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IDENTIFICATION OF EPIGENETIC MARKERS FOR ALLERGIC DISEASES VIA GENOME-SCALE ASSOCIATION STUDIES

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IDENTIFICATION OF EPIGENETIC MARKERS FOR ALLERGIC DISEASES VIA GENOME-SCALE ASSOCIATION STUDIES

by

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Dedication

I dedicate this dissertation to my loving and caring wife, Rutu Rathod. Her love, support and care have been invaluable to my success, and it is my honor to share this accomplishment with her. I thank my parents, Dr. Bhadresh Rathod and Poorvaxi Rathod for instilling the value of education and hard work in me, and for their constant love, support, and encouragement. I also thank my sister Mrunande and her husband Michael III, for their support throughout this journey. I also dedicate this achievement to our son, Shivansh Rathod. He has given us the most beautiful moments by coming in our lives. I am forever indebted for the unconditional love and support of my family.

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Abstract

Asthma is a global public health concern with limited preventive strategies. Recently, DNA methylation (DNAm) has been studied to understand the underlying pathogenesis of asthma. The role of DNAm in asthma acquisition from pre- to post- adolescence is unclear, and how its role changes from adolescence to adulthood is also unknown. The studies in this dissertation were carried out using data in two birth cohorts with one as a discovery cohort and the other as replication cohort. Longitudinal assessments in both cohorts revealed that the associations of DNAm at 62 Cytosine-Guanine sites (CpG sites) with asthma acquired during adolescence were different from those with asthma acquired in young adulthood since post-adolescence. Asthma can be atopic and non-atopic, and their underlying mechanisms are likely to be different in terms of DNAm markers. To this end, I further examined the mediating role of atopy in childhood on the association of DNAm in newborns with childhood asthma acquisition. I identified 30 CpGs that showed only indirect effects, i.e., DNAm in newborns at these CpGs might play a role in the development of atopic asthma with atopy being a mediator. Also, I found 103 CpGs showing only direct effects, which may contribute to the occurrence of non-atopic asthma. Asthma and rhinitis commonly coexist and share common biomarkers. I examined CpGs in newborns for their association in DNAm with these two allergic conditions during pre-adolescence. I detected 133 CpGs at birth that were associated with preadolescent asthma and/or rhinitis in both cohorts. Further, for all the studies, pathway enrichment analyses were conducted to understand the biological functionality of the identified CpGs. Additionally, biological relevance of the CpGs showing consistent findings between the two cohorts was evaluated using gene expressions. Findings from this dissertation will help identify epigenetic biomarkers for asthma acquisition and coexisting asthma and/or rhinitis as well as understand the underlying pathogenesis of these

conditions. More importantly, it will benefit our future efforts in allergic disease prediction and consequently prevention of these common allergic conditions.

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Chapter 1. Introduction

Epigenetics represents mitotically heritable and reversible changes in gene expression without changes to the DNA sequence [1, 2]. It was first coined as the 'study of the interactions between genes and their products that bring the phenotype into being' by Conrad Hal Waddington in 1942 [3]. It plays an important role in transcription, nuclear organization, genome stability and imprinting [1]. Environmental exposures and genetics only partly explain the pathogenesis of a disease, and recent epidemiologic research have demonstrated epigenetics as an important missing link in the etiological puzzle between genes and phenotypes/exposures [1, 2, 4]. Epigenetic epidemiology has the potential to help explain underlying biological mechanisms for diseases. It may play a mechanistic etiologic role by serving as a biomarker of exposure or disease [1]. Altered epigenetics has been shown to be associated with several exposures and diseases [5]. The clinical utility of epigenetic data may include its use as a biomarker for diagnosis, prognosis, treatment or as a performance metric in clinical trials [1]. DNA methylation, histone modifications, microRNA and prions are different types of epigenetic mechanisms (Figure 1). Most epigenetic studies focus on DNA methylation (DNAm) because of its long-term stable nature and availability of several analytical platforms [2, 6].

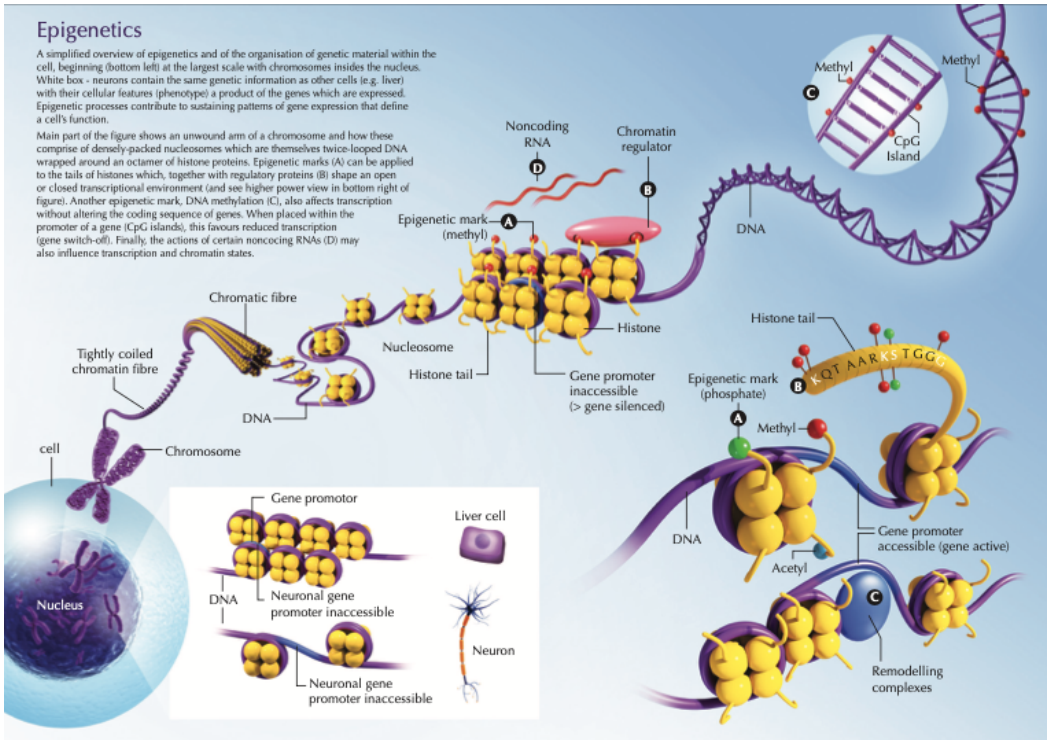

Figure 1. Overview of epigenetic mechanisms. Epigenetic processes contribute to sustaining patterns of gene expression that define a cell's function. DNA methylation (labeled C in the figure) affects transcription without altering the coding sequence of genes. When placed within the promoter of a gene (CpG islands), it favors reduced transcription (gene switch-off) [7].

DNAm at Cytosine-phosphate-Guanine (CpG) site is an addition of a methyl group (CH3) to the DNA strand. DNAm is mitotically heritable, highly stable and plays an important role in gene expression regulation [6]. As DNAm can be influenced by both genetic and environmental factors, it can be an exposure (risk factor), mediator or consequence of a disease. Therefore, DNAm can serve as biomarker of exposure or risk factor, and disease. Several epigenome-wide association studies (EWAS) have demonstrated the association between DNAm and exposures such as smoking [8-12], body mass index [13-16], air pollution [17-19], breastfeeding [20-23], alcohol [24-26], drugs [27, 28]. Similarly, studies have shown association of DNAm with several diseases such as cancers [29, 30], autoimmune [31-34], allergic [35-37], metabolic [38-41],

neurological [42, 43], cardiovascular [44-46] diseases. My dissertation focuses on allergic diseases including asthma and rhinitis.

The prevalence of allergic diseases is increasing globally with children and young adults bearing a large burden. According to World Allergy Organization and World Health Organization, more than 300 million people worldwide suffer from asthma and 400 million from rhinitis [47]. Asthma is responsible for 250,000 deaths annually worldwide [47]. The prevalence of allergic diseases is steadily increasing in the United States and 23 million people have asthma, of which 7 million are children [47]. Allergic diseases are a global public health concern and preventive efforts are needed to reduce its prevalence, death, and economic costs [47]. Several epidemiologic studies have identified prenatal and early-life environmental exposures such as tobacco smoke [47-49], air pollution [47, 48, 50, 51], allergen exposure [48, 52] that contribute towards the increasing burden of asthma and allergic diseases. Control measures for these exposures will prevent the incidence of asthma and allergic diseases. Apart from these exposures, genetics also play an important role in the susceptibility and development of asthma and allergic diseases. Studies have identified several loci related to asthma [53-56] and allergic rhinitis [57]; however, these explain only a fraction of variation in the disease risk and its replication in other populations have largely failed [58]. Because of these limitations, recently there has been an increased focus towards epigenetic studies to understand the pathogenesis of asthma and allergic rhinitis.

Several EWAS studies have demonstrated association of DNAm with the status of asthma [59-62] and rhinitis [35, 63, 64], and identified biomarkers for the same. However, the role of DNAm in asthma acquisition, especially during the critical transition period from pre- to post-adolescence, and how its role changes over time, e.g., from adolescence to adulthood, is

unknown. Atopy is a risk factor for asthma acquisition [65], but asthma can also be non-atopic. The underlying mechanisms of different types of asthma may be explainable by DNAm at earlier ages. Additionally, co-existence of asthma and rhinitis is common and have been known to share common genetic variants [57]. However, it is unclear whether these two conditions share common epigenetic factors, and if so, whether they are consistent with findings in genetic studies. These "unknowns" motivated the projects of this dissertation, as findings in these areas will improve our understanding of allergic disease development from the angle of epigenetics and benefit allergic disease prediction at a much earlier age. In the next chapter, I will outline the projects and related study questions.

Chapter 2. Aims and Research Questions

The proposed dissertation is comprised of three aims with an emphasis on identification of epigenetic markers that has the potential to explain the underlying pathogenesis of allergic diseases in childhood and early adulthood. In aim 1, using an epigenome-wide approach, I will identify novel epigenetic loci during pre- and post- adolescence that are associated with asthma acquisition during adolescence and in later adulthood in males and females separately. In aim 2, using a longitudinal epigenome-wide approach, the direct and indirect effects of DNA methylation (DNAm) in newborns on asthma acquisition across adolescence via pre-adolescence atopy will be evaluated in both sexes separately. In aim 3, I will examine sex-specific associations of DNAm in newborns and pre-adolescence asthma and rhinitis in an epigenome-wide study. Pathway enrichment analysis and association of gene expression with DNAm will be assessed for all the aims to gain better understanding elucidating the biological significance of the identified CpGs.

Aim 1

To examine the association of pre- and post-adolescence DNAm with asthma acquisition during adolescence and in later adulthood.

Research question 1.1: Are pre- and post-adolescence (age 10 and 18 years) DNAm associated with asthma acquisition during adolescence (age 10 to 18 years) and in later adulthood (age 18 to 26 years) for each gender in discovery cohort, Isle of Wight Birth Cohort (IOWBC)?

Research question 1.2: Does replication analysis in an independent cohort, ALSPAC support the findings from the IOWBC?

Research question 1.3: Are there any differentially methylated regions (DMRs) at preadolescent DNAm associated with asthma acquisition from pre- to post-adolescence.

Research question 1.4: What are the biological pathways of genes corresponding to the identified CpGs in IOWBC?

Research question 1.5: Is there an association between DNAm at ages 10 and 18 years and gene expression of nearby genes i.e., within 250kb upstream and downstream region of the identified CpGs at 26 years?

Aim 2

To examine whether atopy in childhood mediates the association of DNAm in newborns with asthma acquisition across adolescence.

Research question 2.1: Does pre-adolescence atopy mediate the association of DNAm in newborns with asthma acquisition across adolescence in IOWBC?

Research question 2.2: Can the findings of research question 2.1 be replicated in ALSPAC?

Research question 2.3: What are the biological pathways of genes corresponding to the identified CpGs in IOWBC?

Research question 2.4: Is there an association between DNAm at age 26 years and gene expression of nearby genes i.e., within 250kb upstream and downstream region of the identified CpGs at 26 years?

Aim 3

To examine sex-specific associations of DNAm in newborns with pre-adolescence asthma and/or rhinitis

Research question 3.1: Is the association of DNAm in newborns with pre-adolescence asthma and/or rhinitis sex-specific?

Research question 3.2: What are the biological pathways of genes corresponding to the identified CpGs in IOWBC?

Research question 3.3: Is there a genetic influence on the identified CpGs, i.e., are they methQTLs?

Research question 3.4: Is there an association between DNAm at age 26 years and gene expression of nearby genes i.e., within 250kb upstream and downstream region of the identified CpGs at 26 years?

Research question 3.5: Is there a genetic influence on DNAm at the replicated CpGs, i.e., are there any methQTLs?

Chapter 3

Aim 1: To examine the association of pre- and post-adolescence DNAm with asthma acquisition during adolescence and in later adulthood.

Background

Asthma is the most prevalent chronic respiratory condition[66] affecting 1-18% of population in several countries[67]. Over recent decades, childhood asthma has become a major public health issue[68] with an increasing prevalence worldwide[69]. Environmental factors such as air pollution, infectious agents, and tobacco smoke have been shown to be associated with the development of asthma[70].

DNA methylation (DNAm), a robust and stable epigenetic mark, represents a potential mechanism mediating environmental impacts on human diseases[71]. Recent studies suggest that DNAm signatures of cytosine-phosphate-guanines (CpG) sites are associated with asthma[58, 61, 72]. Since peripheral blood is readily obtainable and easy to handle in laboratory processing, and information of immune cells in blood is relevant to asthma pathogenesis[73], DNAm in peripheral blood cells has been commonly examined in epigenome-wide studies of asthma[62, 74, 75].

While the development of asthma clearly reflects the combination of inherited susceptibility and environmental exposures, the pathogenesis and underlying biological mechanisms involved in the onset of asthma later in life are not well understood. Asthma most commonly develops during early childhood[76], and the prevalence of asthma depends on gender and age. Asthma is more prevalent among pre-adolescent boys, while it becomes more prevalent among females after puberty with prevalence in males and females being approximately equal in adulthood[77-

79]. However, the pathogenesis of these sex differences in asthma across adolescence and adulthood remains unclear.

Although previous studies have demonstrated association between DNAm and asthma, the role that DNAm plays in asthma acquisition, especially during the critical transition period from pre- to post- adolescence, and how its role changes over time, e.g., from adolescence to adulthood, are unknown. Findings from this type of studies will not only identify important markers for asthma acquisition, and more importantly, benefit our future efforts in asthma prediction and consequently asthma prevention. To this end, in this study, for each gender, we examined the association between DNAm at pre-adolescence and asthma acquisition from pre- to post-adolescence (10 to 18 years), and between DNAm at post-adolescence and asthma acquisition from post-adolescence to adulthood (18 – 26 years), utilizing genome-wide DNA methylation data. We hypothesized that DNAm at specific CpG sites measured before disease onset, either in pre- or post-adolescence would be associated with asthma acquisition both during adolescence and in later adulthood and that there would be differences in such DNA methylation patterns by time window (adolescence or post-adolescence) and by gender. Additionally, differentially methylated regions (DMRs) were identified to incorporate CpGs located close to one another which may be associated with asthma acquisition as a group or cluster of CpGs. These CpGs might have been missed when looking at the associations using individual CpG sites.

Methods

IOWBC study population

The study population comprised of children born between January 1, 1989 and February 28, 1990 on the Isle of Wight (IoW), UK (IOWBC)[80]. Out of the 1,536 children born and recruited, 1,456 in IOWBC were available for further follow-up at ages 1, 2, 4, 10, 18 and 26

years. Ethics approval was obtained by the local research ethics committee (NRES Committee South Central – Hampshire B) (06/Q1701/34)[81]. The details on study design, enrollment, and follow-up procedures for the IoW birth cohort (IOWBC) are described elsewhere [80, 82].

Asthma acquisition

Questionnaires that included the questions of the International Study of Asthma and Allergy in Childhood (ISAAC) was filled by parents/participants at ages 4, 10, 18 and 26 years[61, 83-85]. Asthma was defined as "physician diagnosed asthma" and "wheezing or whistling in the chest in the last 12 months" or "current treatment for asthma." Subjects with asthma at age four years were excluded. The outcome used in this study, asthma acquisition, was defined as individuals who were asthma free at age 10 years and recorded as having asthma at age 18 years (no→yes). The same definition was applied for asthma acquisition from 18 to 26 years (no→yes). Subjects who did not have asthma at both the transition periods were taken as reference (no→no).

Covariates

Atopic status was evaluated at ages 10 and 18 years based on results from skin prick test (SPT) on 11 common allergens (house dust mite, cat dander, dog dander, grass pollen mix, tree pollen mix, *Alternaria alternate*, *Cladosporium herbarium*, cow's milk, hen's egg, peanut, and cod). Being SPT positive to one or more of the 11 allergens was treated as being atopic. Active smoking status at 18 and 26 years was recorded as 'yes' if the participant was a current smoker at that respective age. Second-hand smoke exposure was coded at age 18- and 26-years using information obtained from smoking status of parents and other smokers in the household. To evaluate the contribution of transition periods, 10-18 and 18-26 years, to the association of DNAm with asthma transition, transition periods will be included in the analyses as adjusting factors.

DNA methylation

Using a standardized salting procedure, DNA was extracted from peripheral whole blood samples collected at ages 10 and 18 years[86]. Fluorometric quantitation was used to estimate DNA concentration. Methylation levels at each CpG site was measured using Illumina Infinium HumanMethylation450 or MethylationEPIC BeadChips (Illumina, Inc., San Diego, ca, USA). Probes that did not reach a p-value of 10^{-16} in at least 95% of samples were exclude. The same criterion was applied to exclude samples, i.e., samples with p-value $>10^{-16}$ in at least 95% of the CpGs. CpGs on sex chromosome were excluded. Probes that contained single nucleotide polymorphisms (SNPs) within 10 base pairs of a targeted CpG site with a minor allele in at least 0.7% subjects (corresponding to at least 10 subjects in IoW with n = 1,456) were excluded due to their influence on the measures of DNAm.

Using CPACOR pipeline, DNA methylation (DNAm) was pre-processed for the data from both HumanMethylation450 and MethylationEPIC. DNAm intensities were quantile normalized using the *minfi* R computing package [87]. The quantile normalized intensities at autosomal probes were then converted to beta values. β values is a ratio of methylated (M) over the sum of methylated and unmethylated (U) probes (β=M/[c+M+U]), where c is a constant to prevent from zero in the denominator. Often β values suffer from severe heteroscedasticity, so in statistical analyses, logit transformed DNAm levels, i.e., M values, were used. Principal components (PCs) inferred based on control probes were used to represent latent chip to chip and technical variation. We determined PCs based on DNAm at shared control probes of the two DNAm platforms HumanMethylation450 and MethylationEPIC. In total, 195 shared control probes were used to calculate the control probe PCs with top 15 PCs included in our study to represent latent batch factors [88]. In this study, CpG sites common between Illumina 450k platform and EPIC

platform will be examined. In additions, CpG sites were excluded if the minor allele frequency of a probe SNP at that site is > 0.7% (i.e., ~ ≥ 10 out of 1456 subjects expected to have the minor allele in the cohort) and the probe SNP was within 10 base pairs of the targeted CpG site. After quality control and pre-processing, 442,475 CpG sites will be included in subsequent analysis. Since whole blood is a mixture of distinct cell types[89], there is a need to adjust for cell type composition to account for their potentially confounding effects[90]. Cell type proportions were estimated using the Bioconductor *minfi* package[91] [92]. The estimated cell type proportions of CD4+ T cells, natural killer cells, neutrophil, B cells, monocytes, and eosinophil cells will be included in the analyses as confounders.

Genome-wide RNA-seq gene expression data generation

Gene expression levels from peripheral blood samples collected at 26 years from the IOWBC was determined using paired-end (2×75 bp) RNA sequencing with the Illumina Tru-Seq Stranded mRNA Library Preparation Kit with IDT for Illumina Unique Dual Index (UDI) barcode primers following the manufacturer's recommendations. All samples were sequenced twice using the identical protocol and for each sample the output from both runs were combined. FASTQC were run to assess the quality of the FASTQ files (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/). Reads were mapped against Human Genome (GRch37 version 75) using HISAT2 (v2.1.0) aligner [93]. The alignment files, produced in the Sequence Alignment Map (SAM) format, were converted into the Binary Alignment Map (BAM) format using SAMtools (v1.3.1) [94]. HTseq (v0.11.1) was used to count the number of reads mapped to each gene in the same reference genome used for alignment [95]. Normalized read count FPKM (Fragments Per Kilobase of transcript per Million

mapped reads) were calculated using the countToFPKM package (https://github.com/AAlhendi1707/countToFPKM) and their log-transformed values were used for data analysis.

Statistical analyses

Research question 1.1: Are pre- and post-adolescence DNAm associated with asthma acquisition during adolescence and in later adulthood for each gender in discovery cohort, Isle of Wight Birth Cohort (IOWBC)?

By regressing the M-values (base-2 logit transformed beta values of DNAm) at each CpG site on the aforementioned 15 PCs and 6 cell type proportions, we obtained cell-type and batch-adjusted DNAm (residuals) at each of the 442,475 CpG sites for each gender in IOWBC. Screening of CpG sites was done to obtain DNAm potentially associated with asthma acquisition from pre- to post-adolescence using simple linear regressions. Here, asthma acquisition from 10 to 18 years of age was the independent variable and DNAm at age 10 years was the dependent variable. The analysis was stratified by gender. For the screening purpose, multiple testing was adjusted by controlling false discovery rate (FDR) at a higher rate of 0.2. CpG sites that pass screening were included in subsequent analyses.

Logistic regressions with repeated measurements were applied to the CpGs that pass screening to evaluate the association of asthma acquisitions (no→yes) at two transition periods (10-18 years and 18-26 years) with DNAm at earlier ages (10 and 18 years, respectively). Adolescence is a period accompanied by significant physical and mental development and such changes gradually stabilize as children enter post-adolescence [96, 97]. The unique phenomenon in each transition period motivated a study question, i.e., are the associations between asthma acquisition and DNAm different at different transition periods, in addition to the main effects of DNAm? To

answer this question, I included an interaction term in the final model to test interaction effects between DNAm and transition period. For both situations (the models with main effects only, and the models that included interaction effects) multiple testing was adjusted by controlling FDR of 0.05.

Research question 1.2: Does replication analysis in an independent cohort, ALSPAC support the findings from the IOWBC?

CpGs showing significant interaction effects with transition periods in IOWBC were further tested in the Avon Longitudinal study of Parents and Children (ALSPAC) cohort [98-100]. Pregnant women residing in the Southwest of England and expecting to deliver between April 1, 1991 and December 31, 1992 were eligible to be recruited. Of the 14,541 pregnant women eligible for recruitment, 13,761 were included in the study with 10,321 participants having their DNA sampled. DNAm in the ALSPAC cohort was assessed using the Infinium HumanMethylation450 BeadChip. DNAm data on 604 children in the ALSPAC cohort are available at ages 7 and 17 years [101]. DNAm pre-processing was performed by correcting for batch effects using the *minfi* package [87] and removing CpGs with detection p-value ≥0.01. Samples were flagged that contained sex-mismatch based on X-chromosome methylation. Estimated cell type proportions of CD4+ T cells, natural killer cells, neutrophil, B cells, monocytes, and granulocytes cells were used in the analyses to adjust for cell heterogeneity. Asthma acquisition status from 7 to 17 years, and 17 to 22 years was included in the analysis. It was defined as having no asthma at age 7 years and having asthma at age 17 years. The same definition was applied for asthma acquisition from 17 to 22 years. Logistic regression with repeated measurements were used with similar covariates (as those in IOWBC) available in ALSPAC, i.e., atopy status at age 7 years and second-hand smoke exposure status at age 17 and

24 years. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

Research question 1.3: Are there any differentially methylated regions (DMRs) at preadolescent DNAm associated with asthma acquisition from pre- to post-adolescence?

Differentially methylated regions (DMRs) were identified using the *DMRcate* package in R[102]. To secure enough CpGs for DMR enrichment analysis and to avoid missing important DMRs, CpGs with DNAm (in M values) associated with asthma acquisition via logistic regression at FDR of 0.4 were included in the analysis.

Research question 1.4: What are the biological pathways of genes corresponding to the identified CpGs in IOWBC?

For CpGs showing associations of DNAm with asthma acquisition status, the genes annotated to the CpGs will be summarized along with information such as gene location, chromosome number based on Illumina's manifest file and USCS genome browser (https://genome.ucsc.edu). Pathway enrichment analysis of the identified CpGs were conducted using the *gometh* function [103] in the R package to better understand their biological functionality.

Research question 1.5: Is there an association between DNAm at ages 10 and 18 years and gene expression of nearby genes i.e., within 250kb upstream and downstream region of the identified CpGs at 26 years?

Genes annotated to the replicated CpGs associated with asthma acquisition were extracted along with information such as gene location, chromosome number from the Illumina's manifest file or UCSC genome browser (https://genome.ucsc.edu/). To assess the biological relevance of these CpGs, linear regressions were applied to test the association of DNAm (in M-values;

independent variable) at ages 10 and 18 years separately at each CpG site with expression of its neighboring genes (250k base pairs [bps] upstream and 250k bps downstream of the CpG site) in blood at 26 years of age. Paired DNAm and expression data of n=140 subjects were included in the analyses. As we previously have found the association between gene expression and DNAm to be different in both males and females, the analysis was stratified by sex [61, 104].

Results

Since our study focused on asthma acquisition starting from age 10 years in IOWBC, subjects with asthma at four years were excluded. Participants in IOWBC with both asthma transition and DNAm data available at ages 10 and 18 years were included in the study. The subsamples represented the complete IOWBC (such that no asthma at age 4 years) with respect to asthma acquisition, active and second-hand smoking, and atopy status, (Table 1 A & B). The flow chart of samples included in the study is in Supplement Figure S3

Table 1(A): Asthma acquisition and never asthma subjects included in the current study compared to subjects in the complete cohort for 10-18 period (IOWBC).

Variables N (%)		Females			Males		
		Subsample N=102; n (%)	Complete cohort N=431; n (%)	p-value	Subsample N=133; n (%)	Complete cohort N=402; n (%)	p-value
Asthma transition	Acquisition	7 (6.86)	41 (9.51)	0.40	11 (8.27)	26 (6.47)	0.98
	Never Asthma	95 (93.14)	390 (90.49)		122 (91.73)	376 (93.53)	
Active smoking	Yes	25 (23.36)	120 (25.86)	0.59	33 (21.85)	105 (22.98)	0.48
	No	82 (76.64)	344 (74.14)		118 (78.15)	352 (77.02)	
Second-hand smoking	Yes	54 (50)	212 (44.92)	0.34	66 (43.42)	204 (43.59)	0.78
	No	54 (50)	260 (55.08)		86 (56.58)	264 (56.41)	

Table 1(A): Continue

Variables N (%)		Females			Males		
Atopy	Yes	14 (12.96)	76 (19.1)	0.14	42 (27.81)	108 (27.91)	0.97
	No	94 (87.04)	322 (80.9)		109 (72.19)	279 (72.09)	

Table 1(B): Asthma acquisition and never asthma subjects included in the current study compared to subjects in the complete cohort for 18-26 period (IOWBC).

Variables N (%)		Females			Males		
		Subsample N=156; n (%)	Complete cohort N=330; n (%)	p-value	Subsample N=121; n (%)	Complete cohort n=286; n (%)	p-value
Asthma transition	Acquisition	5 (3.21)	12 (3.64)	0.81	3 (2.48)	10 (3.5)	0.59
	Never Asthma	151 (96.79)	318 (96.36)		118 (97.52)	276 (96.5)	
Active smoking	Yes	46 (27.54)	107 (26.95)	0.89	46 (31.94)	99 (28.95)	0.51
	No	121 (72.46)	290 (73.05)		98 (68.06)	243 (71.05)	
Second-hand smoking	Yes	35 (20.96)	98 (24.75)	0.33	27 (18.75)	80 (23.39)	0.26
	No	132 (79.04)	298 (75.25)		117 (81.25)	262 (76.61)	
Atopy	Yes	55 (29.73)	115 (32.63)	0.36	73 (42.2)	146 (46.65)	0.35
	No	130(70.27)	227 (66.37)		100 (57.8)	167 (53.35)	

In total, 55 CpGs for males and 183 CpGs for females in IOWBC passed screening based on their potential associations with asthma acquisition from 10 to 18 years of age. These CpGs were included in subsequent analyses for their longitudinal associations of DNAm with asthma acquisition from pre- to post-adolescence and from post-adolescence to young adulthood and for

interaction effects between DNAm and transition periods, using logistic regressions with repeated measurements.

After adjusting for multiple testing by controlling FDR of 0.05, statistically significant interaction effects of DNAm and transition period were observed at 17 CpGs in males and 98 CpGs in females (no common CpGs identified between males and females), controlling for atopy status, active and second-hand smoking (Figures 2 and 3, Supplemental Table S1). Of the 17 identified CpGs in males, 4 CpGs (23.5%) were located in the promoter region, while for the 98 CpGs identified in females, a much larger portion of CpGs (54 CpGs, 55.1%) were in the promoter region. For 7 of the 17 CpGs in males, an increase in DNAm is associated with an increased odds of asthma acquisition in the 10-18 transition period but decreased odds in the 18-26 period (Figures 2A and 2B, Supplemental Table S1a). For 47 of the 98 CpGs in females, an increase in DNAm is associated with a decreased odds of asthma acquisition in the 10-18 transition period, but increased odds in the 18-26 period (Figures 3A and 3B, Supplemental Table S1b). In addition, the overall effect sizes at the first transition period were larger than the effect sizes in the second transition period.

