VRIJE UNIVERSITEIT AMSTERDAM

MASTER THESIS

The Effect of Maternal and Active Smoking on Lung Function: A Mendelian Randomization Approach

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"Since we cannot know all that there is to be known about anything, we ought to know a little about everything."

Blaise Pascal

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Abstract

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by Hans NUIJT MSc

The prevalence of allergic respiratory diseases such as asthma and rhinitis has been increasing over the last 50 years, while the pathogenesis of these diseases is still not fully known. Lung function is an important parameter in evaluating respiratory health. It is likely that maternal smoking during pregnancy and active smoking have impact on lung function and play a role in the development of respiratory diseases. Previous research has indicated that epigenetics such as DNA methylation may mediate the effect of smoking on the respiratory health. In this research we performed causal inference modelling to infer if the effects of environmental exposures on lung function are mediated by DNA methylation changes. To investigate this, an innovative adapted variant of two- sample, two-step Mendelian randomization was proposed. The analyses provided some evidence for the effect of smoking during adolescence on DNA methylation changes, but showed no clear effect of smoking on lung function. However, for DNA methylation that previously has been shown to be associated with maternal or active smoking, the analyses do present evidence that it affects lung function. Among the most significant findings is DNA methylation near the genes REST, MFSD2B and HORMAD2. These genes have previously been shown to play an important role in lung cancer. Importantly, we found evidence that DNA methylation near the HORMAD2 gene has a mediating role in the effect of smoking on lung function. This suggests that smoking might also affect lung cancer through epigenetics.

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List of Abbreviations

A	**A**denine
C	**C**ytosine
CpG	**C**ytosine-**P**hosphate-**G**uanine
CUE	**C**ontinuously **U**pdating **E**stimator
DNA	**D**eoxyribo**N**ucleic **Acid**
EAACI	**E**uropean **A**cademy of **A**llergy and **C**linical **I**mmunology
EWAS	**E**pigenome-**W**ide **A**ssociation **S**tudy
FEV1	**F**orced **E**xpiratory **V**olume in **1** second
FVC	**F**orced **V**ital **C**apacity
G	**G**uanine
GMM	**G**eneralized **M**ethod of **M**oments
GRIAC	**G**roningen **R**esearch **I**nstitute for **A**sthma and **C**OPD
GWAS	**G**enome-**W**ide **A**ssociation **S**tudy
InSIDE	**In**strument **S**trength **I**ndependent of **D**irect **E**ffect
IV	**I**nstrumental **V**ariable
IVW	**I**nverse **V**ariance **W**eighted method
LD	**L**inkage **D**isequilibrium
LIML	**L**imited **I**nformation **M**aximum **L**ikelihood
MeQTL	**Me**thylation **Q**uantitative **T**rait **L**oci
MR	**M**endelian **R**andomization
MR-PRESSO	**M**endelian **R**andomization **P**leiotropy **Res**idual **S**um and **O**utlier
mRNA	**M**essenger **R**ibo**n**ucleic **A**cid
OLS	**O**rdinary **L**east **S**quares
PIAMA	**P**revention and **I**ncidence of **A**sthma and **M**ite **A**llergy
RCT	**R**andomized **C**ontrolled **T**rial
RNA	**R**ibo**N**ucleic **A**cid
SNP	**S**ingle-**N**ucleotide **P**olymorphism
T	**T**hymine
U	**U**racil
2SLS	**Two**-**S**tage **L**east **S**quares

Chapter 1

Introduction: The Importance of Causal Inference in Allergy Research

Allergic diseases such as asthma and hay fever are highly prevalent diseases. There is still much lack of understanding about what causes these complex diseases. It is highly probable, though, that many biological aspects, like hereditary and environmental factors, are related to the development of the diseases. This means that, to unravel the complexities of the biological aspects and to understand allergic diseases, different layers of biological data have to be integrated and investigated. The question of utmost interest is what causes these diseases. The so-called multi-omics research, that uses different layers of biological data, can help to find causal mechanisms that influence allergic diseases and it thus may help to develop medicines for the diseases.

An important indicator for people's respiratory health is the lung function, for instance quantified by how much and how fast one can breathe out. It is also an important parameter in diagnosis of asthma and other respiratory diseases. In this thesis we investigate the effect of maternal smoking during pregnancy and of active smoking during adolescence on the lung function. This will be done using an adapted and innovative variant of the two-sample, two-step Mendelian randomization framework. The Mendelian randomization technique has been applied much in other researches, but the variant we will use is very new in the field of (epi)genetic research. In the end we aim for obtaining knowledge about biological mechanisms underlying people's respiratory health. These mechanisms are still not fully known and hence our research is both innovative and relevant. In Section 1.5 we state the aims of the research more specifically. Before that, we give relevant background in the next sections, which will help to better understand the concepts needed to grasp the problem statement.

1.1 Prevalence of allergies

Allergy is the most common chronic disease in Europe. At the start of the 20th century allergies were not highly prevalent. However, in 2015 approximately 150 million Europeans suffered from chronic allergic diseases. This is probably an underestimation, since many patients are not correctly diagnosed or do not report their symptoms. Three main allergic diseases are allergic rhinitis (hay fever), asthma and food allergy, with 100, 70 and 17 million Europeans suffering from them, respectively. The prevalence of allergic diseases is still rising, such that it is expected that in 2025 more than 50 percent of all Europeans will suffer from at least one allergic disease (EAACI, 2016).

The impact of allergic diseases on the patient's quality of life is often considerable. As most allergic diseases start in childhood, allergic reactions during school hours can heavily affect children's educational performance. Furthermore, the productivity of people in their high-productivity years can substantially reduce due to allergies. It is estimated that asthma and allergic rhinitis alone result in more than 100 million lost workdays and schooldays in Europe every year. Appropriate treatment of these patients can have a major impact, also in financial terms: up to 142 billion euro per year could be saved in Europe (EAACI, 2016).

There are several allergies that are associated with each other. In a couple of studies the co-occurrence of asthma, allergic rhinitis and eczema have been investigated (Gough et al., 2015; Ziyab, 2017; Steiner et al., 2018). It was shown that the prevalence of this allergic multimorbidity (co-existence) is common among different populations. 20 to 50 percent of patients with rhinitis also suffer from asthma (Sibbald and Rink, 1991; Wright et al., 1994; Leynaert et al., 1999; Yawn et al., 1999). It was also found that rhinitis occurs in up to 80 percent of the asthma patients (Leynaert et al., 1999). It is hypothesized that rhinitis is an independent risk factor of asthma (Bousquet, Vignola, and Demoly, 2003). Because of this association between these diseases it seems clear that research that focuses on causes of only one of the diseases may miss important links. However, to investigate this, we should first have a better view on what these diseases mean and what symptoms they imply.

1.1.1 Asthma

Asthma is a chronic disease affecting the airways of a person. It is characterized by chronic airway inflammation and is associated with airway hyperresponsiveness and airway obstruction. It can cause couging, wheezing, shortness of breath and difficulties in breathing. The airway hyperresponsiveness and airflow obstruction are often reversible, either spontaneously or via treatment. Acute exacerbations can be triggered by inadequate treatment or environmental factors like cold air, physical activity or exposure to tobacco smoke. The diagnosis of asthma is often based on patient history and symptoms of wheeze, cough and shortness of breath. The increasing prevalence of asthma worldwide is assessed by standardized questionnaires (Pawankar et al., 2011).

1.1.2 Allergic rhinitis

Allergic rhinitis is characterized by nasal congestion, a runny nose, sneezing and nasal itching. These symptoms are caused by inflammation in the nasal epithelium and occur when the patient breathes in something he or she is allergic for, like dust or pollen. Allergic rhinitis often co-occurs with allergic conjunctivitis, of which the symptoms include itchy and red eyes and sometimes swelling around the eyes. Rhinitis can have physical implications like fatigue and sleep disturbances, but it can also interfere with social interactions causing people to come in social isolation and limit them in activities. There are effective anti-inflammatory drugs available for allergic rhinitis: antihistamines and intranasal corticosteroids among others (Pawankar et al., 2011).

1.1.3 Atopic eczema

Atopic eczema is a chronic, inflammatory skin disease. It causes the skin becoming itchy, red, cracked and rough. Sometimes blisters occur. The dry skin is a result of a dysfunctioning epidermal barrier, which leads to an increased penetration of environmental allergens. It is assumed that patients who suffer from atopic eczema are likely to develop other atopic diseases, in the form of allergic rhinitis or asthma. Atopic eczema's symptoms vary both with age and over the course of the disease. It can be mild, but can also take the form of generalized body eczema. The drugs that are available to reduce the symptoms of eczema include emollients and anti-inflammatory drugs (Pawankar et al., 2011).

1.2 DNA and genomics

Allergies are complex diseases. A better understanding of those will probably involve several aspects, among which explanations at the level of genetics. Genetics explains many facets of how the body works. As such, understanding genetics may help to understand diseases. Therefore, we will first provide some necessary background on basic cell biology and on genetic variation. We will focus on the essentials. For more elaborate explanations excellent textbooks are available, like Jorde, Carey, and Bamshad (2015).

1.2.1 Basic cell biology

The basic units of inheritance are genes. Genes are contained in chromosomes and are composed of deoxyribonucleic acid (DNA). This DNA supplies the genetic blueprint for all the proteins in the body. Proteins are at the very core of the human body's functioning. For example they are needed for growth and maintenance of the body, they provide structure to cells and have a role in digestion. Humans have approximately 20,000 to 25,000 genes. There are two types of cells in the body, namely somatic cells and gametes. In the human body the former contain 23 pairs of chromosomes and are hence called diploid. The latter are haploid and have a total of 23 chromosomes.

The main components of DNA are the four nucleotide bases adenine (A), thymine (T), cytosine (C) and guanine (G). These bases form a double helix structure, where A binds with T and C with G. Different sequences of these nucleotide bases specify different proteins. In total the DNA specifies the composition of all human proteins. When cells are copied by division, the DNA has to be replicated in order to incorporate it in the new cell. This replication process consists of several phases. It starts with the breaking of the weak hydrogen bonds between the bases, which produces single DNA strands with unpaired bases. When the bonds are broken, the bases in the strands can pair with free bases to form new double strands. Several enzymes are involved in the process. For example, DNA polymerase travels along the DNA strand and adds nucleotides to the strand. See Figure 1.1 for a graphical representation.

Proteins are not formed in the cell nucleus, but in the cytoplasm. Therefore, the information contained in the DNA must be transported out of the cell nucleus to the cytoplasm, where it can inform the composition of proteins. This process consists of two parts: transcription and translation. In the transcription DNA code is transcribed to messenger ribonucleic acid (mRNA). This mRNA can leave the cell

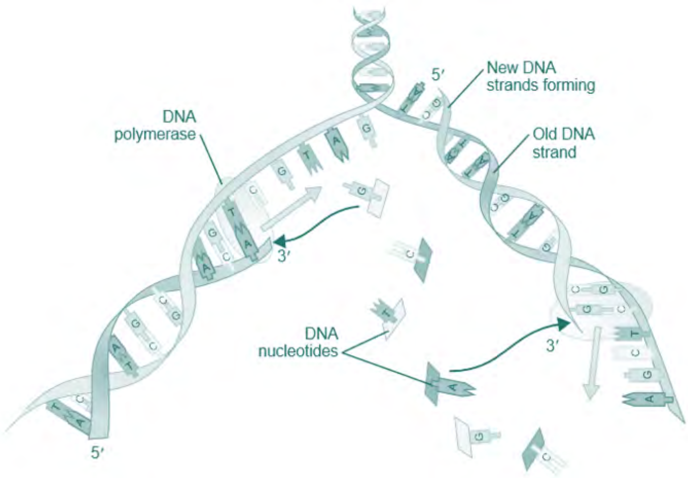


FIGURE 1.1: Graphical representation of the start of the DNA replication process. (From Jorde, Carey, and Bamshad (2015))

nucleus to the cytoplasm, where it can be translated into proteins. Proteins are composed of amino acids. These are encoded by units of three mRNA bases, called codons. There are 64 possible codons and 20 amino acids. RNA resembles DNA, with a main difference that it contains uracil (U) instead of thymine and a ribose sugar instead of deoxyribose. Furthermore, RNA is single stranded whereas DNA takes the form of a double strand.

DNA can be classified into several categories. The first category is single-copy DNA. These sequences are seen only once or a few times in the genome and they make up approximately half of the genome. The other half is repetitive DNA: sequences that occur repeatedly, often thousands of times. Repetitive DNA in turn can be divided into dispersed repetitive DNA and satellite DNA. In the former the DNA is repeated throughout the genome, whereas the latter has its repetitions clustered together. In the end only one to two percent of the 3 billion nucleotide pairs in the human genome encode proteins.

Genetic variation is the result of mutation: a change in the DNA sequence. This makes that a gene can differ between different persons. Such differing sequences are called alleles. An allele is located on the chromosome and this location is called a locus. If someone has the same allele on both members of a chromosome pair, the person is homozygoes and otherwise the person is heterozygoes. Together the alleles make up the genotype of a person. Different DNA sequences that can occur, are named polymorphisms and the loci that contain multiple alleles, are called polymorphic. The most frequent type of polymorphisms are single nucleotide polymorphisms (SNP), which are variants at single nucleotide positions.

Mutation can take several forms. Important types of mutation are base-pair substitution, deletions and insertions. In base-pair substitution a base pair is replaced by another base pair. Many of these mutations do not change the amino acid sequence, but some can result in a change. Deletions and insertions of base pairs often lead to missing or added amino acids. In the end, mutations can result in a gain or loss of function of the protein product. The cause of mutations can lie within the cell, for example during DNA replication. These mutations are called spontaneous.

However, mutations can also occur as a result of environmental causes. An example of these mutagens is radiation.

Gene function also can be changed by DNA methylation. This means that a methyl grou is attached to the C-base. Typical hotspots for methylation are CG dinucleotides. DNA methylation can change the activity of the DNA, although the sequence itself is not changed. Approximately 80 percent of CG dinucleotides in mammals are methylated. These dinucleotide sequences are called cytosine-phosphate-guanine (CpG). A methylated cytosine loses an amino group and is thus converted to thymine. CpGs play a role in several human diseases (Jorde, Carey, and Bamshad, 2015). It is also a very important factor in silencing or activating genes and thus in gene regulation.

1.2.2 The study of DNA

The study of genes and their role in heredity is called genetics (Griffiths et al., 2005). There are several subfields of genetics, among which epigenetics. Epigenetics is the study of heritable gene function changes that do not entail a change in the DNA sequence (Dupont, Armant, and Brenner, 2009). An important example of a mechanism that is studied in epigenetics is DNA methylation. Although sometimes used interchangeably, genetics is not exactly the same as genomics. Genomics is the study of the whole of the genome and how genes in the genome interact with each other and with the environment. Furthermore, in epigenomics all epigenetic modifications on the genetic material are studied.

In genetic studies often the array of DNA base pairs that make up a gene, has to be determined. Previously, the methods for this were quite slow. However, nowadays advanced methods like high-throughput DNA sequencing, have decreased the costs of sequencing, since millions of DNA fragments can be sequenced simultaneously. This means that in the past years an enormous amount of DNA became available, which offers many possibilities and challenges for analysis (Jorde, Carey, and Bamshad, 2015).

1.2.3 Multi-omics

High-throughput technologies provide large data sets. These genome-scale data sets are called omics data (Joyce and Palsson, 2006). It is a challenging task to identify, extract and interpret biological insights from these data sets. Recently, researchers have tried to do so by integrating multiple omics data sets. Examples of omics data sets are genomics, transcriptomics (data about presence and relative abundance of RNA transcripts), proteomics (data about cellular levels of each protein that is encoded by the genome) and metabolomics (data about the set of metabolites of the cell). These multi-omics data have to be integrated in order to unravel complexities of fundamental biology, to find the interdependencies between the layers and to explain or predict disease risk. Several methods for this are discussed in Joyce and Palsson (2006), Zhang, Li, and Nie (2010), Ritchie et al. (2015), Hasin, Seldin, and Lusis (2017), and Lin and Lane (2017).

1.3 Causes of allergies

With the basic biology knowledge in mind, we can have a closer look at the potential causes of allergies. Research on the causes of allergies is an active field of research.

Although much is still unknown, it is currently believed that asthma and allergies are caused by both genetic and environmental factors. Gref (2017) gives an overview of some factors that, according to the current state of knowledge, are important factors in the development of asthma and allergies.

1.3.1 Environmental factors

Previous research has focused on several types of environmental factors. A main environmental factor associated with asthma and allergies is indoor mold and dampness. It is regarded as a large public health problem, causing microorganisms to flourish, which in turn results in exposure to microbial agents, like inflammatory substances and allergens (Mudarri and Fisk, 2007; Cho, Cox-Ganser, and Park, 2016). Several studies have found associations between indoor mold and dampness and allergies, see e.g. Fisk, Lei-Gomez, and Mendell (2006), Mendell et al. (2011), Quansah et al. (2012), and Jaakkola et al. (2013).

Another factor that is suspected to negatively affect asthma and allergies is traffic-related air pollution. This pollution consists of a mixture of components, such as nitrogen oxides (NO_x) and particulate matter (PM). It is almost impossible to measure an individual's exposure to air pollution, therefore most studies have focused on the association between proxies for air pollution exposure and diseases. In these studies associations were found with lung function development in children (see e.g. Gauderman et al. (2004), Schultz et al. (2012), and Gehring et al. (2013)) and with childhood asthma development (see e.g. Health Effects Institute (2010), Bowatte et al. (2015), and Gehring et al. (2015)). Also, smoke, either due to maternal smoking during pregnancy, active smoking or second hand smoking, may contribute to the development of allergic diseases (see a.o Burke et al. (2012) and Tommola et al. (2018)).

Dietary intake may play a role in relation to allergic diseases. It has been hypothesized that decreasing the intake of antioxidants and omega-3 fatty acids and increasing omega-6 polyunsaturated fatty acids may increase asthma and allergic diseases. The anti-oxidative and anti-inflammatory properties of foods with antioxidants and omega-3 fatty acids may have beneficial effects (Devereux and Seaton, 2005; Allan, Kelly, and Devereux, 2010). However, finding causal mechanisms is challenging. It is difficult to measure dietary intake. Furthermore, allergic diseases may change one's diet, impeding the search for cause and effect (Rosenlund et al., 2011).

1.3.2 Genetic factors

As the human genome is very complex, there are lots of factors from different omics layers that may be related to asthma and allergies. Several genetic factors have been found on both DNA level and epigenetic level.

On the genetic level often variations in single nucleotides are studied. If SNPs are in regulatory regions, gene expression could be affected. SNPs in coding regions can alter the function of a gene and the gene product. Via linkage studies several candidate genes have been investigated for their relationship with asthma and allergies. Examples are Laitinen et al. (2004), Ober and Hoffjan (2006), and Aoki et al. (2006). Furthermore, genome-wide association studies (GWAS) are used to search for possibly related SNPs. In this hypothesis-free approach the whole genome is studied in relationship with an outcome of interest. A recent overview of the GWAS studies on asthma can be found in Kim and Ober (2019).

The relationship between DNA methylation and gene regulation is complex. Furthermore, it may be that environmental factors induce epigenetic effects in the form of methylation. To study methylation different approaches are available: targeted locus-specific, epigenome-wide and global methylation approaches. The latter give only information about the total methylated CpG sites in a sample. Epigenome-wide assocation studies (EWAS) have been performed to study the relationship between environmental exposures and methylation and between asthma and methylation and several associations were found (Joubert et al., 2016; Gruzieva et al., 2017).

1.4 Focus points in allergic diseases research

In the previous section we mentioned a lot of factors that possibly have an effect on the development of asthma and allergies. However, much is still unknown about the causal mechanisms that induce asthma and allergies. Given the abounding prevalence of those diseases and the significant burden they induce, research on them is higly relevant. Therefore the European Academy of Allergy and Clinical Immunology (EAACI) has determined the following research priorities. First of all, in the strive towards personalized allergy medicine, clinical syndromes should be categorized into more uniform and treatment-responsive groups. Furthermore, research that tries to unveil pathways and mechanisms of allergies should be supported. Besides, the surveillance and monitoring of allergy trends in Europe should be increased by means of allergy bio-banks and registries. Fourth, biotechnological innovations should be brought closer to clinical practice and lastly more research should be done to prevent and cure allergic diseases (EAACI, 2016).

Research focusing on the integration of multi-omics data mostly focuses on understanding the diseases. Thus, this type of research on asthma and allergies fits very well into the focus points as pointed out by the EAACI. Specifically, multi-omics research can help to find pathways and causal mechanisms. As such, its results may help to improve personalized medicines and ultimately, it can help to prevent and cure allergic diseases.

1.5 Problem statement and thesis structure

To investigate the interactions between multi-omics layers and allergic diseases, the Groningen Research Institute for Asthma and COPD (GRIAC) has done a large cohort study, the PIAMA cohort. The data from this cohort consists of approximately 2000 samples. The different data layers are genotype data (millions of variables), DNA methylation data (from blood and nasal epithelial cells, hundreds of thousands of variables), RNA sequencing data (thousands of variables) and environmental factors. The blood methylation data and the environmental factors are also recorded over time. We will extensively introduce the data in the next chapter.

GRIAC has hypothesized the following:

1. Environmental factors in various stages of childhood may differentially affect the development of allergic respiratory diseases; epigenetic changes in the respiratory epithelium form an important mechanism in this development.

2. In the respiratory epithelium, combinations of environmental factors, genetic and epigenetic variation affect gene expression, leading to causal relationships with asthma development.

Among the environmental factors (also known as exposures) that are regarded to be very relevant in the development of asthma and allergic diseases are smoking and maternal smoking during pregnancy. To investigate the effect of these environmental factors, the respiratory health has to be measured. This can be done in several ways. For instance, one can use the prevalence of asthma or allergies as indicator for one's respiratory health, but it is also possible to investigate related measures like lung function. At this moment it is still unknown what the exact causal relationships are between environmental factors (active smoking and maternal smoking) and diseases (asthma, allergy) or disease-related measurements (lung function). To investigate this problem, a crucial step is to perform causal inference modelling to infer if the effects of exposures on disease are mediated by gene methylation changes. This is the focus of this thesis. Specifically, the goal is as follows:

> *Perform causal inference modelling to infer if the effects of environmental exposures on lung function are mediated by gene methylation changes.*

The purpose is hence to get a better understanding of respiratory diseases, by investigating the role that DNA methylation plays in the development of diseases.

The causal inference modelling is done using an adapted variant of two-sample, two-step Mendelian randomization. This method can help in discovering causal relationships. It is based on the framework of Mendelian randomization and is meant to investigate the causal relationship between an exposure (in our case smoking or maternal smoking), DNA methylation and outcome (for us: lung function). In short: 'The two-step approach first uses a genetic proxy for the exposure of interest to assess the causal relationship between exposure and methylation. A second step then utilizes a genetic proxy for DNA methylation to interrogate the causal relationship between DNA methylation and outcome' (Relton and Smith, 2012). The Mendelian randomization framework is used to investigate the effect of smoking on specific CpG sites and to investigate how the methylation of specific CpG sites affects lung function. Hence, the analysis is not epigenome-wide, meaning that we should restrict ourselves to a small number of CpGs. Selecting which CpGs are worth investigating by means of Mendelian randomization is done using epigenome-wide association studies. The Mendelian randomization itself in turn, is done using an instrumental variable approach.

The rest of this thesis is structured as follows. In Chapter 2 we extensively introduce the data, its source and characteristics. Then we will proceed by explaining the background and method of Mendelian randomization, two-sample, two-step Mendelian randomization and how these are related to the method of instrumental variables in Chapter 3. This theoretical background enables us to create a structured methodology, which we will outline in Chapter 4. The reader who is familiar with the idea of Mendelian Randomization and its mathematical techniques may skip Chapter 3. However, for the interested reader or one who is not familiar with

Mendelian randomization this chapter forms a complete overview of the techniques used. After outlining the methodology we present the results and discussion thereof in Chapter 5. Finally we conclude in Chapter 6.

Chapter 2

Data

2.1 The PIAMA cohort

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study started in 1996. It was set up with two aims:

1. To investigate the effect of mite-allergen avoidance on the incidence of asthma in childhood (Intervention Study).
2. To investigate the incidence of asthma in children from zero to eight years (Natural History Study).

The cohort was set up because of the increasing prevalence of asthma in The Netherlands, mainly among children. In 1992, the Public Health Council of The Netherlands questioned whether decrease of exposure to indoor allergens early in life would prevent or delay the development of allergies and asthma in children. They recommended an intervention study to measure effectiveness of reducing early postnatal exposure to indoor allergens. Together with this intervention study, the natural history study was started to further investigate the incidence of asthma and allergies. Official documentation on the cohort can be found at the websites of birthcohorts.net[1] and of the PIAMA research project[2]. The design and profile of the study also has been described in literature, in Brunekreef et al. (2002) and Wijga et al. (2013).

The study population consists of 3963 children born in 1996-1997 in The Netherlands. The locations of the communities from which children are included are given in Figure 2.1. Of these children, 3291 participated in the natural history study. The parents of the children were asked to fill in several questionnaires, during pregnancy, at the child's 3 months age and 1 years age and then annually until the children were 8 years. Furthermore, home visits and clinical examinations were performed several times. After the first 8 years the study was extended and this resulted in information about the children's exposures, development and health and data from biological samples up till the time they were eighteen years old. Our study will focus on the data of the 16 years old, as this was also the focus of previous studies.

2.2 Characteristics of the data

The data we will be looking at, consists of four data sets, indicated in Table 2.1 as 'combined' data sets. Not all data is available for an equal number of participants,

1. http://www.birthcohorts.net/birthcohorts/birthcohort/?id=244
2. http://piama.iras.uu.nl/index-en.php

FIGURE 2.1: Study area PIAMA cohort
Study area of the PIAMA cohort study. (From `http://piama.iras.uu.nl/`)

resulting in differing number of samples between the data sets. For the persons in the study multiple characteristics are available. Table 2.2 lists how the main discrete covariates in the data sets are distributed and Table 2.3 shows the distribution of the main continuous covariates.

TABLE 2.1: Number of variables in the data sets.

Type	**Dataset**	**N**
Methylation	Nasal methylation	478
	Blood methylation	640
Lung function	Lung function	799
Phenotype	Diseases+some covariates	455
	Height	2671
	Blood cell count	613
	Maternal smoking	3964
	Active smoking	1454
Combined	Blood methylation - phenotype - lung function	611
	Blood methylation - phenotype - smoking	510
	Nasal methylation - phenotype - lung function	452
	Nasal methylation - phenotype - smoking	384

The main outcome variable for this research is the lung function of the participants. The lung function can be measured in several ways. For the PIAMA cohort we have data about the forced expiratory volume in one second (FEV1) and forced vital capacity (FVC). Figure 2.2 shows how these are distributed within the data set.

The methylation data constitutes 436,824 columns. These columns indicate per CpG site to what extent it is methylated. This methylation level is given as a number

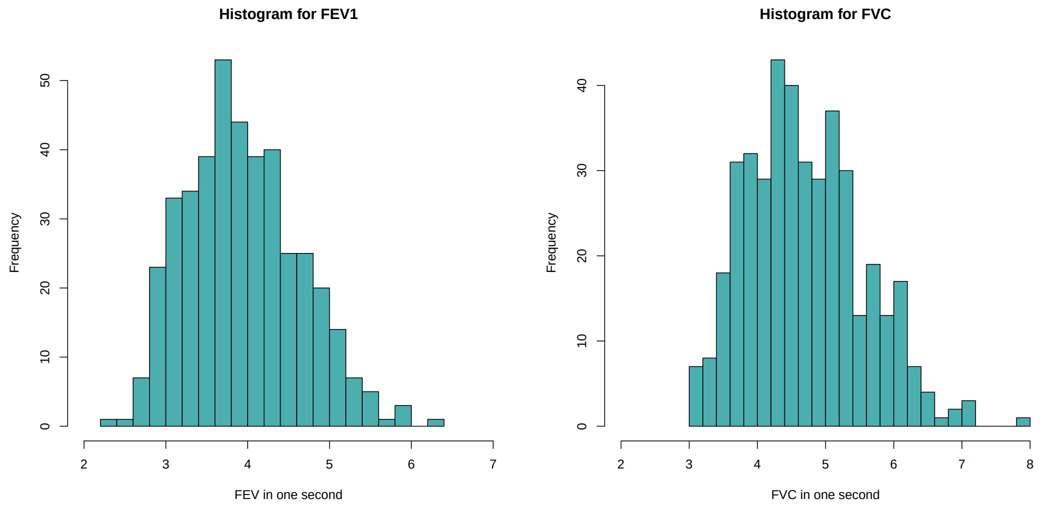
TABLE 2.2: Distribution of the main covariates in the four combined data sets in percentages.

		Blood methylation		Nasal methylation	
		Lung function	Smoking	Lung function	Smoking
N		**611**	**510**	**452**	**384**
Gender	Male	51	51	52	52
	Female	49	49	48	48
Batch	1	66	67	67	67
	2	34	33	33	33
Study center	Groningen	45	44	54	53
	Utrecht	55	56	46	47
Ethniticity	1	93	94	95	95
	2	4	3	4	3
	3	3	3	1	1
Maternal smoking	No		91		90
	Yes		9		10
Active smoking	No		87		89
	Yes		13		11
Allergy	No	52	52	54	55
	Yes	48	48	46	45
Rhinitis	No	53	54	55	56
	Yes	47	46	45	44
Asthma	No	91	92	92	92
	Yes	9	8	8	8

TABLE 2.3: Characteristics of the main continuous variables in the four combined data sets (mean, sd). The latter seven variables are all related to blood cell count.

	Blood methylation		Nasal methylation	
	Lung function	Smoking	Lung function	Smoking
Height	176.0 (8.79)		175.7 (8.62)	
Age	16.3 (0.21)	16.3 (0.21)	16.3 (0.20)	16.3 (0.19)
FEV1	4.0 (0.72)		3.9 (0.69)	
FVC	4.7 (0.87)		4.7 (0.85)	
CD8T	1.0E-01 (0.05)	1.0E-01 (0.05)		
CD4T	1.4E-01 (0.05)	1.4E-01 (0.05)		
NK	2.7E-02 (0.03)	2.6E-02 (0.03)		
Bcell	6.8E-02 (0.03)	6.8E-02 (0.03)		
Mono	7.7E-02 (0.02)	7.6E-02 (0.02)		
Neu	5.8E-01 (0.10)	5.9E-01 (0.10)		
Eos	3.6E-03 (0.02)	3.6E-03 (0.02)		

between zero and one. Table 2.4 shows the overall mean and standard deviation of the methylation levels. Furthermore, it shows that there is much variation between the methylation levels of different CpG sites, this is in line with what we would expect, given the very different roles CpG sites can have in diseases but also in the normal functioning of the body.



(A) Forced expiratory volume in one second (B) Forced vital capacity

FIGURE 2.2: Histograms of the lung function of PIAMA participants at their sixteenth year.

TABLE 2.4: Mean and standard deviation of the overall methylation levels in the PIAMA data of the CpG sites with the highest or lowest mean. The CpG site with the lowest mean is in both blood and nasal methylation data cg02461388 and the one with the highest mean is cg06096175 in blood and cg16706374 in nasal methylation. The total number of CpG sites is 436,824.

	Blood	**Nasal**
All	0.49 (0.342)	0.48 (0.334)
Lowest	0.02 (0.005)	0.03 (0.006)
Highest	0.98 (0.004)	0.98 (0.004)

2.3 Findings from the PIAMA cohort

The data from the PIAMA cohort has been used in many studies. On the website of the PIAMA project the results are divided into ten categories. These range from studies related to asthma and allergies to studies on overweight. Table 2.5 summarizes the main study topics.

Our research fits within four of the categories in Table 2.5: environmental factors, lifestyle factors, interaction between genetic predisposition and environment, and lastly the effect of circumstances during pregnancy and birth. Of particular interest for this thesis are the PIAMA studies that focus on asthma and allergies. As this is one of the main study areas of the PIAMA cohort, many articles have been published related to this subject. Within this study area the most relevant papers are those on the relationship between environmental factors and allergies or asthma and on the relationship between DNA methylation and those diseases. Recently Forno et al. (2019) published on the latter, where they identified CpG sites associated with asthma. Also some studies on the effects of maternal smoking were performed, for

TABLE 2.5: Categories in which results have been published originating from the PIAMA cohort

	Example paper	
Category	**Subject**	**Reference**
Living with asthma	Use of asthma medication	Wijga et al. (2014)
Environmental factors	Traffic-related air pollution and development of asthma	Gehring et al. (2015)
Lifestyle factors	Relationship between overweight and asthma	Scholtens et al. (2009)
Dietary intake	Relationship between dietary and asthma	Willers et al. (2011)
Airway tests	Relationship between exhaled NO and asthma	Brussee et al. (2005)
Allergy and other diseases in family	Allergy occurrence in children from (non)-allergic parents	Strien et al. (2002)
Interaction between genetic predisposition and environment	Association between COPD related genes and lung function in early childhood	Kerkhof et al. (2014)
The use of allergen impermeable mattress covers	Effect of mite-impermeable mattress covers	Gehring et al. (2012)
Effect of circumstances during pregnancy and birth	Relationship between cesarean delivery, overweight and blood pressure	Pluymen et al. (2016)
Pain	Musculoskeletal complaints while growing up	Picavet et al. (2016)

instance, by Thacher et al. (2018) who found that maternal smoking during pregnancy is associated with increased odds of prevalent asthma. However, the effects of smoking during adolescence have not much been studied yet.

Chapter 3

Statistical Background

The main technique that we employed to perform causal inference is an adapted variant of two-sample, two-step Mendelian randomization. This technique makes use of the approach that is known in econometrics as the instrumental variable approach. Central in the Mendelian randomization approach is the idea that if a certain phenotype like smoking causes a disease, than also a genetic variant that is related to smoking must be associated with the disease. In this chapter we elaborate on the background of Mendelian randomization and the specific variant that is called two-sample, two-step Mendelian randomization. Furthermore, given the relationship between Mendelian randomization and instrumental variables, we give the necessary theoretical background on instrumental variables.

3.1 Mendelian randomization

3.1.1 The limitations of observational epidemiology

Observational epidemiological research has revealed many associations relevant in epidemiology. However, this form of epidemiology has been shown to have several serious limitations. The main limitation is that observational epidemiology fails to discern causal association from other types of association. For example, the effect of β-carotene on smoking-related cancers was based on epidemiological research believed to be risk-reducing. However, randomized controlled trials (RCT) did not affirm this (Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group, 1994). The main reason that such epidemiological results are found is probably confounding. Confounding is the case where a factor that is not causally related to a disease, is related to other factors that in turn increase disease risk. One might think, for instance, of factors like socioeconomic position and health service utilization (Smith and Ebrahim, 2003).

3.1.2 An alternative: Mendelian randomization

In 1986, Katan (1986) came up with an idea how to distinguish confounding from causation in epidemiological studies. At that time low serum cholesterol levels were associated with an increased risk of cancer. The causal mechanism was not understood: it might be that early-stage cancer causes low cholesterol levels or that there are confounding factors. Katan's idea was to test whether polymorphic forms of a gene related to cholesterol levels were also related to an increased risk of cancer. If the low cholesterol levels caused cancer, then people with a polymorphism related to low cholesterol levels would have a higher risk of cancer than other individuals. Katan did not have the data to study this, so this only was a study design. However, this idea became influential and more widely adopted in the years that followed.

In 1991, a similar approach was first named 'Mendelian randomization' (Gray and Wheatley, 1991). Katan's idea is central in the Mendelian randomization approach, hence it is vital that the reader fully grasps it.

Mendelian randomization (MR) is based on Mendel's second law, which states that inheritance of one trait is independent of inheritance of other traits. Hence, we say that genes are randomly assigned. MR uses this random assignment of genes to reduce confouding when investigating the association between an exposure and a disease. The idea is as follows. Assume that a polymorphism at a locus produces different phenotypes. If these phenotypes mirror the biological effect of modifiable environmental exposures that alter disease risk, then the polymorphisms should be related to disease risk, to the extent predicted by their influence on the phenotype. For instance, several SNPs have been found to be related to smoking, implying that certain genetic profiles make it more plausible that people smoke. Hence, if smoking causes differential DNA methylation, we also expect to find a relationship between the SNPs and DNA methylation. Since the distribution of polymorphisms is hardly related to confounders, this approach has advantages over observational epidemiology. Two types of polymorphisms are particularly interesting for Mendelian randomization: those that regulate the level of the product coded by a gene and those that influence the structure and function of gene products (Smith and Ebrahim, 2003).

Assumptions

There are three main assumptions that must be fulfilled in a Mendelian randomization framework (Sekula et al., 2016).

1. The genetic variant (SNP) must be strongly associated with the exposure (e.g. smoking).
2. It must not be associated with confounders.
3. It may only be associated with the outcome (e.g. lung function) through the exposure.

In Figure 3.1 this is graphically depicted. Of these assumptions only the first is empirically verifiable.

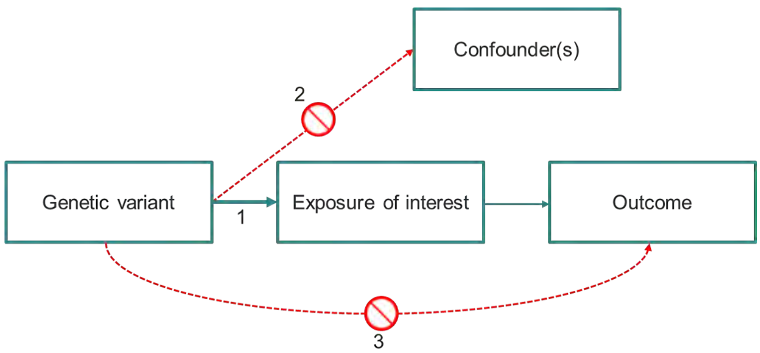


FIGURE 3.1: Graphical representation of Mendelian randomization framework, including its core assumptions (1-3).

Advantages

The use of genetic variants as proxies for environmentally modifiable exposures, as done in Mendelian randomization, has three large advantages (Relton and Smith, 2012). First, Mendelian randomization overcomes the confounding that can occur in observational epidemiology. Many environmentally modifiable exposures are associated with behavioural, social or physiological factors. However, genetic variants that are used as proxy for these exposures do not suffer from this limitation. Furthermore, also the problem of reverse causation can be overcome. In epigenetic studies in particular, this can be a major issue for observational studies. It could be that a disease influences the level of an exposure, like alcohol drink. This reverse causation is not an issue when the genetic variant is used, as the genetic variants are randomly allocated during meiosis. Lastly, Mendelian randomization is robust to temporal variation. Some phenotypes may have high levels of variability. Hence, single measures of these may wrongly estimate the strength of the association between this phenotype and a disease. Genetic variants that are proxies for exposures, reflect the long-term levels of exposure, and are hence more robust.

Limitations

Despite the major advantages that Mendelian randomization offers, there are some limitations that have to be considered carefully (Smith and Ebrahim, 2003; Relton and Smith, 2012; Sekula et al., 2016). The first limitation is that many Mendelian randomization studies have a low statistical power, due to modest effect sizes and relatively small samples. Furthermore, there are several problems related to spurious relationships and confounding. Population stratification (confounding of a genotype-disease association due to factors related to a subpopulation) can be a problem, but can be overcome by applying standard genetic epidemiological methodologies. Confounding can also occur through pleiotropy and linkage disequilibrium (LD). Pleiotropy means that one polymorphism influences more than one intermediate phenotype. LD is the non-random assocation of alleles at multiple loci. It can lead to confounding if the genetic variant under study is in LD with another variant. Another serious threat for Mendelian randomization is canalization. During development the effect of a polymorphism may be compensated. Hence, the phenotypic pertubation that would follow a genetic variant is countered. Lastly, there may be a lack of genetic variants that can be used to proxy for the exposure of interest and the associations might be that complex that misleading inferences may be drawn.

3.1.3 Two-sample Mendelian randomization

In recent years it has become increasingly popular to use summary data for Mendelian randomization (Hartwig et al., 2017). For this type of MR only instrument-exposure and instrument-outcome association results from e.g. publicly available GWAS summary statistics are used to obtain causal estimates of the effect of exposure on the outcome. These association results however do not have to originate from the same sample. The technique in which summary-level results from different samples are used for MR is called two-sample MR (Pierce and Burgess, 2013). Given the developments of increasing availability of public GWAS results, it has become easy to apply this potentially powerful technique.

Advantages and limitations

Two-sample MR has some large advantages. First, since the availability of public GWAS results is strongly increasing, MR can be applied to investigate a wide range of associations. Furthermore, given the often large sample sizes of GWASs, two-sample MR may yield much more power than conventional one-sample MR. However, also some challenges arise. First, as Zhao, Wang, et al. (2018) point out, when the selection of instruments is done using the same sample as the estimation of the instrument-exposure association, a selection bias comes in. This even happens when the selection threshold is very stringent. Furthermore, not all assumptions of the IV analysis can be tested in the same way as in one-sample MR. For example, the association between confounders and the instrument can often not be tested, as this data is not available in GWAS results. Thirdly, one should take care that the data from the two samples are harmonized correctly (Hartwig et al., 2017). For instance, when the effect allele is not the same in both samples, MR results are distorted and hence not reliable. Lastly, pleiotropy may still cause confounding, just as in one-sample MR.

3.1.4 Two-step Mendelian randomization in epigenetics

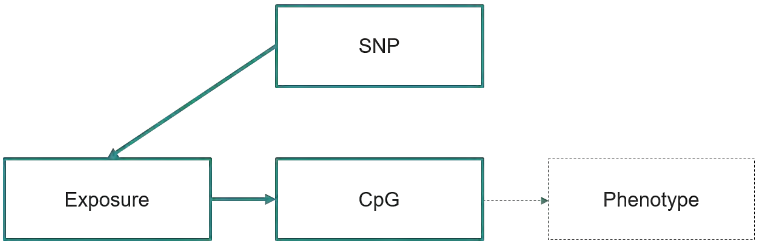
The idea of Mendelian randomization can also be extended to examine the role of methylation as mediator in the causal relation between an environmental exposure like smoking and a disease outcome. This idea originates from Relton and Smith (2012). We here take a look at the most important components of this approach, which are also graphically depicted in Figure 3.2.

In the first step of two-step MR the relationship between an environmental exposure and DNA methylation is investigated. The central idea of MR is employed for this: if an environmental exposure is causally related to a disease outcome, then there must be an (indirect) association between genetic variants that are related to the exposure on the on side and disease outcome on the other side. Hence, a genetic proxy for the environmental exposure can be used. The main prerequisites are to find the genetic variants that can serve as the proxy or instrumental variable for the exposure, and to find which regions of the epigenome should be investigated, thus the methylated CpG sites of interest have to be chosen.

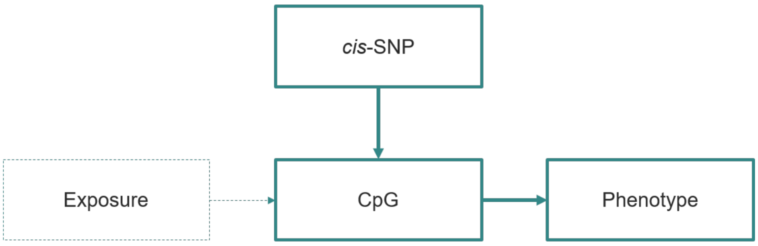
The second second step utilizes a genetic proxy for DNA methylation to evaluate the relationship between DNA methylation and a disease outcome. The idea is again the same as in the original MR: if DNA methylation at a certain CpG site is causally related to a disease outcome, then there must also be an association between genetic variants that are related to the DNA methylation at that particular site on the one hand and the disease outcome on the other hand. In practice this can be applied as follows. As genetic proxy for methylation levels *cis*-SNPs can be used, i.e. SNPs in the locality of the CpG site that correlate with methylation level of the CpG. This genetic proxy can then be used to infer the causal relationship between DNA methylation and a disease outcome.

Advantages and limitations

Two-step MR can help to really understand the role of DNA methylation as a mediator of the influence of an environmental exposure on diseases. This is of particular importance, since DNA methylation plays a role in multiple clinical pictures



(A) First step of the two-step Mendelian randomization: a genetic variant (SNP) is used as proxy for the environmental exposure (smoking) to assess the relationship between exposure and DNA methylation.



(B) Second step of the two-step Mendelian randomization: a genetic variant (*cis*-SNP) is used as proxy for DNA methylation to assess the relationship between DNA methylation and a disease outcome (lung function).

FIGURE 3.2: Graphical representation of the two-step Mendelian randomization framework.

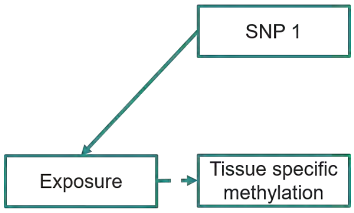
(Robertson, 2005). As Relton and Smith (2012) point out, the technique has the ability to distinguish between intervention targets and epiphenomena which may be only biomarkers for a disease. However, the technique has not been applied much yet. This implies that it offers a great research potential that we also try to utilize in this thesis. On the other hand, two-step MR also has some limitations, which are the same as in the normal MR. Hence, one has to be aware of possible limitations like population stratification and confounding through pleiotropy and linkage disequilibrium, when applying the technique.

3.1.5 Two-sample, two-step Mendelian randomization

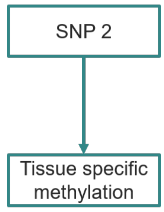
The two former methods, two-sample MR and two-step MR, can also be combined into two-sample, two-step MR. To the best of our knowledge this method has only been described conceptually in literature, without any practical application. Smith and Hemani (2014) introduce this method as a way to investigate mediation of tissue-specific phenotypes, like DNA methylation. Since tissue-specific data is often not available for many individuals, it is advantageous to combine two-sample and two-step MR in the following way. First, in a small sample (for which DNA methylation data is available) the causal effect of the exposure on tissue-specific DNA methylation and of a *cis*-SNP on methylation can be investigated. Then, in a large sample the relationship between exposure and outcome can be investigated. This idea is illustrated in Figure 3.3.

3.2 Instrumental variables

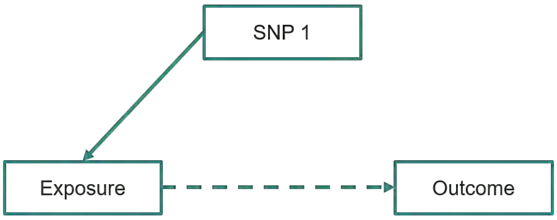
The properties of Mendelian randomization define in fact an instrumental variable approach. This technique is well-known in econometrics and in the literature on



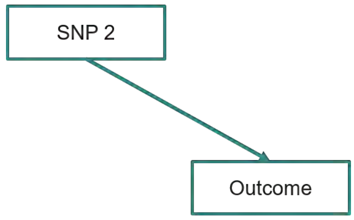
(A) **Sample 1:** Investigate association between exposure and tissue-specific methylation using MR.



(B) **Sample 1:** Find *cis*-SNP associated with methylation differences but not related to exposure.



(C) **Sample 2:** Relate SNP 1 to exposure and to outcome. If the exposure data is not available, relate the SNP only to the outcome.



(D) **Sample 2:** Relate SNP 2 to the outcome.

FIGURE 3.3: Graphical representation of two-sample, two-step Mendelian randomization. Two samples are used: a small sample (sample 1) and a large population-based sample (sample 2).

causal inference. In this section we explain this link and describe the conditions and assumptions for genetic variants to be used as instruments, like described by Didelez and Sheehan (2007) and Hinke et al. (2016). Furthermore, we elaborate on the instrumental variable estimators for MR, in the literature for example described by Burgess, Small, and Thompson (2017). First of all, however, we explain the theoretical background and actual concept of instrumental variables.

3.2.1 Background and concept

In econometrics it is often desirable to find the magnitude and direction of causation in, for instance, a policy analysis. However, inferring these using regression analysis will often result in flawed results, due to the well-known fact that correlation does not imply causation. A specific case where regression analysis will give flawed results is when there is an endogenous variable (i.e. a variable that is correlated with the error term in the regression). Then the parameter estimation becomes inconsistent. Let us consider this in a simple linear regression case. An Ordinary Least Squares (OLS) regression model specifies

$$y_i = \beta_0 + \beta_1 x_{i1} + ... + \beta_p x_{ip} + \varepsilon_i, \quad i = 1, ..., n$$

where y_i is the dependent variable, x_{ij}, for $j = 1, .., p$ are the independent variables, β_j are the parameters of interest and ε_i the unobserved errors. In matrix notation we can write the model as

$$y = X\beta + \varepsilon$$

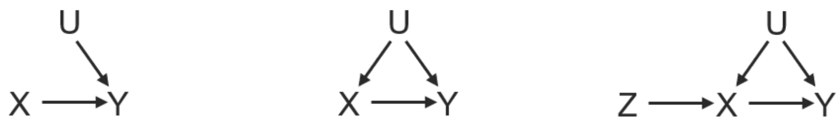
One of the assumptions of OLS is that X is not correlated to ε_i, which is a necessary assumption to ensure consistency of the OLS estimator $\hat{\beta}$. This is visualized as a directed acyclic graph (DAG) in Figure 3.4a. In this figure the arrows indicate conditional dependencies rather than causal dependencies. However, in situations when there are measurement errors or omitted variables in the regression, there may occur association between the predictors X and the erors ε (see Figure 3.4b). Assume that we can decompose the error term $\varepsilon = u(X) + \epsilon$, where $u(X)$ is the part that depends on X and ϵ is the independent part. When we for simplicity leave out the intercept and consider only one predictor x, we have

$$y = \beta x + u(x) + \epsilon. \tag{3.1}$$

Suppose that the dependence of u on x is described by $u = \beta_u x$, then Equation (3.1) becomes

$$y = (\beta + \beta_u)x + \epsilon.$$

Consequently, the OLS estimator $\hat{\beta}$ for β measures the total effect $\beta + \beta_u$, instead of β alone: the estimator becomes inconsistent. A solution is to find an instrument z that is correlated with x and only affects y through x (see Figure 3.4c).



(A) x is correlated to y, but not correlated with the error term.

(B) The predictor x is correlated with both the dependent variable y and the error term.

(C) When the predictor x is correlated with the error term, an instrument z can be used that affects y only through x.

FIGURE 3.4: Directed acyclic graph of the cases where x is independent of the error term (A), x is associated with the error term (B) and z is used as instrumental variable for the endogenous variable x.

The assumptions that must hold for a variable z in order to be used as an instrumental variable are as follows, in terms of conditional independence (Didelez and Sheehan, 2007):

1. z must not be (marginally) independent of x.
2. z must be (marginally) independent of the confounder u.
3. conditionally on x and the confounder u, the instrument and the response are independent.

In the previous section we discussed the assumptions that must hold in order to apply the concept of MR. These are exactly the assumptions that must hold for a variable to be used as an instrumental variable. Hence we can use the techniques and estimators for instrumental variable analysis that are known from econometrics. Because we apply these techniques in our research, we will discuss those below. The techniques known from econometrics are mostly techniques for which data is needed on individual level. So, we start by discussing estimators for this situation.

3.2.2 Instrumental variable estimators for data on individual level

There are several methods available for instrumental variable (IV) estimation. Burgess, Small, and Thompson (2017) give a clear overview of these estimators and discuss their application to Mendelian randomization. We discuss the four methods they mention: ratio, two-stage, likelihood-based and semi-parametric methods.

Ratio of coefficients method

The ratio of coefficients method is a method that can incorporate only one IV. It first regresses the exposure on the IV, yielding the coefficient $\hat{\beta}_{x|z}$, and then it regresses the outcome on the IV, which gives $\hat{\beta}_{y|z}$. The estimator of the causal effect β is then

$$\text{Ratio method estimator} = \frac{\hat{\beta}_{y|z}}{\hat{\beta}_{x|z}}. \tag{3.2}$$

Two-stage least squares

In contrast to the ratio of coefficients method two-stage methods can handle multiple IVs. The method, in the case of a continuous outcome and a linear model, is known as two-stage least squares (2SLS). It is a generalization of the ratio estimation in the sense that 2SLS can be viewed as a weighted average of the ratio estimators calculated with one instrument at a time and then weighted by the relative strength of the instruments in the first stage of the regression. Mathematically, 2SLS works as follows. Given J IVs and sample size N, the first stage is

$$x_i = \alpha_0 + \sum_j \alpha_j z_{ij} + \varepsilon_{xi}, \quad i = 1, ..., N; j = 1, ..., J, \tag{3.3}$$

where x_i is the endogenous regressor, z_{ij} are the instrumental variables, α_k the estimated regression coefficients and ε_{xi} are the errors. The fitted values $\hat{x}_i$ can then be used in the second stage:

$$y_i = \beta_0 + \beta_1 \hat{x}_i + \varepsilon_{yi}. \tag{3.4}$$

We are interested in the coefficient β_1. When estimating both models with OLS, the assumption is that the error terms are homoscedastic and are stricty exogenous. Furthermore, it is important to recognize that the standard errors from the second stage are not correct, because uncertainty from the first stage is not taken into account.

Likelihood methods

Likelihood methods form another alternative estimation method for IVs. Since the two stages are performed simultaneously in these methods, uncertainty in the first stage is taken into account, unlike 2SLS. An example of a likelihood method is limited information maximum likelihood (LIML), in which only limited information on the structure of the model is used. In this method we assume a model

$$\begin{aligned} x_i &= \alpha_0 + \sum_j \alpha_j z_{ij} + \varepsilon_{xi}, \quad i = 1, ..., N; j = 1, ..., J \\ y_i &= \beta_0 + \beta_1 x_i + \varepsilon_{yi}, \end{aligned} \tag{3.5}$$

where the error terms have a bivariate normal distribution. Consequently the maximum likelihood estimates of the coefficients can be calculated, which is exactly what

LIML does. For weak instruments (instruments for which the statistical evidence of association with the exposure is not strong) likelihood-based models may perform better than 2SLS, since the uncertainty in the first stage is better represented in the estimate of the parameter β_1.

Semi-parametric models

Fully parametric models are not always robust to model misspecification. To overcome this, semi-parametric models are designed. These models typically assume a parametric form for the model that relates outcome to the exposure, but do not assume a specific distribution of the errors. For example, the generalized method of moments (GMM) is a flexible form of 2SLS, specifically meant to deal with heteroscedasticity in errors and non-linearity in the second stage. When we have the model

$$Y = X\beta + \varepsilon, \quad \varepsilon \sim (0, \Omega)$$

where X is the $N \times k$ matrix of the k regressors, Z is the $N \times J$ matrix of instruments and $E(z_i \varepsilon_i) = 0$. Then, the J instruments give rise to J moments:

$$f_i(\hat{\beta}) = z_i' \hat{\varepsilon}_i = z_i'(y_i - x_i\beta), \quad i = 1, ..., N$$

Each f_i a J-vector. GMM considers each moment equation as a sample moment, estimated by

$$\bar{f}(\beta) = \frac{1}{N} \sum_{i=1}^{N} z_i(y_i - x_i\beta) = \frac{1}{N} Z' \varepsilon \tag{3.6}$$

Then, the estimation is chosen such that $\bar{f}(\hat{\beta}_{GMM}) = 0$. GMM has less stringent assumptions than other methods and is hence more flexible. Furthermore, Davies et al. (2015) showed that a GMM variant, namely the continuously updating estimator (CUE) can perform better than 2SLS en LIML in terms of consistency when the MR problem contains many weak instruments.

Remarks

As shown, there are multiple estimators that can be used in an instrumental variable analysis. The differences between these estimators become particularly clear when there are weak instruments. However, as Burgess, Small, and Thompson (2017) point out, there is not a single best IV estimation method. The different methods should rather be used to perform sensitivity analyses. The general ways to perform sensitivity analyses are described in Section 3.2.4.

3.2.3 Instrumental variable estimators for summary data

The summary statistics of a GWAS on a certain exposure generally consist of gene-exposure regression coefficients. Hence, for each genetic variant there is one coefficient with the accompanying standard error and p-value. Nowadays there are summary statistics of many GWASs available. When we have the summary statistics of a GWAS on an exposure like smoking and one on an outcome like lung function, we can obtain an estimate of the causal effect of smoking on lung function by comparing per genetic variant the two GWAS coefficients using MR. The rise of MR using summary data resulted in an increased need for methods particularly suited for summary data. Originally, some techniques were already developed in econometrics (see e.g. Angrist and Krueger (1992) and Inoue and Solon (2010)), but more recently, methods were developed that are based on methods for meta-analysis. We here discuss the main methods for MR using summary data.

Inverse-variance weighted method

Above we defined the ratio of coefficients estimator in Equation (3.2) as the regression coefficient from the regression of exposure on the IV divided by the coefficient from the regression of outcome on the IV. Hence, a ratio of coefficients or Wald ratio estimator can also be used with summarized data, when there is only one instrumental variable. For this only the gene-outcome and gene-exposure coefficients are needed, which are typically contained in GWAS summary statistics. However, when there are multiple instruments, this method cannot be used. In that case a summary-level equivalent of 2SLS is needed, which is the inverse-variance weighted (IVW) method (Burgess, Butterworth, and Thompson, 2013). This approach originates from the meta-analysis literature. When we define the gene-outcome coefficients $\hat{\Gamma}_j$ from the GWAS summary statistics and the gene-exposure coefficients $\hat{\gamma}_j$ from the summary statistics of another GWAS, the IVW combines the Wald ratios for J instruments into an estimate of the causal effect of the exposure on the outcome as

$$\hat{\beta}_{IVW} = \frac{\sum_{j=1}^{J} \hat{\gamma}_j^2 \sigma_{yj}^{-2} \hat{\beta}_j}{\sum_{j=1}^{J} \hat{\gamma}_j^2 \sigma_{yj}^{-2}}, \tag{3.7}$$

where $\hat{\beta}_j$ is the Wald ratio $\frac{\hat{\Gamma}_j}{\hat{\gamma}_j}$ and σ_{yj} is the standard error in the regression of outcome on the jth genetic variant. The standard error of the IVW estimator is

$$se(\hat{\beta}_{IVW}) = \sqrt{\frac{1}{\sum_{j=1}^{J} \hat{\gamma}_j^2 \sigma_{yj}^{-2}}}.$$

The IVW estimate is asymptotically equal to the 2SLS estimate. Furthermore, it is a consistent estimate when all genetic variants satisfy the IV assumptions.

Median based methods

When at least one genetic variant is an invalid IV, the IVW method becomes inconsistent. Put differently, it has a breakdown level of zero percent, meaning that zero percent of the genetic variants is allowed to be an invalid IV. An estimator that is more robust to invalid IVs is the median ratio estimator (Han, 2008). This estimator is consistent when up to 50 percent of the genetic variants is invalid. Given there are J genetic variants and $\hat{\beta}_j$ is the jth ordered ratio estimate, the median ratio estimator is defined as

$$\hat{\beta}_{Med} = \begin{cases} \hat{\beta}_{k+1}, & \text{if } J \text{ is odd, } J = 2k+1 \\ \frac{1}{2}(\hat{\beta}_k + \hat{\beta}_{k+1}), & \text{if } J \text{ is even, } J = 2k. \end{cases} \tag{3.8}$$

This estimator is not efficient, though. Hence, Bowden et al. (2016) introduced an adapted variant of the estimator that accounts for this inefficiency: the weighted median estimator. This estimator is defined as follows. When w_j is the weight of the jth ordered ratio estimate, we define $s_j = \sum_{k=1}^{j} w_k$ as the sum of the weights of all the ordered ratio estimates up to j, where $s_J = 1$. The weighted median estimator is then defined as the median of the distribution where $\hat{\beta}_j$ is the p_jth percentile ($p_j = 100(s_j - \frac{w_j}{2})$). Hence, the contribution of each genetic variant to the empirical distribution is weighted by w_j. This is a generalization of the simple median estimator. Bowden et al. (2016) propose to use the inverse of the variance of the ratio estimates as weights, after standardizing them.

Although the median estimators we described are more robust against invalid IVs than the IVW method, the estimate of the causal effect may still be biased when the estimates from the invalid IVs are not well-balanced, i.e. when all estimates are either larger than the true effect or smaller than the true effect. This problem can be partially overcome by using a penalized weighted median estimator (Bowden et al., 2016). The idea behind this estimator is as follows. One can assess the heterogeneity between estimates using Cochran's Q statistic:

$$Q = \sum_j Q_j = \sum_j w'_j(\hat{\beta}_j - \hat{\beta})^2,$$

where $\hat{\beta}$ is the IVW estimator and w'_j are the standardized weights of the median estimator. Under the null hypothesis that all IVs are valid this statistic follows a chisquared distribution with $J - 1$ degrees of freedom. Q_j then follows a chisquared distribution with 1 degrees of freedom. Hence, genetic variants that have a very large Q_j statistic can be penalized, to make the median estimator more robust. Bowden et al. (2016) propose to penalize genetic variants where the Q_j statistic yield a $p < 0.05$ by multiplying the weight by 20 times the p-value.

MR-Egger regression

Even if all genetic variants are invalid, it may be possible to obtain consistent estimates of the causal effect. This is what Bowden, Smith, and Burgess (2015) showed, using a method named MR-Egger regression. They view MR using multiple genetic variants as meta-analysis of the estimates of each variant. Further, they adapt Egger regression, a method to detect small study bias in meta-analysis, to test for bias due to pleiotropy. MR-egger performs a weighted linear regression of the gene-outcome coefficients $\hat{\Gamma}_j$ on the gene-exposure coefficients $\hat{\gamma}_j$:

$$\hat{\Gamma}_j = \beta_{0E} + \beta_E \hat{\gamma}_j. \tag{3.9}$$

To ensure that the results from this regression are usable and comparable, the gene-exposure coefficients $\hat{\gamma}_j$ have to be positive. Based on this regression several conclusions can be drawn. First, when $\hat{\beta}_{0E} = 0$, no pleiotropic effect is detected and $\hat{\beta}_E$ will equal the IVW estimate. Secondly, when there is a pleiotropic effect, and thus the third IV assumption is not satisfied, MR-egger may still give a consistent estimate of the causal effect, when one additional assumption holds. This assumption, known as InSIDE (Instrument Strength Independent of Direct Effect), states that the pleiotropic effects δ_j must be distributed independently of the instrument strength γ_j, when the association of genetic variant j with the outcome is expressed as $\Gamma_j = \beta\gamma_j + \delta_j$.

The fact that MR-Egger enables one to obtain consistent causal estimates when genetic variants are invalid IVs, offers opportunities to use many genetic variants as

IVs. However, Bowden, Smith, and Burgess (2015) warn not to use MR-Egger with large number of genetic variants without prior assessment of the validity of the IV assumptions. MR-Egger should rather be used complementary to other techniques, as a means of sensitivity analysis.

Mendelian randomization using robust adjusted profile score

The main problem of the former mentioned problems is that they make unrealistic simplifying assumptions or that they are not theoretically well-founded, in terms of statistical consistency and limiting distributions of the estimators. For this reason, Zhao, Wang, et al. (2018) propose a method, applicable on summary data, that has good theoretical properties. It is a likelihood-based approach that, for J genetic variants, has the following key modelling assumption.

There exists a real number β_0, such that $\Gamma_j = \beta_0 \gamma_j$, for almost all $j \in 1, ..., J$.

The authors model this as an errors-in-variables regression problem, where $\hat{\Gamma}_j$ is regressed on $\hat{\gamma}_j$, a noisy observation of γ_j. The log-likelihood of GWAS summary data can then be written as

$$l(\beta, \gamma_1, ..., \gamma_J) = -\frac{1}{2}\left[\sum_{j=1}^{J} \frac{(\hat{\gamma}_j - \gamma_j)^2}{\sigma_{Xj}^2} + \sum_{j=1}^{J} \frac{(\hat{\Gamma}_j - \gamma_j \beta)^2}{\sigma_{Yj}^2}\right]$$

The parameter of interest is β, so $\gamma := (\gamma_1, .., \gamma_p)$ can be profiled out, yielding the profile log-likelihood:

$$l(\beta) = \max_{\gamma} l(\beta, \gamma) = -\frac{1}{2}\sum_{j=1}^{J} \frac{(\hat{\Gamma}_j - \beta\hat{\gamma}_j)^2}{\sigma_{Xj}^2 \beta^2 + \sigma_{Yj}^2}.$$

The maximum likelihood estimator (LIML) is $\hat{\beta} = \arg\max_{\beta} l(\beta)$. The profile score is defined as the derivative of the profile log-likelihood:

$$\phi(\beta) := -l'(\beta) = \sum_{j=1}^{J} \frac{(\hat{\Gamma}_j - \beta\hat{\gamma}_j)(\hat{\Gamma}_j \sigma_{Xj}^2 \beta + \hat{\gamma}_j \sigma_{Yj}^2)}{(\sigma_{Xj}^2 \beta^2 + \sigma_{Yj}^2)^2}$$

The authors use this profile score to prove the asymptotic normality of $\hat{\beta}$ when there is no pleiotropy. Further, they show how the profile score can be adjusted robustly in case there is systematic or idiosyncratic pleiotropy. For exact derivations we refer to their paper. The authors show that the Robust Adjusted Profile Score (RAPS) estimator outperforms all other methods in their numerical examples, so its use is highly recommended.