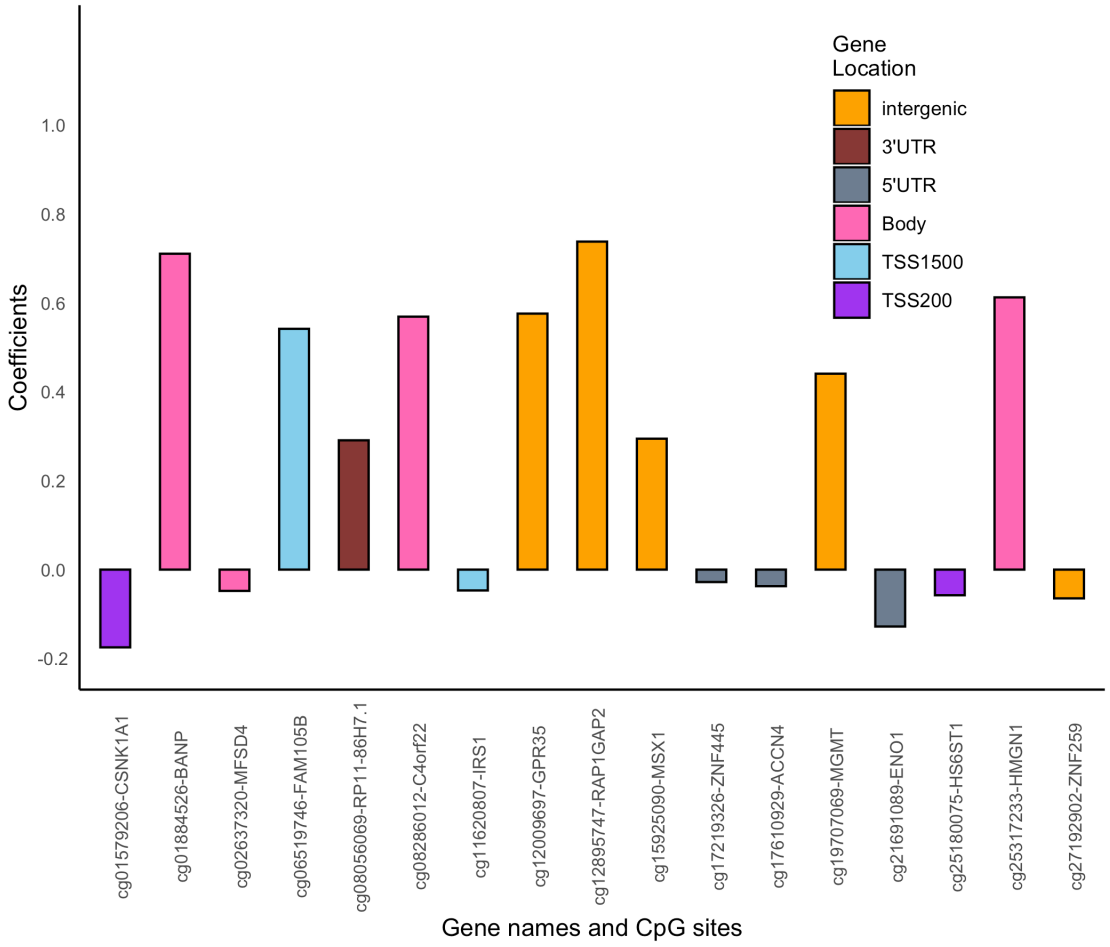

Figure 2 (A): Bar graph showing the direction of DNAm effect at each of the 17 identified CpGs in IOWBC from pre- to post-adolescence asthma acquisition in males. Gene names corresponding to each CpG site are also labeled on the X-axis.

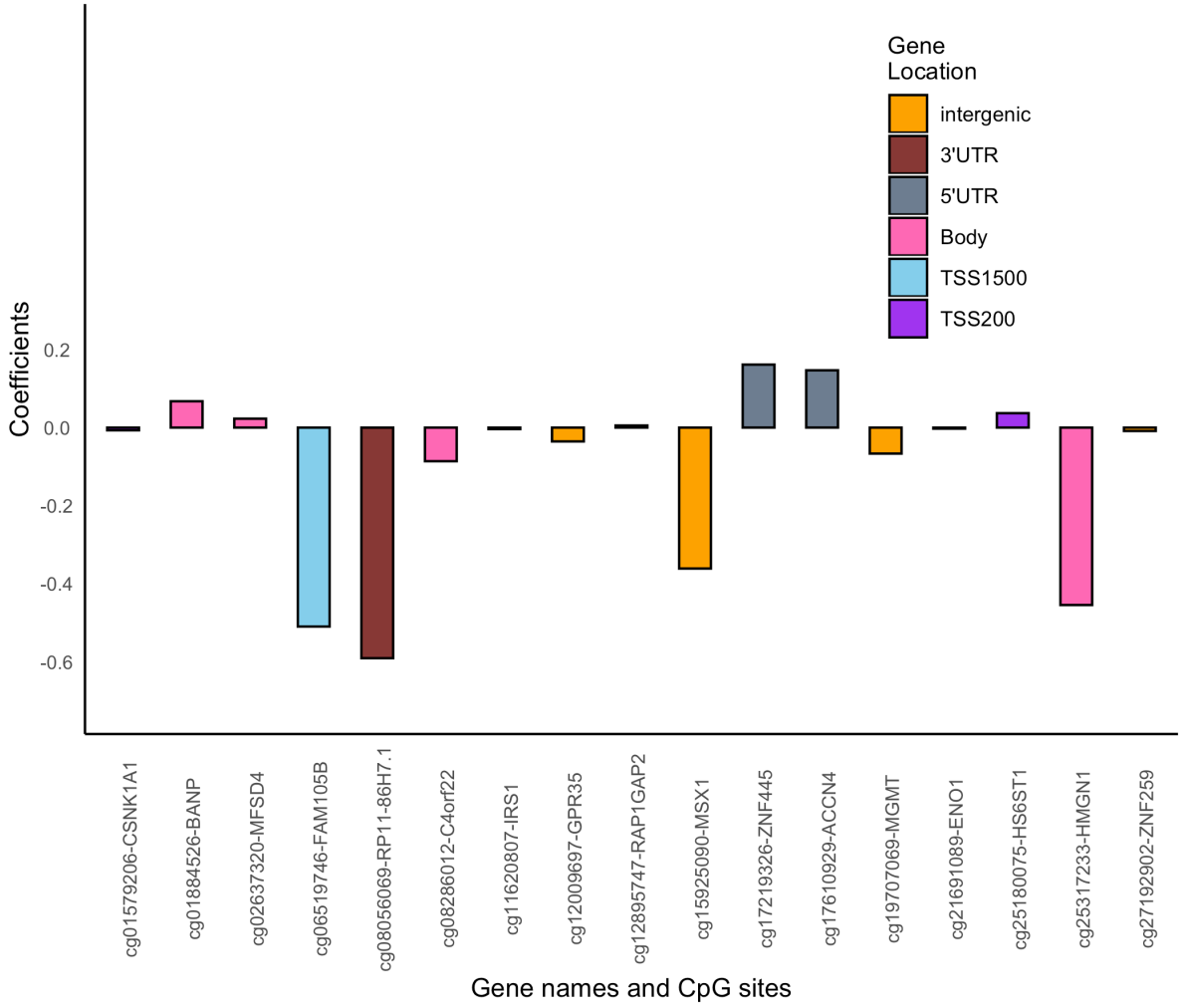

Figure 2(B): Bar graph showing the direction of effect at each of the 17 identified CpGs in IOWBC from post-adolescence to adulthood asthma acquisition in males. Gene names corresponding to each CpG site are also labeled on the X-axis.

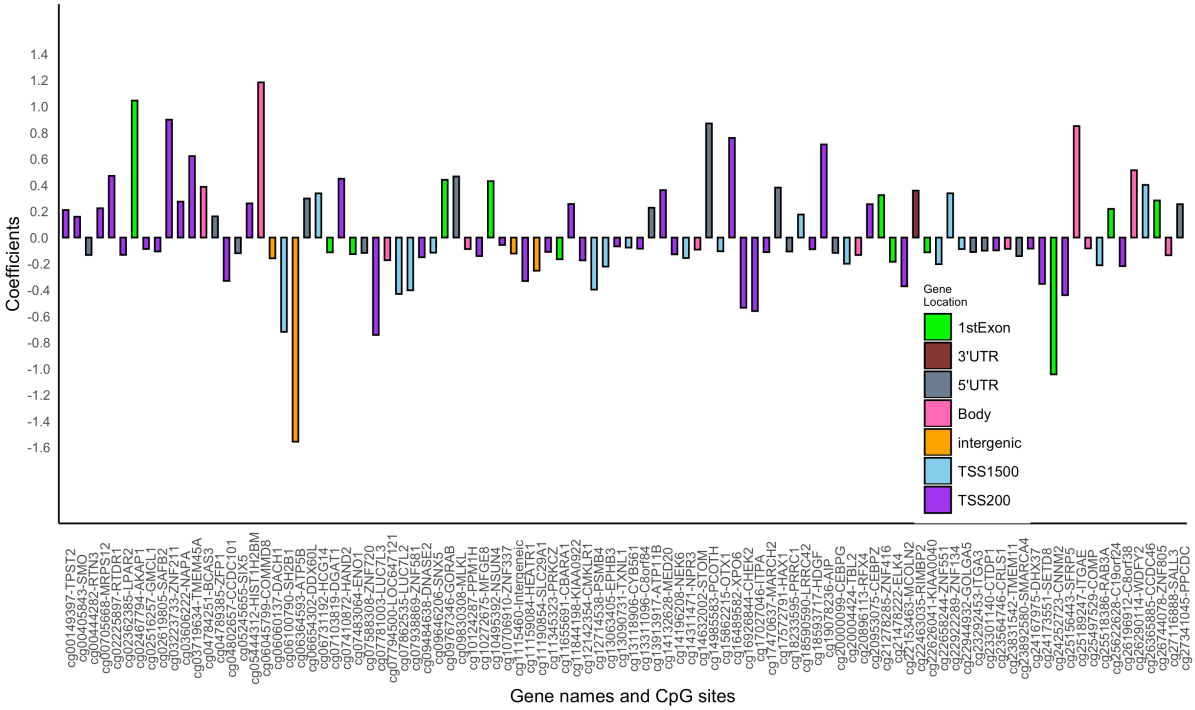

Figure 3(A): Bar graph showing the direction of effect at each of the 98 identified CpGs in IOWBC from pre- to post-adolescence asthma acquisition in females. Gene names corresponding to each CpG site are also labeled on the X-axis.

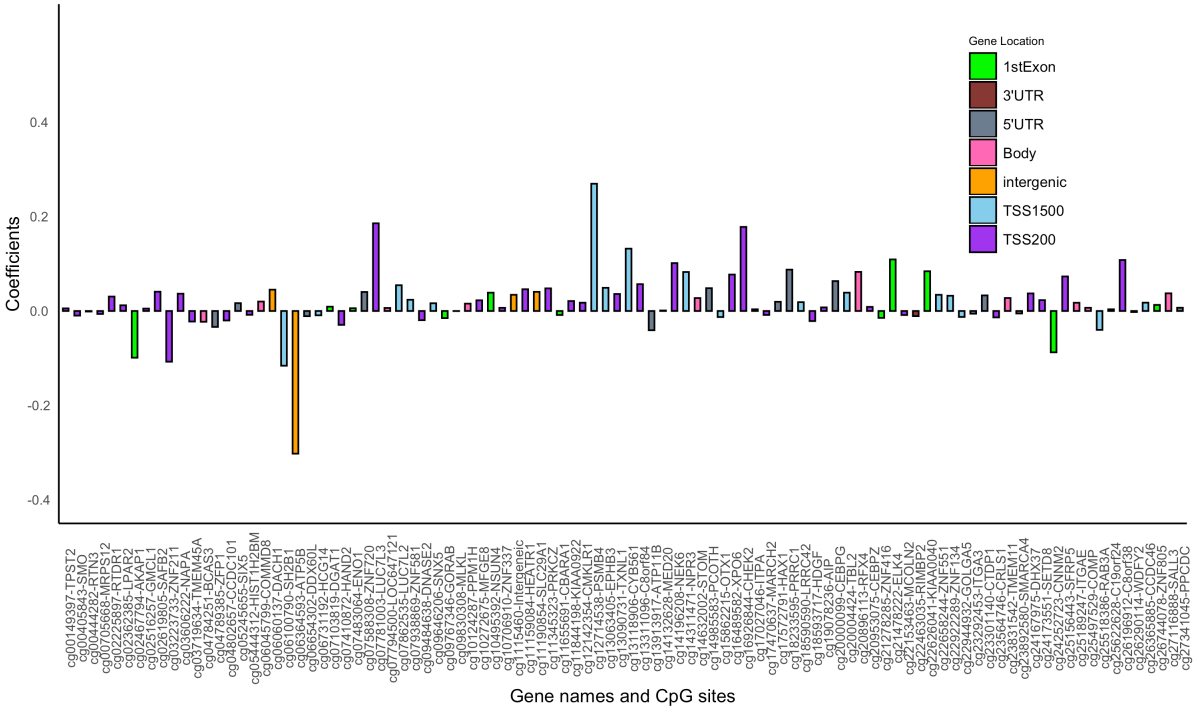

Figure 3(B): Bar graph showing the direction of effect at each of the 17 identified CpGs in IOWBC from post-adolescence to adulthood asthma acquisition in females. Gene names corresponding to each CpG site are also labeled on the X-axis.

For CpGs not showing significant interaction effects between DNAm and transition period, we assessed the main effects of DNAm on asthma acquisition via logistic regression models with repeated measures. After adjusting for multiple testing at FDR=0.05, we identified 38 CpGs in males and 52 CpGs in females (Figure 4, Supplemental Table 3S.2) showing association of DNAm with asthma acquisition status (no common CpGs between males and females). Of the 38 CpGs in males, 13 CpGs (34.2%) were in the promoter region, while for the 52 CpGs identified in females, a much larger portion of CpGs (25 CpGs, 48.1%) were in the promoter region. At 25 of the 38 CpGs in males, an increase in DNAm is associated with a decreased odds of asthma acquisition (Supplemental Table S2a). At 45 of the 52 CpGs in females, an increase in DNAm is associated with a decreased odds of asthma acquisition (Supplemental Table S2b). Overall, the

effect sizes of DNAm on asthma acquisition were larger in males than in females.

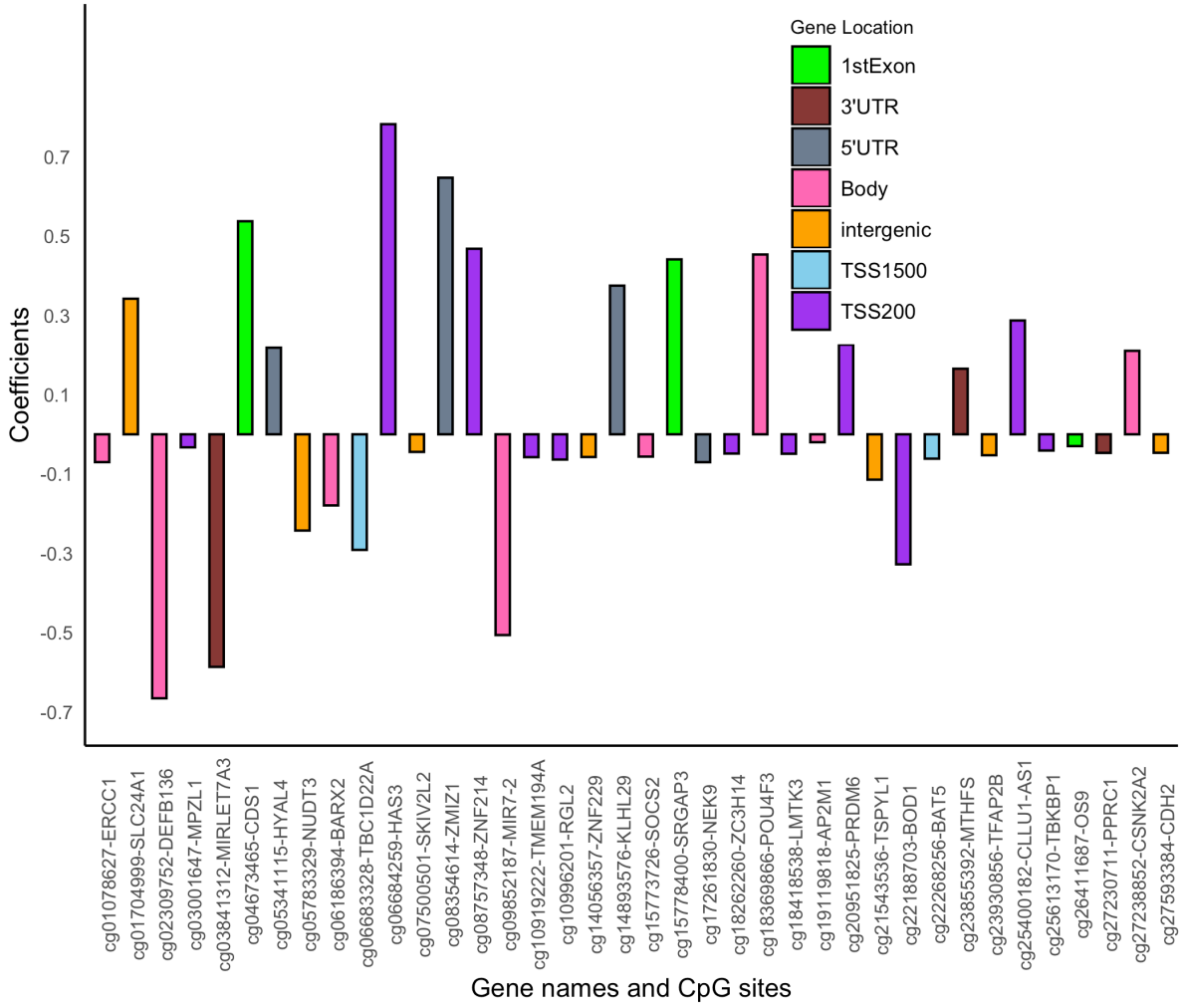

Figure 4(A): Bar graph showing the main effects of DNAm on asthma acquisition at each of the 38 identified CpGs in IOWBC in males. Gene names corresponding to each CpG site are also labeled on the X-axis.

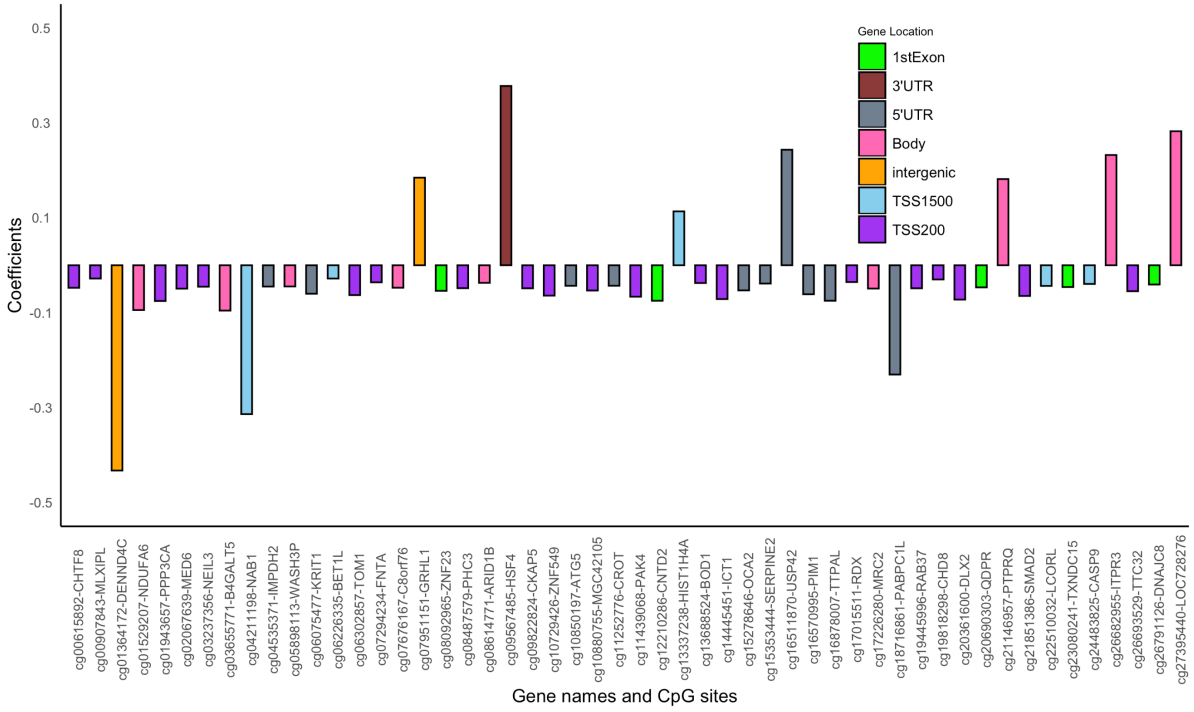

Figure 4(B): Bar graph showing the main effects of DNAm on asthma acquisition at each of the 52 identified CpGs in IOWBC in females. Gene names corresponding to each CpG site are also labeled on the X-axis.

Altogether, we identified 115 CpGs (17 in males) showing interactions with transition period and 90 CpGs (38 in males) showing main effects (excluded CpGs with interaction effects), leading to a total of 205 identified CpGs. We further tested these CpGs in the ALSPAC cohort. For the 115 CpGs (17 in males) showing interaction effects in IOWBC, consistent directions of interaction effects were observed at 9 CpGs in males, with 1 CpG being statistically significant, and 53 CpGs in females, with 3 CpGs being statistically significant, compared to the directions of associations identified in the IOWBC (Supplemental Tables S1a and S1b). Of the 9 CpGs showing consistent interactions in males, 2 CpGs (22.2%) were in the body region of gene, while of the 53 such CpGs in females, 34 (64.2%) were in the promoter region. For the 90 CpGs (38 in males) showing main effects on asthma acquisition, 13 CpGs in males (3 CpGs [23.1%] in the

promoter region) and 37 CpGs in females (19 CpGs [51.4%] in the promoter region) showed consistent directions of main effects (Supplemental Table S2a and S2b) between the two cohorts. The flowchart of the study along with brief summaries of results is in Figure 5.

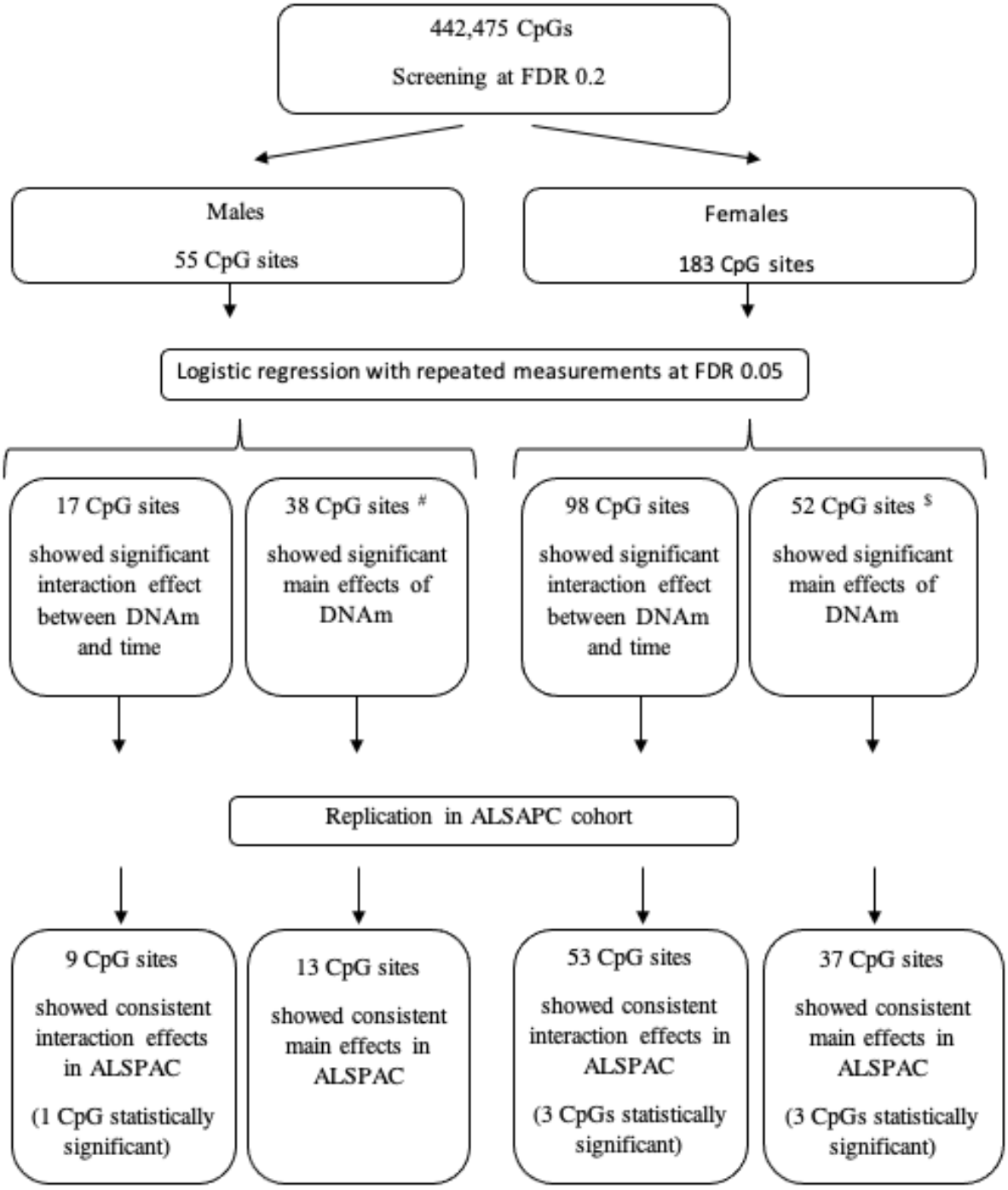

Figure 5. Flowchart of the study design and brief summaries of findings in each step.

- Out of 38 CpGs after excluding significant interaction
$ = Out of 85 CpGs after excluding significant interaction

.

Pathway enrichment analyses was conducted based on CpGs identified for each sex (55 in males and 150 in females with 205 CpGs in total) to better understand their biological functionality. These CpGs were mapped to 54 and 149 genes in males and females respectively. Using these CpGs in the *gometh* function in R, we identified 212 biological processes in males and 228 in females that were enriched at p-value of 0.05. Although none of the biological processes survived multiple testing at FDR of 0.05, genes involved in the top processes for each sex based on statistical significance (top 10 processes in Table 2) were potentially important and may deserve a further assessment. For males, multiple biological processes among the top 10 for males focus on catabolic processes (breakdown glucose for energy), while for females they are biosynthetic processes (synthesizing glucose from food). Among these top processes identified for males, 13 genes corresponding to the identified CpGs were involved in those processes, and for females, 60 genes were involved (Supplemental Table S3).

Table 2(A): Top 10 most statistically significant GO terms and its biological processes from pathway enrichment analysis along with the number of genes in each pathway for males, for the identified CpGs.

GO term	Biological processes	P-value	No. of Genes
GO:1901575	organic substance catabolic process	0.0005	12
GO:0046657	folic acid catabolic process	0.001	1
GO:0042219	cellular modified amino acid catabolic process	0.002	1
GO:0038111	interleukin-7-mediated signaling pathway	0.002	2
GO:1990261	pre-mRNA catabolic process	0.002	1
GO:0071544	diphosphoinositol polyphosphate catabolic process	0.002	1
GO:0042365	water-soluble vitamin catabolic process	0.003	1
GO:0009056	catabolic process	0.003	13
GO:0098760	response to interleukin-7	0.003	2

Table 2 (A): continue

GO term	Biological processes	P-value	No. of Genes
GO:0098761	cellular response to interleukin-7	0.003	2

Table 2(B): Top 10 most statistically significant GO terms and its biological processes from pathway enrichment analysis along with the number of genes in each pathway for females, for the identified CpGs.

GO term	Biological processes	P-value	No. of Genes
GO:0019438	aromatic compound biosynthetic process	0.0004	57
GO:0032774	RNA biosynthetic process	0.0007	49
GO:0008589	regulation of smoothened signaling pathway	0.0007	5
GO:0018130	heterocycle biosynthetic process	0.0008	56
GO:1903506	regulation of nucleic acid-templated transcription	0.0008	49
GO:2001141	regulation of RNA biosynthetic process	0.0008	49
GO:1901362	organic cyclic compound biosynthetic process	0.001	57
GO:0034654	nucleobase-containing compound biosynthetic process	0.001	55
GO:0006355	regulation of transcription, DNA-templated	0.001	48
GO:0009757	hexose mediated signaling	0.001	2

For DMR enrichment analysis, we used CpGs in the screening process that were statistically significant at FDR of 0.4 to cover epigenetic information comprehensively on asthma acquisition. In total, 427 CpGs in males and 372 CpGs in females were included in the DMR analysis. We identified three DMRs in males and three DMRs in females after adjusting for multiple testing at FDR=0.05 level based on the Stouffer test statistics. (Table 3).

Table 3: Differentially methylated regions (DMRs) for asthma acquisition identified by *DMRcate* package for males and females.

Sex	Chr.[$]	Start[#]	End[&]	Gene[£]	CpGs[¥]	P-value
M	3	196065106	196065569	*TM4SF19*	cg05556202, cg05445326	$4.89*10^{-206}$
	12	57472396	57472611	*TMEM194A*	cg10919222, cg09934365	$3.03*10^{-150}$
	17	27899874	27899966	*TP53I13*	cg05877788, cg04498198	$2.69*10^{-53}$
F	2	224903369	224903487	*SERPINE2*	cg15353444, cg11719885	$5.84*10^{-177}$
	1	156721844	156722068	*HDGF*	cg04402095, cg18593717	$5.35*10^{-162}$
	17	79633496	79633565	*CCDC137, C17orf90*	cg199963747, cg11820993	$1.70*10^{-160}$

[$]Chr.: Chromosome
[#]Start: Start position of the region
[&]End: End position of the region
[£]Gene: Genes corresponding to the CpGs in the region
[¥]CpGs: CpGs in the region

To assess the biological relevance of CpGs showing consistent association with asthma acquisition in both cohorts, we evaluated the association of DNAm at the identified 113 CpGs (22 in males) with the expression of genes that the CpGs were mapped to. Nearby genes were also examined defined as genes in a window of 500k base pairs (bps) of each identified CpG site (250k bps up and down stream). In this analysis, DNAm was measured at 10 and 18 years and gene expression levels were assessed at age 26 years. Significant effects of DNAm at 10 years were observed at 14 CpGs on their association with expression of 29 genes in males, and at 73 CpGs with expression of 321 genes in females. Similarly, for DNAm at 18 years, significant associations were found at 10 and 51 CpGs with expression of 29 and 117 genes in males and

females, respectively (Table 4 and Supplemental Table S4). Of the 350 genes' expression (29 in males) associated with DNAm at 10 years, increased DNAm was associated with increased expression of 310 genes (18 in males). Similarly, of the 146 gene expressions associated with DNAm at 18 years, increased DNAm was associated with increased expression of 91 genes (24 in males). Of the CpGs showing associations with expression of their neighbouring genes, 8 genes in males and 39 in females were commonly identified at both ages (10 and 18 years). Among the top 5 most significant associations for each age and sex, 4 genes associated with 3 CpGs in males were found to be common at both ages, i.e., they may represent stable biological relevance of the CpGs during adolescence.

Table 4: Top 5 most significant associations of DNAm with expression of neighboring mapped genes.

CpG site	**DNAm age in years**	**Gene name**	**Estimate**	**P-value**	**Sex**
cg06684259	10	*ACAA2*	0.57	0.0006	Males
	18		0.84	3.40×10^{-5}	Males
	10	*ACP2*	0.67	0.001	Males
	18		0.60	2.08×10^{-5}	Males
cg09852187	10	*ABCD3*	0.53	0.0006	Males
	18		0.48	3.40×10^{-5}	Males
cg08354614	10	*CPM*	0.42	0.003	Males
cg12009697	10	*ABAT*	0.27	0.004	Males
	18		0.40	0.0003	Males

Table 4: Continue

CpG site	DNAm age in years	Gene name	Estimate	P-value	Sex
cg25518386	10	*AKAP10*	0.89	1.24×10^{-10}	Females
cg26791126	10	*AIM1*	0.30	5.14×10^{-10}	Females
cg24173551	10	*ALKBH5*	0.75	5.64×10^{-10}	Females
cg06060137	10	*ACE*	0.84	1.31×10^{-9}	Females
cg25156443	10	*ACVRL1*	0.87	2.27×10^{-9}	Females
cg14056357	18	*ACSF3*	0.45	0.0002	Males
cg13063405	18	*C5*	-0.11	0.0002	Females
		MRC2	-0.11	0.0008	Females
cg02516257	18	*ZHX3*	0.73	0.0003	Females
cg00907843	18	*SOS1*	0.67	0.0007	Females
cg04535371	18	*AKR7A3*	-0.75	0.002	Females

Note: Top 5 most statistically significant associations for each sex and age are shown here.

Discussion

Strengths and limitations

The strength of this study exists in its focus on longitudinal assessment of asthma acquisition at two important transition periods, pre- to post-adolescence and to later adulthood, along with DNAm at two critical time points, pre- and post-adolescence. Although for the CpGs discovered in IOWBC, more than 50% showed consistent findings in ALSPAC, statistical significance was observed at a small number of CpG sites. One reason for this lack of significance might be the age differences between the two cohorts. In addition, there is a potential concern of data double dipping. However, we do not see this as a significant concern in that the statistical model applied

in the screening process (linear regression without covariates such as atopic and smoking status) was different from the model in the final analyses (logistic regression with potential covariates). Another potential limitation is in the design of data analyses, which focused on each individual CpG site. However, CpG sites might be correlated and work jointly to impact the risk of asthma acquisition, which certainly deserves future investigations accompanied by carefully designed analytical plans. Finally, both cohorts, although independent, are mainly Caucasians. Thus, our findings are likely limited to only this population.

Innovation

To our knowledge, this is the first study to examine the epigenetics of asthma acquisition from pre- to post- adolescence, and post-adolescence to young adulthood with respect to gender and transition period specificity.

Conclusion

We assessed the longitudinal association of DNAm measured at earlier ages with asthma acquisition at later ages for each sex based on data in two independent cohorts with IOWBC as the discovery cohort and ALSPAC as the replication cohort. In the IOWBC, at 205 CpGs, pre-adolescence DNAm was shown to be associated with the odds of asthma acquisition from pre- to post-adolescence, and post-adolescence DNAm was associated with asthma acquisition from post-adolescence to adulthood. At 112 of these 205 CpGs, (54.6%), consistent associations were observed in the ALSPAC cohort, including statistically significant findings at 7 CpGs. These 112 CpGs included 62 CpGs (9 in males) showing transition-specific associations with asthma acquisition in that the association of DNAm with asthma acquisition at these 62 CpGs was different between the pre- to post-adolescence transition period and the post- to adulthood transition period. The identified CpGs based on two independent cohorts have a potential to

guide future studies in asthma acquisition prediction at different transition periods. Assessment of biological relevance of the identified CpGs indicated a potential epigenetic regulatory functionality of these CpGs on expression of their mapped and neighboring genes using a window size of 500 kbps.

Our findings also indicated significant differences between males and females. For the 62 CpGs showing consistent transition-specific effects between the two cohorts, at most of the CpGs in males, we found that an increase in DNAm was associated with an increased odds of asthma acquisition during the period from pre- to post-adolescence transition, while for the next transition period, at most of the CpGs, increased DNAm was associated with decreased odds. However, in females, at most of the CpGs, the associations were opposite compared to those in males; in females, an increase in DNAm was shown to be associated with a decreased odds of asthma acquisition from pre- to post-adolescence at most CpGs, but with increased odds at most of the CpGs in the transition period from post-adolescence to adulthood. Among the 50 CpGs (13 in males) showing main effects on asthma acquisition, although at most of the CpGs, an increase in DNAm was associated with a decreased odds of asthma acquisition for both males and females, the proportion of such CpGs was larger in females than in males. Furthermore, the effect sizes were overall weaker in females than in males. Before adolescence, asthma is more prevalent in males but during adolescence, more females acquire asthma and the prevalence of asthma in females surpasses that of males. The unique CpGs identified for each sex without any overlap and the inconsistent associations of DNAm with asthma acquisition between males and females seemed to be related to the gender-reversal phenomenon of asthma prevalence from pre- to post-adolescence.

In order to make sure that the identified CpGs are unique to each sex, the CpGs that were replicated in both cohorts were re-analyzed in opposite sex. For this, CpGs identified in males were evaluated for their association with asthma acquisition in females, and vice-versa. But I did not identify significant associations in either sex through this re-analysis. This ensures that the identified CpGs are unique to each sex.

Although we did not identify statistically significant biological processes after adjusting for multiple testing, biological processes involved in host immune function related to IL7 (i.e., interleukin-7-mediated signaling pathway, response to interleukin-7, cellular response to interleukin-7) were among the top processes determined based on statistical significance. IL7 signaling has been suggested to promote immunopathogenesis of asthma [105, 106], indicating the potentially informativity of the identified CpGs on asthma acquisition. In addition, the *TMEM194A* gene identified based on DMR analyses in males has been previously shown to be associated with asthma in GWAS catalog [107]. For females, gene *SERPINE2* in one of the identified DMRs has been connected with asthma based on genetic studies [108].

The gene *AKAP1*, mapped to the CpG showing consistent and statistically significant interaction effects in both cohorts in females, has been showed to be associated with asthma in the Agricultural Lung Health Study[109]. Although there was no overlap in identified CpGs between males and females, the gene *ENO1* was among the mapped genes of the associated CpGs in both sexes. The detection of IgG autoantibodies to alpha-enolase has been shown to be the most significant indicator for distinguishing severe asthma from mild-to-moderate asthma (OR= 5.2, 95% CI= 2.1-12.9, p-value < .001). It has been shown that alpha-enolase, an autoantigen, was associated with severe asthma[110]. The connection of gene *ENO1* with asthma acquisition

shown in our study is consistent with its differentiation between severe and mild-to-moderate asthma.

Chapter 4

Aim 2: To examine whether atopy in childhood mediates the association of DNAm in newborns with asthma acquisition across adolescence.

Background

Asthma is a common chronic respiratory condition and a major public health concern. Globally, it is ranked 16th among the leading causes of years lived with disability and 28th among the leading causes of burden of disease, as measured by disability-adjusted life years [111]. Atopy is defined as tendency to produce immunoglobulin E (IgE) antibodies in response to small amounts of common environmental exposures. It is a risk factor of asthma incidence [112] and affects 10-30% of general population in developed countries [113]. A number of studies have shown atopic diseases in early childhood are associated with asthma development later in life [114-116]. Carroll et.al. have shown a dose-response relationship in the association of atopic sensitization and asthma among children, i.e., the severity of asthma increases with increase in atopic sensitization to allergens [117].

For childhood asthma, a gender reversal in asthma prevalence from pre- to post-adolescence has been observed; more boys remit asthma than girls during adolescence whereas more girls acquire asthma than boys [118-121]. The underlying mechanisms involved in these sex differences of asthma across adolescence are unclear. The pathogenesis of asthma reflects a combination of genetic and epigenetic components; however, genetics explain only a fraction of variation in asthma risk. In addition to the effect of genetic factors, their interaction with changing environmental factors may also be responsible for atopy susceptibility and consequently contribute to the increase in prevalence of atopy-related disorders [122]. Several studies have explained the role of epigenetics in response to environmental factors in the development of

asthma [123-125]. One of the widely studied epigenetic mechanism is DNA methylation (DNAm) [71, 126]. DNAm or longitudinal changes in DNAm at specific cytosine-phosphate-guanine (CpG) sites have been shown to be associated with both atopy [127-130] and asthma or asthma acquisition [58, 59, 61, 75, 129, 130] in children and young adults. Among these studies, most utilized cross-sectional design to assess the associations of DNAm with atopy or asthma, except for the studies of Danielewicz, et al. and Reese, et al. Danielewicz, et al., via an epigenome-wide association study of 96 mother-child pairs, identified 83 CpG sites in cord blood of newborns that were associated with maternal atopy [127]. Reese et.al. demonstrated using 8 cohort studies that 9 CpGs in newborns were differentially methylated in relation to asthma [59]. However, no studies have focused on identification of methylation sites in newborns that are associated with these chronic conditions at later age.

DNAm in embryonic and pluripotent stem cell is close to zero [131] and it changes extensively from fertilization to implantation [132]. DNAm in newborns has been shown to be influenced by several maternal factors, such as smoking during pregnancy, pre-pregnancy BMI and gestational weight gain [133-136], potentially increase their offspring's risk of atopy and asthma. DNAm in newborns, as a memory of accumulated prenatal exposure, may serve as effective markers and be applied to predict the risk of later age atopy and asthma at a much earlier age.

However, as a risk factor of asthma, the role of atopy on the association of DNAm in newborns with asthma at a later age is unknown. Asthma can be atopic and non-atopic, and the underlying mechanisms is likely to be different in terms of DNAm markers. That is, at certain CpGs, it is possible that effects of DNAm at these CpGs in newborns on asthma at a later age are not mediated by atopy, and these CpGs might play a role in the development of non-atopic rather than atopic asthma. All these motivated the current study. In particular via path analyses, we

examine whether atopy in childhood mediates the association of DNAm in newborns with asthma acquisition at a later age. In addition to using SPT to determine atopic status, specific IgE have been used to assess the status of allergic sensitization against a specific allergen. The agreement between these two methods has been demonstrated in the literature [137]. Furthermore, one of our earlier studies showed that specific IgE-based and SPT-based assessment of atopic status were consistent in terms of their association with DNAm [138]. Such an agreement further supported the use of atopic status determined based on SPT in this study. We specifically focus on asthma acquisition from pre- to post-adolescence to identify epigenetic markers in newborns to facilitate our understanding of the phenomenon on gender reversal of asthma prevalence during this period. Direct and indirect effects (via pre-adolescence atopy status) of DNAm in newborns on asthma acquisition are evaluated using path analyses, based on which we identify potential epigenetic markers for asthma acquisition and at least some of the markers are associated with asthma acquisition via atopy.

Methods

IOWBC Study Population, asthma acquisition and gene expression at 26 years were explained previously in Chapter 3.

Covariates

Information regarding sex, breastfeeding duration in weeks and age at specific pubertal events, i.e., age at onset of voice deepening in males and age at onset of menarche in females, was extracted from questionnaire data. Socio-economic status (SES) was defined based on household income, number of rooms and maternal education. Active smoking status at 18 years was recorded as ‘yes’ if the participant was a current smoker. Second-hand smoke exposure at 18 years was determined using information obtained for tobacco smoke exposure from mother,

father, others, or outside home. Smoke exposure at 18 years was defined by combing active and second-hand smoke exposure at 18 years.

DNA methylation

DNA was extracted from Guthrie cards (blood collected within 5 days of birth) using standard procedures. One microgram of DNA was bisulfite-treated for cytosine to thymine conversion using the EZ 96-DNA methylation kit (Zymo Research, Irvine, CA, USA) for each sample, following the manufacturer's standard protocol. Genome-wide DNAm for each CpG was assessed using the Infinium MethylationEPIC BeadChip (Illumina, Inc, San Diego, CA, USA), which interrogate>850,000 CpG sites. Arrays were processed using a standard protocol as described elsewhere [139], with multiple identical control samples assigned to each bisulfite conversion batch to assess assay variability.

Preprocessing and quantile-normalization of DNAm intensity data was done similarly as explained previously for ages 10 and 18 years. The R package *ComBat* [140] was then applied to the M-values to adjust for batch effects. Cell type compositions were adjusted similarly as explained for ages 10 and 18 years.

Statistical analysis

Chi-square tests for categorical variables and one-sample t-tests for continuous variables were applied, stratified by sex to examine whether the analytic sample (n= 796) reasonably represents the complete cohort (n=1456). Considering the observed phenomenon of gender reversal in asthma prevalence from pre-adolescence to post-adolescence, we performed the analyses separately for each sex.

Research question 2.1: Does pre-adolescence atopy mediate the association of DNAm in newborns with asthma acquisition across adolescence in IOWBC?

Screening for CpGs related to atopy status at 10 years and asthma acquisition at 18 years

Regression of M-values of DNAm at each CpG site on the 6 cell type proportions [92] was done to obtain cell-type-adjusted DNAm (residuals) for each sex, and residuals were used in the subsequent analyses. Genome-wide screening of CpGs in newborns for their potential association with atopic status at 10 years and asthma acquisition from 10 to 18 years was done separately using an R package, *ttScreening* [141]. The screenings were performed on 551,710 CpGs separately for each sex.

In addition, via epigenome-wide DNAm data, we identified candidate CpGs based on detection of differentially methylated regions (DMRs) for their association with asthma acquisition from 10 to 18 years using *DMRff* package in R [142]. *DMRff* overcomes the shortcomings of *DMRcate* by consistently controlling for false positive rates, and more importantly, considers the uneven distribution of CpGs on the arrays. CpGs in DMRs that were statistically significant, after adjusting for multiple testing by controlling false discovery rate (FDR) of 0.2, along with CpGs that passed *ttScreening*, were included in subsequent analysis as candidate CpGs.

Structural equation analyses

We evaluated the mediating effects of atopy at 10 years in the association of DNAm in newborns and asthma acquisition from 10 to 18 years using structural equation analyses (Figure 6), with potential confounders included in each path. The path coefficients (direct and indirect estimates) represent a partial correlation between the independent and dependent variables after adjusting for confounders and covariates in the model [143]. An R package, *MplusAutomation*, was

implemented to iteratively call *MPlus* from R to perform structural equation analyses with each CpGs as an independent variable (Figure 6) [144]. Goodness of fit was determined using Chi-square test p-value >0.05, RMSEA ≤0.06, TLI ≥0.95, and CFI ≥0.95 [145].

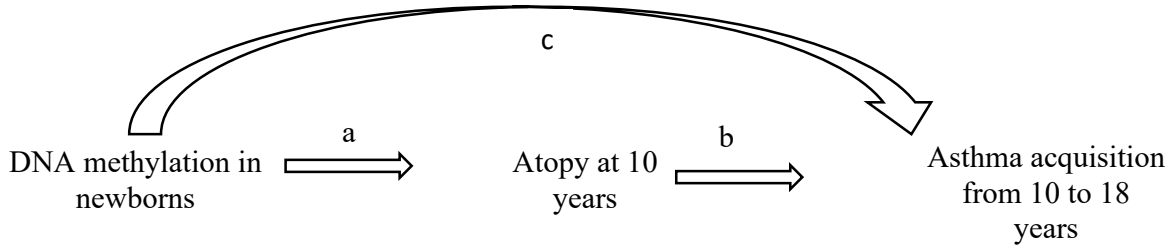

Figure 6: Structural equation analyses model with atopy at 10 years as the mediator in the association of DNAm in newborns with asthma acquisition at young adulthood
a=effects of DNAm in newborns on atopic status at 10 years, controlled for socio-economic status (SES) and breastfeeding duration
b= effects of atopy at 10 years on asthma acquisition from 10 to 18 years, controlled for breastfeeding duration, socio-economic status (SES), smoke exposure at 18 years, pubertal events (age at onset of voice deepening in males and age at onset of menarche in females)
c= direct effects of DNAm in newborns on asthma acquisition from 10 to 18 years

Research question 2.2: Can the findings of research question 2.1 be replicated in ALSPAC?

CpGs in newborns showing association with asthma acquisition from 10 to 18 years via atopy at 10 years were further tested in an independent cohort, the Avon Longitudinal Study of Children and Parents (ALSPAC) [98-100]. DNAm from cord blood in the ALSPAC cohort was assessed using the Infinium HumanMethylation450 BeadChip. The pre-processing of DNAm was performed using the *minfi* package [87] and CpGs with detection p-value ≥0.01 were excluded. Samples that contained sex-mismatch based on X-chromosome methylation were also excluded. In total, 420,399 probes are available for analysis after excluding probes that failed quality control. Estimated cell type proportions of CD4+ T cells, natural killer cells, B cells, monocytes, and granulocytes cells were adjusted to control for cell heterogeneity in the analysis. DNAm in

newborns was included in our study and its residuals were calculated by regression of M-values on cell type proportions (cell-type adjusted DNAm).

Asthma acquisition was assessed from 7 to 17 years, i.e., not having asthma at 7 years and having asthma at 17 years (no→yes). Identical structural equation analyses_models with comparable covariates available in ALSPAC, including SES, breastfeeding duration, smoke exposure at 15 and 17 years and pubertal events were used.

Research question 2.3: What are the biological pathways of genes corresponding to the identified CpGs in IOWBC?

Using the screened CpGs in newborns showing potential association with atopy and/or asthma acquisition, the genes annotated to the CpGs were summarized based on Illumina's manifest file. Pathway enrichment analysis of the genes were conducted using *gometh* package [146] in R software [147] using statistical significance level of 0.05.

Research question 2.4: Is there an association between DNAm at age 26 years and gene expression of nearby genes i.e., within 250kb upstream and downstream region of the identified CpGs at 26 years?

Genes annotated to the replicated CpGs showing indirect and direct effects on asthma acquisition were extracted along with information such as gene location, chromosome number from the Illumina's manifest file or UCSC genome browser (https://genome.ucsc.edu/). To assess the biological relevance of these CpGs, linear regressions were applied to test the association of DNAm (in M- values; independent variable) at age 26 years at each CpG site with expression of its neighboring genes (250k base pairs [bps] upstream and 250k bps downstream of the CpG site) in blood at 26 years of age. Paired DNAm and expression data of n=140 subjects were included

in the analyses. As we previously have found the association between gene expression and DNAm to be different in both males and females, the analysis was stratified by sex [61, 104].

Results

We included 401 male and 395 female participants in our study. Our subsample represented the complete cohort in terms of variables included in our study, shown by p-value > 0.05 in Table 5. The flow chart of sample selection for the present study is in Supplement Figure S4.

Table 5: Comparison of analytical subsample with complete cohort

Variables		Males			Females		
Categorical variables		Subsample (n=285); n (%)	Complete cohort (n=401); n (%)	P-value	Subsample (n=323); n (%)	Complete cohort (n=395); n (%)	P-value
Asthma transition	Acquisition	27 (9.47)	36 (5.87)	0.23	43 (13.31)	59 (9.50)	0.28
	Never asthma	258 (90.53)	473 (77.16)		280 (86.69)	485 (78.10)	
Atopy at 10 years	Yes	111 (31.18)	160 (31.01)	0.96	87 (24.37)	119 (22.88)	0.61
	No	245 (68.82)	356 (68.99)		270 (75.63)	401 (77.12)	
Socio-economic status	Low	61 (15.52)	106 (15.5)	0.68	48 (12.37)	103 (15.30)	0.38
	Mid	303 (77.1)	517 (75.58)		307 (79.12)	520 (77.27)	
	High	29 (7.38)	61 (8.92)		33 (8.51)	50 (7.43)	
Smoke exposure (18 years)	Yes	241 (65.85)	428 (65.64)	0.95	250 (66.31)	451 (68.33)	0.51
	No	125 (34.15)	224 (34.36)		127 (33.69)	209 (31.67)	
Continuous variables		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age at puberty		14.21 ± 1.23	14.24 ± 1.24	0.67	12.74 ± 1.39	12.72 ± 1.42	0.69
Duration of breastfeeding		14.95 ± 14.18	14.55 ± 14.62	0.65	14.37 ± 15.05	13.99 ± 14.99	0.62

The *ttScreening* package in R was applied to 551,710 CpGs to identify candidate CpGs potentially associated with atopy at 10 years or asthma acquisition from 10 to 18 years, stratified by sex. In males, 126 CpGs were potentially associated with atopy at 10 years of age and 93 CpG with asthma acquisition from 10 to 18 years. In females, 196 CpGs were potentially associated with atopy and 182 CpG with asthma acquisition. No common CpGs were found between atopy and asthma in both sexes, and there were no overlapping CpGs between males and females. Thus, in total 597 CpGs passed screening by use of the *ttScreening* package in R. To incorporate CpG sites located in differentially methylated regions into the analyses, we further analyzed DNAm at the genome-scale to identify DMRs with respect to asthma acquisition as an additional screening process. At FDR=0.2, in males, we identified one DMR located on chromosome 6. The region starts at nucleotide position 33255784 and covers 432 base pairs. Four CpGs, cg17131579, cg19048360 and cg27355501 on gene *PFDN6* and cg02272258 on *WDR46*, are in this region. For females, no DMRs were identified. Altogether, 223 CpGs in males and 378 CpGs in females (in total, 601 CpGs) were analyzed for their enrichment in pathways or biological processes and tested via path analysis to assess their effects on asthma acquisition in adolescence via childhood atopy.

To better understand the biological function of the screened CpGs showing potential association with atopy and asthma acquisition (223 CpGs in males and 378 CpGs in females), pathway enrichment analyses was conducted for. The 223 CpGs in males were mapped to 192 genes and 378 CpGs in females to 324 genes. Using these CpGs in *gometh* package in R, we identified 152 biological processes in males and 215 in females that were enriched at p-value <0.05. Among the total 192 and 324 genes in males and females respectively, 45 genes in males and 82 in females

were involved in the identified pathways (Table 6 and Supplemental Table S5). No common biological processes were identified between males and females.

Table 6(A): Top 10 most statistically significant GO terms and its biological processes from pathway enrichment analysis in each pathway for males, for the identified CpGs.

GO term	Biological processes	P-value
GO:0046380	N-acetylneuraminate biosynthetic process	0.005
GO:0035459	vesicle cargo loading	0.006
GO:0042700	luteinizing hormone signaling pathway	0.007
GO:0033140	negative regulation of peptidyl-serine phosphorylation of STAT protein	0.007
GO:0032462	regulation of protein homooligomerization	0.008
GO:0006045	N-acetylglucosamine biosynthetic process	0.008
GO:1901073	glucosamine-containing compound biosynthetic process	0.008
GO:0072665	protein localization to vacuole	0.009
GO:0044727	DNA demethylation of male pronucleus	0.009
GO:1903895	negative regulation of IRE1-mediated unfolded protein response	0.009

Table 6(B): Top 10 most statistically significant GO terms and its biological processes from pathway enrichment analysis in each pathway for females, for the identified CpGs.

GO term	Biological processes	P-value
GO:1901985	positive regulation of protein acetylation	0.0009
GO:0033144	negative regulation of intracellular steroid hormone	0.001
GO:0051582	positive regulation of neurotransmitter uptake	0.002
GO:0045214	sarcomere organization	0.003
GO:0021853	cerebral cortex GABAergic interneuron migration	0.003
GO:1904936	interneuron migration	0.003
GO:0001188	RNA polymerase I preinitiation complex assembly	0.004
GO:0043438	acetoacetic acid metabolic process	0.004

Table 6(B): continue

GO term	Biological processes	P-value
GO:0035066	positive regulation of histone acetylation	0.004
GO:0021894	cerebral cortex GABAergic interneuron development	0.004

After controlling for confounders, DNAm in newborns at 68 CpGs in males and 41 CpGs in females were found to be indirectly associated with asthma acquisition via atopy. It is worth noting that at 60 of the 68 and 37 of the 41 CpGs, only indirect effects were statistically significant. Of these, at 21 CpGs in males and 18 CpGs in females, a higher DNAm was indirectly associated with an increased risk of asthma acquisition via an increased risk of atopy. Whereas, at the remaining CpGs (39 CpGs in males and 19 CpGs in females), an increase in DNAm was indirectly associated with decreased risk of asthma acquisition via decreased risk of atopy (Supplemental Table S6). DNAm at certain number of CpGs only showed direct effects on asthma acquisition; in particular, DNAm in newborns at 99 CpGs in males and 192 CpGs in females were directly associated with asthma acquisition from 10 to 18 years age. Of these, for 50 (51%) CpGs in males and 72 (38%) CpGs in females, an increase in DNAm was directly associated with an increase in the risk of asthma acquisition (Supplemental Table S7).

CpGs showing indirect associations in IOWBC were further tested in the ALSPAC cohort to assess their potential of reproducibility. In ALSPAC cohort, DNAm data in newborns was available for 41 CpGs (of the 68 in IOWBC) in males and 18 CpGs (of the 41 in IOWBC) in females. Of these, the direction of indirect effects was consistent with those in IOWBC at 20 (49%) CpGs in males and 10 (56%) CpGs in females, although none of these CpGs were statistically significant. It is worth mentioning that of the 20 and 10 CpGs in males and females, all CpGs showed only indirect effects (Supplement Table S6). For CpGs showing only direct

effects in IOWBC (99 in males and 192 in females), DNAm in ALSPAC was available for 54 and 113 CpGs in males and females respectively. Of these, at 25 CpGs in males and 78 CpGs in females were in the same direction with one CpG (cg12938020) in males and 11 in females as being statistically significant (Supplemental Table S7).

The biological relevance of CpGs showing consistent direct and indirect effects on asthma acquisition between the two cohorts were further assessed. We evaluated the association of DNAm at the identified 133 CpGs (45 in males) with the expression of nearby genes (measure at age 26 years) that the CpGs were mapped to. To identify nearby genes, we used a range of 500k base pairs (bps) (i.e., 250k bps up and down stream) of the CpG site were also included in the assessment. In this analysis, DNAm and gene expression levels were assessed at age 26 years. Significant effects of DNAm were observed at 35 CpGs on their association with expression of 213 genes in males, and at 61 CpGs with expression of 357 genes in females (Table 7 and Supplement Table S8). Of the 570 genes' expression (213 in males) associated with DNAm, increased DNAm was associated with increased expression of 289 genes (130 in males).

Table 7: Top 5 most significant associations of DNAm with expression of neighboring mapped genes in each sex.

CpG site	Gene name	Estimate	P-value	Sex
cg25121621	*COPRS*	1	5.14×10^{-11}	Males
	PAGR1	1.34	1.48×10^{-9}	
	GDPD3	0.79	7.66×10^{-9}	
	TBX6	0.52	1.16×10^{-8}	
	LTN1	0.65	1.85×10^{-8}	
cg04720635	*CCDC7*	-1.84	3.01×10^{-26}	Females

Table 7: Continue

CpG site	Gene name	Estimate	P-value	Sex
	TP53INP2	-0.93	5.38×10^{-10}	Females
	MAK16	-0.69	2.16×10^{-9}	
	AQP3	-1.36	3.74×10^{-9}	
	N4BP2L2	-0.40	3.79×10^{-8}	

Note: Top 5 most statistically significant associations for each sex are shown here.

Connections with findings in Chapter 3. There was no overlap in the CpGs identified in this study (indirect or direct) and those identified in aim 1 for both sexes. DNAm in aim 1 was measured at 10 and 18 years while in aim 2 was at birth. The different sets of identified CpGs at this two time points may reflect potential dynamicity of epigenetic markers of asthma acquisition. Denser DNAm assessment between birth and age 10 years may help reveal the drifting effects of DNAm at birth as markers for asthma acquisition during adolescence. Atopic status at 10 years of age was included as a mediator in the assessment on the association of DNAm in newborns with asthma acquisition in aim 2. While in aim 1, atopic status at 10 years was used as a confounder. It is possible that atopic status in aim 1 may have played a role as a mediator as well. However, since atopic status determination and DNAm assessment both happened at the same age (10 years), the role of atopic status as a mediator conceptually may not hold under this specific design, but rather a potential confounder as done in aim 1. Nevertheless, it will be of interest to examine the role of atopy as a mediator at different time points.

Discussion

Strengths and limitations

The availability of asthma status at two key time points, pre- and post-adolescence, offered the possibility to examine asthma acquisition during adolescence. Identification of DNAm markers in newborns provides epigenetic insights in fetal life that potentially offered us an opportunity to predict the risk of later-life allergic and respiratory morbidity much earlier before disease manifestation. This study design with a clear time order (birth, pre-adolescence, and post-adolescence) allowed dissection of the total effects of DNAm in newborns on the risk of childhood asthma and whether and how atopy played a role in between.

Although the direction of mediating effects was consistent between the two cohorts at 16 and 7 CpG sites in males and females, respectively, none of them were statistically significant in the ALSPAC cohort. A possible reason for the statistical insignificance in the ALSPAC cohort might be due to the differences in the ages of assessment. In the ALSPAC cohort, atopy at age 7 years and asthma acquisition from 7 to 17 years was included, while in IOWBC, atopy was at age 10 years and asthma acquisition from 10 to 18 years. It is possible that the effect of DNAm in newborns on atopy was not strong enough to be detected at age 7 years. In addition, DNAm in IOWBC was measured in Guthrie cards while DNAm in ALSPAC was measured in cord blood. A recent study noted that when outcome or exposure are binary, agreement in findings between these two sources is expected to be at 70% of all CpGs under investigation [148]. This discrepancy between these two different sources of DNA might also have affected the statistical power in the replication analyses in the ALSPAC cohort.

In addition, our study evaluated the contributions of each individual CpG site. These CpGs may be correlated and jointly impact asthma acquisition, which could not be addressed by the present

study. Nevertheless, the consistency in the results between the two cohorts indicate that the identified CpGs in newborns are likely to play a role in the underlying mechanisms of asthma acquisition across adolescence. The recognized CpGs have a potential to improve our understanding of different underlying pathways (through atopy or not) from DNAm in newborns to asthma acquisition during adolescence.

Innovation

To our knowledge, this is the first study to examine the direct and indirect effects of DNAm in newborns on asthma acquisition from pre- to post-adolescence via pre-adolescence atopy status.

Conclusion

We examined the direct and indirect effects of DNAm in newborns on asthma acquisition from pre- to post-adolescence via pre-adolescence atopy status in two independent cohorts. In the IOWBC discovery cohort, DNAm in newborns at 68 CpGs in males and 41 CpGs in females were found to be indirectly associated with asthma acquisition from 10 to 18 years via atopy. Of these discovered CpGs that were available in the ALSPAC replication cohort (41 CpGs in males and 18 in females), 20 (49%) CpGs in males and 10 (56%) in females showed consistent direction of mediation effects in the ALSPAC, although not statistically significant. All these 30 CpGs showed only indirect effects. Of these 30 CpGs, at six CpGs in males and two CpGs in females, an increase in DNAm was indirectly associated with an increase in asthma acquisition risk via an increase in risk of atopy. For the remaining 22 of the 30 CpGs, an increase in DNAm was indirectly associated with decreased risk of asthma acquisition via decreased risk of atopy at 14 CpGs in males and eight CpGs in females.

In addition to these CpGs showing an effect on asthma acquisition via atopy, we discovered in total 291 CpGs (99 in males) that only had direct effects on asthma acquisition. Among these

291 CpGs, 103 showed consistent direction of effects in the ALSPAC cohort (25 in males) with one CpG site (cg12938020) in males and 11 in females showing statistical significance at 0.05, and at about half of these CpGs, a higher DNAm was associated with a higher odds of asthma acquisition.

Re-analysis of the DNAm sites (direct and indirect) replicated in both cohorts were evaluated in opposite sex. For this, CpGs identified in males were analyzed in females for their association with asthma acquisition, and vice versa. At 4 CpGs in males and 4 in females, statistically significant direct effects of DNAm on asthma acquisition were detected. Of these 8 CpGs (4 in males), 4 CpGs (3 in males) had same direction of effects. These 4 CpGs (cg18694780, cg16622920, cg06365057 in males and cg13331559 in females) may represent common underlying mechanisms for non-atopic asthma development during adolescence in both sexes. No such CpGs were identified for atopic asthma.

Assessment of biological relevance of the replicated CpGs indicated a potential epigenetic regulatory functionality of these CpGs on expression of their neighboring genes using a window size of 500 kbps. DNAm at 35 CpGs were associated with expression of 213 genes in males, and at 61 CpGs with expression of 357 genes in females. At 130 of the 213 genes in males and at 159 of the 357 genes in females, an increase in DNAm was associated with increased gene expression levels.