Following their paper on MR-RAPS, the authors proposed an extension to the method in order to increase statistical power when some genetic instruments are strong but the most are weak (Zhao, Chen, et al., 2018). By using an estimator that adaptively assigns weights to the IVs based on their strength, the power is increased. The method is based on an empirical partially Bayes approach. Again, for the details we refer to the original paper.

3.2.4 Sensitivity analyses

In previous sections we already mentioned the limitations MR can suffer from. Hence, MR analyses should always be accompanied with sensitivity analyses in order to provide robust and reliable statistical results. There are several aspects of the analysis that should be verified and checked for robustness. Here we discuss how the main assumptions and results can be investigated.

Relevance of instruments

The first assumption of IV and MR analysis is that the instruments are relevant, i.e. the genetic variants to be used as IVs should be correlated with the exposure. Traditionally this is tested using the F-statistic of a joint test whether all excluded instruments (z_i which are not in x_i) are significantly different from zero. The rule of thumb for a single endogenous regressor is that the F-statistic should be larger than 10. Equivalently, in a two-sample setting the strength of each genetic variant j can be tested by comparing $\hat{\gamma}_j^2/\sigma_{xj}^2$ (where σ_{Xj} is the standard error in the regression of exposure on the jth genetic variant) with the quantiles of χ_1^2, given that the genetic variants are independent. In general, instruments are said to be weak when the F-statistic is less than 10. In that case asymptotic inference can become problematic (Bound, Jaeger, and Baker, 1995). The F-statistic assumes a homoskedastic setting. It is known that LIML is generally less biased than 2SLS in the case of weak instruments (Burgess, Thompson, and Collaboration, 2011). However, it has been shown by J. A. Hausman et al. (2012) that the LIML estimator is biased when there are many weak instruments and the errors are conditionally heteroskedastic. The CUE estimator is still consistent under those conditions and that is the reason Davies et al. (2015) propose to use this estimator in empirical applications. In a two-sample setting, MR-RAPS is more robust to weak instruments than the other methods, and thus it is a good sensitivity analysis for other estimation methods.

Effective random assignment

In order to serve as a valid IV, the genetic variant should not be associated with confounders. In a two-sample setting this cannot easily be checked, whereas in a one-sample setting the measured covariates can be tested for association with the genetic variants. However, lack of association with measured confounders does not automatically imply lack of association with unmeasured confounders. Therefore the assumption of effective random assignment remains only partially testable.

Exclusion restriction

For the third IV assumption, stating that the genetic variant is conditionally independent of the outcome given the exposure and exposure-outcome confounders, different testing procedures have been developed. In a one-sample setting one can perform the Sargan test, which tests whether all instrumental variables are exogenous. In the two-sample setting there are different testing procedures. These sensitivity analyses basically test whether pleiotropy is present. Pleiotropy arises in two ways. If a SNP influences a trait which in turn infuences another trait, it is called vertical pleiotropy. More problematic is horizontal pleiotropy, where SNPs influence two traits through independent pathways (Hemani, Bowden, and Smith, 2018). Testing the third IV assumption is strongly connected to testing the second IV assumption.

Firstly, when it is assumed that all genetic variants that are valid instruments display the same causal effect, we expect that this is reflected when we plot the genetic associations with the outcome against the genetic associations with the exposure. Hence, a scatter plot can be used to assess the heterogeneity in causal estimates based on individual variants. If the points substantially deviate from a straight line through the origin, this may indicate pleiotropy. As stated before, the heterogeneity can also be assessed using Cochran's Q statistic. Another plot that can be used to assess potential pleiotropy is a funnel plot of the instrumental variable's precision $\hat{\beta}_{xj}/SE(\hat{\beta}_{yj})$ against the instrumental variable estimates $\hat{\beta}_{yj}/\hat{\beta}_{xj}$, which originates from meta-analysis literature (Sterne et al., 2011). In the case of no pleiotropy one would expect that more precise estimates are less variable. Hence, an asymmetric funnel plot is an indication of directional pleiotropy.

Very recently another test for directional or horizontal pleiotropy was developed, named Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) (Verbanck et al., 2018). This test has three components: detection of horizontal pleiotropy (global test), removal of horizontal pleiotropy by removing outliers (outlier test) and testing for significant difference between causal estimates before and after removing the outliers (distortion test). For the exact steps we refer to the aforementioned paper. The authors show that the method outperforms several other method, like using the Q statistic. Hence, it is a good addition to other methods.

Besides investigating pleiotropy using plots and test statistics, sensitivity analyses involve the estimation of causal effects using estimators with different degree of robustness. We already described how median estimators are more robust to invalid IVs than the IVW estimator. Hence, differing estimates from median estimators and IVW are an indication of pleiotropy. MR-Egger regression offers an additional advantage over median estimators. Under the InSIDE assumption the intercept of MR-Egger regression is the average pleiotropic effect of a genetic variant (Bowden, Smith, and Burgess, 2015). Furthermore, under the same assumption, the slope coefficient estimates the causal effect, even if there is evidence for pleiotropy. To provide a complete sensitivity analysis one should of course also compare the estimates of the former methods to the estimates of MR-RAPS, since that is a very robust method.

Lastly, it is useful to investigate whether the MR estimate is driven by a single SNP that might have a horizontal pleiotropic effect. To do so, one can estimate the effect sequentially, dropping one SNP at a time. This leave-one-out analysis will indicate whether the effect substantially changes when one SNP is removed from the analysis and hence, it informs how sensitive the analysis is to outliers. Besides, investigating the causal effect from single SNPs can give insight into the robustness of the analysis results.

Chapter 4

Methods

To infer the role of DNA methylation in the relationship between (maternal) smoking and lungfunction several steps had to be taken. First of all we had to investigate which CpG sites are most likely to be causally related to smoking and differential lung function. We did this by means of epigenome-wide association studies and by investigating published research. Then we selected the genetic variants to use as instrumental variables and we did this based on exposure-outcome associations that we found in literature. Using the selected CpG sites and SNPs we performed an adapted version of two-sample, two-step MR, where we applied an IV approach. To the best of our knowledge, this MR approach has not been applied before. In this chapter we describe the methodology as just outlined, in more detail.

4.1 Epigenome-wide association studies

Before we could apply Mendelian randomization to infer the effect of smoking on DNA methylation at specific CpG sites, we first had to find CpG sites for which the methylation level is associated with (maternal) smoking. To put it even stronger, CpG sites that are shown to be both associated with (maternal) smoking and lung function are the most interesting to investigate for a mediating role between smoking and lung function. Hence, we investigated the associations between DNA methylation on the one hand and lung function, smoking or maternal smoking on the other hand. We did this by means of epigenome-wide association studies (EWAS).

4.1.1 How epigenome-wide association studies were performed

Epigenome-wide association studies work as follows. First the DNA methylation level is measured for many CpG sites. In this research we used methylation levels obtained by Illumina Infinium Human Methylation 450K BeadChip. This results in methylation levels for approximately 450,000 CpG sites. Then, for each CpG site a regression is performed with the methylation level at that site as dependent variable and the maternal smoking, smoking or lung function as independent variable, together with adjustment variables like age and gender. Then the p-value for the independent variable is retrieved from each regression and the CpG sites for which the coefficient of the independent variable is significantly different from zero after correcting for multiple testing, is considered to be associated with the independent variable.

Before performing the EWASs, we prepared the methylation data. The original methylation data consisted of ratios of methylation intensities, where 1 indicates a fully methylated CpG site and 0 an unmethylated CpG site. These ratios are called beta values. We transformed these to M-values, defined as:

$$M = \log_2 \left(\frac{\beta}{1 - \beta} \right)$$

These M-values are shown to possess distributional properties that are preferred over those of beta values for differential methylation analysis (Du et al., 2010). After transforming, the outliers were set to the median, using Tukey's method (Tukey, 1977). This method defines an outlier as a datapoint that falls outside the range [1^{st} quantile - 3 $\times$ IQR; 3^{rd} quantile + 3 $\times$ IQR]. As there was both nasal and blood methylation data available, we did this for both types of methylation. Then, three types of EWAS were performed: to investigate the association between methylation on the one hand and smoking, maternal smoking or lung function on the other hand.

Robust regression

For each EWAS we used robust regression, as implemented in the R package *MASS*. Robust regression is robust in the sense that the results are not overly affected by violations of the assumptions of OLS regression. We used the M-estimation as introduced by Huber (1992). This method is robust to outliers in the response variable. All the regressions had the methylation M-value at a CpG site as the dependent variable and the exposure and adjustment variables as independent variables. Since there are 436,824 CpG sites in the data, each EWAS consists of that many regressions, with approximately 400 samples per regression, depending on the EWAS. To perform these regressions in an efficient way, we parallelized the calculations, using twenty cores. For each regression we calculated the coefficients and their standard error and the sample size. Furthermore we calculated for each EWAS the inflation factor λ_{gc}. This inflation factor is a means of genomic control, as described by Devlin and Roeder (1999) among others. The idea behind this is to investigate markers with a low prior probability of association with the outcome. The observed median of the chi-squared statistics of these markers is divided by the expected median of the chi-squared statistic. If the λ_{gc} is larger than one, there is evidence for systematic biases due to population structure. To correct for this, the p-values are divided by the inflation factor (Hinrichs, Larkin, and Suarez, 2009).

4.1.2 Which epigenome-wide association studies were performed

In this research we had to do twelve EWASs in total. The EWASs on smoking and maternal smoking for both nasal and blood methylation resulted in four EWASs. Besides, lung function is measured in two ways: forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1). For both measures we performed EWASs on both nasal and blood methylation. These EWASs on lung function were done separately for the study centers Utrecht and Groningen, resulting in eight EWASs on lung function. The EWASs are summarized in Table 4.1 and are explained in more detail in the next subsections.

EWAS methylation - smoking

For the EWASs regarding methylation and smoking we took as independent variable the binary indicator whether the person was a smoker. Furthermore we adjusted for age, gender, batch and study center. Besides, for the nasal brush samples we used the R package *sva* to adjust for latent factors such as cell type (Leek et al., 2017). For the blood samples we adjusted for the blood cell count. In total this yielded two EWASs, as summarized in Table 4.1.

EWAS methylation - maternal smoking

The EWASs on maternal smoking were performed using the same covariates as the EWASs on active smoking. In this case, however, we used active smoking of the mother during the third trimester of pregnancy. Naturally, one would expect that the effect of maternal smoking during the third trimester is larger than during the first trimester. Mothers who smoked during the first trimester may have stopped smoking in a very early stage of pregnancy. Hence, taking maternal smoking during third trimester of pregnancy may yield stronger relationship with differential DNA methylation.

EWAS methylation - lung function

To assess the relationship between methylation and lung function, two variables are of interest: FVC and FEV1, which both quantify the lung function. As the used spirometer may have an effect on the measured lung function, we did the EWASs for both study centers (Groningen and Utrecht) separately. Furthermore we adjusted the models for age, gender, batch and height (logarithmic). Here we also adjusted the nasal samples for latent factors, using *sva* and we adjusted the blood samples for blood cell count. In total this resulted in eight EWASs, also summarized in Table 4.1. After these EWASs we did meta-analysis using the inverse variance based method to join the EWAS results from both study centers. (Willer, Li, and Abecasis, 2010).

TABLE 4.1: List of performed epigenome-wide association studies. Besides the specific covariates mentioned in this table, each EWAS was adjusted for age, gender and batch. s.v = surrogate variable.

Independent variable	**Tissue**	**Study center**	**Specific covariates**
Active smoking	Blood	All	Study center, blood cell count
Active smoking	Nasal	All	Study center, *sva*: 1 s.v.
Maternal smoking	Blood	All	Study center, blood cell count
Maternal smoking	Nasal	All	Study center, *sva*: 1 s.v.
FVC	Blood	Groningen	Log(height), blood cell count
FVC	Blood	Utrecht	Log(height), blood cell count
FVC	Nasal	Groningen	Log(height), *sva*: 1 s.v.
FVC	Nasal	Utrecht	Log(height), *sva*: 7 s.v.
FEV1	Blood	Groningen	Log(height), blood cell count
FEV1	Blood	Utrecht	Log(height), blood cell count
FEV1	Nasal	Groningen	Log(height), *sva*: 1 s.v.
FEV1	Nasal	Utrecht	Log(height), *sva*: 7 s.v.

4.2 An adapted variant of two-sample, two-step Mendelian randomization

After performing EWASs we used the Mendelian randomization framework to investigate causal relationships between the exposures smoking and maternal smoking, the possible mediator DNA methylation and the outcome lung function. We used an adapted variant of two-sample, two-step MR, which we explain in detail below. To the best of our knowledge this methodology that we propose has not been applied yet and as such, it is an innovation with respect to other MR studies.

In Figure 3.3 we schematically depicted the framework of two-sample, two-step MR. In its original form the method comprises the use of two samples: one small sample and one much larger sample, and for each of these samples two methodological steps. In total this yields four steps, three of which we adapted in our research. We here explain these methodological steps, together with the data we used for those. We focused on two exposures, namely smoking and maternal smoking, the possible mediator blood methylation and as outcome variable FEV1.

4.2.1 Step one: association between exposure and methylation

The first step in two-sample, two-step MR is to investigate the relationship between exposure and tissue specific methylation by means of IV analysis in a small sample for which methylation data is available (see Figure 3.3a). The sample that is available to us is the data from the PIAMA cohort, which contains methylation data. To perform the IV analysis we first had to find genetic variants that can serve as instrumental variables for the exposure. For the exposure maternal smoking we cannot perform this step, since we would then need to have genetics data of the mothers. For the exposure active smoking on the other hand, we could perform this step. To do so, we selected the genetic variants that would serve as instrumental variables in the following way. The largest GWASs on smoking are, as far as we know, the ones performed by Liu et al. (2019). From these GWASs we selected all the SNPs that were significantly related to smoking initiation in the corresponding GWAS.

To prevent pleiotropy we used two selection criteria: the SNPs should not be in LD with other SNPs from the set of SNPs and the SNPs should not be associated with other traits. To meet the first criterium the LD between SNPs was estimated using the European samples of the 1000 Genomes Project (Siva, 2008). Then, for SNPs within 10,000 kb distance from each other and an LD R^2 larger than 0.001 the SNP with the highest p-value in the GWAS used in Step 3 was removed. The second criterium could be met by searching in the GWAS catalog (Buniello et al., 2018) which of the SNPs that were significant in the smoking GWAS were also significant in GWAS of any other trait or exposure and excluding those SNPs. After selecting the SNPs we investigated which of those passed the quality control (QC) of the data. For SNPs that did not pass the QC we took a SNP in LD that did pass the QC. To find SNPs in LD we used the R package *LDLinkR*, which uses the data from the 1000 Genomes Project. SNPs were considered to be in LD with another SNP when it is within a distance of 10,000 kb and when it has an $R^2 > 0.8$. Only European samples were used for LD calculation, since that corresponds best to the samples in the PIAMA cohort.

Besides selecting genetic variants, also the CpG sites had to be selected, since we only wanted to investigate the CpG sites that are most likely to be associated with smoking. Given the results of the EWASs (see Chapter 5) we decided to select the CpG sites based on literature. The largest meta-analysed EWAS on smoking we found was done by Joehanes et al. (2016). From this EWAS we selected all the significant CpGs.

Instrumental variable analysis and sensitivity analyses

The association between smoking and methylation was in first instance investigated for all the selected CpGs by means of LIML (see Equation (3.5)). In this analysis y was the DNA methylation at one CpG site, x the exposure active smoking and instrumental variables z were the SNPs, hence this analysis was done for each CpG site we selected in step one. The LIML estimator was preferred over 2SLS because of the large number of instruments. Hence, for each CpG site a regression was performed, with the methylation level at that site as dependent variable, smoking as independent variable and the SNPs as instrumental variables for smoking. As a means of sensitivity analysis the results of LIML were compared to the results when the IV analysis was done by means of 2SLS (Equation (3.4)) or using the CUE estimator (see Equation (3.6)). Furthermore we investigated the validity of the assumptions using the F-statistic, the Hausman-Wu test and Sargan's test.

4.2.2 Step two: SNPs associated with differential methylation levels

In the original two-sample, two-step MR the second step (Figure 3.3b) is also performed using the small sample. The idea is to find which *cis*-SNPs are correlated with methylation at a specific CpG site and to utilize these SNPs as proxies for methylation levels. We slightly adapted this second step by not using the data from the relatively small PIAMA sample, but from the mQTL Database (Gaunt et al., 2016). For this database the large Accessible Resource for Integrated Epigenomic Studies (ARIES) dataset was used to investigate which SNPs are correlated with differential methylation levels. This type of analysis, named methylation quantitative trait loci (MeQTL), resembles GWASs in the sense that genetic variants are investigated. The main difference is that in MeQTL the relationship between methylation and genetic variants is investigated instead of the relationship between a trait or exposure and genetic variants. The reason we chose to use the mQTL database to find SNPs that are associated with differential methylation levels, is that this database contains the results of an analysis that had more statistical power than we could obtain using the PIAMA data. Hence, the associations found in those analyses are more robust. This second step of our MR analysis was performed for both CpG sites related to active smoking (as retrieved from Joehanes et al. (2016)) and those related to maternal smoking (as retrieved from Joubert et al. (2016)). This enabled us to investigate in Step four how DNA methylation associated with either active or maternal smoking influences lung function. It must be noted that not necessarily for every CpG site a significantly related SNP could be found.

4.2.3 Step three: association between exposure and outcome

In step one the association between smoking and methylation levels was investigated. If methylation levels are a mediator for the effect of smoking on lung function, one would expect to observe an effect of smoking on lung function. To investigate this, the association between smoking and lung function was examined in the third step of our approach. Originally, Smith and Hemani (2014) proposed to compare in a large sample the gene-exposure associations to the gene-outcome associations (Figure 3.3c). However, we believe this step could be performed in a more robust and general way. Since gene-exposure associations are also compared to gene-outcome associations in two-sample MR, this third step can be done using two-sample MR. That means that not one large sample is needed, but that the results of two large published GWASs can be used: one on the association between genetic variants and smoking and one on the association with lung function. We decided to use the large smoking GWAS from Liu et al. (2019) to infer the gene-exposure associations $\hat{\gamma}_j$. To obtain an estimate of the causal effect of smoking on lung function we retrieved for the SNPs that were significant in the smoking GWAS the gene-outcome associations $\hat{\Gamma}_j$ from a large GWAS on lung function from the UK Biobank (Shrine et al., 2019). Then we used the different methods for instrumental variable analysis using summary data to robustly investigate whether we observe a causal effect of smoking on lung function.

Sensitivity analyses

The causal effect was estimated using methods of differing robustness: IVW, median based estimators and MR-Egger (see respectively Equation (3.7), Equation (3.8) and Equation (3.9)). We compared the resulting estimates of the causal effect and we investigated violations of the IV assumptions using a heterogeneity plot, funnel plot and using the MR-PRESSO test. Besides, the impact of single SNPs was investigated using leave-one-out analysis and by examining the effect of single SNPs.

4.2.4 Step four: association between methylation and outcome

The last step is to explore how the methylation levels are related to lung function (see Figure 3.3d). In step two the SNPs were found that serve as proxy for methylation levels at certain CpG sites. For the CpG sites for which such associated SNPs were found, the relation to the lung function could be determined. Here we also used a slightly different approach than Smith and Hemani (2014) proposed. They proposed to use the larger sample to investigate the association between the SNPs from step two and the outcome. However, this step can also be generalized using a two-sample MR approach. Since MR can give more evidence for causality than the coefficients from a GWAS, our approach is to be preferred. Hence, for the SNPs found in step two we retrieved the gene-methylation coefficients (i.e. in terms of two-sample MR the coefficients $\hat{\gamma}_j$ with their standard errors from the mQTL database. Then, for the same SNPs, we retrieved the gene-outcome coefficients $\hat{\Gamma}_j$ from the GWAS on lung function. After that, a two-sample MR was performed for each CpG site from Step two. Again, these analyses were accompanied with the sensitivity analyses we described in the previous chapter.

4.2.5 Remark

At the time that we just had implemented the aforementioned approach of adapted two-sample, two-step MR, an article appeared in pre-print, which has a goal and methodology that resembles our research (Jamieson et al., 2019). Specifically, those authors investigated by means of MR techniques whether smoking related DNA methylation has an effect on lung function as measured by FEV1. However, we defined our research goal and methodology completely independent of that research, so we did not copy anything from that research. Furthermore, there are some important differences. First, Jamieson et al. (2019) only considered the effect of smoking related DNA methylation on lung function. So, they did not look at DNA methylation related to maternal smoking and they also did not investigate by means of MR the effect of smoking on DNA methylation. Furthermore, the adapted variant of two-sample, two-step MR that we propose, is still an MR variant that we have not seen applied yet in other studies.

Chapter 5

Results and Discussion

5.1 Epigenome-wide association studies

We performed twelve EWASs, to find CpG sites for which the methylation levels are related to lung function and the two environmental exposures maternal smoking and active smoking. In Table 5.1 the inflation factors λ_{gc} of these are given. In general we were able to adjust for population stratification quite well, as reflected in the inflation factors around one. For the EWASs with inflation factor larger than one, we corrected the p-values. The results of the EWASs were combined to find CpGs that were significantly related to both lung function and active smoking. This approach yielded no CpG sites that were significant in both the EWAS of exposure and methylation and the one of methylation and lung function. The CpG sites that were found to be significant in one of the EWASs are shown in Table 5.2. The lack of significant results may be explained by the sample size, which may be too small. As p-values are a function of the sample size, a larger sample size may yield more significant results.

5.2 Mendelian randomization

Since there were only a few significant results, probably due to lack of statistical power, the results of the EWASs we performed could not be used as starting point for the MR analysis. However, by tying together results from different EWASs and GWASs in other cohorts and data from the PIAMA cohort, we set up an MR framework that is both new and innovative. This framework consisted of four steps: finding the association between exposure and methylation, finding SNPs associated with differential methylation levels, exploring the association between exposure and outcome and lastly examining the relationship between DNA methylation and the outcome. These steps were done using the PIAMA data, but also using publicly available summary statistics from GWASs, EWASs and a MeQTL.

5.2.1 Step one: association between exposure and methylation

The GWAS on smoking in Liu et al. (2019) resulted in total in 378 significant SNPs. These are given in Appendix A. For each of these SNPs it is indicated whether we removed it due to LD with other SNPs and whether it was found to be associated with any other trait or exposure in other GWASs. The CpGs that passed the significance level in the meta-analysed EWAS on smoking in Joehanes et al. (2016) can be found in the Appendix of that paper. Most CpG sites that passed the significance level are contained in the PIAMA data, except the 815 CpGs listed in Appendix C. In total the study resulted in 18760 CpGs that were significant at FDR 0.05, so only a small portion is not contained in the PIAMA data.

TABLE 5.1: List of epigenome-wide association studies with their inflation factors.

Exposure category	Exposure	Tissue	Study center	Sample size	Inflation factor
Smoking	Active smoking	Blood	All	510	0.92
	Active smoking	Nasal	All	374	2.13
	Maternal smoking	Blood	All	508	0.98
	Maternal smoking	Nasal	All	383	0.92
Lung function	FVC	Blood	Groningen	179	1.01
	FVC	Blood	Utrecht	229	0.98
	FVC	**Blood**	**All**	**408**	0.99
	FVC	Nasal	Groningen	165	1.05
	FVC	Nasal	Utrecht	150	1.04
	FVC	**Nasal**	**All**	**315**	1.03
	FEV1	Blood	Groningen	179	1.00
	FEV1	Blood	Utrecht	229	0.92
	FEV1	**Blood**	**All**	**408**	0.91
	FEV1	Nasal	Groningen	165	1.02
	FEV1	Nasal	Utrecht	150	0.96
	FEV1	**Nasal**	**All**	**315**	0.96

TABLE 5.2: List of CpGs that were found significant in the EWASs. The rows without CpG indicate EWASs where no significant CpGs where found after Bonferroni correction.

Exposure/outcome	Tissue	CpG	β	SE	P
Active smoking	Blood	-			
	Nasal	cg26498396	-0.192	0.0331	1.52E-08
		cg09591663	0.228	0.0421	1.14E-07
Maternal smoking	Blood	cg04180046	-0.313	0.0464	4.38E-11
		cg12803068	-0.456	0.0799	1.97E-08
		cg22132788	-0.519	0.0956	8.96E-08
	Nasal	-			
FVC	Blood	-			
	Nasal	-			
FEV1	Blood	-			
	Nasal	-			

For every CpG site that was significantly related to smoking in Joehanes et al. (2016) and that was contained in our data, an instrumental variable analysis was run. We used the SNPs from Appendix A as instrumental variables for active smoking, excluding the SNPs in LD with other SNPs, i.e. strongly correlated SNPs, and SNPs related to other traits. In addition, for SNPs that did not pass the QC in the data from the PIAMA cohort, a SNP in LD was used. This resulted in a list of SNPs given in Appendix B.

In Table 5.3 the top 25 CpGs with the lowest p-value from the LIML estimation (using heteroskedastic robust standard errors) are listed. In total the analysis yielded 301 significant CpGs after correcting for multiple testing using the Bonferroni correction. All the results can be found in Appendix D. Comparing these results to the results from 2SLS and CUE, we observe that the significant CpGs are not significant in the 2SLS analysis, but CUE does support most of the significant LIML results: 194 CpGs are significant in both the LIML and CUE estimations. Besides, CUE yields a lot more significant results: in total 8929 CpGs. Furthermore, the diagnostics reveal several things. The p-value of the F-statistics suggest that the instruments are relevant. For most of the significant results the Wu-Hausman test indicates that 2SLS is to be preferred over OLS, confirming the validity of using IV analysis. Lastly, the Sargan tests never reject the null hypothesis of instrument validity for these CpGs.

The differences in results from LIML and CUE on the one hand and on the other hand 2SLS deserve some clarification. It has been shown in literature that LIML performs better than 2SLS when there are many instruments (see a.o. Chao and Swanson (2005) and Hansen, Hausman, and Newey (2008)). Likewise, Davies et al. (2015) showed the benefit of using CUE in a MR context instead of 2SLS and LIML when there are many weak instruments. However, other researchers state that CUE should be expected to perform poorly in finite samples under weak identification (J. Hausman et al., 2011). To test for weak identification, we followed other MR papers which generally use the F-statistic. In the econometric context though, the use of this statistic has been questioned and alternatives have been proposed (Andrews and Stock, 2018). In general, the use and validity of different IV estimation and testing methods has not got the attention in MR literature as it has in econometric literature.

To conclude on this first step: we have evidence for an effect of active smoking during adolescence on DNA methylation. Given the analysis setup with many instruments, the choice not to use 2SLS as primary method seems valid. With the current theoretical knowledge of how CUE performs compared to LIML in MR applications, it is difficult to draw strong conclusions from the difference we see in number of significant results from these two methods. This is a great future research potential.

5.2.2 Step two: SNPs associated with differential methylation levels

The second step could be performed to investigate both maternal smoking and active smoking, as opposed to step one, for which we did not have all the necessary data. Not nearly all CpG sites listed in Joehanes et al. (2016) (CpGs related to active smoking) and Joubert et al. (2016) (CpGs related to maternal smoking) have a significantly correlated *cis*-SNP in the mQTL database. In total 3656 CpGs have at least one *cis*-SNP in the database. These CpGs are given in Appendix E, together with the *cis*-SNPs. Only for these CpGs step 4 can be performed. Most CpGs only have one significantly related *cis*-SNP, but 640 have multiple *cis*-SNPs.

5.2.3 Step three: association between exposure and outcome

We assessed the association between active smoking and lung function by means of several MR techniques. Table 5.4 shows the estimates of the IVW, median and MR-Egger method. Counter-intuitively these estimates show a positive effect of smoking

TABLE 5.3: Top 25 CpGs from the first step of the two-sample, two-step MR. Results are given as β coefficient, standard error and p-value from the LIML, 2SLS and CUE estimators. Besides, the p-values of the following diagnostic statistics and tests are given: F statistic, Wu-Hausman test and Sargan test.

	LIML			**CUE**			**2SLS**			**Diagnostics**			
CpG	**Beta**	**SE**	**P**	**Beta**	**Std**	**P**	**Beta**	**SE**	**P**	**F**	**Wu-Hausman**	**Sargan**	**Gene**
cg08396096	0.0322	0.0051	4.58E-10	0.0040	0.0007	3.7E-08	0.0057	0.0017	0.0011	7.79E-11	4.08E-05	0.6144	VPS37C
cg14851482	0.0409	0.0066	1.02E-09	0.0174	0.0017	1.4E-22	0.0061	0.0020	0.0031	7.79E-11	0.0002	0.4893	SNAP25
cg19618984	-0.0498	0.0081	1.60E-09	-0.0388	0.0029	7.9E-35	-0.0113	0.0032	0.0004	7.79E-11	0.0020	0.8155	
cg24663971	0.1082	0.0181	4.63E-09	0.0094	0.0035	8.3E-03	0.0156	0.0062	0.0122	7.79E-11	0.0012	0.6366	
cg08834436	-0.2513	0.0421	4.75E-09	-0.0869	0.0079	4.7E-25	-0.0434	0.0143	0.0026	7.79E-11	0.0022	0.6603	
cg26878870	0.1326	0.0223	5.11E-09	0.0402	0.0041	8.2E-21	0.0209	0.0077	0.0069	7.79E-11	0.0011	0.6651	ZNF608
cg27289478	0.0672	0.0113	5.78E-09	0.0162	0.0018	1.9E-18	0.0071	0.0029	0.0162	7.79E-11	0.0011	0.2767	RNF4
cg01592687	0.0756	0.0128	7.51E-09	0.0522	0.0044	5.4E-29	0.0122	0.0052	0.0188	7.79E-11	0.0006	0.8259	ZBTB45
cg21664281	-0.2276	0.0387	7.69E-09	-0.0950	0.0105	2.8E-18	-0.0306	0.0120	0.0113	7.79E-11	0.0004	0.5391	
cg18780100	0.1488	0.0255	9.56E-09	0.0267	0.0038	1.1E-11	0.0206	0.0071	0.0038	7.79E-11	0.0023	0.4359	RPTOR
cg13187188	0.0754	0.0130	1.09E-08	0.0363	0.0025	8.6E-39	0.0121	0.0039	0.0024	7.79E-11	0.0056	0.5608	GPR152
cg14094639	0.0678	0.0117	1.14E-08	0.0007	0.0022	7.4E-01	0.0118	0.0044	0.0078	7.79E-11	0.0013	0.7764	AURKAIP1
cg02010963	0.1104	0.0192	1.60E-08	-0.0033	0.0030	2.8E-01	0.0134	0.0051	0.0085	7.79E-11	0.0007	0.3776	FAM100A
cg07648709	0.0595	0.0104	1.78E-08	0.0152	0.0019	2.6E-14	0.0073	0.0032	0.0248	7.79E-11	0.0029	0.5567	ARHGEF17
cg10592926	-0.1128	0.0198	2.05E-08	-0.0413	0.0038	1.5E-24	-0.0115	0.0052	0.0285	7.79E-11	0.0047	0.3580	ZDHHC14
cg03233332	0.0917	0.0162	2.38E-08	-0.0066	0.0032	4.1E-02	0.0128	0.0057	0.0256	7.79E-11	0.0026	0.7081	
cg24207161	0.1241	0.0219	2.50E-08	0.0353	0.0053	7.4E-11	0.0236	0.0078	0.0028	7.79E-11	0.0045	0.7487	TIAM2
cg12856392	0.2617	0.0466	3.38E-08	0.0895	0.0091	6.7E-21	0.0383	0.0125	0.0022	7.79E-11	0.0053	0.4585	ZNF107
cg21611682	-0.0691	0.0123	3.52E-08	-0.0061	0.0021	4.6E-03	-0.0151	0.0041	0.0003	7.79E-11	0.0153	0.7113	LRP5
cg06644428	0.0683	0.0122	3.62E-08	-0.0040	0.0017	1.9E-02	0.0092	0.0039	0.0184	7.79E-11	0.0101	0.6063	
cg19297232	-0.2019	0.0361	3.78E-08	-0.0459	0.0065	4.7E-12	-0.0269	0.0114	0.0184	7.79E-11	0.0031	0.6015	SMPD3
cg14205519	0.0892	0.0160	3.78E-08	0.0139	0.0028	1.2E-06	0.0116	0.0046	0.0122	7.79E-11	0.0036	0.5103	C9orf139;FUT7
cg16254309	-0.0419	0.0075	4.47E-08	-0.0348	0.0027	4.1E-32	-0.0069	0.0030	0.0226	7.79E-11	0.0028	0.8306	CNTNAP2
cg00575674	0.1368	0.0247	4.69E-08	0.0157	0.0047	8.5E-04	0.0145	0.0083	0.0824	7.79E-11	0.0016	0.6520	
cg09109520	-0.1563	0.0283	5.20E-08	-0.0046	0.0041	2.7E-01	-0.0142	0.0072	0.0486	7.79E-11	0.0036	0.3419	GPR56

on lung function. However, when we view the heterogeneity plot (Figure 5.1), where we plot the individual SNP-lung function effects against the SNP-smoking effects, we observe a large heterogeneity. This is also clear from the Q statistic, which equals 659. This means that no clear causal conclusion can be drawn from the analysis. The leave-one-out plot (Appendix F) shows that the estimate is not mainly driven by a single SNP. On the other hand, the causal estimates from individual variants differ a lot (Appendix G).

TABLE 5.4: Estimates of the causal effect of smoking on lung function using different methods.

Method	**Beta**	**SE**	**P**
Inverse variance weighted	0.0489	0.0164	2,94E-03
Simple median	0.0530	0.0135	9,03E-01
Weighted median	0.0602	0.0143	2,47E-01
Penalised weighted median	0.0636	0.0147	1,53E-01
MR Egger	0.1101	0.0687	1,11E-05
MR-RAPS	0.0532	0.0155	6.05E-04
MR-PRESSO	0.0551	0.0126	2.36E-05

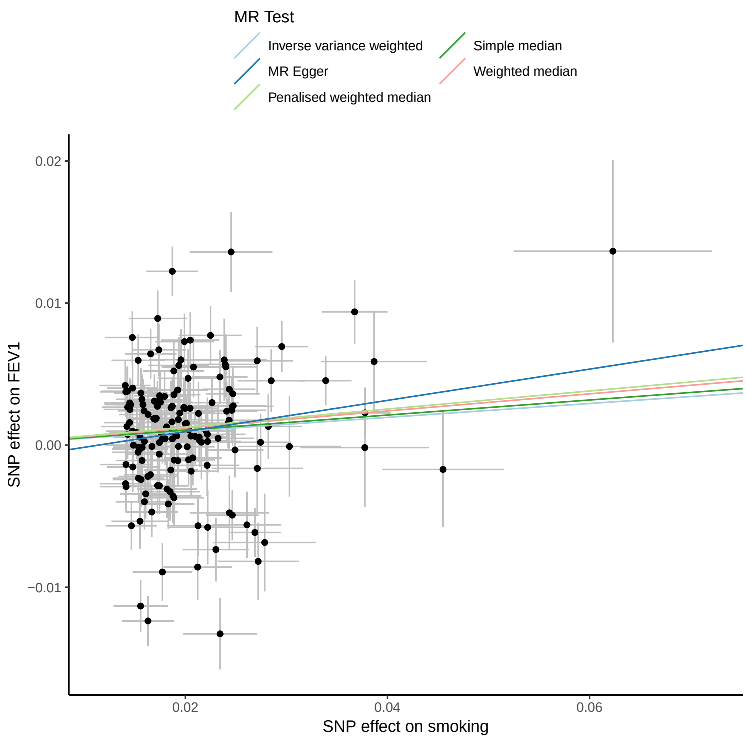


FIGURE 5.1: Heterogeneity plot of SNP-FEV1 effects versus SNP-smoking effects. The bars indicate the standard errors from both GWASs.

The funnel plot in Figure 5.2 does not clearly indicate directional pleiotropy. Also, MR-Egger does not provide clear evidence for pleiotropy, since its estimate of the pleiotropic effect is -0.001 (p-value 0.36). The MR-PRESSO global test, on the other hand, does point towards directional pleiotropy (p-value < 1E-04). However, it does not show a significant distortion (p-value 0.47) in the causal estimate before and after removal of the outliers by means of the MR-PRESSO outlier test. Hence, there is some evidence that there may be pathways other than via the variable active smoking, via which the SNPs influence lung function. We took precautionary measures to prevent pleiotropy affecting our results, but since we were not able to fully remove pleiotropic effects, the obtained causal estimate is not very reliable.

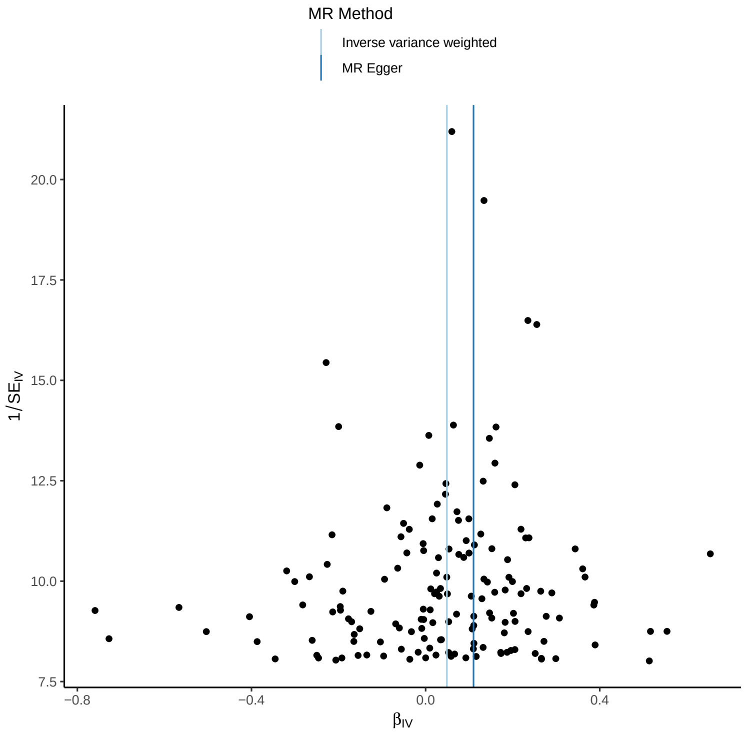


FIGURE 5.2: Funnel plot of the SNP-FEV1 estimate precisions versus their effect size.

5.2.4 Step four: association between methylation and outcome

To investigate the effect of DNA methylation on lung function, we performed two-sample MR. The CpG sites that we investigated were the same as those given in step one and retrieved from Joehanes et al. (2016), with the restriction that significantly related *cis*-SNPs were available (see step two). In addition, we also investigated the CpG sites that have been shown to be related to maternal smoking in Joubert et al. (2016), again with the restriction that significantly related *cis*-SNPs were available. For these CpG sites we obtained the SNP-methylation coefficients from the mQTL database. On the other hand, the SNP-FEV1 coefficients were retrieved from the UK Biobank GWAS on lung function (Shrine et al., 2019). We found that 86 CpGs that had only one significant *cis*-SNP are significantly related to lung function in the two-sample MR, after correcting for multiple testing using the conservative Bonferroni correction. The top 25 CpGs are shown in Table 5.5 and the complete list can be found in Appendix H Table H.1. From the CpGs that had multiple *cis*-SNPs only one CpG (cg17976873) was significant after multiple testing (see Appendix H Table H.2). However, the more robust weighted median and MR-Egger methods did not result in a significant result for this CpG site. The second most significant CpG however, shows more consistent results on all the three methods. This CpG (cg15212369) is near to the STMN3 gene, of which it has been suggested that it is induced by nicotine to promote proliferation of non-small cell lung cancer (Nair et al., 2014). As a last note: for quite a few CpGs with multiple *cis*-SNPs the different estimation methods (IVW, median, MR-Egger) gave very different results, Hence, IVW results display a lack of robustness and may therefore be not very reliable.

TABLE 5.5: Top 25 CpGs of the fourth step of the adapted variant of two-sample, two-step MR. Beta, SE, P are β coefficient, standard error and p-value from IVW estimate. F: F statistic. Exposure: Exposure to which the methylation was previously linked; either active smoking, maternal smoking or both.

CpG	Beta	SE	P	F	Exposure	Gene
cg11939399	-0.0388	0.0041	1.04E-21	42	Active smoking	REST
cg12565126	0.0533	0.0057	1.40E-20	49	Active smoking	MFSD2B
cg21356710	0.0286	0.0031	1.40E-20	187	Active smoking	MFSD2B
cg17632937	0.0518	0.0057	1.33E-19	74	Active smoking	HORMAD2
cg23268208	0.0482	0.0053	1.47E-19	81	Active smoking	HORMAD2
cg25313468	-0.0316	0.0036	7.63E-19	79	Both	REST
cg20099806	-0.0534	0.0060	7.87E-19	49	Maternal smoking	CCDC47
cg19409163	0.0242	0.0028	3.04E-18	250	Active smoking	
cg16426321	0.0461	0.0053	6.65E-18	76	Maternal smoking	ITPK1
cg04788957	-0.0404	0.0055	3.06E-13	69	Active smoking	SH3PXD2A
cg14150774	0.0224	0.0031	1.07E-12	270	Maternal smoking	QSOX2
cg16174681	0.0492	0.0072	9.06E-12	35	Active smoking	FER
cg12616487	-0.0501	0.0074	1.00E-11	37	Both	ROM1
cg20242066	0.0205	0.0030	1.26E-11	316	Active smoking	LCT
cg18611245	0.0265	0.0039	1.62E-11	102	Both	ZGPAT
cg13456470	0.0228	0.0034	1.88E-11	55	Active smoking	PTCH1
cg02812767	-0.0216	0.0032	2.03E-11	234	Both	LOXL1
cg14164839	-0.0146	0.0022	2.60E-11	1003	Active smoking	
cg20642413	0.0229	0.0035	6.81E-11	163	Both	ZGPAT
cg03354707	-0.0214	0.0034	2.17E-10	130	Active smoking	LTBP4
cg21806580	0.0331	0.0053	3.26E-10	62	Active smoking	
cg11478024	-0.0346	0.0056	6.27E-10	134	Maternal smoking	ANKS1A
cg26860257	-0.0236	0.0038	7.52E-10	148	Active smoking	ERF
cg24748631	-0.0501	0.0083	1.49E-09	46	Maternal smoking	
cg10315249	0.0209	0.0035	2.41E-09	207	Active smoking	PELI3

For three of the CpG sites for which we found evidence that they significantly affect the lung function we also found in the first step of our MR framework that their methylation levels are affected by active smoking, according to the LIML estimations. These three CpGs are cg17632937, cg23268208 (both near HORMAD2 gene) and cg09817016 (near KDM3B gene). For the latter two the results of LIML were confirmed by the estimations from the CUE.

Investigating the genes that are nearest to the most significant CpGs reveals some interesting patterns. First, it has been shown that the regulation of the REST gene, which is the nearest gene of the top CpG, affect small-cell lung cancer by methylation (Kreisler et al., 2010). The gene MFSD2B is also important in lung cancer: it may be a risk or protect factor in prognosis of lung adenocarcinoma according to Bao et al. (2016). Further, HORMAD2 is a gene that has been shown to be ectopically expressed in lung cancer tissues (Liu et al., 2012). Our analyses show that methylation at CpG sites near to this gene is also likely to affect lung function. Besides, for a CpG site near the HORMAD2 gene we also found evidence that the methylation levels are significantly affected by active smoking. These findings are very interesting, since there is a close link between lung function and lung cancer: lung function is a good predictor for lung cancer and it probably is a biomarker of susceptibility to smoking for both COPD and lung cancer (Calabrò et al., 2010; Young and Hopkins, 2010).

Concluding, at many CpG sites we see evidence for an effect of smoking during adolescence on DNA methylation. One caveat here is that different estimation methods gave very different results. What also should be realised, is that the participants were investigated during adolescence, and hence do not have smoked for many years. We did not find clear evidence for a causal effect of smoking on lung function, but interestingly, our results do indicate that DNA methylation associated with maternal or active smoking affect lung function. On top of that, genes near the CpGs for which we have the most evidence that their methylation levels affect lung function, have all been shown to be related to lung cancer. In particular, we found substantial evidence for a mediating effect of the CpG cg23268208, which is near the HORMAD2 gene that in turn is ectopically expressed in lung cancer tissues. Hence, our research has revealed some fascinating relations.

Chapter 6

Conclusion

The prevalence of asthma and allergies is strongly increasing. Therefore, research on the causes of these diseases has gained much interest in the past decades. However, due to the complexities of the underlying biology, much is still unknown about the causes of the diseases. Several factors are under suspicion for their possible negative effects on the respiratory health. Among these factors are maternal smoking during pregnancy and active smoking. Recent technological advances have resulted in an increasing availability of multi-omics data like genetics and epigenetics. This in turn enabled researchers to get a deeper understanding of the relationship between heritable factors, environmental factors and diseases. However, the effect of maternal smoking and smoking on one's respiratory health is still not nearly fully understood. It is hypothesized that these factors affect the development of asthma and allergies and that epigenetic changes in the form of DNA methylation play an important role in this. These hypotheses can be investigated in many ways. For example, one could investigate the association between genetics, epigenetics and the prevalence of diseases. However, a measure that may comprise more information is the lung function, as measured by FEV1 or FVC, since those are continuously valued instead of binary indicators. Hence, to investigate the effect of environmental factors on the respiratory health and to investigate the role of DNA methylation in this mechanishm, we stated the following goal for our research:

> *Perform causal inference modelling to infer if the effects of environmental exposures on lung function are mediated by gene methylation changes.*

We performed several steps to get a better understanding of the effect of maternal smoking and active smoking on lung function and the role of DNA methylation herein. First we investigated by means of epigenome-wide association studies in the PIAMA cohort which CpG sites are related to maternal smoking during the third trimester of pregnancy, active smoking during adolescence and lung function (FEV1 and FVC). Probably due to modest sample sizes and hence a lack of statistical power, we found only a few CpG sites related to active smoking or maternal smoking and no CpG sites significantly related to lung function. To overcome the lack of statistical power, we performed a different method to select CpGs for further investigations. We took large meta-analyses of EWASs on active smoking and on maternal smoking and selected the CpGs that were significant in those EWASs. This resulted in 23457 CpGs (18760 related to active smoking, 6073 to maternal smoking, with an overlap of 1376 CpGs). For these CpGs we investigated whether there is evidence for a causal effect of the exposures on the CpGs and of the CpGs on lung function (FEV1) using a Mendelian randomization-based framework.

Specifically, we proposed an adapted variant of two-sample, two-step Mendelian randomization, in order to utilize previous research in the form of GWASs, EWASs and MeQTL and the PIAMA data as much as possible. The two-sample, two-step MR framework has only been described conceptually in literature and our proposed variant is an innovation with respect to that framework. It has never actually been applied in literature as far as we know. Our methodology consisted of four consecutive steps. First, we examined the association between exposure and methylation in the PIAMA cohort by means of MR. Since genetic variants are needed as proxy for the exposure and no genetic data of the mothers of the PIAMA participants were collected, we could only perform this step for the exposure active smoking. For many CpGs we found evidence that their methylation levels are affected by smoking. The only caveat is that different estimation methods that were performed as a means of sensitivity analysis indicated a possible lack of robustness for the estimated effect of smoking on quite a few CpG sites. Hence, our analysis results stress the importance of further investigation of these CpGs in a population that has smoked for a longer time.

The second step of our methodology consisted of finding genetic variants related to differential methylation levels at CpG sites that have been found to be related to either maternal smoking or active smoking. For those CpG sites for which we found significantly related *cis*-SNPs in the ARIES MeQTL study we could perform our fourth step. However, before that, we investigated the association between exposure and outcome by means of two-sample MR. This third step could only be done for the exposure active smoking. We did not find a clear effect of smoking on lung function. The most remarkable result was the large heterogeneity in the estimated effect of smoking on lung function using different genetic variants. Hence, possibly a better procedure to find genetic variants that can serve as instrumental variable for the exposure should be developed.

In the fourth and last step of our methodology we explored the association between methylation and lung function. For quite some CpG sites we see evidence for a causal effect on lung function. The most remarkable is that the top six CpGs from our analysis results previously all have been shown to be related to lung cancer. There are three CpG sites that were significant in both step two and step four, indicating that they may have a mediating role in the effect of smoking on lung function. One of these three CpGs was in the top six results of the fourth step and is near the HORMAD2 gene. This gene is differentially expressed in lung cancer tissues.

In conclusion, we find some evidence for a causal effect of active smoking during adolescence on DNA methylation. Furthermore, the effect of smoking on lung function does not become clear from our analysis. However, we see a clear effect of DNA methylation at several CpG sites related to maternal smoking or active smoking on lung function. We have to be aware, though, that we used the same GWASs for the selection of the genetic variant and to find the corresponding gene-exposure coefficient. This may induce a selection bias, as we described earlier. Binding together the results of the different steps we see evidence for a mediating role of DNA methylation at three CpG sites in the effect of smoking on lung function. Given the nature of

MR analyses, we now have more evidence for a number of causal relationships between smoking, DNA methylation and lung function, than previously known by association studies. For more evidence on these causal relationships, replication studies should be done and the biology behind these factors should be investigated in further detail. What is most worth mentioning about our results is that they suggest that there is a biological link between lung function and lung cancer.

Our research shows the benefits of combining different sources of data and analysis results. We used information from two GWASs, two EWASs, a MeQTL and data from the PIAMA cohort to come to our conclusions. Using this approach we could increase statistical power with respect to only using the PIAMA data. Further, the adapted two-sample, two-step MR methodology we propose, is an efficient way to draw inferences using those different studies and data sets. The largest innovation we have shown is hence how MR can be applied three times (in both one-sample and two-sample form) to infer whether DNA methylation mediates the effect of an exposure on a disease outcome.

Flowing from our research, several future research directions can be defined. These can be categorised into three main topics: first, studies on the relationship between smoking, DNA methylation and lung function; secondly, research into the link between lung function and lung cancer and thirdly study of the theoretical properties of IV estimators with a focus on MR applications. Regarding the first topic, the following topics are particularly interesting. First, the effect of smoking on lung function should be further investigated by reconsidering the genetic variants to use as instrumental variables. Further, the effect of maternal smoking and active smoking on DNA methylation could be further investigated. The first one should be done in a cohort in which genetic data of the mothers is available. The second could either be done in this cohort at the time that some participants have had a longer smoking history or in another cohort consisting of mature people. Even better would be to use a longitudinal cohort study, which enables researchers to investigate the effect of smoking over time. A further refinement on our study would be to investigate the effect of DNA methylation at multiple CpG sites on lung function at the same time, using multivariable MR (Sanderson et al., 2018). Using this approach we would be able to estimate the direct effect of DNA methylation at a certain CpG site on lung function, instead of the total effect which may comprise other pathways.

In our research we showed that DNA methylation near genes that have a close link to lung cancer is likely to have an effect on lung function. Previous research has also pointed out that lung function can be a biomarker of lung cancer. How the biology behind these relationships work is still not completely clear. If studies can reveal the biological relationships, this may hopefully lead to an increased ability to detect lung cancer in an early stage. Hence, this research direction is absolutely promising and relevant.

The first step of our MR framework yielded much heterogeneity in the results. Estimates of different estimators were quite different. In econometric context several IV estimators have been studied thoroughly. However, in MR studies it seems that this knowledge is not fully utilized. Therefore, within the MR framework the properties of different estimators should be studied more deeply and comparisons on their behaviour is highly relevant for future MR studies. There is a number of testing and estimation methods available, for which it is often not clear which of those are most relevant for MR. Investigating their relevance can result in more reliable MR analyses. Lastly, to utilize the possibilities of MR even more, we propose to use our adapted variant of two-sample, two-step MR more widely, to investigate the effect of a range of exposures on disease outcomes and to examine the role of DNA methylation herein. Using this approach one efficiently combines data, resulting in an increased statistical power with respect to using one-sample MR.

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Appendix A

SNPs Associated with Smoking Initiation

TABLE A.1: SNPs reported in Liu et al. (2019) as associated with smoking initiation. Rsid: SNP. Ref: reference allele. Alt: alternative allele. Freq: frequency of reference/alternative allele. LD: 1 indicates that SNP was found to be in LD with another SNP in the set and was removed as it had a higher p-value in the GWAS than the SNP with which it is in LD. Other trait: 1 indicates that SNP is associated with any other trait or exposure in other GWASs and therefore removed from the set. The SNPs in LD that were already removed, were not investigated for association with any other trait.

Rsid	Ref	Alt	Alt. Freq	Ref.Freq	LD	Other trait
rs12130857	G	A	0.324968	0.675032	0	0
rs301807	A	G	0.57	0.43	1	
rs3820277	G	T	0.526	0.474	0	0
rs1889571	T	G	0.131	0.869	0	0
rs10914684	G	A	0.324	0.676	0	1
rs2637869	G	A	0.297	0.703	1	
rs12755632	A	G	0.316	0.684	1	
rs951740	G	A	0.625	0.375	0	0
rs925524	A	G	0.71	0.29	1	
rs12022778	A	C	0.202	0.798	0	0
rs11587399	A	T	0.221	0.779	1	
rs4912332	C	T	0.491	0.509	0	0
rs1937443	C	G	0.563	0.437	1	
rs1022528	G	A	0.344	0.656	1	
rs12740789	G	A	0.178	0.822	1	
rs80054503	T	C	0.116	0.884	0	1
rs10789369	A	G	0.615	0.385	0	1
rs1514176	G	A	0.58	0.42	0	0
rs10873871	A	G	0.207	0.793	1	
rs11162019	C	T	0.363	0.637	0	1
rs1008078	C	T	0.402	0.598	0	1
rs1935571	T	G	0.48	0.52	1	
rs12027999	T	C	0.12	0.88	0	0
rs45444697	C	G	0.212	0.788	0	1
rs2901785	G	A	0.446	0.554	0	1
rs147052174	G	T	0.0171	0.9829	0	0
rs35656245	G	A	0.276	0.724	0	0
rs12739243	T	C	0.221	0.779	0	0
rs12563365	G	A	0.556	0.444	1	
rs876793	T	C	0.349262	0.650738	0	1
rs114976176	A	C	0.351571	0.648429	1	
rs62106258	T	C	0.047329	0.952671	1	
rs6731872	T	G	0.826	0.174	0	1
rs1022376	T	C	0.515821	0.484179	0	0
rs61533748	T	C	0.384	0.616	0	0
rs72790288	G	A	0.0282	0.9718	1	
rs2710634	T	C	0.521	0.479	0	1
rs62137126	A	G	0.121094	0.878906	1	
rs1004787	G	A	0.552	0.448	1	
rs7598402	C	G	0.492084	0.507916	0	0
rs10490159	C	T	0.394	0.606	0	0
rs1518393	A	C	0.619	0.381	1	
rs17616642	A	G	0.24687	0.75313	1	
rs6730325	G	A	0.609782	0.390218	1	
rs2539706	G	A	0.529947	0.470053	1	
rs7585579	C	G	0.499	0.501	1	
rs1863161	G	A	0.56094	0.43906	1	
rs359247	A	T	0.638652	0.361348	0	0
rs62180324	G	A	0.212	0.788	1	
rs6750107	G	A	0.386875	0.613125	1	
rs12714017	T	C	0.511	0.489	0	0
rs56208390	A	G	0.123	0.877	1	
rs11692435	G	A	0.0848	0.9152	1	
rs13392222	A	C	0.139	0.861	0	0
rs1901477	A	G	0.511	0.489	0	0
rs11889814	A	C	0.128	0.872	1	
rs3811038	T	C	0.279	0.721	0	0
rs75210106	C	T	0.176676	0.823324	1	
rs34399632	A	G	0.232	0.768	0	0
rs74697736	G	A	0.287239	0.712761	1	
rs6756212	C	T	0.535	0.465	0	0
rs3076896	G	A	0.38988	0.61012	1	
rs16826827	T	C	0.124	0.876	0	0
rs1445649	T	C	0.538	0.462	0	0
rs1722666	C	T	0.732	0.268	1	
rs11678980	G	A	0.45	0.55	1	
rs12474587	G	T	0.429	0.571	0	0
rs357304	T	C	0.727	0.273	1	
rs13007361	G	A	0.208	0.792	0	0
rs7600835	G	A	0.342	0.658	1	
rs6750529	C	T	0.744	0.256	0	0
rs17229285	C	T	0.505	0.495	0	1
rs3115418	T	C	0.454	0.546	1	
rs62193862	G	A	0.0999	0.9001	0	0
rs4674916	C	A	0.327671	0.672329	1	
rs4674993	A	G	0.2	0.8	0	0
rs11713899	A	C	0.171	0.829	0	0
rs748832	A	G	0.371	0.629	0	1
rs10446419	A	G	0.207	0.793	1	
rs13319205	T	A	0.29	0.71	1	
rs3172494	G	T	0.115	0.885	1	
rs2526390	C	T	0.334	0.666	0	0
rs2276825	T	C	0.245	0.755	1	
rs2306866	A	T	0.614	0.386	1	
rs73831818	A	G	0.057	0.943	1	
rs1910236	G	A	0.469	0.531	1	
rs7640107	C	T	0.430789	0.569211	1	
rs2734390	A	G	0.372	0.628	1	
rs221988	A	C	0.384	0.616	0	1
rs2196356	G	C	0.288886	0.711114	1	
rs11128203	T	A	0.53	0.47	0	1
rs62246017	G	A	0.322639	0.677361	0	1
rs4543050	A	T	0.816	0.184	1	
rs6782116	C	T	0.415	0.585	1	
rs13066050	C	T	0.208	0.792	1	
rs12633090	G	C	0.182	0.818	0	0
rs1549979	C	T	0.615	0.385	0	0
rs74664784	T	C	0.376	0.624	1	
rs57153235	T	G	0.318	0.682	1	
rs6437769	C	T	0.581	0.419	0	0
rs9288999	G	A	0.735	0.265	0	0
rs6438436	C	T	0.816	0.184	0	0
rs12053870	T	G	0.541511	0.458489	1	
rs9826984	G	A	0.542	0.458	0	0
rs2279829	C	T	0.216	0.784	0	1

rs2319545	C	A	0.149099	0.850901	0	0
rs10935779	C	T	0.415	0.585	1	
rs963354	C	A	0.687	0.313	1	
rs1714521	A	C	0.411	0.589	0	0
rs1449012	C	T	0.463	0.537	0	0
rs9850597	G	A	0.816	0.184	1	
rs1187820	C	T	0.439	0.561	0	0
rs16828799	G	T	0.156	0.844	1	
rs9841807	C	T	0.273	0.727	1	
rs7631379	T	C	0.206	0.794	0	0
rs4140932	T	A	0.431	0.569	0	0
rs12642744	G	T	0.744	0.256	1	
rs59537158	C	T	0.214	0.786	0	0
rs1389171	T	A	0.241	0.759	1	
rs55944129	T	C	0.267	0.733	1	
rs58400863	G	A	0.347	0.653	0	1
rs7657022	A	G	0.489	0.511	1	
rs55900829	A	T	0.334806	0.665194	1	
rs112725451	C	T	0.169	0.831	0	0
rs1160685	C	G	0.45	0.55	0	0
rs1435479	G	T	0.28748	0.71252	1	
rs3934797	G	A	0.182	0.818	0	0
rs71602617	C	T	0.216	0.784	0	0
rs7696257	G	A	0.366	0.634	0	0
rs13109980	G	A	0.326	0.674	1	
rs1116690	A	G	0.742	0.258	0	0
rs13110073	T	C	0.395	0.605	0	0
rs28717373	C	T	0.356165	0.643835	1	
rs62340589	G	C	0.201	0.799	0	0
rs12517438	T	G	0.538	0.462	0	1
rs35375873	G	C	0.11	0.89	0	1
rs986714	A	T	0.445	0.555	1	
rs71592686	T	C	0.274	0.726	0	0
rs2028269	G	A	0.399	0.601	1	
rs6874731	T	G	0.484	0.516	0	0
rs6452785	C	T	0.474	0.526	0	0
rs10805858	A	T	0.335286	0.664714	1	
rs181508347	T	G	0.00965	0.99035	1	
rs42417	C	T	0.691	0.309	0	0
rs72780746	T	C	0.173	0.827	0	1
rs10060196	C	A	0.580606	0.419394	1	
rs72789626	T	A	0.136	0.864	1	
rs17165769	A	G	0.394872	0.605128	1	
rs329124	A	G	0.428	0.572	0	1
rs1385108	C	T	0.239	0.761	0	0
rs1173461	C	T	0.327	0.673	1	
rs11956866	T	G	0.567	0.433	1	
rs3909281	T	G	0.536	0.464	1	
rs3843905	C	T	0.403	0.597	1	
rs79476395	A	G	0.0726	0.9274	1	
rs6890961	C	T	0.624	0.376	0	0
rs4044321	A	G	0.644	0.356	0	0
rs2173019	T	A	0.177	0.823	0	0
rs10042827	T	C	0.681	0.319	1	
rs359431	C	T	0.56	0.44	1	
rs1059490	T	C	0.367	0.633	1	
rs6932350	T	A	0.454655	0.545345	1	
rs1150668	T	G	0.419	0.581	0	1
rs1632941	T	C	0.46	0.54	1	
rs3218116	C	T	0.256	0.744	0	0
rs160631	T	G	0.731	0.269	0	0
rs7743165	T	G	0.495	0.505	0	0
rs79180767	C	T	0.253	0.747	1	
rs10945141	G	A	0.263	0.737	0	0
rs17554906	G	C	0.444	0.556	0	0
rs619087	A	G	0.422	0.578	1	
rs6568832	G	A	0.753851	0.246149	0	0
rs12195240	G	A	0.285	0.715	0	0
rs6936160	C	T	0.698	0.302	0	0
rs12530388	A	C	0.511	0.489	1	
rs3800227	A	G	0.742	0.258	1	
rs118202	G	T	0.812	0.188	0	0
rs73008357	A	C	0.121	0.879	1	
rs9331343	T	C	0.568	0.432	1	
rs10698713	G	A	0.0544	0.9456	1	
rs1737329	C	G	0.742	0.258	0	1
rs10272990	T	C	0.327622	0.672378	1	
rs6948707	T	G	0.419	0.581	0	0
rs10259715	T	A	0.209918	0.790082	1	
rs13237637	G	C	0.485	0.515	1	
rs79631993	A	C	0.216281	0.783719	1	
rs7809303	G	A	0.325	0.675	0	0
rs7802996	C	T	0.166	0.834	1	
rs1030015	G	T	0.519564	0.480436	0	0
rs4727189	T	C	0.344	0.656	0	0
rs76841737	C	G	0.103	0.897	1	
rs11768481	C	A	0.34	0.66	0	0
rs1799068	G	T	0.379	0.621	1	
rs13437771	A	G	0.155	0.845	0	0
rs11766326	T	C	0.506	0.494	1	
rs6968380	G	A	0.681	0.319	1	
rs112913817	A	G	0.011318	0.988682	1	
rs10233018	A	G	0.516	0.484	0	1
rs10953957	G	A	0.386	0.614	0	1
rs77283305	G	A	0.305819	0.694181	0	0
rs10279261	G	A	0.618	0.382	0	0
rs1561112	T	C	0.412815	0.587185	1	
rs2952251	A	G	0.74437	0.25563	1	
rs4326350	C	G	0.493	0.507	0	0
rs11780471	G	A	0.063121	0.936879	1	
rs11783093	C	T	0.158	0.842	0	1
rs1565735	T	A	0.204463	0.795537	1	
rs7836565	C	T	0.718	0.282	0	0
rs13261666	G	T	0.517	0.483	0	0
rs3850736	C	G	0.474	0.526	0	0
rs2063976	C	T	0.664955	0.335045	0	0
rs6993429	C	A	0.453	0.547	1	
rs6986430	T	C	0.222377	0.777623	0	0
rs9987376	T	G	0.574251	0.425749	1	
rs290601	C	T	0.274	0.726	0	0
rs3847244	C	T	0.47	0.53	0	0
rs11791671	C	T	0.067315	0.932685	0	0
rs7024924	T	C	0.174	0.826	0	0
rs6474609	T	A	0.586731	0.413269	1	
rs1931431	G	C	0.478	0.522	1	
rs7867822	A	G	0.673	0.327	1	
rs10966092	T	C	0.267	0.733	0	0
rs10969352	T	A	0.5	0.5	1	
rs4877285	G	A	0.668249	0.331751	0	1
rs1930371	C	T	0.241	0.759	1	
rs2378662	G	A	0.541	0.459	0	1
rs1927901	T	C	0.553	0.447	1	
rs4837631	C	T	0.446	0.554	0	0
rs1759433	G	A	0.48	0.52	1	
rs34553878	A	G	0.111	0.889	0	0
rs7026534	T	G	0.703821	0.296179	1	
rs10858334	C	G	0.14	0.86	0	1
rs10905461	T	C	0.748	0.252	1	
rs7920501	T	A	0.465	0.535	0	0
rs1291821	A	G	0.534	0.466	0	0
rs11258417	C	T	0.391	0.609	1	
rs7072776	A	G	0.712	0.288	0	1
rs2796793	G	A	0.452	0.548	0	0
rs1733760	T	C	0.51	0.49	0	0
rs7921378	G	C	0.482	0.518	0	0
rs7901883	G	A	0.230322	0.769678	1	
rs11594623	T	C	0.234241	0.765759	0	0
rs11191269	C	G	0.193294	0.806706	1	
rs28408682	A	G	0.600019	0.399981	1	
rs12244388	G	A	0.35	0.65	0	1
rs111842178	A	G	0.231008	0.768992	1	
rs34970111	C	T	0.458	0.542	1	
rs9787523	T	C	0.418	0.582	1	
rs11192347	G	A	0.104	0.896	1	
rs10885480	T	C	0.284	0.716	0	0
rs4752018	C	A	0.231	0.769	0	0
rs9423279	C	G	0.645	0.355	0	0
rs6265	C	T	0.188	0.812	0	1
rs4275621	A	G	0.382	0.618	1	
rs62618693	C	T	0.0428	0.9572	1	
rs2939756	G	A	0.48	0.52	0	0
rs1381775	T	C	0.712	0.288	0	0
rs2959084	G	A	0.704674	0.295326	1	
rs3740977	T	C	0.167	0.833	1	
rs61886926	C	T	0.384	0.616	0	0
rs61884449	C	T	0.149183	0.850817	1	
rs644740	C	T	0.457	0.543	0	0
rs7943721	G	A	0.829	0.171	0	0
rs7929518	A	G	0.773	0.227	0	0
rs586699	G	A	0.543	0.457	1	
rs76460663	C	G	0.041056	0.958944	1	
rs2155646	T	C	0.4	0.6	0	0
rs78239456	A	T	0.376527	0.623473	1	
rs1713676	A	G	0.522512	0.477488	0	1
rs238896	G	A	0.49	0.51	1	
rs540860	A	G	0.543	0.457	0	0
rs1944689	G	T	0.785911	0.214089	1	
rs1834306	A	G	0.579399	0.420601	1	
rs1106363	C	T	0.344579	0.655421	0	0
rs2010921	G	A	0.311	0.689	0	0

rs11057005	A	G	0.441	0.559	0	0
rs13906	C	T	0.109	0.891	0	0
rs4759229	A	G	0.656	0.344	0	0
rs7969559	A	G	0.713	0.287	0	0
rs7134009	T	C	0.287	0.713	0	0
rs77215829	A	C	0.131	0.869	0	0
rs1109480	G	A	0.384	0.616	0	0
rs11611651	G	A	0.0868	0.9132	0	0
rs17197663	G	A	0.125	0.875	0	0
rs4264267	C	T	0.527042	0.472958	0	0
rs61959481	G	A	0.21	0.79	0	0
rs3098272	A	C	0.798794	0.201206	1	
rs9538162	T	C	0.415874	0.584126	1	
rs1413119	C	T	0.396318	0.603682	1	
rs56367474	C	T	0.304	0.696	1	
rs55786907	A	G	0.162492	0.837508	0	0
rs4886207	T	C	0.637	0.363	1	
rs9540731	C	T	0.509	0.491	0	0
rs9545155	T	C	0.478	0.522	0	0
rs1772572	C	A	0.324132	0.675868	0	0
rs75674569	G	A	0.0997	0.9003	1	
rs7333559	G	A	0.783	0.217	1	
rs1108130	T	A	0.212	0.788	0	0
rs12855717	C	T	0.538	0.462	1	
rs12878369	C	A	0.414762	0.585238	0	0
rs2145451	T	C	0.193	0.807	1	
rs9323328	A	G	0.537	0.463	0	0
rs1811739	G	A	0.248	0.752	0	0
rs8005334	T	G	0.36	0.64	0	0
rs34940743	A	G	0.346	0.654	1	
rs2925128	C	T	0.385191	0.614809	0	0
rs1381287	C	T	0.467	0.533	0	1
rs55913542	G	T	0.175	0.825	1	
rs1435672	T	C	0.56	0.44	0	0
rs281296	G	A	0.357	0.643	0	0
rs1435741	G	A	0.432951	0.567049	1	
rs56902655	T	G	0.136	0.864	1	
rs2289791	G	T	0.247	0.753	0	0
rs60833441	A	G	0.461	0.539	1	
rs62007780	G	T	0.416	0.584	0	0
rs12442563	G	T	0.223	0.777	1	
rs4310804	C	G	0.247	0.753	0	0
rs8027457	T	C	0.511	0.489	1	
rs1139897	G	A	0.23	0.77	0	0
rs11076962	T	C	0.279	0.721	0	1
rs7192140	T	C	0.498	0.502	1	
rs9922607	C	T	0.2	0.8	0	0
rs9941217	C	G	0.352204	0.647796	0	1
rs7188873	A	G	0.612998	0.387002	1	
rs6497840	G	A	0.707	0.293	0	0
rs4785187	G	A	0.223	0.777	1	
rs8050598	C	T	0.254117	0.745883	1	
rs12918191	A	G	0.243	0.757	0	1
rs9302604	A	G	0.435	0.565	0	0
rs9936784	T	G	0.53418	0.46582	1	
rs62052916	A	T	0.0701	0.9299	1	
rs4788676	T	C	0.228528	0.771472	1	
rs61537885	T	C	0.037215	0.962785	1	
rs117657830	A	G	0.0417	0.9583	0	0
rs1050847	C	T	0.559	0.441	0	1
rs11642231	G	A	0.369	0.631	0	0
rs4790874	C	T	0.532	0.468	0	0
rs11078713	A	G	0.419348	0.580652	1	
rs28441558	T	C	0.0563	0.9437	0	1
rs11651955	G	A	0.499	0.501	1	
rs67777803	G	T	0.172	0.828	0	0
rs2344976	T	C	0.612	0.388	1	
rs3764351	G	A	0.657	0.343	0	0
rs72836318	T	C	0.246	0.754	0	0
rs17692129	C	T	0.331	0.669	1	
rs75919030	T	C	0.267	0.733	0	0
rs2938134	C	A	0.673	0.327	1	
rs2587507	T	C	0.502	0.498	0	0
rs34342129	T	C	0.509	0.491	0	0
rs4476253	G	A	0.24	0.76	0	0
rs7505855	C	T	0.586	0.414	1	
rs8096225	A	C	0.703	0.297	0	0
rs67050670	A	G	0.229	0.771	0	0
rs2359180	A	G	0.369	0.631	1	
rs72898831	A	G	0.155	0.845	1	
rs8083764	G	T	0.306171	0.693829	1	
rs1373178	T	G	0.588	0.412	0	0
rs62098013	G	A	0.365322	0.634678	1	
rs72938304	G	A	0.113	0.887	0	0
rs11872397	G	A	0.253	0.747	1	
rs71367544	C	T	0.203	0.797	0	0
rs76608582	C	A	0.0489	0.9511	0	1
rs10853981	G	A	0.33036	0.66964	0	1
rs113230003	G	A	0.255	0.745	0	1
rs8103660	T	C	0.354431	0.645569	1	
rs117734003	G	C	0.0673	0.9327	0	0
rs1126757	C	T	0.473	0.527	0	1
rs6050446	A	G	0.971	0.029	0	1
rs6058782	C	T	0.908	0.092	1	
rs1555445	A	T	0.318	0.682	1	
rs6073075	T	A	0.824	0.176	0	0
rs910912	T	C	0.739	0.261	1	
rs6011779	C	T	0.806	0.194	1	
rs3810496	T	C	0.619436	0.380564	0	0
rs4818005	G	A	0.581	0.419	0	0
rs139896	T	C	0.648	0.352	1	
rs4822102	C	T	0.618	0.382	0	0
rs9627272	G	C	0.407	0.593	1	

Appendix B

SNPs Used in Step One of our MR Framework

TABLE B.1: SNPs that were used in the first step of our MR-based methodology. Input SNP: SNP found in Liu et al. (2019) to be associated with smoking. SNP used: available SNP in PIAMA cohort that is correlated to the input SNP. Chr: chromosome. Pos: position. MAF: minor allele frequency. Distance: distance between the input SNP and the used SNP. R^2: R^2 between the two SNPs in the 1000 Genomes Project.