Allergic asthma can be atopic or non-atopic asthma. Atopic asthma is IgE mediated while non-atopic asthma is non-IgE mediated, i.e., eosinophilic or Th2 (T-helper 2) asthma.

We postulate that the 30 CpGs showing only indirect effects might play a role in the development of atopic asthma due to the involvement of atopy as a mediator. On the other hand, the 103 CpGs showing direct effects only may contribute to the occurrence of non-atopic asthma

since whether an individual was atopic or non-atopic did not influence the association of DNAm in newborns with asthma acquisition. CpG site cg12938020 showing significant direct effects in both cohorts is mapped to *HOXD3* gene, and Wang et.al. have shown rs10954213, located in *HOXD3* gene, influences *IRF5* gene expression, which is further linked to asthma [149].

In the top biological pathways detected through enrichment analysis based on CpGs that passed screening, several pathways and biological processes drew our attention and have been suggested to play an important role in the pathogenesis of asthma and allergy. In relation to the luteinizing hormone signaling pathway identified based on CpGs that passed screening for males, studies have shown lower levels of luteinizing hormone in patients with bronchial asthma [150, 151]. Annotated genes of the CpGs that passed screening were possibly also enriched in two biological processes related to biosynthesis of glucosamine, N-acetylglucosamine biosynthetic process and glucosamine-containing compound biosynthetic process, and glucosamine has been linked to atopy and respiratory tract secretions of asthmatic patients [152]. For the identified pathways of positive regulation of protein acetylation and histone acetylation, they are likely to be involved in the development of allergic diseases and asthma [153, 154]. The airway epithelium from asthmatic subjects displayed increased histone acetylation levels compared to non-asthmatic subjects [155]. These previous studies support the findings from our enrichment analyses and strengthen the possible connection between those CpGs with atopy and/or asthma. *PEX14* gene was involved in the top biological processes in males and also showed only indirect effects in both the cohorts. It has been found to be associated with asthma [156-158] as well as atopy [159]. *TMED10*, *BFAR* in males and *OBSL1* in females were among the top 10 biological processes and showed only direct effects in both cohorts. Previous studies have shown *TMED10* to be differentially- expressed in severe asthma [160], and *OBSL1* is overexpressed in asthma

cases compared to controls (foldchange= 1.305937, FDR p-value= 0.00217526) [161]. These findings may support the role of *PEX14* gene in atopic asthma while *TMED10* and *OBSL1* gene in non-atopic asthma. The identified CpGs from both cohorts may serve as biomarkers of atopic and non-atopic asthma. Future studies are encouraged to investigate the role of DNAm at these CpGs as mediator in the association of exposures during fetal development with asthma.

Chapter 5

Aim 3: To examine sex-specific associations of DNAm in Guthrie cards of newborns with pre-adolescence asthma and/or rhinitis

Background

Asthma affects more than 300 million people worldwide [162], and is ranked 16th among the leading causes of years lived with disability. Asthma most often originates in childhood and so higher incidence and prevalence is found among children. Asthma incidence and prevalence is different between males and females. A higher incidence, prevalence and hospitalization is seen in pre-pubertal boys than girls of same age, while a reverse trend is observed during adolescence [61, 163]. Another closely related airway disease, rhinitis, has been treated as a risk factor of asthma [164]. Among different types of rhinitis, allergic rhinitis affects 10-40% of world population with a prevalence of 8.4% in children and 14.9% in adolescents. It is the most common allergic disease among children [165] leading to long-term consequences in adulthood. Asthma and rhinitis are common chronic conditions that occur as comorbidities. About 40% of patients with allergic rhinitis have asthma, and 94% of patients with allergic asthma have allergic rhinitis [166-169]. Another study found allergic rhinitis patients have three times increased risk of developing asthma. Also, relief of rhinitis symptoms over time had a correlation with improvement in asthma symptoms, and subjects with severe and persistent rhinitis are at increased risk of developing asthma [170]. It has been found that the prevalence of coexisting asthma and allergic rhinitis in pre-adolescence is predominant in males[171].

Both these conditions have complex etiologies involving both genetic and epigenetic mechanisms. The heritability estimates representing genetic contribution vary substantially, 35-95% for asthma and 33-91% for allergic rhinitis [172]. Studies have found genetic similarities

between asthma and rhinitis as shared phenotypes [57, 173] explained by concept of united airway disease, IgE and non-IgE sensitizations [174]. Recent studies further incorporated epigenetics to explain the pathogenesis of asthma [58] and allergic conditions due to its ability to mediate environmental effects. DNA methylation (DNAm) at 5'-C-phosphate-G-3' (CpG) sites is one of the most studied epigenetic mechanisms. Several studies have shown an association of DNAm in blood with the status of asthma [13, 58, 61] and allergic diseases [175-177]. A recent meta-analysis demonstrated that DNAm in newborns was associated with asthma in school-aged children in 8 cohorts [59]. However, literature on the connection between DNAm and rhinitis is limited. A study of allergic rhinitis (AR) participants identified 42 CpG sites showing correlations of AR symptoms with DNAm [64].

In this study, we focused on subjects with asthma and/or rhinitis (Ast_Rh) and aim to identify CpG sites with DNAm in newborns associated with these two allergic diseases, asthma, and rhinitis, among pre-adolescent children. Genome-scale DNAm data and clinical data collected in the Isle of Wight birth cohort (IOWBC) were included in the study. Previously, a cross-sectional study with focus on Ast_Rh was conducted among children aged 16 years based on DNAm in nasal epithelium [63]. Our study, on the other hand, is longitudinal with DNAm in blood on Guthrie cards of newborns. Findings from this study has a potential to identify individuals with higher risk of Ast_Rh at a much earlier age.

Methods

IOWBC Study Population and gene expression data at 26 years was explained in Chapter 3. DNAm at birth is explained in Chapter 4.

Asthma and/or Rhinitis (Ast_Rh)

Asthma at 10 years was defined using ISAAC questionnaire as “ever had asthma” and “wheezing or whistling in the chest in the last 12 months” and/or “current treatment for asthma”. Based on responses to these questions, a participant was determined to have asthma if she/he had experienced recurrent wheezing in the last 12 months and been given a clinical diagnosis of asthma by the physician with or without being treated with asthma medications. Rhinitis at 10 years was defined as ‘In the past 12 months have you had a problem with sneezing or a runny or a blocked nose when you did not have a cold or the flu?’ [180]. The outcome of the study was asthma and/or rhinitis (Ast_Rh) at 10 years, i.e., subjects with asthma only, rhinitis only, or both asthma and rhinitis were included in the study. Participants who did not have asthma nor rhinitis at 10 years were included in our study as a reference group.

Covariates

Atopic status at 10 years and SES are explained in Chapter 4. Second-hand smoke exposure at 10 years was determined using information obtained from tobacco smoke exposure from mother, father, others, or outside home at 1, 2, 4 and 10 years.

Statistical analysis

Chi-square tests for categorical variables and one-sample t-tests for continuous variables were applied, stratified by sex to examine whether the analytic sample (n=796) reasonably represents the complete cohort (n=1456).

Research question 3.1: Is the association of DNAm in newborns with pre-adolescence asthma and/or rhinitis sex-specific?

<u>Screening for CpGs in newborns related to asthma and/or rhinitis at 10 years</u>

Regression of M-values of DNAm at each CpG site on the 6 cell type proportions [92] was done to obtain cell-type-adjusted DNAm (residuals) for each sex, and residuals were used in the subsequent analyses.

Screening of genome-scale CpGs potentially associated with Ast_Rh was performed from two directions, separately for each sex, with the first direction focusing on individual CpGs and the second on CpGs in regions. To screen individual CpGs with DNAm in newborns possibly associated with Ast_Rh at 10 years, an R package, *ttScreening* [141], was implemented. The method implemented in *ttScreening* can control both type I and type II errors.

In the second approach of screening, we identified candidate CpGs based on detection of differentially methylated regions (DMRs) for their association with Ast_Rh at 10 years using the *DMRff* package in R [142]. CpGs in DMRs that were statistically significant at the level of false discovery rate (FDR) of 0.2 along with CpGs that passed *ttScreening* were included in subsequent analysis as candidate CpGs.

Association of DNAm in newborns with Ast_Rh at 10 years

Multivariable logistic regression analysis was conducted to evaluate the association of DNAm in newborns (independent variable) at CpGs that passed screening with Ast_Rh at 10 years (dependent variable). Sex, SES, duration of breastfeeding, atopy, and second-hand smoke at 10 years were included in the model as potential confounders. An interaction term of DNAm and sex was included in the model as an attempt to address sex difference in childhood asthma or rhinitis prevalence. For CpGs not showing significant interaction effects, their main effects were evaluated. In both situations (the models with main effects only, and the models that included interaction effects) multiple testing was adjusted by controlling FDR of 0.05.

Research question 3.2: What are the biological pathways of genes corresponding to the identified CpGs in IOWBC?

For candidate CpGs showing associations of DNAm with Ast_Rh, genes annotated to the CpGs were summarized along with information including gene location and chromosome number extracted from the Illumina's manifest file and USCS genome browser (https://genome.ucsc.edu). Pathway enrichment analysis of the identified candidate CpGs was conducted using the R function *gometh* [103] to gain insight of their biological functionality.

Research question 3.3: Can the findings of research question 3.1 be replicated in ALSPAC?

CpGs in newborns showing association with Ast_Rh at 10 were further tested in an independent cohort, the Avon Longitudinal Study of Children and Parents (ALSPAC) [98-100]. DNAm measurement from cord blood has been explained previously in Chapter 4 (Research question 2.2).

Ast_Rh was assessed at 7 years, i.e., subjects with asthma only, rhinitis only, or both asthma and rhinitis. Logistic regressions with comparable covariates available in ALSPAC, including SES, sex, atopy at 7 years and second-hand smoke at 7 years were used.

Research question 3.4: Is there an association between DNAm at age 26 years and gene expression of nearby genes i.e., within 250kb upstream and downstream region of the identified CpGs at 26 years?

Genes annotated to the replicated CpGs showing association with Ast_Rh were extracted along with information such as gene location, chromosome number from the Illumina's manifest file or UCSC genome browser (https://genome.ucsc.edu/). To assess the biological relevance of these CpGs, linear regressions were applied to test the association of DNAm (in M- values; independent variable) at age 26 years at each CpG site with expression of its neighboring genes

(250k base pairs [bps] upstream and 250k bps downstream of the CpG site) in blood at 26 years of age. Paired DNAm and expression data of n=140 subjects were included in the analyses. As we previously have found the association between gene expression and DNAm to be different in both males and females, the analysis was stratified by sex [61, 104].

Research question 3.5: Is there a genetic influence on DNAm at the replicated CpGs, i.e., are there any methQTLs?

Single nucleotide polymorphisms (SNPs) associated with methylation levels of CpGs are known as methQTLs [179]. SNPs to be included in the analyses for methQTL assessment were the ones located on the CpGs' mapping genes using the Illumina manifestation file. Linear regression was used to evaluate this association where DNAm at birth was the dependent variables and SNPs was independent variables. CpGs with p-value <0.05 indicated its statistical significance on its association with SNPs (as methQTLs).

Results

Descriptive statistics on the status of Ast_Rh and variables potentially associated with the childhood asthma and rhinitis indicated that the subsamples represented the complete IOWBC (Table 8). The consort diagram for the study on samples included in the analyses is in Supplement Figure S5. Additionally, I looked at atopic status to make sure not all participants in Ast_Rh are atopic (Supplement Figure S6).

Table 8: Comparison of analytical subsample with complete cohort

Variables		Males			Females		
Categorical variables		Subsample (n=392); n (%)	Complete cohort (n=401); n (%)	P-value	Subsample (n=387); n (%)	Complete cohort (n=395); n (%)	P-value
Ast_Rh	Yes	144 (36.7)	222 (31.9)	0.1	119 (30.8)	192 (28.4)	0.42
	No	248 (63.3)	475 (68.1)		268 (69.2)	484 (71.6)	
Atopy at 10 years	Yes	111 (31.2)	160 (31.01)	0.9	87 (24.4)	119 (22.88)	0.61
	No	245 (68.8)	356 (68.99)		270 (75.6)	401 (77.12)	
Socio-economic status	Low	61 (15.5)	106 (15.5)	0.68	48 (12.4)	103 (15.30)	0.38
	Mid	303 (77.1)	517 (75.58)		307 (79.1)	520 (77.27)	
	High	29 (7.4)	61 (8.92)		33 (8.5)	50 (7.43)	
Second-hand smoke at age 10 years	Yes	266 (66.8)	489 (64.3)	0.38	246 (62.3)	445 (68.4)	0.77
	No	132 (33.2)	272 (35.7)		149 (37.7)	280 (31.6)	
Continuous variables		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Duration of breastfeeding		14.95 ± 14.81	14.55 ± 14.62	0.6	14.37 ± 15.05	13.99 ± 14.99	0.63

To identify candidate CpGs potentially associated with Ast_Rh at 10 years of age, *ttScreening* stratified by sex was applied to 551,710 CpGs using residuals (cell-type adjusted DNAm) in newborns. In total, 154 CpGs in males and 339 in females in IOWBC passed screening. There were no overlapping CpGs between males and females, and union of these CpGs, i.e., 493 CpGs, were included in subsequent analyses. Additionally, using the R package *DMRff*, at FDR 0.2 level, we identified one DMR with 2 CpGs (cg00701456, cg08196106) in females on chromosome 12. As these 2 CpGs were in one DMR, they may work together. We treated these two CpGs as one CpG unit and used the mean of their cell-type-adjusted DNAm levels to represent DNAm of the CpG unit. No DMRs were identified in males. One CpG (cg08196106)

was common between the CpGs identified via *ttScreening* and those by *DMRff*. Thus, in total, 492 CpGs plus one CpG unit were included in further analyses.

Pathway enrichment analysis was conducted to better understand the biological functionality of the 154 screened CpGs in males and 340 CpGs (=339 CpGs from *ttScreening* + 1 CpG from *DMRff*) in females. The 154 CpGs in males were mapped to 123 genes, and 340 CpGs were mapped to 266 genes. Using these CpGs in *gometh* package in R, we identified 110 biological processes in males and 278 in females that were enriched at p-value <0.05. Among the mapped 123 and 266 genes in males and females respectively, 10 genes in males and 29 in females were involved in the identified pathways (Table 9 and Supplemental Table S9). No common biological processes were identified between males and females.

Table 9(A): Top 10 most statistically significant GO terms and its biological processes from pathway enrichment analysis in each pathway for males, for the CpGs that passed screening.

GO term	Biological processes	P-value
GO:0045116	protein neddylation	0.001
GO:0033622	integrin activation	0.004
GO:0045956	positive regulation of calcium ion-dependent exocytosis	0.004
GO:1905078	positive regulation of interleukin-17 secretion	0.004
GO:0008049	male courtship behavior	0.004
GO:0042407	cristae formation	0.005
GO:0006393	termination of mitochondrial transcription	0.006
GO:1904235	regulation of substrate-dependent cell migration, cell attachment to substrate	0.006
GO:1904237	positive regulation of substrate-dependent cell migration, cell attachment to substrate	0.006
GO:0002636	positive regulation of germinal center formation	0.007

Table 9(B): Top 10 most statistically significant GO terms and its biological processes from pathway enrichment analysis in each pathway for females, for the CpGs that passed screening.

GO term	Biological processes	P-value
GO:0014834	skeletal muscle satellite cell maintenance involved in skeletal muscle regeneration	0.0007
GO:0035264	multicellular organism growth	0.001
GO:0001678	cellular glucose homeostasis	0.002
GO:0089718	amino acid import across plasma membrane	0.002
GO:0071499	cellular response to laminar fluid shear stress	0.003
GO:0035902	response to immobilization stress	0.003
GO:0043090	amino acid import	0.003
GO:1904491	protein localization to ciliary transition zone	0.003
GO:0060563	neuroepithelial cell differentiation	0.003
GO:0046324	regulation of glucose import	0.003

Via logistic regressions, we examined the interaction effects of DNAm and sex on the odds of Ast_Rh at the 492 CpGs and one CpG unit, controlling for second-hand smoke exposure at 10 years, SES, duration of breastfeeding and atopy. After adjusting for multiple testing by controlling FDR at 0.05 level, 404 CpGs and one CpG unit showed significant interaction with sex. Of these, opposite effects of DNAm were observed at 330 CpGs in males and females, i.e., at 130 CpGs, an increase in DNAm was associated with a decreased odds of Ast_Rh in males but increased odds in females. And at 199 CpGs and one CpG unit, an increase in DNAm was associated with an increased odds of Ast_Rh in males but decreased odds in females. (Supplemental Table S10a). For CpGs not showing interaction effects between DNAm and sex, main effects of DNAm were assessed at 88 CpGs. After adjusting for FDR at 0.05 level, we identified 70 CpGs showing association of DNAm with Ast_Rh controlling for sex and

previously mentioned covariates. At 32 of the 70 CpGs, an increase in DNAm was associated with an increased odds of Ast_Rh while at the remaining 38 CpGs, the association was in the opposite direction (Supplemental Table S10b).

Altogether, we identified 475 (=405+70) CpGs in newborns with DNAm associated with Ast_Rh at 10 years. We further tested these CpGs in the ALSPAC cohort. For the 405 CpGs showing interaction effects in IOWBC, consistent directions of interaction effects were observed at 116 CpGs of the available 242 CpGs, with 3 CpGs being statistically significant in ALSPAC. For the 70 CpGs showing main effects in IOWBC, 17 CpGs of the available 37 CpGs in ALSPAC showed same directions of associations identified in the IOWBC.

To assess the biological relevance of replicated CpGs showing association with Ast_Rh, we evaluated the association of DNAm at the identified 129 CpGs with the expression of genes that the CpGs were mapped to as well as their nearby genes by considering a window of 500k base pairs (bps) of the CpG site (250k bps up and down stream). In this analysis, DNAm and gene expression levels were assessed at age 26 years. Significant effects of DNAm were observed at 86 CpGs on their association with expression of 396 genes in males, and at 96 CpGs with expression of 589 genes in females (Table 10 and Supplemental Table S11). Of the genes' expression associated with DNAm, increased DNAm was associated with increased expression of 208 genes in males and 345 genes in females.

Table 10: Top 5 most significant associations of DNAm with expression of neighboring mapped genes in each sex.

CpG site	Gene name	Estimate	P-value	Sex
cg01662869	*DPYSL4*	0.92	4.30×10^{-7}	Males
	QRFP	0.83	6.55×10^{-7}	
cg19248893	*RGS6*	-1.8	8.53×10^{-7}	Males
cg01662869	*JADE2*	1.05	1.56×10^{-6}	Males
	JAM3	1.92	2.18×10^{-6}	
	JADE2	0.93	1.72×10^{-11}	Females
	DPYSL4	0.83	2.99×10^{-10}	
	MOSPD1	0.56	8.41×10^{-8}	
	GLB1L2	0.62	1.66×10^{-7}	
	LAMC3	0.68	1.67×10^{-7}	

Note: Top 5 most statistically significant associations for each sex are shown here.

For replicated 133 CpGs, their genetic influence was further assessed by evaluating if those CpGs had methQTLs. SNPs were extracted using the Illumina manifestation file and SNPs on the mapping genes of these CpGs were included in the analyses. In total, 791 SNPs for 47 CpGs were included in the analyses to assess methQTL. The analysis was sex stratified. We identified 29 CpGs in males and 31 CpGs in females (25 CpGs in common) showing association with SNPs i.e., methQTLs existed at those CpGs (Supplement Table S12).

Discussion

Strengths and limitations

The strength of this study exists in its focus on a longitudinal assessment of DNAm at a critical time point, less than a week after birth, with pre-adolescent asthma and/or rhinitis. In addition to assess contribution of individual CpG sites, we examined joint effects of CpGs identified via DMR analyses and some of those CpGs were otherwise excluded from analyses based on individual CpGs. Several limitations of the study exist. First, the study population was mainly Caucasians. This may be a limiting factor in the external validity of findings, and hence generalization of these findings should be implemented with caution. Second, the focus of the study was on associations rather than causality, and this analytical approach does not allow predictions or inferring causality. Third, DNA was extracted from blood cells while asthma and rhinitis primarily affect cells of the respiratory tract. Although DNAm of the blood cells has concordance with that of the respiratory system cells [181], some differences exist between the two. Hence, DNAm in blood may not fully reflect the DNAm in respiratory tract cells.

Innovation

To our knowledge, this is the first longitudinal study to examine the association of epigenetics in newborns with pre-adolescent asthma and/or rhinitis in blood with respect to gender specificity.

Conclusion

We assessed the longitudinal association of DNAm in newborns with pre-adolescent asthma and/or rhinitis. At 404 CpGs and a CpG unit of cg00701456 and cg08196106, we identified significant interaction effects of DNAm and sex in the association with Ast_Rh at FDR 0.05 level. Of these, an increase in DNAm at 199 CpGs and one CpG unit was associated with an increased odds of Ast_Rh in males but a decreased odds in females. Of the CpGs not showing

interaction effects, 70 CpGs were found to be associated with Ast_Rh adjusting for sex, of which an increase in DNAm at 32 CpGs was associated with an increased odds of Ast_Rh. Of the 404 CpGs and a CpG unit showing significant interaction effects in IOWBC, at 116 of the available 242 CpGs, (48%), consistent associations were observed in the ALSPAC cohort, including statistically significant findings at 3 CpGs. Of the 70 CpGs showing main effects in IOWBC, 17 of the available 37 CpGs (46%) showed same direction of association in ALSPAC.

Assessment of biological relevance of the replicated CpGs indicated a potential epigenetic regulatory functionality of these CpGs on expression of their neighboring genes using a window size of 500 kbps. DNAm at 86 CpGs were associated with expression of 396 genes in males, and at 96 CpGs with expression of 589 genes in females. At 208 of the 396 genes in males and at 345 of the 589 genes in females, an increase in DNAm was associated with increased gene expression levels. Of the replicated 133 CpGs, 29 CpGs in males and 31 CpGs in females were linked to genetic variants (methQTLs) indicating potential contribution of genetic factors on the identified CpGs. It is worth noting that between these 29 and 31 CpGs, 25 were in common, strengthening the existence of methQTLs. That is, the observed epigenetic effects at these CpG sites were likely due to the contribution of genetic factors, supporting the findings on the genetic connection between asthma and rhinitis [57, 173]. On the other hand, CpGs with DNAm not associated with SNPs may represent epigenetic effects only without significant genetic contribution.

Although we did not identify statistically significant biological processes after adjusting for multiple testing, biological processes such as integrin activation and interleukin-17 secretion were among the top processes determined based on statistical significance. Activation of integrins have been shown to be correlated with eosinophil recruitment and pulmonary

function in asthma [182]. Eosinophil arrest and recruitment to the airway in asthma are mediated, at least in part, by integrins [182-184]. Therefore, antagonists targeting integrins may potentially be involved in asthma treatment [184]. Expression of IL-17A in nasal mucosa is associated with pathophysiology of allergic rhinitis including its severity and nasal eosinophilia [185]. Neutralization of IL-17 has been found to improve symptoms of allergic rhinitis [186].

Chapter 6. Summary

Epigenetic investigations of asthma will help us better understand its etiology and help direct preventive measures. The summary of main findings of this dissertation from two independent cohorts are:

- I identified DNAm at 62 CpGs (9 in males) showing transition-specific associations with asthma acquisition (AA) such that the associations were different between the pre- to post-adolescence transition period and the post- to adulthood transition period. I also found significant differences between males and females at these CpGs i.e., at most of the CpGs in males, an increase in DNAm was associated with an increased odds of AA from pre- to post-adolescence transition, while from post-adolescence to adulthood, increased DNAm at most of the CpGs was associated with decreased odds. The associations in females for both transition periods were opposite compared to those in males. Among the 50 CpGs (13 in males) showing main effects on AA, at most of the CpGs, an increase in DNAm was associated with a decreased odds of AA for both males and females, although the proportion of such CpGs was larger in females than in males. Furthermore, the effect sizes were weaker in females than in males.
- I identified 30 CpGs (20 in males) in newborns that are associated with AA via atopy. Of these, an increase in DNAm at 22 CpGs (14 in males) was indirectly associated with decreased risk of AA via decreased risk of atopy. These CpGs might play a role in atopic asthma. At 103 CpGs, only direct effects of DNAm in newborns on AA during adolescence were observed which might contribute towards non-atopic asthma.
- Sex-specific effects of DNAm in newborns on preadolescent Ast_Rh were observed at 116 CpGs, and at most CpGs opposite effects in males and females were detected.

For each aim, it will be informative to examine DNAm trajectories at the identified CpGs and the longitudinal associations between DNAm and the endpoint (asthma acquisition or asthma/rhinitis status). Such an investigation will allow us to assess the potential of dynamicity of DNAm along with its potentially changing effect, if any.

Within each aim, it was noticed that a small number of CpGs in IOWBC were replicated in ALSPAC showing the same direction of effects with statistical significance. There is a possibility of false-positive findings. Other factors such as age and sources of DNAm might have also caused the discrepancy in the findings between the two cohorts. Further assessment of the identified CpGs is desired in large scale cohort studies.

In addition, none of the identified CpGs showed overlap in these 3 studies, which was expected. The DNAm was assessed at 10 and 18 years for aim 1, while in newborns for aim 2 and 3. Reflected in my analyses was that CpGs identified in newborns are likely not to continue their association at ages 10 or 18 years with AA at later ages. This may be the result of changes in environmental exposures over time, from birth to adolescence. Also, the outcomes for the three studies are different. Aim 1 and 2 focused on AA, i.e., transition during adolescence (while the DNAm ages were different) and aim 3 focused on the status of preadolescent Ast_Rh rather than changes in asthma status. The CpGs identified in aim 1 and 2 may represent involvement in the development of asthma during a critical period of adolescent, while those in aim 3 are related to the status of asthma and/or rhinitis before adolescence (i.e., conditions are already developed, and some may have persistent asthma).

The unique CpGs identified for each sex without any overlap in these findings and the inconsistent associations of DNAm with AA between males and females might be related to the gender-reversal phenomenon of asthma prevalence from pre- to post-adolescence. It is worth

noting that for most of the associations of DNAm with AA, a greater number of CpGs were identified in females compared to males. The reason for this observation is unknown and remains to be biologically determined through future investigations. I speculate that X chromosome inactivation due to genetic mechanism may be related to such a difference in number of identified CpGs in each sex [187]. These identified CpGs can guide future studies in AA prediction at different transition periods in both sexes, whether atopic or non-atopic asthma. The biological functionality of the identified CpGs will strengthen their potential as causal factors in addition to epigenetic markers. The CpGs identified in this dissertation have a potential to serve as epigenetic biomarkers due to the strength of associations assessed based on statistical significance.

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Appendix

Supplement Table S1 (A): Association of DNAm with asthma acquisition from pre- to post-adolescence, and post-adolescence to young adulthood at 17 CpGs in males that are transition period specific. Significant interaction between DNAm and transition period on asthma acquisition identified in the IoW(a) cohort were further tested in the ALSPAC(b) cohort. 10-18transition period is the reference group.

CpG sites	IoW Main estimates (10-18 years)	IoW Interaction Estimates	Raw p value Int	FDR p value Int	Gene	CpG islands	Gene location	Chromosome
cg01579206	-0.17	0.17	0.002	0.019	*CSNK1A1*	Island	TSS200	5
cg01884526	0.71	-0.64	0.015	0.048	*BANP*		Body	16
cg02637320	-0.05	0.07	0.009	0.048	*MFSD4*	Island	Body	1
cg06519746	0.54	-1.05	0.002	0.019	*FAM105B*	Island	TSS1500	5
cg08056069	0.29	-0.88	0.002	0.020	*RP11-86H7.1*		3'UTR	1
cg08286012	0.57	-0.66	0.000	0.008	*C4orf22*	Island	Body	4
cg11620807	-0.05	0.04	0.012	0.048	*IRS1*	Island	TSS1500	2
cg12009697	0.58	-0.61	0.014	0.048	*GPR35*	N_Shore		2
cg12895747	0.74	-0.73	0.004	0.030	*RAP1GAP2*	Island		17
cg15925090	0.29	-0.66	0.001	0.015	*MSX1*	Island		4
cg17219326	-0.03	0.19	0.011	0.048	*ZNF445*	N_Shore	5'UTR	3
cg17610929	-0.04	0.18	0.006	0.039	*ACCN4*	S_Shore	5'UTR	2
cg19707069	0.44	-0.51	0.013	0.048	*MGMT*			10
cg21691089	-0.13	0.13	0.010	0.048	*ENO1*	Island	1stExon	1
cg25180075	-0.06	0.09	0.011	0.048	*HS6ST1*	Island	TSS200	2
cg25317233	0.61	-1.07	0.000	0.000	*HMGN1*	N_Shelf	Body	21
cg27192902	-0.06	0.06	0.015	0.048	*ZNF259*	Island		11

CpG sites	Gene	ALSPAC Main Estimates (7-17 years)	ALSPAC Interaction Estimates	ALSPAC estimates (17-22 years)	ALSPAC p value
cg01579206	*CSNK1A1*	0.07	-0.11	-0.04	0.644
cg01884526	*BANP*	0.00	-0.24	-0.25	0.217
cg02637320	*MFSD4*	0.01	-0.13	-0.12	0.682
cg06519746	*FAM105B*	-0.02	0.43	0.42	0.071
cg08056069	*RP11-86H7.1*	0.07	-0.28	-0.21	0.079
cg08286012	*C4orf22*	0.04	0.46	0.50	0.167
cg11620807	*IRS1*	0.01	0.11	0.13	0.829
cg12009697	*GPR35*	0.00	-0.29	-0.29	0.065
cg12895747	*RAP1GAP2*	0.02	0.16	0.18	0.389
cg15925090	*MSX1*	0.06	0.26	0.33	0.213
cg17219326	*ZNF445*	0.03	0.02	0.05	0.887
cg17610929	*ACCN4*	0.09	-0.05	0.04	0.836
cg19707069	*MGMT*	0.02	-0.82	-0.80	0.043
cg21691089	*ENO1*	-0.01	0.27	0.27	0.521
cg25180075	*HS6ST1*	0.07	-0.25	-0.18	0.402
cg25317233	*HMGN1*	-0.02	-0.04	-0.06	0.808
cg27192902	*ZNF259*	0.00	0.30	0.30	0.311

Note: (a) For the analysis in IoW, logistic regression with repeated measurements were adjusted for atopic status at ages 10 and 18 years, active smoking, and secondhand smoke exposure at age 18 and 26 years, transition period 10-18 and 18-26 years.
(b) Analysis of ALSPAC used similar available covariates: atopic status at age 7 years, secondhand smoke exposure at age 17 and 24 years.
Interaction effects consistent between the two cohorts are with bold fonts of CpG.

Supplement Table S1 (B): Association of DNAm with asthma acquisition from pre- to post-adolescence, and post-adolescence to young adulthood at 98 CpGs in females that are transition period specific. Significant interaction between DNAm and transition period on asthma acquisition identified in the IoW(a) cohort were further tested in the ALSPAC(b) cohort. 10-18transition period is the reference group.