Input SNP	SNP used	Chr	Pos	Alleles	MAF	Distance	R^2	Correlated alleles
rs12027999	rs12027999	1	154206358	(T/C)	0.1521	0	1	T=T,C=C
rs147052174	rs147052174	1	179783167	(G/T)	0.0149	0	1	G=G,T=T
rs3820277	rs3820277	1	18436657	(G/T)	0.4573	0	1	G=G,T=T
rs35656245	rs35656245	1	190957480	(G/A)	0.2823	0	1	G=G,A=A
rs12739243	rs12739243	1	210302043	(T/C)	0.2624	0	1	T=T,C=C
rs12563365	rs12563365	1	236872829	(G/A)	0.4463	0	1	G=G,A=A
rs1889571	rs1889571	1	32195819	(T/G)	0.1143	0	1	T=T,G=G
rs2637869	rs2637869	1	38757237	(G/A)	0.2843	0	1	G=G,A=A
rs12755632	rs12755632	1	41776623	(A/G)	0.3091	0	1	A=A,G=G
rs951740	rs951740	1	44011737	(G/A)	0.3658	0	1	G=G,A=A
rs925524	rs925524	1	46496709	(A/G)	0.2604	0	1	A=A,G=G
rs12022778	rs12022778	1	50603995	(A/C)	0.1909	0	1	A=A,C=C
rs11587399	rs11587399	1	50861071	(A/T)	0.2177	0	1	A=A,T=T
rs4912332	rs4912332	1	58815243	(C/T)	0.497	0	1	C=C,T=T
rs1937443	rs1937443	1	66469643	(C/G)	0.4314	0	1	C=C,G=G
rs1022528	rs1022528	1	71490122	(G/A)	0.338	0	1	G=G,A=A
rs12740789	rs12740789	1	72752073	(G/A)	0.174	0	1	G=G,A=A
rs80054503	rs80054503	1	72900406	(T/C)	0.174	0	1	T=T,C=C
rs1514176	rs1514176	1	74991596	(G/A)	0.4284	0	1	G=G,A=A
rs10873871	rs10873871	1	76689019	(A/G)	0.1789	0	1	A=A,G=G
rs12130857	rs12130857	1	7791461	(G/A)	0.2853	0	1	G=G,A=A
rs301807	rs301807	1	8484823	(A/G)	0.4722	0	1	A=A,G=G
rs11162019	rs11162019	1	87913176	(C/T)	0.3797	0	1	C=C,T=T
rs1935571	rs1935571	1	96414335	(T/G)	0.492	0	1	T=T,G=G
rs7920501	rs7920501	10	10043159	(T/A)	0.493	0	1	T=T,A=A
rs7901883	rs7901883	10	103186838	(G/A)	0.2584	0	1	G=G,A=A
rs11594623	rs11594623	10	103960351	(T/C)	0.2445	0	1	T=T,C=C
rs11191269	rs11191269	10	104120522	(C/G)	0.1899	0	1	C=C,G=G
rs28408682	rs28408682	10	104403310	(A/G)	0.3648	0	1	A=A,G=G
rs111842178	rs111842178	10	104852121	(A/G)	0.4076	0	1	A=A,G=G
rs34970111	rs34970111	10	106078937	(C/T)	0.4751	0	1	C=C,T=T
rs9787523	rs9787523	10	106460460	(T/C)	0.4493	0	1	T=T,C=C
rs11192347	rs11192347	10	106929313	(G/A)	0.0964	0	1	G=G,A=A
rs1291821	rs1291821	10	11133823	(A/G)	0.4433	0	1	A=A,G=G
rs10885480	rs10885480	10	115378364	(T/C)	0.2873	0	1	T=T,C=C
rs4752018	rs4752018	10	118678712	(C/A)	0.2296	0	1	C=C,A=A
rs9423279	rs9423279	10	125680419	(C/G)	0.3628	0	1	C=C,G=G
rs11258417	rs11258417	10	13533053	(C/T)	0.336	0	1	C=C,T=T
rs2796793	rs2796793	10	36634124	(G/A)	0.4583	0	1	G=G,A=A
rs1733760	rs1733760	10	56698174	(T/C)	0.494	0	1	T=T,C=C
rs7921378	rs7921378	10	63674885	(G/C)	0.4901	0	1	G=G,C=C
rs10905461	rs10905461	10	8803551	(T/C)	0.2634	0	1	T=T,C=C
rs76460663	rs76460663	11	111979741	(C/G)	0.0497	0	1	C=C,G=G
rs2155646	rs2155646	11	112912811	(T/C)	0.4364	0	1	T=T,C=C
rs78239456	rs78239456	11	112984491	(A/T)	0.4791	0	1	A=A,T=T
rs238896	rs238896	11	113994505	(G/A)	0.4861	0	1	G=G,A=A
rs540860	rs540860	11	121530888	(A/G)	0.4374	0	1	A=A,G=G
rs1944689	rs1944689	11	121634334	(G/T)	0.2406	0	1	G=G,T=T
rs1834306	rs1834306	11	122023187	(A/G)	0.4274	0	1	A=A,G=G
rs1106363	rs1106363	11	131966264	(C/T)	0.3698	0	1	C=C,T=T
rs2010921	rs2010921	11	132098205	(G/A)	0.34	0	1	G=G,A=A
rs4275621	rs4275621	11	28652996	(A/G)	0.3777	0	1	A=A,G=G
rs62618693	rs62618693	11	32956492	(C/T)	0.0338	0	1	C=C,T=T
rs2939756	rs2939756	11	41436297	(G/A)	0.4891	0	1	G=G,A=A
rs1381775	rs1381775	11	42442826	(T/C)	0.2594	0	1	T=T,C=C
rs2959084	rs2959084	11	46078656	(G/A)	0.325	0	1	G=G,A=A
rs3740977	rs3740977	11	46393574	(T/C)	0.168	0	1	T=T,C=C

rs61886926	rs61886926	11	64133552	(C/T)	0.3708	0	1	C=C,T=T
rs61884449	rs61884449	11	64485193	(C/T)	0.1491	0	1	C=C,T=T
rs644740	rs644740	11	65561468	(C/T)	0.4583	0	1	C=C,T=T
rs7943721	rs7943721	11	73309393	(G/A)	0.1551	0	1	G=G,A=A
rs7929518	rs7929518	11	85980958	(A/G)	0.2276	0	1	A=A,G=G
rs586699	rs586699	11	92289734	(G/A)	0.4722	0	1	G=G,A=A
rs77215829	rs77215829	12	112618346	(A/C)	0.1332	0	1	A=A,C=C
rs1109480	rs1109480	12	121083279	(G/A)	0.3757	0	1	G=G,A=A
rs11611651	rs11611651	12	133380790	(G/A)	0.0716	0	1	G=G,A=A
rs11057005	rs11057005	12	16748721	(A/G)	0.4473	0	1	A=A,G=G
rs13906	rs13906	12	49952394	(C/T)	0.1133	0	1	C=C,T=T
rs4759229	rs4759229	12	56474480	(A/G)	0.336	0	1	A=A,G=G
rs7969559	rs7969559	12	69655167	(A/G)	0.3181	0	1	A=A,G=G
rs7134009	rs7134009	12	75263193	(T/C)	0.3131	0	1	T=T,C=C
rs7333559	rs7333559	13	100546450	(G/A)	0.2087	0	1	G=G,A=A
rs1108130	rs1108130	13	100648356	(T/A)	0.2107	0	1	T=T,A=A
rs12855717	rs12855717	13	101252635	(C/T)	0.4384	0	1	C=C,T=T
rs17197663	rs17197663	13	38172867	(G/A)	0.1203	0	1	G=G,A=A
rs4264267	rs4264267	13	38359676	(C/T)	0.4563	0	1	C=C,T=T
rs61959481	rs61959481	13	55834929	(G/A)	0.2028	0	1	G=G,A=A
rs3098272	rs3098272	13	55931424	(A/C)	0.1948	0	1	A=A,C=C
rs9538162	rs9538162	13	59265043	(T/C)	0.3847	0	1	T=T,C=C
rs1413119	rs1413119	13	59339281	(C/T)	0.3767	0	1	C=C,T=T
rs56367474	rs56367474	13	59454139	(C/T)	0.3211	0	1	C=C,T=T
rs55786907	rs55786907	13	59871584	(A/G)	0.1849	0	1	A=A,G=G
rs4886207	rs4886207	13	60705792	(T/C)	0.3946	0	1	T=T,C=C
rs9540731	rs9540731	13	66949370	(C/T)	0.494	0	1	C=C,T=T
rs9545155	rs9545155	13	80191873	(T/C)	0.498	0	1	T=T,C=C
rs1772572	rs1772572	13	81191176	(C/A)	0.338	0	1	C=C,A=A
rs75674569	rs75674569	13	96823724	(G/A)	0.0994	0	1	G=G,A=A
rs12878369	rs12878369	14	28346502	(C/A)	0.4066	0	1	C=C,A=A
rs9323328	rs9323328	14	58653514	(A/G)	0.4732	0	1	A=A,G=G
rs1811739	rs1811739	14	77529375	(G/A)	0.2674	0	1	G=G,A=A
rs8005334	rs8005334	14	79563654	(T/G)	0.338	0	1	T=T,G=G
rs34940743	rs34940743	14	80102233	(A/G)	0.334	0	1	A=A,G=G
rs2925128	rs2925128	14	98362355	(C/T)	0.3787	0	1	C=C,T=T
rs55913542	rs55913542	14	99693843	(G/T)	0.17	0	1	G=G,T=T
rs1435672	rs1435672	15	36399479	(T/C)	0.4185	0	1	T=T,C=C
rs281296	rs281296	15	47685010	(G/A)	0.3559	0	1	G=G,A=A
rs1435741	rs1435741	15	47935843	(G/A)	0.4274	0	1	G=G,A=A
rs56902655	rs56902655	15	63898709	(T/G)	0.1521	0	1	T=T,G=G
rs2289791	rs2289791	15	67476952	(G/T)	0.2406	0	1	G=G,T=T
rs60833441	rs60833441	15	74048768	(A/G)	0.4871	0	1	A=A,G=G
rs62007780	rs62007780	15	78025464	(G/T)	0.4095	0	1	G=G,T=T
rs4310804	rs4310804	15	96858409	(C/G)	0.2117	0	1	C=C,G=G
rs8027457	rs8027457	15	99204101	(T/C)	0.4871	0	1	T=T,C=C
rs7192140	rs7192140	16	10173748	(T/C)	0.4851	0	1	T=T,C=C
rs9922607	rs9922607	16	17570220	(C/T)	0.2087	0	1	C=C,T=T
rs7188873	rs7188873	16	24727064	(A/G)	0.3827	0	1	A=A,G=G
rs6497840	rs6497840	16	25351633	(G/A)	0.2863	0	1	G=G,A=A
rs4785187	rs4785187	16	49766772	(G/A)	0.2445	0	1	G=G,A=A
rs8050598	rs8050598	16	49891964	(C/T)	0.2416	0	1	C=C,T=T
rs9302604	rs9302604	16	69576894	(A/G)	0.4334	0	1	A=A,G=G
rs1139897	rs1139897	16	720986	(G/A)	0.2575	0	1	G=G,A=A
rs9936784	rs9936784	16	72230694	(T/G)	0.4841	0	1	T=T,G=G
rs62052916	rs62052916	16	72574550	(A/T)	0.0616	0	1	A=A,T=T
rs4788676	rs4788676	16	72950468	(T/C)	0.2167	0	1	T=T,C=C
rs61537885	rs61537885	16	75620118	(T/C)	0.0427	0	1	T=T,C=C
rs117657830	rs117657830	16	75766873	(A/G)	0.0378	0	1	A=A,G=G
rs11642231	rs11642231	16	89608702	(G/A)	0.3509	0	1	G=G,A=A
rs11651955	rs11651955	17	16235462	(G/A)	0.493	0	1	G=G,A=A
rs4790874	rs4790874	17	1995177	(C/T)	0.4453	0	1	C=C,T=T
rs67777803	rs67777803	17	27323322	(G/T)	0.163	0	1	G=G,T=T
rs2344976	rs2344976	17	30685935	(T/C)	0.3608	0	1	T=T,C=C
rs3764351	rs3764351	17	37824339	(G/A)	0.34	0	1	G=G,A=A
rs17692129	rs17692129	17	44793283	(C/T)	0.34	0	1	C=C,T=T
rs75919030	rs75919030	17	50193197	(T/C)	0.2346	0	1	T=T,C=C
rs2938134	rs2938134	17	50243397	(C/A)	0.3221	0	1	C=C,A=A
rs2587507	rs2587507	17	77790135	(T/C)	0.496	0	1	T=T,C=C
rs11078713	rs11078713	17	7795972	(A/G)	0.4076	0	1	A=A,G=G
rs4476253	rs4476253	18	25253297	(G/A)	0.2425	0	1	G=G,A=A
rs7505855	rs7505855	18	31696075	(C/T)	0.4026	0	1	C=C,T=T
rs8096225	rs8096225	18	36921851	(A/C)	0.3022	0	1	A=A,C=C
rs67050670	rs67050670	18	39297254	(A/G)	0.2396	0	1	A=A,G=G
rs2359180	rs2359180	18	41314171	(A/G)	0.4493	0	1	A=A,G=G
rs72898831	rs72898831	18	42658643	(A/G)	0.1322	0	1	A=A,G=G
rs8083764	rs8083764	18	49874515	(G/T)	0.2942	0	1	G=G,T=T
rs1373178	rs1373178	18	49967811	(T/G)	0.3907	0	1	T=T,G=G
rs62098013	rs62098013	18	50863861	(G/A)	0.3429	0	1	G=G,A=A
rs72938304	rs72938304	18	53661743	(G/A)	0.0954	0	1	G=G,A=A
rs34342129	rs34342129	18	5872472	(T/C)	0.492	0	1	T=T,C=C
rs11872397	rs11872397	18	72535282	(G/A)	0.2555	0	1	G=G,A=A
rs71367544	rs71367544	18	77574374	(C/T)	0.161	0	1	C=C,T=T
rs8103660	rs8103660	19	18566395	(T/C)	0.3628	0	1	T=T,C=C
rs117734003	rs117734003	19	51129745	(G/C)	0.0487	0	1	G=G,C=C
rs13392222	rs13392222	2	100672408	(A/C)	0.1203	0	1	A=A,C=C
rs1901477	rs1901477	2	104126983	(A/G)	0.4364	0	1	A=A,G=G
rs11889814	rs11889814	2	104432494	(A/C)	0.1133	0	1	A=A,C=C
rs3811038	rs3811038	2	113240183	(T/C)	0.2594	0	1	T=T,C=C
rs75210106	rs75210106	2	113246436	(C/T)	0.2117	0	1	C=C,T=T
rs34399632	rs34399632	2	137571174	(A/G)	0.1839	0	1	A=A,G=G
rs74697736	rs74697736	2	145412271	(G/A)	0.3062	0	1	G=G,A=A
rs6756212	rs6756212	2	146140132	(C/T)	0.495	0	1	C=C,T=T
rs16826827	rs16826827	2	147825689	(T/C)	0.1173	0	1	T=T,C=C
rs1445649	rs1445649	2	155682556	(T/C)	0.4801	0	1	T=T,C=C
rs1722666	rs1722666	2	161816880	(C/T)	0.2515	0	1	C=C,T=T
rs11678980	rs11678980	2	162101261	(G/A)	0.4304	0	1	G=G,A=A
rs12474587	rs12474587	2	162802993	(G/T)	0.3986	0	1	G=G,T=T

rs357304	rs357304	2	164862639	(T/C)	0.2793	0	1	T=T,C=C
rs13007361	rs13007361	2	166250244	(G/A)	0.1899	0	1	G=G,A=A
rs7600835	rs7600835	2	172521827	(G/A)	0.3221	0	1	G=G,A=A
rs6750529	rs6750529	2	182027603	(C/T)	0.2495	0	1	C=C,T=T
rs3115418	rs3115418	2	200936399	(T/C)	0.4573	0	1	T=T,C=C
rs62193862	rs62193862	2	202843875	(G/A)	0.1054	0	1	G=G,A=A
rs1022376	rs1022376	2	22067213	(T/C)	0.4781	0	1	T=T,C=C
rs4674916	rs4674916	2	225365635	(C/A)	0.331	0	1	C=C,A=A
rs61533748	rs61533748	2	22582968	(T/C)	0.3777	0	1	T=T,C=C
rs4674993	rs4674993	2	226332033	(A/G)	0.1909	0	1	A=A,G=G
rs114976176	rs114976176	2	264621	(A/C)	0.3469	0	1	A=A,C=C
rs72790288	rs72790288	2	29513404	(G/A)	0.0249	0	1	G=G,A=A
rs62106258	rs62106258	2	417167	(T/C)	0.0437	0	1	T=T,C=C
rs62137126	rs62137126	2	44250149	(A/G)	0.1183	0	1	A=A,G=G
rs1004787	rs1004787	2	45159091	(G/A)	0.4602	0	1	G=G,A=A
rs7598402	rs7598402	2	50735943	(C/G)	0.492	0	1	C=C,G=G
rs10490159	rs10490159	2	51341259	(C/T)	0.4115	0	1	C=C,T=T
rs1518393	rs1518393	2	58171220	(A/C)	0.4066	0	1	A=A,C=C
rs17616642	rs17616642	2	59022210	(A/G)	0.2256	0	1	A=A,G=G
rs6730325	rs6730325	2	59315828	(G/A)	0.3807	0	1	G=G,A=A
rs2539706	rs2539706	2	59819545	(G/A)	0.4573	0	1	G=G,A=A
rs7585579	rs7585579	2	60024857	(C/G)	0.4821	0	1	C=C,G=G
rs1863161	rs1863161	2	60139524	(G/A)	0.4374	0	1	G=G,A=A
rs359247	rs359247	2	60477052	(A/T)	0.3757	0	1	A=A,T=T
rs62180324	rs62180324	2	63416606	(G/A)	0.2097	0	1	G=G,A=A
rs6750107	rs6750107	2	80748807	(G/A)	0.3728	0	1	G=G,A=A
rs12714017	rs12714017	2	80999398	(T/C)	0.4662	0	1	T=T,C=C
rs56208390	rs56208390	2	83247997	(A/G)	0.1213	0	1	A=A,G=G
rs11692435	rs11692435	2	98275354	(G/A)	0.0835	0	1	G=G,A=A
rs6058782	rs6058782	20	29946968	(C/T)	0.0795	0	1	C=C,T=T
rs1555445	rs1555445	20	31175258	(A/T)	0.2763	0	1	A=A,T=T
rs6073075	rs6073075	20	42015801	(T/A)	0.1809	0	1	T=T,A=A
rs910912	rs910912	20	54462393	(T/C)	0.2803	0	1	T=T,C=C
rs6011779	rs6011779	20	61984317	(C/T)	0.1909	0	1	C=C,T=T
rs3810496	rs3810496	20	62406886	(T/C)	0.3807	0	1	T=T,C=C
rs4818005	rs4818005	21	40588819	(G/A)	0.3976	0	1	G=G,A=A
rs139896	rs139896	22	38397797	(T/C)	0.3499	0	1	T=T,C=C
rs4822102	rs4822102	22	42698430	(C/T)	0.3966	0	1	C=C,T=T
rs9627272	rs9627272	22	46442288	(G/C)	0.3897	0	1	G=G,C=C
rs6437769	rs6437769	3	107997514	(C/T)	0.4076	0	1	C=C,T=T
rs9288999	rs9288999	3	114147927	(G/A)	0.2475	0	1	G=G,A=A
rs6438436	rs6438436	3	117822149	(C/T)	0.2048	0	1	C=C,T=T
rs12053870	rs12053870	3	118302515	(T/G)	0.4771	0	1	T=T,G=G
rs9826984	rs9826984	3	131945722	(G/A)	0.4473	0	1	G=G,A=A
rs2319545	rs2319545	3	147719648	(C/A)	0.164	0	1	C=C,A=A
rs10935779	rs10935779	3	149543102	(C/T)	0.4165	0	1	C=C,T=T
rs963354	rs963354	3	157393770	(C/A)	0.2952	0	1	C=C,A=A
rs1714521	rs1714521	3	158284861	(A/C)	0.3787	0	1	A=A,C=C
rs1449012	rs1449012	3	159048333	(C/T)	0.4712	0	1	C=C,T=T
rs9850597	rs9850597	3	161761866	(G/A)	0.175	0	1	G=G,A=A
rs1187820	rs1187820	3	173072584	(C/T)	0.4712	0	1	C=C,T=T
rs16828799	rs16828799	3	173353739	(G/T)	0.1491	0	1	G=G,T=T
rs9841807	rs9841807	3	175718927	(C/T)	0.2813	0	1	C=C,T=T
rs7631379	rs7631379	3	181409057	(T/C)	0.1829	0	1	T=T,C=C
rs11713899	rs11713899	3	2365026	(A/C)	0.1779	0	1	A=A,C=C
rs10446419	rs10446419	3	25725501	(A/G)	0.2038	0	1	A=A,G=G
rs13319205	rs13319205	3	47800216	(T/A)	0.2922	0	1	T=T,A=A
rs3172494	rs3172494	3	48731487	(G/T)	0.1243	0	1	G=G,T=T
rs2526390	rs2526390	3	50192760	(C/T)	0.3241	0	1	C=C,T=T
rs2276825	rs2276825	3	52886605	(T/C)	0.2753	0	1	T=T,C=C
rs2306866	rs2306866	3	53766212	(A/T)	0.3887	0	1	A=A,T=T
rs73831818	rs73831818	3	55988394	(A/G)	0.0596	0	1	A=A,G=G
rs1910236	rs1910236	3	59434420	(G/A)	0.4523	0	1	G=G,A=A
rs7640107	rs7640107	3	59966156	(C/T)	0.4543	0	1	C=C,T=T
rs2734390	rs2734390	3	60459291	(A/G)	0.3767	0	1	A=A,G=G
rs221988	rs221988	3	64234307	(A/C)	0.4274	0	1	A=A,C=C
rs2196356	rs2196356	3	70890288	(G/C)	0.2674	0	1	G=G,C=C
rs4543050	rs4543050	3	74954560	(A/T)	0.1779	0	1	A=A,T=T
rs6782116	rs6782116	3	77176032	(C/T)	0.4324	0	1	C=C,T=T
rs13066050	rs13066050	3	81325861	(C/T)	0.1928	0	1	C=C,T=T
rs12633090	rs12633090	3	83241365	(G/C)	0.1988	0	1	G=G,C=C
rs1549979	rs1549979	3	85460131	(C/T)	0.3807	0	1	C=C,T=T
rs74664784	rs74664784	3	85475292	(T/C)	0.3817	0	1	T=T,C=C
rs57153235	rs57153235	3	85902536	(T/G)	0.3419	0	1	T=T,G=G
rs3934797	rs3934797	4	112467612	(G/A)	0.172	0	1	G=G,A=A
rs71602617	rs71602617	4	136406155	(C/T)	0.2147	0	1	C=C,T=T
rs7696257	rs7696257	4	137474783	(G/A)	0.3449	0	1	G=G,A=A
rs13109980	rs13109980	4	140886963	(G/A)	0.3022	0	1	G=G,A=A
rs1116690	rs1116690	4	143510148	(A/G)	0.2783	0	1	A=A,G=G
rs13110073	rs13110073	4	147797913	(T/C)	0.3787	0	1	T=T,C=C
rs28717373	rs28717373	4	147985231	(C/T)	0.3181	0	1	C=C,T=T
rs4140932	rs4140932	4	15458598	(T/A)	0.4374	0	1	T=T,A=A
rs62340589	rs62340589	4	176875795	(G/C)	0.1998	0	1	G=G,C=C
rs12642744	rs12642744	4	28027176	(G/T)	0.2425	0	1	G=G,T=T
rs59537158	rs59537158	4	28246049	(C/T)	0.2326	0	1	C=C,T=T
rs1389171	rs1389171	4	28822284	(T/A)	0.2276	0	1	T=T,A=A
rs55944129	rs55944129	4	29082156	(T/C)	0.2276	0	1	T=T,C=C
rs7657022	rs7657022	4	35501032	(A/G)	0.4632	0	1	A=A,G=G
rs55900829	rs55900829	4	35514712	(A/T)	0.4652	0	1	A=A,T=T
rs112725451	rs112725451	4	68017710	(C/T)	0.168	0	1	C=C,T=T
rs1160685	rs1160685	4	94052854	(C/G)	0.4533	0	1	C=C,G=G
rs1435479	rs1435479	4	94550450	(G/T)	0.2684	0	1	G=G,T=T
rs10060196	rs10060196	5	106455988	(C/A)	0.4245	0	1	C=C,A=A
rs72789626	rs72789626	5	106825618	(T/A)	0.1312	0	1	T=T,A=A
rs17165769	rs17165769	5	107365642	(A/G)	0.3897	0	1	A=A,G=G
rs1385108	rs1385108	5	154839646	(C/T)	0.2396	0	1	C=C,T=T
rs1173461	rs1173461	5	157707571	(C/T)	0.3082	0	1	C=C,T=T
rs11956866	rs11956866	5	161018271	(T/G)	0.4672	0	1	T=T,G=G

rs3909281	rs3909281	5	165096435	(T/G)	0.4692	0	1	T=T,G=G
rs3843905	rs3843905	5	165427280	(C/T)	0.3827	0	1	C=C,T=T
rs79476395	rs79476395	5	166063680	(A/G)	0.0606	0	1	A=A,G=G
rs6890961	rs6890961	5	166778503	(C/T)	0.3648	0	1	C=C,T=T
rs4044321	rs4044321	5	166989513	(A/G)	0.331	0	1	A=A,G=G
rs2173019	rs2173019	5	167614971	(T/A)	0.172	0	1	T=T,A=A
rs10042827	rs10042827	5	170299916	(T/C)	0.3201	0	1	T=T,C=C
rs359431	rs359431	5	173288534	(C/T)	0.4145	0	1	C=C,T=T
rs986714	rs986714	5	50821338	(A/T)	0.4284	0	1	A=A,T=T
rs71592686	rs71592686	5	60121271	(T/C)	0.2813	0	1	T=T,C=C
rs2028269	rs2028269	5	79308315	(G/A)	0.4185	0	1	G=G,A=A
rs6874731	rs6874731	5	80263865	(T/G)	0.4811	0	1	T=T,G=G
rs6452785	rs6452785	5	87685500	(C/T)	0.494	0	1	C=C,T=T
rs10805858	rs10805858	5	88873832	(A/T)	0.3449	0	1	A=A,T=T
rs181508347	rs181508347	5	91366274	(T/G)	0.008	0	1	T=T,G=G
rs42417	rs42417	5	94198290	(C/T)	0.3042	0	1	C=C,T=T
rs6936160	rs6936160	6	100347745	(C/T)	0.325	0	1	C=C,T=T
rs12530388	rs12530388	6	101329173	(A/C)	0.4901	0	1	A=A,C=C
rs3800227	rs3800227	6	108994161	(A/G)	0.3201	0	1	A=A,G=G
rs118202	rs118202	6	111658371	(G/T)	0.2117	0	1	G=G,T=T
rs73008357	rs73008357	6	156431856	(A/C)	0.1074	0	1	A=A,C=C
rs9331343	rs9331343	6	157738258	(T/C)	0.4543	0	1	T=T,C=C
rs1059490	rs1059490	6	26171250	(T/C)	0.332	0	1	T=T,C=C
rs6932350	rs6932350	6	26571629	(T/A)	0.4155	0	1	T=T,A=A
rs1632941	rs1632941	6	29796685	(T/C)	0.4324	0	1	T=T,C=C
rs3218116	rs3218116	6	41901763	(C/T)	0.2445	0	1	C=C,T=T
rs160631	rs160631	6	52895230	(T/G)	0.2714	0	1	T=T,G=G
rs7743165	rs7743165	6	67521222	(T/G)	0.4781	0	1	T=T,G=G
rs79180767	rs79180767	6	67540984	(C/T)	0.3668	0	1	C=C,T=T
rs10945141	rs10945141	6	69470709	(G/A)	0.2565	0	1	G=G,A=A
rs17554906	rs17554906	6	92226609	(G/C)	0.4066	0	1	G=G,C=C
rs619087	rs619087	6	94175279	(A/G)	0.4264	0	1	A=A,G=G
rs6568832	rs6568832	6	97702876	(G/A)	0.2266	0	1	G=G,A=A
rs12195240	rs12195240	6	98636905	(G/A)	0.3042	0	1	G=G,A=A
rs11766326	rs11766326	7	111100585	(T/C)	0.4811	0	1	T=T,C=C
rs6968380	rs6968380	7	114940159	(G/A)	0.3141	0	1	G=G,A=A
rs112913817	rs112913817	7	115077394	(A/G)	0.006	0	1	A=A,G=G
rs10953957	rs10953957	7	121954709	(G/A)	0.3698	0	1	G=G,A=A
rs77283305	rs77283305	7	132593831	(G/A)	0.3042	0	1	G=G,A=A
rs10279261	rs10279261	7	133589846	(G/A)	0.3698	0	1	G=G,A=A
rs1561112	rs1561112	7	133840652	(T/C)	0.4712	0	1	T=T,C=C
rs10272990	rs10272990	7	1703675	(T/C)	0.329	0	1	T=T,C=C
rs6948707	rs6948707	7	1870794	(T/G)	0.4076	0	1	T=T,G=G
rs10259715	rs10259715	7	3329967	(T/A)	0.3042	0	1	T=T,A=A
rs13237637	rs13237637	7	3503207	(G/C)	0.499	0	1	G=G,C=C
rs79631993	rs79631993	7	69432311	(A/C)	0.2704	0	1	A=A,C=C
rs7809303	rs7809303	7	69484366	(G/A)	0.2853	0	1	G=G,A=A
rs7802996	rs7802996	7	77771983	(C/T)	0.159	0	1	C=C,T=T
rs1030015	rs1030015	7	78139581	(G/T)	0.4722	0	1	G=G,T=T
rs4727189	rs4727189	7	88442568	(T/C)	0.3688	0	1	T=T,C=C
rs76841737	rs76841737	7	91281409	(C/G)	0.0855	0	1	C=C,G=G
rs11768481	rs11768481	7	96629103	(C/A)	0.3608	0	1	C=C,A=A
rs1799068	rs1799068	7	97707069	(G/T)	0.3946	0	1	G=G,T=T
rs13437771	rs13437771	7	99071478	(A/G)	0.165	0	1	A=A,G=G
rs2952251	rs2952251	8	10143164	(A/G)	0.2525	0	1	A=A,G=G
rs4326350	rs4326350	8	10763655	(C/G)	0.4891	0	1	C=C,G=G
rs290601	rs290601	8	115374642	(C/T)	0.2813	0	1	C=C,T=T
rs11780471	rs11780471	8	27344719	(G/A)	0.0755	0	1	G=G,A=A
rs1565735	rs1565735	8	27426077	(T/A)	0.1998	0	1	T=T,A=A
rs7836565	rs7836565	8	52569449	(C/T)	0.3042	0	1	C=C,T=T
rs13261666	rs13261666	8	59814666	(G/T)	0.4394	0	1	G=G,T=T
rs3850736	rs3850736	8	64912021	(C/G)	0.496	0	1	C=C,G=G
rs2063976	rs2063976	8	91096366	(C/T)	0.3191	0	1	C=C,T=T
rs6993429	rs6993429	8	92733282	(C/A)	0.4811	0	1	C=C,A=A
rs6986430	rs6986430	8	93048104	(T/C)	0.2356	0	1	T=T,C=C
rs9987376	rs9987376	8	93190014	(T/G)	0.4304	0	1	T=T,G=G
rs6474609	rs6474609	9	10981069	(T/A)	0.4185	0	1	T=T,A=A
rs1931431	rs1931431	9	11161799	(G/C)	0.494	0	1	G=G,C=C
rs1927901	rs1927901	9	120519111	(T/C)	0.4394	0	1	T=T,C=C
rs4837631	rs4837631	9	122061948	(C/T)	0.4592	0	1	C=C,T=T
rs1759433	rs1759433	9	128073097	(G/A)	0.4821	0	1	G=G,A=A
rs34553878	rs34553878	9	134334588	(A/G)	0.1153	0	1	A=A,G=G
rs7026534	rs7026534	9	134907263	(T/G)	0.2932	0	1	T=T,G=G
rs7867822	rs7867822	9	20676454	(A/G)	0.3072	0	1	A=A,G=G
rs10966092	rs10966092	9	23831658	(T/C)	0.2714	0	1	T=T,C=C
rs10969352	rs10969352	9	29747488	(T/A)	0.4801	0	1	T=T,A=A
rs3847244	rs3847244	9	3025368	(C/T)	0.4811	0	1	C=C,T=T
rs11791671	rs11791671	9	3398679	(C/T)	0.0537	0	1	C=C,T=T
rs1930371	rs1930371	9	81444104	(C/T)	0.2266	0	1	C=C,T=T
rs7024924	rs7024924	9	8282399	(T/C)	0.1839	0	1	T=T,C=C
rs10698713	rs28581547	6	158882320	(G/A)	0.0527	0	1	G=G,A=A
rs12442563	rs7167340	15	83888602	(C/T)	0.1968	-4641	1	G=C,T=T
rs2145451	rs138088001	14	29316842	(T/C)	0.2157	0	1	T=T,C=C
rs3076896	rs151291990	2	146283610	(G/A)	0.3936	0	1	G=G,A=A
rs72836318	.	17	44121579	(T/C)	0.2137	0	1	T=T,C=C

Appendix C

CpGs not Contained in PIAMA

TABLE C.1: CpGs that are related to active smoking in Joehanes et al. (2016), but that are not present in the PIAMA data and therefore could not be investigated for a causal effect of smoking on the methylation levels. Chr: chromosome. Pos: position.

CpG	Chr	Pos	Gene
cg03792876	16	73.243	
cg26856289	1	24.307.516	SFRS13A
cg01017464	18	47.018.095	SNORD58A; SNORD58B; RPL17
cg11263997	11	70.257.280	CTTN
cg23576855	5	373.299	AHRR
cg17619208	5	175.623.192	
cg25560398	2	233.252.170	ECEL1P2
cg20727233	7	97.501.946	ASNS
cg24947694	11	86.387.554	
cg03188382	2	233.245.886	ALPP
cg08825291	16	16.327.241	NOMO3
cg25006998	11	119.897.638	
cg08257009	14	94.812.770	
cg22499893	1	24.307.535	SFRS13A
cg06360776	16	30.545.507	ZNF747
cg19593285	20	32.267.661	E2F1
cg02377704	12	53.075.359	KRT1
cg17767185	10	22.944.961	PIP4K2A
cg02672759	19	39.739.058	
cg04692023	16	33.815.990	
cg13772815	17	20.492.631	
cg17341790	14	106.361.618	
cg02226079	3	190.971.216	
cg00153942	11	71.249.212	KRTAP5-8
cg23573114	20	34.634.400	LOC647979
cg17990365	11	319.718	IFITM3
cg23950232	2	233.323.030	ALPI
cg02985540	13	46.964.186	
cg06697407	12	3.305.394	TSPAN9
cg08049592	2	241.623.436	AQP12B
cg07525202	17	30.591.850	RHBDL3
cg13755776	11	3.602.845	
cg03399898	1	148.603.739	
cg02150926	14	106.361.667	
cg06716508	7	99.816.473	GATS;PVRIG
cg07764473	X	40.037.510	BCOR
cg05183538	16	88.536.950	ZFPM1
cg05986195	18	43.608.509	PSTPIP2
cg11195909	14	106.383.155	KIAA0125
cg07753510	3	171.111.243	TNIK
cg06909288	17	29.302.666	RNF135; DPRXP4
cg16241684	14	101.711.890	
cg10780313	6	33.501.379	
cg01434349	11	118.900.337	SLC37A4
cg04907849	6	30.459.317	HLA-E
cg12901451	X	48.620.161	GLOD5
cg02370022	11	68.866.745	
cg19020103	1	147.999.849	
cg19713851	2	233.246.594	ALPP
cg14554488	9	90.538.261	FAM75C1
cg15331301	6	150.381.200	
cg27592424	16	31.515.409	C16orf58
cg09607043	17	17.295.349	
cg17334970	6	33.218.094	VPS52
cg04315923	16	29.634.191	
cg05252279	10	81.588.174	
cg08955792	8	105.338.401	
cg14647125	5	403.112	AHRR
cg18979623	20	62.434.140	ZBTB46
cg10573751	7	27.144.391	
cg02931644	1	25.747.376	RHCE
cg26554302	15	22.467.326	
cg11647478	6	170.497.869	
cg09122035	11	319.667	
cg27550441	16	14.530.550	PARN
cg25317941	2	233.351.153	ECEL1
cg07121312	17	77.970.193	TBC1D16
cg21125207	15	22.547.896	
cg00689360	4	100.273.995	ADH1C
cg20167216	7	142.353.463	
cg00340584	1	149.512.963	
cg13338350	19	53.238.337	ZNF611
cg04701181	11	1.606.344	HCCA2; LOC338651; KRTAP5-1
cg03789791	16	29.166.049	
cg12212060	6	28.323.405	ZNF323; ZKSCAN3
cg17483411	5	72.114.851	TNPO1
cg10583893	19	53.039.743	ZNF808
cg02543363	X	129.252.577	
cg17533477	7	97.501.010	ASNS
cg13328614	X	48.775.123	PIM2
cg01052864	5	215.875	CCDC127
cg02388253	9	123.640.363	PHF19
cg15087369	1	226.681.523	
cg09974965	14	106.361.640	
cg11465939	22	23.923.462	IGLL1
cg18406801	2	109.294.820	LIMS1
cg16592596	17	79.620.347	PDE6G
cg04922188	9	139.527.675	
cg10424892	12	9.602.245	DDX12
cg03287929	6	168.682.455	
cg25670900	X	77.914.054	ZCCHC5
cg07502868	16	979.898	LMF1
cg12728240	2	73.870.294	NAT8
cg12421513	1	25.599.066	RHD
cg27016114	14	101.712.466	
cg01763916	1	40.849.202	SMAP2
cg25530944	X	130.964.695	LOC286467
cg01824063	11	71.276.654	KRTAP5-10
cg22261987	8	256.888	
cg23413924	15	45.427.734	DUOX1
cg06153467	16	29.647.520	
cg12297125	1	2.996.522	PRDM16
cg19925186	1	89.725.637	GBP5
cg12504098	7	38.298.908	
cg24050109	1	6.501.240	ESPN
cg13383814	10	98.745.012	C10orf12
cg14387414	22	39.377.930	APOBEC3B
cg23629561	11	71.238.382	KRTAP5-7
cg15305732	2	86.155.886	
cg16734191	21	40.194.848	ETS2
cg26790897	7	56.147.772	SUMF2
cg04143805	16	89.395.205	ANKRD11
cg10906108	4	330.163	ZNF141
cg06203720	1	1.309.641	AURKAIP1
cg25318364	1	147.719.101	
cg19600442	3	129.800.495	ALG1L2
cg27644672	7	1.858.694	MAD1L1
cg17362247	19	39.788.647	IL29
cg25234732	7	56.183.885	LOC389493
cg16702690	19	51.686.316	
cg00706683	2	233.251.030	ECEL1P2
cg11436767	11	46.401.422	MDK; DGKZ
cg14191036	X	48.335.457	FTSJ1

cg05755017	11	122.929.522	HSPA8
cg01157559	16	29.166.162	
cg09011576	1	149.193.534	
cg11750165	13	112.722.233	SOX1
cg19784262	X	153.166.733	AVPR2
cg08152331	4	73.632.683	
cg21771528	5	18.745.861	
cg27497831	X	153.171.917	AVPR2
cg25582185	14	106.032.933	
cg20329220	15	78.286.521	LOC91450
cg19376664	6	32.153.575	PBX2
cg12058781	1	89.663.896	GBP4
cg21873567	7	99.816.750	GATS; PVRIG
cg06715352	16	66.729.204	CMTM4
cg14558880	19	1.271.275	C19orf23; CIRBP
cg11896066	8	8.821.111	
cg02471940	15	62.535.343	
cg08522831	3	152.074.401	MBNL1
cg10054984	12	129.329.790	
cg02389252	8	104.152.279	BAALC; C8orf56
cg00960209	16	29.165.693	
cg22177227	15	59.125.919	FAM63B
cg09591533	3	197.382.671	
cg05190516	X	99.891.595	TSPAN6
cg26424645	1	227.729.598	
cg08356705	11	68.148.006	LRP5
cg17755386	1	45.242.191	SNORD46; RPS8; SNORD38A
cg26712680	12	8.542.524	LOC389634
cg23206289	19	43.891.866	TEX101
cg16488174	1	16.971.585	MST1P2
cg07685606	12	132.116.798	
cg05922028	1	207.669.334	CR1
cg27064949	X	69.397.448	DGAT2L6
cg21157094	17	25.958.282	LGALS9
cg26659404	1	25.747.437	RHCE
cg25861453	6	31.867.906	ZBTB12
cg02188225	6	30.459.255	HLA-E
cg03274069	X	153.171.699	AVPR2
cg05858130	X	48.929.808	PRAF2
cg22136749	12	2.041.419	
cg11586158	1	175.013.920	
cg08609845	X	45.060.113	CXorf36
cg06987369	7	127.899.681	
cg13838634	6	31.785.399	HSPA1A
cg27239828	3	185.136.561	MAP3K13
cg03736201	11	117.848.510	
cg11331769	X	153.639.287	TAZ; DNASE1L1
cg04340203	19	891.986	MED16
cg16370863	5	76.210.838	S100Z
cg12539124	6	21.948.636	FLJ22536
cg24911837	7	65.227.864	CCT6P1
cg03099849	19	39.755.959	
cg16893618	19	14.491.899	CD97
cg13218284	X	38.662.289	MID1IP1
cg18061395	5	16.754.384	MYO10
cg03292040	2	132.286.665	CCDC74A
cg16279576	10	43.361.553	
cg09186748	17	73.577.594	
cg05662829	1	787.423	LOC643837
cg02707162	19	632.675	POLRMT
cg12614667	1	89.663.868	GBP4
cg20539430	2	233.762.570	NGEF
cg06796482	7	74.378.824	GATSL1
cg01454237	19	55.314.879	KIR2DL4
cg02050232	16	29.296.614	
cg26564117	22	28.249.567	PITPNB
cg16351010	5	221.513	SDHA
cg12408911	16	87.903.671	SLC7A5
cg27108577	7	74.573.749	NCF1C
cg23591536	12	6.299.538	
cg00805874	6	31.867.847	ZBTB12
cg25420507	19	39.261.921	LGALS7
cg10786986	X	13.711.087	RAB9A
cg25470384	6	31.867.836	ZBTB12
cg21097504	7	63.151.988	
cg01273344	19	11.998.201	ZNF69
cg05248067	10	43.361.339	
cg27448496	10	130.868.409	
cg21002146	14	92.303.622	TC2N
cg10573235	X	123.480.277	SH2D1A
cg16355771	3	13.242.707	
cg03025569	17	15.586.426	TRIM16
cg06636203	6	31.867.788	ZBTB12
cg09788778	6	31.867.822	ZBTB12
cg00657202	10	131.309.164	MGMT
cg17202706	3	195.453.369	MUC20
cg22388316	2	2.000.192	MYT1L
cg24581845	1	168.513.242	XCL2
cg04037732	X	70.364.775	NLGN3
cg11148381	2	2.000.815	MYT1L
cg22649124	19	39.282.077	LGALS7B
cg11553721	13	114.287.546	TFDP1
cg01308549	21	38.592.416	DSCR9
cg24955592	6	26.271.227	HIST1H3G
cg10631854	3	197.383.170	
cg20896063	11	5.274.883	HBG2
cg25614935	10	1.084.866	C10orf110
cg27603055	8	29.172.360	
cg10692693	7	101.688.648	CUX1
cg00152644	1	153.068.236	SPRR2E
cg21230425	7	64.533.826	
cg08326410	19	55.314.884	KIR2DL4
cg05468303	22	18.894.389	DGCR6
cg26627129	19	49.552.470	CGB8
cg12067024	1	153.387.689	S100A7A
cg04774770	5	754.668	
cg19274680	4	26.143.392	
cg25469474	4	2.749.501	TNIP2
cg19418648	5	176.789.979	RGS14
cg03073000	X	130.964.931	LOC286467
cg21171639	9	7.478.307	
cg22322928	X	45.060.415	CXorf36
cg09726125	17	77.685.623	
cg01577700	22	24.641.314	GGT5
cg02057598	16	87.904.547	SLC7A5
cg26328180	2	91.874.214	
cg17473580	3	197.382.627	
cg06477464	5	68.790.044	OCLN
cg00141845	X	74.493.352	UPRT
cg14995803	17	21.455.116	C17orf51
cg20965017	5	231.967	SDHA
cg21085701	19	12.033.228	
cg11433672	17	26.578.289	
cg00941203	10	31.016.591	
cg02177607	X	128.924.261	SASH3
cg02574805	12	131.814.178	
cg24693803	4	171.013.537	
cg10424125	8	124.194.624	FAM83A
cg09205156	7	101.991.189	SPDYE6
cg25085729	10	16.949.847	CUBN
cg23623364	3	49.726.785	MST1; RNF123
cg23374847	2	34.720.275	
cg04375087	X	48.166.824	SSX9
cg23840219	6	109.381.072	SESN1
cg06462796	9	79.634.861	FOXB2
cg03528016	2	73.871.942	ALMS1P
cg09647375	8	12.578.896	
cg15466862	13	112.722.333	SOX1
cg17385225	X	118.750.273	SEPT6
cg10714111	2	233.244.503	ALPP
cg26605073	X	100.333.473	TMEM35
cg07660283	22	51.223.343	RPL23AP82; RABL2B
cg11497169	1	247.333.735	ZNF124
cg00054352	13	114.891.672	RASA3
cg25701114	6	26.031.939	HIST1H3B
cg13434308	12	29.936.486	TMTC1
cg09872233	17	4.544.925	ALOX15
cg19260144	22	49.763.965	
cg01307555	2	73.871.915	ALMS1P
cg17935703	9	139.642.998	LCN6
cg19369616	19	53.447.272	ZNF321
cg21008363	7	75.053.134	POM121C
cg12338731	7	7.031.197	
cg24180805	6	32.556.093	HLA-DRB1
cg19241305	2	162.137.625	
cg06128881	X	46.616.842	SLC9A7
cg15903280	1	793.962	
cg19367951	7	75.072.658	POM121C
cg13127825	6	31.867.919	ZBTB12
cg00718129	X	10.084.289	WWC3
cg21347444	2	107.107.664	
cg00986824	12	75.601.465	KCNC2
cg14455613	3	125.648.160	LOC100125556; ALG1L
cg18789636	18	14.430.708	
cg20244073	X	10.851.627	MID1
cg16659202	13	32.205.404	
cg01310750	19	52.996.548	ZNF578

cg26089827	12	132.116.780	
cg03392753	7	1.005.576	COX19
cg08146256	14	21.734.410	HNRNPC
cg18002437	1	144.522.237	LOC728875
cg07124956	1	236.273.335	
cg17672846	X	11.774.782	MSL3
cg02940661	14	106.382.755	KIAA0125
cg11193416	1	4.471.975	LOC284661
cg22499139	6	29.759.718	HCG4
cg10587047	4	2.956.821	NOP14
cg06824467	1	149.223.316	
cg02902412	18	77.087.900	ATP9B
cg09408951	1	187.673.731	
cg08061040	7	149.746.077	
cg25424250	11	71.421.380	
cg22483030	6	33.043.849	HLA-DPB1
cg18847118	7	56.953.025	
cg00853671	12	129.331.490	
cg03216698	6	32.021.500	TNXB
cg15221579	7	38.298.966	
cg05343105	16	29.801.371	KIF22
cg25253815	X	153.170.555	AVPR2
cg27270684	7	55.757.158	FKBP9L
cg13197450	7	89.853.852	STEAP2
cg26813458	19	42.260.485	CEACAM6
cg14523706	1	16.347.701	CLCNKA
cg05626738	19	53.238.413	ZNF611
cg16114213	6	33.165.592	RXRB
cg11279857	11	64.009.878	FKBP2
cg13613146	16	29.625.989	SLC7A5P1
cg01444579	16	87.925.584	CA5A
cg15296538	5	178.203.469	AACSL
cg24539569	12	10.028.003	
cg23850283	2	114.261.369	
cg07961098	14	64.228.680	
cg16719099	X	139.007.085	MIR505
cg01828661	1	16.971.394	MST1P2
cg09535841	5	177.576.684	NHP2
cg03104055	3	75.705.922	
cg21031692	3	39.321.710	CX3CR1
cg25137968	1	120.905.306	HIST2H2BA
cg00014561	16	56.762.906	NUP93
cg27574287	10	42.641.430	
cg10182404	2	96.078.823	FAHD2A
cg21330641	X	118.780.930	SEPT6; MIR766
cg23617947	3	195.347.035	
cg10609310	8	38.722.935	
cg04224247	X	9.984.515	WWC3
cg04603811	6	31.867.873	ZBTB12
cg07148697	6	31.323.253	HLA-B
cg18704218	5	33.162.408	
cg19127840	X	65.238.616	MIR223
cg19927565	17	74.023.625	EVPL
cg09367126	16	89.242.147	CDH15
cg15779702	7	72.722.304	NSUN5
cg15225364	7	1.859.172	MAD1L1
cg21518974	3	85.553.266	CADM2
cg11872645	17	75.186.962	SEC14L1
cg02407068	4	39.771.851	UBE2K
cg03234702	6	26.225.539	HIST1H3E
cg01945822	6	33.313.399	
cg15599437	5	40.676.198	
cg00801716	22	47.074.280	GRAMD4
cg03597525	19	51.920.435	SIGLEC10; LOC100129083
cg11322877	X	130.965.143	LOC286467
cg15965241	12	121.570.571	P2RX7
cg26461666	7	142.353.864	
cg04630982	X	139.006.339	MIR505
cg15929297	X	99.667.528	
cg23873735	17	4.539.072	ALOX15
cg27629311	2	68.906.885	
cg17385749	2	96.675.342	LOC729234
cg05796223	16	21.532.721	SLC7A5P2
cg03116676	19	12.371.283	
cg04532200	X	153.033.893	PLXNB3
cg06939402	13	114.876.521	RASA3
cg17010905	X	153.365.806	
cg11657258	X	114.546.354	
cg19506407	X	5.811.303	NLGN4X
cg01832487	11	59.787.020	
cg04976697	22	30.938.784	
cg04768713	19	53.073.334	ZNF701
cg02833725	1	156.696.768	ISG20L2; C1orf66
cg03440535	X	110.867.852	

cg23725323	X	20.163.796	
cg00187768	3	186.617.977	
cg07885785	X	30.591.068	CXorf21
cg05996573	12	66.627.943	IRAK3
cg08267258	14	106.150.738	
ch.1.839062R	1	25.282.539	RUNX3
cg00949249	2	97.776.919	
cg16002248	1	155.699.008	DAP3
cg23417743	X	129.086.838	
cg04691277	1	6.479.352	HES2
cg01523316	3	172.585.684	
cg05719181	4	2.956.957	NOP14
cg21915074	7	72.351.001	POM121
cg22349387	12	9.600.060	DDX12
cg14071186	14	71.635.288	
cg14996583	13	24.478.590	
cg08160826	3	137.491.164	
cg10139889	7	5.863.510	ZNF815
cg03791917	X	100.641.287	BTK
cg03152870	18	77.088.134	ATP9B
cg00318897	16	88.268.362	
cg09898573	Y	14.100.824	
cg26188131	14	106.095.796	
cg09027357	8	256.911	
cg11264997	5	177.395.755	
cg03965496	1	147.718.157	
cg18503052	X	49.028.039	PLP2
cg25691526	X	130.964.707	LOC286467
cg05017760	8	117.544.399	
cg06964738	7	977.190	ADAP1
cg08704250	15	31.115.839	
cg15819955	1	168.510.365	XCL2
cg10514593	10	134.578.406	INPP5A
cg21872009	17	26.573.693	PPY2
cg03163767	16	66.969.506	FAM96B; CES2
cg00982805	11	1.619.030	HCCA2; KRTAP5-2; LOC338651
cg03049125	6	168.687.955	
cg07381669	12	125.369.317	
cg16491050	12	6.818.455	
cg03725115	6	30.458.102	HLA-E
cg25692507	19	5.866.076	FUT5
cg07699845	8	38.068.205	BAG4
cg03833774	X	77.914.149	ZCCHC5
cg20207784	X	71.494.120	RPS4X
cg07071615	14	106.214.478	
cg08647652	17	18.538.582	
cg06737484	14	96.972.280	PAPOLA
cg15114045	5	138.906.052	
cg09574997	7	2.718.222	AMZ1
cg06219204	16	88.299.223	
cg02147592	19	4.090.388	MAP2K2
cg06598386	12	67.830.705	
cg13407883	19	51.627.843	SIGLEC9
cg05184256	16	88.155.593	
cg24886414	19	53.290.126	ZNF600
cg10244368	19	53.039.145	ZNF808
cg27441045	X	100.446.383	
cg09569868	19	53.028.694	
cg12718339	12	29.936.407	TMTC1
cg04351258	16	30.569.043	ZNF764
cg12910810	2	96.662.438	
cg08042799	16	15.490.293	MPV17L
cg24261529	17	66.194.137	LOC440461
cg20638644	12	64.937.971	
cg12763118	1	9.711.304	PIK3CD
cg12164975	7	156.665.847	LMBR1
cg24385450	4	2.957.128	NOP14
cg04008601	12	103.696.126	C12orf42
cg04653083	X	118.827.004	SEPT6
cg08271622	20	37.053.969	LOC388796; SNORA71B
cg16101962	6	3.064.937	
cg10461895	15	66.795.834	SNORD18A; RPL4; SNORD18B; SNORD16
cg15788580	4	144.832.211	
cg01596349	X	153.627.775	RPL10;SNORA70
cg26181840	13	114.869.338	RASA3
cg10199040	1	89.592.995	GBP2
cg26988585	17	13.926.488	CDRT15P
cg17656474	12	176.424	IQSEC3
cg21912308	X	48.929.987	PRAF2
cg14945456	17	79.791.791	DYSFIP1; FAM195B
cg06614118	5	180.414.906	BTNL3

cg01490258	X	40.030.456	BCOR
cg25653296	15	35.413.975	
cg08510934	19	55.361.935	KIR3DL2
cg16439324	2	242.927.580	
cg25570486	20	61.621.446	
cg14172454	14	106.190.169	
cg04248512	12	133.016.503	
cg24542766	22	39.713.532	RPL3; RNU86
cg00171192	22	17.518.345	CECR7
cg07465140	4	171.013.671	
cg17079026	2	95.858.880	
cg04602755	1	154.935.120	SHC1; PYGO2
cg19866040	11	1.619.381	HCCA2; KRTAP5-2; LOC338651
cg17863923	2	87.170.602	RGPD1; RGPD2
cg24799729	5	161.178.484	
cg26398510	15	45.328.217	SORD
cg23418965	11	125.170.859	PKNOX2
cg23148631	17	6.950.669	
cg22228134	14	25.078.609	GZMH
cg01836906	2	192.792.315	
cg27639408	4	155.662.375	
cg19178479	2	112.124.118	
cg21114303	X	54.069.147	PHF8
cg26062172	5	94.775.923	FAM81B
cg16301758	6	150.275.521	
cg22950493	7	32.805.364	
cg09069886	8	131.000.415	
cg27150460	16	67.515.916	ATP6V0D1
cg17278295	19	2.131.861	AP3D1
cg03128614	16	30.534.807	
cg26101890	2	228.185.396	
cg23599683	1	40.235.372	BMP8B;OXCT2
cg10607675	X	21.674.415	KLHL34
cg12056733	20	43.535.593	YWHAB
cg09076821	X	47.052.506	UBA1
cg13226290	20	1.448.595	NSFL1C
cg09215282	16	811.744	MSLN
cg15189233	19	35.939.766	FFAR2
cg15657641	11	47.939.769	
cg19492036	19	55.249.782	KIR2DL3
cg15644764	1	202.592.914	SYT2
cg25729060	17	17.088.577	MPRIP
cg21175761	X	70.273.254	
cg07143583	2	85.776.941	GGCX
cg17281297	3	134.207.444	CEP63
cg23035602	19	53.935.117	ZNF761; LOC147804
cg05967389	X	40.948.142	USP9X
cg13769609	11	70.669.673	SHANK2
cg10862981	11	46.164.774	
cg07844659	16	86.601.361	FOXC2
cg22099398	16	32.823.584	
cg27360158	X	41.133.058	
cg08617020	16	87.894.491	SLC7A5
cg19950606	17	76.121.276	TMC6
cg18422972	X	40.029.227	BCOR
cg11704818	3	47.517.781	SCAP
cg06128598	17	26.552.870	PYY2
cg02690169	18	14.430.704	
cg16717008	3	148.037.650	
cg06299783	11	133.872.222	
cg08146495	1	182.911.555	C1orf14
cg08153621	19	53.561.441	
cg12699187	21	15.354.157	C21orf81
cg00893045	15	66.795.844	SNORD18A; RPL4; SNORD18B; SNORD16
cg27112809	17	16.736.463	LOC400578
cg19203575	6	28.322.086	ZNF323; ZKSCAN3
cg15871544	20	52.211.744	
cg06408533	X	67.867.352	STARD8
cg17718576	17	36.883.244	MLLT6
cg10753398	19	39.896.713	ZFP36
cg21447170	4	188.686.763	
cg00252529	4	148.730.174	ARHGAP10
cg24470206	6	33.165.598	RXRB
cg12748000	12	6.299.601	
cg15558102	1	148.242.521	
cg12795731	13	114.287.498	TFDP1
cg18489146	19	39.759.357	IL28A
cg16709512	5	101.297.174	
cg19792027	X	118.922.222	SNORA69;RPL39
cg10053473	17	62.856.997	LRRC37A3
cg07859138	X	118.751.995	SEPT6
cg04023663	7	7.031.200	
cg18547838	10	63.800.880	ARID5B
cg01634664	14	91.580.142	C14orf159
cg07578331	16	15.237.722	
cg03588189	17	61.988.802	CSHL1
cg22537843	19	298.437	
cg00166770	20	55.043.239	C20orf43
cg26324366	6	99.283.652	POU3F2
cg02093833	17	16.287.835	
cg11800635	2	74.783.088	DOK1
cg06948553	X	40.037.418	BCOR
cg13279774	X	102.632.528	NGFRAP1
cg01502484	16	67.192.220	TRADD
cg02675179	16	20.686.073	ACSM1
cg09552402	20	62.282.821	STMN3
cg13778815	4	190.949.272	FRG2
cg03537673	15	92.398.483	SLCO3A1
cg22090266	11	60.106.260	MS4A6E
cg24268343	X	56.260.186	KLF8
cg08026791	16	5.134.964	FAM86A; ALG1
cg12112110	6	32.009.422	TNXB
cg07417990	1	224.051.868	
cg14805882	X	101.381.594	TCEAL2
cg15100535	2	134.866.137	
cg20675040	8	143.813.288	C8orf55
cg01507577	7	146.484.609	CNTNAP2
cg15057581	20	1.875.084	SIRPA
cg26613586	1	16.847.289	
cg11117255	X	40.008.202	BCOR
cg05560472	X	99.986.046	SYTL4
cg04304019	16	12.146.023	SNX29; RUNDC2A
cg16555411	14	107.062.160	
cg06542928	2	171.608.308	
cg04214399	5	35.532.928	
cg16383910	15	78.287.672	TBC1D2B; LOC91450
cg16112904	14	106.015.656	
cg10277548	22	17.517.062	CECR7
cg16930947	8	88.984.447	
cg22290284	3	49.726.443	MST1; RNF123
cg01435401	17	263.615	C17orf97
cg14924510	3	195.682.365	
cg07871633	19	41.639.260	
cg04835653	13	19.956.749	
cg06911487	19	10.024.282	OLFM2
cg09665844	2	4.720.659	
cg03797305	16	30.209.202	SULT1A3; SULT1A4
cg23267872	1	8.937.087	ENO1
cg09865026	1	222.645.903	
cg18299157	10	131.904.410	
cg11509733	X	99.892.000	TSPAN6
cg25140188	X	31.087.348	
cg02816727	10	125.042.097	
cg14545834	9	8.713.437	PTPRD
cg13572146	19	5.832.296	FUT6
cg13064305	1	144.567.670	
cg02118671	8	143.660.412	
cg20430101	X	47.003.160	NDUFB11; RBM10
cg12664806	6	108.882.981	FOXO3
cg05508793	12	133.433.300	CHFR
cg06837067	22	39.381.429	APOBEC3B
cg04840108	4	38.859.339	TLR6
cg02412123	19	51.628.204	SIGLEC9
cg11856308	1	1.449.956	ATAD3A
cg16115418	X	3.630.582	PRKX
cg09717585	16	87.517.852	ZCCHC14
cg01586208	19	22.806.647	
cg26159184	7	62.528.610	
cg19928997	22	24.642.243	GGT5
cg07390373	X	43.741.933	MAOB
cg02368737	12	27.273.951	
cg07166654	12	52.652.220	
cg02842889	Y	2.803.127	ZFY
cg22964346	X	109.411.307	TMEM164
cg01152168	17	18.280.011	EVPLL
cg23730037	7	158.596.552	ESYT2
cg09048404	2	91.937.754	
cg13478010	1	222.224.088	
cg00423700	16	66.982.435	
cg24156613	X	39.950.501	BCOR
cg22049321	1	207.669.116	CR1
cg05886469	17	66.205.079	
cg08251248	10	74.086.590	
cg02018040	22	27.152.963	
cg20631224	7	99.934.059	PILRB; PMS2L1
cg25248094	X	123.480.304	SH2D1A
cg06099703	16	2.569.920	AMDHD2; ATP6V0C

cg00605988	16	31.548.698	
cg26129027	X	38.662.279	MID1IP1
cg17114866	19	35.222.640	
cg13487284	17	26.794.878	
cg26618874	16	75.572.883	TMEM231
cg26932054	1	1.606.361	LOC728661; CDK11B
cg15782228	20	60.932.415	LAMA5
cg16861845	17	15.652.329	
cg26286239	6	157.285.705	ARID1B
cg22433141	1	45.243.377	SNORD38A; RPS8; SNORD38B
cg13378486	6	32.115.221	
cg03544771	X	38.661.483	MID1IP1
cg05554718	6	26.235.699	HIST1H1D
cg24866308	3	75.671.115	
cg26212966	11	71.351.271	
cg13817994	X	152.600.484	ZNF275
cg00405494	9	7.797.524	C9orf123
cg13001844	5	1.513.791	LPCAT1
cg13377102	17	7.832.764	KCNAB3
cg24099067	6	26.758.750	
cg25359908	7	149.918.047	
cg24456744	13	114.849.719	RASA3
cg26326746	X	139.006.401	MIR505
cg12904531	11	67.572.716	LOC645332
cg08676755	19	49.520.359	LHB
cg13028630	6	31.964.754	C4B;C4A
cg13913130	9	141.045.017	TUBBP5
cg16335841	2	233.246.214	ALPP
cg06346138	1	17.086.071	MST1P9
cg07704242	1	108.766.057	NBPF4
cg05893029	8	88.760.082	
cg23604959	X	153.283.694	IRAK1
cg14873885	3	49.726.775	MST1; RNF123
cg06694641	12	133.533.079	ZNF605
cg15060599	3	13.974.467	
cg10064060	16	15.603.154	C16orf45
cg14345215	2	212.388.373	ERBB4
cg03963784	7	144.114.242	
cg09208740	6	29.856.353	HLA-H
cg18439080	X	70.273.384	
cg18526140	14	106.444.894	
cg27054055	6	142.290.983	
cg05428888	6	165.236.522	
cg00423291	7	40.855.639	C7orf10
cg25529393	6	27.858.380	HIST1H3J
cg05407003	7	23.246.146	
cg08021532	16	50.321.878	ADCY7
cg17004975	10	81.743.287	
cg14741114	Y	14.774.198	TTTY15
cg17213462	6	29.795.411	HLA-G
cg25786265	6	30.458.998	HLA-E
cg00615794	X	102.943.966	MORF4L2
cg02615352	2	73.928.500	NAT8B
cg15786732	13	33.933.471	
cg21911143	17	58.197.134	
cg18512780	17	76.117.734	TMC6
cg14996916	X	147.131.122	
cg15850390	X	72.668.487	CDX4
cg02677388	6	26.045.788	HIST1H3C
cg25356951	8	25.023.246	
cg18298815	1	161.519.989	FCGR3A
cg06945563	16	88.153.548	
cg23016632	1	1.396.169	ATAD3C
cg16927664	17	18.575.710	ZNF286B; FOXO3B
cg08130275	3	171.773.170	FNDC3B
cg24781299	13	114.807.826	RASA3
cg14996291	X	69.662.278	
cg25849281	1	8.937.077	ENO1
cg08824291	9	136.428.028	ADAMTSL2
cg02864732	X	130.192.365	FLJ30058
cg26040075	1	1.034.421	C1orf159
cg04246864	16	33.357.426	
cg20469935	X	130.964.757	LOC286467
cg25559322	7	74.304.373	STAG3L2
cg08413390	15	84.944.048	
cg00470565	22	22.469.147	
cg20277250	5	74.061.999	NSA2; GFM2
cg22193924	19	35.850.463	FFAR3
cg23928118	5	140.215.201	PCDHA6; PCDHA2; PCDHA1; PCDHA7; PCDHA5; PCDHA3; PCDHA4
cg12105899	X	125.715.154	
cg09013789	7	138.776.683	ZC3HAV1
cg09677082	7	62.514.572	
cg17326835	X	153.688.618	PLXNA3
cg17680813	3	172.394.387	NCEH1
cg01718222	4	298.277	
cg00456637	14	37.050.455	NKX2-8
cg12432010	12	176.081	IQSEC3
cg20364183	3	115.758.614	LSAMP
cg00353643	16	1.458.060	UNKL
cg27055580	X	69.396.942	DGAT2L6
cg03119454	17	78.850.480	RPTOR
cg07473909	15	41.782.961	
cg15818604	8	94.713.593	FAM92A1
cg07536161	2	87.085.357	CD8B
cg23735003	X	70.331.762	IL2RG
cg00404599	X	107.018.431	TSC22D3
cg10693635	6	16.215.614	
cg18669823	7	30.725.669	
cg24681408	17	79.887.046	LOC92659; MAFG
cg18026626	15	78.286.614	LOC91450
cg11586216	7	76.750.857	CCDC146
cg26982829	17	29.335.153	
cg20559943	4	185.820.756	
cg18396832	X	8.700.172	KAL1
cg00156057	6	169.391.744	
cg02078896	20	15.176.557	MACROD2
cg04265051	11	68.079.686	LRP5
cg06538336	X	150.346.599	GPR50
cg07980988	X	123.480.013	SH2D1A
cg13668005	2	131.278.268	CFC1B; CFC1
cg18449462	X	77.155.144	COX7B
cg17329835	2	38.204.832	FAM82A1
cg05403433	2	87.088.843	CD8B
cg00869530	6	32.155.124	PBX2
cg19259829	6	46.743.446	
cg13541257	9	44.873.530	
cg15656181	5	71.654.404	PTCD2
cg02057716	2	218.807.759	TNS1
cg04338134	16	66.969.401	FAM96B; CES2
cg08476485	3	122.684.038	SEMA5B
cg15885337	11	132.813.819	OPCML
cg17186328	1	168.545.835	XCL1
cg25104430	14	78.128.179	
cg27550498	X	70.340.920	MED12
cg15176306	2	224.813.276	
cg00692088	6	161.622.097	AGPAT4
cg24326574	X	153.713.930	UBL4A
cg03267151	16	30.347.240	LOC595101
cg20708061	12	131.958.981	
cg12686920	17	41.739.806	MEOX1
cg09944171	16	56.669.778	
cg07420720	4	178.113.740	
cg03573109	16	85.849.619	
cg03311682	19	47.127.856	PTGIR
cg07193998	20	4.707.860	PRND
cg04984422	7	2.614.081	IQCE
cg16691557	6	115.562.132	
cg26486069	X	48.434.354	RBM3
cg14038878	9	86.431.343	GKAP1
cg07564837	8	58.126.962	
cg12879539	X	45.607.438	MIR222
cg26793320	1	147.719.039	
cg01645955	4	39.371.148	
cg14505256	22	20978594	
cg02305961	14	105157042	INF2
cg14423168	8	41400312	GINS4
cg11507793	6	29856363	HLA-H
cg26707149	16	68033301	DPEP2
cg05336395	13	53421688	PCDH8
cg03004249	14	83560039	
cg02772106	X	152992265	ABCD1
cg00681003	20	23586547	CST9
cg07478007	1	1411602	ATAD3B
cg19781248	1	144340161	LOC728855; LOC728875
cg12549079	17	6756796	ALOX12P2
cg20400795	12	133516439	ZNF605
cg14992964	22	17001515	
cg01785719	8	143404187	TSNARE1
cg10018203	14	106179136	
cg21558614	5	754184	
cg01089751	22	39378425	APOBEC3B
cg03330485	8	21647596	GFRA2
cg24104627	2	52006728	

cg07251872	6	41169918	TREML2
cg14677013	8	75512167	
cg24198059	6	27839751	HIST1H3I
cg24828683	6	29856210	HLA-H
cg15162219	8	29952246	LEPROTL1
cg26899005	X	153213140	HCFC1
cg00555036	22	16213781	
cg20063270	1	158146122	
cg02105352	2	73929892	NAT8B
cg15320148	14	70449448	SMOC1
cg23114772	17	80622243	RAB40B
cg15188084	9	135947049	CEL
cg14042931	14	106791268	
cg20767845	X	128926467	SASH3
cg12131827	8	21640270	GFRA2
cg16708281	2	114256673	FOXD4L1
cg08224217	17	18562111	ZNF286B
cg15389519	5	140769585	PCDHGB4; PCDHGA4; PCDHGA6; PCDHGA1; PCDHGA5; PCDHGB1;PCDHGA3; PCDHGA2; PCDHGA7; PCDHGB2; PCDHGB3
cg13385794	1	248469461	
cg10180404	6	32632334	HLA-DQB1
cg01745539	6	32632331	HLA-DQB1
cg24658321	7	138776717	ZC3HAV1
cg10790704	17	78701084	RPTOR
cg05278186	2	131303925	LOC150527
cg06752398	15	79053858	ADAMTS7
cg07990036	12	122982870	ZCCHC8
cg10060918	6	29080437	OR2J3
cg21302017	X	14048278	GEMIN8
cg14580349	1	25664531	TMEM50A
cg21500538	X	152683655	ZFP92

Appendix D

Results of First Step of our MR Framework

TABLE D.1: Results of the first step of our MR framework. Results are given as β coefficient, standard error and p-value from both LIML and CUE estimation.

	LIML			CUE		
CpG	**Beta**	**SE**	**P**	**Beta**	**Std**	**P**
cg08396096	0.0322	0.0051	4.58E-10	0.0040	0.0007	3.7E-08
cg14851482	0.0409	0.0066	1.02E-09	0.0174	0.0017	1.4E-22
cg19618984	-0.0498	0.0081	1.60E-09	-0.0388	0.0029	7.9E-35
cg24663971	0.1082	0.0181	4.63E-09	0.0094	0.0035	8.3E-03
cg08834436	-0.2513	0.0421	4.75E-09	-0.0869	0.0079	4.7E-25
cg26878870	0.1326	0.0223	5.11E-09	0.0402	0.0041	8.2E-21
cg27289478	0.0672	0.0113	5.78E-09	0.0162	0.0018	1.9E-18
cg01592687	0.0756	0.0128	7.51E-09	0.0522	0.0044	5.4E-29
cg21664281	-0.2276	0.0387	7.69E-09	-0.0950	0.0105	2.8E-18
cg18780100	0.1488	0.0255	9.56E-09	0.0267	0.0038	1.1E-11
cg13187188	0.0754	0.0130	1.09E-08	0.0363	0.0025	8.6E-39
cg14094639	0.0678	0.0117	1.14E-08	0.0007	0.0022	7.4E-01
cg02010963	0.1104	0.0192	1.60E-08	-0.0033	0.0030	2.8E-01
cg07648709	0.0595	0.0104	1.78E-08	0.0152	0.0019	2.6E-14
cg10592926	-0.1128	0.0198	2.05E-08	-0.0413	0.0038	1.5E-24
cg03233332	0.0917	0.0162	2.38E-08	-0.0066	0.0032	4.1E-02
cg24207161	0.1241	0.0219	2.50E-08	0.0353	0.0053	7.4E-11
cg12856392	0.2617	0.0466	3.38E-08	0.0895	0.0091	6.7E-21
cg21611682	-0.0691	0.0123	3.52E-08	-0.0061	0.0021	4.6E-03
cg06644428	0.0683	0.0122	3.62E-08	-0.0040	0.0017	1.9E-02
cg19297232	-0.2019	0.0361	3.78E-08	-0.0459	0.0065	4.7E-12
cg14205519	0.0892	0.0160	3.78E-08	0.0139	0.0028	1.2E-06
cg16254309	-0.0419	0.0075	4.47E-08	-0.0348	0.0027	4.1E-32
cg00575674	0.1368	0.0247	4.69E-08	0.0157	0.0047	8.5E-04
cg09109520	-0.1563	0.0283	5.20E-08	-0.0046	0.0041	2.7E-01
cg00202479	-0.0806	0.0146	5.31E-08	-0.0280	0.0028	4.6E-22
cg27576485	-0.1476	0.0268	5.77E-08	-0.0283	0.0056	6.2E-07
cg10928294	0.0918	0.0167	6.56E-08	0.0240	0.0038	9.1E-10
cg21400170	0.1114	0.0204	7.34E-08	0.0451	0.0050	2.9E-18
cg00849642	-0.1053	0.0193	7.41E-08	-0.0427	0.0048	1.4E-17
cg11151251	0.0526	0.0096	7.58E-08	-0.0034	0.0018	6.3E-02
cg20385395	0.1005	0.0184	7.68E-08	0.0275	0.0034	7.6E-15
cg26510500	-0.0670	0.0123	7.88E-08	-0.0168	0.0021	7.4E-15
cg15209808	-0.1422	0.0261	8.48E-08	-0.0601	0.0053	1.2E-26
cg01834573	0.0468	0.0086	8.51E-08	0.0350	0.0028	1.3E-30
cg16474684	0.1014	0.0187	8.77E-08	0.0506	0.0038	2.0E-34
cg02604522	0.0737	0.0136	9.36E-08	0.0194	0.0024	1.9E-15
cg13240704	0.0835	0.0154	9.41E-08	-0.0071	0.0025	4.8E-03
cg19645639	0.1091	0.0201	9.65E-08	0.0645	0.0054	2.7E-29
cg23198793	-0.0901	0.0166	9.71E-08	-0.0200	0.0032	9.3E-10
cg21381845	0.1625	0.0301	1.09E-07	0.0538	0.0049	1.4E-25
cg20087093	0.0757	0.0140	1.09E-07	0.0273	0.0033	8.8E-16
cg19018709	0.0787	0.0146	1.14E-07	0.0380	0.0033	5.6E-27
cg03440944	0.0774	0.0144	1.15E-07	0.0446	0.0037	4.9E-30
cg05057834	-0.1016	0.0189	1.18E-07	-0.0266	0.0043	1.1E-09
cg00241664	-0.0558	0.0104	1.20E-07	-0.0123	0.0018	7.8E-12
cg14535531	0.2352	0.0438	1.22E-07	0.0658	0.0071	7.5E-19
cg21035374	-0.0466	0.0087	1.35E-07	-0.0290	0.0028	1.6E-22
cg16622652	0.1159	0.0217	1.36E-07	0.0725	0.0059	4.9E-30
cg10171489	0.1095	0.0205	1.40E-07	-0.0319	0.0036	3.3E-17
cg15802263	-0.1904	0.0357	1.46E-07	-0.0439	0.0060	8.1E-13
cg06590434	0.0614	0.0115	1.48E-07	0.0256	0.0022	1.5E-28
cg04392488	-0.1528	0.0287	1.51E-07	-0.0608	0.0060	3.3E-22
cg20663495	-0.0669	0.0126	1.53E-07	-0.0240	0.0029	1.0E-15
cg03619472	0.0786	0.0148	1.74E-07	0.0372	0.0032	5.1E-28
cg15421321	0.0470	0.0089	1.77E-07	0.0120	0.0016	8.4E-13
cg11669285	-0.1238	0.0234	1.90E-07	-0.0180	0.0057	1.6E-03
cg01973695	0.1285	0.0243	1.91E-07	0.0465	0.0043	2.0E-24
cg06000951	-0.0295	0.0056	1.98E-07	-0.0060	0.0011	1.7E-07
cg03280245	-0.0725	0.0138	2.00E-07	-0.0176	0.0019	8.1E-19
cg04018738	-0.0781	0.0148	2.13E-07	-0.0388	0.0050	2.9E-14
cg00674004	-0.1135	0.0216	2.15E-07	-0.0100	0.0057	7.8E-02
cg00997990	0.0432	0.0082	2.27E-07	-0.0049	0.0015	9.2E-04
cg23930945	0.0290	0.0055	2.35E-07	0.0079	0.0012	2.2E-10
cg19545472	-0.0870	0.0166	2.45E-07	-0.0130	0.0046	4.8E-03
cg07886712	0.0719	0.0137	2.52E-07	0.0049	0.0019	9.5E-03
cg13244241	-0.0728	0.0139	2.60E-07	-0.0380	0.0027	2.6E-38
cg00840332	-0.0893	0.0171	2.64E-07	-0.0420	0.0038	8.6E-26
cg08844770	0.0969	0.0186	2.64E-07	0.0147	0.0024	2.5E-09
cg20348746	-0.1874	0.0359	2.66E-07	-0.0378	0.0066	1.7E-08
cg22586569	-0.1426	0.0273	2.66E-07	-0.0093	0.0046	4.4E-02
cg23378941	0.1538	0.0295	2.74E-07	0.0430	0.0041	5.1E-23
cg08848462	0.1094	0.0210	2.75E-07	0.0666	0.0065	2.3E-22
cg07281948	-0.0237	0.0045	2.80E-07	0.0001	0.0005	8.7E-01
cg15843572	0.0911	0.0175	2.84E-07	0.0220	0.0035	5.0E-10
cg00401753	-0.0643	0.0124	3.00E-07	-0.0349	0.0031	3.2E-26
cg02634816	0.1206	0.0232	3.12E-07	0.0321	0.0039	1.2E-15
cg23268208	-0.1255	0.0242	3.13E-07	-0.0313	0.0043	8.8E-13
cg04258124	-0.0887	0.0171	3.23E-07	0.0095	0.0026	2.3E-04
cg23084416	-0.1132	0.0219	3.27E-07	-0.0124	0.0026	1.8E-06
cg18817459	-0.1706	0.0330	3.43E-07	0.0188	0.0050	1.9E-04
cg11413133	0.0896	0.0173	3.48E-07	-0.0382	0.0042	2.7E-18
cg00776080	-0.0458	0.0089	3.70E-07	-0.0041	0.0015	5.1E-03
cg16375265	0.1040	0.0202	3.75E-07	0.0088	0.0035	1.2E-02
cg15683295	0.0560	0.0109	3.97E-07	0.0030	0.0017	7.8E-02
cg11190156	0.0761	0.0148	3.98E-07	0.0134	0.0023	1.5E-08
cg06800840	0.0749	0.0146	4.05E-07	0.0286	0.0027	5.1E-24
cg06652329	-0.0955	0.0186	4.11E-07	-0.0279	0.0029	1.0E-20
cg05433557	0.1047	0.0204	4.15E-07	0.0098	0.0033	3.6E-03
cg16489259	0.1092	0.0213	4.19E-07	0.0679	0.0051	4.1E-35
cg08354093	0.0431	0.0084	4.33E-07	0.0207	0.0014	7.3E-43
cg19864758	-0.0414	0.0081	4.35E-07	-0.0050	0.0013	1.2E-04
cg23435671	-0.1102	0.0215	4.44E-07	-0.0167	0.0039	2.1E-05
cg00232827	0.1781	0.0348	4.45E-07	-0.0482	0.0055	2.3E-17
cg24496475	-0.1347	0.0263	4.49E-07	-0.0099	0.0041	1.6E-02
cg01316047	-0.0222	0.0043	4.52E-07	0.0008	0.0007	2.4E-01
cg06346307	0.1015	0.0198	4.56E-07	0.0593	0.0056	1.3E-23
cg09975715	-0.1096	0.0214	4.59E-07	-0.0430	0.0038	4.3E-26
cg01575601	0.0823	0.0161	4.59E-07	0.0078	0.0031	1.2E-02
cg18701970	-0.0679	0.0133	4.70E-07	-0.0012	0.0020	5.7E-01
cg05510665	-0.0589	0.0115	4.73E-07	-0.0222	0.0022	1.9E-22
cg12499872	-0.1199	0.0235	4.74E-07	-0.0459	0.0045	1.9E-22
cg09130658	0.0590	0.0116	4.76E-07	0.0172	0.0022	9.9E-14
cg07675477	-0.0761	0.0149	4.76E-07	-0.0073	0.0029	1.3E-02
cg10164592	-0.0226	0.0044	4.76E-07	0.0000	0.0006	1.0E+00
cg11851792	0.1093	0.0214	4.89E-07	-0.0083	0.0038	2.8E-02
cg01453052	0.2057	0.0403	4.93E-07	0.0108	0.0044	1.4E-02
cg00072689	0.1788	0.0351	4.96E-07	-0.0309	0.0061	5.1E-07
cg24218620	-0.0716	0.0141	4.98E-07	-0.0605	0.0065	2.4E-19
cg17165055	-0.0409	0.0080	4.98E-07	-0.0056	0.0016	7.6E-04
cg17076667	-0.0549	0.0108	5.00E-07	-0.0060	0.0029	3.5E-02
cg05336115	-0.0365	0.0072	5.00E-07	0.0004	0.0010	6.7E-01
cg20328456	-0.1147	0.0225	5.01E-07	-0.0947	0.0070	1.6E-35
cg24024660	-0.2058	0.0404	5.02E-07	-0.1065	0.0083	1.0E-32
cg13956645	-0.0423	0.0083	5.06E-07	-0.0035	0.0015	1.6E-02
cg19825437	0.0638	0.0125	5.11E-07	-0.0086	0.0022	8.6E-05
cg07219769	0.1002	0.0197	5.36E-07	0.0375	0.0044	2.5E-16

cg20977024	0.0932	0.0184	5.59E-07	0.0576	0.0055	3.3E-23	cg25687179	-0.1353	0.0277	1.36E-06	-0.0232	0.0054	2.0E-05
cg00466334	-0.0513	0.0101	5.64E-07	0.0061	0.0018	9.4E-04	cg09581137	0.1983	0.0405	1.37E-06	0.0119	0.0047	1.1E-02
cg07026010	0.1609	0.0317	5.70E-07	0.0177	0.0030	4.2E-09	cg13594463	-0.0350	0.0072	1.38E-06	-0.0157	0.0018	3.1E-16
cg02573176	-0.1049	0.0207	5.74E-07	0.0076	0.0048	1.2E-01	cg11136250	0.0613	0.0125	1.40E-06	0.0105	0.0030	4.7E-04
cg19235026	0.0665	0.0131	5.84E-07	0.0572	0.0035	4.9E-48	cg19757631	0.0858	0.0176	1.42E-06	0.0524	0.0041	6.2E-33
cg02275418	0.0502	0.0099	5.90E-07	0.0189	0.0022	4.6E-16	cg19712600	0.1417	0.0290	1.42E-06	0.0267	0.0039	2.5E-11
cg15787039	-0.0753	0.0149	5.90E-07	0.0208	0.0047	1.0E-05	cg06893362	0.1056	0.0216	1.42E-06	0.0295	0.0045	1.0E-10
cg27640528	-0.0822	0.0162	5.92E-07	-0.0376	0.0031	5.3E-30	cg10583997	0.1767	0.0362	1.44E-06	0.0048	0.0042	2.5E-01
cg03962950	0.0573	0.0113	5.92E-07	0.0325	0.0032	8.1E-22	cg16555466	0.1316	0.0270	1.46E-06	0.0276	0.0053	2.4E-07
cg00566158	-0.1062	0.0210	5.93E-07	0.0030	0.0027	2.8E-01	cg04287574	-0.3227	0.0662	1.47E-06	-0.0202	0.0095	3.3E-02
cg21922810	0.1463	0.0289	5.94E-07	0.0145	0.0033	1.8E-05	cg21777095	0.0782	0.0161	1.48E-06	-0.0014	0.0025	5.8E-01
cg25646708	-0.1896	0.0375	6.24E-07	-0.0898	0.0070	1.8E-32	cg18699466	-0.0611	0.0125	1.49E-06	-0.0163	0.0018	3.2E-18
cg19737746	0.0720	0.0143	6.30E-07	-0.0159	0.0024	5.4E-11	cg26416159	0.0518	0.0106	1.49E-06	0.0041	0.0018	2.7E-02
cg18443253	-0.0622	0.0123	6.36E-07	-0.0064	0.0015	2.4E-05	cg01205935	-0.2078	0.0427	1.51E-06	-0.0497	0.0068	1.2E-12
cg08173263	-0.1378	0.0274	6.66E-07	-0.0033	0.0040	4.1E-01	cg24146100	-0.0852	0.0175	1.52E-06	-0.0244	0.0046	2.0E-07
cg17632937	-0.1216	0.0242	6.87E-07	0.0031	0.0039	4.4E-01	cg15961920	-0.1072	0.0220	1.54E-06	-0.0219	0.0033	1.3E-10
cg04630292	-0.0438	0.0087	6.93E-07	-0.0317	0.0027	2.7E-28	cg26371327	-0.2563	0.0527	1.55E-06	-0.0937	0.0070	9.0E-35
cg09573843	0.0232	0.0046	6.96E-07	0.0064	0.0012	9.1E-08	cg10517222	-0.0735	0.0151	1.56E-06	-0.0079	0.0021	1.6E-04
cg08782337	-0.0297	0.0059	6.96E-07	-0.0008	0.0012	5.1E-01	cg05656688	0.1079	0.0222	1.56E-06	0.0101	0.0038	8.4E-03
cg22800233	-0.1417	0.0282	7.00E-07	0.0173	0.0042	5.1E-05	cg17379828	-0.0424	0.0087	1.57E-06	-0.0131	0.0017	4.1E-14
cg06361405	-0.0245	0.0049	7.04E-07	-0.0067	0.0009	1.4E-13	cg01637175	0.1824	0.0375	1.57E-06	-0.0223	0.0082	7.0E-03
cg15389749	0.0508	0.0101	7.07E-07	-0.0036	0.0024	1.4E-01	cg01254555	0.0195	0.0040	1.60E-06	0.0186	0.0014	5.1E-35
cg20343063	0.0928	0.0185	7.14E-07	0.0403	0.0036	1.7E-25	cg23856299	-0.0722	0.0149	1.60E-06	0.0119	0.0029	5.9E-05
cg08681689	0.0696	0.0139	7.20E-07	0.0119	0.0021	3.3E-08	cg13596235	0.0561	0.0115	1.60E-06	0.0032	0.0022	1.6E-01
cg20591407	0.1042	0.0208	7.27E-07	0.0285	0.0027	3.2E-24	cg03227184	0.0305	0.0063	1.60E-06	-0.0007	0.0008	3.9E-01
cg04444027	0.0801	0.0160	7.36E-07	0.0039	0.0022	8.2E-02	cg14209165	0.0875	0.0180	1.63E-06	0.0152	0.0025	1.9E-09
cg19850024	-0.1699	0.0339	7.43E-07	-0.2290	0.0221	6.7E-23	cg21436456	0.0626	0.0129	1.64E-06	-0.0146	0.0019	1.2E-13
cg19793809	-0.1196	0.0239	7.65E-07	-0.0205	0.0025	2.9E-15	cg05940672	-0.0975	0.0201	1.64E-06	0.0146	0.0024	1.6E-09
cg26139080	-0.1271	0.0254	7.66E-07	-0.0081	0.0036	2.5E-02	cg12065779	-0.0599	0.0123	1.65E-06	-0.0390	0.0037	4.4E-23
cg05789250	0.1393	0.0278	7.85E-07	0.0466	0.0055	3.7E-16	cg07422042	-0.1134	0.0234	1.65E-06	-0.0139	0.0050	5.5E-03
cg14340889	0.0510	0.0102	8.17E-07	-0.0026	0.0019	1.6E-01	cg12776033	0.1302	0.0269	1.68E-06	0.0133	0.0027	1.0E-06
cg23035209	0.0901	0.0180	8.23E-07	0.0271	0.0031	2.9E-17	cg21640865	-0.1765	0.0364	1.69E-06	-0.1145	0.0105	8.8E-25
cg13631094	0.1338	0.0268	8.29E-07	0.0413	0.0039	8.3E-24	cg04360793	-0.0583	0.0120	1.70E-06	-0.0338	0.0037	1.9E-18
cg08774868	-0.0626	0.0125	8.29E-07	0.0147	0.0021	2.2E-11	cg03950655	0.0480	0.0099	1.70E-06	0.0133	0.0017	3.0E-14
cg16437021	-0.1288	0.0258	8.30E-07	-0.0581	0.0046	1.0E-31	cg20912770	0.0319	0.0066	1.70E-06	0.0015	0.0009	7.9E-02
cg16302655	0.1455	0.0291	8.30E-07	0.0503	0.0053	1.2E-19	cg07860918	-0.0248	0.0051	1.71E-06	-0.0115	0.0013	1.4E-18
cg02803819	0.0670	0.0134	8.34E-07	0.0283	0.0027	7.2E-24	cg18431951	0.1412	0.0292	1.74E-06	-0.0134	0.0041	1.2E-03
cg06437209	-0.1369	0.0275	8.67E-07	0.0141	0.0037	1.4E-04	cg09325711	0.0523	0.0108	1.76E-06	0.0161	0.0018	1.5E-17
cg23909633	0.0827	0.0166	8.74E-07	0.0099	0.0022	6.8E-06	cg01153817	0.1207	0.0249	1.76E-06	0.0246	0.0045	6.8E-08
cg17024919	0.1953	0.0392	8.82E-07	0.1433	0.0125	4.4E-27	cg26614073	0.0935	0.0193	1.77E-06	0.0165	0.0033	6.9E-07
cg12423733	-0.1068	0.0215	9.02E-07	-0.0372	0.0057	2.2E-10	cg22805381	0.1048	0.0217	1.80E-06	-0.0001	0.0033	9.7E-01
cg15169121	0.1188	0.0239	9.09E-07	0.0145	0.0038	1.5E-04	cg13139848	-0.0626	0.0129	1.81E-06	-0.0191	0.0025	5.1E-14
cg06631810	0.0762	0.0153	9.26E-07	0.0280	0.0030	7.4E-19	cg18082112	-0.0490	0.0102	1.83E-06	-0.0071	0.0020	3.6E-04
cg09390001	-0.0795	0.0160	9.38E-07	-0.0033	0.0036	3.6E-01	cg04736217	0.1218	0.0252	1.84E-06	0.0810	0.0083	9.7E-21
cg14180029	-0.0559	0.0112	9.40E-07	-0.0203	0.0027	3.6E-13	cg12474798	0.1655	0.0343	1.84E-06	0.0365	0.0058	5.9E-10
cg05284727	0.1722	0.0347	9.50E-07	0.0852	0.0091	2.1E-19	cg04477431	-0.0813	0.0168	1.85E-06	-0.0191	0.0025	1.2E-13
cg02891728	0.1012	0.0204	9.53E-07	0.0631	0.0039	7.1E-48	cg17322044	-0.2730	0.0566	1.86E-06	-0.0607	0.0091	6.6E-11
cg16508714	0.0883	0.0178	9.65E-07	0.0041	0.0028	1.4E-01	cg27312961	0.1995	0.0413	1.87E-06	0.0997	0.0071	6.4E-38
cg09817016	0.1625	0.0328	9.71E-07	0.0841	0.0059	2.8E-38	cg12708802	0.0834	0.0173	1.87E-06	0.0184	0.0035	1.6E-07
cg18912541	0.0750	0.0151	9.94E-07	0.0207	0.0025	4.1E-15	cg06244240	0.1001	0.0208	1.92E-06	0.0499	0.0042	3.2E-28
cg23430652	-0.1425	0.0288	9.95E-07	-0.0432	0.0051	2.0E-16	cg02257550	0.1268	0.0263	1.92E-06	0.0321	0.0045	2.4E-12
cg23110422	-0.1139	0.0230	9.99E-07	-0.0106	0.0024	1.0E-05	cg13706582	0.1415	0.0294	1.95E-06	0.0581	0.0056	5.8E-23
cg03633120	0.0750	0.0151	1.00E-06	0.0459	0.0038	4.9E-29	cg13541527	0.1700	0.0353	1.97E-06	0.0357	0.0063	3.1E-08
cg22383924	0.1010	0.0204	1.00E-06	0.0225	0.0030	4.2E-13	cg26140749	0.1537	0.0319	1.97E-06	0.0088	0.0033	8.4E-03
cg01871127	0.0404	0.0081	1.00E-06	-0.0042	0.0013	1.3E-03	cg18390683	-0.1321	0.0274	1.98E-06	-0.0308	0.0037	7.7E-16
cg19221489	0.0587	0.0119	1.04E-06	-0.0033	0.0021	1.2E-01	cg15114651	0.0555	0.0115	1.98E-06	-0.0042	0.0023	6.8E-02
cg08463485	-0.0632	0.0128	1.06E-06	-0.0339	0.0034	2.5E-21	cg00249383	-0.1346	0.0280	2.00E-06	-0.0298	0.0055	8.3E-08
cg11238048	-0.0543	0.0110	1.07E-06	-0.0243	0.0023	1.0E-23	cg15435170	0.2006	0.0417	2.04E-06	-0.0279	0.0074	1.7E-04
cg00563932	-0.0617	0.0125	1.08E-06	-0.0422	0.0040	5.5E-24	cg08537737	0.0997	0.0207	2.06E-06	0.0394	0.0037	1.6E-23
cg09874659	0.0580	0.0117	1.08E-06	-0.0045	0.0023	5.4E-02	cg07580975	-0.1256	0.0261	2.06E-06	-0.0089	0.0031	4.2E-03
cg14330585	0.2543	0.0515	1.08E-06	-0.0111	0.0071	1.2E-01	cg24761597	0.0584	0.0122	2.07E-06	0.0272	0.0029	1.0E-18
cg11730703	-0.1074	0.0218	1.09E-06	-0.0203	0.0032	4.7E-10	cg24796272	0.0604	0.0126	2.08E-06	0.0421	0.0031	1.7E-35
cg05506292	-0.0572	0.0116	1.12E-06	0.0034	0.0022	1.2E-01	cg26825412	0.1161	0.0242	2.09E-06	0.0228	0.0036	3.9E-10
cg10689438	0.0667	0.0135	1.13E-06	-0.0225	0.0026	5.7E-17	cg13312458	0.0664	0.0138	2.10E-06	0.0282	0.0037	1.1E-13
cg19031085	0.2840	0.0576	1.14E-06	0.0837	0.0079	1.3E-23	cg11231349	0.0625	0.0130	2.14E-06	0.0014	0.0025	5.9E-01
cg17247190	-0.0613	0.0124	1.15E-06	-0.0171	0.0019	9.4E-19	cg25453677	-0.1118	0.0233	2.18E-06	-0.0568	0.0046	5.9E-31
cg18973586	0.1003	0.0204	1.15E-06	0.0273	0.0031	1.4E-17	cg10773526	-0.0537	0.0112	2.20E-06	-0.0483	0.0036	1.0E-34
cg01321673	-0.0860	0.0175	1.15E-06	-0.0141	0.0036	9.7E-05	cg15777335	-0.0516	0.0108	2.21E-06	0.0019	0.0016	2.3E-01
cg03533561	0.0547	0.0111	1.15E-06	-0.0022	0.0018	2.3E-01	cg24688690	0.0547	0.0114	2.22E-06	0.0095	0.0020	2.7E-06
cg15743533	0.0624	0.0127	1.17E-06	0.0354	0.0039	1.1E-18	cg23198623	0.0989	0.0207	2.23E-06	0.0031	0.0051	5.5E-01
cg18432895	-0.2078	0.0423	1.20E-06	0.0074	0.0058	2.1E-01	cg24533564	0.0584	0.0122	2.24E-06	0.0055	0.0021	9.5E-03
cg27332104	-0.0720	0.0146	1.20E-06	-0.0047	0.0038	2.2E-01	cg07285237	0.3898	0.0814	2.25E-06	0.0868	0.0163	1.6E-07
cg14509967	0.0987	0.0201	1.21E-06	-0.0050	0.0040	2.1E-01	cg21538924	-0.0528	0.0110	2.26E-06	-0.0106	0.0018	1.7E-08
cg14404318	0.1443	0.0294	1.24E-06	-0.0033	0.0021	1.2E-01	cg21392700	0.0582	0.0122	2.30E-06	0.0668	0.0057	5.8E-28
cg26079699	0.0597	0.0122	1.25E-06	0.0268	0.0023	2.4E-28	cg01697865	0.0733	0.0153	2.34E-06	0.0787	0.0079	3.4E-21
cg26933683	0.0760	0.0155	1.25E-06	-0.0062	0.0031	4.8E-02	cg12312338	0.0526	0.0110	2.41E-06	0.0174	0.0019	1.2E-18
cg25923345	0.0757	0.0154	1.26E-06	0.0149	0.0021	2.1E-12	cg15010140	-0.0871	0.0183	2.41E-06	1.8542	0.2259	2.0E-15
cg09033638	0.1307	0.0267	1.28E-06	0.0368	0.0040	6.2E-19	cg00968167	0.1440	0.0302	2.42E-06	-0.0413	0.0059	7.8E-12
cg23891364	0.1694	0.0345	1.29E-06	0.0169	0.0028	2.7E-09	cg14706579	0.0508	0.0106	2.43E-06	0.0118	0.0017	7.7E-12
cg08097581	0.1189	0.0243	1.29E-06	-0.0106	0.0031	6.5E-04	cg05514971	-0.1141	0.0239	2.44E-06	-0.0319	0.0037	1.7E-16
cg04300115	0.0990	0.0202	1.30E-06	0.0210	0.0032	1.2E-10	cg12590902	-0.0955	0.0200	2.46E-06	-0.0174	0.0035	9.8E-07
cg23124451	-0.0968	0.0198	1.31E-06	-0.0268	0.0024	1.4E-25	cg12916723	0.1348	0.0283	2.49E-06	0.0055	0.0027	4.0E-02
cg22533317	-0.0948	0.0194	1.32E-06	-0.0091	0.0038	1.9E-02	cg15326320	0.0093	0.0020	2.53E-06	-0.0002	0.0004	6.9E-01
cg10549018	-0.0867	0.0177	1.33E-06	-0.0171	0.0036	2.5E-06	cg14635955	-0.0521	0.0109	2.59E-06	0.0063	0.0018	4.8E-04
cg25974380	0.1273	0.0260	1.35E-06	0.0153	0.0033	4.3E-06	cg25464787	0.1227	0.0258	2.61E-06	-0.0175	0.0043	5.1E-05

cg13384850	0.0608	0.0128	2.62E-06	0.0192	0.0023	5.4E-16	cg05532892	0.0331	0.0071	4.18E-06	0.0506	0.0060	2.6E-16
cg00522883	0.0519	0.0109	2.64E-06	-0.0037	0.0021	7.2E-02	cg24608218	0.0622	0.0134	4.21E-06	0.0174	0.0016	5.8E-24
cg17220161	-0.1140	0.0240	2.65E-06	-0.0832	0.0061	8.0E-36	cg08376824	0.1998	0.0430	4.24E-06	0.0700	0.0067	5.6E-23
cg27226949	-0.0962	0.0202	2.67E-06	-0.0156	0.0018	9.8E-17	cg26131026	-0.0527	0.0113	4.26E-06	-0.0163	0.0020	1.5E-15
cg11680605	0.0574	0.0121	2.69E-06	0.0654	0.0066	4.9E-21	cg26892308	0.0358	0.0077	4.29E-06	0.0017	0.0019	3.8E-01
cg00643086	-0.0344	0.0072	2.70E-06	-0.0209	0.0017	1.1E-29	cg02358653	0.0698	0.0150	4.32E-06	-0.0026	0.0026	3.2E-01
cg25918821	0.1028	0.0216	2.71E-06	-0.0207	0.0028	3.6E-13	cg02204046	-0.0421	0.0091	4.33E-06	-0.0169	0.0014	9.0E-29
cg27308982	-0.0456	0.0096	2.72E-06	-0.0590	0.0044	8.8E-35	cg12827530	-0.0723	0.0156	4.34E-06	-0.0177	0.0045	1.1E-04
cg09594075	0.0699	0.0147	2.72E-06	0.0077	0.0027	4.5E-03	cg00187059	0.0556	0.0120	4.35E-06	0.0112	0.0025	7.1E-06
cg06930757	0.0808	0.0170	2.73E-06	0.0470	0.0041	7.1E-27	cg11625077	0.0805	0.0173	4.37E-06	-0.0209	0.0026	1.5E-14
cg12166080	0.0591	0.0124	2.76E-06	0.0433	0.0043	1.7E-21	cg04211179	0.1477	0.0318	4.38E-06	0.0101	0.0040	1.2E-02
cg11454936	0.2508	0.0529	2.76E-06	0.0061	0.0043	1.6E-01	cg21963854	-0.0615	0.0133	4.47E-06	-0.0648	0.0051	5.6E-32
cg14765414	-0.0664	0.0140	2.77E-06	-0.0013	0.0035	7.0E-01	cg16619991	0.1821	0.0392	4.48E-06	0.0092	0.0057	1.1E-01
cg20161791	0.0680	0.0143	2.78E-06	0.0436	0.0040	7.3E-25	cg10166277	0.0653	0.0141	4.49E-06	0.0309	0.0030	1.7E-22
cg25191628	-0.0260	0.0055	2.81E-06	-0.0023	0.0012	4.7E-02	cg08330950	-0.2330	0.0502	4.51E-06	0.0014	0.0080	8.6E-01
cg24541550	0.0662	0.0140	2.82E-06	-0.0130	0.0020	1.2E-10	cg04479212	-0.2727	0.0588	4.52E-06	-0.0299	0.0055	1.1E-07
cg06234201	0.1102	0.0233	2.84E-06	0.0392	0.0037	2.5E-23	cg09643139	0.2139	0.0461	4.54E-06	-0.0134	0.0049	6.4E-03
cg12171761	-0.1443	0.0305	2.84E-06	-0.1190	0.0114	5.2E-23	cg27202646	0.0510	0.0110	4.57E-06	-0.0151	0.0022	4.5E-11
cg25314111	0.1002	0.0212	2.84E-06	0.0141	0.0037	1.6E-04	cg07435331	-0.1036	0.0223	4.57E-06	0.0153	0.0044	4.9E-04
cg23055003	0.0513	0.0108	2.87E-06	0.0088	0.0024	2.0E-04	cg02585702	-0.0484	0.0104	4.59E-06	0.0061	0.0011	3.5E-08
cg27252776	0.1103	0.0233	2.88E-06	-0.0044	0.0037	2.3E-01	cg18474153	0.0954	0.0206	4.59E-06	0.0144	0.0029	1.5E-06
cg13039251	-0.1167	0.0246	2.90E-06	0.0004	0.0035	9.0E-01	cg15689795	0.0497	0.0107	4.59E-06	0.0069	0.0020	7.5E-04
cg12269161	0.0600	0.0127	2.91E-06	0.0368	0.0033	1.7E-26	cg24310500	-0.0806	0.0174	4.65E-06	-0.0315	0.0036	5.6E-17
cg16029875	-0.1330	0.0281	2.92E-06	0.0026	0.0048	5.8E-01	cg27286011	-0.1150	0.0248	4.68E-06	-0.0336	0.0052	2.5E-10
cg03773862	-0.1648	0.0348	2.93E-06	-0.0370	0.0037	2.3E-21	cg13573210	0.1577	0.0341	4.69E-06	0.0416	0.0042	6.9E-21
cg26837800	-0.0567	0.0120	2.93E-06	-0.0051	0.0021	1.5E-02	cg07723114	0.0597	0.0129	4.71E-06	0.0218	0.0023	6.3E-20
cg13485366	-0.1141	0.0241	2.93E-06	-0.0099	0.0043	2.2E-02	cg06397161	-0.1141	0.0247	4.79E-06	-0.0568	0.0049	4.6E-28
cg15611912	0.1163	0.0246	2.95E-06	0.0412	0.0051	7.6E-15	cg09373227	-0.0663	0.0143	4.82E-06	0.0014	0.0016	4.0E-01
cg02553516	-0.0270	0.0057	2.98E-06	-0.0048	0.0008	1.3E-08	cg02365303	-0.0675	0.0146	4.85E-06	0.0070	0.0015	2.0E-06
cg04149916	0.2419	0.0512	2.99E-06	0.0394	0.0056	5.7E-12	cg09205438	-0.1677	0.0363	4.89E-06	-0.0184	0.0032	2.4E-08
cg03078400	0.0655	0.0139	2.99E-06	0.0177	0.0034	3.4E-07	cg17873465	0.0285	0.0062	4.91E-06	-0.0043	0.0006	5.1E-11
cg12534424	-0.0748	0.0158	2.99E-06	-0.0085	0.0037	2.2E-02	cg11834658	-0.0479	0.0104	4.91E-06	-0.0131	0.0021	8.8E-10
cg11835068	-0.0475	0.0101	3.01E-06	-0.0119	0.0019	1.3E-09	cg24566824	0.0317	0.0069	4.95E-06	-0.0111	0.0018	4.0E-09
cg16906964	0.1541	0.0326	3.01E-06	-0.0377	0.0098	1.3E-04	cg18439734	0.0343	0.0074	4.96E-06	0.0016	0.0012	1.7E-01
cg10986043	-0.0865	0.0183	3.07E-06	0.0024	0.0032	4.6E-01	cg01882991	0.1145	0.0248	4.98E-06	0.0262	0.0033	3.0E-14
cg10672726	0.1158	0.0245	3.09E-06	0.0427	0.0038	1.1E-25	cg02832224	-0.0666	0.0144	5.03E-06	-0.0745	0.0070	7.7E-24
cg02145310	-0.0647	0.0137	3.11E-06	-0.0232	0.0027	3.2E-16	cg02574073	0.3144	0.0681	5.04E-06	-0.0085	0.0112	4.5E-01
cg00788170	0.0644	0.0137	3.11E-06	0.0170	0.0022	3.8E-14	cg27514333	0.1081	0.0234	5.05E-06	0.0306	0.0033	2.5E-19
cg24446586	-0.0487	0.0103	3.11E-06	-0.0059	0.0013	1.2E-05	cg13617561	-0.1067	0.0231	5.06E-06	0.0025	0.0031	4.0E-01
cg14469684	-0.1734	0.0368	3.12E-06	-0.0282	0.0047	3.5E-09	cg01415909	-0.0477	0.0103	5.08E-06	0.0016	0.0014	2.4E-01
cg01241007	0.0798	0.0169	3.15E-06	0.0284	0.0029	3.5E-21	cg17955729	-0.1045	0.0227	5.09E-06	-0.0524	0.0049	6.1E-24
cg22497969	-0.2008	0.0426	3.16E-06	0.1024	0.0110	5.3E-19	cg03540589	-0.0920	0.0199	5.09E-06	-0.0010	0.0019	6.0E-01
cg26180015	-0.0290	0.0062	3.16E-06	0.0016	0.0008	5.3E-02	cg06700146	0.0608	0.0132	5.12E-06	0.0112	0.0015	6.5E-13
cg13518625	0.1594	0.0338	3.18E-06	0.0058	0.0042	1.6E-01	cg24483576	-0.1177	0.0255	5.13E-06	-0.0164	0.0022	9.5E-13
cg17141902	0.0514	0.0109	3.20E-06	0.0055	0.0025	2.7E-02	cg16565409	0.1699	0.0369	5.14E-06	0.0125	0.0047	8.0E-03
cg01613691	0.1335	0.0283	3.21E-06	0.0222	0.0039	1.4E-08	cg05318142	-0.0841	0.0182	5.18E-06	-0.0012	0.0042	7.8E-01
cg18919541	0.1376	0.0292	3.23E-06	0.0167	0.0046	3.3E-04	cg26574777	0.1442	0.0313	5.21E-06	0.0069	0.0037	5.9E-02
cg23418645	-0.0601	0.0128	3.24E-06	-0.0172	0.0023	8.1E-13	cg18047662	0.1415	0.0307	5.32E-06	0.0102	0.0027	1.6E-04
cg18605031	-0.1596	0.0339	3.24E-06	-0.0261	0.0041	4.6E-10	cg12356266	-0.2233	0.0485	5.33E-06	-0.1017	0.0088	2.4E-27
cg00241281	-0.0826	0.0175	3.25E-06	-0.0164	0.0033	1.2E-06	cg08899667	-0.0820	0.0178	5.41E-06	-0.0122	0.0033	2.9E-04
cg01995548	0.0752	0.0160	3.26E-06	0.0350	0.0035	6.8E-22	cg15603548	0.0854	0.0186	5.51E-06	0.0202	0.0021	2.1E-19
cg13578465	-0.1451	0.0308	3.27E-06	-0.0072	0.0044	1.0E-01	cg06002516	0.0871	0.0190	5.53E-06	0.0061	0.0045	1.8E-01
cg07177756	0.1245	0.0265	3.31E-06	0.0299	0.0042	5.8E-12	cg02993991	0.2069	0.0450	5.55E-06	0.0521	0.0052	1.8E-21
cg11945474	-0.1583	0.0336	3.32E-06	-0.0279	0.0063	1.0E-05	cg02032125	-0.0695	0.0151	5.57E-06	-0.0182	0.0031	5.9E-09
cg11557492	-0.2801	0.0595	3.33E-06	-0.0247	0.0092	7.8E-03	cg01465102	0.0741	0.0161	5.57E-06	0.0087	0.0018	1.8E-06
cg11679455	0.0771	0.0164	3.35E-06	0.0170	0.0024	9.0E-12	cg17890233	-0.0640	0.0139	5.60E-06	-0.0253	0.0026	4.1E-20
cg16536918	-0.0697	0.0148	3.36E-06	-0.0818	0.0068	2.3E-29	cg13291570	-0.2653	0.0578	5.65E-06	0.1004	0.0101	3.4E-21
cg23899057	0.0807	0.0172	3.41E-06	0.0029	0.0018	1.1E-01	cg17514353	-0.0795	0.0173	5.65E-06	-0.0081	0.0022	2.9E-04
cg02311932	-0.1399	0.0298	3.43E-06	-0.0139	0.0050	5.5E-03	cg07899551	-0.1203	0.0262	5.66E-06	-0.0460	0.0042	9.2E-25
cg06661266	-0.1039	0.0221	3.44E-06	-0.0066	0.0035	5.8E-02	cg03333101	0.0973	0.0212	5.67E-06	0.0000	0.0020	9.9E-01
cg05600496	0.1143	0.0244	3.47E-06	0.0721	0.0067	3.1E-24	cg12590600	-0.0599	0.0130	5.68E-06	-0.0122	0.0027	7.4E-06
cg18631996	-0.0666	0.0142	3.50E-06	-0.0373	0.0038	3.5E-21	cg03882585	0.0466	0.0102	5.69E-06	0.0399	0.0040	1.4E-21
cg15614119	0.0895	0.0191	3.56E-06	0.0280	0.0033	5.4E-16	cg15962267	0.0647	0.0141	5.69E-06	0.0172	0.0034	6.4E-07
cg12214451	-0.1087	0.0232	3.57E-06	-0.0251	0.0044	2.6E-08	cg15963463	0.1138	0.0248	5.69E-06	0.0099	0.0029	8.2E-04
cg21448513	0.0899	0.0192	3.62E-06	0.0234	0.0026	2.6E-18	cg08262002	0.0908	0.0198	5.75E-06	-0.0003	0.0037	9.4E-01
cg19828220	0.2416	0.0516	3.64E-06	-0.0375	0.0075	9.2E-07	cg20408175	0.0755	0.0165	5.79E-06	0.0104	0.0017	5.0E-09
cg23798387	0.1308	0.0279	3.65E-06	0.0147	0.0028	1.6E-07	cg27467282	-0.0678	0.0148	5.80E-06	-0.0287	0.0025	2.3E-27
cg09026994	0.0988	0.0211	3.65E-06	-0.0069	0.0025	5.5E-03	cg04970434	-0.1197	0.0261	5.80E-06	-0.0298	0.0036	9.7E-16
cg24771152	-0.0713	0.0152	3.66E-06	-0.0200	0.0033	4.2E-09	cg15965301	0.1574	0.0343	5.84E-06	0.0512	0.0046	1.4E-25
cg16517298	-0.1444	0.0309	3.79E-06	0.0083	0.0059	1.6E-01	cg05287480	0.1027	0.0224	5.84E-06	-0.0178	0.0024	3.0E-13
cg10163776	0.0338	0.0072	3.79E-06	-0.0001	0.0006	8.3E-01	cg14242246	-0.2717	0.0593	5.85E-06	-0.0363	0.0061	5.7E-09
cg19787076	-0.1021	0.0219	3.86E-06	-0.0146	0.0037	8.4E-05	cg19108771	0.1997	0.0436	5.86E-06	0.0151	0.0041	2.6E-04
cg24418941	0.1107	0.0237	3.90E-06	0.0281	0.0023	9.1E-31	cg14264316	-0.1132	0.0247	5.89E-06	0.0443	0.0062	4.1E-12
cg03567830	-0.0701	0.0150	3.90E-06	0.0097	0.0014	2.1E-11	cg09489128	-0.0573	0.0125	5.91E-06	0.0144	0.0025	2.1E-08
cg03523676	0.1099	0.0235	3.95E-06	0.0202	0.0032	7.7E-10	cg18877361	0.0983	0.0215	5.93E-06	0.0256	0.0033	1.0E-13
cg26942124	0.1369	0.0293	3.95E-06	-0.0074	0.0044	9.4E-02	cg27403406	-0.1384	0.0302	5.96E-06	-0.0891	0.0063	9.0E-39
cg21227253	0.1107	0.0237	3.96E-06	-0.0412	0.0038	2.5E-24	cg09717146	-0.0783	0.0171	5.98E-06	0.0010	0.0026	7.1E-01
cg24804279	-0.1178	0.0253	4.10E-06	-0.0816	0.0075	8.8E-25	cg06035600	-0.1492	0.0326	6.01E-06	-0.0191	0.0064	2.9E-03
cg00424286	0.1050	0.0225	4.11E-06	0.0196	0.0042	4.1E-06	cg15763258	0.1239	0.0271	6.04E-06	0.0058	0.0025	2.2E-02
cg26971042	-0.1080	0.0232	4.12E-06	-0.0443	0.0034	2.8E-33	cg03750587	-0.0471	0.0103	6.07E-06	0.0116	0.0018	7.3E-10
cg21253721	-0.1160	0.0249	4.12E-06	-0.0004	0.0031	8.9E-01	cg26844633	0.1042	0.0228	6.09E-06	0.0597	0.0049	6.6E-30
cg25064395	0.1475	0.0317	4.14E-06	0.0503	0.0063	1.4E-14	cg04861271	0.1534	0.0336	6.13E-06	-0.0025	0.0032	4.3E-01
cg07044859	0.4264	0.0916	4.15E-06	0.1093	0.0105	4.8E-23	cg02566861	0.1471	0.0322	6.14E-06	-0.0111	0.0056	4.7E-02
cg08639339	-0.1027	0.0220	4.16E-06	-0.0265	0.0045	9.1E-09	cg24522654	0.1142	0.0250	6.15E-06	0.0091	0.0041	2.5E-02
cg14011327	-0.0420	0.0090	4.17E-06	-0.0253	0.0022	4.7E-28	cg11840984	-0.1177	0.0257	6.16E-06	-0.0504	0.0046	1.0E-24