CpG sites	IoW Main estimates (10-18 years)	IoW Interaction Estimates	Raw p value Int	FDR p value Int	Gene	CpG islands	Gene location	Chromosome
cg00149397	0.21	-0.20	8E-06	0.0004	*TPST2*	Island	TSS200	22
cg00405843	0.16	-0.17	2E-03	0.0111	*SMO*	Island	TSS200	7
cg00444282	-0.13	0.13	1E-02	0.0284	*RTN3*	Island	5'UTR	11
cg00705668	0.22	-0.23	2E-03	0.0111	*MRPS12*	Island	TSS200	19
cg02225897	0.47	-0.44	5E-03	0.0182	*RTDR1*	S_Shore	TSS200	22
cg02362385	-0.13	0.14	2E-02	0.0414	*LPAR2*	Island	TSS200	19
cg02467794	1.04	-1.14	1E-02	0.0338	*AKAP1*	Island	1stExon	17
cg02516257	-0.09	0.09	2E-02	0.0424	*GMCL1*	Island	TSS200	2
cg02619805	-0.11	0.15	4E-04	0.0037	*SAFB2*	Island	TSS200	19
cg03223733	0.90	-1.01	6E-04	0.0052	*ZNF211*	Island	TSS200	19
cg03606222	0.27	-0.24	6E-04	0.0052	*NAPA*	Island	TSS200	19
cg03719634	0.62	-0.64	5E-04	0.0045	*TMEM45A*	Island	TSS200	3
cg04784251	0.39	-0.41	1E-02	0.0371	*BCAS3*		Body	17
cg04789385	0.16	-0.20	2E-04	0.0029	*ZFP1*	Island	5'UTR	16
cg04802657	-0.33	0.31	4E-03	0.0158	*CCDC101*	Island	TSS200	16
cg05245655	-0.12	0.14	9E-03	0.0271	*SIX5*	Island	5'UTR	19
cg05444312	0.26	-0.27	1E-02	0.0342	*HIST1H2BM*	S_Shore	TSS200	6
cg06045799	1.18	-1.16	1E-03	0.0065	*COMMD8*	Island	Body	4
cg06060137	-0.16	0.20	1E-02	0.0336	*DACH1*			13
cg06100790	-0.72	0.60	5E-03	0.0187	*SH2B1*	Island	TSS1500	16
cg06364593	-1.56	1.25	2E-02	0.0424	*ATP5B*			12
cg06654302	0.30	-0.31	4E-08	0.0000	*DDX60L*	Island	5'UTR	4
cg06731192	0.34	-0.35	2E-03	0.0111	*HCG14*	S_Shore	TSS1500	6

cg07103819	-0.11	0.12	1E-02	0.0359	*DGAT1*	Island	1stExon	8
cg07410872	0.45	-0.48	2E-04	0.0030	*HAND2*	Island	TSS200	4
cg07483064	-0.13	0.13	2E-02	0.0383	*ENO1*	Island	1stExon	1
cg07588308	-0.12	0.16	2E-02	0.0456	*ZNF720*	N_Shore	5'UTR	16
cg07781003	-0.74	0.93	2E-02	0.0474	*LUC7L3*	Island	TSS200	17
cg07794500	-0.17	0.18	1E-02	0.0342	*LOC647121*	Island	Body	1
cg07862535	-0.43	0.48	1E-02	0.0342	*LUC7L2*	N_Shore	TSS1500	7
cg07938869	-0.40	0.43	2E-04	0.0030	*ZNF581*	Island	TSS1500	19
cg09484638	-0.15	0.13	3E-02	0.0478	*DNASE2*	Island	TSS200	19
cg09646206	-0.12	0.13	2E-02	0.0470	*SNX5*	Island	TSS1500	20
cg09767346	0.44	-0.46	1E-03	0.0064	*GORAB*		1stExon	1
cg09830308	0.47	-0.47	5E-05	0.0014	*MLKL*	Island	5'UTR	16
cg10124287	-0.09	0.10	5E-03	0.0174	*PPM1H*	Island	Body	12
cg10272675	-0.14	0.16	2E-03	0.0111	*MFGE8*	Island	TSS200	15
cg10495392	0.43	-0.39	2E-02	0.0474	*NSUN4*	Island	1stExon	1
cg10706910	-0.06	0.06	2E-02	0.0462	*ZNF337*	Island	TSS200	20
cg1115460	-0.12	0.16	2E-02	0.0385	*Intergeneic*			
cg11159084	-0.33	0.38	2E-03	0.0105	*HEATR1*	Island	TSS200	1
cg11190854	-0.25	0.29	2E-02	0.0456	*SLC29A1*			6
cg11345323	-0.11	0.16	2E-03	0.0111	*PRKCZ*	Island	TSS200	1
cg11655691	-0.17	0.16	2E-02	0.0383	*CBARA1*	Island	1stExon	10
cg11844198	0.26	-0.24	4E-03	0.0168	*KIAA0922*	Island	TSS200	4
cg12142354	-0.17	0.19	1E-02	0.0359	*CMKLR1*		TSS200	12
cg12714538	-0.40	0.67	1E-05	0.0004	*PSMB4*	Island	TSS1500	1
cg13063405	-0.22	0.27	7E-04	0.0052	*EPHB3*	Island	TSS1500	3
cg13090731	-0.07	0.10	2E-02	0.0373	*TXNL1*	Island	TSS200	18
cg13118906	-0.08	0.21	6E-05	0.0014	*CYB561*	Island	TSS1500	17
cg13311096	-0.08	0.14	1E-04	0.0026	*C8orf84*	Island	TSS200	8
cg13913917	0.23	-0.27	1E-06	0.0001	*ATP11B*	Island	5'UTR	3

cg14132628	0.36	-0.36	1E-02	0.0284	*MED20*	Island	TSS200	6
cg14196208	-0.13	0.23	9E-04	0.0060	*NEK6*	N_Shore	TSS200	9
cg14311471	-0.16	0.24	2E-03	0.0111	*NPR3*	Island	TSS1500	5
cg14632002	-0.09	0.12	9E-03	0.0271	*STOM*	Island	Body	9
cg14985583	0.87	-0.82	5E-03	0.0185	*PCOTH*	Island	5'UTR	13
cg15862215	-0.10	0.09	2E-02	0.0474	*OTX1*	Island	TSS1500	2
cg16489582	0.76	-0.68	3E-03	0.0135	*XPO6*	Island	TSS200	16
cg16926844	-0.53	0.71	4E-04	0.0037	*CHEK2*	Island	TSS200	22
cg17027046	-0.56	0.56	1E-02	0.0339	*ITPA*	Island	TSS200	20
cg17470637	-0.11	0.10	2E-02	0.0456	*MARCH2*	Island	TSS200	19
cg17572791	0.38	-0.36	6E-05	0.0014	*HAX1*	Island	5'UTR	1
cg18233595	-0.11	0.19	2E-04	0.0030	*PRRC1*	Island	5'UTR	5
cg18590590	0.18	-0.16	5E-03	0.0188	*LRRC42*	Island	TSS1500	1
cg18593717	-0.09	0.07	1E-02	0.0359	*HDGF*	Island	TSS200	1
cg19078236	0.71	-0.70	8E-03	0.0255	*AIP*	N_Shore	TSS200	11
cg20000099	-0.12	0.18	8E-04	0.0056	*CEBPG*	Island	5'UTR	19
cg20004424	-0.20	0.24	2E-04	0.0030	*TBL2*	S_Shore	TSS1500	7
cg20896113	-0.13	0.22	5E-03	0.0174	*RFX4*		Body	12
cg20953075	0.25	-0.25	2E-04	0.0029	*CEBPZ*	Island	TSS200	2
cg21278285	0.32	-0.34	1E-03	0.0075	*ZNF416*	Island	1stExon	19
cg21478222	-0.18	0.29	2E-02	0.0456	*ELK4*	S_Shore	1stExon	1
cg22153463	-0.37	0.36	7E-03	0.0235	*MCOLN2*	Island	TSS200	1
cg22463035	0.36	-0.37	9E-03	0.0271	*RIMBP2*	Island	3'UTR	12
cg22626041	-0.11	0.20	4E-03	0.0171	*KIAA0040*	Island	1stExon	1
cg22658244	-0.20	0.24	2E-02	0.0456	*ZNF551*	N_Shore	TSS1500	19
cg22922289	0.34	-0.31	6E-03	0.0216	*ZNF134*	Island	TSS1500	19
cg22944932	-0.09	0.08	3E-02	0.0478	*GOLGA5*	Island	TSS1500	14
cg23292453	-0.11	0.10	1E-02	0.0284	*ITGA3*	Island	5'UTR	17
cg23301140	-0.10	0.13	8E-04	0.0056	*CTDP1*	Island	5'UTR	18

cg23564746	-0.10	0.08	2E-02	0.0383	*CRLS1*	Island	TSS200	20
cg23831542	-0.09	0.11	5E-04	0.0045	*TMEM11*	Island	Body	17
cg23892580	-0.14	0.14	9E-03	0.0284	*SMARCA4*	Island	5'UTR	19
cg24167975	-0.08	0.12	2E-02	0.0393	*DHX37*	Island	TSS200	12
cg24173551	-0.35	0.38	2E-02	0.0385	*SETD8*	Island	TSS200	12
cg24252723	-1.04	0.96	3E-03	0.0114	*CNNM2*	Island	1stExon	10
cg25156443	-0.44	0.51	3E-04	0.0037	*SFRP5*	Island	TSS200	10
cg25189247	0.85	-0.83	2E-03	0.0111	*ITGAE*		Body	17
cg25497529	-0.08	0.09	1E-02	0.0335	*COMP*	Island	Body	19
cg25518386	-0.21	0.17	2E-02	0.0474	*RAB3A*	S_Shore	TSS1500	19
cg25622628	0.22	-0.21	2E-02	0.0456	*C19orf24*	Island	1stExon	19
cg26196912	-0.22	0.33	3E-03	0.0114	*C8orf38*	Island	TSS200	8
cg26290114	0.51	-0.52	8E-04	0.0056	*WDFY2*	S_Shore	Body	13
cg26365885	0.40	-0.38	5E-06	0.0003	*CCDC46*	TSS1500	Island	17
cg26744078	0.28	-0.27	2E-03	0.0105	*ZNF805*	Island	1stExon	19
cg27116888	-0.13	0.17	8E-03	0.0254	*SALL3*		Body	18
cg27341045	0.25	-0.25	1E-03	0.0062	*PPCDC*	Island	5'UTR	15

CpG sites	Gene	ALSPAC Main Estimates (7-17 years)	ALSPAC Interaction Estimates	ALSPAC estimates (17-22 years)	ALSPAC P value
cg00149397	*TPST2*	0.01	0.31	0.31	0.093
cg00405843	*SMO*	-0.25	0.13	-0.12	0.676
cg00444282	*RTN3*	-0.02	0.00	-0.02	0.979
cg00705668	*MRPS12*	-0.04	-0.09	-0.14	0.707
cg02225897	*RTDR1*	-0.01	-0.16	-0.17	0.142

cg02362385	*LPAR2*	-0.04	0.44	0.40	0.147
cg02467794	*AKAP1*	0.03	-0.37	-0.33	0.026
cg02516257	*GMCL1*	-0.08	0.39	0.31	0.116
cg02619805	*SAFB2*	-0.09	0.16	0.07	0.601
cg03223733	*ZNF211*	-0.01	-0.18	-0.19	0.307
cg03606222	*NAPA*	-0.07	0.61	0.54	0.072
cg03719634	*TMEM45A*	-0.09	-0.16	-0.25	0.343
cg04784251	*BCAS3*	-0.01	-0.08	-0.09	0.476
cg04789385	*ZFP1*	-0.09	0.24	0.15	0.407
cg04802657	*CCDC101*	-0.03	-0.03	-0.05	0.934
cg05245655	*SIX5*	-0.29	0.12	-0.16	0.665
cg05444312	*HIST1H2BM*	0.03	0.05	0.07	0.552
cg06045799	*COMMD8*	-0.05	0.23	0.18	0.392
cg06060137	*DACH1*	0.00	0.02	0.02	0.893
cg06100790	*SH2B1*	0.06	-0.10	-0.04	0.646
cg06364593	*ATP5B*	0.10	-0.02	0.09	0.888
cg06654302	*DDX60L*	-0.15	0.31	0.17	0.151
cg06731192	*HCG14*	-0.02	-0.06	-0.08	0.719
cg07103819	*DGAT1*	-0.12	0.11	-0.01	0.693
cg07410872	*HAND2*	-0.01	0.29	0.28	0.220
cg07483064	*ENO1*	-0.12	-0.22	-0.35	0.335
cg07588308	*ZNF720*	-0.04	0.22	0.19	0.408
cg07781003	*LUC7L3*	0.01	-0.13	-0.13	0.447
cg07794500	*LOC647121*	0.07	-0.21	-0.14	0.337
cg07862535	*LUC7L2*	0.01	-0.29	-0.28	0.103
cg07938869	*ZNF581*	-0.23	0.23	0.00	0.377
cg09484638	*DNASE2*	-0.11	0.17	0.06	0.598
cg09646206	*SNX5*	-0.05	0.09	0.04	0.773
cg09767346	*GORAB*	0.01	-0.03	-0.02	0.885

cg09830308	*MLKL*	-0.07	0.05	-0.02	0.853
cg10124287	*PPM1H*	-0.01	-0.07	-0.08	0.833
cg10272675	*MFGE8*	-0.03	-0.02	-0.05	0.875
cg10495392	*NSUN4*	-0.02	0.21	0.19	0.099
cg10706910	*ZNF337*	-0.06	0.11	0.05	0.601
cg1115460	*Intergeneic*	0.02	-0.04	-0.02	0.780
cg11159084	*HEATR1*	0.06	-0.18	-0.12	0.548
cg11190854	*SLC29A1*	-0.16	0.28	0.12	0.184
cg11345323	*PRKCZ*	-0.06	0.11	0.06	0.623
cg11655691	*CBARA1*	0.08	-0.21	-0.14	0.303
cg11844198	*KIAA0922*	-0.01	-0.38	-0.40	0.174
cg12142354	*CMKLR1*	0.03	0.00	0.03	0.999
cg12714538	*PSMB4*	0.03	-0.09	-0.06	0.634
cg13063405	*EPHB3*	-0.08	0.24	0.16	0.419
cg13090731	*TXNL1*	-0.13	0.29	0.16	0.228
cg13118906	*CYB561*	0.02	0.25	0.27	0.238
cg13311096	*C8orf84*	-0.03	-0.09	-0.12	0.723
cg13913917	*ATP11B*	-0.17	-0.02	-0.19	0.955
cg14132628	*MED20*	0.10	0.00	0.11	0.983
cg14196208	*NEK6*	-0.47	0.40	-0.07	0.092
cg14311471	*NPR3*	0.04	0.08	0.12	0.521
cg14632002	*STOM*	-0.06	0.27	0.21	0.303
cg14985583	*PCOTH*	-0.09	0.07	-0.02	0.731
cg15862215	*OTX1*	-0.02	0.02	0.00	0.817
cg16489582	*XPO6*	0.01	0.11	0.12	0.319
cg16926844	*CHEK2*	-0.02	0.12	0.10	0.438
cg17027046	*ITPA*	-0.08	0.22	0.15	0.207
cg17470637	*MARCH2*	-0.20	0.40	0.20	0.019
cg17572791	*HAX1*	-0.04	-0.04	-0.08	0.595

cg18233595	*PRRC1*	-0.08	0.10	0.02	0.652
cg18590590	*LRRC42*	-0.07	0.16	0.09	0.285
cg18593717	*HDGF*	-0.10	0.05	-0.05	0.826
cg19078236	*AIP*	-0.04	-0.11	-0.14	0.510
cg20000099	*CEBPG*	-0.13	0.10	-0.03	0.741
cg20004424	*TBL2*	0.02	0.02	0.04	0.850
cg20896113	*RFX4*	0.08	-0.13	-0.06	0.044
cg20953075	*CEBPZ*	-0.11	0.40	0.29	0.091
cg21278285	*ZNF416*	-0.03	-0.22	-0.25	0.387
cg21478222	*ELK4*	-0.06	-0.47	-0.53	0.060
cg22153463	*MCOLN2*	0.00	0.16	0.16	0.034
cg22463035	*RIMBP2*	0.03	0.24	0.27	0.190
cg22626041	*KIAA0040*	-0.09	0.20	0.11	0.537
cg22658244	*ZNF551*	0.06	-0.06	0.00	0.766
cg22922289	*ZNF134*	-0.21	0.50	0.29	0.136
cg22944932	*GOLGA5*	-0.20	0.05	-0.15	0.855
cg23292453	*ITGA3*	-0.05	0.26	0.21	0.239
cg23301140	*CTDP1*	-0.09	0.15	0.06	0.616
cg23564746	*CRLS1*	-0.02	-0.09	-0.11	0.733
cg23831542	*TMEM11*	-0.02	-0.12	-0.15	0.656
cg23892580	*SMARCA4*	-0.15	0.32	0.17	0.238
cg24167975	*DHX37*	0.05	0.12	0.17	0.670
cg24173551	*SETD8*	-0.07	0.27	0.19	0.394
cg24252723	*CNNM2*	-0.02	-0.18	-0.20	0.309
cg25156443	*SFRP5*	-0.17	0.26	0.09	0.072
cg25189247	*ITGAE*	-0.05	0.10	0.06	0.404
cg25497529	*COMP*	-0.07	-0.15	-0.22	0.398
cg25518386	*RAB3A*	0.00	0.24	0.24	0.124
cg25622628	*C19orf24*	-0.13	0.24	0.11	0.450

cg26196912	*C8orf38*	-0.05	-0.32	-0.37	0.349
cg26290114	*WDFY2*	0.04	0.00	0.04	0.992
cg26365885	*CCDC46*	-0.03	0.00	-0.03	0.995
cg26744078	*ZNF805*	-0.23	0.33	0.11	0.166
cg27116888	*SALL3*	0.03	0.01	0.04	0.956
cg27341045	*PPCDC*	-0.22	0.37	0.15	0.195

Note: (a) For the analysis in IoW, logistic regression with repeated measurements were adjusted for atopic status at ages 10 and 18 years, active smoking, and secondhand smoke exposure at age 18 and 26 years, transition period 10-18 and 18-26 years.
(b) Analysis of ALSPAC used similar available covariates: atopic status at age 7 years, secondhand smoke exposure at age 17 and 24 years.
Interaction effects consistent between the two cohorts are with bold fonts of CpG.

Supplement Table S2 (A): Association of DNAm with asthma acquisition from pre- to post-adolescence, and post-adolescence to young adulthood at 38 CpGs in males that are transition period non-specific. Significant effects of DNAm on asthma acquisition identified in the IoW(a) cohort were further tested in the ALSPAC(b) cohort.

CpG sites	IoW Estimates	Raw p value Int	FDR p value Int	Gene	CpG islands	Gene location	Chr.	ALSPAC Estimates	ALSPAC P value
cg01078627	-0.07	2E-06	3E-05	*ERCC1*	Island	Body	19	0.07	0.52
cg01704999	0.34	1E-02	1E-02	*SLC24A1*			15	-0.03	0.54
cg02309752	-0.67	5E-04	1E-03	*DEFB136*		Body	8	0.03	0.59
cg03001647	-0.03	5E-03	7E-03	*MPZL1*	S_Shore	TSS200	1	0.00	0.98
cg03841312	-0.59	6E-06	5E-05	*MIRLET7A3*		3'UTR	22	0.02	0.62
cg04673465	0.54	1E-03	2E-03	*CDS1*		1stExon	4	-0.03	0.60
cg05341115	0.22	1E-03	2E-03	*HYAL4*		5'UTR	7	0.06	0.28
cg05783329	-0.24	1E-03	2E-03	*NUDT3*	Island		6	0.03	0.42
cg06186394	-0.18	7E-03	8E-03	*BARX2*	S_Shore	Body	11	-0.04	0.22
cg06683328	-0.29	1E-03	2E-03	*TBC1D22A*	S_Shelf	TSS1500	22	-0.06	0.27
cg06684259	0.78	3E-07	1E-05	*HAS3*	N_Shore	TSS200	16	0.01	0.90
cg07500501	-0.04	5E-04	1E-03	*SKIV2L2*	Island		5	0.02	0.89
cg08354614	0.65	2E-05	1E-04	*ZMIZ1*		5'UTR	10	0.00	0.95

cg08757348	0.47	6E-05	2E-04	*ZNF214*	Island	TSS200	11	-0.03	0.38
cg09852187	-0.51	2E-05	1E-04	*MIR7-2*		Body;	15	-0.01	0.77
cg10919222	-0.06	8E-04	2E-03	*TMEM194A*	Island	TSS200	12	0.03	0.70
cg10996201	-0.06	1E-03	2E-03	*RGL2*	Island	TSS200	6	-0.06	0.61
cg14056357	-0.06	4E-06	5E-05	*ZNF229*	Island		19	-0.01	0.62
cg14893576	0.37	3E-04	8E-04	*KLHL29*	N_Shelf	5'UTR	2	0.03	0.26
cg15773726	-0.06	2E-03	2E-03	*SOCS2*	Island	Body	12	0.02	0.85
cg15778400	0.44	3E-04	8E-04	*SRGAP3*		1stExon	3	0.01	0.88
cg17261830	-0.07	2E-03	2E-03	*NEK9*	Island	5'UTR	14	0.03	0.50
cg18262260	-0.05	2E-05	9E-05	*ZC3H14*	Island	TSS200	14	0.04	0.37
cg18369866	0.45	1E-03	2E-03	*POU4F3*	Island	Body	5	-0.02	0.71
cg18418538	-0.05	9E-06	5E-05	*LMTK3*	Island	TSS200	19	0.07	0.08
cg19119818	-0.02	9E-03	9E-03	*AP2M1*	Island	Body	3	0.01	0.91
cg20951825	0.23	7E-03	8E-03	*PRDM6*		TSS200	5	-0.02	0.75
cg21543536	-0.11	8E-03	9E-03	*TSPYL1*	S_Shore		6	0.00	0.92
cg22188703	-0.33	9E-05	3E-04	*BOD1*	S_Shelf	TSS200	5	0.02	0.69
cg22268256	-0.06	2E-04	5E-04	*BAT5*	Island	TSS1500	6	0.01	0.86
cg23855392	0.17	3E-03	5E-03	*MTHFS*	S_Shore	3'UTR	15	-0.02	0.62
cg23930856	-0.05	8E-06	5E-05	*TFAP2B*	N_Shore		6	0.09	0.23
cg25400182	0.29	2E-02	2E-02	*CLLU1-AS1*		TSS200	12	-0.04	0.35
cg25613170	-0.04	2E-03	2E-03	*TBKBP1*	Island	TSS200	17	0.05	0.20
cg26411687	-0.03	3E-02	3E-02	*OS9*	Island	1stExon	12	-0.06	0.08
cg27230711	-0.05	4E-03	5E-03	*PPRC1*	Island	3'UTR	10	-0.02	0.82
cg27238852	0.21	1E-03	2E-03	*CSNK2A2*		Body	16	-0.04	0.22
cg27593384	-0.05	3E-05	1E-04	*CDH2*	Island		18	-0.01	0.82

Note: (a) For the analysis in IoW, logistic regression with repeated measurements were adjusted for atopic status at ages 10 and 18 years, active smoking and second-hand smoke exposure at age 18 and 26 years, transition period 10-18 and 18-26 years.
(b) Analysis of ALSPAC used similar available covariates: atopic status at age 7 years, second-hand smoke exposure at age 17 and 24 years.
Interaction effects consistent between the two cohorts are with bold fonts of CpG.

Supplement Table S2 (B): Association of DNAm with asthma acquisition from pre- to post-adolescence, and post-adolescence to young adulthood at 53 CpGs in females that are transition period non-specific. Significant effects of DNAm on asthma acquisition identified in the IoW(a) cohort were further tested in the ALSPAC(b) cohort.

CpG sites	IoW Estimates	Raw p value Int	FDR p value Int	Gene	CpG islands	Gene location	Chr.	ALSPAC Estimates	ALSPAC P value
cg00615892	-0.05	0.0030	0.0126	*CHTF8*	Island	TSS200	16	0.01	0.90
cg00907843	-0.03	0.0163	0.0342	*MLXIPL*	Island	TSS200	7	0.00	0.97
cg01364172	-0.43	0.0110	0.0274	*DENND4C*	N_Shore		9	-0.02	0.68
cg01529207	-0.09	0.0225	0.0407	*NDUFA6*	N_Shore	Body	22	0.04	0.14
cg01943657	-0.08	0.0001	0.0020	*PPP3CA*	Island	TSS200	4	-0.08	0.33
cg02067639	-0.05	0.0131	0.0293	*MED6*		TSS200	14	-0.14	0.07
cg03237356	-0.05	0.0054	0.0165	*NEIL3*	Island	TSS200	4	0.03	0.68
cg03655771	-0.10	0.0122	0.0289	*B4GALT5*	Island	Body	20	-0.03	0.38
cg04211198	-0.31	0.0001	0.0019	*NAB1*	Island	TSS1500	2	-0.15	0.04
cg04535371	-0.04	0.0052	0.0162	*IMPDH2*	Island	5'UTR	3	-0.10	0.32
cg05898113	-0.04	0.0175	0.0346	*WASH3P*	Island	Body	15	-0.01	0.90
cg06075477	-0.06	0.0001	0.0019	*KRIT1*	Island	5'UTR	7	-0.06	0.59
cg06226335	-0.03	0.0264	0.0449	*BET1L*	Island	TSS1500	11	-0.06	0.14
cg06302857	-0.06	0.0011	0.0079	*TOM1*	Island	TSS200	22	-0.18	0.09
cg07294234	-0.04	0.0169	0.0342	*FNTA*	Island	TSS200	8	0.06	0.49
cg07676167	-0.05	0.0014	0.0084	*C8orf76*	Island	Body	8	0.05	0.16
cg07951151	0.18	0.0289	0.0482	*GRHL1*			2	-0.04	0.27
cg08092965	-0.05	0.0001	0.0019	*ZNF23*	Island	1stExon	16	-0.06	0.50
cg08487579	-0.05	0.0007	0.0069	*PHC3*	Island	TSS200	3	-0.09	0.02
cg08614771	-0.04	0.0199	0.0376	*ARID1B*		Body	6	-0.04	0.39
cg09567485	0.38	0.0041	0.0150	*HSF4*	N_Shore	3'UTR	16	-0.19	0.03
cg09822824	-0.05	0.0208	0.0385	*CKAP5*	Island	TSS200	11	-0.01	0.72
cg10729426	-0.06	0.0009	0.0074	*ZNF549*	Island	TSS200	19	0.00	0.99
cg10850197	-0.04	0.0155	0.0337	*ATG5*	Island	5'UTR	6	-0.01	0.78

cg10880755	-0.05	0.0029	0.0126	*MGC42105*	Island	TSS200	5	-0.09	0.27
cg11252776	-0.04	0.0166	0.0342	*CROT*	Island	5'UTR	7	-0.05	0.57
cg11439068	-0.07	0.0002	0.0021	*PAK4*	Island	TSS200	19	-0.11	0.20
cg12210286	-0.07	0.0010	0.0074	*CNTD2*	Island	1stExon	19	-0.18	0.02
cg13337238	0.11	0.0033	0.0128	*HIST1H4A*	Island	TSS1500	6	0.04	0.19
cg13688524	-0.04	0.0072	0.0211	*BOD1*	Island	TSS200	5	0.02	0.80
cg14445451	-0.07	0.0000	0.0019	*ICT1*	Island	TSS200	17	-0.14	0.11
cg15278646	-0.05	0.0076	0.0211	*OCA2*	Island	5'UTR	15	-0.04	0.58
cg15353444	-0.04	0.0091	0.0241	*SERPINE2*	Island	5'UTR	2	0.01	0.89
cg16511870	0.24	0.0016	0.0091	*USP42*	Island	5'UTR	7	-0.02	0.79
cg16570995	-0.06	0.0002	0.0020	*PIM1*	Island	5'UTR	6	-0.04	0.56
cg16878007	-0.07	0.0033	0.0128	*TTPAL*	Island	5'UTR	20	-0.06	0.45
cg17015511	-0.04	0.0261	0.0449	*RDX*	Island	TSS200	11	-0.11	0.19
cg17226280	-0.05	0.0049	0.0161	*MRC2*	Island	Body	17	-0.02	0.75
cg18716861	-0.23	0.0095	0.0244	*PABPC1L*	Island	5'UTR	20	-0.09	0.21
cg19445996	-0.05	0.0014	0.0084	*RAB37*	Island	TSS200	17	-0.12	0.22
cg19818298	-0.03	0.0077	0.0211	*CHD8*		TSS200	14	0.16	0.01
cg20361600	-0.07	0.0192	0.0371	*DLX2*	Island	TSS200	2	-0.10	0.29
cg20690303	-0.05	0.0305	0.0498	*QDPR*	Island	1stExon	4	-0.04	0.58
cg21146957	0.18	0.0026	0.0126	*PTPRQ*		Body	12	-0.02	0.43
cg21851386	-0.06	0.0128	0.0293	*SMAD2*	Island	TSS200	18	-0.11	0.25
cg22510032	-0.04	0.0234	0.0415	*LCORL*	S_Shore	TSS1500	4	0.02	0.44
cg23080241	-0.05	0.0023	0.0122	*TXNDC15*	Island	1stExon	5	-0.10	0.25
cg24483825	-0.04	0.0049	0.0161	*CASP9*	Island	TSS1500	1	-0.01	0.78
cg26682955	0.23	0.0115	0.0280	*ITPR3*	S_Shelf	Body	6	-0.05	0.33
cg26693529	-0.05	0.0000	0.0019	*TTC32*	Island	TSS200	2	-0.01	0.93
cg26791126	-0.04	0.0029	0.0126	*DNAJC8*	Island	1stExon	1	-0.01	0.76
cg27395440	0.28	0.0047	0.0161	*LOC728276*		Body	16	-0.04	0.32

Note: (a) For the analysis in IoW, logistic regression with repeated measurements were adjusted for atopic status at ages 10 and 18 years, active smoking and second hand smoke exposure at age 18 and 26 years, transition period 10-18 and 18-26 years.
(b) Analysis of ALSPAC used similar available covariates: atopic status at age 7 years, second hand smoke exposure at age 17 and 24 years.
Interaction effects consistent between the two cohorts are with bold fonts of CpG.

Supplement Table S3 (A): Top 10 most statistically significant GO terms and its biological processes from pathway enrichment analysis along with their genes names in each pathway for males, for the identified CpGs.

GO term	Biological processes	P-value	Genes
GO:0009056	catabolic process	0.003682	*AP2M1, CSNK1A1, CSNK2A2,* ***ENO1****,* ***IRS1****, MTHFS,* ***OS9,*** *NUDT3,* ***HYAL4****,* ***BANP****, ZC3H14, MIRLET7A3*
GO:0038111	interleukin-7-mediated signaling pathway	0.002124	***IRS1*** *SOCS2*
GO:0042219	cellular modified amino acid catabolic process	0.002071	*MTHFS*
GO:0042365	water-soluble vitamin catabolic process	0.003378	*MTHFS*
GO:0046657	folic acid catabolic process	0.001542	*MTHFS*
GO:0071544	diphosphoinositol polyphosphate catabolic process	0.002544	*NUDT3*
GO:0098760	response to interleukin-7	0.003907	***IRS1*** *SOCS2*
GO:0098761	cellular response to interleukin-7	0.003907	***IRS1*** *SOCS2*
GO:1901575	organic substance catabolic process	0.000585	*AP2M1, CSNK1A1, CSNK2A2,* ***ENO1****,* ***IRS1****, MTHFS,* ***OS9****, NUDT3,* ***HYAL4****,* ***BANP****, ZC3H14, MIRLET7A3*

Note: CpGs mapped to genes in bold font showed consistent associations (interaction or main effects) between two cohorts.