cg05539265	0.0712	0.0156	6.16E-06	-0.0421	0.0043	1.8E-20	cg22595230	0.2787	0.0618	8.11E-06	0.0239	0.0072	9.7E-04
cg24399529	-0.0799	0.0175	6.17E-06	-0.0093	0.0028	1.2E-03	cg18091264	0.1173	0.0260	8.11E-06	0.0053	0.0034	1.2E-01
cg17979068	0.1450	0.0317	6.18E-06	0.0457	0.0060	1.1E-13	cg21010646	-0.1129	0.0250	8.11E-06	-0.0033	0.0029	2.6E-01
cg06526721	0.1648	0.0361	6.20E-06	0.0346	0.0056	1.4E-09	cg00261569	0.1171	0.0260	8.13E-06	0.0181	0.0052	5.6E-04
cg17547897	0.1381	0.0302	6.27E-06	0.0237	0.0033	1.7E-12	cg19711268	-0.1522	0.0337	8.16E-06	-0.0144	0.0038	1.4E-04
cg21723559	0.0651	0.0143	6.27E-06	0.0001	0.0024	9.8E-01	cg03163525	-0.1660	0.0368	8.18E-06	-0.1569	0.0145	1.6E-24
cg16554099	-0.1200	0.0263	6.30E-06	-0.0117	0.0034	5.8E-04	cg12371991	0.1515	0.0336	8.18E-06	0.0105	0.0047	2.6E-02
cg05389183	-0.0796	0.0174	6.30E-06	0.0025	0.0020	2.1E-01	cg00063111	0.1093	0.0242	8.20E-06	-0.0153	0.0038	7.3E-05
cg25767433	0.0944	0.0207	6.33E-06	0.0234	0.0032	1.0E-12	cg17214107	-0.1067	0.0237	8.24E-06	-0.0251	0.0036	1.5E-11
cg03806501	0.1487	0.0326	6.33E-06	0.0148	0.0055	7.7E-03	cg04002235	0.1768	0.0392	8.25E-06	0.0476	0.0081	8.7E-09
cg06000610	-0.0940	0.0206	6.34E-06	0.0143	0.0023	7.6E-10	cg09983216	0.1764	0.0391	8.27E-06	-0.0220	0.0052	2.7E-05
cg00813509	0.1052	0.0230	6.34E-06	0.0202	0.0033	3.1E-09	cg00471696	0.0665	0.0148	8.30E-06	0.0061	0.0023	7.7E-03
cg14142087	-0.0734	0.0161	6.34E-06	0.0148	0.0028	2.1E-07	cg21766667	0.1354	0.0301	8.33E-06	-0.0202	0.0059	7.5E-04
cg22950598	0.0872	0.0191	6.35E-06	0.0690	0.0074	4.5E-19	cg22544863	-0.0563	0.0125	8.36E-06	-0.0177	0.0024	4.7E-13
cg03844211	0.0543	0.0119	6.37E-06	0.0031	0.0019	1.1E-01	cg01960979	-0.0554	0.0123	8.41E-06	-0.0007	0.0016	6.8E-01
cg27381979	-0.0757	0.0166	6.38E-06	-0.0410	0.0032	8.0E-33	cg03400139	-0.1454	0.0323	8.46E-06	-0.0549	0.0057	4.4E-20
cg14712058	0.0798	0.0175	6.39E-06	0.0171	0.0028	3.4E-09	cg01272400	-0.0505	0.0112	8.46E-06	-0.0101	0.0018	2.3E-08
cg16914953	0.0752	0.0165	6.51E-06	0.0357	0.0032	1.2E-25	cg12304113	0.0952	0.0212	8.48E-06	0.0334	0.0028	6.0E-29
cg22009923	0.0917	0.0201	6.53E-06	0.0073	0.0030	1.6E-02	cg24090911	-0.1564	0.0348	8.52E-06	0.0402	0.0053	2.2E-13
cg16685832	0.0597	0.0131	6.59E-06	0.0068	0.0015	4.8E-06	cg08969823	-0.0490	0.0109	8.53E-06	0.0030	0.0014	3.7E-02
cg01205831	0.0744	0.0163	6.63E-06	-0.0002	0.0021	9.2E-01	cg20661257	-0.1456	0.0324	8.57E-06	0.0019	0.0050	7.0E-01
cg05316650	-0.0553	0.0121	6.68E-06	-0.0118	0.0019	1.4E-09	cg13662290	0.2096	0.0466	8.62E-06	-0.0188	0.0063	2.9E-03
cg07478098	0.0554	0.0122	6.71E-06	0.0152	0.0018	5.8E-16	cg18824549	-0.1293	0.0287	8.63E-06	-0.0037	0.0033	2.6E-01
cg11323506	-0.0841	0.0185	6.74E-06	0.0042	0.0050	4.0E-01	cg12097550	0.1114	0.0248	8.65E-06	0.0643	0.0055	6.5E-28
cg00510160	0.1025	0.0225	6.75E-06	0.0510	0.0056	1.3E-18	cg27297137	-0.1505	0.0335	8.68E-06	0.0203	0.0030	3.7E-11
cg01701585	0.0793	0.0174	6.75E-06	0.0264	0.0029	4.6E-18	cg03316237	0.0945	0.0210	8.73E-06	-0.0248	0.0024	1.4E-22
cg00064778	-0.0872	0.0192	6.77E-06	-0.0587	0.0058	8.2E-22	cg25332357	0.0990	0.0220	8.80E-06	0.0180	0.0030	2.9E-09
cg11032534	-0.0473	0.0104	6.79E-06	-0.0154	0.0022	1.2E-11	cg23938300	0.0287	0.0064	8.81E-06	-0.0063	0.0014	8.3E-06
cg11288801	0.0735	0.0162	6.84E-06	-0.0213	0.0044	1.5E-06	cg02976588	-0.0941	0.0209	8.84E-06	-0.0896	0.0090	1.7E-21
cg25135322	0.1463	0.0322	6.85E-06	-0.0170	0.0046	2.3E-04	cg13299325	0.1105	0.0246	8.86E-06	0.0009	0.0041	8.2E-01
cg05335186	-0.0750	0.0165	6.86E-06	-0.0199	0.0037	8.0E-08	cg09166091	-0.1029	0.0229	8.90E-06	-0.0167	0.0035	2.8E-06
cg16794579	-0.0738	0.0162	6.86E-06	-0.0154	0.0042	2.7E-04	cg13046524	0.0686	0.0153	8.92E-06	-0.0182	0.0028	3.1E-10
cg16848873	0.2636	0.0580	6.94E-06	0.1271	0.0117	7.5E-25	cg26550068	-0.0968	0.0216	8.93E-06	0.0430	0.0043	7.7E-22
cg23904955	0.3335	0.0734	6.94E-06	0.0643	0.0080	6.8E-15	cg01176694	-0.1188	0.0265	8.94E-06	0.1193	0.0115	4.9E-23
cg04675251	-0.1129	0.0248	6.94E-06	-0.0191	0.0034	2.9E-08	cg04368724	-0.0747	0.0167	9.00E-06	-0.0018	0.0033	5.8E-01
cg06405563	-0.1559	0.0343	6.96E-06	-0.0179	0.0038	2.3E-06	cg03990033	-0.0775	0.0173	9.02E-06	-0.0009	0.0016	5.6E-01
cg11830695	0.1402	0.0308	6.96E-06	0.0099	0.0033	2.9E-03	cg25097946	0.1420	0.0316	9.03E-06	0.0069	0.0025	5.7E-03
cg16546376	-0.0736	0.0162	6.97E-06	0.0033	0.0023	1.6E-01	cg13598881	-0.0725	0.0162	9.10E-06	-0.0467	0.0050	5.5E-19
cg13442016	0.1535	0.0338	6.98E-06	0.0079	0.0030	7.7E-03	cg08091666	0.0649	0.0145	9.10E-06	0.0152	0.0027	4.3E-08
cg01986016	0.2555	0.0563	7.04E-06	-0.0551	0.0063	3.5E-17	cg10959726	0.0593	0.0132	9.12E-06	-0.0005	0.0017	7.6E-01
cg07180646	0.1648	0.0363	7.04E-06	0.0201	0.0039	3.1E-07	cg11224946	0.0721	0.0161	9.14E-06	0.0036	0.0026	1.7E-01
cg17033287	0.1040	0.0229	7.05E-06	0.0025	0.0022	2.6E-01	cg12910797	0.0867	0.0193	9.23E-06	0.0363	0.0034	3.6E-24
cg22784258	0.0770	0.0170	7.10E-06	0.0047	0.0018	1.1E-02	cg14526039	-0.0670	0.0149	9.25E-06	-0.1060	0.0092	2.5E-27
cg09009466	0.0509	0.0112	7.11E-06	0.0134	0.0023	1.3E-08	cg16597045	-0.0909	0.0203	9.31E-06	0.0085	0.0024	4.6E-04
cg05634915	-0.0734	0.0162	7.17E-06	0.0058	0.0020	3.7E-03	cg07312601	0.0621	0.0139	9.31E-06	0.0088	0.0026	8.5E-04
cg03630015	-0.0972	0.0214	7.18E-06	-0.0276	0.0032	1.3E-16	cg25607920	-0.1706	0.0381	9.33E-06	-0.1020	0.0105	1.6E-20
cg13515808	0.0562	0.0124	7.19E-06	0.0023	0.0016	1.5E-01	cg21443659	0.2253	0.0503	9.33E-06	-0.0074	0.0053	1.6E-01
cg26362453	0.0807	0.0178	7.24E-06	0.0051	0.0029	7.5E-02	cg11601297	0.1458	0.0325	9.35E-06	0.0175	0.0032	8.4E-08
cg11152384	0.1286	0.0283	7.25E-06	0.0203	0.0036	1.9E-08	cg15711727	-0.0319	0.0071	9.35E-06	0.0012	0.0017	4.6E-01
cg20495333	0.1015	0.0224	7.26E-06	-0.0433	0.0038	4.1E-27	cg05185748	0.1262	0.0282	9.38E-06	0.0105	0.0038	5.8E-03
cg18468088	0.0611	0.0135	7.26E-06	0.0088	0.0015	7.5E-09	cg11649376	-0.0687	0.0153	9.44E-06	-0.0356	0.0026	3.4E-36
cg07466622	-0.0642	0.0142	7.28E-06	0.0040	0.0028	1.6E-01	cg06008724	-0.0478	0.0107	9.49E-06	-0.0249	0.0026	1.4E-20
cg27200006	0.1605	0.0354	7.29E-06	0.0607	0.0054	1.3E-26	cg22587479	-0.0360	0.0080	9.49E-06	-0.0080	0.0010	6.2E-15
cg01268763	-0.0756	0.0167	7.29E-06	-0.0338	0.0035	2.1E-20	cg23708624	-0.1690	0.0378	9.51E-06	-0.1496	0.0129	9.8E-28
cg15701047	-0.0534	0.0118	7.30E-06	-0.0444	0.0037	1.3E-29	cg02767841	-0.0421	0.0094	9.52E-06	0.0081	0.0013	2.1E-09
cg19445684	0.0704	0.0155	7.32E-06	0.0079	0.0017	2.5E-06	cg24349832	-0.1011	0.0226	9.52E-06	-0.0002	0.0034	9.4E-01
cg02978297	0.0440	0.0097	7.34E-06	0.0146	0.0016	3.7E-19	cg27262054	0.1095	0.0245	9.53E-06	-0.0135	0.0032	3.1E-05
cg22365446	0.0913	0.0201	7.41E-06	-0.0059	0.0029	4.2E-02	cg07666840	-0.0717	0.0160	9.63E-06	-0.0128	0.0026	1.0E-06
cg06677021	-0.1799	0.0397	7.42E-06	-0.0170	0.0058	3.8E-03	cg23149687	0.2610	0.0584	9.66E-06	0.0570	0.0069	1.9E-15
cg02594345	0.1593	0.0352	7.44E-06	0.0213	0.0039	9.9E-08	cg04873169	0.0747	0.0167	9.66E-06	0.0118	0.0023	3.7E-07
cg05888755	0.2313	0.0511	7.50E-06	0.1542	0.0122	7.7E-32	cg13993176	-0.0551	0.0123	9.71E-06	-0.0365	0.0036	9.8E-22
cg01756424	-0.0864	0.0191	7.50E-06	-0.0070	0.0031	2.5E-02	cg01518508	0.0519	0.0116	9.78E-06	-0.0092	0.0019	1.7E-06
cg11370064	0.1765	0.0390	7.55E-06	0.0140	0.0052	7.5E-03	cg25309041	0.0685	0.0153	9.83E-06	0.0272	0.0030	1.0E-18
cg01987516	0.1991	0.0440	7.55E-06	0.0049	0.0046	2.9E-01	cg03217253	-0.0384	0.0086	1.00E-05	0.0080	0.0011	2.7E-13
cg26754262	0.1258	0.0278	7.60E-06	-0.0293	0.0052	2.8E-08	cg26780705	0.0958	0.0215	1.00E-05	-0.0200	0.0034	7.1E-09
cg10321404	-0.3190	0.0705	7.65E-06	0.0726	0.0117	1.3E-09	cg21649580	0.1087	0.0244	1.03E-05	0.0435	0.0035	2.8E-31
cg10510742	0.0390	0.0086	7.65E-06	0.0068	0.0023	2.8E-03	cg13950558	0.1120	0.0251	1.03E-05	0.0253	0.0031	1.4E-15
cg18676967	-0.1205	0.0266	7.65E-06	-0.0082	0.0039	3.5E-02	cg03886681	0.0821	0.0184	1.03E-05	0.0226	0.0037	1.8E-09
cg18055007	0.0447	0.0099	7.69E-06	0.0136	0.0024	2.3E-08	cg19618279	0.1413	0.0317	1.03E-05	0.0180	0.0030	2.6E-09
cg04716530	0.0844	0.0187	7.70E-06	0.0369	0.0042	1.6E-17	cg04885336	-0.0653	0.0147	1.03E-05	0.0125	0.0023	1.5E-07
cg09890374	0.1168	0.0258	7.73E-06	0.0341	0.0036	1.1E-19	cg09023869	-0.0831	0.0186	1.03E-05	-0.0073	0.0024	3.0E-03
cg03227037	-0.1170	0.0259	7.79E-06	0.0092	0.0039	1.9E-02	cg13197521	0.0726	0.0163	1.04E-05	0.0362	0.0034	3.0E-24
cg00621943	0.0991	0.0219	7.80E-06	0.0019	0.0019	3.3E-01	cg07289618	0.0712	0.0160	1.04E-05	0.0176	0.0024	5.5E-13
cg00330825	0.0712	0.0158	7.86E-06	-0.0200	0.0029	1.0E-11	cg08623535	0.0597	0.0134	1.04E-05	0.0186	0.0025	1.1E-12
cg07058988	-0.0756	0.0167	7.87E-06	-0.0217	0.0034	3.6E-10	cg10775991	0.0764	0.0171	1.04E-05	-0.0044	0.0021	3.9E-02
cg06520846	-0.1282	0.0284	7.89E-06	-0.0139	0.0032	2.0E-05	cg23802419	-0.0476	0.0107	1.04E-05	-0.0006	0.0010	5.8E-01
cg23297413	0.0567	0.0126	7.90E-06	-0.0047	0.0024	4.7E-02	cg17113856	-0.1608	0.0361	1.05E-05	-0.0780	0.0063	1.8E-30
cg09071896	-0.2165	0.0479	7.92E-06	-0.0439	0.0061	2.1E-12	cg19409133	0.1138	0.0256	1.05E-05	0.0682	0.0064	5.1E-24
cg25966016	-0.1077	0.0239	7.97E-06	-0.0181	0.0036	8.6E-07	cg01293143	0.0898	0.0202	1.05E-05	0.0068	0.0028	1.4E-02
cg00127150	-0.0877	0.0194	7.98E-06	0.0012	0.0027	6.6E-01	cg16174029	-0.0405	0.0091	1.05E-05	0.0006	0.0011	6.0E-01
cg07141605	-0.1680	0.0372	8.01E-06	-0.0997	0.0083	5.0E-29	cg17929687	-0.0454	0.0102	1.06E-05	-0.0041	0.0011	3.3E-04
cg19040266	-0.1009	0.0224	8.02E-06	0.0156	0.0030	3.0E-07	cg13424229	-0.0917	0.0206	1.06E-05	0.0064	0.0034	6.1E-02
cg01287088	-0.1654	0.0367	8.05E-06	-0.0543	0.0063	6.5E-17	cg09071762	-0.2104	0.0473	1.06E-05	0.0088	0.0089	3.2E-01
cg03575122	0.0615	0.0136	8.05E-06	0.0060	0.0028	3.4E-02	cg13573346	0.0982	0.0221	1.06E-05	-0.0021	0.0030	4.9E-01
cg15891850	-0.0793	0.0176	8.10E-06	-0.0196	0.0033	7.5E-09	cg25212453	0.1408	0.0316	1.06E-05	0.0013	0.0030	6.6E-01

cg14663208	0.0636	0.0143	1.07E-05	0.0705	0.0071	3.0E-21	cg09787315	-0.0666	0.0152	1.40E-05	-0.0059	0.0019	2.5E-03
cg23267759	-0.0307	0.0069	1.07E-05	-0.0101	0.0015	5.8E-11	cg14119236	-0.0983	0.0224	1.42E-05	-0.0177	0.0046	1.5E-04
cg07987890	-0.0573	0.0129	1.07E-05	0.0044	0.0031	1.6E-01	cg26013992	-0.0947	0.0216	1.42E-05	0.0123	0.0036	7.8E-04
cg16332631	0.1039	0.0234	1.08E-05	-0.0296	0.0030	1.4E-20	cg10260711	0.0787	0.0180	1.43E-05	0.0364	0.0033	4.9E-25
cg09658183	0.0551	0.0124	1.08E-05	0.0164	0.0022	4.8E-13	cg10096929	-0.0885	0.0202	1.43E-05	0.0274	0.0058	2.7E-06
cg02787917	-0.0525	0.0118	1.08E-05	-0.0095	0.0015	4.8E-10	cg04468198	0.1076	0.0246	1.44E-05	0.0697	0.0055	7.9E-32
cg03116948	0.0700	0.0158	1.09E-05	0.0205	0.0019	7.9E-25	cg02161701	-0.0634	0.0145	1.44E-05	-0.0237	0.0045	1.8E-07
cg25839482	0.1099	0.0247	1.09E-05	0.1250	0.0121	7.8E-23	cg10513161	0.1308	0.0299	1.45E-05	0.0148	0.0031	1.9E-06
cg09907758	-0.1118	0.0251	1.09E-05	-0.0412	0.0045	9.4E-19	cg02029843	0.0650	0.0148	1.45E-05	0.0061	0.0032	5.7E-02
cg18684142	0.2442	0.0549	1.09E-05	0.0215	0.0126	8.9E-02	cg16757281	0.0590	0.0135	1.46E-05	-0.0015	0.0013	2.5E-01
cg25464840	0.1273	0.0287	1.10E-05	0.0569	0.0046	3.0E-31	cg11808677	0.0347	0.0079	1.47E-05	0.0108	0.0016	7.4E-11
cg18956562	0.1163	0.0262	1.10E-05	-0.0213	0.0029	1.2E-12	cg15043720	0.0396	0.0090	1.47E-05	-0.0061	0.0010	4.6E-09
cg12226453	0.0817	0.0184	1.10E-05	-0.0051	0.0044	2.5E-01	cg09247392	0.0596	0.0136	1.47E-05	0.0059	0.0022	6.6E-03
cg18153326	0.0217	0.0049	1.11E-05	0.0086	0.0010	5.3E-18	cg24825210	0.0517	0.0118	1.47E-05	-0.0041	0.0024	8.3E-02
cg24989962	-0.0568	0.0128	1.11E-05	-0.0108	0.0019	8.8E-09	cg19483007	0.1246	0.0285	1.48E-05	0.1004	0.0088	1.1E-26
cg17777683	0.1000	0.0225	1.11E-05	-0.0181	0.0039	4.9E-06	cg26669717	0.0796	0.0182	1.49E-05	0.0247	0.0026	2.0E-19
cg04834228	0.0699	0.0158	1.11E-05	-0.0024	0.0017	1.5E-01	cg05928051	-0.0434	0.0099	1.50E-05	-0.0147	0.0013	3.4E-25
cg02547426	-0.0806	0.0181	1.11E-05	-0.0018	0.0031	5.7E-01	cg26416971	-0.0835	0.0191	1.50E-05	-0.0435	0.0051	1.2E-16
cg11753018	0.1256	0.0283	1.12E-05	0.0144	0.0033	1.2E-05	cg00253658	-0.1120	0.0256	1.51E-05	0.1052	0.0081	3.9E-33
cg16836589	0.1702	0.0384	1.13E-05	0.0204	0.0046	1.3E-05	cg14291900	-0.0425	0.0097	1.51E-05	0.0085	0.0018	3.2E-06
cg27546241	-0.0626	0.0141	1.13E-05	-0.0122	0.0030	6.6E-05	cg04276536	-0.0539	0.0123	1.51E-05	-0.0115	0.0025	6.3E-06
cg22417398	-0.0693	0.0156	1.13E-05	-0.0091	0.0023	9.5E-05	cg23025459	-0.1413	0.0323	1.51E-05	-0.0079	0.0050	1.2E-01
cg11344744	-0.1329	0.0300	1.14E-05	-0.0230	0.0030	1.7E-13	cg06626750	0.0907	0.0208	1.52E-05	0.0341	0.0038	4.2E-18
cg06447341	0.0677	0.0153	1.14E-05	0.0048	0.0025	5.5E-02	cg05914034	-0.1892	0.0433	1.52E-05	0.0287	0.0060	2.1E-06
cg04347708	0.1029	0.0232	1.15E-05	0.0135	0.0023	7.8E-09	cg06538684	0.1237	0.0283	1.52E-05	-0.0054	0.0039	1.7E-01
cg09180848	0.0494	0.0111	1.15E-05	0.0005	0.0010	6.6E-01	cg00574958	-0.0582	0.0133	1.53E-05	-0.0446	0.0048	3.4E-19
cg25823085	-0.2126	0.0480	1.16E-05	-0.0826	0.0066	3.7E-31	cg26294551	0.0564	0.0129	1.53E-05	-0.0109	0.0028	1.5E-04
cg14770389	0.0538	0.0121	1.16E-05	-0.0047	0.0022	2.9E-02	cg24987622	0.0577	0.0132	1.53E-05	0.0016	0.0028	5.7E-01
cg16478236	-0.0386	0.0087	1.16E-05	0.0027	0.0013	3.6E-02	cg20831648	-0.1318	0.0302	1.54E-05	-0.0404	0.0048	2.9E-16
cg06507285	-0.0765	0.0173	1.17E-05	-0.0873	0.0082	7.0E-24	cg03812323	-0.1361	0.0312	1.54E-05	0.0113	0.0035	1.4E-03
cg16810293	-0.0775	0.0175	1.17E-05	0.0109	0.0028	1.1E-04	cg25264101	0.0528	0.0121	1.54E-05	0.0053	0.0023	2.1E-02
cg01672129	-0.1574	0.0356	1.17E-05	-0.0109	0.0039	6.1E-03	cg13071386	-0.0512	0.0117	1.55E-05	-0.0430	0.0040	2.4E-24
cg23749482	0.1496	0.0338	1.18E-05	0.1247	0.0104	2.9E-29	cg13785196	0.1289	0.0295	1.55E-05	0.0271	0.0034	8.3E-15
cg10158821	0.0672	0.0152	1.18E-05	-0.0115	0.0025	4.2E-06	cg00342313	0.0629	0.0144	1.55E-05	0.0097	0.0019	3.4E-07
cg01115923	0.0486	0.0110	1.18E-05	0.0088	0.0022	6.8E-05	cg05670885	-0.0503	0.0115	1.55E-05	0.0029	0.0017	9.7E-02
cg05707236	0.0544	0.0123	1.18E-05	-0.0051	0.0021	1.3E-02	cg11084718	0.0757	0.0173	1.55E-05	0.0046	0.0030	1.2E-01
cg11978634	-0.0874	0.0197	1.19E-05	-0.0407	0.0042	9.0E-21	cg02641676	0.1099	0.0252	1.55E-05	0.0025	0.0032	4.4E-01
cg25224090	0.0753	0.0170	1.19E-05	0.0115	0.0023	8.0E-07	cg18759081	-0.2900	0.0665	1.56E-05	-0.0423	0.0071	4.6E-09
cg11178863	-0.0582	0.0132	1.19E-05	-0.0051	0.0014	3.3E-04	cg24442740	-0.1420	0.0325	1.57E-05	-0.0486	0.0059	2.8E-15
cg00321234	0.0665	0.0150	1.19E-05	-0.0038	0.0017	2.7E-02	cg19202384	0.0898	0.0206	1.57E-05	0.0224	0.0036	1.5E-09
cg06925984	0.1137	0.0257	1.20E-05	0.0436	0.0037	7.6E-28	cg06196801	0.1095	0.0251	1.57E-05	0.0230	0.0037	1.6E-09
cg05682333	-0.0836	0.0189	1.20E-05	0.0213	0.0045	2.5E-06	cg24239148	-0.0533	0.0122	1.57E-05	-0.0069	0.0016	3.3E-05
cg21649604	0.1000	0.0226	1.20E-05	0.0170	0.0037	6.7E-06	cg23981354	-0.0492	0.0113	1.57E-05	0.0026	0.0023	2.7E-01
cg10108468	0.0759	0.0172	1.20E-05	0.0108	0.0031	5.5E-04	cg13077865	-0.0698	0.0160	1.58E-05	0.0385	0.0043	7.3E-18
cg04388657	0.1086	0.0245	1.20E-05	-0.0016	0.0040	6.9E-01	cg00375250	-0.0487	0.0112	1.58E-05	0.0102	0.0020	7.9E-07
cg09358973	-0.1954	0.0442	1.21E-05	-0.0704	0.0069	2.9E-22	cg24237439	-0.0820	0.0188	1.58E-05	-0.0088	0.0020	1.7E-05
cg12771187	0.0959	0.0217	1.21E-05	0.0439	0.0047	2.4E-19	cg22670759	-0.1518	0.0348	1.59E-05	-0.0671	0.0066	3.1E-22
cg23998635	0.1024	0.0232	1.21E-05	0.0129	0.0028	5.8E-06	cg00159523	0.3279	0.0752	1.59E-05	-0.3294	0.0415	1.5E-14
cg25949550	0.0601	0.0136	1.22E-05	0.0343	0.0033	2.0E-23	cg11214576	0.0873	0.0200	1.59E-05	0.0113	0.0022	3.1E-07
cg20478120	0.1374	0.0311	1.22E-05	0.0181	0.0038	3.4E-06	cg04816394	-0.0828	0.0190	1.59E-05	-0.0050	0.0046	2.7E-01
cg11924638	0.0745	0.0169	1.23E-05	0.0298	0.0039	8.2E-14	cg26337070	-0.1241	0.0285	1.60E-05	-0.0530	0.0056	1.3E-19
cg08666707	0.0906	0.0205	1.23E-05	0.0142	0.0025	1.6E-08	cg13645530	0.0961	0.0220	1.60E-05	0.0248	0.0039	4.6E-10
cg02714677	0.0409	0.0093	1.23E-05	0.0032	0.0023	1.6E-01	cg05007549	0.0986	0.0226	1.60E-05	0.0042	0.0025	9.7E-02
cg01777397	-0.0553	0.0125	1.24E-05	-0.0265	0.0025	2.4E-24	cg14122633	0.0752	0.0172	1.60E-05	-0.0024	0.0018	1.9E-01
cg19854698	-0.1418	0.0321	1.24E-05	-0.0051	0.0031	1.0E-01	cg26801014	-0.0843	0.0194	1.61E-05	-0.0233	0.0029	1.4E-14
cg07099000	0.0403	0.0091	1.25E-05	0.0091	0.0019	3.1E-06	cg09664550	-0.0650	0.0149	1.61E-05	-0.0122	0.0017	2.8E-12
cg09470638	0.0872	0.0198	1.25E-05	0.0072	0.0032	2.4E-02	cg05460226	-0.2309	0.0530	1.61E-05	-0.0187	0.0046	6.2E-05
cg08309251	0.1166	0.0264	1.26E-05	0.0523	0.0048	4.6E-25	cg16789230	0.3153	0.0724	1.61E-05	0.0053	0.0078	5.0E-01
cg25503804	0.1281	0.0290	1.26E-05	0.0867	0.0084	1.5E-22	cg03639897	-0.0745	0.0171	1.62E-05	-0.0193	0.0025	4.5E-14
cg10007927	0.0801	0.0182	1.26E-05	0.0035	0.0019	6.4E-02	cg27589809	0.0529	0.0121	1.62E-05	0.0079	0.0023	6.1E-04
cg25287482	-0.1052	0.0239	1.27E-05	-0.0286	0.0030	1.1E-19	cg12281620	0.0623	0.0143	1.63E-05	0.0113	0.0025	1.0E-05
cg19427610	-0.0518	0.0118	1.28E-05	0.0095	0.0017	4.6E-08	cg07915896	0.0457	0.0105	1.63E-05	0.0030	0.0010	2.4E-03
cg24671760	-0.1502	0.0341	1.28E-05	-0.0314	0.0082	1.4E-04	cg05122026	-0.0747	0.0172	1.64E-05	-0.0244	0.0025	4.7E-21
cg12085044	-0.0454	0.0103	1.28E-05	-0.0043	0.0017	9.8E-03	cg01513063	-0.0678	0.0156	1.64E-05	-0.0080	0.0019	3.1E-05
cg02876297	-0.0703	0.0160	1.29E-05	-0.0174	0.0024	6.6E-13	cg24582007	-0.0560	0.0129	1.64E-05	0.0002	0.0029	9.6E-01
cg00524271	0.0547	0.0124	1.30E-05	0.0099	0.0025	8.7E-05	cg21756647	-0.0434	0.0100	1.65E-05	-0.0289	0.0024	2.1E-29
cg24144105	-0.0807	0.0183	1.31E-05	-0.0260	0.0021	1.9E-30	cg10175583	0.0804	0.0185	1.65E-05	0.0156	0.0020	4.1E-14
cg12528835	0.1006	0.0228	1.31E-05	-0.0515	0.0053	1.7E-20	cg16436711	-0.1791	0.0412	1.66E-05	-0.0623	0.0061	3.4E-22
cg11363234	0.1421	0.0323	1.31E-05	0.0172	0.0030	1.1E-08	cg20684110	0.0859	0.0197	1.66E-05	0.0399	0.0052	6.2E-14
cg18935353	-0.0868	0.0197	1.31E-05	-0.0104	0.0024	1.5E-05	cg01239651	0.1497	0.0344	1.66E-05	0.0185	0.0041	6.0E-06
cg01475577	-0.0518	0.0118	1.31E-05	-0.0090	0.0031	3.9E-03	cg05177776	-0.0720	0.0166	1.66E-05	-0.0051	0.0022	2.2E-02
cg13242944	0.0596	0.0135	1.32E-05	0.0274	0.0029	1.1E-19	cg00305993	0.0990	0.0228	1.67E-05	0.0254	0.0025	5.2E-22
cg00237010	0.0703	0.0160	1.32E-05	0.0028	0.0028	3.2E-01	cg10043058	0.0478	0.0110	1.67E-05	0.0149	0.0029	3.8E-07
cg16541026	0.0918	0.0209	1.33E-05	0.0133	0.0031	2.1E-05	cg15899053	-0.1407	0.0323	1.67E-05	0.0136	0.0035	1.2E-04
cg09282085	0.0715	0.0162	1.33E-05	0.0080	0.0029	5.4E-03	cg08962798	0.1003	0.0231	1.68E-05	0.0148	0.0025	7.3E-09
cg03628800	0.0625	0.0142	1.34E-05	-0.0035	0.0024	1.6E-01	cg14391586	0.1009	0.0232	1.68E-05	0.0230	0.0046	7.5E-07
cg07368443	-0.0844	0.0192	1.35E-05	-0.0220	0.0028	2.8E-14	cg14221612	0.0591	0.0136	1.70E-05	0.0238	0.0023	6.2E-23
cg00455216	-0.0275	0.0063	1.36E-05	-0.0057	0.0010	1.6E-08	cg25445101	-0.0456	0.0105	1.70E-05	0.0185	0.0025	1.4E-12
cg13716409	0.0285	0.0065	1.36E-05	0.0010	0.0018	5.7E-01	cg23231163	0.1405	0.0323	1.70E-05	0.0379	0.0052	1.5E-12
cg01440841	-0.0420	0.0096	1.38E-05	-0.0190	0.0019	1.6E-21	cg20422417	-0.1423	0.0327	1.70E-05	-0.0443	0.0065	2.2E-11
cg06652085	0.0526	0.0120	1.38E-05	0.0110	0.0032	6.1E-04	cg19589396	0.1328	0.0306	1.70E-05	0.0233	0.0038	1.3E-09
cg11927233	0.1151	0.0262	1.39E-05	0.0582	0.0051	9.3E-27	cg04452713	-0.0904	0.0208	1.70E-05	0.0051	0.0021	1.7E-02
cg08050115	-0.0833	0.0190	1.39E-05	-0.0262	0.0033	8.3E-15	cg02597894	-0.1023	0.0236	1.71E-05	-0.0343	0.0034	7.3E-22
cg00969323	0.0400	0.0091	1.39E-05	-0.0086	0.0022	8.6E-05	cg01810111	0.1240	0.0285	1.71E-05	0.0029	0.0023	2.1E-01
cg27135286	-0.0813	0.0185	1.39E-05	-0.0072	0.0028	9.3E-03	cg00152340	0.0766	0.0177	1.73E-05	0.0298	0.0024	1.6E-30

cg03316570	0.0999	0.0230	1.73E-05	-0.0166	0.0033	7.9E-07
cg11067714	-0.0701	0.0162	1.73E-05	-0.0100	0.0026	1.3E-04
cg03747309	0.0314	0.0072	1.73E-05	-0.0040	0.0013	2.5E-03
cg10976961	-0.0732	0.0169	1.75E-05	0.0106	0.0028	1.4E-04
cg07702888	-0.0987	0.0228	1.75E-05	0.0099	0.0030	8.6E-04
cg04920385	0.0428	0.0099	1.76E-05	0.0003	0.0019	8.8E-01
cg12435134	-0.0902	0.0208	1.77E-05	-0.0914	0.0073	1.5E-31
cg11573219	-0.1240	0.0286	1.77E-05	-0.0138	0.0030	5.5E-06
cg24500972	-0.1599	0.0369	1.78E-05	-0.0536	0.0046	5.3E-28
cg08370173	0.0506	0.0117	1.78E-05	0.0146	0.0029	5.1E-07
cg05837435	0.0781	0.0180	1.79E-05	0.0558	0.0054	1.5E-22
cg26640901	-0.1007	0.0232	1.79E-05	-0.0226	0.0028	2.5E-15
cg15855924	0.0969	0.0224	1.79E-05	0.0194	0.0040	1.7E-06
cg02156769	-0.0953	0.0220	1.79E-05	0.0029	0.0034	3.9E-01
cg02594183	0.0450	0.0104	1.80E-05	-1.4003	0.1721	3.4E-15
cg08394896	-0.0964	0.0223	1.80E-05	0.0261	0.0046	1.9E-08
cg03477904	0.0920	0.0212	1.80E-05	-0.0129	0.0031	4.8E-05
cg00945209	0.1585	0.0366	1.81E-05	0.0731	0.0061	3.8E-29
cg25898192	-0.0935	0.0216	1.81E-05	0.0173	0.0020	2.3E-16
cg05389935	0.0508	0.0117	1.81E-05	0.0180	0.0024	1.0E-13
cg03127898	-0.0609	0.0141	1.81E-05	-0.0078	0.0039	5.0E-02
cg21644856	-0.0678	0.0157	1.82E-05	-0.0134	0.0022	1.3E-09
cg22995106	0.0652	0.0151	1.83E-05	0.0268	0.0021	2.4E-31
cg19721221	0.0476	0.0110	1.83E-05	-0.0216	0.0020	7.1E-25
cg12817782	0.0644	0.0149	1.84E-05	0.0186	0.0025	8.4E-13
cg25991761	-0.2401	0.0555	1.84E-05	-0.0289	0.0049	9.3E-09
cg02000426	-0.1730	0.0400	1.84E-05	-0.0205	0.0049	3.0E-05
cg03665078	0.0875	0.0202	1.84E-05	0.0096	0.0025	1.8E-04
cg06002638	-0.0763	0.0176	1.85E-05	-0.0242	0.0025	1.8E-20
cg05711036	-0.1772	0.0410	1.86E-05	0.0354	0.0065	9.5E-08
cg00269659	0.0464	0.0107	1.86E-05	-0.0007	0.0020	7.5E-01
cg11051055	0.0466	0.0108	1.87E-05	0.0606	0.0061	3.4E-21
cg18673409	0.1453	0.0336	1.87E-05	0.0295	0.0037	6.6E-15
cg13918042	0.1002	0.0232	1.87E-05	0.0183	0.0035	2.9E-07
cg10586546	0.0791	0.0183	1.87E-05	0.0039	0.0030	2.0E-01
cg03084901	-0.0456	0.0106	1.89E-05	-0.0206	0.0018	1.5E-26
cg23480021	-0.1937	0.0448	1.89E-05	-0.0481	0.0062	4.4E-14
cg12303813	-0.0966	0.0224	1.89E-05	0.0192	0.0034	2.8E-08
cg20098659	0.2396	0.0555	1.89E-05	-0.0042	0.0082	6.1E-01
cg23902550	0.1005	0.0233	1.90E-05	0.0650	0.0060	9.6E-25
cg04179952	-0.3553	0.0823	1.92E-05	-0.0648	0.0116	4.2E-08
cg03423767	0.2081	0.0482	1.92E-05	0.0208	0.0070	3.2E-03
cg03752977	0.0840	0.0195	1.93E-05	0.0868	0.0093	4.8E-19
cg18121224	-0.2094	0.0485	1.93E-05	0.0225	0.0082	6.1E-03
cg15705813	0.1289	0.0299	1.94E-05	-0.0004	0.0042	9.3E-01
cg05473289	-0.1321	0.0306	1.95E-05	-0.0116	0.0034	6.3E-04
cg04497512	-0.0977	0.0227	1.97E-05	-0.0143	0.0022	1.3E-10
cg15950273	-0.1143	0.0265	1.97E-05	-0.0167	0.0050	8.7E-04
cg00504285	0.1182	0.0274	1.98E-05	0.0455	0.0038	1.0E-28
cg11998932	0.1251	0.0290	1.98E-05	0.1070	0.0090	1.0E-28
cg24420089	-0.1235	0.0287	1.98E-05	0.0198	0.0035	2.6E-08
cg00565090	0.0738	0.0171	1.99E-05	0.0167	0.0026	2.0E-10
cg04424621	0.0734	0.0170	1.99E-05	-0.0034	0.0034	3.2E-01
cg07901199	0.1304	0.0303	2.00E-05	0.0397	0.0044	4.4E-18
cg05483571	0.0879	0.0204	2.01E-05	0.0460	0.0051	5.4E-18
cg21737444	0.1177	0.0273	2.01E-05	0.0313	0.0045	7.4E-12
cg16209444	0.0601	0.0140	2.01E-05	0.0138	0.0022	3.0E-10
cg11424376	0.0351	0.0082	2.01E-05	0.0062	0.0019	1.6E-03
cg04687241	-0.1200	0.0279	2.02E-05	0.0019	0.0032	5.6E-01
cg05308656	-0.1641	0.0381	2.03E-05	-0.1018	0.0080	3.5E-32
cg23746574	0.0377	0.0087	2.03E-05	0.0124	0.0013	2.7E-21
cg14351425	0.0863	0.0201	2.04E-05	0.0265	0.0037	1.8E-12
cg15123573	-0.1063	0.0247	2.04E-05	-0.0222	0.0042	1.6E-07
cg07850982	-0.0458	0.0106	2.04E-05	-0.0073	0.0018	5.4E-05
cg15976709	-0.0634	0.0147	2.04E-05	-0.0009	0.0021	6.9E-01
cg18745507	-0.0658	0.0153	2.05E-05	-0.0245	0.0034	4.1E-12
cg15699524	0.1114	0.0259	2.05E-05	0.0158	0.0032	7.7E-07
cg21473814	-0.1724	0.0401	2.07E-05	-0.0386	0.0043	7.3E-18
cg22260869	-0.0371	0.0086	2.07E-05	-0.0093	0.0013	1.3E-11
cg16183122	0.0799	0.0186	2.07E-05	-0.0053	0.0021	1.3E-02
cg15772157	-0.1142	0.0266	2.08E-05	0.0805	0.0074	1.4E-24
cg14183865	-0.1098	0.0256	2.08E-05	-0.0254	0.0037	2.8E-11
cg14899046	0.0578	0.0134	2.08E-05	0.0025	0.0021	2.2E-01
cg17584477	-0.0432	0.0101	2.09E-05	-0.0181	0.0018	2.5E-22
cg04258133	-0.0567	0.0132	2.09E-05	-0.0200	0.0029	8.8E-12
cg23680518	-0.1418	0.0330	2.09E-05	-0.0219	0.0043	5.8E-07
cg21003380	-0.0908	0.0211	2.09E-05	-0.0100	0.0046	3.0E-02
cg20152539	0.1385	0.0322	2.10E-05	0.0680	0.0056	1.1E-29
cg00117335	0.0455	0.0106	2.10E-05	0.0532	0.0053	7.3E-22
cg03985801	0.0699	0.0163	2.10E-05	0.0080	0.0024	1.1E-03
cg25747670	-0.0759	0.0177	2.10E-05	-0.0016	0.0020	4.4E-01
cg08972170	-0.1046	0.0244	2.11E-05	-0.0462	0.0053	4.9E-17
cg05462761	-0.0710	0.0165	2.11E-05	-0.0188	0.0031	2.6E-09
cg07169826	0.0986	0.0229	2.11E-05	0.0142	0.0029	1.9E-06
cg04931184	0.0668	0.0155	2.11E-05	0.0050	0.0026	5.5E-02
cg14266248	0.1061	0.0247	2.12E-05	0.0187	0.0031	2.1E-09
cg26832142	0.0500	0.0117	2.13E-05	0.0144	0.0014	1.1E-22
cg03643998	0.0919	0.0214	2.14E-05	-0.0111	0.0029	1.8E-04
cg00842549	-0.1120	0.0261	2.14E-05	-0.0034	0.0043	4.2E-01
cg21750887	-0.1433	0.0334	2.16E-05	-0.0529	0.0044	9.2E-30
cg12622182	-0.0800	0.0187	2.16E-05	-0.0202	0.0031	8.6E-11
cg24249791	-0.1712	0.0399	2.16E-05	-0.0219	0.0050	1.4E-05
cg10589447	-0.0987	0.0230	2.17E-05	-0.0378	0.0036	9.1E-24
cg18331348	-0.0715	0.0167	2.18E-05	-0.0120	0.0035	5.9E-04
cg09620718	-0.1671	0.0390	2.19E-05	0.0329	0.0048	1.6E-11
cg06401414	0.0939	0.0219	2.19E-05	0.0135	0.0045	2.8E-03
cg02749735	0.0630	0.0147	2.19E-05	-0.0008	0.0017	6.2E-01
cg21733098	-0.1220	0.0285	2.20E-05	0.0458	0.0061	2.0E-13
cg07303275	-0.0831	0.0194	2.20E-05	-0.0207	0.0032	3.0E-10
cg03438552	0.2243	0.0523	2.20E-05	0.0195	0.0037	1.5E-07
cg10906729	0.2568	0.0599	2.21E-05	0.3720	0.0389	6.0E-20
cg12528056	-0.0638	0.0149	2.21E-05	0.0092	0.0023	6.1E-05
cg01836137	-0.1101	0.0257	2.21E-05	-0.0117	0.0043	6.1E-03
cg24091104	-0.1061	0.0248	2.22E-05	-0.0547	0.0039	4.2E-37
cg16615058	-0.0438	0.0102	2.23E-05	-0.0317	0.0025	4.7E-31
cg25718035	-0.0687	0.0160	2.23E-05	-0.0083	0.0012	5.2E-11
cg18212762	0.0378	0.0088	2.23E-05	0.0036	0.0017	3.7E-02
cg00640376	0.0565	0.0132	2.25E-05	0.0071	0.0022	1.0E-03
cg04811945	-0.0758	0.0177	2.25E-05	-0.0030	0.0021	1.5E-01
cg17082568	-0.2342	0.0547	2.26E-05	-0.0562	0.0065	5.2E-17
cg14817490	0.1494	0.0349	2.26E-05	0.0413	0.0052	2.0E-14
cg23291900	-0.0759	0.0178	2.27E-05	0.0163	0.0027	2.7E-09
cg26573704	-0.0504	0.0118	2.27E-05	-0.0057	0.0010	7.2E-09
cg19586143	-0.1290	0.0302	2.27E-05	0.0076	0.0027	5.0E-03
cg13065683	0.0923	0.0216	2.27E-05	0.0028	0.0023	2.2E-01
cg01986630	0.0636	0.0149	2.28E-05	0.0158	0.0025	3.3E-10
cg06531870	0.1677	0.0392	2.28E-05	0.0145	0.0040	2.8E-04
cg11599526	0.0773	0.0181	2.29E-05	-0.0120	0.0019	2.7E-10
cg03132729	0.0830	0.0194	2.30E-05	0.0263	0.0034	8.6E-14
cg08126789	0.0860	0.0201	2.30E-05	0.0089	0.0021	3.0E-05
cg11664544	-0.0964	0.0226	2.32E-05	-0.0358	0.0035	1.4E-22
cg22361106	0.0877	0.0205	2.33E-05	0.0322	0.0033	6.0E-21
cg14505741	0.0797	0.0187	2.33E-05	0.0213	0.0035	2.0E-09
cg08998192	0.1446	0.0339	2.34E-05	0.0115	0.0032	4.1E-04
cg11255208	-0.1192	0.0279	2.34E-05	-0.0040	0.0023	7.7E-02
cg06335008	-0.1352	0.0317	2.34E-05	0.0021	0.0030	4.8E-01
cg13472610	-0.0829	0.0194	2.36E-05	0.0796	0.0080	2.0E-21
cg00587301	0.0971	0.0227	2.36E-05	0.0088	0.0018	2.8E-06
cg11452501	0.2548	0.0597	2.37E-05	0.0304	0.0035	3.9E-17
cg13065228	-0.2879	0.0675	2.39E-05	-0.0293	0.0061	1.8E-06
cg16267979	0.0649	0.0152	2.39E-05	0.0014	0.0028	6.2E-01
cg25649826	-0.0816	0.0191	2.40E-05	-0.0426	0.0039	3.7E-25
cg14886849	-0.1957	0.0459	2.40E-05	-0.2360	0.0263	5.8E-18
cg18758585	-0.0514	0.0121	2.41E-05	-0.0187	0.0025	2.4E-13
cg14411670	0.1111	0.0261	2.41E-05	-0.0221	0.0030	7.6E-13
cg01692482	0.1082	0.0254	2.42E-05	-0.0701	0.0066	1.5E-23
cg06742077	-0.1126	0.0264	2.42E-05	-0.0337	0.0080	3.1E-05
cg23686403	0.0336	0.0079	2.42E-05	0.0012	0.0012	2.9E-01
cg09757644	0.0958	0.0225	2.43E-05	0.0402	0.0051	3.2E-14
cg02802420	0.0856	0.0201	2.43E-05	0.0121	0.0028	1.7E-05
cg11838299	-0.0752	0.0177	2.43E-05	-0.0063	0.0019	7.5E-04
cg06358322	0.0875	0.0205	2.43E-05	-0.0002	0.0025	9.3E-01
cg19097280	0.1050	0.0246	2.44E-05	0.0266	0.0033	8.1E-15
cg24283019	0.0791	0.0186	2.44E-05	0.0010	0.0028	7.1E-01
cg20204415	-0.0420	0.0099	2.45E-05	-0.0104	0.0017	1.5E-09
cg20011983	0.1404	0.0330	2.45E-05	-0.0065	0.0057	2.6E-01
cg19907915	0.3109	0.0730	2.45E-05	-0.0015	0.0078	8.5E-01
cg00169122	0.2250	0.0528	2.46E-05	0.0732	0.0059	1.6E-30
cg19499581	0.0585	0.0137	2.46E-05	0.0500	0.0055	3.7E-18
cg21661344	0.0354	0.0083	2.47E-05	0.0284	0.0025	1.3E-26
cg05652328	0.0528	0.0124	2.47E-05	0.0176	0.0019	1.7E-18
cg07765674	-0.0738	0.0173	2.47E-05	0.0189	0.0025	3.3E-13
cg05513300	0.0478	0.0112	2.47E-05	-0.0057	0.0019	2.2E-03
cg27209072	0.0683	0.0160	2.48E-05	-0.0579	0.0048	8.2E-30
cg20904286	0.0324	0.0076	2.48E-05	0.0134	0.0019	2.5E-12
cg04256516	-0.0513	0.0121	2.49E-05	-0.0005	0.0026	8.6E-01
cg12926404	0.0412	0.0097	2.50E-05	0.0252	0.0028	6.2E-18
cg19903927	0.2317	0.0545	2.50E-05	0.0442	0.0051	3.6E-17
cg13487575	-0.0735	0.0173	2.50E-05	0.0079	0.0021	1.7E-04
cg07900344	0.0432	0.0102	2.51E-05	0.0065	0.0029	2.5E-02
cg17972162	0.1557	0.0366	2.54E-05	0.0152	0.0030	5.3E-07
cg20054157	0.1080	0.0254	2.55E-05	0.0679	0.0059	3.6E-27
cg03274391	-0.2636	0.0620	2.55E-05	-0.0222	0.0066	8.7E-04
cg05023903	0.0818	0.0192	2.55E-05	-0.0024	0.0023	3.1E-01
cg23913941	-0.0346	0.0081	2.58E-05	-0.0174	0.0017	1.6E-21
cg06679720	-0.0569	0.0134	2.58E-05	-0.0144	0.0018	2.9E-14
cg05650171	0.1075	0.0253	2.60E-05	0.0253	0.0026	7.1E-20
cg07564108	-0.0941	0.0222	2.61E-05	-0.0209	0.0028	5.1E-13
cg12105382	-0.0864	0.0204	2.61E-05	0.0042	0.0020	3.9E-02
cg19668034	0.1519	0.0358	2.62E-05	0.0176	0.0037	2.2E-06

cg05194300	0.0619	0.0146	2.63E-05	0.0299	0.0028	1.8E-24
cg08604596	0.0484	0.0114	2.63E-05	0.0059	0.0020	3.6E-03
cg05713794	0.1034	0.0244	2.64E-05	0.0419	0.0036	3.1E-28
cg20188739	0.1045	0.0246	2.65E-05	0.0302	0.0044	2.0E-11
cg05357209	0.1254	0.0296	2.65E-05	0.0441	0.0070	6.3E-10
cg17459635	-0.0599	0.0141	2.66E-05	-0.0760	0.0059	8.4E-33
cg07374224	0.1590	0.0375	2.67E-05	0.0094	0.0039	1.6E-02
cg27366280	0.0552	0.0130	2.67E-05	-0.0038	0.0022	8.6E-02
cg04263702	-0.1590	0.0375	2.68E-05	0.0762	0.0064	3.6E-29
cg22719241	-0.1212	0.0286	2.70E-05	-0.0896	0.0075	3.0E-29
cg09735822	-0.1313	0.0310	2.70E-05	-0.0168	0.0026	2.8E-10
cg09684846	-0.2141	0.0505	2.71E-05	-0.0284	0.0079	3.8E-04
cg21429551	0.1193	0.0282	2.72E-05	0.0657	0.0070	2.2E-19
cg08537367	-0.0593	0.0140	2.73E-05	-0.0383	0.0035	2.7E-25
cg24199599	0.1273	0.0301	2.73E-05	0.0289	0.0051	1.8E-08
cg07400063	0.0828	0.0196	2.73E-05	0.0035	0.0022	1.2E-01
cg19726321	-0.1712	0.0404	2.73E-05	0.0001	0.0034	9.8E-01
cg02616604	-0.0827	0.0195	2.74E-05	-0.0449	0.0044	2.8E-22
cg03456213	-0.1260	0.0298	2.74E-05	-0.0060	0.0035	8.6E-02
cg14398883	-0.1953	0.0461	2.74E-05	0.0020	0.0040	6.2E-01
cg17240987	-0.0297	0.0070	2.76E-05	-0.0036	0.0015	1.9E-02
cg18362281	0.1423	0.0336	2.77E-05	0.0572	0.0058	9.7E-21
cg15577373	-0.0736	0.0174	2.77E-05	-0.0179	0.0030	4.7E-09
cg05044291	-0.4154	0.0981	2.77E-05	0.0016	0.0124	9.0E-01
cg24576804	0.0889	0.0210	2.77E-05	-0.0004	0.0030	9.0E-01
cg10791541	0.1249	0.0295	2.78E-05	0.0237	0.0035	2.3E-11
cg10179300	0.0851	0.0201	2.78E-05	0.0057	0.0028	3.9E-02
cg02970525	-0.0393	0.0093	2.78E-05	-0.0030	0.0018	9.0E-02
cg05654103	-0.0513	0.0121	2.79E-05	-0.0197	0.0029	2.2E-11
cg17230002	-0.0640	0.0151	2.79E-05	0.0110	0.0037	3.0E-03
cg19949550	0.0585	0.0138	2.80E-05	-0.0118	0.0022	1.0E-07
cg19602315	-0.1032	0.0244	2.81E-05	-0.0337	0.0040	2.2E-16

Appendix E

CpGs with *cis*-SNP

TABLE E.1: CpGs that are either related to maternal or active smoking with their significantly correlated *cis*-SNP(s) as obtained from the mQTL database (Gaunt et al., 2016). EAF: effect allele frequency. Beta: beta coefficient from the mQTL database. SE: standard error from the mQTL. P: *p*-value corresponding to the beta coefficient.

CpG	Chr	Pos	cis-SNP	Gene	Effect allele	Other allele	EAF	Beta	SE	P
cg00002033	19	39798481	rs30458	LRFN1	G	A	0.106	0.7355	0.0730	3.57E-19
cg00003298	12	113901210	rs4838851	LHX5	A	G	0.2366	0.4446	0.0478	7.51E-16
cg00022866	11	64108440	rs7122759	CCDC88B	T	C	0.3265	0.9746	0.0340	2.13E-176
cg00024404	5	79552470	rs1126176	SERINC5	A	G	0.3834	0.3333	0.0425	2.36E-11
cg00028929	12	52908478	rs199774989	KRT5	I	NA	0.1468	0.7419	0.0480	4.04E-49
cg00045902	10	134222218	rs117974416	PWWP2B	T	C	0.0452	1.096	0.0859	1.51E-32
cg00049323	5	472564	rs2672758	LOC25845	C	G	0.3689	0.9422	0.0273	1.00E-200
cg00054774	21	43373079	rs12185822	C2CD2	A	G	0.2227	0.4369	0.0457	5.52E-17
cg00057272	8	135726252	rs148316606	ZFAT	A	C	0.1702	0.5645	0.0523	1.69E-22
cg00059225	5	151304357	rs2071220	GLRA1	T	C	0.4548	0.3075	0.0332	8.81E-16
cg00061520	16	4070371	rs2239311	ADCY9	C	T	0.0692	0.5884	0.0802	1.09E-08
cg00070899	6	34024479	rs6905327	GRM4	T	A	0.2048	0.5656	0.0505	1.81E-25
cg00072689	17	46681111	rs11079830	LOC404266	G	A	0.4124	0.2295	0.0422	2.77E-03
cg00073460	6	149806502	rs62439783	ZC3H12D	T	C	0.06529	0.5973	0.0731	1.52E-11
cg00073543	1	38941882	rs2265999		A	C	0.2517	0.3935	0.0443	3.30E-14
cg00096536	4	154711906	rs74549610		G	C	0.2556	0.4633	0.0367	8.41E-32
cg00099441	2	11264766	rs72785429		T	C	0.2037	0.4099	0.0493	4.91E-13
cg00115288	11	705892	rs7118663	EPS8L2	T	C	0.4754	0.3282	0.0395	4.85E-12
cg00118978	3	14597418	rs35997780		D	NA	0.2606	0.5395	0.0452	3.43E-28
cg00134210	10	14644132	rs72770512	FAM107B	T	A	0.1741	0.4605	0.0475	1.51E-17
cg00142036	10	13388442	rs825645	SEPHS1	G	A	0.4386	0.6788	0.0357	5.01E-76
cg00151370	6	16323285	rs11758500	ATXN1	C	T	0.01953	14.088	0.1340	3.75E-21
			rs2073519	ATXN1	G	T	0.207	0.244342	0.0444	1.89E-03
cg00152644	1	153068236	rs310096	SPRR2E	T	G	0.04576	-1.068	0.0947	8.74E-25
cg00153942	11	71249212	rs17363723	KRTAP5-8	A	G	0.442	0.4081	0.0255	3.82E-53
cg00156057	6	169391744	rs4708401		G	A	0.3198	0.3712	0.0447	4.83E-12
cg00175403	1	12223543	rs590314		A	G	0.4029	0.2304	0.0336	3.59E-08
cg00177243	10	18434068	rs77286225	CACNB2	C	T	0.04408	1.578	0.0922	6.18E-61
cg00178850	1	236559675	rs61833985	EDARADD	G	T	0.4129	0.3551	0.0429	5.91E-13
cg00186954	11	8933980	rs2742520	ST5	T	C	0.346	0.6418	0.0357	9.80E-68
cg00205605	1	2516401	rs4385650		A	G	0.332	0.5551	0.0312	3.81E-66
cg00218893	17	73073239	rs61370032		T	C	0.04855	0.6175	0.0945	3.22E-06
cg00223867	8	86087386	rs7017323		G	C	0.1562	0.3738	0.0476	1.93E-10
cg00232827	5	172096764	rs7718156	NEURL1B	A	C	0.1696	0.5493	0.0562	7.38E-18
cg00233028	11	44642914	rs7122659		T	C	0.1412	0.5487	0.0509	2.00E-22
cg00237010	12	772861	rs12312948	NINJ2	G	A	0.3739	0.5613	0.0371	5.19E-47
cg00238349	3	52187791	rs876782	WDR51A	C	T	0.07422	0.6241	0.0804	4.04E-10
cg00249383	16	2287763	rs3114130	DNASE1L2	T	C	0.05022	0.7606	0.0958	1.04E-10
cg00261569	3	119216728	rs4688009	C3orf1	T	C	0.1864	0.7597	0.0523	4.61E-43
cg00291478	10	121301041	rs6585552	RGS10	G	C	0.08147	0.5165	0.0621	4.29E-12
cg00292029	6	36703127	rs236448		C	A	0.3979	0.3657	0.0392	5.76E-16
cg00312553	5	157098553	rs7712133	C5orf52	C	T	0.3638	0.343	0.0447	8.65E-10
cg00313914	1	201618901	rs11587986	NAV1	G	A	0.4252	0.537841	0.0409	8.44E-35
			rs61333833	NAV1	G	A	0.2528	0.575936	0.0466	2.38E-30
cg00335892	22	21213899	rs13054456	SNAP29	C	T	0.4308	0.7612	0.0366	3.18E-91
cg00338002	1	28198813	rs12062621	C1orf38	G	A	0.3633	0.4271	0.0421	1.61E-19
cg00344801	22	46685728	rs9615933	TTC38	A	G	0.09933	0.7266	0.0505	3.05E-42
cg00347798	3	45077649	rs4683021		A	G	0.4872	0.383917	0.0652	1.91E-05
			rs9868885		A	G	0.4252	0.469747	0.0667	9.10E-08
cg00353643	16	1458060	rs1987071	UNKL	G	C	0.1256	0.4495	0.0448	5.58E-19
cg00356499	4	3516065	rs3135165	LRPAP1	C	G	0.2098	0.7218	0.0453	1.86E-52
cg00377358	20	61639277	rs2427460	BHLHE23	C	T	0.4766	0.3138	0.0427	9.50E-09
cg00378510	19	2291020	rs148145895	LINGO3	D	NA	0.4107	0.4722	0.0331	1.63E-41
cg00383167	18	77616694	rs62103233		G	A	0.2824	0.337	0.0433	3.57E-10
cg00386101	2	11621399	rs11893713		G	A	0.4537	0.4616	0.0389	9.98E-28
cg00395296	22	42481778	rs5758553	NDUFA6	A	G	0.4955	0.1687	0.0307	1.99E-03
cg00411097	7	1596050	rs10715883	TMEM184A	D	NA	0.4079	0.6971	0.0306	7.47E-110
cg00426968	19	47138284	rs12462989	GNG8	T	C	0.2958	0.4169	0.0443	2.37E-16
cg00451105	13	29104082	rs75196973		G	A	0.05357	0.6714	0.0895	3.18E-09
cg00461022	5	16618052	rs35004	FAM134B	A	C	0.471	0.4979	0.0291	5.50E-61
cg00464046	7	134854551	rs75588101	C7orf49	G	A	0.09598	0.8139	0.0685	7.75E-28
cg00465247	13	50703477	rs9316484		C	T	0.2087	0.843	0.0394	1.26E-96
cg00471190	16	3115809	rs13335800	IL32	A	T	0.365	0.2923	0.0308	1.10E-16
cg00472373	3	9833414	rs4686371	ARPC4	C	T	0.2333	0.5913	0.0401	1.73E-44

cg00475085	11	60674473	rs1224036	PRPF19	C	T	0.3532	0.325	0.0430	2.18E-09
cg00491255	16	58019984	rs9924293	TEPP	C	G	0.159	0.3241	0.0595	2.58E-03
cg00498211	2	65217568	rs35375623	SLC1A4	G	A	0.1345	0.303153	0.0555	2.35E-03
			rs6546118	SLC1A4	G	A	0.149	0.759407	0.0511	2.59E-45
cg00502062	1	201578212	rs1267139		C	T	0.221	0.3579	0.0461	4.10E-10
cg00506935	15	89169262	rs12440303	AEN	C	G	0.1853	0.5333	0.0465	9.99E-26
cg00522231	2	9549277	rs11692768	ITGB1BP1	A	G	0.2188	0.312199	0.0379	9.17E-12
			rs7564165	ITGB1BP1	T	C	0.4018	0.785972	0.0333	2.59E-118
cg00540464	19	16655751	rs11371657		I	NA	0.09319	0.6215	0.0609	9.48E-20
cg00541303	1	208962374	rs61815842		T	A	0.1189	0.5268	0.0621	1.14E-12
cg00541638	16	9056115	rs61426394	USP7	C	G	0.07366	0.5604	0.0659	9.28E-13
cg00544337	10	82116203	rs12411833	DYDC2	C	T	0.1401	0.351341	0.0558	1.49E-05
			rs4146515	DYDC2	G	A	0.4844	0.321639	0.0391	9.71E-12
cg00549219	5	177370476	rs113821938		T	C	0.02567	-1.342	0.1239	1.18E-22
cg00550955	22	22012657	rs450129		T	G	0.3577	0.2513	0.0427	1.99E-04
cg00566899	1	216058191	rs76363249	USH2A	C	T	0.09487	0.418	0.0613	4.69E-07
cg00569896	4	204382	rs57867809		C	T	0.3934	0.2536	0.0384	1.92E-07
cg00574379	7	38344455	rs76532745		C	T	0.2388	0.7546	0.0403	1.28E-73
cg00575674	1	61314297	rs11808039		G	A	0.178	0.386944	0.0490	1.50E-10
			rs310179		T	C	0.2567	0.459038	0.0423	8.96E-23
cg00579402	19	5838999	rs778798	FUT6	A	C	0.2578	0.6112	0.0370	1.05E-56
cg00580497	5	1153746	rs11133652		A	G	0.3398	0.5154	0.0420	6.54e-35
cg00581603	1	53442535	rs200702147	SCP2	I	NA	0.4353	0.2754	0.0422	3.48E-06
cg00587301	6	156717406	rs1078299		C	A	0.09989	0.6166	0.0681	6.62E-15
cg00589617	1	230415343	rs3213495	GALNT2	A	G	0.12	0.409361	0.0644	1.02E-05
			rs9431818	GALNT2	C	T	0.4922	0.320495	0.0430	4.76E-09
cg00605523	2	238523251	rs4271721		A	G	0.4263	0.4414	0.0374	2.04E-27
cg00605988	16	31548698	rs12596058		A	T	0.3661	0.536066	0.0389	1.35E-38
			rs140805916		T	G	0.04129	-106.725	0.0933	1.36E-25
cg00622799	20	62318588	rs201926957	RTEL1	I	NA	0.245	0.3145	0.0406	4.61E-10
cg00627029	17	72322791	rs7209183	KIF19	C	G	0.3705	0.3105	0.0419	6.57E-09
cg00637477	20	62525797	rs6062333	DNAJC5	C	T	0.04353	0.5797	0.0802	2.48E-08
cg00664609	16	2198075	rs258281	RAB26	A	G	0.178	0.4264	0.0442	2.64E-17
cg00668559	6	44230977	rs730775	NFKBIE	G	A	0.4403	0.7684	0.0326	1.71E-118
cg00674004	10	101280750	rs11190133		T	C	0.2991	0.4556	0.0442	3.36E-20
cg00675878	22	23521267	rs2071431	BCR	G	T	0.2355	0.3272	0.0402	1.92E-11
cg00689225	14	35871954	rs12435366	NFKBIA	T	C	0.2316	0.473	0.0353	3.52E-36
cg00689360	4	100273995	rs4147531	ADH1C	A	G	0.4509	0.4438	0.0386	7.08E-26
cg00706994	11	59190310	rs11604472	OR5A2	T	G	0.284	0.431	0.0406	1.33E-21
cg00710862	2	85545908	rs16346	TGOLN2	D	NA	0.1384	0.8857	0.0483	1.66E-70
cg00711496	19	50191497	rs4964614	C19orf76	T	G	0.3929	0.3481	0.0435	5.95E-11
cg00723017	8	124953650	rs7837731	FER1L6	C	T	0.4258	0.3127	0.0398	1.87E-10
cg00726046	20	43161260	rs6031646	PKIG	T	C	0.07422	-1.262	0.0566	1.38E-105
cg00729885	13	36046056	rs9544300	NBEA	T	G	0.159	0.4354	0.0535	2.10E-11
cg00752969	2	70311984	rs6546568		T	C	0.05859	0.6266	0.0754	4.88E-12
cg00756943	15	91208460	rs35907368		T	C	0.2026	0.426397	0.0438	9.95E-18
			rs79722842		C	G	0.04074	123.246	0.0897	2.74E-38
cg00761968	13	53314142	rs9527001	LECT1	C	T	0.4794	0.3946	0.0376	5.08E-21
cg00770316	2	146509846	rs113608643		I	NA	0.101	0.4517	0.0534	1.40E-12
cg00772091	10	124914911	rs11248425	BUB3	A	G	0.1194	0.452	0.0605	4.16E-09
cg00782645	16	90115048	rs9934403	LOC100130015	T	C	0.226	0.4668	0.0464	4.42E-19
cg00785482	1	208058986	rs2745950		A	G	0.3945	0.1684	0.0298	7.57E-04
cg00794673	6	35016449	rs2689091	ANKS1A	A	G	0.4715	0.3116	0.0385	2.79E-11
cg00804043	17	8771331	rs12939015	PIK3R6	A	G	0.3287	0.3006	0.0355	1.23E-12
cg00804078	6	110736941	rs4445085	DDO	T	A	0.4353	0.7671	0.0325	8.11E-119
cg00806481	1	2996650	rs1569419	PRDM16	T	C	0.2511	0.9698	0.0373	5.48E-144
cg00812761	4	53799391	rs17082147	SCFD2	T	C	0.08092	0.6284	0.0706	2.65E-14
cg00826902	1	3563954	rs35440906	WDR8	I	NA	0.1819	0.2987	0.0516	3.61E-04
cg00830420	12	5758014	rs11063846	ANO2	C	T	0.1138	0.6765	0.0612	9.74E-24
			rs1984479	ANO2	A	C	0.3359	0.302333	0.0426	6.20E-08
cg00830767	16	19098198	rs17357834		A	G	0.1814	0.4596	0.0482	8.14E-17
cg00835193	19	2291780	rs3795039	LINGO3	C	G	0.4068	0.4679	0.0416	1.27E-24
cg00849642	12	109106495	rs9783411	CORO1C	A	C	0.4654	0.442	0.0279	8.84E-52
cg00852783	1	26633632	rs11247887	UBXN11	C	T	0.3438	0.4593	0.0379	4.24E-30
cg00854314	15	89180799	rs11073795	ISG20	A	G	0.3929	0.233	0.0300	4.09E-10
cg00857907	2	202896898	rs6730625		T	C	0.3041	0.286338	0.0532	3.63E-03
			rs7592801		T	C	0.4358	0.35737	0.0498	3.72E-08
cg00865973	4	102709336	rs11097755		C	T	0.4609	0.8573	0.0318	1.56E-155
cg00893045	15	66795844	rs524612	SNORD18A	C	A	0.3945	0.7291	0.0271	3.48E-155
cg00893603	13	26587011	rs9553698	ATP8A2	C	A	0.3426	0.477	0.0400	3.68E-28
cg00901598	3	172164984	rs61017161	GHSR	A	G	0.4754	0.3072	0.0367	2.62E-12
cg00917251	1	24829987	rs80007720	RCAN3	T	C	0.05804	0.7373	0.0870	1.13E-13
cg00925802	1	10732558	rs284317	CASZ1	A	G	0.4961	0.2825	0.0407	1.86E-07
cg00929860	10	73846448	rs1245546	SPOCK2	T	C	0.4515	0.2441	0.0321	1.37E-09
cg00941203	10	31016591	rs3124191		T	C	0.2042	0.360787	0.0432	3.15E-13
			rs7924137		T	C	0.3828	0.744243	0.0355	4.51E-93
cg00945209	17	76801579	rs4796817	USP36	T	C	0.2115	0.3656	0.0391	3.98E-16
cg00949249	2	97776919	rs13411628		C	T	0.3488	0.2952	0.0337	1.02E-13
cg00960209	16	29165693	rs252285		T	C	0.1769	0.717	0.0460	5.24E-50
cg00971747	1	200864307	rs184164	C1orf106	C	T	0.3795	0.4259	0.0337	7.96E-32
cg00976097	5	421733	rs11745813	AHRR	C	A	0.1596	0.536094	0.0577	7.21E-17
			rs3815928	AHRR	G	C	0.4425	0.355612	0.0428	4.63E-12
cg00981651	20	44574847	rs11906879	PCIF1	C	T	0.4665	0.3895	0.0397	5.41E-18
cg00981877	20	50366841	rs200371476	ATP9A	I	NA	0.0385	0.8553	0.1073	8.02E-11
cg00983437	20	592164	rs282165	TCF15	C	T	0.2254	0.4708	0.0536	8.49E-14
cg00986580	14	22951241	rs227860		A	T	0.1278	0.7818	0.0555	2.04E-40
cg00995520	1	111218282	rs2821557	KCNA3	C	T	0.4408	0.3141	0.0391	4.56E-11
cg00996827	1	2838805	rs936251		C	T	0.236	0.9269	0.0405	2.52E-111
cg01016119	3	56835282	rs35983891	ARHGEF3	T	C	0.4286	0.335	0.0268	3.23E-31
cg01020987	1	3816166	rs7513321	C1orf174	A	G	0.1579	0.6349	0.0558	2.90E-25
cg01030476	1	236686564	rs2759007	LGALS8	G	C	0.2545	0.5435	0.0410	1.75E-35
cg01052864	5	215875	rs113513945	CCDC127	A	G	0.1479	0.412282	0.0523	1.64E-10
			rs7734433	CCDC127	G	A	0.3672	0.369151	0.0389	1.26E-16
cg01062937	16	88537260	rs870021	ZFPM1	A	T	0.3158	0.2256	0.0298	1.77E-09
cg01073837	8	38757859	rs117064964	PLEKHA2	T	C	0.159	0.5933	0.0557	7.73E-22
cg01077185	7	149562623	rs10807975	ZNF862	G	C	0.3756	0.3124	0.0377	6.20E-12
cg01081636	6	33994263	rs6905327	GRM4	T	A	0.2048	0.4258	0.0479	3.28E-14
cg01084740	14	61748243	rs17806459	TMEM30B	G	A	0.08873	0.846174	0.0657	2.80E-33

			rs200538787	TMEM30B	I	NA	0.2924	0.552739	0.0399	4.84E-39
cg01090821	2	239066990	rs73094343		C	A	0.466	0.3128	0.0373	2.57E-12
cg01109535	16	24856104	rs11644562	SLC5A11	A	C	0.1903	0.5087	0.0455	2.73E-25
cg01119319	7	38356808	rs11769443		C	T	0.3783	0.3743	0.0413	6.60E-15
cg01131866	5	61601529	rs10062757	KIF2A	C	T	0.4235	0.2504	0.0345	1.99E-08
cg01135546	17	45949828	rs56006220		C	T	0.07143	0.6274	0.0780	4.26E-11
cg01139039	7	150778208	rs2303942	FASTK	A	G	0.4989	0.2095	0.0288	1.79E-08
cg01148088	2	7057227	rs17606606	RNF144A	A	G	0.3064	0.64041	0.0385	1.87E-57
			rs454999	RNF144A	G	A	0.3811	0.33696	0.0366	1.86E-15
			rs771290	RNF144A	A	G	0.07924	0.456312	0.0658	2.04E-07
cg01148741	2	96811453	rs2969489	DUSP2	T	C	0.4481	0.6406	0.0289	1.83E-104
cg01152624	11	106239635	rs11211831		T	G	0.1406	0.8921	0.0535	7.82E-58
cg01157559	16	29166162	rs252285		T	C	0.1769	0.9251	0.0412	4.98E-107
cg01161042	4	2322052	rs55997253	ZFYVE28	D	NA	0.3354	0.2178	0.0310	1.14E-07
cg01185345	13	99218287	rs9517338	STK24	A	G	0.1886	0.4967	0.0480	2.00E-20
cg01238669	7	21797276	rs6942457	DNAH11	A	G	0.1618	0.976652	0.0474	1.05E-89
			rs6979777	DNAH11	A	C	0.05915	0.729541	0.0703	1.56E-20
cg01240931	5	112074043	rs60532731	APC	C	T	0.01562	0.978538	0.1403	1.51E-07
			rs66911377	APC	D	NA	0.4604	0.462162	0.0335	1.74E-38
cg01252219	12	110302105	rs4766637	GLTP	A	C	0.4554	0.406	0.0253	1.79E-53
cg01271455	7	157362062	rs221291	PTPRN2	A	G	0.03795	0.850341	0.0963	5.14E-14
			rs73163812	PTPRN2	A	G	0.3638	0.258517	0.0393	2.48E-07
cg01286935	16	89778247	rs12860610	C16orf7	G	A	0.4972	0.4261	0.0336	3.30E-32
cg01289343	13	114814401	rs7999377	RASA3	A	G	0.4392	0.5342	0.0322	3.24E-57
cg01294327	19	2291373	rs148145895	LINGO3	D	NA	0.4107	0.742	0.0335	5.93E-104
cg01310750	19	52996548	rs5828508	ZNF578	D	NA	0.03125	0.8809	0.1134	4.07E-10
cg01314044	11	94246036	rs141125338		D	NA	0.4314	0.4494	0.0428	4.22E-21
cg01321673	22	50438363	rs4838818	IL17REL	A	G	0.1211	0.4396	0.0495	3.58E-14
cg01328473	2	1711966	rs13401942	PXDN	G	A	0.2355	0.3996	0.0395	2.43E-19
cg01360605	20	58983676	rs6015692		C	G	0.2785	0.3322	0.0457	1.84E-08
cg01400685	11	61598025	rs61897793	FADS2	A	G	0.1814	0.7203	0.0473	1.17E-47
cg01405107	17	46671635	rs4793589	LOC404266	C	G	0.178	0.508296	0.0515	2.74E-18
			rs6504411	LOC404266	T	C	0.0904	0.509016	0.0693	1.03E-08
cg01413354	9	136017755	rs12348227	RALGDS	T	G	0.3761	0.9595	0.0321	2.09E-191
cg01435643	13	113689776	rs3011511	MCF2L	A	G	0.2595	0.3215	0.0464	2.18E-08
cg01436487	7	1890148	rs4639400	MAD1L1	G	T	0.389	0.4081	0.0394	2.00E-20
cg01439670	11	76381165	rs4945097	LRRC32	G	A	0.481	0.291	0.0415	1.23E-07
cg01447281	1	8482689	rs301805	RERE	T	G	0.4397	0.3296	0.0344	4.28E-17
cg01447828	19	40919465	rs116866864	PRX	T	C	0.03292	-1.402	0.1080	7.29E-34
cg01455178	1	205648187	rs6673687	SLC45A3	T	A	0.4196	0.3919	0.0378	1.62E-20
cg01465596	1	42381916	rs783629	HIVEP3	C	T	0.4364	0.4456	0.0339	9.53E-36
cg01471372	8	38592365	rs34153723	TACC1	C	A	0.2031	0.6149	0.0440	9.50E-40
cg01476739	2	241853884	rs4417704		A	G	0.2533	0.5568	0.0406	4.36E-38
cg01478234	12	107975299	rs1991310	BTBD11	A	G	0.4481	0.2699	0.0405	1.30E-06
cg01486260	16	31379850	rs10782004	ITGAX	A	G	0.3426	0.186094	0.0310	1.01E-04
			rs4264407	ITGAX	C	G	0.07812	0.476053	0.0540	5.93E-14
cg01498900	14	74035742	rs143643216	ACOT2	D	NA	0.2919	0.3701	0.0429	2.99E-14
cg01503516	15	85202406	rs17532346	NMB	C	A	0.2584	0.7097	0.0373	7.80E-76
cg01538731	16	87757018	rs12447906	KLHDC4	T	C	0.433	0.585388	0.0360	1.07E-54
			rs2115396	KLHDC4	A	T	0.4314	0.35876	0.0358	6.42E-19
cg01548777	20	62433998	rs4538263	ZBTB46	A	G	0.1356	0.4696	0.0572	1.16E-11
cg01553004	14	77495672	rs61991619	C14orf4	G	A	0.2695	0.3676	0.0390	2.25E-16
cg01561259	17	78560781	rs4889872	RPTOR	A	G	0.2667	0.3685	0.0432	6.86E-13
cg01565703	14	103245090	rs11850030	TRAF3	G	C	0.1819	0.371	0.0543	4.18E-07
cg01570068	8	1937676	rs4410948	KBTBD11	T	C	0.07701	0.9509	0.0764	6.78E-31
cg01572694	17	46657555	rs145663483	MIR10A	I	NA	0.1853	0.3655	0.0469	3.29E-10
cg01575652	22	38077606	rs2899292		G	A	0.3086	0.4549	0.0339	2.79E-36
cg01577700	22	24641314	rs35720801	GGT5	A	G	0.2533	0.4323	0.0410	2.81E-21
cg01581360	12	122986464	rs11354559	ZCCHC8	D	NA	0.1272	0.7381	0.0574	4.05E-33
cg01588379	7	151433326	rs117728810	PRKAG2	A	G	0.05022	-10.079	0.0845	4.03E-28
			rs6464166	PRKAG2	C	T	0.1842	0.360667	0.0488	7.28E-09
cg01595951	5	54834655	rs10041669		C	T	0.1429	0.4144	0.0490	1.34E-12
cg01598596	3	187464648	rs4271904	BCL6	C	T	0.4888	0.3411	0.0354	2.65E-17
cg01610165	5	124071029	rs6421891	ZNF608	C	G	0.3744	0.4012	0.0416	2.60E-17
cg01613691	19	1105380	rs4807542	GPX4	A	G	0.1663	0.4743	0.0504	2.31E-16
cg01617750	3	32279261	rs4955268	CMTM8	G	A	0.2634	0.5509	0.0428	2.78E-33
cg01620165	12	113530915	rs1674092	DTX1	C	T	0.2065	0.3299	0.0366	9.02E-15
cg01626885	15	45937757	rs74244958	SQRDL	A	T	0.08705	0.4169	0.0536	3.61E-10
cg01637175	17	21281507	rs12935991	KCNJ12	C	T	0.4526	0.9266	0.0326	1.14E-172
cg01639898	1	32083012	rs7529064	HCRTR1	C	A	0.4425	0.5072	0.0390	5.93E-34
cg01643605	16	29040623	rs7202069		T	A	0.293	0.3854	0.0396	9.93E-18
cg01645955	4	39371148	rs10033019		A	G	0.4849	0.2657	0.0394	7.93E-07
cg01649611	2	43521066	rs6715059	THADA	T	C	0.1791	0.304	0.0451	7.90E-07
cg01651915	8	55795551	rs1498170		T	A	0.3493	0.2754	0.0440	1.99E-05
cg01676795	7	75586348	rs59882870	POR	A	G	0.1769	0.4	0.0435	1.82E-16
cg01687189	12	102225365	rs76300806	GNPTAB	NA	D	0.495	0.5704	0.0335	2.51E-61
cg01735049	16	9187613	rs34839208	C16orf72	C	G	0.1791	0.3768	0.0512	8.99E-09
cg01735398	17	18907305	rs2074271	SLC5A10	A	G	0.04632	0.8233	0.0981	2.40E-13
cg01751245	2	65593761	rs934734	SPRED2	A	G	0.4732	0.2865	0.0390	9.54E-09
cg01785359	8	38757652	rs117064964	PLEKHA2	T	C	0.159	0.5098	0.0537	1.12E-16
cg01785719	8	143404187	rs72687386	TSNARE1	T	C	0.2355	0.765417	0.0405	6.24E-75
			rs9886385	TSNARE1	T	C	0.1278	0.321425	0.0530	6.78E-05
cg01802117	1	53393560	rs1242331	SCP2	A	G	0.3516	0.4877	0.0442	1.39E-23
cg01815128	13	31480003	rs17599975	C13orf33	T	C	0.1278	0.4799	0.0626	8.85E-10
cg01824603	8	1878323	rs4876271	ARHGEF10	A	G	0.1283	0.4468	0.0600	4.74E-09
cg01838544	16	57576594	rs6499882	GPR114	G	A	0.3069	0.7061	0.0413	8.09E-61
cg01873977	8	125699897	rs28502052	MTSS1	A	G	0.3326	0.3633	0.0424	5.49E-13
cg01887374	2	129077404	rs12469358	HS6ST1	C	T	0.1652	0.6744	0.0532	4.48E-32
			rs141232401	HS6ST1	T	C	0.02344	0.96921	0.1296	3.84E-09
cg01899318	16	71523395	rs67540871	ZNF19	D	NA	0.1334	0.3623	0.0538	8.07E-07
cg01919939	15	35990007	rs2647676		A	G	0.1925	0.841705	0.0571	2.10E-44
			rs55928440		G	A	0.1099	0.463875	0.0738	1.61E-05
cg01927745	5	72677723	rs7726687		T	A	0.0692	0.541	0.0748	2.29E-08
cg01933695	14	77495691	rs61991619	C14orf4	G	A	0.2695	0.4128	0.0461	1.80E-14
cg01934408	1	6085799	rs76852674	KCNAB2	G	A	0.1016	0.8689	0.0638	1.41E-37
cg01937809	1	37941854	rs115755325	ZC3H12A	A	G	0.01339	-1.061	0.1317	3.88E-11
cg01939428	7	156931170	rs2286130	UBE3C	T	C	0.2333	0.473237	0.0590	5.03E-11
			rs3815217	UBE3C	G	A	0.4827	0.290569	0.0532	2.42E-03

cg01940297	8	129061191	rs2720660	MIR1207	A	G	0.3683	0.5173	0.0404	6.54E-33
cg01946401	6	45296101	rs641011	SUPT3H	C	G	0.06194	0.6079	0.0897	6.23E-07
cg01955025	14	91091782	rs67690838	TTC7B	A	G	0.1205	0.3097	0.0506	4.57E-05
cg01957582	22	32341780	rs35719902	C22orf24	I	NA	0.2963	0.352424	0.0440	5.56E-11
			rs9621371	C22orf24	G	T	0.2494	0.284883	0.0489	2.77E-04
cg01973695	11	128560328	rs55635129		D	NA	0.3131	0.4466	0.0435	4.93E-20
cg01987516	10	101282726	rs11190133		T	C	0.2991	0.719	0.0419	3.66E-61
cg01991752	14	101014148	rs6575784	BEGAIN	C	T	0.3845	0.3255	0.0376	2.68E-13
cg01999046	9	139779708	rs2811761	TRAF2	C	T	0.2176	0.3386	0.0545	2.66E-05
cg02008416	1	55445880	rs2059688	TMEM61	G	A	0.2288	0.6196	0.0497	5.39E-31
cg02010760	21	38934792	rs2236605		G	C	0.4732	0.2995	0.0338	3.90E-14
cg02028663	11	128557589	rs55635129		D	NA	0.3131	0.5738	0.0427	2.19E-37
cg02030270	15	84215725	rs2732153	SH3GL3	G	T	0.1702	0.9895	0.0414	1.43E-121
cg02032558	4	155662438	rs3836690		D	NA	0.4526	0.3297	0.0432	1.09E-09
cg02056062	3	149374914	rs4681535	WWTR1	G	A	0.4107	0.2814	0.0357	1.54E-10
cg02057716	2	218807759	rs11676955	TNS1	G	C	0.07087	0.5251	0.0740	6.50E-08
cg02058108	12	26348117	rs17380837	SSPN	T	C	0.3041	0.5834	0.0445	1.22E-34
cg02061173	5	77805555	rs16875564	LHFPL2	C	G	0.2958	0.3207	0.0476	8.26E-07
cg02068690	2	25600451	rs2304426	DTNB	G	A	0.3694	0.1975	0.0323	4.87E-05
cg02072018	3	9884995	rs57223920	RPUSD3	T	C	0.06194	0.903562	0.0749	8.06E-29
			rs9812740	RPUSD3	A	G	0.1669	0.766349	0.0491	2.52E-50
cg02078896	20	15176557	rs35319766	MACROD2	D	NA	0.409	0.4602	0.0407	6.82E-25
cg02085294	2	65220148	rs2922288	SLC1A4	C	T	0.4035	0.3386	0.0325	1.07E-20
cg02086839	8	144403439	rs66944623	TOP1MT	C	G	0.2963	0.5299	0.0386	3.17E-38
cg02103401	3	37033373	rs35149869	EPM2AIP1	D	NA	0.2076	0.2891	0.0415	1.64E-07
cg02118194	19	46404538	rs7250721	MYPOP	C	T	0.2104	0.4793	0.0496	2.25E-17
cg02147592	19	4090388	rs60505738	MAP2K2	T	C	0.09375	0.8323	0.0602	9.11E-39
cg02148654	7	157296159	rs17667159		C	A	0.3131	0.561589	0.0431	4.53E-35
			rs7246000		T	C	0.389	0.338254	0.0401	1.72E-13
cg02156769	9	139872246	rs12343591	PTGDS	A	C	0.2467	0.5194	0.0470	9.70E-24
cg02158978	12	133134938	rs4475994	FBRSL1	C	G	0.4548	0.3466	0.0353	5.22E-18
cg02162897	2	38300537	rs4646429	CYP1B1	T	C	0.284	0.3489	0.0410	9.34E-14
cg02175308	1	109941060	rs10858088	SORT1	C	T	0.284	0.7881	0.0417	7.18E-75
cg02186444	17	73120977	rs6501762	ARMC7	G	A	0.3465	0.2493	0.0386	5.49E-06
cg02187522	20	3065488	rs2740191	AVP	T	C	0.1529	0.5236	0.0511	5.90E-20
cg02218324	19	46318439	rs35226705	RSPH6A	C	A	0.4475	0.2383	0.0414	4.35E-04
cg02225599	7	27143252	rs2465275	HOXA2	A	G	0.1021	0.6372	0.0624	8.31E-20
cg02231590	2	231737958	rs60237566	ITM2C	G	T	0.2388	0.3043	0.0394	5.94E-10
cg02243303	6	52147973	rs9474192	MCM3	G	T	0.3393	0.4532	0.0357	3.70E-32
cg02257517	9	136340262	rs3124760	SLC2A6	C	T	0.1529	0.3453	0.0524	2.11E-06
cg02270010	5	175958651	rs10050798	RNF44	G	A	0.1842	0.409015	0.0502	1.84E-11
			rs4868642	RNF44	T	C	0.3086	0.464468	0.0425	4.49E-23
cg02272278	6	158448578	rs6455950	SYNJ2	A	G	0.4001	0.3817	0.0434	7.34E-14
cg02279625	15	78384520	rs12910083	SH2D7	T	C	0.04353	1.016	0.0904	1.26E-24
cg02299328	17	38346960	rs56357916	RAPGEFL1	A	G	0.1417	0.9631	0.0500	5.01E-78
cg02331830	8	145008288	rs62522556	PLEC1	C	T	0.3839	-147.482	0.0687	1.24E-97
			rs7833924	PLEC1	G	A	0.418	0.437131	0.0694	1.49E-05
cg02339793	17	79225573	rs148056883	SLC38A10	I	NA	0.3253	0.457764	0.0391	6.04E-27
			rs72850649	SLC38A10	T	C	0.08873	0.348387	0.0651	4.39E-03
cg02345399	11	65195039	rs550015		A	G	0.111	0.3596	0.0509	8.28E-08
cg02354658	5	95151391	rs2007	GLRX	C	G	0.2148	0.835	0.0447	2.44E-73
cg02359132	6	111279585	rs6925571	GTF3C6	T	C	0.1568	1.009	0.0458	5.09E-103
cg02373104	7	147601429	rs2710119	MIR548F3	T	C	0.365	0.41	0.0400	5.40E-20
cg02375208	5	77804381	rs36037001	LHFPL2	D	NA	0.2573	0.3472	0.0369	2.35E-16
cg02380595	16	85160569	rs11641810		C	T	0.2673	0.406	0.0464	1.12E-13
cg02390801	15	74528565	rs351174	CCDC33	G	A	0.3761	0.4118	0.0363	4.41E-25
cg02405476	20	44441818	rs6032535	UBE2C	T	C	0.3164	0.3613	0.0372	1.23E-17
cg02449762	10	5661741	rs10752145		C	T	0.3237	0.3931	0.0389	2.71E-20
cg02462416	11	2036573	rs7107675		A	T	0.2372	0.7198	0.0439	8.43E-56
cg02464912	14	64319543	rs111680529	SYNE2	T	C	0.2349	0.3342	0.0452	7.16E-09
cg02473781	22	22007095	rs112381187	MIR130B	A	G	0.365	0.3733	0.0433	3.10E-13
cg02484127	3	128723005	rs1075509	CCDC48	A	G	0.2433	0.3317	0.0413	5.14E-11
cg02489552	19	15121531	rs58827655	CCDC105	D	NA	0.2221	0.7622	0.0456	5.45E-58
cg02493846	1	151809534	rs4845624	LOC100132111	G	A	0.2829	0.2186	0.0364	9.33E-05
cg02501827	11	11862879	rs57910734	USP47	C	T	0.1468	0.7148	0.0456	1.18E-51
cg02503850	10	72432552	rs34821335	ADAMTS14	D	NA	0.269	0.4401	0.0493	2.12E-14
cg02508743	8	56903623	rs72653917	LYN	A	T	0.2093	0.3807	0.0496	8.31E-10
cg02532700	22	37257404	rs4821544	NCF4	C	T	0.3108	0.4712	0.0402	4.63E-27
cg02547426	4	3371236	rs910568	RGS12	A	G	0.3968	0.2854	0.0343	4.68E-12
cg02549628	4	88896208	rs2853749	SPP1	T	C	0.2907	0.3287	0.0410	5.53E-11
cg02550277	6	137815699	rs6909916	OLIG3	G	C	0.4961	0.2368	0.0344	2.72E-07
cg02550691	17	7255736	rs61759532	KCTD11	T	C	0.2411	0.8611	0.0388	1.49E-104
cg02558476	16	2880326	rs4786328	ZG16B	T	C	0.3253	0.3555	0.0364	7.03E-18
cg02564061	12	49998963	rs2720305	FAM186B	A	G	0.3153	0.3944	0.0376	4.52E-21
cg02569613	10	50323127	rs1986725	C10orf72	A	C	0.3845	0.4024	0.0376	5.77E-22
cg02574073	17	46682398	rs11079830	LOC404266	G	A	0.4124	0.24	0.0420	5.44E-04
cg02574805	12	131814178	rs114936273		T	C	0.0971	0.607656	0.0620	5.49E-18
			rs12815095		G	T	0.284	0.285926	0.0403	6.49E-08
cg02577773	2	208027870	rs67686520	KLF7	A	G	0.3052	0.3233	0.0383	1.50E-12
cg02577963	19	5041570	rs113840751	KDM4B	G	A	0.06473	0.8682	0.0664	2.34E-34
cg02580626	22	18572133	rs464385	PEX26	G	A	0.3538	0.4127	0.0328	1.53E-31
cg02586730	11	65639869	esv2676573	EFEMP2	D	NA	0.3421	0.4528	0.0437	1.86E-20
cg02594345	10	133956183	rs2637624	JAKMIP3	A	G	0.4743	0.36835	0.0495	5.19E-09
			rs2818385	JAKMIP3	C	T	0.3125	0.317498	0.0535	1.46E-04
cg02629070	6	41394156	rs13219238		T	C	0.1741	0.3896	0.0586	1.51E-06
cg02635932	10	18549778	rs16916956	CACNB2	C	A	0.04632	0.9917	0.0921	2.31E-22
cg02660097	11	68866761	rs150950408		D	NA	0.4632	0.310523	0.0558	1.28E-03
			rs2305498		A	G	0.1401	0.554424	0.0494	1.56E-24
			rs3829241		A	G	0.4381	0.391561	0.0522	3.19E-09
cg02672759	19	39739058	rs4803217		A	C	0.2963	0.285	0.0440	4.77E-07
cg02673986	1	27683912	rs79512993	MAP3K6	G	C	0.01562	-1.153	0.1721	1.05E-06
cg02688118	13	114918456	rs7332249		T	C	0.351	0.218	0.0329	1.67E-06
cg02695349	7	38269241	rs10226230	STARD3NL	A	G	0.4542	0.3915	0.0394	1.35E-18
cg02704502	11	2036580	rs7107675		A	T	0.2372	0.6627	0.0436	1.68E-48
cg02710860	15	42065401	rs17678552	MAPKBP1	C	T	0.3477	0.6087	0.0355	3.47E-61
cg02713960	16	746048	rs7205124	FBXL16	T	C	0.2193	0.3277	0.0499	2.49E-06
cg02736016	12	1017144	rs1986231	WNK1	G	A	0.3945	0.2215	0.0405	2.22E-03
cg02736908	17	29887376	rs1548470		A	G	0.3237	0.4436	0.0418	1.17E-22

cg02745045	17	63150820	rs12453132	RGS9	G	A	0.07087	0.9967	0.0639	3.26E-50
cg02745912	7	142494204	rs56352733		G	A	0.4727	0.4917	0.0378	4.41E-34
cg02750743	12	117477837	rs7979546	TESC	T	C	0.1172	0.4023	0.0477	1.71E-12
cg02757488	19	41193662	rs2561537	NUMBL	G	A	0.4994	0.252	0.0315	6.62E-11
cg02762115	11	640446	rs117429558	DRD4	A	G	0.05022	0.934694	0.0784	4.57E-28
			rs150403728	DRD4	D	NA	0.3008	0.356688	0.0378	1.72E-16
cg02771260	11	59836817	rs12221875	MS4A3	C	G	0.3064	0.847086	0.0348	2.86E-126
			rs560238	MS4A3	A	G	0.2997	0.283853	0.0350	2.70E-11
cg02776313	22	50965782	rs131805	TYMP	T	C	0.2165	0.8013	0.0457	5.47E-64
cg02780017	11	64981227	rs239258	SLC22A20	C	G	0.4715	0.687	0.0316	6.26E-100
cg02780210	17	37732690	rs200972378		I	NA	0.2584	0.3714	0.0476	3.06E-10
cg02780269	17	80292252	rs1132114	SECTM1	G	A	0.4431	0.362	0.0398	4.74E-16
cg02782510	3	160820084	rs9869430	B3GALNT1	A	C	0.02623	0.7692	0.1074	4.04E-08
cg02786012	4	57371589	rs199942666	ARL9	I	NA	0.317	0.4629	0.0457	2.02E-19
cg02787737	11	133928346	rs80235995		T	C	0.1133	0.5281	0.0682	5.04E-10
cg02797195	21	43185674	rs8126778	RIPK4	T	A	0.2824	0.4753	0.0470	2.62E-19
cg02812767	15	74218468	rs16958477	LOXL1	C	A	0.3895	0.5515	0.0360	3.57E-48
cg02818189	1	25173236	rs2185151		A	G	0.3253	0.4272	0.0381	1.75E-24
cg02826890	7	149319535	rs354051	ZNF767	C	G	0.3493	0.767386	0.0421	2.23E-69
			rs7801550	ZNF767	G	C	0.3477	0.236662	0.0423	1.11E-03
cg02838492	9	116861288	rs34721942	KIF12	T	A	0.183	0.785394	0.0456	1.17E-62
			rs72760628	KIF12	T	G	0.1479	0.428435	0.0502	7.47E-13
cg02840794	10	103825777	rs11191205	HPS6	A	G	0.1735	0.3409	0.0523	3.42E-06
cg02841155	5	128301328	rs2577539	SLC27A6	A	G	0.3873	0.7031	0.0359	1.04E-81
cg02845204	11	71259439	rs7940512	KRTAP5-9	C	T	0.4152	0.2452	0.0316	4.33E-10
cg02856338	8	101822108	rs7004284		A	G	0.3962	0.2913	0.0365	7.20E-11
cg02869364	7	1081709	rs2030959	C7orf50	T	C	0.4118	0.236438	0.0328	2.81E-08
			rs6951245	C7orf50	A	G	0.1496	0.630054	0.0455	5.64E-39
cg02871659	16	2014063	rs758335	SNHG9	A	G	0.1953	0.7859	0.0459	5.77E-61
cg02886591	17	45773570	rs4794052	TBKBP1	T	C	0.4096	0.3694	0.0409	8.94E-15
cg02890250	19	16243834	rs7250023	HSH2D	C	T	0.3287	0.365	0.0426	5.42E-13
cg02895669	4	81104762	rs6810403		C	T	0.495	0.6378	0.0359	4.29E-66
cg02902946	20	57617168	rs144360277	SLMO2	D	NA	0.02846	-1.366	0.1151	8.26E-28
cg02930200	1	38022384	rs4535966	DNALI1	C	T	0.4576	0.3343	0.0434	6.41E-10
cg02947253	1	112046700	rs12127443	ADORA3	T	A	0.2561	0.7893	0.0307	9.29E-141
cg02959759	12	2801584	rs11062335	CACNA1C	T	C	0.1356	0.5535	0.0600	1.45E-15
cg02962602	17	80171413	rs12946944	CCDC57	T	C	0.3359	0.4036	0.0374	1.79E-23
cg02962647	6	158655004	rs75187010		I	NA	0.3683	0.2393	0.0332	2.84E-08
cg02968508	3	9956698	rs201142544	IL17RE	D	NA	0.4621	0.2292	0.0313	1.25E-08
cg02983759	21	43098598	rs11273403	NCRNA00111	I	NA	0.389	0.25	0.0469	4.83E-03
cg02983950	1	38942220	rs1329818		C	T	0.2595	0.3836	0.0443	2.45E-13
cg02996131	6	152958598	rs62435218	SYNE1	T	C	0.1356	0.653221	0.0532	5.45E-30
			rs9322384	SYNE1	A	G	0.4453	0.625022	0.0354	5.84E-65
cg02998240	1	16508668	rs6677710		T	C	0.3689	0.6775	0.0345	2.87E-83
cg02999476	16	427684	rs3785289	TMEM8A	C	G	0.4414	0.301	0.0418	3.08E-08
cg03004599	9	114937770	rs4978476	SUSD1	C	T	0.2204	0.5198	0.0468	5.91E-24
cg03015498	10	7517765	rs113639463		I	NA	0.144	0.5879	0.0487	7.05E-29
cg03025569	17	15586426	rs11867308	TRIM16	C	T	0.05078	0.4241	0.0595	5.30E-08
cg03033176	11	65343929	rs143834068	EHBP1L1	A	G	0.01395	1.484	0.1613	1.80E-15
cg03043406	1	45242356	rs143095450	RPS8	D	NA	0.1462	0.3818	0.0529	2.57E-08
cg03051880	6	119662024	rs195075	MAN1A1	C	T	0.2517	0.3986	0.0419	8.73E-17
cg03054277	1	228400217	rs2298014	OBSCN	A	G	0.3616	0.3917	0.0388	2.93E-19
cg03062454	21	30362034	rs112167519	RNF160	C	T	0.09821	0.4936	0.0622	1.09E-10
cg03062881	21	47844012	rs9975345	PCNT	T	C	0.4794	0.2116	0.0339	2.12E-07
cg03099849	19	39755959	rs35790907		T	A	0.2818	0.5531	0.0408	4.17E-38
cg03120475	10	15411913	rs7915196	FAM171A1	C	T	0.2891	0.3629	0.0455	7.42E-11
cg03132729	1	21947437	rs55722102	RAP1GAP	C	T	0.1953	0.400558	0.0485	7.34E-12
			rs66871026	RAP1GAP	T	C	0.4219	0.267147	0.0362	7.68E-09
			rs710946	RAP1GAP	A	C	0.1769	0.628125	0.0488	2.78E-33
cg03144619	1	230415668	rs12058500	GALNT2	G	C	0.3025	0.347832	0.0427	1.76E-11
			rs3213495	GALNT2	A	G	0.12	0.382089	0.0613	2.22E-05
			rs9431818	GALNT2	C	T	0.4922	0.294532	0.0404	1.64E-08
			rs9432148	GALNT2	C	T	0.2366	0.309939	0.0482	6.33E-06
cg03152092	19	41869545	rs4803459	B9D2	T	C	0.2935	0.460942	0.0407	4.80E-25
			rs73931466	B9D2	G	A	0.08259	0.586422	0.0707	5.33E-12
cg03155159	16	59627519	rs12709032		T	C	0.2874	0.3736	0.0461	2.49E-11
cg03158561	11	8705959	rs7123653	RPL27A	C	A	0.4146	0.2396	0.0389	3.49E-05
cg03163525	10	2357283	rs10794903		C	G	0.2093	0.4848	0.0512	1.43E-16
cg03164928	16	89005932	rs1617734	CBFA2T3	C	G	0.3493	0.5493	0.0349	5.64E-51
cg03171770	10	43393728	rs1775062		T	C	0.4202	0.4375	0.0411	8.54E-23
cg03177666	16	54365103	rs4784362		T	A	0.2874	0.3367	0.0393	5.67E-14
cg03188382	2	233245886	rs144000513	ALPP	G	A	0.07533	0.4862	0.0777	1.91E-06
cg03192897	1	170115351	rs11360504	METTL11B	D	NA	0.3008	0.3295	0.0447	8.88E-09
cg03219657	11	64981125	rs239258	SLC22A20	C	G	0.4715	0.3763	0.0380	2.07E-18
cg03222009	2	129077232	rs12469358	HS6ST1	C	T	0.1652	0.5457	0.0571	6.57E-17
cg03229780	12	108238372	rs7957874		A	T	0.4548	0.2239	0.0403	1.38E-03
cg03233332	7	66118400	rs1615892		A	G	0.1233	0.631	0.0694	4.61E-15
cg03233656	2	65214625	rs10170033	SLC1A4	C	T	0.2623	0.8645	0.0374	1.02E-113
			rs6546118	SLC1A4	G	A	0.149	0.827635	0.0450	8.48E-71
cg03234777	11	118095544	rs1793185	AMICA1	A	C	0.2093	0.5539	0.0403	3.08E-38
cg03237218	17	33760527	rs772286	SLFN12	T	G	0.49	0.291375	0.0323	8.90E-16
			rs9893390	SLFN12	A	T	0.08817	0.608031	0.0553	2.24E-23
cg03262802	2	234118754	rs4663834		T	G	0.245	0.3415	0.0427	6.22E-11
cg03263730	1	7841722	rs697681		G	A	0.1328	0.5087	0.0569	1.86E-15
cg03273183	10	90761751	rs1159120	FAS	T	C	0.1222	0.3738	0.0565	1.91E-06
cg03292040	2	132286665	rs11666876	CCDC74A	C	A	0.01228	1.642	0.1778	1.27E-15
cg03295852	8	131308988	rs7008182	ASAP1IT1	T	A	0.4972	0.3308	0.0356	7.81E-16
cg03316864	19	17906309	rs117328795	B3GNT3	T	C	0.06529	0.503153	0.0806	2.16E-05
			rs34262244	B3GNT3	A	G	0.3108	0.284799	0.0435	2.81E-06
cg03332701	15	63793652	rs144268704		I	NA	0.3477	0.4769	0.0407	5.74E-27
cg03333699	7	966569	rs4722409	ADAP1	C	T	0.4079	0.4176	0.0380	2.00E-23
cg03345145	18	47341300	rs2956987	ACAA2	G	C	0.4637	0.3124	0.0393	1.01E-11
cg03345232	14	92981121	rs10147664	RIN3	A	G	0.3421	0.496663	0.0376	3.69E-35
			rs77826962	RIN3	G	A	0.1484	0.614515	0.0500	4.76E-30
cg03346521	4	7740503	rs12507674	SORCS2	T	C	0.1105	0.5385	0.0646	3.88E-12
cg03354707	19	41115390	rs11667772	LTBP4	G	A	0.375	0.475181	0.0417	2.23E-25
			rs12974270	LTBP4	T	C	0.1021	0.351545	0.0656	4.24E-03
cg03355526	5	178368415	rs111995800	ZNF454	I	NA	0.3326	0.4557	0.0395	4.99E-26

cg03366574	7	2764599	rs199654941		I	NA	0.2221	0.368388	0.0443	4.43E-12
			rs798539		A	G	0.1646	0.374678	0.0496	2.20E-09
cg03366850	7	28998595	rs1006521	TRIL	G	A	0.3292	0.649	0.0383	1.17E-59
cg03368358	17	3820044	rs11659011	P2RX1	A	G	0.4498	0.3442	0.0313	2.39E-23
cg03373393	17	39890193	rs8074419	HAP1	C	G	0.1758	0.552	0.0554	1.10E-18
cg03376308	10	3497811	rs56111506		A	G	0.2695	0.2499	0.0423	1.71E-04
cg03399898	1	148603739	rs114337666		A	G	0.03181	0.787296	0.1203	2.97E-06
			rs80314439		G	A	0.05915	0.517919	0.0907	5.56E-04
cg03400139	1	201619900	rs1267119	NAV1	T	C	0.07812	-120.357	0.0676	3.69E-66
			rs17428998	NAV1	A	G	0.4241	0.252477	0.0378	1.17E-06
cg03407228	22	18921705	rs2016118	PRODH	T	C	0.4381	0.3354	0.0376	2.38E-14
cg03407441	22	21310727	rs111493256		I	NA	0.2003	0.6066	0.0490	1.79E-30
cg03423767	13	114876390	rs11147312	RASA3	T	C	0.1484	0.946754	0.0438	5.24E-99
			rs9590436	RASA3	T	C	0.2288	0.685264	0.0376	1.27E-69
cg03437912	13	29232327	rs17087026	POMP	T	C	0.1546	0.4678	0.0524	2.14E-14
cg03440944	7	45023329	rs67396798	C7orf40	D	NA	0.159	0.2781	0.0509	2.32E-03
cg03449398	7	92673015	rs113289498		T	C	0.0692	1.198	0.0682	2.04E-64
cg03456213	9	97767954	rs143845824	C9orf3	I	NA	0.07254	0.5572	0.0729	1.03E-09
cg03466342	12	52753899	rs1791627	KRT85	A	T	0.4693	0.3222	0.0345	5.25E-16
cg03471047	15	51455849	rs57053639		D	NA	0.1713	0.6027	0.0516	9.15E-27
cg03475293	6	7051303	rs7772284		G	A	0.1423	0.6664	0.0553	1.06E-28
cg03477904	2	242040840	rs76534319	MTERFD2	A	G	0.1456	0.3386	0.0563	9.28E-05
cg03480383	16	89930147	rs11076633	SPIRE2	G	C	0.3114	0.2079	0.0355	2.38E-04
cg03480935	15	67417860	rs990986	SMAD3	G	A	0.3147	0.3273	0.0357	2.50E-15
cg03483626	1	111218276	rs6668335	KCNA3	C	G	0.1685	0.2986	0.0528	7.64E-04
cg03499581	15	78384868	rs12910083	SH2D7	T	C	0.04353	0.5695	0.0775	1.03E-08
cg03519967	1	26010346	rs3014710	MAN1C1	A	G	0.08984	0.5894	0.0615	4.75E-17
cg03528016	2	73871942	rs114029547	ALMS1P	A	G	0.1401	0.497006	0.0520	6.47E-18
			rs6740766	ALMS1P	G	A	0.2461	0.306977	0.0428	3.48E-08
cg03531326	19	39443344	rs9676853	FBXO17	T	G	0.1189	0.5551	0.0565	4.47E-18
cg03544771	X	38661483	rs198773	MID1IP1	G	A	0.2965	0.3611	0.0235	1.11E-48
cg03550773	14	35163458	rs11845203		G	A	0.2896	0.2107	0.0331	9.97E-06
cg03554335	17	62075151	rs3764868	C17orf72	A	G	0.3783	0.3203	0.0356	1.08E-14
cg03560586	2	239334908	rs35982899	ASB1	I	NA	0.4163	0.6838	0.0364	5.61E-74
cg03565777	12	125028339	rs4765577		G	C	0.4888	0.3743	0.0431	2.04E-13
cg03573529	5	177412586	rs4072924		C	T	0.428	0.3329	0.0351	1.20E-16
cg03589001	15	79164714	rs117776652	MORF4L1	T	C	0.04855	0.633457	0.0917	2.40E-07
			rs12911969	MORF4L1	C	T	0.1607	0.566525	0.0502	7.66E-25
cg03591238	11	64885558	rs10501396	ZNHIT2	A	C	0.2294	0.3687	0.0559	2.13E-07
cg03591499	3	16555620	rs1366700	RFTN1	C	T	0.3142	0.590001	0.0367	2.26E-53
			rs34240418	RFTN1	C	G	0.1004	0.709568	0.0594	3.23E-28
cg03594868	19	18234829	rs11666281	MAST3	T	C	0.2824	0.6648	0.0387	1.88E-61
cg03597525	19	51920435	rs34785289	SIGLEC10	G	A	0.1646	0.7398	0.0479	3.90E-49
cg03599037	10	82172508	rs151006313	C10orf58	A	G	0.0385	0.7116	0.1027	2.16E-08
cg03603530	16	69365009	rs8061352	PDF	A	T	0.2835	0.5785	0.0418	6.88E-39
cg03609435	17	34965792	rs76784277		C	T	0.4107	0.244	0.0371	2.28E-06
cg03609639	10	101291397	rs5787350	NKX2-3	I	NA	0.284	0.4841	0.0439	1.24E-23
cg03617683	16	85060908	rs904813	KIAA0513	A	G	0.2132	0.3942	0.0534	7.47E-09
cg03622666	16	49499091	rs2111568		C	G	0.2422	0.339118	0.0395	4.32E-13
			rs9928763		G	A	0.1155	105.364	0.0516	4.37E-88
cg03626278	9	98278383	rs28485705	PTCH1	G	C	0.2182	0.4467	0.0493	6.09E-15
cg03626672	2	237478664	rs7602374	CXCR7	T	C	0.07031	-1.212	0.0699	1.25E-62
cg03631078	3	114290368	rs11714846	ZBTB20	C	A	0.08594	0.7934	0.0635	4.36E-31
cg03631656	8	6420770	rs17063453	ANGPT2	C	A	0.07366	0.7006	0.0765	2.50E-15
cg03634479	10	18430412	rs72109948	CACNB2	D	NA	0.1356	0.749	0.0578	1.06E-34
cg03636183	19	17000585	rs773902	F2RL3	A	G	0.1864	0.322	0.0537	1.01E-05
cg03638795	11	416499	rs4076104	SIGIRR	A	G	0.1741	0.4391	0.0481	3.28E-15
cg03642518	8	28175003	rs73570753	PNOC	T	C	0.05804	1.228	0.0860	1.63E-41
cg03646605	11	86383804	rs10583492	ME3	D	NA	0.1161	0.3829	0.0688	1.34E-03
cg03650189	19	10405083	rs901886	ICAM5	C	T	0.4771	0.3667	0.0391	3.14E-17
cg03653399	8	142233436	rs10875467	SLC45A4	C	A	0.4046	0.531319	0.0438	4.05E-29
			rs4961341	SLC45A4	A	C	0.2712	0.281678	0.0483	2.81E-04
cg03662545	16	85254209	rs141538436		I	NA	0.01283	-1.791	0.1518	1.96E-27
cg03677069	10	88718317	rs7919325	SNCG	A	G	0.4325	0.5819	0.0351	6.79E-57
cg03680338	6	22043967	rs10440834	FLJ22536	T	C	0.07422	0.84904	0.0695	1.31E-29
			rs1736512	FLJ22536	G	A	0.4364	0.287719	0.0368	2.85E-11
cg03684807	22	46457384	rs56161057		D	NA	0.3739	0.6788	0.0385	8.15E-65
cg03693486	1	20914322	rs140348786	CDA	I	NA	0.3895	0.196868	0.0354	1.30E-03
			rs35463327	CDA	A	G	0.06529	0.447987	0.0687	3.48E-06
cg03704673	17	4692287	rs77362751	GLTPD2	C	A	0.4637	0.4144	0.0380	5.50E-23
cg03710029	17	79265601	rs10445406	SLC38A10	A	G	0.2098	0.550044	0.0330	1.03E-57
			rs12103824	SLC38A10	C	T	0.1256	0.227902	0.0420	2.83E-03
cg03720745	8	22561445	rs10112699		T	C	0.4559	0.32657	0.0506	5.46E-06
			rs12549847		A	G	0.4431	0.671063	0.0503	5.95E-36
cg03731740	1	29062689	rs4654370	YTHDF2	A	G	0.3912	0.3678	0.0412	2.32E-14
cg03737367	19	50005045	rs1316885	MIR150	C	T	0.1077	0.5047	0.0483	7.43E-21
cg03741458	2	200468445	rs12613262		T	C	0.1741	1.016	0.0451	1.60E-107
cg03759239	1	192626671	rs4147217	RGS13	A	C	0.4805	0.3742	0.0397	2.39E-17
cg03763518	1	150245044	rs138605093	C1orf54	A	G	0.02176	1.263	0.1446	1.23E-13
cg03766449	15	89920918	rs150294	LOC254559	G	A	0.3906	0.2241	0.0350	7.63E-06
cg03769383	12	41583367	rs143678681	PDZRN4	D	NA	0.3566	0.292	0.0436	1.02E-06
cg03776060	9	133972575	rs2478784	AIF1L	T	G	0.1981	0.256634	0.0462	1.43E-03
			rs353538	AIF1L	C	T	0.4794	0.734661	0.0367	1.49E-84
cg03780701	8	38965386	rs11985898	ADAM32	A	G	0.4615	0.7909	0.0340	9.00E-115
cg03785755	6	26196794	rs74660303		T	C	0.04688	0.7388	0.0870	1.06E-12
cg03789791	16	29166049	rs252283		A	C	0.1763	0.4788	0.0534	1.56E-14
cg03792876	16	73243	rs79269981		A	G	0.139	0.3491	0.0565	3.16E-05
cg03814093	4	154410006	rs2190690	KIAA0922	C	G	0.2567	0.4134	0.0369	2.02E-24
cg03826252	7	151095023	rs11761588	WDR86	T	C	0.2879	0.7235	0.0386	7.56E-74
cg03832522	2	218898668	rs1077362		T	C	0.4035	0.5834	0.0374	2.71E-50
cg03851835	11	107711742	rs580100	SLC35F2	T	G	0.1116	0.8504	0.0534	2.65E-52
cg03858448	13	20138965	rs9508194		G	A	0.2243	0.3636	0.0487	3.93E-09
cg03864215	11	17408437	rs5213	KCNJ11	C	T	0.356	0.4334	0.0420	2.56E-20
cg03871267	5	67483475	rs7703736		C	T	0.4129	0.362932	0.0405	1.63E-14
			rs7734077		G	A	0.07366	0.587992	0.0786	3.83E-09
cg03873281	5	131608955	rs270622	PDLIM4	C	T	0.09375	0.5949	0.0762	2.98E-10
cg03884592	1	42384474	rs4660585	HIVEP3	G	A	0.2779	0.274072	0.0480	5.71E-04
			rs783629	HIVEP3	C	T	0.4364	0.557009	0.0441	7.83E-33

cg03890167	1	203242638	rs2486935		C	G	0.4581	0.6754	0.0334	4.27E-86
cg03906843	3	151157436	rs7621142	IGSF10	T	G	0.3778	0.4726	0.0414	1.62E-25
cg03912703	1	45279349	rs11211037	BTBD19	C	A	0.3532	0.3009	0.0394	1.19E-09
cg03914735	3	140953689	rs6439984	ACPL2	A	C	0.2081	0.6313	0.0457	9.52E-39
cg03928546	19	15121591	rs60417800	CCDC105	A	G	0.2232	0.5466	0.0451	4.70E-29
cg03929796	3	52231840	rs230508	ALAS1	A	G	0.3359	0.2962	0.0401	7.69E-09
cg03962527	10	111766879	rs61881648	ADD3	A	G	0.1222	0.6347	0.0553	8.17E-27
cg03970900	1	222440048	rs11485169		T	C	0.3722	0.5759	0.0334	6.24E-62
cg03985801	1	202182603	rs12122827	LGR6	G	T	0.2634	0.3846	0.0460	3.32E-12
cg03987653	16	90024450	rs12597913	DEF8	G	A	0.06641	0.5516	0.0803	3.28E-07
cg03991871	5	368447	rs199905289	AHRR	D	NA	0.03069	-1.33	0.1244	5.44E-22
cg03994942	11	45943979	rs72902474	GYLTL1B	T	C	0.2188	0.3056	0.0487	1.78E-05
cg03995300	17	5019989	rs2585266	ZNF232	T	C	0.09654	0.455	0.0701	4.15E-06
cg03997139	2	11485552	rs10173492	ROCK2	G	A	0.1708	0.8221	0.0482	1.40E-60
cg04002235	11	128560443	rs2155132		T	C	0.2946	0.277743	0.0446	2.40E-05
			rs55635129		D	NA	0.3131	0.69621	0.0439	6.16E-53
cg04011173	3	10326540	rs35681	GHRLOS	T	C	0.4732	0.6394	0.0352	7.72E-69
cg04011995	1	41326317	rs17357593		A	C	0.1021	0.4212	0.0424	1.32E-18
cg04017131	8	6419570	rs10101475	ANGPT2	T	C	0.07254	0.601623	0.0730	8.21E-12
			rs10108504	ANGPT2	C	T	0.06864	0.80917	0.0739	3.27E-24
			rs2442626	ANGPT2	C	T	0.0519	0.728226	0.0821	3.68E-15
cg04019522	2	127852450	rs78908164	BIN1	T	G	0.05301	0.6735	0.0810	4.42E-12
cg04019636	1	201977390	rs2819360		T	C	0.4481	0.339	0.0359	1.83E-16
cg04023663	7	7031200	rs10011678		C	T	0.1244	0.5215	0.0526	1.74E-18
cg04031093	1	233027124	rs200168344		I	NA	0.1797	0.504371	0.0445	4.84E-25
			rs6424258		G	A	0.07533	0.611471	0.0653	3.69E-17
cg04036898	1	46664598	rs7521617	POMGNT1	T	C	0.3583	0.3073	0.0374	1.08E-11
cg04063345	6	152130058	rs3020341	ESR1	C	G	0.2874	0.4109	0.0446	1.44E-15
cg04064380	11	117688259	rs610226		G	C	0.3343	0.3156	0.0439	3.21E-08
cg04065210	7	35074628	rs9691668	DPY19L1	G	C	0.4821	0.2979	0.0392	1.57E-09
cg04071812	10	131926270	rs7026259		G	A	0.4414	0.2955	0.0388	1.31E-09
cg04077047	2	75361945	rs12713832	TACR1	C	T	0.486	0.5391	0.0409	5.32E-35
cg04078896	20	62338273	rs1048665	ZGPAT	G	T	0.2472	0.3479	0.0528	2.30E-06
cg04088152	1	6062462	rs531099		G	A	0.4983	0.247697	0.0358	2.29E-07
			rs58640305		T	C	0.1462	0.412413	0.0490	1.81E-12
cg04104776	17	3439336	rs401643	TRPV3	C	T	0.1373	0.4883	0.0556	7.56E-15
cg04111478	11	1991677	rs112493		A	G	0.3566	0.484	0.0409	1.10E-27
cg04115307	14	101539612	rs45496396		G	C	0.0385	0.589456	0.0938	1.67E-05
			rs5811024		D	NA	0.4554	0.544588	0.0360	7.12E-47
cg04120546	8	125740895	rs148014058	MTSS1	D	NA	0.09542	0.5902	0.0723	1.69E-11
cg04144533	1	206681983	rs72752997	RASSF5	G	A	0.3599	0.5574	0.0406	4.14E-38
cg04164838	19	14591148	rs2287699	GIPC1	A	G	0.1579	0.4867	0.0559	1.51E-13
cg04180046	7	45002736	rs6976664	MYO1G	T	C	0.2305	0.3912	0.0522	3.38E-09
cg04192740	5	171605778	rs3797326	STK10	C	T	0.3571	0.6526	0.0387	3.13E-59
cg04201373	6	33551533	rs530878	GGNBP1	G	A	0.2204	0.2782	0.0448	2.67E-05
cg04209460	17	4711018	rs10852865	PLD2	A	C	0.1669	0.9246	0.0442	2.16E-92
cg04220047	8	65714735	rs4471086		T	A	0.1814	0.3866	0.0548	8.85E-08
cg04220636	16	89034088	rs57706252	CBFA2T3	C	T	0.1423	0.6977	0.0502	3.12E-39
cg04220930	8	52814681	rs34677273		T	C	0.1763	0.461	0.0505	3.51E-15
cg04223006	5	82845599	rs3839293	VCAN	D	NA	0.2757	0.5086	0.0465	4.09E-23
cg04230060	9	114937992	rs12344169	SUSD1	C	T	0.2913	0.220098	0.0316	1.52E-07
			rs3849121	SUSD1	T	C	0.2199	-103.875	0.0339	1.00E-200
cg04232972	16	30671644	rs72793363		T	C	0.05357	0.6106	0.0879	1.85E-07
cg04233669	5	135173201	rs11738241	LOC153328	G	T	0.3968	0.438	0.0403	8.07E-23
cg04236263	1	17305798	rs4920588	MFAP2	C	T	0.1769	0.5021	0.0511	4.37E-18
cg04236329	5	443585	rs13356700	EXOC3	A	G	0.4621	0.2836	0.0360	1.77E-10
cg04236334	1	26487591	rs72666338	GRRP1	T	A	0.2963	0.5	0.0397	1.03E-32
cg04246864	16	33357426	rs1876006		T	G	0.4118	0.3791	0.0440	3.33E-13
cg04248512	12	133016503	rs4883600		T	C	0.07533	-1.105	0.0729	2.89E-47
cg04255391	8	145008397	rs113513807	PLEC1	A	G	0.02344	0.8656	0.0915	1.51E-16
			rs62522556	PLEC1	C	T	0.3839	0.920442	0.0284	1.00E-200
cg04259904	1	44399492	rs12127737	ARTN	G	A	0.2405	0.4319	0.0378	1.37E-25
cg04263702	7	5528266	rs4559154	FBXL18	G	T	0.317	0.6196	0.0416	1.50E-45
cg04277125	14	22309073	rs12879132		C	T	0.3906	0.6355	0.0359	3.08E-65
cg04287574	1	201619622	rs12725631	NAV1	T	C	0.4442	0.387618	0.0424	3.24E-15
			rs7364578	NAV1	A	G	0.2427	0.434535	0.0499	1.67E-13
cg04290171	1	207924482	rs2796259	CD46	G	T	0.4581	0.3051	0.0406	2.81E-09
cg04300115	20	62200199	rs310665	PRIC285	A	G	0.07868	0.6397	0.0797	5.04E-13
cg04307083	4	57521138	rs4324602	HOPX	C	G	0.4643	0.2816	0.0366	7.04E-10
cg04308185	17	38084377	rs35557848	ORMDL3	T	C	0.245	0.464887	0.0448	1.56E-20
			rs3744246	ORMDL3	T	C	0.2227	0.346335	0.0489	7.04E-09
cg04314261	12	10163030	rs61913541	CLEC12B	C	T	0.2812	0.284655	0.0477	1.21E-06
			rs6488242	CLEC12B	G	A	0.4621	0.352099	0.0457	6.91E-10
cg04316941	1	202224262	rs35703788	LGR6	D	NA	0.4955	0.2423	0.0380	9.06E-06
cg04321555	19	34285737	rs1139231		C	T	0.4018	0.7765	0.0359	7.86E-99
cg04328562	19	11649701	rs585790	CNN1	C	T	0.05022	0.955	0.0842	3.76E-25
cg04337534	11	65816809	rs2430978	GAL3ST3	C	G	0.486	0.2717	0.0372	1.43E-08
cg04343971	20	62570696	rs112813285		T	C	0.07701	0.558483	0.0796	1.12E-07
			rs145136929		A	G	0.06417	0.60504	0.0816	6.00E-09
			rs76766334		T	C	0.2003	0.390431	0.0541	2.63E-08
cg04361926	16	89070185	rs140355859		T	C	0.05859	0.558	0.0999	1.16E-03
cg04363470	11	7597814	rs72849046	PPFIBP2	A	C	0.03013	-1.597	0.0929	1.34E-61
cg04364261	2	219233650	rs28472297		G	C	0.394	0.2975	0.0301	2.49E-20
cg04392488	1	3644226	rs70940310	TP73	I	NA	0.3192	0.541	0.0443	1.31E-29
cg04392554	22	46685472	rs9615933	TTC38	A	G	0.09933	0.9324	0.0496	5.15E-74
cg04396998	19	49376722	rs564196	PPP1R15A	A	G	0.1367	0.7165	0.0606	1.41E-28
cg04404772	19	46876609	rs1024782	PPP5C	T	C	0.2785	0.2807	0.0334	2.05E-12
cg04411044	1	36191660	rs11264194		T	C	0.06473	0.78452	0.0734	5.99E-22
			rs75639682		C	T	0.05636	0.656131	0.0807	2.09E-12
cg04423209	2	85663660	rs6729475	SH2D6	A	C	0.2366	0.3181	0.0401	1.03E-10
cg04447128	16	74771998	rs4999690	FA2H	A	G	0.3281	0.4752	0.0374	2.71E-32
cg04456238	11	32450104	rs12293603	WT1	A	C	0.2065	0.4064	0.0549	6.46E-10
cg04460372	9	130661175	rs73602391	ST6GALNAC6	A	G	0.0452	0.8229	0.1106	5.13E-09
cg04472726	8	41386353	rs117086399	GINS4	G	C	0.1155	0.336079	0.0590	5.96E-04
			rs1559739	GINS4	G	A	0.3996	0.442333	0.0385	6.95E-26
cg04473569	7	100881007	rs10230349	CLDN15	C	T	0.0519	0.7313	0.0830	6.30E-15
cg04477962	12	51317375	rs2111958	METTL7A	A	G	0.3588	0.2463	0.0407	7.00E-05
cg04494136	10	126703576	rs11245468	CTBP2	C	T	0.02288	104.845	0.1230	7.94E-13

			rs117854848	CTBP2	G	A	0.02344	103.196	0.1222	1.54E-12
			rs4962722	CTBP2	T	A	0.3694	0.426329	0.0393	1.11E-22
cg04498198	17	27899966	rs497993	TP53I13	T	C	0.2969	0.6585	0.0407	3.83E-54
cg04503968	5	122423530	rs4262105	PRDM6	G	A	0.3555	0.3101	0.0454	4.26E-07
cg04506190	3	129323941	rs140808581	PLXND1	D	NA	0.3248	0.3807	0.0447	8.62E-13
cg04508951	1	193456140	rs79987731		C	T	0.03237	0.9759	0.1139	5.17E-13
cg04516112	3	124303404	rs6771416	KALRN	A	G	0.4782	0.3697	0.0361	5.73E-20
cg04517524	14	94405342	rs2180085	ASB2	T	C	0.1579	0.4573	0.0598	1.03E-10
cg04534765	18	74962369	rs2850889	GALR1	C	T	0.4548	0.3623	0.0416	1.41E-13
cg04545296	12	48745243	rs2468943	ZNF641	G	T	0.3281	0.4926	0.0412	2.93E-28
cg04545963	14	35872393	rs12435366	NFKBIA	T	C	0.2316	0.6076	0.0335	1.30E-68
cg04552852	11	844390	rs200031456	TSPAN4	D	NA	0.4682	0.3262	0.0365	2.11E-14
cg04566512	22	46457588	rs56161057		D	NA	0.3739	0.6476	0.0403	1.77E-53
cg04569233	3	39321449	rs13062158	CX3CR1	C	T	0.2712	0.3104	0.0441	9.65E-08
cg04599946	16	85936480	rs144009594	IRF8	I	NA	0.4425	0.2457	0.0414	1.49E-05
cg04602696	16	88846723	rs9933309	FAM38A	T	C	0.3125	0.9455	0.0346	3.81E-160
cg04614290	19	2327696	rs148145895	LSM7	D	NA	0.4107	0.7196	0.0343	5.23E-94
cg04630273	20	62406879	rs4809229	ZBTB46	C	T	0.1328	0.3901	0.0664	2.07E-06
cg04632887	20	3065559	rs2740191	AVP	T	C	0.1529	0.4883	0.0512	7.65E-17
cg04636402	5	139284774	rs35316811	NRG2	A	G	0.1529	0.5541	0.0490	6.78E-25
cg04666465	16	23520563	rs2040574	GGA2	A	G	0.1501	-1.028	0.0458	9.18E-107
cg04667538	2	105372176	rs365389		T	G	0.3767	0.5307	0.0382	4.40E-39
cg04671541	3	111717682	rs41270435	TAGLN3	T	G	0.07422	-1.148	0.0702	2.18E-55
cg04675251	7	6702706	rs56281415		G	A	0.08371	0.4903	0.0813	8.04E-05
cg04677123	5	90466501	rs4537089		C	T	0.1663	0.5692	0.0424	2.31E-36
cg04677158	5	78279841	rs62377912	ARSB	G	A	0.1886	0.9413	0.0415	4.63E-109
cg04678936	15	43802612	rs2584727	TP53BP1	C	T	0.361	0.265879	0.0407	3.06E-06
			rs28628574	TP53BP1	C	A	0.12	0.474425	0.0604	1.90E-11
cg04685387	10	34925640	rs12416511	PARD3	C	T	0.1585	0.437	0.0558	2.33E-10
cg04703696	9	136036629	rs111381411	GBGT1	D	NA	0.1892	0.7028	0.0500	3.72E-40
cg04707715	5	148785250	rs353298	LOC728264	G	A	0.4018	0.2756	0.0404	4.52E-07
cg04718447	16	85518989	rs7200732		T	C	0.356	0.3645	0.0416	9.72E-14
cg04726446	2	26624865	rs34436433	C2orf39	G	T	0.3488	0.337	0.0425	1.15E-10
cg04754011	11	60623144	rs3862662	GPR44	T	A	0.26	0.303052	0.0436	1.72E-07
			rs4939469	GPR44	G	A	0.1066	0.603108	0.0592	1.05E-19
cg04788957	10	105438008	rs10786773	SH3PXD2A	T	A	0.3465	0.3272	0.0394	4.64E-12
cg04806562	17	80316908	rs79159073	TEX19	G	A	0.04855	0.7728	0.0847	3.61E-15
cg04816394	5	80529067	rs750728	RNU5E	T	C	0.2785	0.4509	0.0430	5.35E-21
cg04829830	14	105339549	rs28460540	KIAA0284	G	C	0.4654	0.679	0.0373	2.53E-69
cg04848349	1	117882838	rs1418452		T	G	0.1283	0.6991	0.0632	8.80E-24
cg04852348	6	170463167	rs12526455		T	C	0.293	0.39727	0.0451	6.45E-14
			rs3012407		G	A	0.4537	0.323029	0.0415	3.32E-10
cg04860432	14	52783454	rs1390376	PTGER2	C	T	0.1641	0.323231	0.0549	1.96E-04
			rs80066383	PTGER2	C	G	0.08482	0.477774	0.0747	8.16E-06
cg04864179	7	128579964	rs113478424	IRF5	D	NA	0.4342	0.350454	0.0286	6.19E-30
			rs11767834	IRF5	T	C	0.02344	0.797721	0.0941	1.17E-13
cg04889800	1	16163555	rs10803401	FLJ37453	A	G	0.3281	0.227687	0.0401	6.63E-04
			rs12738340	FLJ37453	C	A	0.106	0.763514	0.0602	3.62E-32
cg04890576	17	73032613	rs113682539		T	C	0.05246	0.712	0.0891	6.57E-11
cg04905201	16	89119709	rs11862059		T	C	0.106	0.5051	0.0705	4.01E-08
cg04907151	3	135684161	rs9289502	PPP2R3A	A	G	0.3231	0.42	0.0440	7.43E-17
cg04907244	7	22894795	rs11983782	SNORD93	G	C	0.4738	0.5135	0.0382	1.48E-36
cg04910877	16	88988235	rs57920860	CBFA2T3	A	C	0.3527	0.3811	0.0400	8.39E-17
cg04928670	2	89128459	rs17038731		C	T	0.3823	0.3188	0.0384	4.95E-12
cg04956306	22	50700563	rs9617126	MAPK12	T	C	0.3265	0.4727	0.0338	7.22E-40
cg04961911	9	35079141	rs2252749	FANCG	T	C	0.2573	0.5273	0.0453	1.47E-26
cg04972979	20	749148	rs6117544	C20orf54	A	G	0.1529	0.4498	0.0563	6.56E-12
cg04986591	17	41723953	rs12451525	MEOX1	C	T	0.428	0.4709	0.0377	3.47E-31
cg04990372	20	47895899	rs237738	SNORD12B	T	C	0.1791	0.3554	0.0440	3.28E-11
cg05005217	8	25317638	rs11775241	CDCA2	A	G	0.3354	0.5104	0.0434	3.30E-27
cg05022105	11	32460980	rs7943101	WIT1	T	C	0.1842	0.5537	0.0512	1.41E-22
cg05044291	1	202172867	rs12122827	LGR6	G	T	0.2634	1.023	0.0352	1.78E-181
cg05053979	14	89681043	rs7146342	FOXN3	T	C	0.2204	0.3697	0.0520	6.02E-08
cg05057834	3	37495654	rs17227306	ITGA9	T	C	0.1317	0.8298	0.0509	3.84E-55
cg05085585	16	30420623	rs12921440	ZNF771	C	T	0.3956	0.5365	0.0403	9.84E-36
cg05098037	17	78753327	rs35926934	RPTOR	A	G	0.1127	0.5336	0.0491	9.03E-23
cg05105913	17	48422990	rs12450449	XYLT2	C	A	0.2584	0.5951	0.0423	2.79E-40
cg05111603	4	38213171	rs11096936		G	A	0.4799	0.50594	0.0407	7.93E-31
			rs11730174		A	C	0.3499	0.273492	0.0433	1.40E-05
cg05122453	9	130532879	rs10760499	SH2D3C	C	G	0.3504	0.3837	0.0424	6.61E-15
cg05129050	1	7178026	rs9434845	CAMTA1	C	T	0.399	0.3131	0.0388	3.53E-11
cg05136169	20	3065473	rs2740191	AVP	T	C	0.1529	0.4689	0.0523	1.63E-14
cg05136804	18	32849113	rs62096498	ZNF397OS	C	G	0.04743	1.003	0.0781	4.56E-33
cg05147525	12	6717762	rs7134035	CHD4	C	T	0.1685	0.5224	0.0479	5.91E-25
cg05155319	4	109355164	rs28488539		A	G	0.332	0.2917	0.0304	4.62E-17
cg05157251	18	57566460	rs4349252	PMAIP1	A	C	0.3544	0.498985	0.0430	1.73E-26
			rs62094888	PMAIP1	A	G	0.1177	0.397131	0.0648	4.50E-05
cg05157625	14	93153553	rs7159005	RIN3	A	G	0.3477	1	0.0314	1.00E-200
cg05162032	7	6310773	rs7791225	CYTH3	G	A	0.08929	0.3786	0.0667	7.04E-04
cg05163057	19	2329403	rs3795039	SPPL2B	C	G	0.4068	0.4384	0.0377	1.48E-26
cg05168580	14	103572194	rs1052823	C14orf73	T	G	0.0971	0.517	0.0640	3.39E-11
cg05173758	13	27335096	rs7990675	GPR12	T	G	0.2969	0.5588	0.0398	4.53E-40
cg05176958	8	142316435	rs12677618		T	C	0.2533	0.3248	0.0409	9.31E-11
cg05183538	16	88536950	rs36024491	ZFPM1	T	C	0.3041	0.2766	0.0389	5.46E-09
cg05190516	X	99891595	rs8780	TSPAN6	C	G	0.34	0.2756	0.0250	1.34E-23
cg05204104	2	235403141	rs1464264	ARL4C	G	A	0.4358	0.257875	0.0344	3.42E-10
			rs28621759	ARL4C	G	A	0.4565	0.263355	0.0342	6.94E-10
cg05209515	22	37585549	rs229527	C1QTNF6	A	C	0.4319	0.4068	0.0421	2.16E-17
cg05214460	10	111766841	rs6584970	ADD3	C	T	0.1244	0.5974	0.0551	9.98E-23
cg05236720	2	37893255	rs35100295	CDC42EP3	A	G	0.05804	0.477711	0.0746	7.67E-06
			rs6544098	CDC42EP3	T	C	0.4565	0.258875	0.0337	8.36E-10
cg05247391	8	71581649	rs6998397	XKR9	G	A	0.4866	0.3108	0.0410	1.62E-09
cg05265359	11	45943572	rs11038709	GYLTL1B	C	T	0.2952	0.4491	0.0447	5.03E-19
cg05266212	17	45822969	rs11657479	TBX21	C	T	0.2366	1.061	0.0331	1.00E-200
cg05267427	4	146831054	rs12510175	ZNF827	G	C	0.361	0.7918	0.0341	6.67E-115
cg05272587	13	111038400	rs55940034	COL4A2	G	A	0.2946	0.353789	0.0538	2.32E-06
			rs9515199	COL4A2	C	T	0.3867	-108.154	0.0492	2.22E-102
cg05301188	2	10184457	rs4669520	KLF11	A	G	0.221	0.517905	0.0492	2.95E-21