Supplement STable 3 (B): Top 10 most statistically significant GO terms and its biological processes from pathway enrichment analysis along with their genes names in each pathway for females, for the identified CpGs.

GO term	Biological processes	P-value	Genes
GO:0019438	aromatic compound biosynthetic process	0.00045	*ATP5F1B,* ***CEBPG****,* ***CMKLR1****,* ***DACH1****,* ***DLX2****, ELK4, ENO1,* ***HDGF****, HSF4,* ***IMPDH2****, ITPA,* ***SMAD2****,* ***NAB1****,* ***OCA2****,* ***OTX1****,* ***PIM1****,* ***PPP3CA****,* ***PRKCZ****, PSMB4,* ***QDPR****, TRIM27, RFX4,* ***SFRP5****,* ***SMARCA4****, SMO,* ***ZNF23****, ZNF41, ZNF134,* ***AIP****,* ***CTDP1****, HAND2, MED20,* ***SAFB2****,* ***MED6****, CEBPZ,* ***HAX1****,* ***ZNF211****,* ***CHEK2,*** *SH2B1,* ***ZNF337****,* ***SALL3****, GRHL1,* ***MLXIPL****,* ***ZNF581****,* ***BCAS3****, CHTF8, HEATR1,* ***ARID1B****, CHD8, PPCDC,* ***PABPC1L****, ZNF551,* ***ZNF720****, ZFP1, LCORL,* ***ZNF549****, ZNF805*
GO:0032774	RNA biosynthetic process	0.000704	***CEBPG****,* ***CMKLR1****,* ***DACH1****,* ***DLX2****, ELK4, ENO1,* ***HDGF****, HSF4,* ***SMAD2****,* ***NAB1****,* ***OTX1****,* ***PIM1****,* ***PPP3CA****,* ***PRKCZ****, PSMB4, TRIM27, RFX4,* ***SFRP5****,* ***SMARCA4****, SMO,* ***ZNF23****, ZNF41, ZNF134,* ***AIP****,* ***CTDP1,*** *HAND2, MED20,* ***SAFB2****,* ***MED6****, CEBPZ,* ***HAX1****,* ***ZNF211****,* ***CHEK2****,* ***ZNF337****,* ***SALL3****, GRHL1,* ***MLXIPL,*** ***ZNF581****,* ***BCAS3****, HEATR1,* ***ARID1B****, CHD8,* ***PABPC1L****, ZNF551,* ***ZNF720****, ZFP1, LCORL,* ***ZNF549****, ZNF805*
GO:0008589	regulation of smoothened signaling pathway	0.000747	*SERPINE, RFX4, SMO,* ***SALL3****,* ***GORAB***
GO:0018130	heterocycle biosynthetic process	0.000804	*ATP5F1B,* ***CEBPG****,* ***CMKLR1****,* ***DACH1****,* ***DLX2****, ELK4, ENO1,* ***HDGF****, HSF4,* ***IMPDH2****, ITPA,* ***SMAD2****,* ***NAB1****,* ***OCA2****,* ***OTX1****,* ***PIM1****,* ***PPP3CA****,* ***PRKCZ,*** *PSMB4,* ***QDPR****, TRIM27, RFX4,* ***SFRP5****,* ***SMARCA4****, SMO,* ***ZNF23****, ZNF41, ZNF134,* ***AIP****,* ***CTDP1****, HAND2, MED20,* ***SAFB2****,* ***MED6****, CEBPZ,* ***HAX1****,* ***ZNF211****,* ***CHEK2****, SH2B1,* ***ZNF337****,* ***SALL3****, GRHL1,* ***MLXIPL****,* ***ZNF581****,* ***BCAS3****, CHTF8, HEATR1,* ***ARID1B****, CHD8, PPCDC,* ***PABPC1L****, ZNF551,* ***ZNF720****, ZFP1, LCORL,* ***ZNF549****, ZNF805*

GO:1903506	regulation of nucleic acid-templated transcription	0.00087	***CEBPG***, ***CMKLR1***, ***DACH1***, ***DLX2***, *ELK4, ENO1,* ***HDGF***, *HSF4,* ***SMAD2***, ***NAB1***, ***OTX1***, ***PIM1***, ***PPP3CA***, ***PRKCZ***, *PSMB4, TRIM27, RFX4,* ***SFRP5***, ***SMARCA4***, *SMO,* ***ZNF23***, *ZNF41, ZNF134,* ***AIP***, ***CTDP1***, *HAND2, MED20,* ***SAFB2***, ***MED6***, *CEBPZ,* ***HAX1***, ***ZNF211***, ***CHEK2***, ***ZNF337***, ***SALL3***, *GRHL1,* ***MLXIPL***, ***ZNF581***, ***BCAS3***, *HEATR1,* ***ARID1B***, *CHD8,* ***PABPC1L***, *ZNF551,* ***ZNF720***, *ZFP1, LCORL,* ***ZNF549***, *ZNF805*
GO:2001141	regulation of RNA biosynthetic process	0.000893	***CEBPG***, ***CMKLR1***, ***DACH1***, ***DLX2***, *ELK4, ENO1,* ***HDGF***, *HSF4,* ***SMAD2***, ***NAB1***, ***OTX1***, ***PIM1***, ***PPP3CA***, ***PRKCZ***, *PSMB4,* ***QDPR***, *TRIM27, RFX4,* ***SFRP5***, ***SMARCA4***, *SMO,* ***ZNF23***, *ZNF41, ZNF134,* ***AIP***, ***CTDP1,*** *HAND2, MED20,* ***SAFB2***, ***MED6***, *CEBPZ,* ***HAX1***, ***ZNF211***, ***CHEK2***, *SH2B1,* ***ZNF337***, ***SALL3***, *GRHL1,* ***MLXIPL***, ***ZNF581***, ***BCAS3***, *CHTF8, HEATR1,* ***ARID1B***, *CHD8, PPCDC,* ***PABPC1L***, *ZNF551,* ***ZNF720***, *ZFP1, LCORL,* ***ZNF549***, *ZNF805*
GO:1901362	organic cyclic compound biosynthetic process	0.00101	*ATP5F1B,* ***CEBPG***, ***CMKLR1***, ***DACH1***, ***DLX2***, *ELK4, ENO1,* ***HDGF***, *HSF4,* ***IMPDH2***, *ITPA,* ***SMAD2***, ***NAB1***, ***OTX1***, ***PIM1***, ***PPP3CA***, ***PRKCZ***, *PSMB4, TRIM27, RFX4,* ***SFRP5, SMARCA4***, *SMO,* ***ZNF23***, *ZNF41, ZNF134,* ***AIP***, ***CTDP1***,
GO:0034654	nucleobase-containing compound biosynthetic process	0.001032	

			HAND2, MED20, ***SAFB2****,* ***MED6****, CEBPZ,* ***HAX1****,* ***ZNF211****,* ***CHEK2****, SH2B1,* ***ZNF337****,* ***SALL3****, GRHL1,* ***MLXIPL****,* ***ZNF581****,* ***BCAS3****, CHTF8, HEATR1,* ***ARID1B****, CHD8, PPCDC,* ***PABPC1L****, ZNF551,* ***ZNF720****, ZFP1, LCORL,* ***ZNF549****, ZNF805*
GO:0006355	regulation of transcription, DNA-templated	0.001117	***CEBPG****,* ***CMKLR1****,* ***DACH1****,* ***DLX2****, ELK4, ENO1,* ***HDGF****, HSF4,* ***SMAD2****,* ***NAB1****,* ***OTX1****,* ***PIM1****,* ***PPP3CA****,* ***PRKCZ,*** *PSMB4, TRIM27, RFX4,* ***SFRP5****,* ***SMARCA4****, SMO,* ***ZNF23****, ZNF41, ZNF134,* ***CTDP1****, HAND2, MED20,* ***SAFB2****,* ***MED6****,* ***CEBPZ****,* ***HAX1****,* ***ZNF211****,* ***CHEK2****,* ***ZNF337****,* ***SALL3****, GRHL1,* ***MLXIPL****,* ***ZNF581****,* ***BCAS3****, HEATR1,* ***ARID1B****, CHD8,* ***PABPC1L****, ZNF551,* ***ZNF720****, ZFP1, LCORL,* ***ZNF549****, ZNF805*
GO term	Biological processes	P-value	Genes
GO:0019438	aromatic compound biosynthetic process	0.001203	*ATP5F1B,* ***CEBPG****,* ***CMKLR1****,* ***DACH1****,* ***DLX2****, ELK4, ENO1****,* ***HDGF****, HSF4,* ***IMPDH2****, ITPA,* ***SMAD2****,* ***NAB1****,* ***OCA2****,* ***OTX1****,* ***PIM1****,* ***PPP3CA****,* ***PRKCZ****, PSMB4,* ***QDPR****, TRIM27, RFX4,* ***SFRP5****,* ***SMARCA4****, SMO,* ***ZNF23****, ZNF41, ZNF134,* ***AIP****,* ***CTDP1****, HAND2, MED20,* ***SAFB2****,* ***MED6****, CEBPZ,* ***HAX1****,* ***ZNF211****,* ***CHEK2,*** *SH2B1,* ***ZNF337****,* ***SALL3****, GRHL1,* ***MLXIPL****,* ***ZNF581****,* ***BCAS3****, CHTF8, HEATR1,* ***ARID1B****, CHD8, PPCDC,* ***PABPC1L****, ZNF551,* ***ZNF720****, ZFP1, LCORL,* ***ZNF549****, ZNF806*
GO:0032774	RNA biosynthetic process	0.001274	***CEBPG****,* ***CMKLR1****,* ***DACH1****,* ***DLX2****, ELK4, ENO1,* ***HDGF****, HSF4,* ***SMAD2****,* ***NAB1****,* ***OTX1****,* ***PIM1****,* ***PPP3CA****,* ***PRKCZ****, PSMB4, TRIM27, RFX4,* ***SFRP5****,* ***SMARCA4****, SMO,* ***ZNF23****, ZNF41, ZNF134,* ***AIP****,* ***CTDP1,*** *HAND2, MED20,* ***SAFB2****,* ***MED6****, CEBPZ,* ***HAX1****,* ***ZNF211****,* ***CHEK2****,* ***ZNF337****,* ***SALL3****, GRHL1,* ***MLXIPL,*** ***ZNF581****,* ***BCAS3****, HEATR1,* ***ARID1B****, CHD8,* ***PABPC1L****,*

			ZNF551, ***ZNF720****, ZFP1, LCORL,* ***ZNF549****, ZNF806*
GO:0008589	regulation of smoothened signaling pathway	0.001345	*SERPINE, RFX4, SMO,* ***SALL3****,* ***GORAB*** *ATP5F1B,* ***CEBPG****,* ***CMKLR1****,* ***DACH1****,* ***DLX2****, ELK4, ENO1,* ***HDGF****, HSF4,* ***IMPDH2****, ITPA,* ***SMAD2****,* ***NAB1****,* ***OCA2****,* ***OTX1****,* ***PIM1****,* ***PPP3CA****,* ***PRKCZ,*** *PSMB4,* ***QDPR****, TRIM27, RFX4,* ***SFRP5****,* ***SMARCA4****, SMO,* ***ZNF23****, ZNF41, ZNF134,* ***AIP****,* ***CTDP1****, HAND2, MED20,* ***SAFB2****,* ***MED6****, CEBPZ,* ***HAX1****,* ***ZNF211****,* ***CHEK2****, SH2B1,* ***ZNF337****,* ***SALL3****, GRHL1,* ***MLXIPL****,* ***ZNF581****,* ***BCAS3****, CHTF8, HEATR1,* ***ARID1B****, CHD8, PPCDC,* ***PABPC1L****, ZNF551,* ***ZNF720****, ZFP1, LCORL,* ***ZNF549****, ZNF806*
GO:0018130	heterocycle biosynthetic process	0.001416	***CEBPG****,* ***CMKLR1****,* ***DACH1****,* ***DLX2****, ELK4, ENO1,* ***HDGF****, HSF4,* ***SMAD2****,* ***NAB1****,* ***OTX1****,* ***PIM1****,* ***PPP3CA****,* ***PRKCZ****, PSMB4, TRIM27, RFX4,* ***SFRP5****,* ***SMARCA4****, SMO,* ***ZNF23****, ZNF41, ZNF134,* ***AIP****,* ***CTDP1****, HAND2, MED20,* ***SAFB2****,* ***MED6****, CEBPZ,* ***HAX1****,* ***ZNF211****,* ***CHEK2****,* ***ZNF337****,* ***SALL3****, GRHL1,* ***MLXIPL****,* ***ZNF581****,* ***BCAS3****, HEATR1,* ***ARID1B****, CHD8,* ***PABPC1L****, ZNF551,* ***ZNF720****, ZFP1, LCORL,* ***ZNF549****, ZNF805*
GO:1903506	regulation of nucleic acid-templated transcription	0.001487	

GO:2001141	regulation of RNA biosynthetic process	0.001558	***CEBPG***, ***CMKLR1***, ***DACH1***, ***DLX2***, *ELK4, ENO1,* ***HDGF***, *HSF4,* ***SMAD2***, ***NAB1***, ***OTX1***, ***PIM1***, ***PPP3CA***, ***PRKCZ***, *PSMB4, TRIM27, RFX4,* ***SFRP5***, ***SMARCA4***, *SMO,* ***ZNF23***, *ZNF41, ZNF134,* ***AIP, CTDP1***, *HAND2, MED20,* ***SAFB2***, ***MED6***, *CEBPZ,* ***HAX1***, ***ZNF211***, ***CHEK2***, ***ZNF337***, ***SALL3***, *GRHL1,* ***MLXIPL***, ***ZNF581***, ***BCAS3***, *HEATR1,* ***ARID1B***, *CHD8,* ***PABPC1L***, *ZNF551,* ***ZNF720***, *ZFP1, LCORL,* ***ZNF549***, *ZNF805*
GO term	Biological processes	P-value	Genes
GO:0019438	aromatic compound biosynthetic process	0.001203	*ATP5F1B,* ***CEBPG***, ***CMKLR1***, ***DACH1***, ***DLX2***, *ELK4, ENO1,* ***HDGF***, *HSF4,* ***IMPDH2***, *ITPA,* ***SMAD2***, ***NAB1***, ***OCA2***, ***OTX1***, ***PIM1***, ***PPP3CA***, ***PRKCZ***, *PSMB4,* ***QDPR***, *TRIM27, RFX4,* ***SFRP5***, ***SMARCA4***, *SMO,* ***ZNF23***, *ZNF41, ZNF134,* ***AIP***, ***CTDP1***, *HAND2, MED20,* ***SAFB2***, ***MED6***, *CEBPZ,* ***HAX1***, ***ZNF211***, ***CHEK2,*** *SH2B1,* ***ZNF337***, ***SALL3***, *GRHL1,* ***MLXIPL***, ***ZNF581***, ***BCAS3***, *CHTF8, HEATR1,* ***ARID1B***, *CHD8, PPCDC,* ***PABPC1L***, *ZNF551,* ***ZNF720***, *ZFP1, LCORL,* ***ZNF549***, *ZNF806*
GO:0032774	RNA biosynthetic process	0.001274	***CEBPG***, ***CMKLR1***, ***DACH1***, ***DLX2***, *ELK4, ENO1,* ***HDGF***, *HSF4,* ***SMAD2***, ***NAB1***, ***OTX1***, ***PIM1***, ***PPP3CA***, ***PRKCZ***, *PSMB4, TRIM27, RFX4,* ***SFRP5***, ***SMARCA4***, *SMO,* ***ZNF23***, *ZNF41, ZNF134,* ***AIP***, ***CTDP1,*** *HAND2, MED20,* ***SAFB2***, ***MED6***, *CEBPZ,* ***HAX1***, ***ZNF211***, ***CHEK2***, ***ZNF337***, ***SALL3***, *GRHL1,* ***MLXIPL, ZNF581***, ***BCAS3***, *HEATR1,* ***ARID1B***, *CHD8,* ***PABPC1L***, *ZNF551,* ***ZNF720***, *ZFP1, LCORL,* ***ZNF549***, *ZNF806*
GO:0008589	regulation of smoothened signaling pathway	0.001345	*SERPINE, RFX4, SMO,* ***SALL3***, ***GORAB***

GO:0018130	heterocycle biosynthetic process	0.001416	*ATP5F1B*, ***CEBPG***, ***CMKLR1***, ***DACH1***, ***DLX2***, *ELK4, ENO1*, ***HDGF***, *HSF4*, ***IMPDH2***, *ITPA*, ***SMAD2***, ***NAB1***, ***OCA2***, ***OTX1***, ***PIM1***, ***PPP3CA***, ***PRKCZ,*** *PSMB4*, ***QDPR***, *TRIM27, RFX4*, ***SFRP5***, ***SMARCA4***, *SMO*, ***ZNF23***, *ZNF41, ZNF134*, ***AIP***, ***CTDP1***, *HAND2, MED20*, ***SAFB2***, ***MED6***, *CEBPZ*, ***HAX1***, ***ZNF211***, ***CHEK2***, *SH2B1*, ***ZNF337***, ***SALL3***, *GRHL1*, ***MLXIPL***, ***ZNF581***, ***BCAS3***, *CHTF8, HEATR1*, ***ARID1B***, *CHD8, PPCDC*, ***PABPC1L***, *ZNF551*, ***ZNF720***, *ZFP1, LCORL*, ***ZNF549***, *ZNF806*

Note: CpGs mapped to genes in bold font showed consistent associations (interaction or main effects) between two cohorts.

Supplement Table S4 (A): Association of DNAM at 10 years in males with neighboring gene expression at 26 years (n=55)

coefficient	Pvalue	CpGs	Genes
1	0	cg01884526	*A2M*
0.574357	0.000603	cg06684259	*ACAA2*
0.52864	0.000603	cg09852187	*ABCD3*
0.673389	0.001496	cg06684259	*ACP2*
0.417462	0.002771	cg08354614	*CPM*
0.266446	0.00353	cg12009697	*ABAT*
0.533883	0.00372	cg08056069	*ACOT8*
0.266522	0.0069	cg14056357	*ABCG2*
0.397577	0.007577	cg14056357	*ISG20*
-0.58998	0.012191	cg10996201	*ELOVL4*
0.248885	0.012797	cg14056357	*AEN*
0.697283	0.012797	cg14893576	*ACSS2*
0.117351	0.012923	cg21691089	*TRPS1*
-0.42789	0.01339	cg19707069	*VN1R1*
-0.7264	0.016615	cg19707069	*ZNF776*
-0.59436	0.018257	cg08354614	*CORO2B*
0.311837	0.020645	cg14056357	*ACSF3*
-0.43218	0.026245	cg19707069	*MMP15*

0.795243	0.027506	cg19707069	*ZNF552*
-0.63205	0.030349	cg06684259	*CDK16*
0.230713	0.030425	cg27230711	*RAMP3*
-0.60773	0.030815	cg06684259	*CELSR1*
-0.50637	0.032182	cg15778400	*IRS1*
0.203504	0.036249	cg19707069	*AGAP2*
0.450854	0.036863	cg10996201	*ANTXR2*
-0.41133	0.040424	cg27593384	*PPP1R3E*
0.404555	0.043048	cg06684259	*TTC7A*
-0.70604	0.044696	cg19707069	*ZNF550*
-0.55431	0.049689	cg06684259	*USP11*

Supplement Table S4 (B): Association of DNAM at 10 years in females with neighboring gene expression at 26 years (n=85)

coefficient	Pvalue	CpGs	Genes
1	0	cg18593717	*AGPAT3*
0.888376	1.24E-10	cg25518386	*AKAP10*
0.300261	5.14E-10	cg26791126	*AIM1*
0.751707	5.64E-10	cg24173551	*ALKBH5*
0.839157	1.31E-09	cg06060137	*ACE*
0.873602	2.27E-09	cg25156443	*ACVRL1*
1.13045	5.53E-09	cg06302857	*AGAP2*
2.361207	2.25E-08	cg23892580	*ABCC13*
0.413501	3.67E-08	cg12210286	*AHRR*
2.299555	4.43E-08	cg23892580	*AGMAT*
0.504819	1.78E-07	cg27116888	*ACER3*
0.241357	2.33E-07	cg07938869	*WBSCR27*
0.201176	4.79E-07	cg23292453	*AACS*
0.798827	8.28E-07	cg25156443	*ABHD14A*
0.471668	8.61E-07	cg06075477	*AARS*
0.54115	1.63E-06	cg08092965	*ACSF2*
-0.46654	1.81E-06	cg04535371	*AKR7A2*

-0.72349	2.23E-06	cg14632002	*ABCA9*
0.82532	7.86E-06	cg21278285	*AIF1L*
1.415142	8.13E-06	cg21278285	*AKR1B1*
0.236382	8.69E-06	cg06060137	*AHSA2*
1.294485	1.15E-05	cg01943657	*ABHD3*
0.609914	1.23E-05	cg11190854	*ADA*
0.520721	2.69E-05	cg10850197	*ADA*
0.906162	2.99E-05	cg07862535	*AHCY*
0.859667	3.07E-05	cg20690303	*ALKBH5*
0.492038	3.64E-05	cg11190854	*ACKR2*
0.340205	5.01E-05	cg10706910	*ACTR5*
0.088196	7.88E-05	cg11252776	*GPRC5C*
0.25099	8.53E-05	cg27116888	*WDR41*
-0.31279	9.27E-05	cg24167975	*AAED1*
0.370447	0.000116	cg10850197	*AMBRA1*
0.703841	0.00013	cg14311471	*ADAL*
0.376625	0.000162	cg22153463	*MSH6*
1.160843	0.000184	cg19445996	*ADAM19*
2.072194	0.000218	cg02619805	*ADAR*
0.341148	0.000294	cg11190854	*ADAM11*
0.884396	0.000328	cg06226335	*ACTB*
0.308443	0.000509	cg07862535	*HDAC1*
1.303444	0.000687	cg14632002	*ABCA10*
0.211341	0.000712	cg11252776	*NAP1L2*
0.693113	0.000804	cg18233595	*ABHD6*
0.047971	0.000943	cg07938869	*SFXN5*
0.648877	0.000953	cg16570995	*AIF1*
0.252745	0.001	cg02516257	*RINL*
0.208035	0.001025	cg11345323	*DUSP4*
0.286072	0.001072	cg14311471	*SLC2A1*
0.90579	0.001279	cg06302857	*ABHD6*

0.198105	0.001319	cg22153463	*TEC*
0.119485	0.001438	cg11345323	*GOLGA8M*
0.108483	0.00155	cg07862535	*FRY*
0.181572	0.001705	cg11345323	*SNX29P2*
0.148416	0.001761	cg23292453	*CPXM2*
0.106252	0.001798	cg02516257	*IDO2*
0.157721	0.001809	cg11252776	*POM121*
0.335936	0.001906	cg23892580	*HACL1*
0.608771	0.001994	cg14445451	*NPIPB8*
0.301212	0.002129	cg22153463	*TXK*
0.185306	0.002142	cg02516257	*SYNGR1*
0.464686	0.002169	cg09822824	*ADCY6*
0.28933	0.002182	cg14445451	*GOLGA8M*
0.217725	0.00232	cg17015511	*UBE2S*
1.113797	0.002549	cg23892580	*ADORA2B*
1.009593	0.002617	cg14632002	*AAGAB*
-0.304	0.002695	cg23080241	*MYLK3*
0.21046	0.003009	cg22153463	*FOXD2*
0.093079	0.00308	cg11345323	*FLT1*
0.097257	0.003171	cg11190854	*NIM1K*
-0.461	0.003209	cg04535371	*AKR7A3*
0.982721	0.003293	cg14632002	*ADHFE1*
0.09392	0.003303	cg18233595	*CDK4*
0.118872	0.003399	cg11345323	*RABEP2*
0.511332	0.003584	cg20000099	*MRPS14*
0.491325	0.003712	cg14632002	*ABCA5*
0.186914	0.003803	cg07588308	*ARF5*
0.117059	0.003885	cg24483825	*KSR1*
-1.03374	0.003967	cg04535371	*AKAP10*
0.555959	0.003986	cg09646206	*ADAMTS1*
0.139283	0.004017	cg10850197	*SIX5*

0.406413	0.004197	cg14445451	*FOSL2*
1.38477	0.004331	cg14632002	*ALDH3B2*
0.445959	0.004403	cg14445451	*CCDC91*
0.345893	0.004436	cg14445451	*TBC1D29*
0.201845	0.004626	cg07862535	*TMEM39B*
0.383383	0.004954	cg23892580	*CA5BP1*
0.254905	0.004969	cg08487579	*MEPCE*
0.157746	0.005062	cg07588308	*FSCN3*
0.204396	0.005281	cg10729426	*PDE4D*
0.101371	0.005432	cg11844198	*TMEM232*
0.359739	0.00562	cg02516257	*MGAT3*
0.144734	0.005636	cg06226335	*CD274*
0.064974	0.005768	cg09822824	*GRWD1*
0.174955	0.005776	cg07862535	*TOPORS*
0.309503	0.005987	cg10729426	*DACT1*
0.232715	0.006084	cg11252776	*ATG16L2*
1.337492	0.006164	cg23080241	*ALS2CL*
0.275666	0.006423	cg11345323	*ADAP2*
0.65345	0.006622	cg08487579	*AGFG2*
0.211885	0.006667	cg22944932	*PDIA6*
0.16493	0.00701	cg06060137	*FADS1*
0.179453	0.007129	cg11252776	*FZD9*
0.153677	0.007242	cg08092965	*PTPRJ*
0.219345	0.007584	cg07862535	*PRRG4*
0.095669	0.007783	cg11190854	*DCAKD*
0.214516	0.007824	cg22944932	*TMED1*
0.488059	0.007986	cg14445451	*CREB5*
-0.33983	0.007992	cg25518386	*ZNF486*
0.075498	0.008149	cg24483825	*NINL*
-0.11709	0.008162	cg02467794	*NPW*
0.1244	0.008215	cg06060137	*DIDO1*

0.134268	0.008446	cg07588308	*NR5A1*
0.064015	0.008466	cg26693529	*CDK4*
0.200741	0.009018	cg27116888	*USP36*
0.17143	0.009109	cg22153463	*NFXL1*
0.120691	0.009175	cg17226280	*TSPAN15*
0.138499	0.009215	cg24483825	*STXBP6*
0.19066	0.00943	cg20361600	*CAMK1D*
0.118233	0.009512	cg24483825	*UBE3A*
0.127302	0.009838	cg11252776	*FCHSD2*
0.35321	0.009941	cg22153463	*ZNF589*
0.261091	0.010027	cg23892580	*CD38*
0.165408	0.010228	cg09484638	*C8orf76*
0.432855	0.010269	cg18233595	*AGAP2*
0.562242	0.010276	cg14445451	*YTHDF2*
0.068661	0.010437	cg06075477	*MXD1*
0.348048	0.010508	cg14445451	*DSG2*
-0.2666	0.010599	cg14445451	*CPD*
0.132616	0.010677	cg13118906	*UBAP2L*
0.261382	0.011236	cg14445451	*RABEP2*
0.081197	0.011259	cg06060137	*CHD7*
0.771824	0.011868	cg01943657	*ACER2*
0.167747	0.012137	cg02516257	*DAAM2*
0.172042	0.012161	cg22153463	*SAMD14*
0.230787	0.012285	cg13063405	*RORA*
0.255171	0.012446	cg14311471	*PSTPIP2*
0.105338	0.012743	cg24483825	*SMIM20*
0.414708	0.012748	cg08487579	*ADH5*
0.108698	0.012813	cg15278646	*DGAT1*
0.146354	0.012913	cg11844198	*SYPL2*
0.201808	0.012988	cg11345323	*CD19*
1.415696	0.013211	cg19078236	*ALPK3*

0.308108	0.013217	cg10729426	*TRIM28*
0.477289	0.013491	cg16570995	*AHSP*
-0.07232	0.013606	cg26693529	*KATNB1*
0.306907	0.013813	cg06060137	*FADS2*
0.193982	0.013861	cg17027046	*UNC5B*
0.097766	0.013873	cg11190854	*PTCRA*
0.262559	0.013992	cg14445451	*SULT1A1*
0.120031	0.014409	cg20690303	*TBC1D5*
0.1334	0.014485	cg07588308	*PRRC1*
0.090816	0.014543	cg09484638	*ATAD2*
0.146585	0.014627	cg07862535	*SUB1*
0.091332	0.014653	cg11439068	*ANKIB1*
0.117631	0.014678	cg02516257	*SMIM14*
-0.30739	0.01486	cg23080241	*ARHGAP1*
0.425008	0.015032	cg14445451	*TUFM*
0.238878	0.015329	cg07862535	*C14orf1*
0.130402	0.016059	cg16878007	*CAMSAP1*
0.127401	0.016448	cg11345323	*TRIM27*
0.181908	0.016487	cg09484638	*KALRN*
0.261328	0.016539	cg18593717	*FAM118A*
-0.05506	0.016588	cg22944932	*TDH*
0.073876	0.01703	cg09822824	*KCND1*
0.055871	0.017189	cg09822824	*TFE3*
-0.0944	0.017231	cg03223733	*SART3*
0.124885	0.017491	cg09822824	*TMEM143*
0.405711	0.017501	cg14632002	*ABCA6*
0.10987	0.01779	cg22153463	*HUS1*
0.609012	0.017815	cg25156443	*ACY1*
0.315088	0.018045	cg14445451	*TRIM27*
0.166978	0.018069	cg08487579	*MOSPD3*
0.129654	0.019052	cg06060137	*DCAF7*

0.078161	0.019151	cg02516257	*SEC23A*
0.117782	0.019189	cg11345323	*CHN2*
0.128839	0.019413	cg11252776	*STARD10*
0.08526	0.019436	cg20361600	*IQSEC1*
0.193252	0.019447	cg22153463	*PDK2*
0.13776	0.019525	cg09484638	*PLEKHA1*
0.139026	0.019561	cg11190854	*AKAP11*
0.068892	0.019567	cg16878007	*MRPS22*
0.074482	0.019882	cg07938869	*FCHSD2*
0.07278	0.019962	cg24483825	*TOP2B*
0.148083	0.020036	cg13063405	*TAF4*
0.11141	0.020149	cg02516257	*LRFN1*
0.06483	0.020342	cg09822824	*PPP1R3F*
0.082667	0.020355	cg11252776	*MSC*
0.370583	0.020575	cg14445451	*PAN3*
0.114661	0.020627	cg02516257	*PROSER1*
0.162122	0.020746	cg11252776	*TRIM50*
0.164265	0.020758	cg09484638	*TMED2*
0.135721	0.021347	cg13063405	*PHLPP1*
0.332998	0.021397	cg14445451	*RRN3P2*
-0.10097	0.021702	cg17226280	*ENAM*
-0.08553	0.021756	cg26791126	*PRKAR2B*
0.18429	0.02189	cg11345323	*WAC*
-0.09223	0.021967	cg08487579	*TFR2*
0.12065	0.022173	cg20361600	*GPRC5D*
0.576207	0.022292	cg16570995	*H3F3C*
0.322268	0.022435	cg22626041	*PEAK1*
0.076311	0.022677	cg11252776	*RYBP*
0.127784	0.022684	cg20690303	*ARRDC2*
0.074269	0.022826	cg15278646	*CYHR1*
0.19467	0.023022	cg22153463	*PTPRJ*