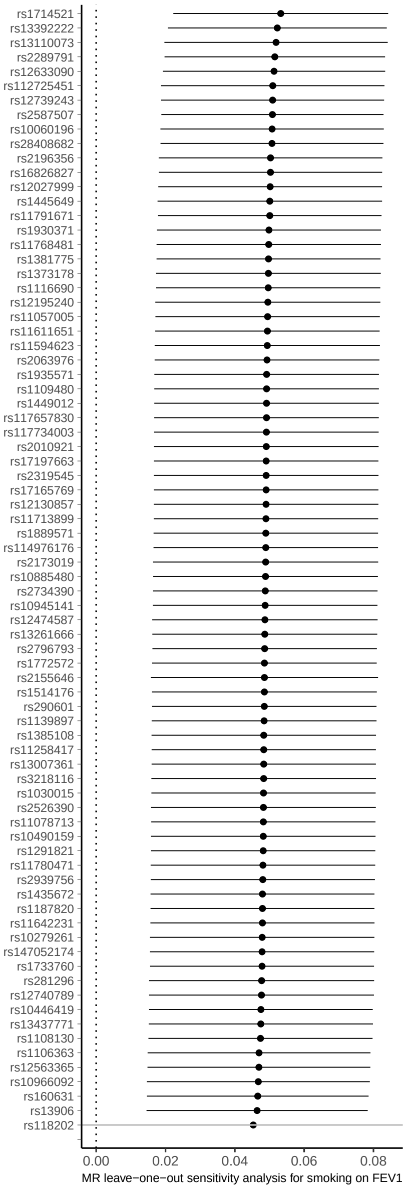
			rs6747078	KLF11	G	A	0.2494	0.296943	0.0470	1.29E-05
cg05306310	21	43186286	rs77007684	RIPK4	C	T	0.2215	0.4585	0.0504	4.71E-15
cg05308656	2	235406291	rs34613023	ARL4C	G	C	0.2517	0.379676	0.0491	5.22E-10
			rs6731739	ARL4C	A	G	0.08259	0.525089	0.0765	3.27E-08
cg05310240	17	47979069	rs271681		G	A	0.4219	0.357899	0.0466	7.98E-10
			rs56065835		G	T	0.2333	0.319836	0.0570	1.03E-03
cg05310309	2	109257429	rs201355324	LIMS1	I	NA	0.4342	0.4522	0.0387	9.03E-27
cg05331807	7	157224035	rs12698057		A	G	0.4782	0.2891	0.0412	1.14E-07
cg05335186	13	53173507	rs61958074		G	C	0.05636	0.30634	0.0514	1.28E-04
			rs9526950		A	C	0.3638	0.580008	0.0241	2.99E-123
cg05357209	7	872208	rs4721600	UNC84A	T	C	0.159	0.9283	0.0413	3.41E-107
cg05368038	15	31621727	rs4779516	KLF13	C	T	0.4665	0.3129	0.0341	2.18E-16
cg05379350	17	27917157	rs55644350	GIT1	T	C	0.4074	0.3774	0.0390	2.12E-18
cg05389183	5	122372942	rs10061195	PPIC	C	A	0.1373	0.49559	0.0593	3.27E-12
			rs7723798	PPIC	C	G	0.3237	0.246338	0.0440	1.07E-03
cg05403689	12	89748932	rs10506971		G	A	0.4503	0.6645	0.0370	2.26E-67
cg05407003	7	23246146	rs7808488		C	T	0.3839	0.668351	0.0380	2.23E-64
			rs858254		C	G	0.0385	0.629374	0.0933	7.78E-07
cg05423018	7	36193854	rs199728313	EEPD1	I	NA	0.1607	0.4686	0.0523	1.52E-14
cg05462761	1	6545157	rs12733111	PLEKHG5	G	A	0.135	0.349574	0.0579	7.76E-05
			rs3007430	PLEKHG5	C	A	0.1133	0.522019	0.0617	1.30E-12
cg05468303	22	18894389	rs372055	DGCR6	G	A	0.2042	0.3934	0.0478	8.91E-12
cg05471495	2	101369330	rs13026445		C	G	0.4632	0.386	0.0388	1.22E-18
cg05482864	3	32799602	rs6550155	CNOT10	G	A	0.2137	0.3051	0.0409	4.55E-09
cg05483076	5	74347539	rs6895821		T	C	0.2628	0.6382	0.0404	2.02E-51
cg05508558	1	207627372	rs61821106	CR2	A	C	0.1155	0.3272	0.0577	6.92E-05
cg05512100	7	32109997	rs11770184	PDE1C	C	T	0.08371	0.524569	0.0791	1.62E-06
			rs199708405	PDE1C	D	NA	0.4135	0.387932	0.0361	2.72E-22
			rs715454	PDE1C	T	C	0.2054	0.565227	0.0530	7.56E-22
cg05514971	9	130329588	rs2249452	FAM129B	C	T	0.2991	0.27527	0.0461	1.20E-05
			rs2249453	FAM129B	C	G	0.4704	0.536142	0.0409	1.30E-34
cg05516537	13	114239958	rs201010335	TFDP1	D	NA	0.3465	0.3945	0.0420	2.66E-16
cg05517541	6	112115209	rs9481189	FYN	C	T	0.1239	0.9878	0.0524	1.90E-74
cg05529343	3	22412124	rs12638680		C	T	0.2863	0.6004	0.0374	2.02E-53
cg05533340	11	20496110	rs10833332	PRMT3	A	G	0.4247	0.3182	0.0403	1.34E-10
cg05542681	16	744328	rs9921161	FBXL16	G	A	0.2271	0.5301	0.0473	1.69E-24
cg05547853	5	180236251	rs59424661	MGAT1	G	T	0.08482	0.7943	0.0521	1.03E-47
cg05560472	X	99986046	rs73557596	SYTL4	A	G	0.02507	0.8764	0.0873	5.32E-19
cg05564831	3	52568323	rs7614981	NT5DC2	C	A	0.4704	0.6578	0.0387	2.96E-60
cg05584950	2	86012847	rs750443	ATOH8	A	G	0.2467	0.5506	0.0423	4.79E-35
cg05586607	11	1965447	rs217252		T	C	0.1429	0.6344	0.0526	7.72E-29
cg05589489	12	89748821	rs3990314		C	T	0.4475	0.737	0.0356	1.58E-90
cg05593667	6	35490744	rs7755718		G	A	0.04576	-1.146	0.0868	4.07E-35
cg05599106	19	12251511	rs3760779	ZNF20	T	C	0.1211	0.7318	0.0636	6.41E-26
cg05612654	6	2375895	rs150684632		A	G	0.01172	-1.359	0.1661	1.37E-12
cg05620288	2	129076914	rs13385412	HS6ST1	T	C	0.1161	0.438719	0.0579	1.74E-09
			rs61732881	HS6ST1	T	C	0.4453	0.33604	0.0377	2.54E-14
			rs66708634	HS6ST1	D	NA	0.08817	0.566505	0.0631	1.38E-14
cg05624954	5	179340170	rs26074		T	C	0.3806	0.3211	0.0379	1.11E-12
cg05661533	5	1495043	rs1971941	LPCAT1	T	G	0.2015	0.279	0.0399	1.39E-07
cg05662829	1	787423	rs115485097	LOC643837	A	C	0.03013	1.016	0.1267	5.43E-12
cg05682333	2	233274291	rs72617176	ALPPL2	A	G	0.07143	0.8364	0.0564	4.77E-45
cg05695937	1	201618003	rs11587986	NAV1	G	A	0.4252	0.496567	0.0434	1.37E-25
			rs71635553	NAV1	C	A	0.2383	0.319136	0.0515	2.91E-05
cg05697274	1	230415377	rs2273968	GALNT2	C	T	0.1066	0.537242	0.0676	9.20E-11
			rs9793529	GALNT2	A	G	0.1942	0.32571	0.0520	1.82E-05
cg05705813	11	86383809	rs10583492	ME3	D	NA	0.1161	0.4451	0.0667	1.29E-06
cg05709437	1	186426136	rs12754662	PDC	A	G	0.1367	0.4685	0.0650	2.96E-08
cg05711037	2	234359783	rs73117559	DGKD	A	C	0.09598	0.464	0.0704	2.16E-06
cg05719818	4	8106273	rs4696758	ABLIM2	G	A	0.4604	0.5319	0.0409	6.66E-34
cg05720226	7	116786597	rs56680066	ST7	A	G	0.1412	0.3635	0.0449	2.73E-11
cg05724492	16	979662	rs111820009	LMF1	C	G	0.1373	0.7646	0.0604	5.25E-32
cg05779990	3	128292593	rs2734047	C3orf27	A	G	0.3739	0.2944	0.0390	2.33E-09
cg05795313	12	48745136	rs7134565	ZNF641	A	T	0.4604	0.2558	0.0326	2.04E-10
cg05805236	11	65401703	rs10896026	PCNXL3	T	C	0.3521	0.981	0.0329	2.68E-190
cg05830220	16	87757033	rs12933978	KLHDC4	T	C	0.1596	0.487609	0.0549	3.15E-15
			rs13330114	KLHDC4	T	C	0.4671	0.267272	0.0488	2.15E-03
			rs13339331	KLHDC4	A	G	0.2751	0.285817	0.0511	1.09E-03
cg05858126	10	104196213	rs149003255	MIR146B	G	A	0.0279	0.8788	0.1348	3.59E-06
cg05877104	6	167507447	rs150111		T	C	0.05413	0.6696	0.0875	9.81E-10
cg05877788	17	27899874	rs497993	TP53I13	T	C	0.2969	0.6374	0.0373	1.00E-60
cg05878630	15	91474889	rs10048033	HDDC3	G	C	0.2751	0.757	0.0466	1.39E-55
cg05879418	5	54455955	rs78240897	CDC20B	T	G	0.1339	0.5254	0.0604	1.67E-15
cg05886626	15	39873553	rs45461294	THBS1	A	G	0.1708	0.3531	0.0498	6.61E-08
cg05903720	14	104663241	rs72198203		D	NA	0.09989	0.8233	0.0651	5.69E-32
cg05908442	15	77800637	rs2055902		G	A	0.1021	0.5918	0.0617	4.36E-19
cg05914034	7	5528179	rs4559154	FBXL18	G	T	0.317	0.5081	0.0428	9.69E-28
cg05923226	19	15121516	rs60417800	CCDC105	A	G	0.2232	0.6301	0.0463	1.56E-37
cg05951221	2	233284402	rs2245452		C	T	0.4007	0.264567	0.0440	9.02E-05
			rs58457058		A	C	0.0731	0.496608	0.0836	1.41E-04
cg05955436	20	17660838	rs3790315	RRBP1	C	T	0.418	0.4453	0.0351	4.24E-32
cg05958910	10	21796441	rs200627011		D	NA	0.008929	-1.516	0.2117	3.96E-08
cg05962511	10	102730022	rs10883565		C	T	0.1992	0.4934	0.0534	1.32E-15
cg05965387	13	51418053	rs59551851	DLEU7	A	G	0.04855	0.5486	0.0940	2.64E-04
cg05976753	8	29205988	rs57393868	DUSP4	G	A	0.2338	0.5344	0.0468	1.54E-27
cg05987787	6	158448508	rs7776378	SYNJ2	T	C	0.495	0.3653	0.0408	1.86E-14
cg05999189	20	18545071	rs6136430		T	A	0.3717	0.5067	0.0422	1.62E-28
cg06002516	12	57666521	rs11172211	R3HDM2	G	C	0.5	0.232663	0.0375	2.74E-05
			rs60651196	R3HDM2	A	T	0.02846	0.808248	0.1156	1.34E-07
cg06008724	22	45403507	rs4823435	PHF21B	T	C	0.3326	0.4756	0.0383	1.22E-30
cg06009448	7	1102226	rs77868187	C7orf50	C	A	0.1468	0.7733	0.0513	1.06E-46
cg06010163	6	156885985	rs79713442		C	T	0.1323	0.3868	0.0639	7.21E-05
cg06011067	6	110677913	rs4445085	C6orf186	T	A	0.4353	0.203637	0.0368	1.61E-03
			rs6939019	C6orf186	G	A	0.4911	0.337714	0.0368	2.16E-15
			rs756487	C6orf186	C	T	0.2165	0.342179	0.0458	4.17E-09
			rs7738520	C6orf186	A	C	0.2734	0.353189	0.0396	2.60E-14
cg06023570	2	7058545	rs28649623	RNF144A	A	C	0.2606	0.474269	0.0470	3.06E-19
			rs56941243	RNF144A	T	A	0.2556	0.28338	0.0472	9.70E-05

cg06024215	17	75210996	rs13334205	SEC14L1	G	A	0.1306	0.4481	0.0546	1.13E-12
cg06033254	16	66613355	rs138122225	CMTM2	C	T	0.03181	1.543	0.0988	2.52E-50
cg06065019	2	177356276	rs72922974		A	G	0.1032	0.9655	0.0527	3.51E-70
cg06088623	19	8274890	rs7258249	LASS4	G	A	0.4978	0.3967	0.0380	7.30E-22
cg06090684	12	101672472	rs1304615	UTP20	G	A	0.3722	0.367201	0.0413	2.76E-14
			rs703721	UTP20	T	C	0.3555	0.495449	0.0439	6.80E-25
cg06099431	20	44451667	rs380973		A	G	0.3432	0.4143	0.0459	8.54E-15
cg06100161	15	60987894	rs8042370	RORA	T	C	0.236	0.6301	0.0375	8.42E-59
cg06128881	X	46616842	rs5906273	SLC9A7	T	C	0.2994	0.2669	0.0242	1.39E-23
cg06152215	12	124422259	rs35794481	CCDC92	A	G	0.04855	0.5995	0.0852	9.75E-08
cg06155229	7	102937535	rs75341923	PMPCB	G	A	0.04576	-1.615	0.0880	1.42E-70
cg06166490	7	27143334	rs1725074	HOXA2	T	C	0.1356	0.5779	0.0600	2.82E-17
cg06167719	21	38362727	rs1892915	HLCS	T	C	0.2227	0.337323	0.0472	4.48E-08
			rs2187102	HLCS	A	G	0.2935	0.650828	0.0369	5.32E-65
			rs28593435	HLCS	C	T	0.3878	0.247257	0.0401	3.51E-05
cg06177555	16	29678624	rs11150562	SPN	G	T	0.06362	0.5878	0.0726	2.95E-11
cg06179486	20	36148320	rs2425348	BLCAP	C	G	0.2243	0.3663	0.0468	2.65E-10
cg06193043	1	11908199	rs198361	NPPA	C	T	0.1205	-1.122	0.0495	3.85E-109
cg06196801	12	121164025	rs35525135	ACADS	C	T	0.2467	0.336107	0.0592	7.01E-04
			rs695948	ACADS	G	A	0.4302	0.311512	0.0511	5.56E-05
cg06197751	3	153912866	rs449292	SGEF	G	A	0.361	0.3286	0.0394	4.05E-13
cg06208288	1	58858074	rs12118488		A	C	0.1797	0.558087	0.0304	1.21E-70
			rs338928		C	T	0.481	0.234206	0.0247	1.12E-16
cg06219995	1	16374768	rs9659483	CLCNKB	A	C	0.3186	0.3126	0.0366	6.56E-13
cg06230839	21	43189892	rs36230813		D	NA	0.3951	0.3388	0.0415	1.58E-11
cg06238004	17	42029727	rs162430		A	G	0.08761	0.688647	0.0722	6.99E-17
			rs1731890		T	C	0.3142	0.366455	0.0435	1.69E-12
			rs72540152		I	NA	0.3393	0.289295	0.0386	3.52E-09
cg06240690	2	158114069	rs11899353	GALNT5	A	T	0.1055	0.3958	0.0682	3.33E-04
cg06261052	10	13545875	rs11258422	BEND7	C	A	0.3365	0.3436	0.0376	3.14E-15
cg06270615	17	40516068	rs8069645	STAT3	G	A	0.2757	0.8298	0.0403	2.01E-89
cg06279471	11	67806118	rs4147780	TCIRG1	G	A	0.4961	0.4868	0.0387	1.24E-31
cg06283478	4	7649606	rs34846328	SORCS2	T	C	0.2773	0.4295	0.0425	2.67E-19
cg06320277	2	105980029	rs62155873	FHL2	T	C	0.1345	0.9167	0.0491	4.67E-73
cg06321596	16	17562960	rs11647637	XYLT1	G	T	0.4665	0.3576	0.0431	5.39E-12
cg06329491	17	49031751	rs7212757		T	C	0.3756	0.3944	0.0420	3.17E-16
cg06334495	16	1020046	rs2729595	LMF1	A	G	0.3047	0.392501	0.0475	6.92E-12
			rs72769435	LMF1	G	C	0.1166	0.651244	0.0713	3.41E-15
cg06355422	22	50013649	rs135872	C22orf34	T	C	0.2667	0.8308	0.0371	2.41E-106
cg06357748	12	1025529	rs4766370	RAD52	T	A	0.4621	0.4292	0.0395	8.28E-23
cg06360427	18	74962672	rs11662010	GALR1	G	A	0.4531	0.255226	0.0476	4.23E-03
			rs2850909	GALR1	T	C	0.3778	0.48963	0.0481	1.26E-19
cg06362313	12	6645287	rs7978461	GAPDH	T	C	0.4866	0.2308	0.0422	2.30E-03
cg06382664	11	73098877	rs7115605	RELT	T	C	0.221	0.4167	0.0440	1.37E-17
cg06393589	16	84581885	rs2013838		T	C	0.07533	0.552449	0.0839	2.28E-06
			rs4782636		T	A	0.1881	0.354179	0.0593	1.15E-04
			rs6564059		T	G	0.4213	0.390059	0.0418	5.70E-16
cg06394247	9	36986788	rs3174276	PAX5	T	C	0.2472	0.3804	0.0476	6.72E-11
cg06395298	17	46651225	rs9905793	HOXB3	A	G	0.08259	0.7903	0.0715	1.08E-23
cg06400428	10	102107666	rs201238033	SCD	I	NA	0.404	0.3175	0.0415	1.07E-09
cg06401979	7	27143717	rs11564055	HOXA2	G	A	0.1016	0.5726	0.0675	1.15E-12
cg06407111	17	73872650	rs4600514	TRIM47	A	G	0.1501	0.5687	0.0528	2.46E-22
cg06417962	11	507970	rs7983	RNH1	C	G	0.317	0.6846	0.0418	1.62E-55
cg06418475	19	17008851	rs2608732	CPAMD8	G	C	0.4704	0.5775	0.0384	2.00E-46
cg06432655	19	36523405	rs141529354	CLIP3	I	NA	0.1161	0.4982	0.0562	3.71E-14
cg06433467	5	67730071	rs16897819		G	T	0.07422	0.7576	0.0710	7.56E-22
cg06435765	18	596713	rs12957470	CLUL1	C	G	0.298	0.301475	0.0484	2.34E-06
			rs7244330	CLUL1	T	C	0.2712	0.310409	0.0504	3.65E-05
cg06449334	20	17593441	rs1132274		A	C	0.1501	0.3962	0.0507	2.91E-10
cg06458086	6	131162400	rs146810684	EPB41L2	D	NA	0.1451	0.3933	0.0540	1.67E-08
cg06459104	18	5456880	rs112527405	EPB41L3	C	A	0.02846	104.454	0.1154	6.99E-15
			rs12962743	EPB41L3	T	G	0.3644	0.472312	0.0414	1.63E-26
			rs1965652	EPB41L3	A	G	0.269	0.329763	0.0458	2.87E-08
cg06478823	16	20774873	rs34869903	ACSM3	D	NA	0.1334	0.8341	0.0608	4.42E-38
cg06484000	19	46998383	rs11670534	PNMAL2	T	C	0.173	0.758919	0.0552	2.22E-38
			rs12974870	PNMAL2	A	G	0.3571	0.358547	0.0441	2.29E-11
cg06484123	19	53107200	rs61486719		C	A	0.1116	0.4722	0.0526	1.40E-14
cg06490839	18	24240815	rs34134107		A	G	0.3744	0.4317	0.0336	4.98E-34
cg06490845	16	88858315	rs860762		T	C	0.351	0.4636	0.0390	6.47E-28
cg06505619	16	698072	rs1128550	WDR90	G	A	0.3482	0.2982	0.0386	5.61E-10
cg06521852	22	38141419	rs202179193	TRIOBP	D	NA	0.05246	0.577674	0.0796	1.91E-08
			rs4396807	TRIOBP	C	G	0.3287	0.337342	0.0377	1.95E-14
cg06522681	19	15121596	rs73510283	CCDC105	C	A	0.2015	0.3888	0.0519	3.46E-09
cg06526721	5	119799384	rs78057302	PRR16	T	G	0.1724	0.589	0.0521	5.91E-25
cg06532880	5	176731545	rs6879874	PRELID1	A	T	0.2667	0.307	0.0468	2.69E-06
cg06538684	12	12511223	rs11313889	LOH12CR2	D	NA	0.3443	0.325958	0.0382	7.53E-13
			rs71457148	LOH12CR2	T	C	0.0625	0.492392	0.0752	2.87E-06
cg06578342	16	4349215	rs804175		A	G	0.264	0.4094	0.0483	1.22E-12
cg06589051	2	105946882	rs113067541	TGFBRAP1	T	C	0.1345	0.506053	0.0492	3.84E-20
			rs6749541	TGFBRAP1	C	G	0.101	0.344447	0.0577	1.16E-04
			rs6752669	TGFBRAP1	C	G	0.2388	0.366234	0.0406	9.34E-15
cg06598386	12	67830705	rs35584224		D	NA	0.101	0.797	0.0590	6.73E-37
cg06603074	18	60192893	rs4940559	ZCCHC2	G	C	0.4939	0.3221	0.0396	2.07E-11
cg06614118	5	180414906	rs7710895	BTNL3	C	T	0.2952	0.4555	0.0345	4.94E-35
cg06653796	20	62367805	rs112756706	LIME1	T	A	0.2238	0.3876	0.0445	1.56E-13
cg06661266	3	134027721	rs9881242		A	C	0.4459	0.411	0.0386	9.49E-22
cg06670463	4	103749966	rs7688014	UBE2D3	T	C	0.4888	0.3754	0.0422	3.15E-15
cg06673536	19	45213941	rs62120573	CEACAM16	C	T	0.06194	0.6864	0.0882	3.56E-10
cg06678242	15	93614758	rs11854936	RGMA	C	T	0.4319	0.782947	0.0470	1.64E-57
			rs4777759	RGMA	T	G	0.4459	0.270097	0.0466	3.38E-04
cg06687489	15	52587077	rs5002319	MYO5C	A	G	0.1172	0.703	0.0606	2.14E-26
cg06693983	19	55889216	rs4806665	TMEM190	G	A	0.4749	0.428	0.0388	1.50E-23
cg06711259	22	39095898	rs9611008	JOSD1	C	T	0.3142	0.4245	0.0407	1.03E-20
cg06716182	11	96074944	rs116961539	MAML2	G	C	0.02623	1.432	0.1182	4.64E-29
cg06750167	12	117538458	rs112483974	TESC	I	NA	0.3304	0.4029	0.0422	7.02E-17
cg06752398	15	79053858	rs12906653	ADAMTS7	A	G	0.4012	0.482589	0.0386	4.43E-31
			rs34552906	ADAMTS7	G	A	0.3404	0.265406	0.0406	3.22E-06
cg06753163	14	95760031	rs6575508	CLMN	T	C	0.3588	0.3676	0.0419	8.26E-14

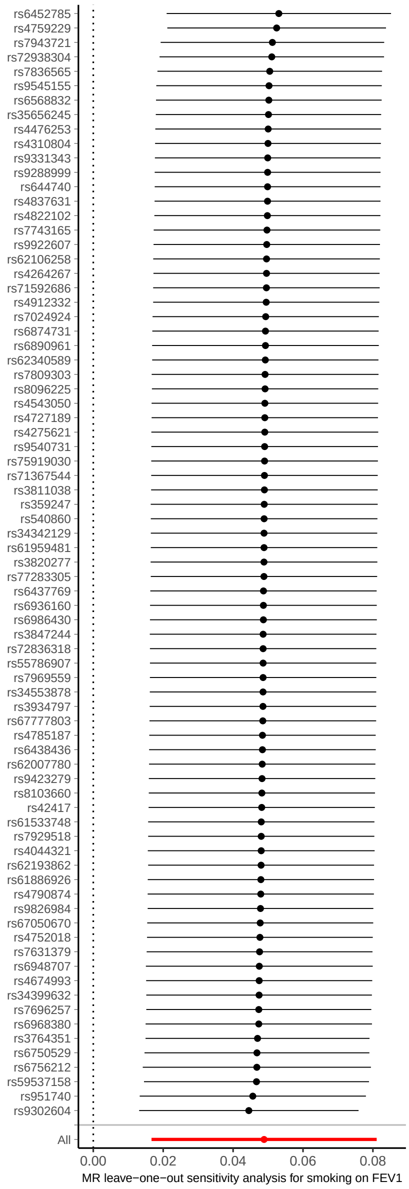
cg06763054	8	17270834	rs75437306	MTMR7	C	T	0.3237	0.279476	0.0429	3.48E-06
			rs9442366	MTMR7	T	C	0.4297	0.343528	0.0409	2.18E-12
cg06766016	1	45278971	rs58320827	BTBD19	A	G	0.3477	0.3351	0.0393	7.59E-13
cg06769377	1	228350860	rs2185544		A	G	0.4079	0.5266	0.0316	9.88E-58
cg06770878	2	105372265	rs36050054		T	G	0.375	0.5263	0.0371	5.76E-41
cg06772580	17	27899576	rs497993	TP53I13	T	C	0.2969	0.8133	0.0409	2.02E-83
cg06779856	11	33209645	rs115743849		A	G	0.04632	-1.568	0.0868	3.51E-68
cg06791426	12	133135361	rs2875247	FBRSL1	C	T	0.4559	0.6228	0.0336	3.96E-73
cg06801385	5	1152362	rs55982000		D	NA	0.4872	0.2633	0.0326	3.09E-11
cg06802630	5	322735	rs12984002	AHRR	T	C	0.06194	0.4775	0.0861	1.47E-03
cg06824013	15	53097247	rs2165991		G	A	0.2511	0.4386	0.0405	1.38E-22
cg06828143	5	10490335	rs2967946		G	A	0.4805	0.287	0.0431	1.32E-06
cg06855485	4	144303008	rs10013047	GAB1	A	G	0.3555	0.3164	0.0302	5.50E-21
cg06855983	19	13984313	rs8104649	MIR181C	C	T	0.2221	0.3633	0.0469	4.65E-10
cg06856720	20	19870217	rs6136874	RIN2	C	T	0.486	0.4745	0.0428	6.90E-24
cg06880612	2	102759576	rs12613301		T	A	0.4565	0.1696	0.0285	1.26E-04
cg06891043	17	7186718	rs2521991	SLC2A4	C	A	0.3811	0.2288	0.0403	7.05E-04
cg06903103	15	34506071	rs7164448		T	A	0.3477	0.3959	0.0431	2.05E-15
cg06922635	4	57371607	rs7700034	ARL9	G	A	0.3225	0.3877	0.0473	1.32E-11
cg06935361	13	32964454	rs9534367	BRCA2	T	C	0.2026	0.3495	0.0469	4.42E-09
cg06935608	8	26309176	rs62491007		A	G	0.2455	0.3394	0.0425	6.85E-11
cg06939852	16	51068651	rs4238819		G	A	0.2584	0.3526	0.0446	1.37E-10
cg06940168	17	64370665	rs79939256	PRKCA	A	G	0.1127	-1.187	0.0556	1.66E-96
cg06949439	1	206729034	rs28362485	RASSF5	D	NA	0.332	0.278233	0.0298	4.61E-16
			rs71633591	RASSF5	A	C	0.2137	0.303921	0.0336	7.24E-15
cg06951627	6	26196580	rs2183948		G	A	0.1395	0.3814	0.0432	5.20E-14
cg06974662	1	8277080	rs478128		G	A	0.1217	0.8432	0.0564	8.50E-46
cg06978288	4	77228884	rs5859507	STBD1	D	NA	0.4286	0.3147	0.0368	6.21E-13
cg06981781	4	110842888	rs10017261	EGF	A	T	0.3432	0.5118	0.0384	7.68E-36
cg06982272	20	2188575	rs6137362		T	G	0.4219	0.465	0.0359	9.86E-34
cg06992846	8	126448837	rs2235108	TRIB1	A	G	0.2801	0.5054	0.0433	9.15E-28
cg06996175	19	2546877	rs6510683	GNG7	C	A	0.09375	0.960372	0.0663	6.56E-43
			rs9304895	GNG7	A	G	0.3756	0.238205	0.0404	1.83E-04
cg06997114	18	21851455	rs17797879	OSBPL1A	C	T	0.4967	0.2762	0.0426	4.51E-06
cg06998765	14	75389618	rs7146041	RPS6KL1	A	G	0.3532	0.5933	0.0361	5.74E-56
cg07005444	17	3820796	rs11078476	P2RX1	G	C	0.3069	0.3903	0.0396	3.04E-18
cg07007550	1	16011710	rs10927840	PLEKHM2	G	A	0.2299	0.3941	0.0467	1.49E-12
cg07027613	12	7260608	rs7709	C1RL	A	C	0.4983	0.2547	0.0391	3.81E-06
cg07029024	11	65249342	rs10896002		T	C	0.1484	0.408907	0.0501	1.73E-12
			rs11227205		A	G	0.1847	0.502865	0.0463	9.29E-23
cg07038400	3	135684163	rs13081105	PPP2R3A	G	A	0.3198	0.4288	0.0430	1.08E-19
cg07048504	1	55829278	rs11206566		T	C	0.2048	0.2296	0.0401	5.23E-04
cg07059784	2	233416233	rs62191568	TIGD1	T	C	0.07701	0.6106	0.0751	2.06E-11
cg07065756	7	2119340	rs3800881	MAD1L1	T	C	0.3845	0.4352	0.0406	4.06E-22
cg07090714	6	6857062	rs12200128		G	T	0.08092	0.558254	0.0638	1.05E-13
			rs73718678		A	C	0.1133	0.542431	0.0532	9.91E-20
cg07091481	10	82169149	rs4934167	C10orf58	A	G	0.4554	0.3051	0.0333	2.84E-15
cg07093324	2	114652143	rs144178686	ACTR3	T	C	0.1462	0.4629	0.0503	1.89E-15
cg07104958	10	46168551	rs73292848	ANUBL1	C	T	0.03181	1.123	0.1028	4.31E-23
cg07109046	13	41204388	rs2701880	FOXO1	C	A	0.0692	0.503009	0.0828	6.11E-05
			rs9549260	FOXO1	A	C	0.2243	0.266694	0.0485	1.88E-03
cg07109801	3	49057661	rs182228347	MIR425	G	T	0.03571	0.8269	0.1000	6.99E-12
cg07112604	14	91836354	rs1285813	CCDC88C	G	A	0.0692	0.3908	0.0541	2.45E-08
cg07124366	3	10361044	rs35682	SEC13	G	A	0.4799	0.3113	0.0340	2.77E-15

Appendix F

Leave-one-out Analysis



(A) First half of SNPs

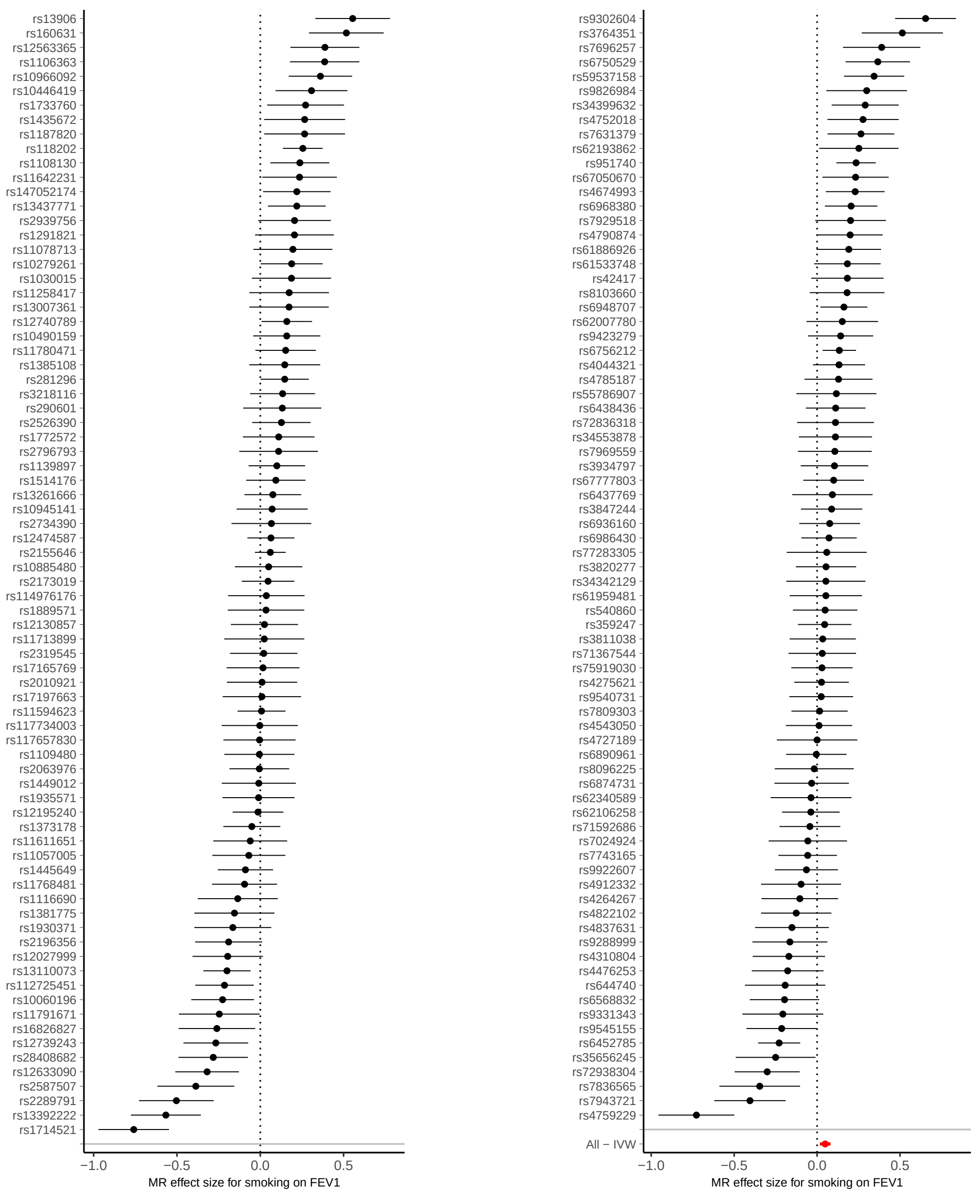


(B) Second half of SNPs

FIGURE F.1: Leave-one-out plot of the effect of smoking on lung function, excluding one smoking-related SNP at a time.

Appendix G

Single SNP analysis



(A) First half of SNPs

(B) Second half of SNPs

FIGURE G.1: Single SNP analysis of the estimated causal effect of smoking on lung function using one SNP as instrumental variable at a time.

Appendix H

Results of Fourth Step of our MR Framework

TABLE H.1: Results of the fourth step of our MR framework, where a single *cis*-SNP was available for the CpGs related to maternal or active smoking. Beta, SE, P are β coefficient, standard error and p-value from IVW estimate. F: F statistic. Exposure: Exposure to which the methylation was previously linked; either active smoking, maternal smoking or both.

CpG	Beta	SE	P	F	Exposure	Gene
cg11939399	-0.0388	0.0041	1.04E-21	42	Active smoking	REST
cg12565126	0.0533	0.0057	1.40E-20	49	Active smoking	MFSD2B
cg21356710	0.0286	0.0031	1.40E-20	187	Active smoking	MFSD2B
cg17632937	0.0518	0.0057	1.33E-19	74	Active smoking	HORMAD2
cg23268208	0.0482	0.0053	1.47E-19	81	Active smoking	HORMAD2
cg25313468	-0.0316	0.0036	7.63E-19	79	Both	REST
cg20099806	-0.0534	0.0060	7.87E-19	49	Maternal smoking	CCDC47
cg19409163	0.0242	0.0028	3.04E-18	250	Active smoking	
cg16426321	0.0461	0.0053	6.65E-18	76	Maternal smoking	ITPK1
cg04788957	-0.0404	0.0055	3.06E-13	69	Active smoking	SH3PXD2A
cg14150774	0.0224	0.0031	1.07E-12	270	Maternal smoking	QSOX2
cg16174681	0.0492	0.0072	9.06E-12	35	Active smoking	FER
cg12616487	-0.0501	0.0074	1.00E-11	37	Both	ROM1
cg20242066	0.0205	0.0030	1.26E-11	316	Active smoking	LCT
cg18611245	0.0265	0.0039	1.62E-11	102	Both	ZGPAT
cg13456470	0.0228	0.0034	1.88E-11	55	Active smoking	PTCH1
cg02812767	-0.0216	0.0032	2.03E-11	234	Both	LOXL1
cg14164839	-0.0146	0.0022	2.60E-11	1003	Active smoking	
cg20642413	0.0229	0.0035	6.81E-11	163	Both	ZGPAT
cg03354707	-0.0214	0.0034	2.17E-10	130	Active smoking	LTBP4
cg21806580	0.0331	0.0053	3.26E-10	62	Active smoking	
cg11478024	-0.0346	0.0056	6.27E-10	134	Maternal smoking	ANKS1A
cg26860257	-0.0236	0.0038	7.52E-10	148	Active smoking	ERF
cg24748631	-0.0501	0.0083	1.49E-09	46	Maternal smoking	
cg10315249	0.0209	0.0035	2.41E-09	207	Active smoking	PELI3
cg09006487	-0.0311	0.0053	4.41E-09	66	Both	RYBP
cg06382664	-0.0296	0.0051	7.14E-09	90	Active smoking	RELT
cg19717773	0.0206	0.0036	1.26E-08	46	Both	GNA12
cg16417118	0.0191	0.0034	1.40E-08	33	Active smoking	SKI
cg20674490	0.0143	0.0026	2.07E-08	41	Maternal smoking	RUNX3
cg18685455	0.0149	0.0027	2.25E-08	344	Active smoking	AHI1
cg04337534	0.0358	0.0064	2.34E-08	53	Active smoking	GAL3ST3
cg08968329	0.0316	0.0057	3.41E-08	72	Active smoking	FAM38A
cg01503516	-0.0151	0.0028	4.62E-08	361	Active smoking	NMB
cg22670759	-0.0208	0.0038	5.26E-08	141	Active smoking	CACNA2D2
cg16000022	-0.0215	0.0040	7.67E-08	135	Active smoking	TPCN2
cg10255761	0.0260	0.0049	1.36E-07	116	Active smoking	KLHDC8B
cg16641055	0.0166	0.0032	1.53E-07	37	Maternal smoking	FAM38A
cg21198712	0.0125	0.0024	2.59E-07	539	Maternal smoking	
cg11645556	0.0315	0.0062	3.75E-07	56	Active smoking	RRAS2
cg05607577	-0.0264	0.0052	4.51E-07	125	Maternal smoking	XPO5
cg16737517	-0.0182	0.0037	6.81E-07	149	Active smoking	ZBTB46
cg12283398	-0.0176	0.0035	6.81E-07	122	Maternal smoking	ZBTB46
cg00664609	-0.0262	0.0053	7.04E-07	93	Active smoking	RAB26
cg14251267	-0.0169	0.0034	7.09E-07	165	Both	ZBTB46
cg07262247	0.0181	0.0037	1.05E-06	160	Active smoking	PDLIM4
cg09244707	0.0311	0.0064	1.39E-06	44	Maternal smoking	
cg14977069	0.0317	0.0066	1.40E-06	62	Active smoking	LIME1
cg06653796	0.0252	0.0052	1.40E-06	76	Both	LIME1
cg18786782	-0.0308	0.0064	1.45E-06	39	Maternal smoking	
cg02962602	0.0219	0.0046	2.26E-06	117	Active smoking	CCDC57
cg17924476	0.0337	0.0071	2.27E-06	34	Both	AHRR
cg15247329	0.0114	0.0024	2.48E-06	314	Active smoking	
cg10516117	0.0295	0.0063	2.78E-06	87	Active smoking	SERPINF2
cg09817016	-0.0138	0.0029	2.85E-06	280	Active smoking	KDM3B
cg04078896	0.0269	0.0058	2.89E-06	43	Both	ZGPAT
cg24281267	-0.0155	0.0033	3.27E-06	67	Active smoking	TULP1
cg20595752	-0.0259	0.0056	3.93E-06	71	Maternal smoking	TEAD3
cg20765408	0.0250	0.0054	3.93E-06	80	Maternal smoking	PARP4

cg17094065	-0.0225	0.0049	4.15E-06	69	Active smoking	TENC1
cg11683364	-0.0131	0.0028	4.21E-06	70	Active smoking	LGR6
cg19154600	-0.0241	0.0052	4.38E-06	90	Active smoking	SYNPO2L
cg17901382	0.0109	0.0024	4.50E-06	524	Active smoking	TSEN54
cg18446336	-0.0194	0.0042	4.70E-06	105	Both	GNA12
cg21832243	0.0114	0.0025	5.23E-06	495	Active smoking	TTC3
cg21201401	0.0334	0.0074	5.46E-06	55	Both	LIME1
cg13227481	-0.0117	0.0026	6.47E-06	371	Active smoking	DES
cg06320277	-0.0128	0.0029	6.99E-06	348	Active smoking	FHL2
cg20512303	-0.0247	0.0055	7.43E-06	63	Active smoking	PDLIM4
cg22657492	-0.0257	0.0057	7.76E-06	48	Maternal smoking	GFRA3
cg02512168	0.0147	0.0033	7.79E-06	202	Maternal smoking	ZNF205
cg22598563	-0.0198	0.0044	7.98E-06	138	Active smoking	P4HA2
cg19939077	0.0208	0.0047	8.26E-06	126	Active smoking	PPIF
cg09658497	0.0160	0.0036	8.54E-06	159	Both	GNA12
cg25082487	0.0165	0.0037	9.12E-06	145	Active smoking	
cg20513976	0.0420	0.0095	9.26E-06	36	Both	LIME1
cg14739437	-0.0109	0.0025	1.05E-05	434	Active smoking	LRRC24
cg19139589	0.0456	0.0104	1.06E-05	67	Active smoking	
cg11105358	0.0111	0.0025	1.14E-05	396	Active smoking	
cg11197664	-0.0211	0.0048	1.14E-05	69	Active smoking	
cg02508743	-0.0251	0.0057	1.14E-05	59	Active smoking	LYN
cg00901598	0.0248	0.0057	1.20E-05	70	Active smoking	GHSR
cg23222488	-0.0200	0.0046	1.20E-05	114	Active smoking	
cg00794673	-0.0245	0.0056	1.22E-05	66	Active smoking	ANKS1A
cg13919466	-0.0169	0.0039	1.30E-05	157	Active smoking	COL16A1
cg14061067	0.0161	0.0037	1.51E-05	171	Active smoking	BNC2
cg01476739	-0.0154	0.0036	1.53E-05	188	Active smoking	
cg19430473	-0.0206	0.0048	1.63E-05	81	Active smoking	
cg22998476	0.0216	0.0050	1.70E-05	75	Active smoking	
cg14873022	-0.0091	0.0021	1.79E-05	719	Active smoking	ZNF827
cg20811755	0.0157	0.0037	1.98E-05	83	Active smoking	
cg12974394	0.0207	0.0049	2.07E-05	87	Active smoking	ADAMTSL4
cg03987653	-0.0275	0.0065	2.23E-05	47	Active smoking	DEF8
cg12500956	0.0098	0.0023	2.69E-05	46	Active smoking	TMEM163
cg26520678	-0.0165	0.0039	2.72E-05	129	Active smoking	
cg23083424	0.0156	0.0038	3.04E-05	202	Active smoking	SYNPO2L
cg26613586	-0.0108	0.0026	3.17E-05	540	Active smoking	
cg00356499	0.0122	0.0029	3.45E-05	254	Active smoking	LRPAP1
cg03970900	0.0129	0.0031	3.52E-05	297	Active smoking	
cg05504729	0.0172	0.0042	3.87E-05	112	Maternal smoking	ANKRD11
cg06484000	-0.0108	0.0026	4.02E-05	189	Active smoking	PNMAL2
cg18132076	0.0236	0.0058	4.12E-05	71	Active smoking	GMDS
cg24433016	-0.0107	0.0026	4.13E-05	371	Active smoking	TTK
cg22534374	-0.0146	0.0036	4.46E-05	207	Active smoking	
cg07751331	0.0164	0.0040	4.63E-05	141	Both	KIF3C
cg21187770	0.0218	0.0054	4.63E-05	76	Both	KIF3C
cg06105699	-0.0145	0.0036	4.80E-05	54	Maternal smoking	ASPSCR1
cg14767165	-0.0175	0.0043	4.93E-05	115	Maternal smoking	ACAT2
cg14714797	0.0246	0.0061	5.11E-05	38	Active smoking	AHRR
cg07737182	-0.0217	0.0054	6.09E-05	50	Active smoking	
cg02660097	0.0124	0.0031	6.62E-05	31	Active smoking	
cg11773468	0.0142	0.0036	6.92E-05	170	Active smoking	MAMSTR
cg15043384	0.0180	0.0045	6.98E-05	92	Active smoking	WWTR1
cg25748958	0.0198	0.0050	7.01E-05	92	Active smoking	THADA
cg03133378	-0.0114	0.0029	7.86E-05	261	Maternal smoking	
cg12290671	-0.0107	0.0027	7.86E-05	321	Maternal smoking	
cg24024660	-0.0153	0.0039	7.86E-05	135	Both	
cg00941203	-0.0089	0.0023	8.18E-05	70	Active smoking	
cg06855485	-0.0226	0.0057	8.19E-05	110	Active smoking	GAB1
cg13426079	-0.0162	0.0041	8.30E-05	119	Active smoking	KCNQ4
cg02936049	-0.0125	0.0032	8.89E-05	311	Maternal smoking	ZBTB38
cg16535667	0.0229	0.0058	8.95E-05	50	Maternal smoking	SIPA1
cg12527260	-0.0083	0.0021	9.57E-05	779	Active smoking	RCOR2
cg04865726	0.0141	0.0036	1.04E-04	39	Maternal smoking	
cg22052056	0.0245	0.0063	1.11E-04	78	Active smoking	DNMT3B
cg26117521	0.0317	0.0082	1.12E-04	59	Maternal smoking	EBF1
cg03603530	-0.0128	0.0033	1.12E-04	192	Active smoking	PDF
cg19560927	-0.0133	0.0035	1.18E-04	33	Active smoking	PNMAL2
cg04236263	-0.0174	0.0045	1.20E-04	97	Active smoking	MFAP2
cg25646708	0.0116	0.0030	1.23E-04	37	Active smoking	
cg23681440	-0.0256	0.0067	1.30E-04	38	Active smoking	
cg00541638	0.0236	0.0062	1.42E-04	72	Active smoking	USP7
cg20375836	0.0222	0.0058	1.43E-04	51	Active smoking	STK24
cg22698028	-0.0183	0.0048	1.45E-04	75	Both	AHRR
cg24484352	-0.0194	0.0051	1.49E-04	198	Active smoking	
cg03593471	-0.0209	0.0056	1.73E-04	59	Maternal smoking	
cg21609804	-0.0120	0.0032	1.73E-04	233	Maternal smoking	MARK2
cg07835443	-0.0158	0.0042	1.77E-04	45	Active smoking	C16orf55
cg07029024	-0.0133	0.0036	1.84E-04	67	Active smoking	
cg09387382	-0.0190	0.0051	1.85E-04	67	Active smoking	
cg15037583	0.0257	0.0069	1.89E-04	41	Active smoking	MACROD1
cg01639898	0.0128	0.0034	1.91E-04	169	Active smoking	HCRTR1
cg10068539	0.0182	0.0049	1.97E-04	134	Active smoking	MARK2
cg00732810	0.0131	0.0035	2.00E-04	104	Maternal smoking	RASA3
cg06196801	0.0152	0.0041	2.02E-04	32	Active smoking	ACADS
cg24117468	0.0106	0.0029	2.03E-04	366	Maternal smoking	P4HA2
cg13105904	0.0078	0.0021	2.04E-04	348	Both	CBLN3
cg16002441	-0.0150	0.0041	2.22E-04	135	Active smoking	PPFIA3
cg25114611	-0.0213	0.0058	2.24E-04	42	Both	FKBP5
cg06348134	0.0164	0.0045	2.29E-04	123	Maternal smoking	
cg21235334	0.0243	0.0066	2.29E-04	75	Active smoking	DNMT3B
cg13578465	-0.0160	0.0044	2.42E-04	79	Active smoking	INF2
cg16926213	-0.0105	0.0029	2.53E-04	41	Active smoking	
cg23060272	0.0124	0.0034	2.70E-04	216	Active smoking	LPP
cg17927313	-0.0218	0.0060	2.82E-04	57	Active smoking	PLEKHO2
cg23097139	0.0136	0.0037	2.90E-04	173	Active smoking	SNUPN
cg08301612	0.0174	0.0048	2.95E-04	87	Active smoking	HEXIM1

cg01131866	-0.0254	0.0070	3.14E-04	53	Active smoking	KIF2A
cg24066601	0.0138	0.0038	3.24E-04	216	Maternal smoking	HIST1H3G
cg20630655	-0.0099	0.0028	3.50E-04	281	Active smoking	SNUPN
cg14410964	0.0124	0.0035	3.52E-04	146	Active smoking	NOTCH1
cg09009770	0.0134	0.0037	3.61E-04	371	Active smoking	
cg18436735	0.0304	0.0085	3.62E-04	34	Maternal smoking	FEZ1
cg22078805	-0.0171	0.0048	3.70E-04	71	Active smoking	FAM171A2
cg25809905	0.0148	0.0042	3.70E-04	160	Active smoking	ITGA2B
cg27532360	-0.0298	0.0084	3.70E-04	32	Active smoking	ITGA2B
cg18882449	-0.0080	0.0023	3.93E-04	760	Active smoking	NT5C2
cg11362820	-0.0128	0.0036	4.03E-04	39	Active smoking	
cg07286682	0.0173	0.0049	4.16E-04	66	Active smoking	MIR548H4
cg05005217	0.0126	0.0036	4.23E-04	138	Active smoking	CDCA2
cg15095727	0.0206	0.0058	4.34E-04	89	Active smoking	CEP70
cg17847044	-0.0062	0.0018	4.54E-04	1295	Maternal smoking	MAPKBP1
cg00852783	0.0140	0.0040	4.61E-04	147	Active smoking	UBXN11
cg12269161	-0.0102	0.0029	4.83E-04	306	Active smoking	HIVEP2
cg27110548	-0.0149	0.0043	4.95E-04	145	Active smoking	NAA40
cg18968920	0.0131	0.0038	5.01E-04	187	Active smoking	PRPF40A
cg05389183	0.0145	0.0042	5.06E-04	70	Active smoking	PPIC
cg23352030	0.0232	0.0067	5.10E-04	32	Active smoking	PRIC285
cg14713146	0.0241	0.0069	5.11E-04	109	Active smoking	
cg08237401	-0.0070	0.0020	5.23E-04	654	Active smoking	BCAR3
cg19696491	0.0157	0.0046	5.63E-04	109	Both	CHRNA5
cg22563815	0.0153	0.0044	5.63E-04	138	Active smoking	CHRNA5
cg18537730	-0.0154	0.0045	5.64E-04	85	Maternal smoking	IZUMO1
cg23387569	0.0205	0.0059	5.78E-04	44	Active smoking	AGAP2
cg16416158	0.0126	0.0037	5.85E-04	195	Active smoking	ECE1
cg09206294	-0.0226	0.0066	6.05E-04	43	Active smoking	MAPKBP1
cg17390562	0.0181	0.0053	6.05E-04	104	Active smoking	EZR
cg05695937	0.0106	0.0031	6.06E-04	131	Active smoking	NAV1
cg23232299	-0.0166	0.0048	6.39E-04	76	Maternal smoking	GNG12
cg03292040	-0.0144	0.0042	6.42E-04	85	Active smoking	CCDC74A
cg20124610	0.0175	0.0051	6.47E-04	83	Both	CARS2
cg21117965	-0.0062	0.0018	6.57E-04	893	Active smoking	SPEG
cg16760981	-0.0175	0.0051	6.79E-04	52	Active smoking	
cg15199181	-0.0146	0.0043	6.87E-04	138	Active smoking	
cg05267427	0.0078	0.0023	7.39E-04	541	Active smoking	ZNF827
cg11731596	-0.0154	0.0046	8.04E-04	91	Maternal smoking	
cg01030476	0.0125	0.0037	8.14E-04	176	Active smoking	LGALS8
cg01455178	0.0151	0.0045	8.32E-04	108	Active smoking	SLC45A3
cg08550394	-0.0145	0.0043	8.36E-04	102	Active smoking	ADCY9
cg05858126	-0.0199	0.0060	8.43E-04	42	Active smoking	MIR146B
cg05822532	-0.0162	0.0048	8.47E-04	72	Maternal smoking	ELN
cg19266387	-0.0169	0.0051	8.73E-04	96	Active smoking	PARL
cg06490839	0.0136	0.0041	8.86E-04	165	Active smoking	
cg14759549	-0.0130	0.0039	9.01E-04	146	Active smoking	MAP4K4
cg03164928	-0.0108	0.0033	9.05E-04	247	Active smoking	CBFA2T3
cg19827875	0.0084	0.0025	9.13E-04	182	Active smoking	NAV1
cg15084803	-0.0114	0.0035	9.27E-04	168	Active smoking	CHCHD4
cg13959031	0.0219	0.0066	9.68E-04	48	Active smoking	ISCA1
cg09358973	0.0098	0.0030	9.79E-04	130	Active smoking	NAV1
cg13056510	0.0160	0.0049	9.93E-04	83	Maternal smoking	
cg09713758	0.0190	0.0058	0.0010	95	Active smoking	C16orf67
cg06769377	0.0110	0.0034	0.0010	278	Active smoking	
cg14920846	0.0078	0.0024	0.0011	215	Both	NAV1
cg08549806	-0.0144	0.0044	0.0011	125	Active smoking	
cg10553415	-0.0126	0.0039	0.0011	127	Maternal smoking	
cg27027069	-0.0176	0.0054	0.0011	77	Active smoking	MYO6
cg17301216	0.0102	0.0031	0.0011	178	Active smoking	LOC254559
cg02056062	0.0205	0.0063	0.0011	62	Active smoking	WWTR1
cg02232751	0.0182	0.0056	0.0011	68	Maternal smoking	LDHA
cg15700009	0.0224	0.0069	0.0011	33	Maternal smoking	LDHA
cg20588859	-0.0147	0.0045	0.0011	98	Maternal smoking	LTBP3
cg07563400	0.0198	0.0061	0.0012	55	Maternal smoking	ADORA2B
cg17580614	0.0094	0.0029	0.0012	322	Both	ADORA2B
cg10116432	-0.0198	0.0061	0.0012	55	Active smoking	NT5C2
cg07327299	-0.0251	0.0077	0.0012	31	Active smoking	GRB7
cg03985801	-0.0166	0.0051	0.0012	70	Active smoking	LGR6
cg05044291	0.0062	0.0019	0.0012	847	Active smoking	LGR6
cg19332572	-0.0210	0.0065	0.0012	44	Maternal smoking	LTBP3
cg20072528	0.0069	0.0021	0.0012	778	Active smoking	
cg01447281	0.0172	0.0053	0.0012	92	Active smoking	RERE
cg21091547	-0.0123	0.0038	0.0013	50	Both	CDKN1A
cg05157625	-0.0059	0.0018	0.0013	1014	Active smoking	RIN3
cg04503968	0.0187	0.0058	0.0013	47	Active smoking	PRDM6
cg27058497	0.0296	0.0092	0.0013	54	Maternal smoking	RUNX3
cg11100795	-0.0074	0.0023	0.0014	87	Maternal smoking	AP3B1
cg22171758	0.0210	0.0066	0.0015	65	Maternal smoking	
cg13742400	0.0212	0.0067	0.0015	83	Maternal smoking	DOCK10
cg10920224	-0.0109	0.0034	0.0015	107	Active smoking	TRAF3
cg14886849	-0.0150	0.0047	0.0015	74	Active smoking	TRAF3
cg15950273	-0.0159	0.0050	0.0015	51	Active smoking	TRAF3
cg23231163	0.0083	0.0026	0.0015	423	Active smoking	FUT11
cg12072028	0.0088	0.0028	0.0015	162	Both	RIN3
cg22871253	0.0145	0.0046	0.0015	124	Active smoking	EZR
cg03345232	0.0086	0.0027	0.0015	175	Both	RIN3
cg06270615	-0.0074	0.0023	0.0016	424	Active smoking	STAT3
cg02405476	-0.0161	0.0051	0.0016	94	Active smoking	UBE2C
cg19197419	-0.0153	0.0048	0.0016	97	Active smoking	UBE2C
cg04220636	-0.0109	0.0035	0.0017	193	Active smoking	CBFA2T3
cg07599786	0.0078	0.0025	0.0017	196	Active smoking	NAV1
cg24033122	0.0087	0.0028	0.0017	301	Active smoking	ITGAL
cg03483626	-0.0243	0.0078	0.0017	32	Active smoking	KCNA3
cg07903677	-0.0165	0.0053	0.0017	75	Active smoking	KCNA3
cg14899046	0.0165	0.0053	0.0017	64	Active smoking	
cg09099830	-0.0123	0.0039	0.0017	153	Active smoking	ITGAL
cg27423445	-0.0075	0.0024	0.0018	41	Active smoking	APOLD1

cg08641963	0.0067	0.0021	0.0018	529	Active smoking	TNNC2
cg06099431	0.0137	0.0044	0.0018	82	Active smoking	
cg23599843	-0.0128	0.0041	0.0018	91	Maternal smoking	JPH1
cg06791426	0.0087	0.0028	0.0018	344	Active smoking	FBRSL1
cg15408734	0.0104	0.0033	0.0018	208	Both	
cg05490519	-0.0081	0.0026	0.0018	361	Maternal smoking	PRSS22
cg05895034	-0.0082	0.0026	0.0018	380	Maternal smoking	PRSS22
cg15884713	0.0167	0.0054	0.0019	64	Active smoking	NINJ2
cg21929761	0.0175	0.0056	0.0019	69	Active smoking	
cg18302225	-0.0094	0.0030	0.0019	366	Active smoking	
cg24049468	-0.0164	0.0053	0.0019	70	Both	AK3L1
cg15038286	0.0094	0.0030	0.0020	115	Active smoking	GATA2
cg13935009	-0.0086	0.0028	0.0020	69	Active smoking	CDK18
cg25975805	0.0140	0.0045	0.0020	86	Active smoking	
cg22304262	0.0119	0.0038	0.0020	173	Active smoking	SLC1A5
cg12589431	-0.0172	0.0056	0.0021	32	Active smoking	
cg24119798	0.0168	0.0054	0.0021	85	Maternal smoking	
cg18322510	0.0096	0.0031	0.0021	246	Active smoking	LGALS8
cg08858540	0.0103	0.0034	0.0022	188	Active smoking	AHRR
cg09134760	0.0071	0.0023	0.0022	374	Active smoking	
cg11347139	0.0096	0.0031	0.0022	131	Active smoking	HIAT1
cg02473781	0.0149	0.0049	0.0022	74	Active smoking	MIR130B
cg24766327	0.0189	0.0062	0.0023	71	Maternal smoking	
cg02158978	-0.0154	0.0050	0.0023	96	Active smoking	FBRSL1
cg20454518	-0.0090	0.0029	0.0023	303	Active smoking	FBRSL1
cg05593667	0.0103	0.0034	0.0023	174	Active smoking	
cg21504624	0.0147	0.0048	0.0023	104	Active smoking	IL11RA
cg00706994	0.0138	0.0045	0.0023	113	Active smoking	OR5A2
cg18345369	-0.0080	0.0026	0.0023	251	Maternal smoking	PRSS22
cg13652493	0.0152	0.0050	0.0025	72	Active smoking	
cg11673244	0.0119	0.0039	0.0025	92	Active smoking	MIR130B
cg04287574	0.0098	0.0033	0.0025	83	Active smoking	NAV1
cg05512100	0.0095	0.0032	0.0025	44	Active smoking	PDE1C
cg26659404	-0.0066	0.0022	0.0026	538	Active smoking	RHCE
cg19555986	-0.0103	0.0034	0.0026	172	Active smoking	MAP7
cg16013006	0.0097	0.0032	0.0026	43	Active smoking	HSPBP1
cg06824013	-0.0137	0.0046	0.0027	117	Active smoking	
cg03766449	0.0238	0.0079	0.0028	41	Active smoking	LOC254559
cg14659662	-0.0057	0.0019	0.0028	903	Maternal smoking	GLIS1
cg25653947	-0.0187	0.0063	0.0028	69	Active smoking	
cg26785220	-0.0224	0.0075	0.0028	34	Maternal smoking	
cg00096536	-0.0130	0.0044	0.0028	159	Active smoking	
cg18487309	0.0176	0.0059	0.0029	54	Active smoking	TBC1D9B
cg00464520	0.0169	0.0057	0.0029	54	Maternal smoking	
cg03992168	-0.0140	0.0047	0.0029	99	Maternal smoking	
cg23352722	-0.0116	0.0039	0.0030	29	Active smoking	PHYHIP
cg22736323	0.0196	0.0066	0.0030	40	Active smoking	PDGFRA
cg01802117	0.0111	0.0037	0.0030	122	Active smoking	SCP2
cg17475857	-0.0106	0.0036	0.0031	91	Active smoking	DNMT3B
cg02339793	-0.0266	0.0090	0.0031	137	Active smoking	SLC38A10
cg00541303	-0.0150	0.0051	0.0031	72	Active smoking	
cg24013213	-0.0153	0.0052	0.0031	147	Active smoking	GUCY1B2
cg06891043	-0.0230	0.0078	0.0032	32	Active smoking	SLC2A4
cg16595667	-0.0078	0.0027	0.0032	501	Active smoking	KIAA1737
cg02500990	-0.0166	0.0056	0.0032	41	Maternal smoking	CPNE7
cg21692620	-0.0130	0.0044	0.0032	96	Active smoking	CNTNAP1
cg23541923	-0.0101	0.0034	0.0034	170	Maternal smoking	
cg14409810	0.0170	0.0058	0.0035	57	Active smoking	C9orf167
cg16453665	-0.0166	0.0057	0.0035	48	Active smoking	TTC23L
cg08962185	-0.0097	0.0033	0.0035	284	Maternal smoking	TSNARE1
cg26430287	-0.0113	0.0039	0.0035	42	Active smoking	SMAD3
cg01717649	-0.0149	0.0051	0.0036	86	Maternal smoking	
cg18043888	-0.0088	0.0030	0.0036	215	Maternal smoking	RHOD
cg11657615	0.0260	0.0089	0.0036	31	Active smoking	ZDHHC1
cg17877600	0.0172	0.0059	0.0036	60	Active smoking	
cg15964523	-0.0061	0.0021	0.0036	699	Active smoking	SPTBN2
cg05897163	-0.0244	0.0084	0.0036	31	Maternal smoking	PPP1R1B
cg25749306	-0.0130	0.0045	0.0037	98	Active smoking	PNMAL2
cg01649611	0.0219	0.0075	0.0037	45	Active smoking	THADA
cg18634506	0.0168	0.0058	0.0038	63	Active smoking	BUD31
cg13504055	0.0084	0.0029	0.0039	304	Active smoking	
cg16124934	0.0161	0.0056	0.0039	58	Active smoking	RPS6KL1
cg00475085	0.0163	0.0056	0.0039	57	Active smoking	PRPF19
cg12582317	-0.0072	0.0025	0.0040	603	Active smoking	
cg00313914	0.0069	0.0024	0.0040	173	Active smoking	NAV1
cg15927699	0.0124	0.0043	0.0040	73	Active smoking	
cg08166214	0.0148	0.0052	0.0042	132	Active smoking	
cg04852348	0.0102	0.0036	0.0042	78	Active smoking	
cg21493768	-0.0069	0.0024	0.0043	380	Maternal smoking	
cg08257003	-0.0085	0.0030	0.0043	254	Active smoking	ME1
cg06526721	0.0119	0.0042	0.0044	128	Active smoking	PRR16
cg21633052	0.0134	0.0047	0.0044	92	Active smoking	C4orf38
cg05247391	0.0159	0.0056	0.0045	58	Active smoking	XKR9
cg05471495	0.0129	0.0045	0.0046	99	Active smoking	
cg05265359	0.0121	0.0043	0.0046	101	Active smoking	GYLTL1B
cg12421513	-0.0116	0.0041	0.0047	125	Active smoking	RHD
cg16689434	0.0120	0.0043	0.0050	55	Active smoking	GAS8
cg23365801	-0.0139	0.0050	0.0051	72	Active smoking	KCNAB3
cg18883198	-0.0121	0.0043	0.0051	96	Maternal smoking	TMEM57
cg03304763	-0.0104	0.0037	0.0051	241	Maternal smoking	TEX12
cg03400139	0.0071	0.0025	0.0051	317	Active smoking	NAV1
cg21868031	-0.0094	0.0034	0.0052	173	Active smoking	CD46
cg00237010	0.0090	0.0032	0.0053	229	Active smoking	NINJ2
cg06998765	0.0084	0.0030	0.0055	270	Active smoking	RPS6KL1
cg02464912	-0.0172	0.0062	0.0055	55	Active smoking	SYNE2
cg17830209	0.0114	0.0041	0.0055	156	Active smoking	FLJ90757
cg09138892	0.0172	0.0062	0.0055	74	Active smoking	FLJ90757
cg15758702	0.0077	0.0028	0.0056	254	Active smoking	BAHCC1

cg19045002	0.0080	0.0029	0.0056	252	Active smoking	BAHCC1
cg14170999	0.0071	0.0026	0.0056	342	Both	BAHCC1
cg12121643	-0.0079	0.0029	0.0057	255	Active smoking	DGKG
cg11143953	-0.0089	0.0032	0.0058	236	Maternal smoking	FIP1L1
cg06880612	0.0283	0.0103	0.0059	36	Active smoking	
cg20925954	-0.0117	0.0042	0.0060	102	Active smoking	DUSP5
cg21830368	-0.0130	0.0047	0.0060	67	Maternal smoking	40057
cg11789681	-0.0092	0.0033	0.0061	123	Active smoking	
cg07376232	0.0209	0.0076	0.0061	48	Active smoking	AMICA1
cg17769793	-0.0072	0.0026	0.0061	326	Active smoking	FAM13A
cg00569896	-0.0193	0.0071	0.0061	44	Active smoking	
cg05795313	0.0185	0.0068	0.0064	62	Active smoking	ZNF641
cg23623364	0.0141	0.0052	0.0064	71	Active smoking	MST1
cg09201238	-0.0129	0.0047	0.0065	39	Active smoking	
cg26424147	0.0116	0.0043	0.0066	104	Active smoking	
cg06008724	-0.0106	0.0039	0.0066	154	Active smoking	PHF21B
cg01209566	-0.0137	0.0050	0.0066	93	Maternal smoking	LOC157381
cg13133835	0.0210	0.0078	0.0068	41	Active smoking	
cg04851639	0.0057	0.0021	0.0070	569	Maternal smoking	
cg27386326	-0.0111	0.0041	0.0070	108	Active smoking	
cg08305533	-0.0196	0.0073	0.0070	42	Active smoking	SFI1
cg06449334	-0.0163	0.0061	0.0070	61	Active smoking	
cg15804973	0.0109	0.0041	0.0070	116	Active smoking	MAP3K5
cg16616467	0.0158	0.0059	0.0071	49	Maternal smoking	CPNE7
cg25684105	-0.0109	0.0041	0.0071	130	Active smoking	TXNRD1
cg09065876	-0.0128	0.0048	0.0071	83	Active smoking	
cg06670463	-0.0125	0.0046	0.0073	79	Active smoking	UBE2D3
cg07915896	-0.0104	0.0039	0.0074	113	Active smoking	
cg10694914	0.0078	0.0029	0.0074	327	Active smoking	POU2AF1
cg19148410	0.0071	0.0027	0.0074	597	Active smoking	POU2AF1
cg20140034	0.0091	0.0034	0.0074	290	Active smoking	POU2AF1
cg15109207	-0.0080	0.0030	0.0074	284	Maternal smoking	PLA2G4C
cg18033416	0.0148	0.0055	0.0075	70	Active smoking	RHBDL3
cg01135546	-0.0145	0.0054	0.0075	65	Active smoking	
cg14911856	0.0070	0.0026	0.0076	448	Active smoking	
cg11335411	0.0136	0.0051	0.0077	68	Active smoking	ZNF274
cg08667275	-0.0089	0.0034	0.0077	141	Active smoking	
cg05877788	-0.0079	0.0030	0.0077	292	Active smoking	TP53I13
cg04498198	-0.0077	0.0029	0.0077	262	Active smoking	TP53I13
cg06772580	-0.0062	0.0023	0.0077	396	Active smoking	TP53I13
cg11231069	-0.0164	0.0062	0.0077	65	Active smoking	HDAC4
cg25607948	0.0163	0.0061	0.0077	56	Active smoking	
cg13877106	-0.0113	0.0042	0.0078	86	Active smoking	DCPS
cg01400685	0.0082	0.0031	0.0078	232	Active smoking	FADS2
cg02092181	-0.0144	0.0054	0.0079	53	Maternal smoking	DOT1L
cg09307264	-0.0101	0.0038	0.0079	125	Active smoking	INCA1
cg04990372	-0.0170	0.0064	0.0079	65	Active smoking	SNORD12B
cg16517753	-0.0111	0.0042	0.0083	210	Maternal smoking	TNR
cg17485838	0.0136	0.0052	0.0083	61	Active smoking	
cg14351425	-0.0145	0.0055	0.0083	54	Both	GRK5
cg13937758	-0.0114	0.0043	0.0084	115	Active smoking	
cg03650189	-0.0125	0.0047	0.0084	88	Active smoking	ICAM5
cg15011409	-0.0128	0.0049	0.0084	74	Active smoking	ICAM5
cg04423209	0.0170	0.0065	0.0085	63	Active smoking	SH2D6
cg27107076	0.0074	0.0028	0.0086	116	Active smoking	ADCY3
cg00689225	0.0114	0.0043	0.0087	179	Active smoking	NFKBIA
cg04545963	0.0089	0.0034	0.0087	328	Both	NFKBIA
cg03954086	0.0125	0.0048	0.0088	76	Maternal smoking	
cg09173378	0.0203	0.0077	0.0089	43	Maternal smoking	KCNT2
cg00394823	-0.0203	0.0078	0.0089	29	Maternal smoking	ACSM3
cg13850019	0.0137	0.0053	0.0089	68	Active smoking	
cg00491255	-0.0188	0.0072	0.0089	30	Active smoking	TEPP
cg12614667	0.0135	0.0052	0.0089	84	Active smoking	GBP4
cg26276120	-0.0165	0.0063	0.0090	49	Active smoking	TPI1
cg01873977	0.0135	0.0052	0.0091	73	Active smoking	MTSS1
cg13842240	0.0140	0.0054	0.0091	65	Active smoking	
cg16822035	-0.0172	0.0066	0.0092	53	Active smoking	MCF2L
cg01436487	-0.0115	0.0044	0.0092	107	Active smoking	MAD1L1
cg12091498	0.0082	0.0032	0.0095	133	Maternal smoking	
cg01887374	0.0076	0.0029	0.0095	160	Both	HS6ST1
cg10980495	0.0124	0.0048	0.0095	85	Both	HCCA2
cg14391923	-0.0076	0.0029	0.0095	165	Active smoking	
cg24937136	-0.0057	0.0022	0.0095	400	Active smoking	PARP1
cg11351908	0.0062	0.0024	0.0096	581	Active smoking	40057
cg01119319	-0.0124	0.0048	0.0096	82	Active smoking	
cg24300154	-0.0148	0.0057	0.0096	58	Active smoking	
cg06240690	0.0182	0.0070	0.0097	34	Active smoking	GALNT5
cg11229399	0.0091	0.0035	0.0097	190	Active smoking	
cg07413467	0.0159	0.0062	0.0098	68	Both	CDK6
cg24125710	0.0164	0.0064	0.0098	42	Active smoking	
cg04917446	-0.0092	0.0036	0.0098	58	Maternal smoking	HOXB9
cg05155319	0.0164	0.0064	0.0098	92	Active smoking	
cg03817727	-0.0128	0.0050	0.0099	63	Maternal smoking	
cg10590964	0.0097	0.0038	0.0101	57	Active smoking	
cg01902605	-0.0073	0.0028	0.0102	267	Maternal smoking	BHMT2
cg03400060	-0.0087	0.0034	0.0102	184	Maternal smoking	BHMT2
cg09718037	0.0129	0.0050	0.0103	84	Both	
cg10665891	0.0216	0.0084	0.0103	35	Both	
cg23975840	0.0147	0.0057	0.0103	87	Both	
cg22879098	0.0135	0.0053	0.0103	65	Maternal smoking	TPPP
cg24082121	0.0133	0.0052	0.0103	61	Maternal smoking	TPPP
cg08867399	0.0094	0.0036	0.0103	63	Active smoking	HS6ST1
cg26804772	0.0074	0.0029	0.0106	171	Active smoking	
cg12192566	0.0149	0.0058	0.0107	52	Active smoking	CD14
cg11186344	-0.0099	0.0039	0.0107	121	Active smoking	IFFO2
cg17636752	-0.0115	0.0045	0.0107	130	Maternal smoking	RUNX2
cg27526649	-0.0065	0.0025	0.0107	398	Active smoking	
cg25341925	-0.0088	0.0035	0.0107	110	Active smoking	NPPA

cg11753018	0.0076	0.0030	0.0107	255	Active smoking	RASSF4
cg27139956	0.0070	0.0028	0.0107	280	Active smoking	RASSF4
cg15117739	-0.0103	0.0040	0.0108	68	Maternal smoking	HOXB9
cg18960218	0.0110	0.0043	0.0110	61	Active smoking	SLC7A7
cg02776313	0.0067	0.0026	0.0110	307	Active smoking	TYMP
cg10416593	0.0076	0.0030	0.0110	300	Active smoking	TYMP
cg16367976	0.0129	0.0051	0.0110	73	Active smoking	TYMP
cg15778054	-0.0112	0.0044	0.0111	79	Active smoking	KCTD14
cg12528056	0.0096	0.0038	0.0111	119	Active smoking	GPR44
cg06360427	-0.0082	0.0032	0.0111	29	Active smoking	GALR1
cg02549628	-0.0147	0.0058	0.0112	64	Active smoking	SPP1
cg26548293	-0.0059	0.0023	0.0113	529	Maternal smoking	C1orf77
cg02771260	-0.0053	0.0021	0.0113	593	Active smoking	MS4A3
cg12073833	-0.0073	0.0029	0.0115	338	Active smoking	MAD1L1
cg11590282	0.0112	0.0044	0.0115	129	Active smoking	
cg02462416	0.0074	0.0029	0.0115	269	Both	
cg02704502	0.0081	0.0032	0.0115	231	Both	
cg00061520	0.0142	0.0056	0.0118	54	Active smoking	ADCY9
cg23771366	0.0117	0.0047	0.0118	90	Both	PRSS23
cg08548559	0.0084	0.0034	0.0118	56	Active smoking	PIK3IP1
cg26145504	0.0167	0.0066	0.0119	54	Active smoking	
cg04682135	0.0092	0.0037	0.0120	141	Maternal smoking	C3orf55
cg14903689	-0.0104	0.0041	0.0120	54	Maternal smoking	COL18A1
cg13318071	0.0084	0.0034	0.0120	121	Maternal smoking	MESP2
cg25376651	-0.0101	0.0040	0.0122	100	Active smoking	EEF1DP3
cg04236329	0.0154	0.0061	0.0125	62	Active smoking	EXOC3
cg01328473	0.0129	0.0051	0.0125	102	Active smoking	PXDN
cg01454592	-0.0086	0.0034	0.0127	176	Maternal smoking	CCDC36
cg15089077	0.0086	0.0034	0.0128	141	Active smoking	TTC22
cg19022697	0.0151	0.0061	0.0128	42	Active smoking	TTC22
cg24550149	0.0095	0.0038	0.0128	113	Active smoking	TTC22
cg02272278	0.0116	0.0047	0.0128	77	Active smoking	SYNJ2
cg14548802	-0.0097	0.0039	0.0128	137	Active smoking	COL5A1
cg27661460	-0.0048	0.0019	0.0129	877	Active smoking	FAM38A
cg04602696	0.0050	0.0020	0.0129	749	Active smoking	FAM38A
cg16555417	0.0057	0.0023	0.0130	440	Maternal smoking	
cg02826890	-0.0056	0.0023	0.0130	332	Active smoking	ZNF767
cg14473838	-0.0159	0.0064	0.0132	41	Maternal smoking	
cg10888348	-0.0120	0.0048	0.0133	89	Active smoking	FOXK1
cg04440283	0.0111	0.0045	0.0133	90	Maternal smoking	TRHR
cg04460372	-0.0125	0.0050	0.0134	55	Active smoking	ST6GALNAC6
cg13873269	-0.0050	0.0020	0.0135	57	Active smoking	SUSD1
cg12833872	0.0110	0.0044	0.0135	99	Maternal smoking	SLC9A3
cg22572362	0.0116	0.0047	0.0135	98	Maternal smoking	SLC9A3
cg24466377	0.0115	0.0047	0.0135	39	Active smoking	SIX5
cg18878432	0.0166	0.0067	0.0136	61	Maternal smoking	LOC404266
cg00353643	-0.0140	0.0057	0.0138	101	Active smoking	UNKL
cg00981651	0.0110	0.0045	0.0139	96	Active smoking	PCIF1
cg27529037	0.0054	0.0022	0.0139	606	Active smoking	PCIF1
cg13914531	0.0202	0.0082	0.0139	56	Active smoking	IRF5
cg26359488	-0.0072	0.0029	0.0139	318	Maternal smoking	C1orf77
cg16513459	-0.0104	0.0042	0.0140	106	Active smoking	KCNAB3
cg07554496	-0.0112	0.0045	0.0140	88	Active smoking	HDAC4
cg00377497	-0.0140	0.0057	0.0141	81	Maternal smoking	TRIM35
cg17004975	-0.0167	0.0068	0.0141	53	Active smoking	
cg17979719	-0.0075	0.0031	0.0142	56	Active smoking	SYNE1
cg16597391	-0.0132	0.0054	0.0144	76	Active smoking	
cg13299325	-0.0132	0.0054	0.0146	75	Active smoking	
cg15122985	0.0118	0.0048	0.0147	68	Active smoking	TCEA2
cg15813090	-0.0066	0.0027	0.0147	323	Active smoking	EXOC3
cg17137888	0.0161	0.0066	0.0147	57	Active smoking	
cg15298286	0.0205	0.0084	0.0149	50	Active smoking	C17orf72
cg00506935	0.0102	0.0042	0.0150	131	Active smoking	AEN
cg17696194	0.0059	0.0024	0.0151	51	Active smoking	DTX4
cg21935536	-0.0143	0.0059	0.0151	63	Active smoking	ANPEP
cg09643139	0.0141	0.0058	0.0152	58	Active smoking	TOX
cg25560443	-0.0063	0.0026	0.0153	346	Maternal smoking	KLHL29
cg05182265	-0.0045	0.0018	0.0153	852	Maternal smoking	UBE3C
cg10061906	0.0152	0.0063	0.0154	66	Active smoking	ZNF34
cg14095101	0.0106	0.0044	0.0155	48	Active smoking	TRPM6
cg01016119	-0.0128	0.0053	0.0155	157	Active smoking	ARHGEF3
cg08701566	0.0077	0.0032	0.0156	179	Active smoking	CHRNA3
cg00461022	0.0085	0.0035	0.0156	293	Active smoking	FAM134B
cg25284397	0.0136	0.0056	0.0157	62	Both	CDK6
cg26709300	0.0114	0.0047	0.0157	102	Maternal smoking	YPEL3
cg01570068	0.0080	0.0033	0.0159	155	Active smoking	KBTBD11
cg16509355	0.0138	0.0057	0.0159	60	Active smoking	CC2D2A
cg04598670	0.0105	0.0044	0.0159	68	Maternal smoking	
cg24576425	0.0152	0.0063	0.0160	52	Active smoking	GALNT5
cg27409015	0.0087	0.0036	0.0160	160	Active smoking	GALNT5
cg20469837	0.0101	0.0042	0.0160	105	Both	GALNT5
cg27582124	0.0121	0.0050	0.0160	77	Both	GALNT5
cg23560546	-0.0070	0.0029	0.0162	237	Maternal smoking	DAPL1
cg11042320	-0.0134	0.0056	0.0162	65	Active smoking	PDGFRB
cg23126342	-0.0122	0.0051	0.0164	65	Active smoking	PCDH9
cg12407791	-0.0057	0.0024	0.0164	598	Active smoking	UNC13D
cg23238119	0.0117	0.0049	0.0164	70	Maternal smoking	C6orf147
cg13983063	-0.0070	0.0029	0.0165	244	Active smoking	PPP2R2B
cg15465439	-0.0069	0.0029	0.0165	260	Active smoking	CTTN
cg12763668	0.0137	0.0057	0.0167	52	Active smoking	CAPZB
cg14274621	0.0102	0.0043	0.0168	149	Active smoking	
cg16363586	-0.0106	0.0044	0.0170	108	Maternal smoking	BST2
cg03591499	-0.0061	0.0025	0.0171	258	Active smoking	RFTN1
cg04364261	-0.0142	0.0060	0.0172	98	Active smoking	
cg15794034	-0.0105	0.0044	0.0178	123	Active smoking	AMICA1
cg26645655	-0.0125	0.0053	0.0178	56	Active smoking	
cg18981338	0.0169	0.0071	0.0179	40	Maternal smoking	DHRS4
cg16913064	-0.0116	0.0049	0.0180	79	Active smoking	

cg13897134	0.0137	0.0058	0.0181	62	Maternal smoking	ZIC4
cg02607237	0.0087	0.0037	0.0181	153	Maternal smoking	
cg03234777	-0.0092	0.0039	0.0183	189	Active smoking	AMICA1
cg07839313	0.0112	0.0048	0.0184	81	Active smoking	BST2
cg07929768	0.0060	0.0026	0.0184	38	Both	
cg00854314	0.0184	0.0078	0.0184	60	Active smoking	ISG20
cg26018382	-0.0080	0.0034	0.0185	215	Active smoking	MOSC1
cg18869709	-0.0108	0.0046	0.0186	211	Active smoking	PACSIN2
cg23247955	0.0042	0.0018	0.0186	1193	Maternal smoking	LRRC59
cg15986413	-0.0088	0.0037	0.0186	87	Active smoking	ECEL1
cg15059065	-0.0127	0.0054	0.0186	58	Both	NR2F6
cg04534765	-0.0113	0.0048	0.0187	76	Active smoking	GALR1
cg15176413	0.0110	0.0047	0.0188	32	Active smoking	FOXK1
cg02999476	0.0137	0.0058	0.0188	52	Active smoking	TMEM8A
cg04230060	-0.0046	0.0020	0.0189	49	Active smoking	SUSD1
cg02057716	0.0148	0.0063	0.0189	50	Active smoking	TNS1
cg12157673	0.0115	0.0049	0.0190	60	Active smoking	ZNF578
cg11461808	-0.0127	0.0054	0.0191	74	Active smoking	GPER
cg02886591	0.0112	0.0048	0.0193	81	Active smoking	TBKBP1
cg00147172	-0.0059	0.0025	0.0194	304	Maternal smoking	
cg25985504	-0.0071	0.0030	0.0196	77	Active smoking	
cg19628934	-0.0161	0.0069	0.0197	59	Active smoking	
cg22641093	-0.0100	0.0043	0.0199	121	Active smoking	FAM125A
cg15029032	0.0063	0.0027	0.0199	98	Active smoking	
cg05805236	-0.0043	0.0018	0.0200	887	Active smoking	PCNXL3
cg17823346	-0.0064	0.0028	0.0200	438	Active smoking	ZMIZ1
cg18919659	0.0109	0.0047	0.0203	113	Active smoking	PACSIN2
cg19358608	-0.0127	0.0055	0.0204	107	Active smoking	
cg00574379	-0.0063	0.0027	0.0204	351	Active smoking	
cg26084700	0.0105	0.0045	0.0205	106	Both	
cg05468303	0.0131	0.0056	0.0205	68	Active smoking	DGCR6
cg14191688	-0.0081	0.0035	0.0205	167	Active smoking	CTTN
cg17127702	-0.0055	0.0024	0.0206	601	Active smoking	PARP1
cg23712594	-0.0159	0.0069	0.0206	80	Active smoking	PARP1
cg08572767	-0.0097	0.0042	0.0206	162	Active smoking	CD52
cg13888509	0.0163	0.0070	0.0209	61	Maternal smoking	STRA6
cg26216876	0.0106	0.0046	0.0211	146	Active smoking	SLMO2
cg20011983	0.0046	0.0020	0.0211	652	Active smoking	
cg15253520	-0.0068	0.0030	0.0213	239	Maternal smoking	FAM82B
cg11014740	0.0110	0.0048	0.0214	75	Active smoking	
cg02017109	-0.0140	0.0061	0.0214	49	Maternal smoking	WDR41
cg16617872	0.0133	0.0058	0.0218	78	Maternal smoking	SERPINE1
cg13885120	0.0169	0.0074	0.0219	40	Maternal smoking	COL5A1
cg06022607	0.0206	0.0090	0.0219	32	Maternal smoking	
cg14078579	-0.0044	0.0019	0.0220	948	Maternal smoking	FBRSL1
cg19452802	0.0080	0.0035	0.0220	121	Active smoking	
cg03222009	0.0095	0.0041	0.0220	91	Both	HS6ST1
cg03554335	0.0129	0.0056	0.0221	81	Active smoking	C17orf72
cg15474579	-0.0097	0.0042	0.0222	112	Active smoking	CDKN1A
cg04290171	-0.0130	0.0057	0.0225	56	Active smoking	CD46
cg05839709	0.0082	0.0036	0.0226	135	Maternal smoking	ZC3H12C
cg08869273	0.0096	0.0042	0.0229	111	Maternal smoking	SIGIRR
cg27106909	0.0111	0.0049	0.0231	89	Maternal smoking	YPEL3
cg03789791	0.0110	0.0048	0.0232	80	Active smoking	
cg25361506	0.0142	0.0063	0.0235	83	Active smoking	
cg05734973	0.0057	0.0025	0.0235	212	Maternal smoking	ZFYVE20
cg26910511	0.0085	0.0038	0.0236	92	Active smoking	LRFN1
cg21171704	0.0044	0.0020	0.0237	197	Maternal smoking	BICD2
cg09701700	0.0081	0.0036	0.0238	161	Active smoking	MIR146B
cg22632947	-0.0097	0.0043	0.0241	149	Maternal smoking	PRKCA
cg11660018	0.0137	0.0061	0.0245	58	Active smoking	PRSS23
cg15667844	-0.0115	0.0051	0.0245	63	Active smoking	DUSP5
cg23506842	-0.0093	0.0041	0.0247	68	Active smoking	PTPN7
cg09544050	-0.0053	0.0024	0.0247	367	Active smoking	BAI1
cg12436568	-0.0084	0.0037	0.0248	64	Active smoking	PTPN7
cg03480383	0.0206	0.0092	0.0249	34	Active smoking	SPIRE2
cg12112234	-0.0106	0.0047	0.0251	70	Active smoking	TGM4
cg18824585	0.0114	0.0051	0.0259	67	Active smoking	CSMD3
cg24796998	0.0110	0.0050	0.0260	79	Active smoking	
cg03969515	0.0138	0.0062	0.0261	57	Maternal smoking	
cg22588715	0.0092	0.0041	0.0261	102	Active smoking	MYT1L
cg07341220	0.0077	0.0035	0.0267	175	Maternal smoking	IFT140
cg03759239	0.0104	0.0047	0.0269	89	Active smoking	RGS13
cg02547426	-0.0137	0.0062	0.0269	69	Active smoking	RGS12
cg00175403	0.0168	0.0076	0.0273	47	Active smoking	
cg09119776	0.0149	0.0068	0.0273	49	Both	SUFU
cg00785482	-0.0232	0.0105	0.0277	32	Active smoking	
cg17930194	-0.0132	0.0060	0.0277	49	Active smoking	LHX6
cg11837293	-0.0169	0.0077	0.0278	34	Active smoking	
cg15299997	0.0137	0.0062	0.0282	55	Maternal smoking	UGT1A5
cg15417641	0.0116	0.0053	0.0283	62	Both	CACNA1D
cg21188533	0.0118	0.0054	0.0283	51	Both	CACNA1D
cg12921411	-0.0067	0.0031	0.0288	217	Active smoking	SYNPO
cg11097968	0.0111	0.0051	0.0290	82	Maternal smoking	
cg08563601	-0.0071	0.0032	0.0292	220	Active smoking	BARD1
cg24607575	-0.0082	0.0038	0.0292	153	Active smoking	BARD1
cg20800117	0.0072	0.0033	0.0292	184	Maternal smoking	CAMTA1
cg22311015	0.0144	0.0066	0.0295	54	Active smoking	AQP12A
cg24714497	-0.0089	0.0041	0.0296	105	Active smoking	ELAVL3
cg03399898	0.0102	0.0047	0.0298	43	Active smoking	
cg10536276	0.0119	0.0055	0.0300	80	Maternal smoking	PSD4
cg06532880	0.0137	0.0063	0.0300	43	Active smoking	PRELID1
cg13377102	-0.0147	0.0068	0.0300	52	Active smoking	KCNAB3
cg26585644	-0.0122	0.0056	0.0300	56	Active smoking	DCI
cg09990613	-0.0076	0.0035	0.0301	155	Active smoking	TCEA2
cg27130176	0.0066	0.0031	0.0302	271	Active smoking	CCDC64B
cg00045902	0.0082	0.0038	0.0304	163	Active smoking	PWWP2B
cg08751508	0.0070	0.0032	0.0304	234	Active smoking	PWWP2B

cg25859045	-0.0105	0.0048	0.0305	78	Maternal smoking	SAC3D1
cg24750308	-0.0074	0.0034	0.0306	58	Active smoking	NOX4
cg17801352	-0.0111	0.0051	0.0308	62	Active smoking	PXDN
cg15233611	-0.0183	0.0085	0.0309	39	Both	SETD1B
cg07586008	0.0116	0.0054	0.0313	72	Maternal smoking	PPFIA3
cg06193043	-0.0047	0.0022	0.0315	514	Active smoking	NPPA
cg20202438	-0.0078	0.0036	0.0315	172	Active smoking	NPPA
cg24844545	-0.0048	0.0022	0.0315	522	Active smoking	NPPA
cg14852082	0.0093	0.0043	0.0319	52	Active smoking	
cg03120475	-0.0112	0.0052	0.0321	64	Active smoking	FAM171A1
cg24715680	0.0095	0.0045	0.0322	86	Active smoking	BARD1
cg18480781	0.0166	0.0078	0.0323	33	Both	
cg05624954	-0.0120	0.0056	0.0324	72	Active smoking	
cg01206378	0.0101	0.0047	0.0326	74	Maternal smoking	RWDD3
cg07639376	0.0058	0.0027	0.0326	207	Maternal smoking	IFT140
cg06417962	-0.0058	0.0027	0.0326	268	Active smoking	RNH1
cg24800754	0.0120	0.0056	0.0327	74	Active smoking	MLLT1
cg17892069	-0.0101	0.0047	0.0328	83	Maternal smoking	AUTS2
cg21698310	0.0116	0.0055	0.0332	62	Active smoking	PPP1R9B
cg20490392	-0.0099	0.0046	0.0332	54	Active smoking	ANGPT2
cg25968437	0.0068	0.0032	0.0335	107	Active smoking	
cg17189494	-0.0107	0.0051	0.0335	74	Active smoking	MAD2L2
cg08324115	-0.0126	0.0059	0.0337	73	Active smoking	
cg24247370	-0.0119	0.0056	0.0338	97	Both	STK24
cg01486260	-0.0124	0.0058	0.0340	36	Active smoking	ITGAX
cg12009872	0.0091	0.0043	0.0340	38	Active smoking	CYP19A1
cg22517925	0.0105	0.0050	0.0343	83	Active smoking	TESC
cg01637175	-0.0040	0.0019	0.0344	806	Active smoking	KCNJ12
cg04961911	-0.0077	0.0037	0.0344	135	Active smoking	FANCG
cg21437157	0.0077	0.0036	0.0345	191	Active smoking	
cg00960209	0.0068	0.0032	0.0346	243	Active smoking	
cg01157559	0.0053	0.0025	0.0346	505	Active smoking	
cg10249734	-0.0106	0.0050	0.0349	32	Active smoking	SECTM1
cg08133631	-0.0123	0.0058	0.0352	121	Maternal smoking	CATSPER4
cg20415053	-0.0087	0.0041	0.0352	218	Maternal smoking	CATSPER4
cg18158419	-0.0075	0.0035	0.0353	51	Both	FIS1
cg25491122	-0.0119	0.0057	0.0354	51	Active smoking	PCDH9
cg15692360	0.0098	0.0046	0.0355	78	Maternal smoking	FERMT1
cg10072237	0.0039	0.0019	0.0355	967	Active smoking	
cg14626907	0.0072	0.0034	0.0355	226	Active smoking	
cg14753872	0.0072	0.0034	0.0355	307	Active smoking	
cg12648759	-0.0089	0.0042	0.0357	58	Active smoking	ATF6
cg20712808	0.0142	0.0068	0.0361	48	Active smoking	
cg20329047	0.0055	0.0026	0.0365	396	Both	BOP1
cg01299997	-0.0074	0.0035	0.0366	76	Maternal smoking	FIS1
cg02840794	-0.0139	0.0067	0.0367	43	Active smoking	HPS6
cg17792616	0.0081	0.0039	0.0369	163	Maternal smoking	
cg20654462	0.0095	0.0045	0.0369	123	Maternal smoking	
cg27574595	-0.0128	0.0061	0.0370	57	Active smoking	RARB
cg07791160	-0.0051	0.0025	0.0375	462	Active smoking	
cg24249791	-0.0051	0.0025	0.0375	393	Active smoking	
cg04956306	-0.0081	0.0039	0.0377	196	Active smoking	MAPK12
cg05150608	0.0046	0.0022	0.0378	630	Maternal smoking	
cg23430664	-0.0100	0.0048	0.0378	91	Active smoking	XYLT2
cg10312186	0.0094	0.0045	0.0380	91	Both	
cg14168009	0.0095	0.0046	0.0380	114	Maternal smoking	CARD11
cg08946995	0.0040	0.0019	0.0381	1230	Active smoking	
cg12594615	0.0161	0.0078	0.0382	114	Maternal smoking	TBC1D8
cg12555334	0.0056	0.0027	0.0384	367	Both	CCT6A
cg04477962	0.0153	0.0074	0.0384	37	Active smoking	METTL7A
cg07734975	-0.0082	0.0040	0.0385	134	Active smoking	
cg17344321	-0.0085	0.0041	0.0385	169	Active smoking	
cg21279955	0.0119	0.0058	0.0386	55	Active smoking	SLC27A3
cg09264140	-0.0161	0.0078	0.0387	37	Active smoking	FMNL1
cg18107425	0.0070	0.0034	0.0390	152	Both	MESP2
cg00070899	0.0077	0.0037	0.0391	126	Active smoking	GRM4
cg01081636	0.0102	0.0050	0.0391	79	Active smoking	GRM4
cg10270430	0.0079	0.0039	0.0391	120	Active smoking	GRM4
cg17762073	0.0084	0.0040	0.0391	92	Active smoking	GRM4
cg27198497	0.0071	0.0034	0.0391	237	Active smoking	
cg27351978	0.0095	0.0046	0.0394	49	Maternal smoking	DLGAP2
cg27618939	0.0116	0.0057	0.0396	67	Active smoking	XKR9
cg07578772	0.0129	0.0063	0.0398	130	Active smoking	FAM194A
cg14263391	-0.0108	0.0053	0.0400	71	Maternal smoking	GRB7
cg09895166	-0.0107	0.0052	0.0400	64	Active smoking	LRBA
cg03229780	-0.0160	0.0078	0.0400	31	Active smoking	
cg10819733	0.0092	0.0045	0.0401	57	Active smoking	
cg11323506	0.0088	0.0043	0.0404	120	Active smoking	RNU5E
cg12827530	0.0105	0.0051	0.0404	74	Active smoking	RNU5E
cg26416971	0.0081	0.0039	0.0404	141	Active smoking	RNU5E
cg16858211	-0.0134	0.0065	0.0405	66	Active smoking	AOAH
cg14550518	-0.0094	0.0046	0.0406	81	Active smoking	ZNF385D
cg18503679	-0.0101	0.0049	0.0406	72	Active smoking	ZNF385D
cg20738719	-0.0107	0.0052	0.0408	66	Active smoking	SEMA5B
cg15720112	-0.0060	0.0030	0.0408	95	Maternal smoking	
cg02354563	-0.0086	0.0042	0.0408	99	Maternal smoking	SLC9A3
cg26056498	0.0077	0.0038	0.0409	106	Maternal smoking	
cg23220823	-0.0141	0.0069	0.0411	49	Both	CCM2
cg12150039	0.0079	0.0039	0.0412	170	Active smoking	GRAMD1A
cg06521852	-0.0112	0.0055	0.0413	53	Active smoking	TRIOBP
cg02393699	0.0116	0.0057	0.0415	69	Maternal smoking	PRKCZ
cg23605961	0.0062	0.0030	0.0415	203	Active smoking	PRKAR1B
cg20399011	-0.0071	0.0035	0.0417	212	Maternal smoking	MGAT1
cg09338136	0.0096	0.0047	0.0417	82	Active smoking	AHRR
cg04816394	-0.0088	0.0043	0.0419	110	Active smoking	RNU5E
cg13270236	0.0141	0.0070	0.0421	39	Active smoking	UBR2
cg01405107	-0.0072	0.0035	0.0421	97	Active smoking	LOC404266
cg10009224	-0.0092	0.0045	0.0425	117	Active smoking	PCGF3

cg07109801	0.0123	0.0061	0.0426	68	Active smoking	MIR425
cg17300750	-0.0110	0.0055	0.0429	63	Active smoking	DNASE1L2
cg04180046	-0.0109	0.0054	0.0433	56	Both	MYO1G
cg00142036	-0.0052	0.0026	0.0434	362	Active smoking	SEPHS1
cg22088368	-0.0084	0.0042	0.0435	175	Active smoking	C22orf33
cg23560388	-0.0115	0.0057	0.0436	114	Both	TIAM2
cg02186444	0.0149	0.0074	0.0436	42	Active smoking	ARMC7
cg14526671	0.0098	0.0048	0.0438	85	Active smoking	
cg08922729	-0.0086	0.0043	0.0439	95	Active smoking	
cg14242246	0.0066	0.0033	0.0442	48	Active smoking	C2orf28
cg21683390	-0.0080	0.0040	0.0445	186	Active smoking	C18orf1
cg08845973	0.0079	0.0039	0.0445	96	Active smoking	SPG7
cg11413133	-0.0045	0.0022	0.0446	488	Active smoking	KCNJ12
cg10965975	-0.0070	0.0035	0.0447	163	Active smoking	
cg10465839	0.0057	0.0028	0.0449	82	Maternal smoking	IFT140
cg13809441	0.0079	0.0040	0.0449	123	Both	
cg03591238	0.0113	0.0056	0.0450	43	Active smoking	ZNHIT2
cg00550955	-0.0147	0.0073	0.0450	35	Active smoking	
cg22367556	0.0102	0.0051	0.0451	71	Active smoking	ANKS1B
cg02256631	-0.0107	0.0054	0.0468	62	Maternal smoking	ITGAM
cg14194983	-0.0048	0.0024	0.0469	320	Active smoking	NPPA
cg18008766	-0.0071	0.0036	0.0470	152	Active smoking	SFRS7
cg23484392	-0.0150	0.0075	0.0471	37	Active smoking	CCDC102B
cg11324650	-0.0121	0.0061	0.0476	42	Active smoking	
cg03710029	0.0070	0.0036	0.0482	278	Active smoking	SLC38A10
cg20826740	0.0039	0.0020	0.0486	652	Maternal smoking	
cg17527975	-0.0054	0.0027	0.0492	117	Active smoking	DENND3
cg08240539	0.0049	0.0025	0.0492	375	Active smoking	FTSJ2
cg17177599	-0.0125	0.0063	0.0493	42	Active smoking	
cg19478111	-0.0126	0.0064	0.0501	42	Active smoking	PLEKHB1
cg10373891	-0.0113	0.0058	0.0502	62	Maternal smoking	
cg12377874	0.0063	0.0032	0.0503	169	Active smoking	RAB27B
cg20739013	0.0150	0.0077	0.0503	30	Active smoking	EOMES
cg10531355	0.0166	0.0085	0.0503	31	Active smoking	SERINC5
cg11644052	-0.0078	0.0040	0.0503	151	Active smoking	NFU1
cg00153942	0.0084	0.0043	0.0506	257	Active smoking	KRTAP5-8
cg26618903	-0.0131	0.0067	0.0511	39	Active smoking	PYROXD2
cg01409207	0.0057	0.0029	0.0513	314	Maternal smoking	TESC
cg26003909	-0.0048	0.0024	0.0513	598	Both	
cg11550547	-0.0068	0.0035	0.0522	190	Active smoking	KCTD14
cg10858945	0.0147	0.0076	0.0523	67	Active smoking	
cg02703145	0.0115	0.0059	0.0523	43	Maternal smoking	
cg14598846	0.0033	0.0017	0.0526	1238	Active smoking	PLEC1
cg14920289	0.0160	0.0083	0.0526	31	Active smoking	SLC22A17
cg14334310	-0.0070	0.0036	0.0528	156	Active smoking	
cg04846451	0.0073	0.0038	0.0528	144	Maternal smoking	C2orf63
cg01559770	0.0104	0.0054	0.0532	67	Maternal smoking	KCNH2
cg25689649	0.0089	0.0046	0.0533	104	Active smoking	OCEL1
cg11850468	0.0078	0.0040	0.0533	141	Maternal smoking	MGAT1
cg16211507	0.0102	0.0053	0.0534	85	Active smoking	
cg16274899	-0.0053	0.0027	0.0535	315	Active smoking	PLEKHG3
cg01939428	-0.0067	0.0035	0.0539	64	Active smoking	UBE3C
cg04314261	0.0077	0.0040	0.0542	36	Active smoking	CLEC12B
cg18750087	0.0068	0.0035	0.0545	215	Active smoking	
cg03262802	0.0116	0.0060	0.0546	64	Active smoking	
cg03163525	-0.0085	0.0044	0.0548	90	Active smoking	
cg05886626	-0.0126	0.0065	0.0549	50	Active smoking	THBS1
cg18417061	-0.0118	0.0062	0.0552	73	Active smoking	PRKCH
cg23422170	0.0115	0.0060	0.0553	67	Active smoking	C2orf48
cg07718903	-0.0133	0.0069	0.0556	30	Maternal smoking	FERMT1
cg16659510	-0.0081	0.0042	0.0556	116	Active smoking	BANP
cg13672342	-0.0083	0.0043	0.0557	92	Active smoking	CIAO1
cg00812761	-0.0097	0.0051	0.0557	79	Active smoking	SCFD2
cg09374627	-0.0069	0.0036	0.0561	83	Maternal smoking	
cg25243766	-0.0082	0.0043	0.0562	38	Active smoking	
cg15578140	0.0126	0.0066	0.0567	55	Both	MIR548F3
cg06992846	-0.0072	0.0038	0.0568	136	Active smoking	TRIB1
cg07644039	-0.0047	0.0024	0.0568	458	Active smoking	ARL6IP4
cg14184886	0.0082	0.0043	0.0568	106	Active smoking	
cg05584950	-0.0071	0.0037	0.0570	169	Active smoking	ATOH8
cg08889843	-0.0104	0.0055	0.0570	78	Active smoking	SBK2
cg13847322	0.0171	0.0090	0.0571	35	Active smoking	RXRA
cg22678092	-0.0056	0.0029	0.0576	250	Both	FCRLB
cg07408552	0.0077	0.0041	0.0577	189	Active smoking	ATP6V0A1
cg10509626	0.0049	0.0026	0.0577	353	Active smoking	SHANK2
cg16069986	0.0079	0.0042	0.0577	123	Active smoking	SHANK2
cg17696044	0.0083	0.0044	0.0577	120	Active smoking	SHANK2
cg10707081	0.0054	0.0029	0.0579	219	Maternal smoking	PCDH9
cg19487819	-0.0063	0.0033	0.0580	141	Active smoking	MAD1L1
cg16837557	0.0063	0.0033	0.0580	177	Active smoking	KIRREL3
cg24973226	0.0130	0.0069	0.0583	52	Maternal smoking	STIM1
cg02569613	-0.0084	0.0044	0.0587	114	Active smoking	C10orf72
cg17979068	0.0064	0.0034	0.0594	247	Active smoking	C2orf48
cg10002066	-0.0145	0.0077	0.0594	43	Both	RASA3
cg19038540	-0.0087	0.0046	0.0595	104	Active smoking	S1PR1
cg01075005	0.0061	0.0032	0.0595	154	Maternal smoking	
cg15230883	-0.0060	0.0032	0.0596	160	Active smoking	DCP1A
cg05698090	-0.0088	0.0047	0.0597	53	Maternal smoking	CERK
cg17373345	-0.0090	0.0048	0.0599	85	Active smoking	DNAJC5B
cg26179134	-0.0103	0.0055	0.0603	71	Maternal smoking	DTNB
cg10395101	-0.0078	0.0042	0.0605	40	Active smoking	ANGPT2
cg04300115	0.0096	0.0051	0.0605	64	Active smoking	PRIC285
cg04630273	-0.0123	0.0066	0.0607	35	Active smoking	ZBTB46
cg27631256	-0.0057	0.0031	0.0607	63	Active smoking	TNFSF8
cg01478234	0.0121	0.0065	0.0608	44	Active smoking	BTBD11
cg13935577	0.0085	0.0045	0.0608	91	Active smoking	BTBD11
cg21535366	0.0111	0.0059	0.0608	50	Active smoking	BTBD11
cg27567561	0.0064	0.0034	0.0608	153	Active smoking	BTBD11

cg24718367	-0.0063	0.0034	0.0610	51	Active smoking	MAD2L2
cg07875360	0.0120	0.0064	0.0616	105	Maternal smoking	NDUFS6
cg25508605	0.0097	0.0052	0.0618	71	Active smoking	SLCO3A1
cg05589489	-0.0044	0.0024	0.0622	429	Active smoking	
cg04569233	-0.0116	0.0062	0.0622	50	Active smoking	CX3CR1
cg05529343	-0.0060	0.0032	0.0623	258	Active smoking	
cg15693572	-0.0056	0.0030	0.0623	215	Active smoking	
cg14145338	-0.0121	0.0065	0.0623	40	Active smoking	LCN8
cg13523236	0.0063	0.0034	0.0626	206	Active smoking	
cg24860092	0.0064	0.0035	0.0631	65	Maternal smoking	
cg20059377	-0.0045	0.0024	0.0634	591	Active smoking	TBC1D2B
cg02147592	0.0069	0.0037	0.0636	191	Active smoking	MAP2K2
cg10691866	0.0120	0.0064	0.0638	36	Both	TPST1
cg22637865	0.0075	0.0040	0.0638	62	Active smoking	TTLL1
cg17725019	0.0080	0.0043	0.0638	180	Maternal smoking	PIK3IP1
cg20592017	0.0039	0.0021	0.0642	49	Maternal smoking	
cg27383418	0.0137	0.0074	0.0644	35	Both	
cg23732845	0.0101	0.0055	0.0650	72	Active smoking	AIM1L
cg07919145	0.0120	0.0065	0.0653	66	Active smoking	SYNGR1
cg00347798	-0.0053	0.0029	0.0653	35	Active smoking	
cg26279261	0.0095	0.0051	0.0656	430	Active smoking	NR2F6
cg11063110	-0.0110	0.0060	0.0656	44	Maternal smoking	CPA5
cg09262442	0.0100	0.0054	0.0656	59	Active smoking	C10orf18
cg11730703	-0.0095	0.0052	0.0663	73	Active smoking	INF2
cg04864179	-0.0134	0.0073	0.0664	151	Active smoking	IRF5
cg18286285	-0.0094	0.0051	0.0667	79	Maternal smoking	LDB3
cg01081584	-0.0079	0.0043	0.0673	111	Maternal smoking	EIF2AK4
cg04517524	0.0096	0.0053	0.0673	58	Active smoking	ASB2
cg12195135	-0.0086	0.0047	0.0674	82	Active smoking	ZNF584
cg06598631	0.0105	0.0057	0.0675	94	Maternal smoking	RARS2
cg18055623	-0.0115	0.0063	0.0677	50	Active smoking	CACNG8
cg21946195	-0.0095	0.0052	0.0679	84	Maternal smoking	ATOH8
cg04255391	0.0034	0.0018	0.0684	90	Active smoking	PLEC1
cg13059495	0.0070	0.0038	0.0684	95	Active smoking	TPRG1L
cg17519479	0.0075	0.0041	0.0690	169	Active smoking	
cg01238669	0.0038	0.0021	0.0690	425	Active smoking	DNAH11
cg17826006	-0.0156	0.0086	0.0693	32	Active smoking	
cg16608018	0.0077	0.0043	0.0695	104	Active smoking	
cg19367951	-0.0101	0.0056	0.0698	57	Active smoking	POM121C
cg03631078	-0.0074	0.0041	0.0699	156	Active smoking	ZBTB20
cg11739399	-0.0110	0.0061	0.0700	53	Active smoking	IKBKE
cg19268652	-0.0144	0.0080	0.0700	45	Active smoking	HIVEP1
cg03475293	0.0066	0.0037	0.0702	145	Active smoking	
cg26574777	0.0109	0.0060	0.0705	43	Active smoking	PCCA
cg26130090	0.0112	0.0062	0.0708	55	Active smoking	
cg08951051	0.0088	0.0049	0.0708	80	Maternal smoking	
cg18025831	-0.0060	0.0033	0.0708	194	Active smoking	DCP1A
cg05612654	0.0107	0.0059	0.0710	67	Active smoking	
cg05987787	0.0086	0.0048	0.0711	80	Active smoking	SYNJ2
cg24735226	-0.0050	0.0028	0.0712	266	Active smoking	CACHD1
cg22045942	0.0063	0.0035	0.0713	247	Active smoking	GRAMD1A
cg13717350	0.0038	0.0021	0.0713	711	Active smoking	SARDH
cg02525435	0.0076	0.0042	0.0717	83	Maternal smoking	CBFA2T3
cg25323057	0.0051	0.0028	0.0719	265	Active smoking	C10orf116
cg05379350	-0.0085	0.0047	0.0720	93	Active smoking	GIT1
cg04917197	0.0075	0.0042	0.0721	103	Maternal smoking	
cg11672277	-0.0102	0.0057	0.0724	43	Maternal smoking	MAPRE2
cg07520810	0.0133	0.0074	0.0727	42	Active smoking	ARID5B
cg02869364	-0.0062	0.0034	0.0728	52	Both	C7orf50
cg13451356	0.0056	0.0031	0.0728	209	Maternal smoking	
cg02266399	0.0110	0.0061	0.0728	46	Maternal smoking	FAM115A
cg16329197	-0.0040	0.0022	0.0728	453	Active smoking	
cg11902777	0.0111	0.0062	0.0729	39	Both	AHRR
cg09587957	0.0116	0.0064	0.0730	91	Active smoking	BMF
cg25135322	-0.0045	0.0025	0.0731	376	Active smoking	GSTP1
cg05136804	0.0069	0.0038	0.0732	165	Both	ZNF397OS
cg03638795	0.0096	0.0054	0.0734	83	Active smoking	SIGIRR
cg07890839	-0.0049	0.0027	0.0735	219	Maternal smoking	SMAD3
cg10802414	-0.0095	0.0053	0.0735	71	Maternal smoking	HCN3
cg22472290	0.0061	0.0034	0.0737	189	Active smoking	ZNF577
cg04064380	0.0106	0.0059	0.0737	52	Active smoking	
cg11303839	-0.0099	0.0055	0.0741	71	Active smoking	CCL26
cg18584012	0.0092	0.0051	0.0742	47	Active smoking	CHMP4C
cg11708721	0.0066	0.0037	0.0746	57	Active smoking	PTGFRN
cg04037228	0.0054	0.0030	0.0750	244	Maternal smoking	LIMD1
cg15175162	0.0090	0.0051	0.0751	35	Maternal smoking	FBXL5
cg11530213	-0.0052	0.0029	0.0755	301	Active smoking	PLAT
cg00971695	-0.0090	0.0050	0.0757	70	Maternal smoking	
cg11877254	0.0070	0.0040	0.0766	29	Active smoking	PPAN-P2RY11
cg02780269	-0.0087	0.0049	0.0768	83	Active smoking	SECTM1
cg23395310	0.0057	0.0032	0.0768	232	Both	SNHG7
cg14209784	0.0100	0.0057	0.0774	60	Active smoking	AGAP11
cg05403689	-0.0046	0.0026	0.0774	322	Active smoking	
cg22466678	-0.0049	0.0028	0.0774	278	Active smoking	
cg11298343	-0.0131	0.0074	0.0776	230	Active smoking	EGLN2
cg16417374	-0.0098	0.0056	0.0781	73	Active smoking	MAN1C1
cg14093936	0.0064	0.0037	0.0784	127	Active smoking	SEMA7A
cg00049323	0.0033	0.0019	0.0793	1189	Active smoking	LOC25845
cg09906309	-0.0063	0.0036	0.0793	120	Active smoking	C11orf46
cg26126879	-0.0045	0.0026	0.0794	594	Active smoking	
cg07234199	-0.0072	0.0041	0.0795	122	Active smoking	LOC388796
cg26145228	0.0091	0.0052	0.0798	73	Active smoking	NTNG1
cg01745789	0.0077	0.0044	0.0799	94	Maternal smoking	
cg27056132	-0.0092	0.0052	0.0801	96	Maternal smoking	
cg21717508	0.0095	0.0054	0.0802	75	Active smoking	SNX15
cg20019720	0.0034	0.0019	0.0802	820	Maternal smoking	CNKSR3
cg18745507	0.0102	0.0058	0.0807	71	Active smoking	ZGLP1
cg11609571	-0.0059	0.0034	0.0811	156	Maternal smoking	PRELID2

cg13523245	-0.0063	0.0036	0.0812	168	Active smoking	
cg18026626	0.0166	0.0095	0.0814	37	Active smoking	LOC91450
cg14841514	-0.0131	0.0075	0.0815	30	Active smoking	ZMIZ1
cg07892167	-0.0073	0.0042	0.0815	188	Active smoking	R3HCC1
cg08647652	0.0082	0.0047	0.0821	78	Active smoking	
cg09795027	-0.0070	0.0040	0.0823	161	Active smoking	EVPL
cg11375102	0.0045	0.0026	0.0825	105	Maternal smoking	IFT140
cg04232972	0.0109	0.0063	0.0829	48	Both	
cg08757742	-0.0077	0.0044	0.0829	102	Maternal smoking	RASGRF2
cg18919541	0.0056	0.0033	0.0832	82	Active smoking	
cg00451105	0.0093	0.0054	0.0846	56	Active smoking	
cg10920316	-0.0089	0.0052	0.0847	78	Active smoking	
cg18585107	0.0063	0.0036	0.0851	59	Active smoking	RPS6KA4
cg21757872	0.0137	0.0079	0.0852	33	Active smoking	BTBD11
cg23762517	-0.0042	0.0024	0.0856	392	Active smoking	HIVEP3
cg04972745	0.0093	0.0054	0.0857	71	Maternal smoking	
cg20270653	-0.0092	0.0053	0.0857	63	Active smoking	WBSCR17
cg04685387	0.0091	0.0053	0.0858	61	Active smoking	PARD3
cg17115737	0.0108	0.0063	0.0860	76	Active smoking	POR
cg01240931	0.0146	0.0085	0.0864	49	Active smoking	APC
cg00929860	-0.0123	0.0072	0.0872	58	Active smoking	SPOCK2
cg16294152	-0.0053	0.0031	0.0874	218	Active smoking	AHRR
cg15090440	-0.0062	0.0036	0.0881	159	Both	PRDM16
cg13909895	0.0065	0.0038	0.0883	30	Active smoking	ARSA
cg22881914	-0.0090	0.0053	0.0888	58	Active smoking	NID2
cg03051880	-0.0085	0.0050	0.0890	91	Active smoking	MAN1A1
cg03142697	0.0089	0.0053	0.0895	64	Maternal smoking	RUNX1
cg26576890	0.0073	0.0043	0.0899	102	Maternal smoking	
cg00091064	0.0095	0.0056	0.0899	53	Maternal smoking	
cg00982521	0.0074	0.0044	0.0899	95	Maternal smoking	
cg22789605	0.0097	0.0057	0.0901	48	Active smoking	SLC11A2
cg05272587	-0.0027	0.0016	0.0904	43	Active smoking	COL4A2
cg00233028	0.0074	0.0044	0.0905	116	Active smoking	
cg19870512	-0.0068	0.0040	0.0907	79	Active smoking	KCNA6
cg26201213	-0.0057	0.0034	0.0907	198	Active smoking	MGMT
cg02845204	0.0121	0.0072	0.0914	60	Active smoking	KRTAP5-9
cg19509778	0.0117	0.0069	0.0915	41	Active smoking	FOXI2
cg17937101	0.0074	0.0044	0.0916	93	Active smoking	MIR596
cg06711259	0.0073	0.0043	0.0916	109	Active smoking	JOSD1
cg11328127	-0.0054	0.0032	0.0916	209	Maternal smoking	SIGIRR
cg14399122	-0.0089	0.0053	0.0916	66	Active smoking	COL5A1
cg06407111	-0.0072	0.0043	0.0919	116	Active smoking	TRIM47
cg26703507	-0.0083	0.0049	0.0920	109	Active smoking	SLC20A1
cg06940168	0.0038	0.0022	0.0921	456	Active smoking	PRKCA
cg03573529	0.0089	0.0053	0.0922	90	Active smoking	
cg20322193	0.0087	0.0051	0.0925	74	Active smoking	RALA
cg06433467	0.0074	0.0044	0.0928	114	Active smoking	
cg07785717	-0.0097	0.0058	0.0930	56	Active smoking	CACNG8
cg02558476	0.0089	0.0053	0.0933	96	Active smoking	ZG16B
cg01548777	0.0090	0.0054	0.0934	67	Both	ZBTB46
cg04473569	-0.0089	0.0053	0.0936	78	Active smoking	CLDN15
cg07941108	0.0113	0.0067	0.0939	64	Active smoking	
cg11386711	-0.0113	0.0067	0.0940	55	Maternal smoking	ST6GAL1
cg24933919	0.0064	0.0038	0.0943	280	Maternal smoking	
cg20227259	-0.0065	0.0039	0.0945	135	Active smoking	FAM45B
cg02030270	-0.0040	0.0024	0.0947	571	Active smoking	SH3GL3
cg04031093	-0.0089	0.0053	0.0949	128	Both	
cg05357209	-0.0043	0.0026	0.0953	505	Active smoking	UNC84A
cg12803068	-0.0082	0.0049	0.0954	84	Both	MYO1G

TABLE H.2: Results of the fourth step of our MR framework, where multiple *cis*-SNPs were available for the CpGs related to maternal or active smoking. Results are given as β coefficient, standard error and p-value from IVW, weighted median and MR-Egger estimate. Exposure: Exposure to which the methylation was previously linked; either active smoking, maternal smoking or both.

	IVW			Weighted			MR-Egger						
CpG	**Beta**	**SE**	**P**	**Beta**	**SE**	**P**	**Beta**	**SE**	**P**	**P intercept**	**Nr. SNPs**	**Exposure**	**Gene**
cg17976873	0.0151	0.0031	1.40E-06	0.0134	0.0037	0.0003	0.0092	0.0082	0.2588	0.4379	3	Maternal smoking	REM2
cg15212369	0.0141	0.0033	2.05E-05	0.0180	0.0042	1.80E-05	0.0451	0.0132	6.49E-04	0.0154	3	Active smoking	STMN3
cg06589051	0.0115	0.0034	8.06E-04	0.0140	0.0054	0.0091	0.0639	0.0417	0.1249	0.2016	3	Active smoking	TGFBRAP1
cg18923740	0.0073	0.0022	8.93E-04	0.0086	0.0025	0.0005	0.0112	0.0180	0.5325	0.8254	3	Active smoking	NBL1
cg08883485	0.0063	0.0021	0.0029	0.0045	0.0032	0.1529	-0.0055	0.0243	0.8209	0.6159	3	Both	NAV1
cg16127683	-0.0078	0.0027	0.0044	-0.0074	0.0030	0.0130	-0.0064	0.0059	0.2748	0.7874	3	Maternal smoking	EIF2AK4
cg20255370	-0.0081	0.0032	0.0108	-0.0086	0.0036	0.0167	-0.0096	0.0073	0.1872	0.8151	3	Maternal smoking	EIF2AK4
cg20401567	0.0078	0.0033	0.0182	0.0079	0.0037	0.0355	0.0001	0.0343	0.9976	0.8217	3	Maternal smoking	
cg07277038	0.0051	0.0027	0.0552	0.0062	0.0036	0.0822	-0.0246	0.0145	0.0901	0.0371	3	Active smoking	LRRC33
cg20102019	-0.0035	0.0019	0.0623	-0.0046	0.0020	0.0221	-0.0214	0.0063	0.0006	0.0027	3	Maternal smoking	
cg19757176	0.0059	0.0033	0.0729	0.0047	0.0039	0.2310	0.0057	0.0091	0.5323	0.9803	3	Both	TPM3
cg23161492	-0.0047	0.0031	0.1340	-0.0029	0.0038	0.4371	-0.0175	0.0112	0.1184	0.2347	3	Both	ANPEP
cg12439232	0.0036	0.0024	0.1356	0.0045	0.0026	0.0816	0.0104	0.0055	0.0575	0.1512	3	Active smoking	
cg13483797	0.0033	0.0023	0.1572	0.0036	0.0025	0.1507	-0.0052	0.0069	0.4561	0.1975	3	Active smoking	PRRX2
cg07427475	0.0018	0.0013	0.1808	0.0019	0.0014	0.1895	0.0070	0.0040	0.0767	0.1331	3	Active smoking	PLEC1
cg04017131	-0.0037	0.0027	0.1827	-0.0039	0.0033	0.2422	0.0216	0.0369	0.5576	0.4899	3	Active smoking	ANGPT2
cg16274678	0.0044	0.0033	0.1829	0.0041	0.0039	0.2940	0.0097	0.0166	0.5584	0.7462	3	Active smoking	TPM3
cg23849826	0.0038	0.0030	0.1988	0.0042	0.0034	0.2121	0.0063	0.0092	0.4934	0.7765	3	Maternal smoking	THBS1

cg12848614	0.0019	0.0015	0.2161	0.0040	0.0020	0.0477	0.0622	0.0943	0.5094	0.5220	3	Active smoking	
cg26572811	-0.0047	0.0038	0.2227	-0.0083	0.0051	0.1061	0.0409	0.0603	0.4969	0.4466	3	Active smoking	HS3ST3B1
cg25350011	-0.0031	0.0027	0.2529	-0.0025	0.0031	0.4175	0.0194	0.0219	0.3763	0.2987	3	Active smoking	ANGPT2
cg04494136	-0.0031	0.0029	0.2866	-0.0027	0.0033	0.4143	-0.0050	0.0075	0.5065	0.7884	3	Both	CTBP2
cg10078511	0.0029	0.0028	0.3013	0.0030	0.0033	0.3721	0.0082	0.0118	0.4832	0.6406	4	Maternal smoking	THBS1
cg24192569	-0.0031	0.0031	0.3078	-0.0034	0.0035	0.3347	-0.0115	0.0077	0.1352	0.2357	3	Active smoking	SDK1
cg11718162	-0.0038	0.0038	0.3118	-0.0027	0.0050	0.5876	-0.0107	0.0207	0.6062	0.7220	3	Active smoking	TPM3
cg06167719	0.0022	0.0025	0.3794	0.0024	0.0026	0.3647	-0.0017	0.0063	0.7919	0.5038	3	Both	HLCS
cg18364858	0.0025	0.0028	0.3797	0.0061	0.0038	0.1077	-0.0140	0.0441	0.7511	0.7064	3	Both	
cg19574915	0.0031	0.0038	0.4204	0.0010	0.0046	0.8308	-0.0422	0.0444	0.3419	0.3061	3	Active smoking	ISG20
cg22349387	-0.0010	0.0014	0.4586	-0.0008	0.0015	0.6069	0.0011	0.0023	0.6391	0.2526	5	Active smoking	DDX12
cg09978105	0.0018	0.0025	0.4711	0.0014	0.0027	0.5926	0.0133	0.0060	0.0277	0.0366	3	Maternal smoking	
cg04235768	0.0020	0.0029	0.4892	0.0022	0.0034	0.5128	0.0129	0.0165	0.4363	0.5046	3	Maternal smoking	PRDM8
cg20820876	-0.0023	0.0034	0.4985	-0.0005	0.0041	0.9080	0.0287	0.1352	0.8320	0.8185	3	Active smoking	
cg25215890	0.0022	0.0036	0.5338	0.0031	0.0040	0.4381	0.0033	0.0064	0.6105	0.8448	3	Maternal smoking	CD48
cg15677087	-0.0017	0.0027	0.5344	-0.0016	0.0028	0.5556	0.0008	0.0063	0.8935	0.6604	3	Both	SLC17A9
cg14154784	0.0018	0.0032	0.5740	0.0015	0.0035	0.6607	0.0200	0.0212	0.3460	0.3855	3	Maternal smoking	TLE1
cg21351392	-0.0008	0.0017	0.6269	-0.0004	0.0019	0.8383	0.0024	0.0146	0.8689	0.8132	3	Both	AGPAT4
cg01148088	-0.0009	0.0024	0.7064	-0.0008	0.0026	0.7659	0.0159	0.0085	0.0609	0.0388	3	Active smoking	RNF144A
cg15172061	-0.0013	0.0039	0.7314	-0.0030	0.0054	0.5753	0.0942	0.1576	0.5501	0.5439	3	Maternal smoking	GSDMD
cg03144619	-0.0010	0.0031	0.7401	-0.0014	0.0035	0.6868	0.0059	0.0319	0.8528	0.8272	4	Both	GALNT2
cg05452645	0.0007	0.0024	0.7625	0.0002	0.0027	0.9369	-0.0049	0.0170	0.7749	0.7395	3	Maternal smoking	PRDM8
cg12550496	-0.0008	0.0033	0.8095	-0.0008	0.0047	0.8706	-0.0079	0.0118	0.5042	0.4663	3	Active smoking	
cg06459104	0.0007	0.0028	0.8104	0.0013	0.0031	0.6821	-0.0061	0.0082	0.4564	0.3795	3	Active smoking	EPB41L3
cg05830220	0.0008	0.0034	0.8196	0.0001	0.0039	0.9703	-0.0031	0.0127	0.8071	0.7517	3	Active smoking	KLHDC4
cg23206289	-0.0008	0.0041	0.8389	-0.0006	0.0046	0.8907	-0.0121	0.0144	0.4010	0.4146	3	Active smoking	TEX101
cg06011067	0.0005	0.0030	0.8797	0.0027	0.0037	0.4734	0.0170	0.0148	0.2510	0.2538	4	Active smoking	C6orf186
cg04390734	0.0001	0.0016	0.9413	0.0004	0.0017	0.8256	0.0088	0.0054	0.1033	0.0916	3	Maternal smoking	
cg06393589	0.0001	0.0032	0.9679	0.0001	0.0036	0.9769	0.0003	0.0210	0.9879	0.9927	3	Active smoking	
cg03132729	-0.0001	0.0027	0.9787	0.0002	0.0029	0.9447	0.0024	0.0078	0.7560	0.7333	3	Active smoking	RAP1GAP
cg03463411	0.0000	0.0023	0.9872	0.0000	0.0026	0.9956	-0.0093	0.0242	0.7016	0.7015	3	Maternal smoking	PRDM8