0.07395	0.023044	cg11844198	*AMIGO1*
0.000606	0.023493	cg00705668	*KIF18B*
0.319929	0.023997	cg09646206	*ZKSCAN3*
0.099319	0.02406	cg17015511	*SHISA7*
-0.87798	0.024061	cg03655771	*ADAM20*
0.311103	0.024225	cg10729426	*PPM1D*
0.211358	0.024461	cg08092965	*ZNF589*
-0.17288	0.02471	cg05245655	*HOXC4*
0.165381	0.024764	cg22153463	*TMEM92*
0.080166	0.024854	cg10850197	*EML2*
0.082313	0.02508	cg09484638	*RAB14*
0.071777	0.025104	cg27116888	*SDAD1*
0.064434	0.025164	cg27116888	*CCDC146*
0.404341	0.025482	cg18593717	*NKPD1*
0.365921	0.025759	cg14445451	*EIF3C*
-0.06281	0.026099	cg17572791	*NUP153*
0.265815	0.026231	cg26290114	*ZKSCAN3*
0.377603	0.026967	cg14445451	*BAMBI*
0.250816	0.027274	cg22153463	*SLC48A1*
0.139707	0.027471	cg07862535	*AVL9*
0.075356	0.027557	cg06060137	*LIMD2*
0.264642	0.027658	cg19078236	*GSE1*
-0.1367	0.027772	cg13337238	*NFKBIA*
0.062848	0.027969	cg18233595	*CSNK2A2*
0.082893	0.02798	cg16878007	*QSOX2*
0.106878	0.02799	cg11252776	*TMEM104*
-0.17001	0.028384	cg03719634	*TNRC6B*
0.105043	0.028537	cg22153463	*PPP1R9B*
0.082317	0.028628	cg18233595	*DAB1*
0.154478	0.028823	cg08487579	*TSC22D4*
0.518484	0.029029	cg21278285	*FAM127C*

0.076066	0.029144	cg13063405	*METTL2A*
0.147189	0.02959	cg06060137	*USP34*
0.086846	0.029817	cg08092965	*GDF10*
0.057646	0.030046	cg06075477	*PPFIA1*
0.088114	0.030109	cg11439068	*CKS2*
0.446086	0.03022	cg18593717	*ICOSLG*
0.231993	0.030388	cg16570995	*ZBTB12*
0.231612	0.030407	cg20690303	*CECR1*
0.055203	0.030417	cg20361600	*HEBP1*
0.114795	0.030751	cg10850197	*COG3*
0.141882	0.030824	cg11844198	*GPR61*
0.060141	0.031011	cg09822824	*EMP3*
0.154599	0.031712	cg07862535	*EIF3I*
0.213865	0.032142	cg20690303	*SAAL1*
0.197654	0.032843	cg22153463	*PKD1L1*
0.276256	0.032889	cg20690303	*SERGEF*
0.078173	0.03292	cg08092965	*ELAC1*
0.286654	0.033156	cg22626041	*CLN5*
-0.31037	0.03362	cg23080241	*PNMAL2*
0.027641	0.033646	cg20361600	*GPR19*
0.132506	0.033789	cg10729426	*MYSM1*
0.160547	0.033862	cg22153463	*CAMP*
0.06543	0.03394	cg11190854	*STARD9*
0.355703	0.034437	cg10729426	*ZNF324B*
0.161221	0.034531	cg11252776	*NCF1B*
0.088712	0.034584	cg06060137	*FTH1*
0.278832	0.034593	cg20690303	*LLGL1*
0.053228	0.036078	cg11190854	*RRP7A*
0.067995	0.036689	cg21851386	*RPL22L1*
0.205205	0.036813	cg08487579	*CSTF2*
-0.05727	0.03702	cg06731192	*MTMR6*

0.115821	0.037107	cg26693529	*ZNF549*
0.174823	0.037446	cg08092965	*WAS*
0.127648	0.037691	cg09822824	*WFIKKN2*
0.153353	0.037816	cg20690303	*DRG2*
0.205641	0.03783	cg07862535	*GOLGA8O*
0.042465	0.038065	cg18716861	*SPC25*
0.094512	0.038495	cg11252776	*HEXA*
0.192174	0.039046	cg25518386	*TXNRD2*
0.057479	0.039057	cg09822824	*LMTK3*
0.100064	0.039366	cg20361600	*NFIX*
0.153814	0.039677	cg11252776	*ANKRA2*
0.082017	0.039879	cg18233595	*HEATR6*
0.186668	0.040281	cg26693529	*ZNF319*
0.118191	0.040788	cg13063405	*PPM1A*
0.509216	0.041199	cg26290114	*ADAMTS5*
0.554445	0.041302	cg07862535	*AKAP6*
0.128896	0.041398	cg20690303	*B3GNT3*
0.096139	0.041537	cg09646206	*APOBR*
0.066683	0.041944	cg24483825	*TMEM57*
-0.07588	0.042029	cg03223733	*FICD*
0.104908	0.042173	cg13063405	*PTGDR2*
0.044404	0.042294	cg18233595	*PXK*
0.140154	0.042447	cg09484638	*DAB2IP*
0.111836	0.042461	cg11345323	*DSG2*
0.125699	0.042981	cg06075477	*SNX12*
0.052137	0.043438	cg07938869	*JPX*
0.090521	0.043624	cg15278646	*NBPF10*
0.269335	0.043688	cg23892580	*EPS8*
0.14122	0.043952	cg07862535	*ITCH*
0.325167	0.043979	cg23892580	*SAMSN1*
0.096451	0.044033	cg16570995	*LY6G6F*

0.117322	0.04436	cg06060137	*CCDC6*
0.186628	0.044531	cg13337238	*ZMYM4*
-0.05566	0.04457	cg09822824	*RPL18*
0.123775	0.044692	cg02467794	*MSRB1*
-0.76633	0.044829	cg02067639	*GNPTAB*
0.087099	0.044965	cg08092965	*TEC*
0.279409	0.045238	cg22626041	*RSBN1L*
0.134111	0.0455	cg10706910	*TMEM217*
0.0514	0.045512	cg16878007	*SPOPL*
0.00055	0.045689	cg00705668	*BMS1*
0.123414	0.046412	cg24173551	*FAM106A*
-0.20574	0.046787	cg23080241	*DYM*
0.113827	0.04719	cg14196208	*PA2G4P4*
0.076362	0.047236	cg11190854	*SLC14A2*
0.050291	0.047507	cg16878007	*CLEC2L*
-0.06419	0.047626	cg27116888	*CAPN5*
0.196048	0.048262	cg20690303	*BCL2L13*
0.078915	0.048455	cg11345323	*TTC28*
0.772067	0.04857	cg14632002	*AIP*
-0.04902	0.048673	cg01364172	*CLDN4*
0.049417	0.048706	cg15278646	*POLR3GL*
0.119623	0.04916	cg07862535	*NPR3*
0.148547	0.049259	cg20690303	*TPH1*
0.211489	0.049323	cg24167975	*GJC3*
0.178124	0.049599	cg11190854	*ZNF37BP*

Supplement Table S4 (C): Association of DNAM at 18 years in males with neighboring gene expression at 26 years (n=55)

coefficient	Pvalue	CpGs	Genes
1	0	cg01884526	*A2M*
0.597933	2.08E-05	cg06684259	*ACP2*
0.839567	3.40E-05	cg06684259	*ACAA2*

0.477653	3.40E-05	cg09852187	*ABCD3*
0.449276	0.000163	cg14056357	*ACSF3*
0.404666	0.000291	cg12009697	*ABAT*
0.814954	0.001791	cg09852187	*PDK4*
0.392199	0.008617	cg06683328	*BCORL1*
0.475772	0.016425	cg14893576	*HPCA*
-0.57357	0.017653	cg06684259	*CALM3*
0.352765	0.018762	cg14893576	*ANKRD27*
0.410258	0.019077	cg14893576	*ITCH*
0.656904	0.02035	cg14893576	*AKAP6*
-0.71635	0.026519	cg19707069	*ABHD6*
-0.38708	0.027086	cg06684259	*GNG8*
1.243804	0.027646	cg08056069	*DNTTIP1*
-0.63999	0.029427	cg12009697	*ZNF558*
0.71897	0.029721	cg08056069	*ZNF221*
0.318524	0.030186	cg08056069	*ACOT8*
0.398119	0.031384	cg14893576	*RP9*
0.289631	0.031447	cg14893576	*TARS*
0.268749	0.031529	cg08354614	*CPM*
0.407187	0.032552	cg14893576	*NUDT19*
0.466572	0.032768	cg09852187	*IPPK*
0.381913	0.041659	cg08354614	*SLC35E3*
0.33788	0.044371	cg14893576	*GSS*
0.217225	0.046485	cg14893576	*CCDC7*
-0.44495	0.048569	cg06683328	*GLT1D1*
0.208746	0.049541	cg06683328	*HS6ST1*

Supplement Table S4 (D): Association of DNAm at 18 years in females with neighboring gene expression at 26 years (n=85)

coefficient	Pvalue	CpGs	Genes
1	0	cg18593717	*AGPAT3*
-0.1099	0.000225	cg13063405	*C5*

0.73038	0.000317	cg02516257	*ZHX3*
0.667995	0.000697	cg00907843	*SOS1*
-0.10592	0.000787	cg13063405	*MRC2*
-0.75004	0.001521	cg04535371	*AKR7A3*
-0.35624	0.002559	cg00907843	*MAP4K3*
-0.52457	0.002589	cg00907843	*RFC1*
-0.06047	0.003588	cg07103819	*ITGA4*
0.297358	0.004464	cg13090731	*CLEC4E*
0.569328	0.00448	cg00907843	*CCR8*
-0.4945	0.004484	cg00907843	*DAB2*
0.128192	0.00479	cg06226335	*FBXL18*
-0.1207	0.005752	cg01364172	*RELT*
0.127063	0.005814	cg13063405	*CCDC86*
0.164471	0.006441	cg22944932	*CIITA*
-0.12918	0.006803	cg18233595	*VN1R1*
-0.45974	0.006828	cg00907843	*KCNK5*
0.434352	0.00742	cg00907843	*RRAGC*
0.249222	0.007558	cg10880755	*HSP90AA*
0.191974	0.008024	cg13063405	*LSM14B*
-0.05146	0.008957	cg14196208	*PA2G4P4*
0.141962	0.010234	cg16926844	*PRSS3*
0.161717	0.011979	cg15278646	*LIX1L*
0.064039	0.012347	cg22944932	*KANK2*
0.117817	0.012401	cg13063405	*C1orf87*
0.196124	0.012522	cg16926844	*ZSCAN20*
0.106745	0.012661	cg02225897	*POLR2J4*
0.317295	0.013324	cg23292453	*ALG1L*
-0.07128	0.013947	cg14632002	*DOC2GP*
-0.13769	0.01426	cg20361600	*TMEM40*
-0.32867	0.014397	cg00907843	*CBX7*
-0.15523	0.014576	cg25156443	*FPR3*

0.403932	0.014581	cg03223733	*VAV3*
0.103377	0.014662	cg22153463	*SLAIN2*
-0.07573	0.014712	cg26693529	*MMP15*
-0.63704	0.015586	cg05898113	*KIR3DL2*
-0.0474	0.015609	cg14196208	*C5*
0.063729	0.016289	cg13337238	*ARPP21*
0.093769	0.016879	cg06302857	*CYP27B1*
0.382421	0.017534	cg18233595	*ABHD6*
0.060404	0.018106	cg11345323	*DSG3*
0.348638	0.018425	cg17015511	*ALPK2*
-0.10376	0.018841	cg23292453	*TMEM65*
0.159577	0.019116	cg21278285	*SLC35B4*
-0.06643	0.019191	cg14632002	*KCTD19*
-0.04984	0.019338	cg14632002	*EXOC3L1*
-0.36763	0.0204	cg00907843	*KRT36*
0.141686	0.020467	cg06226335	*FARS2*
-0.06427	0.021495	cg14311471	*PABPC1L*
0.11876	0.022624	cg13063405	*PSMA7*
-0.06758	0.022836	cg20004424	*PCGF5*
-0.11063	0.023231	cg20004424	*FAM174B*
-0.12414	0.023473	cg14632002	*ZDHHC1*
-0.25622	0.023678	cg07862535	*AHCY*
0.144148	0.024605	cg06226335	*TRIM22*
0.079739	0.024788	cg06731192	*LRP5L*
-0.07526	0.024861	cg13063405	*TMEM109*
0.168992	0.025096	cg14196208	*ADAM19*
0.092431	0.0258	cg09822824	*LAMB2*
0.276644	0.026154	cg02467794	*GABRD*
-0.04267	0.026649	cg07862535	*KBTBD2*
0.282605	0.026698	cg10729426	*ZSCAN22*
0.265258	0.027627	cg02467794	*TACC3*

-0.0957	0.027751	cg14632002	*KBTBD8*
0.05973	0.027917	cg22944932	*SPC24*
0.000579	0.028178	cg00705668	*TMEM62*
-0.34917	0.028366	cg00907843	*CX3CR1*
0.173283	0.028434	cg22626041	*CIPC*
0.065801	0.02963	cg22944932	*TVP23A*
-0.06997	0.029705	cg11190854	*ADAM11*
0.157376	0.030261	cg10850197	*MYPOP*
0.059637	0.030444	cg22944932	*TARDBP*
0.237657	0.030861	cg02225897	*ZNF487*
-0.24988	0.031075	cg04784251	*MAGEF1*
0.124215	0.031756	cg09822824	*RB1*
-0.10846	0.031977	cg18593717	*FKBP3*
-0.09946	0.032465	cg26693529	*KIF5A*
0.150788	0.033237	cg16570995	*LY6G6F*
-0.07492	0.03382	cg14311471	*C2CD2*
0.146959	0.034355	cg06226335	*EVC*
0.337518	0.034435	cg12210286	*VPS53*
0.171688	0.034619	cg03223733	*NXT2*
0.131316	0.03579	cg15278646	*ITGA10*
0.107918	0.036703	cg14311471	*ERMAP*
0.149858	0.037092	cg09822824	*KCNJ14*
-0.07324	0.037192	cg20004424	*SMCO4*
-0.08503	0.037263	cg20004424	*EEA1*
0.443	0.037641	cg02067639	*POLR2J2*
-0.07059	0.038317	cg14632002	*SLC9A5*
0.198418	0.03907	cg21278285	*SMIM10*
0.330601	0.039285	cg10880755	*DYNC1H1*
-0.04002	0.039504	cg26693529	*MARS*
-0.08761	0.04063	cg25156443	*MCM3*
0.134894	0.041158	cg18716861	*SEC62*

-0.03786	0.04179	cg26693529	*TUBD1*
0.144014	0.041823	cg10880755	*MOK*
0.095629	0.042829	cg22153463	*LONP2*
0.100274	0.043656	cg13063405	*PHLPP1*
0.056722	0.043709	cg26791126	*CKAP4*
0.323744	0.044327	cg19078236	*ZNF592*
0.053681	0.044349	cg06731192	*BNIP3L*
-0.07178	0.044603	cg08092965	*PLXNB1*
-0.05759	0.044636	cg18593717	*BTBD19*
-0.05312	0.044651	cg26693529	*TSPAN31*
0.381758	0.045081	cg02467794	*LSP1*
-0.17607	0.045187	cg00907843	*CAPN12*
0.072321	0.045349	cg22944932	*HRH1*
0.123413	0.045427	cg25156443	*TMOD3*
0.256165	0.045561	cg09646206	*XPO6*
-0.0974	0.046444	cg25518386	*RTN4R*
0.075735	0.046596	cg11844198	*GPR61*
0.088734	0.046637	cg06226335	*TNRC18*
-0.17589	0.047397	cg14311471	*ZNF691*
-0.06962	0.04749	cg26693529	*CTDSP2*
-0.11971	0.048049	cg20361600	*SPTLC3*
0.067785	0.0492	cg22944932	*STYK1*

Supplement Table S5(A): Statistically significant GO terms and its biological processes from pathway enrichment analysis in each pathway for males, for the identified CpGs.

GO term	Biological Processes	N#	Raw p value
GO:0046380	N-acetylneuraminate biosynthetic process	1	0.0050
GO:0035459	vesicle cargo loading	22	0.0059
GO:0042700	luteinizing hormone signaling pathway	2	0.0075

GO:0033140	negative regulation of peptidyl-serine phosphorylati	2	0.0079
GO:0032462	regulation of protein homooligomerization	20	0.0084
GO:0072665	protein localization to vacuole	63	0.0086
GO:0006045	N-acetylglucosamine biosynthetic process	2	0.0089
GO:1901073	glucosamine-containing compound biosynthetic process	2	0.0089
GO:0044727	DNA demethylation of male pronucleus	2	0.0094
GO:1903895	negative regulation of IRE1-mediated unfolded protei	3	0.0098
GO:0060749	mammary gland alveolus development	18	0.0102
GO:0061377	mammary gland lobule development	18	0.0102
GO:0014822	detection of wounding	1	0.0117
GO:0048567	ectodermal digestive tract morphogenesis	1	0.0117
GO:0048613	embryonic ectodermal digestive tract morphogenesis	1	0.0117
GO:0060461	right lung morphogenesis	1	0.0117
GO:0071373	cellular response to luteinizing hormone stimulus	3	0.0126
GO:0015798	myo-inositol transport	4	0.0129
GO:0044725	chromatin reprogramming in the zygote	3	0.0134
GO:0007034	vacuolar transport	139	0.0137
GO:0061736	engulfment of target by autophagosome	1	0.0139
GO:0061753	substrate localization to autophagosome	1	0.0139
GO:0036250	peroxisome transport along microtubule	1	0.0142
GO:0044721	protein import into peroxisome matrix, substrate rel	1	0.0142
GO:0046105	thymidine biosynthetic process	2	0.0143
GO:0046120	deoxyribonucleoside biosynthetic process	2	0.0143
GO:0046126	pyrimidine deoxyribonucleoside biosynthetic process	2	0.0143
GO:0043126	regulation of 1-phosphatidylinositol 4-kinase activi	1	0.0145
GO:0043128	positive regulation of 1-phosphatidylinositol 4-kina	1	0.0145
GO:1905676	positive regulation of adaptive immune memory respon	1	0.0145
GO:0006227	dUDP biosynthetic process	2	0.0152
GO:0006233	dTDP biosynthetic process	2	0.0152

GO:0009139	pyrimidine nucleoside diphosphate biosynthetic proce	2	0.0152
GO:0009196	pyrimidine deoxyribonucleoside diphosphate metabolic	2	0.0152
GO:0009197	pyrimidine deoxyribonucleoside diphosphate biosynthe	2	0.0152
GO:0046072	dTDP metabolic process	2	0.0152
GO:0046077	dUDP metabolic process	2	0.0152
GO:0055094	response to lipoprotein particle	32	0.0164
GO:2000311	regulation of AMPA receptor activity	24	0.0172
GO:0097029	mature conventional dendritic cell differentiation	4	0.0181
GO:0035621	ER to Golgi ceramide transport	5	0.0184
GO:0006120	mitochondrial electron transport, NADH to ubiquinone	47	0.0185
GO:0090716	adaptive immune memory response	2	0.0188
GO:1905674	regulation of adaptive immune memory response	2	0.0188
GO:0071402	cellular response to lipoprotein particle stimulus	34	0.0192
GO:0016561	protein import into peroxisome matrix, translocation	2	0.0192
GO:0090461	glutamate homeostasis	3	0.0199
GO:0051966	regulation of synaptic transmission, glutamatergic	70	0.0201
GO:0043418	homocysteine catabolic process	3	0.0207
GO:0006352	DNA-templated transcription, initiation	245	0.0209
GO:0035783	CD4-positive, alpha-beta T cell costimulation	3	0.0210
GO:0046836	glycolipid transport	5	0.0212
GO:0006211	5-methylcytosine catabolic process	3	0.0227
GO:0019857	5-methylcytosine metabolic process	3	0.0227
GO:1901090	regulation of protein tetramerization	2	0.0235
GO:1901091	negative regulation of protein tetramerization	2	0.0235
GO:1901093	regulation of protein homotetramerization	2	0.0235
GO:1901094	negative regulation of protein homotetramerization	2	0.0235
GO:0009138	pyrimidine nucleoside diphosphate metabolic process	3	0.0236
GO:0060458	right lung development	2	0.0242
GO:0018023	peptidyl-lysine trimethylation	43	0.0243

GO:0080144	amino acid homeostasis	4	0.0247
GO:0002587	negative regulation of antigen processing and presen	2	0.0248
GO:1905224	clathrin-coated pit assembly	3	0.0253
GO:0006235	dTTP biosynthetic process	4	0.0256
GO:0009212	pyrimidine deoxyribonucleoside triphosphate biosynth	4	0.0256
GO:0046075	dTTP metabolic process	4	0.0256
GO:0034699	response to luteinizing hormone	4	0.0258
GO:0061030	epithelial cell differentiation involved in mammary	4	0.0261
GO:0010257	NADH dehydrogenase complex assembly	58	0.0264
GO:0032981	mitochondrial respiratory chain complex I assembly	58	0.0264
GO:0046813	receptor-mediated virion attachment to host cell	4	0.0266
GO:0007439	ectodermal digestive tract development	2	0.0269
GO:0048611	embryonic ectodermal digestive tract development	2	0.0269
GO:0009249	protein lipoylation	6	0.0271
GO:0035964	COPI-coated vesicle budding	6	0.0273
GO:0048200	Golgi transport vesicle coating	6	0.0273
GO:0048205	COPI coating of Golgi vesicle	6	0.0273
GO:0048009	insulin-like growth factor receptor signaling pathwa	38	0.0276
GO:0045039	protein insertion into mitochondrial inner membrane	8	0.0278
GO:0032459	regulation of protein oligomerization	42	0.0279
GO:0051389	inactivation of MAPKK activity	2	0.0289
GO:0019418	sulfide oxidation	5	0.0290
GO:0070221	sulfide oxidation, using sulfide:quinone oxidoreduct	5	0.0290
GO:1902389	ceramide 1-phosphate transport	8	0.0291
GO:0032963	collagen metabolic process	113	0.0293
GO:0043305	negative regulation of mast cell degranulation	7	0.0295
GO:2001190	positive regulation of T cell activation via T cell	3	0.0299
GO:0120009	intermembrane lipid transfer	8	0.0300
GO:0061462	protein localization to lysosome	40	0.0301

GO:0022602	ovulation cycle process	46	0.0302
GO:0034238	macrophage fusion	6	0.0306
GO:0032417	positive regulation of sodium:proton antiporter acti	4	0.0306
GO:0051668	localization within membrane	93	0.0307
GO:0032365	intracellular lipid transport	45	0.0310
GO:0046104	thymidine metabolic process	5	0.0317
GO:0046125	pyrimidine deoxyribonucleoside metabolic process	5	0.0317
GO:0002584	negative regulation of antigen processing and presen	4	0.0318
GO:0002586	regulation of antigen processing and presentation of	4	0.0325
GO:0071211	protein targeting to vacuole involved in autophagy	4	0.0336
GO:0014905	myoblast fusion involved in skeletal muscle regenera	4	0.0339
GO:0007041	lysosomal transport	103	0.0342
GO:0060750	epithelial cell proliferation involved in mammary gl	4	0.0350
GO:0048371	lateral mesodermal cell differentiation	3	0.0352
GO:0015791	polyol transport	11	0.0353
GO:0071806	protein transmembrane transport	57	0.0353
GO:0044273	sulfur compound catabolic process	53	0.0355
GO:0009211	pyrimidine deoxyribonucleoside triphosphate metaboli	6	0.0356
GO:0009189	deoxyribonucleoside diphosphate biosynthetic process	4	0.0357
GO:0016560	protein import into peroxisome matrix, docking	4	0.0358
GO:2000563	positive regulation of CD4-positive, alpha-beta T ce	5	0.0359
GO:0090131	mesenchyme migration	5	0.0364
GO:0006367	transcription initiation from RNA polymerase II prom	186	0.0364
GO:0002581	negative regulation of antigen processing and presen	3	0.0366
GO:0032962	positive regulation of inositol trisphosphate biosyn	6	0.0366
GO:0048566	embryonic digestive tract development	34	0.0374
GO:0006383	transcription by RNA polymerase III	55	0.0377
GO:0035329	hippo signaling	38	0.0379
GO:0070813	hydrogen sulfide metabolic process	7	0.0384

GO:0032415	regulation of sodium:proton antiporter activity	6	0.0393
GO:0002583	regulation of antigen processing and presentation of	6	0.0394
GO:0046462	monoacylglycerol metabolic process	5	0.0398
GO:0052651	monoacylglycerol catabolic process	5	0.0398
GO:2001188	regulation of T cell activation via T cell receptor	6	0.0398
GO:0033139	regulation of peptidyl-serine phosphorylation of STA	12	0.0400
GO:0034773	histone H4-K20 trimethylation	6	0.0402
GO:0033007	negative regulation of mast cell activation involved	9	0.0407
GO:0070973	protein localization to endoplasmic reticulum exit s	7	0.0409
GO:0060523	prostate epithelial cord elongation	3	0.0410
GO:0035249	synaptic transmission, glutamatergic	93	0.0411
GO:0048369	lateral mesoderm morphogenesis	4	0.0412
GO:0048370	lateral mesoderm formation	4	0.0412
GO:0016191	synaptic vesicle uncoating	5	0.0424
GO:0030579	ubiquitin-dependent SMAD protein catabolic process	6	0.0426
GO:0060751	branch elongation involved in mammary gland duct bra	5	0.0432
GO:0072666	establishment of protein localization to vacuole	49	0.0433
GO:0060426	lung vasculature development	6	0.0439
GO:0002580	regulation of antigen processing and presentation of	5	0.0441
GO:0009120	deoxyribonucleoside metabolic process	8	0.0442
GO:0009202	deoxyribonucleoside triphosphate biosynthetic proces	6	0.0446
GO:0060075	regulation of resting membrane potential	8	0.0453
GO:0009186	deoxyribonucleoside diphosphate metabolic process	6	0.0457
GO:0032526	response to retinoic acid	108	0.0462
GO:0061734	parkin-mediated stimulation of mitophagy in response	6	0.0464
GO:0009221	pyrimidine deoxyribonucleotide biosynthetic process	8	0.0466
GO:0098943	neurotransmitter receptor transport, postsynaptic en	7	0.0466
GO:0048806	genitalia development	47	0.0469
GO:0072318	clathrin coat disassembly	6	0.0473

GO:0060737	prostate gland morphogenetic growth	4	0.0477
GO:0043045	DNA methylation involved in embryo development	8	0.0479
GO:1901538	changes to DNA methylation involved in embryo develo	8	0.0479
GO:0097070	ductus arteriosus closure	5	0.0483
GO:0032960	regulation of inositol trisphosphate biosynthetic pr	7	0.0496

Note: #N: Number of genes involved in the respective pathways

Supplement Table S5 (B): Statistically significant GO terms and its biological processes from pathway enrichment analysis in each pathway for females, for the identified CpGs.

GO term	Biological Processes	N#	Raw P-value
GO:1901985	positive regulation of protein acetylation	43	0.0010
GO:0033144	negative regulation of intracellular steroid hormone	35	0.0011
GO:0051582	positive regulation of neurotransmitter uptake	6	0.0025
GO:0045214	sarcomere organization	53	0.0033
GO:0021853	cerebral cortex GABAergic interneuron migration	6	0.0038
GO:1904936	interneuron migration	6	0.0038
GO:0001188	RNA polymerase I preinitiation complex assembly	9	0.0040
GO:0043438	acetoacetic acid metabolic process	1	0.0041
GO:0035066	positive regulation of histone acetylation	30	0.0043
GO:0021894	cerebral cortex GABAergic interneuron development	7	0.0043
GO:0060415	muscle tissue morphogenesis	82	0.0043
GO:2000758	positive regulation of peptidyl-lysine acetylation	33	0.0054
GO:0048644	muscle organ morphogenesis	88	0.0055
GO:0006308	DNA catabolic process	40	0.0056
GO:0150070	regulation of arginase activity	1	0.0065
GO:0150072	positive regulation of arginase activity	1	0.0065
GO:0006507	GPI anchor release	1	0.0071

GO:0034014	response to triglyceride	1	0.0071
GO:0071401	cellular response to triglyceride	1	0.0071
GO:0097241	hematopoietic stem cell migration to bone marrow	1	0.0071
GO:0043630	ncRNA polyadenylation involved in polyadenylation-de	1	0.0076
GO:1901983	regulation of protein acetylation	72	0.0082
GO:0032651	regulation of interleukin-1 beta production	89	0.0085
GO:0006029	proteoglycan metabolic process	94	0.0090
GO:0030241	skeletal muscle myosin thick filament assembly	11	0.0090
GO:0071688	striated muscle myosin thick filament assembly	11	0.0090
GO:0003139	secondary heart field specification	9	0.0092
GO:0021826	substrate-independent telencephalic tangential migra	9	0.0095
GO:0021830	interneuron migration from the subpallium to the cor	9	0.0095
GO:0021843	substrate-independent telencephalic tangential inter	9	0.0095
GO:0031034	myosin filament assembly	12	0.0100
GO:0030239	myofibril assembly	73	0.0102
GO:0032675	regulation of interleukin-6 production	149	0.0108
GO:0046606	negative regulation of centrosome cycle	14	0.0109
GO:0050652	dermatan sulfate proteoglycan biosynthetic process,	1	0.0113
GO:0150073	regulation of protein-glutamine gamma-glutamyltransf	2	0.0113
GO:0150074	positive regulation of protein-glutamine gamma-gluta	2	0.0113
GO:0032611	interleukin-1 beta production	100	0.0115
GO:0033147	negative regulation of intracellular estrogen recept	13	0.0117
GO:0032652	regulation of interleukin-1 production	100	0.0118
GO:0055008	cardiac muscle tissue morphogenesis	69	0.0119
GO:0021515	cell differentiation in spinal cord	54	0.0121
GO:0021892	cerebral cortex GABAergic interneuron differentiatio	11	0.0122
GO:0030240	skeletal muscle thin filament assembly	14	0.0125
GO:0031033	myosin filament organization	13	0.0125
GO:0033143	regulation of intracellular steroid hormone receptor	75	0.0132

GO:0032635	interleukin-6 production	158	0.0134
GO:0002038	positive regulation of L-glutamate import across pla	2	0.0137
GO:0030166	proteoglycan biosynthetic process	69	0.0140
GO:0030204	chondroitin sulfate metabolic process	39	0.0142
GO:0007517	muscle organ development	406	0.0144
GO:0035020	regulation of Rac protein signal transduction	14	0.0153
GO:0019520	aldonic acid metabolic process	2	0.0154
GO:0019521	D-gluconate metabolic process	2	0.0154
GO:0046176	aldonic acid catabolic process	2	0.0154
GO:0046177	D-gluconate catabolic process	2	0.0154
GO:0030522	intracellular receptor signaling pathway	278	0.0158
GO:0032612	interleukin-1 production	112	0.0160
GO:1900134	negative regulation of renin secretion into blood st	1	0.0164
GO:1904975	response to bleomycin	2	0.0170
GO:1904976	cellular response to bleomycin	2	0.0170
GO:0034147	regulation of toll-like receptor 5 signaling pathway	1	0.0175
GO:0034148	negative regulation of toll-like receptor 5 signalin	1	0.0175
GO:0070429	negative regulation of nucleotide-binding oligomeriz	1	0.0175
GO:0072573	tolerance induction to lipopolysaccharide	1	0.0175
GO:0060766	negative regulation of androgen receptor signaling p	15	0.0186
GO:0050654	chondroitin sulfate proteoglycan metabolic process	44	0.0190
GO:0014866	skeletal myofibril assembly	16	0.0192
GO:0043652	engulfment of apoptotic cell	15	0.0198
GO:0030073	insulin secretion	206	0.0199
GO:2000772	regulation of cellular senescence	52	0.0200
GO:0097154	GABAergic neuron differentiation	14	0.0201
GO:1990918	double-strand break repair involved in meiotic recom	3	0.0204
GO:0035853	chromosome passenger complex localization to spindle	1	0.0205
GO:0016333	morphogenesis of follicular epithelium	1	0.0212

GO:0016334	establishment or maintenance of polarity of follicul	1	0.0212
GO:0042247	establishment of planar polarity of follicular epith	1	0.0212
GO:0048739	cardiac muscle fiber development	18	0.0213
GO:0033233	regulation of protein sumoylation	21	0.0214
GO:0044467	glial cell-derived neurotrophic factor secretion	2	0.0218
GO:1900166	regulation of glial cell-derived neurotrophic factor	2	0.0218
GO:1900168	positive regulation of glial cell-derived neurotroph	2	0.0218
GO:0070428	regulation of nucleotide-binding oligomerization dom	2	0.0219
GO:0062029	positive regulation of stress granule assembly	2	0.0227
GO:0061061	muscle structure development	668	0.0227
GO:0006535	cysteine biosynthetic process from serine	1	0.0234
GO:0046603	negative regulation of mitotic centrosome separation	1	0.0238
GO:2000349	negative regulation of CD40 signaling pathway	2	0.0241
GO:0021527	spinal cord association neuron differentiation	14	0.0242
GO:0051580	regulation of neurotransmitter uptake	20	0.0244
GO:0021953	central nervous system neuron differentiation	183	0.0244
GO:0090291	negative regulation of osteoclast proliferation	2	0.0244
GO:1901741	positive regulation of myoblast fusion	19	0.0245
GO:0043401	steroid hormone mediated signaling pathway	182	0.0247
GO:1904464	regulation of matrix metallopeptidase secretion	5	0.0250
GO:1904465	negative regulation of matrix metallopeptidase secre	5	0.0250
GO:1990773	matrix metallopeptidase secretion	5	0.0250
GO:0035065	regulation of histone acetylation	53	0.0252
GO:0090251	protein localization involved in establishment of pl	1	0.0256
GO:0009051	pentose-phosphate shunt, oxidative branch	3	0.0259
GO:0015798	myo-inositol transport	4	0.0259
GO:0003128	heart field specification	15	0.0266
GO:0007529	establishment of synaptic specificity at neuromuscul	2	0.0270
GO:0071929	alpha-tubulin acetylation	2	0.0273

GO:0048936	peripheral nervous system neuron axonogenesis	2	0.0280
GO:0051151	negative regulation of smooth muscle cell differenti	23	0.0281
GO:0090667	cell chemotaxis to vascular endothelial growth facto	4	0.0287
GO:0090668	endothelial cell chemotaxis to vascular endothelial	4	0.0287
GO:1901739	regulation of myoblast fusion	21	0.0297
GO:0019343	cysteine biosynthetic process via cystathionine	2	0.0301
GO:0007538	primary sex determination	3	0.0305
GO:0090342	regulation of cell aging	60	0.0305
GO:0090277	positive regulation of peptide hormone secretion	96	0.0306
GO:2000111	positive regulation of macrophage apoptotic process	3	0.0308
GO:0043111	replication fork arrest	4	0.0311
GO:2000756	regulation of peptidyl-lysine acetylation	59	0.0313
GO:0050796	regulation of insulin secretion	175	0.0313
GO:0043629	ncRNA polyadenylation	2	0.0316
GO:0071050	snoRNA polyadenylation	2	0.0316
GO:0010983	positive regulation of high-density lipoprotein part	6	0.0318
GO:0000737	DNA catabolic process, endonucleolytic	33	0.0322
GO:0034140	negative regulation of toll-like receptor 3 signalin	3	0.0328
GO:0018335	protein succinylation	4	0.0333
GO:0106077	histone succinylation	4	0.0333
GO:0072719	cellular response to cisplatin	5	0.0333
GO:0000472	endonucleolytic cleavage to generate mature 5'-end o	3	0.0343
GO:0000967	rRNA 5'-end processing	3	0.0343
GO:0035442	dipeptide transmembrane transport	5	0.0344
GO:0042938	dipeptide transport	5	0.0344
GO:0070425	negative regulation of nucleotide-binding oligomeriz	3	0.0347
GO:0070433	negative regulation of nucleotide-binding oligomeriz	3	0.0347
GO:0034146	toll-like receptor 5 signaling pathway	2	0.0354
GO:0070427	nucleotide-binding oligomerization domain containing	4	0.0355

GO:0019322	pentose biosynthetic process	4	0.0355
GO:1902659	regulation of glucose mediated signaling pathway	3	0.0356
GO:1902661	positive regulation of glucose mediated signaling pa	3	0.0356
GO:0006739	NADP metabolic process	31	0.0356
GO:0071787	endoplasmic reticulum tubular network formation	4	0.0357
GO:0060212	negative regulation of nuclear-transcribed mRNA poly	3	0.0357
GO:1900152	negative regulation of nuclear-transcribed mRNA cata	3	0.0357
GO:0050653	chondroitin sulfate proteoglycan biosynthetic proces	2	0.0358
GO:0044550	secondary metabolite biosynthetic process	28	0.0363
GO:0050708	regulation of protein secretion	465	0.0363
GO:0043418	homocysteine catabolic process	3	0.0364
GO:0060143	positive regulation of syncytium formation by plasma	27	0.0366
GO:0002677	negative regulation of chronic inflammatory response	4	0.0367
GO:1990168	protein K33-linked deubiquitination	4	0.0370
GO:0060913	cardiac cell fate determination	3	0.0371
GO:1990809	endoplasmic reticulum tubular network membrane organ	4	0.0378
GO:0010982	regulation of high-density lipoprotein particle clea	7	0.0380
GO:0000706	meiotic DNA double-strand break processing	4	0.0382
GO:0035986	senescence-associated heterochromatin focus assembly	3	0.0385
GO:0035054	embryonic heart tube anterior/posterior pattern spec	3	0.0389
GO:0071657	positive regulation of granulocyte colony-stimulatin	3	0.0390
GO:1901258	positive regulation of macrophage colony-stimulating	3	0.0390
GO:0045589	regulation of regulatory T cell differentiation	32	0.0396
GO:1905319	mesenchymal stem cell migration	3	0.0399
GO:1905320	regulation of mesenchymal stem cell migration	3	0.0399
GO:1905322	positive regulation of mesenchymal stem cell migrati	3	0.0399
GO:0051586	positive regulation of dopamine uptake involved in s	3	0.0400
GO:0051944	positive regulation of catecholamine uptake involved	3	0.0400
GO:1900133	regulation of renin secretion into blood stream	4	0.0401

GO:0150173	positive regulation of phosphatidylcholine metabolic	3	0.0404
GO:2001247	positive regulation of phosphatidylcholine biosynthe	3	0.0404
GO:0021526	medial motor column neuron differentiation	2	0.0405
GO:0030262	apoptotic nuclear changes	34	0.0407
GO:2001025	positive regulation of response to drug	33	0.0415
GO:0009092	homoserine metabolic process	4	0.0415
GO:0019346	transsulfuration	4	0.0415
GO:0045066	regulatory T cell differentiation	34	0.0418
GO:0090289	regulation of osteoclast proliferation	5	0.0418
GO:0030072	peptide hormone secretion	249	0.0419
GO:0060765	regulation of androgen receptor signaling pathway	26	0.0420
GO:1901491	negative regulation of lymphangiogenesis	3	0.0421
GO:0006741	NADP biosynthetic process	3	0.0421
GO:0055003	cardiac myofibril assembly	26	0.0422
GO:0060142	regulation of syncytium formation by plasma membrane	29	0.0426
GO:0090074	negative regulation of protein homodimerization acti	4	0.0427
GO:0097194	execution phase of apoptosis	74	0.0432
GO:0071076	RNA 3' uridylation	4	0.0433
GO:0002036	regulation of L-glutamate import across plasma membr	5	0.0434
GO:0071655	regulation of granulocyte colony-stimulating factor	4	0.0437
GO:0016925	protein sumoylation	79	0.0438
GO:0006361	transcription initiation from RNA polymerase I promo	35	0.0439
GO:0009093	cysteine catabolic process	4	0.0442
GO:0019448	L-cysteine catabolic process	4	0.0442
GO:0046439	L-cysteine metabolic process	4	0.0442
GO:0003215	cardiac right ventricle morphogenesis	20	0.0442
GO:0050707	regulation of cytokine secretion	204	0.0442
GO:0042321	negative regulation of circadian sleep/wake cycle, s	5	0.0443
GO:0030043	actin filament fragmentation	4	0.0450

GO:0048386	positive regulation of retinoic acid receptor signal	4	0.0451
GO:0060488	orthogonal dichotomous subdivision of terminal units	2	0.0451
GO:0060489	planar dichotomous subdivision of terminal units inv	2	0.0451
GO:0060490	lateral sprouting involved in lung morphogenesis	2	0.0451
GO:2000620	positive regulation of histone H4-K16 acetylation	2	0.0455
GO:0042138	meiotic DNA double-strand break formation	6	0.0458
GO:0062028	regulation of stress granule assembly	5	0.0461
GO:0071947	protein deubiquitination involved in ubiquitin-depen	5	0.0464
GO:1905868	regulation of 3'-UTR-mediated mRNA stabilization	3	0.0466
GO:1905870	positive regulation of 3'-UTR-mediated mRNA stabiliz	3	0.0466
GO:0090325	regulation of locomotion involved in locomotory beha	5	0.0471
GO:0010927	cellular component assembly involved in morphogenesi	115	0.0472
GO:0006921	cellular component disassembly involved in execution	36	0.0474
GO:0099552	trans-synaptic signaling by lipid, modulating synapt	3	0.0475
GO:0099553	trans-synaptic signaling by endocannabinoid, modulat	3	0.0475
GO:0043634	polyadenylation-dependent ncRNA catabolic process	7	0.0479
GO:0006552	leucine catabolic process	6	0.0480
GO:0071611	granulocyte colony-stimulating factor production	5	0.0481
GO:0030206	chondroitin sulfate biosynthetic process	26	0.0483
GO:0021895	cerebral cortex neuron differentiation	24	0.0486
GO:0060392	negative regulation of SMAD protein signal transduct	5	0.0487
GO:0070814	hydrogen sulfide biosynthetic process	5	0.0487
GO:0060160	negative regulation of dopamine receptor signaling p	4	0.0495
GO:0021516	dorsal spinal cord development	22	0.0498

Note: #N: Number of genes involved in the respective pathways

Supplement Table S6 (A): Indirect association of DNAm at birth at 68 CpG sites in males, with asthma acquisition from pre- to post-adolescence mediated by pre-adolescent Atopy.

CpGs	IOWBC estimate	IOWBC pvalue	ALSPAC estimate	ALSPAC pvalue	CHR	Gene	Gene location	CpG Island
cg06028605	-0.07	0.01	0.01	0.31	16	*SLC5A11*	5'UTR	
cg00067274	-0.06	0.01	0.00	0.70	4	*DCHS2*	TSS1500	
cg09760697	0.06	0.02	-0.01	0.41	10	*RP11-163F15.1*		
cg25165501	0.06	0.02	0.02	0.11	11	*SLC22A11*	Body	Island
cg25693132	-0.06	0.02	-0.01	0.41	3	*GRM2*	TSS1500	Island
cg22878693	-0.06	0.02	0.01	0.41	17	*RPTOR*	Body	
cg16010911	0.06	0.02	0.00	0.81	17	*C17orf77*	TSS200	
cg01804036	-0.05	0.03	0.00	0.75	12	*TESC*	Body	N_Shore
cg00892999	0.06	0.03	0.00	0.78	4	*GAK*	Body	N_Shore
cg26435502	0.06	0.03	-0.01	0.49	3	*NISCH*	Body	
cg00459447	0.06	0.03	-0.02	0.21	7	*THAP5,DNAJB 9*	TSS200	Island
cg22780731	-0.05	0.03	-0.01	0.40	19	*EVI5L*	5'UTR	N_Shore
cg16781287	-0.05	0.03	-0.01	0.40	11	*UBE4A*	Body	
cg20250341	-0.06	0.03	0.00	0.83	17	*C17orf44*	Body	Island
cg24085655	-0.05	0.03	0.01	0.49	6	*RPL10A*	1stExon	Island
cg26453588	-0.06	0.03	0.00	0.83	22	*BIK*	TSS1500	Island
cg09990169	-0.05	0.03	0.01	0.33	2	*C2orf54*	TSS200	
cg10475970	-0.05	0.03	0.00	0.78	5	*PCDHGA4*	Body	Island
cg08991599	-0.05	0.03	-0.01	0.50	8	*FAM84B*	TSS200	Island
cg18073883	-0.05	0.03	0.00	0.80	6	*HLA-DOB*	3'UTR	
cg03488284	0.06	0.04	0.01	0.40	16	*NDUFAB1*	TSS200	Island
cg17425144	-0.05	0.04	0.01	0.38	1	*PEX14*	Body	
cg02776315	-0.04	0.04	-0.01	0.33	2	*LHCGR*	TSS1500	S_Shore
cg19987540	-0.05	0.04	-0.01	0.57	12	*RAB21*		N_Shelf
cg14551279	0.05	0.04	-0.02	0.24	8	*SLC20A2*	Body	Island

cg22647738	-0.06	0.04	-0.02	0.20	17	*CCL16*	3'UTR	
cg04956882	-0.05	0.04	0.01	0.61	14	*C14orf48*	TSS1500	
cg04432599	-0.05	0.04	-0.01	0.43	17	*GP1BA*	1stExon;5'UTR	
cg22571278	-0.05	0.04	0.02	0.19	17	*RP11-159D12.11*		
cg02820040	-0.05	0.04	0.00	0.82	2	*C2orf54*	TSS1500	
cg04214710	0.05	0.04	0.00	0.83	7	*PTPRN2*	Body	
cg15909600	0.05	0.04	0.00	0.95	22	*MAPK8IP2*	TSS1500	Island
cg06207120	-0.05	0.04	0.01	0.35	15	*CTD-2306A12.1*		Island
cg04940570	0.05	0.05	-0.01	0.29	11	*TEAD1*	5'UTR	Island
cg06391046	0.05	0.05	0.00	0.88	16	*CMIP*	TSS200	Island
cg02366519	0.05	0.05	-0.01	0.34	4	*ABLIM2*	Body	
cg02730843	-0.05	0.05	-0.01	0.35	10	*MCM10*	3'UTR	
cg16347828	0.04	0.05	0.00	0.75	14	*FLJ10357*	TSS1500	Island
cg12156887	-0.04	0.05	0.01	0.36	17	*AKAP10*		S_Shore
cg00615241	-0.04	0.05	0.01	0.45	19	*PRTN3*	TSS1500	N_Shelf
cg13139542	-0.05	0.05	0.00	0.94	2	*LINC00298, LINC0*		
cg00425661	-0.05	0.03			14			
cg00880959	0.05	0.02			5	*PLEKHG4B*	TSS200	
cg01265507	-0.06	0.04			8	*TRAPPC9*	TSS1500	S_Shore
cg02449147	0.05	0.04			22	*NCF4*	Body	
cg03308555	-0.05	0.03			9	*RORB*	Body	
cg04216721	-0.05	0.02			6	*ARHGAP18*	Body	
cg05866778	-0.06	0.02			7	*DBNL*	Body	
cg06795516	0.06	0.01			17	*LRRC75A*	Body;Body	
cg08805613	0.06	0.04			15			
cg09940657	0.06	0.03			15			
cg10727229	0.05	0.05			4			
cg11367790	-0.05	0.03			12	*CACNA1C*	3'UTR;	S_Shore
cg11934012	-0.06	0.03			14	*PNP*	3'UTR	

cg12496108	0.05	0.04	7			
cg12768236	-0.04	0.05	6	*KIF13A*	Body	
cg13611924	-0.06	0.02	14	*TTLL5*	Body	
cg15798462	-0.05	0.04	13	*FLT1*	Body	
cg16664238	-0.05	0.03	16	*IL34*	Body	
cg18498739	0.05	0.04	21	*LTN1*	Body	
cg18635968	0.05	0.05	8	*SPAG1*	Body	Island
cg18925412	-0.05	0.02	2			
cg20304956	-0.05	0.03	8	*MRPS28*	Body	
cg25561286	0.05	0.02	12			
cg26089861	-0.05	0.05	9	*ASTN2*	Body	
cg26225339	-0.05	0.04	3			
cg26729787	-0.05	0.03	10	*ZNF22*	TSS1500	S_Shore
cg27651942	0.06	0.02	1	*SCNN1D*	Body	

Supplement Table S6 (B): Indirect association of DNAm at birth at 42 CpG sites in males, with asthma acquisition from pre- to post-adolescence mediated by pre-adolescent Atopy.

CpGs	IOWBC estimate	IOWBC pvalue	ALSPAC estimate	ALSPAC pvalue	CHR	Gene	Gene location	CpG Island
cg06508623	-0.04	0.04	0.02	0.09	13	*DNAJC15*		
cg02997605	0.04	0.04	-0.01	0.32	16	*LINC02177*		
cg06636625	-0.04	0.04	-0.01	0.41	19	*ZNF17*	Body	S_Shore
cg05934125	-0.04	0.04	-0.01	0.31	1	*NID1*	Body	
cg18844144	-0.04	0.04	-0.01	0.23	14	*ACIN1*	Body	Island
cg04720635	0.04	0.04	0.01	0.50	5	*TNFAIP8*	1stExon;5'UTR	Island
cg13849727	-0.04	0.04	0.01	0.26	9	*C9orf93*	Body	
cg14803350	0.04	0.04	-0.01	0.50	5	*PWWP2A*	1stExon;1stExon	Island
cg04888037	-0.04	0.04	0.00	0.73	12	*RP4-809F18.1*		S_Shore

cg26647291	-0.04	0.04	0.00	0.73	11	*ESRRA*	Body	N_Shelf
cg04466022	-0.04	0.05	0.00	0.79	6	*MDGA1*	Body	Island
cg07621385	-0.04	0.05	0.00	0.86	3	*MYLK*	5'UTR	
cg15761799	-0.04	0.05	-0.01	0.14	17	*AATK*	Body	S_Shore
cg06589109	-0.04	0.05	0.00	0.88	16	*KIAA0182*	Body;Body	
cg08566044	0.04	0.05	0.01	0.37	6	*SNORD48*	5'UTR;	Island
cg11320144	-0.04	0.05	-0.01	0.50	20	*PDYN*	TSS1500	
cg13601799	0.04	0.05	-0.01	0.19	9	*CDKN2A*	1stExon	Island
cg23796713	-0.03	0.05	-0.01	0.60	6	*ZBTB22*	TSS1500	N_Shore
cg00141391	-0.04	0.03			8			
cg01329939	-0.03	0.05			12	*ANO2*	Body	
cg01426804	0.04	0.05			3	*KLHL6*	Body	
cg02115490	0.04	0.05			20			
cg02407116	-0.05	0.02			1	*DUSP12*	TSS1500	N_Shore
cg03727227	0.05	0.04			6	*SRF*	Body;TSS200	Island
cg04878489	0.04	0.04			6	*SRF*	Body;TSS200	Island
cg08587654	0.04	0.05			9	*KLHL9*	TSS200	Island
cg09487370	0.04	0.05			1			
cg11106136	-0.04	0.04			18	*CELF4*	Body	
cg11500743	0.05	0.04			14	*WDR89*	Body	S_Shelf
cg12033528	0.04	0.05			6			
cg12600901	-0.04	0.04			1	*MIR190B*	TSS1500	
cg12884325	-0.04	0.04			10			
cg13006926	-0.04	0.05			7	*CDK14*	Body	
cg13225210	0.05	0.02			1	*TMEM39B*	Body	S_Shelf
cg14325335	0.04	0.05			15	*PARP6*	TSS200	N_Shore
cg14975786	0.04	0.05			12			
cg16716563	0.04	0.05			9	*STXBP1*	Body	
cg20451039	0.04	0.04			15	*ITGA11*	Body	

cg22808375	-0.04	0.04	1			
cg24099241	0.03	0.05	19	*ITPKC*	Body	
cg24206614	-0.04	0.05	1	*KLHDC8A*	TSS200	

Supplement Table S7 (A): Direct association of DNAm at birth at 98 CpG sites in males, with asthma acquisition from pre- to post-adolescence.

CpGs	IOWBC estimate	IOWBC pvalue	ALSPAC estimate	ALSPAC pvalue	CHR	Gene	Gene location	CpG Island
cg03304017	0.23	0	-0.125	0.07	8	*DEFB4*	3'UTR	
cg02582183	-0.238	0	0.136	0.082	11	*TMEM80*	TSS200	Island
cg00800038	-0.235	0	-0.094	0.161	16	*TCF25*	Body	N_Shore
cg08638939	0.314	0	-0.073	0.275	17	*TIMM22*	TSS200	Island
cg14789960	0.26	0	0.056	0.349	17	*MRPS23*	Body	N_Shelf
cg19558503	-0.184	0	-0.051	0.377	7	*PLEKHA8*	TSS1500	Island
cg06226384	0.221	0	-0.028	0.67	17	*CACNG5*	TSS200	
cg20215212	0.238	0	0.024	0.705	17	*BLMH*	Body	N_Shore
cg19780308	0.189	0	-0.026	0.724	4	*MAML3*	Body	
cg01024247	0.2	0	0.018	0.773	7	*MIR589*	TSS200;Body	S_Shore
cg14093886	0.294	0	0.013	0.829	7	*LOC285954*	Body;Body	Island
cg16097124	0.254	0	-0.011	0.86	14	*TMED10*	Body	N_Shore
cg03508095	0.276	0	-0.006	0.92	4	*C4orf39,TRIM61*	3'UTR	S_Shore
cg04355222	-0.254	0	0.002	0.971	11	*CD81*	Body	N_Shore
cg16481969	0.172	0.001	0.072	0.252	16	*CPPED1*	TSS1500	S_Shore
cg17725477	0.207	0.001	0.08	0.289	15	*SNAPC5*	Body	N_Shore
cg24027263	0.265	0.001	-0.049	0.482	3	*ATXN7*	Body	
cg15203632	0.186	0.001	-0.041	0.557	1	*KCNK1*	Body	
cg13331559	0.244	0.001	0.036	0.606	1	*MCOLN3*	TSS1500	Island
cg15391807	-0.22	0.001	0.023	0.733	10	*KCNK18*		N_Shelf
cg07452560	0.216	0.001	0.008	0.9	8	*KIAA1688*	Body	
cg14080518	0.237	0.001	0.008	0.911	7	*SMURF1*	Body	S_Shelf

cg12938020	-0.176	0.002	-0.15	0.027	2	*HOXD3*		N_Shore
cg13425962	-0.191	0.002	-0.079	0.205	9	*EXD3*	5'UTR	Island
cg18809973	-0.207	0.002	0.03	0.686	17	*LINC01987*		
cg09760697	-0.153	0.002	0.012	0.869	10	*RP11-163F15.1*		
cg05541258	0.196	0.003	0.059	0.299	6	*RNU7-26P*		
cg07670736	0.206	0.003	-0.041	0.535	1	*ALG14*	Body	N_Shore
cg22729438	0.233	0.003	-0.041	0.561	15	*TJP1*		N_Shore
cg10855395	0.159	0.003	0.01	0.885	12	*UBC*		Island
cg25121621	0.208	0.004	0.05	0.423	15	*SQRDL*	TSS1500	N_Shore
cg19775582	-0.199	0.004	-0.028	0.66	5	*ODZ2*	Body	
cg22106810	0.183	0.004	-0.026	0.706	12	*PLEKHA5*	Body	Island
cg17675639	-0.219	0.004	0.012	0.845	13	*EEF1DP3*	TSS200	Island
cg07056644	0.149	0.005	-0.038	0.53	16	*FOXF1*	3'UTR	S_Shore
cg18306327	-0.229	0.006	0.052	0.39	16	*BFAR*	TSS200	Island
cg19288752	-0.203	0.006	-0.007	0.907	2	*DTYMK*	TSS200	Island
cg11968414	-0.211	0.007	0.09	0.191	6	*MDCÊ1.00*	5'UTR	Island
cg05616472	0.195	0.007	-0.054	0.42	9	*EHMT1*	Body	S_Shore
cg11170810	0.223	0.008	0.043	0.545	6	*IGF2R*	TSS1500	N_Shore
cg15886596	0.222	0.008	-0.021	0.72	19	*WASH5P*		Island
cg03921529	0.139	0.009	0.061	0.335	13	*LINC00327*		N_Shore
cg25958857	-0.218	0.009	0.037	0.562	12	*TENC1*	Body	Island
cg20318748	0.146	0.011	0.081	0.254	20	*NANP*	TSS1500	Island
cg17117277	0.196	0.015	-0.042	0.517	19	*ZFR2*	Body	Island
cg00067274	0.151	0.016	0.079	0.219	4	*DCHS2*	TSS1500;Body	
cg06028605	0.128	0.016	-0.031	0.669	16	*SLC5A11*	5'UTR	
cg01098234	-0.193	0.018	-0.123	0.077	11	*FAM86GP*		Island
cg11663481	-0.159	0.019	-0.076	0.195	3	*TMEM41A*	Body	Island
cg22878693	0.138	0.033	-0.09	0.207	17	*RPTOR*	Body	
cg06698093	0.165	0.037	-0.053	0.397	8	*AC084082.3*		S_Shore

cg04930211	-0.17	0.037	0.008	0.9	22	*FAM19A5*	Body	
cg00892999	-0.204	0.041	-0.01	0.874	4	*GAK*	Body	N_Shore
cg13918948	-0.151	0.043	-0.084	0.198	10	*DIP2C*	Body	
cg00061313	0.251	0			10			
cg00241558	-0.216	0			10			
cg01181929	0.125	0.013			12	*PLEKHG6*	TSS1500	Island
cg01344289	-0.223	0.002			15	*GNB5*	Body	
cg03137783	-0.215	0			1	*HIVEP3*	5'UTR	
cg03251789	-0.203	0.002			15			
cg04124763	0.213	0.008			19			
cg04400433	-0.27	0.001			6	*PKIB*	5'UTR	
cg04591284	0.205	0.002			22	*CRKL*	TSS1500	N_Shore
cg04854616	-0.21	0.003			22	*ZC3H7B*	5'UTR	
cg04857808	-0.244	0			1	*APH1A*	Body;	N_Shore
cg05271437	-0.18	0.042			8	*NUDCD1*	Body	
cg05747243	0.206	0.004			15	*SQRDL*	TSS1500	N_Shelf
cg06672144	0.209	0			18			
cg06795516	-0.186	0.025			17	*LRRC75A*	Body;Body	
cg06895337	-0.251	0			19	*GLTSCR1*	5'UTR	
cg09961998	-0.155	0.005			7	*TPK1*	Body	
cg11747595	-0.195	0.003			1	*PODN*	TSS1500	N_Shore
cg11764125	-0.155	0.014			1	*GNG12*	5'UTR	
cg11984187	-0.285	0			1	*SH3D21*	Body	N_Shore
cg12154726	-0.184	0.002			22	*MYO18B*	Body	
cg12524068	-0.266	0			1	*LRIG2*	Body	
cg12558795	-0.203	0.001			7			
cg12691745	0.238	0.002			13	*COG6*	Body	
cg12774854	0.236	0.002			17	*ANKFY1*	Body	
cg13246505	-0.195	0			19	*LRFN1*	TSS200	S_Shore

cg13575045	-0.236	0.002	22	*PLA2G3*	TSS1500	
cg13982174	-0.218	0	2			
cg14188354	0.187	0.024	3	*EOMES*	5'UTR	Island
cg14273507	0.197	0.002	18			
cg14715653	-0.203	0.001	17			
cg14894593	0.214	0.001	1			
cg15668843	-0.221	0.001	2			
cg15956957	-0.165	0.004	12	*ENO2*	Body	S_Shelf
cg17097187	-0.271	0	1			S_Shore
cg17697043	0.19	0	20			
cg18005079	0.21	0.001	15			
cg18491851	0.202	0.014	1	*C1orf106*	Body	N_Shore
cg18925412	0.132	0.037	2			
cg19727897	-0.152	0.025	11	*SMTNL1*	TSS200	
cg20587396	-0.266	0	1			
cg21463078	-0.187	0.014	14			
cg21981207	0.24	0	21	*PDXK*	Body	
cg23507180	-0.24	0.001	1	*PAX7*	Body	
cg25561286	-0.138	0.041	12			

Supplement Table S7 (B): Direct association of DNAm at birth at 193 CpG sites in females, with asthma acquisition from pre- to post-adolescence.

CpGs	IOWBC estimate	IOWBC pvalue	ALSPAC estimate	ALSPAC pvalue	CHR	Gene	Gene location	CpG Island
cg07823273	-0.249	0	-0.176	0.002	19	*SYCN*	TSS200	S_Shore
cg04017131	-0.226	0	-0.137	0.015	8	*ANGPT2*	Body	
cg09890200	-0.222	0	-0.116	0.021	2	*PRKRA*	TSS1500	Island
cg14291650	-0.217	0	-0.124	0.022	15	*MTFMT*		S_Shelf
cg04491367	-0.232	0	-0.113	0.023	16	*ZNF778*		Island

cg21330703	-0.235	0	-0.115	0.029	11	*DRD2*	TSS1500	S_Shore
cg22103637	-0.27	0	-0.1	0.055	13	*HS6ST3*	TSS1500	N_Shore
cg26580576	-0.224	0	-0.099	0.068	4	*LOC93622*	TSS200	Island
cg19807836	0.241	0	0.094	0.071	1	*NEK7*		
cg02960777	-0.183	0	0.1	0.082	7	*PHTF2*	Body	
cg07834476	-0.201	0	-0.085	0.091	10	*ENKUR,THNSL1*	TSS1500;5'UTR	Island
cg03016446	-0.249	0	-0.093	0.107	10	*CBARA1*	TSS1500	S_Shore
cg18393722	-0.218	0	-0.086	0.123	15	*UBE2QP1*	Body	Island
cg02054358	-0.233	0	-0.076	0.126	17	*LINC00511*		
cg17339484	-0.227	0	-0.079	0.129	10	*RHOBTB1*	Body	Island
cg22085380	0.236	0	0.09	0.149	3	*FSTL1*		S_Shelf
cg04080041	-0.207	0	-0.073	0.174	5	*PCDHGA4*	Body	Island
cg14714391	-0.24	0	-0.073	0.174	5	*F2R*	TSS1500	N_Shore
cg22708914	-0.209	0	-0.072	0.175	8	*SH2D4A*	TSS1500	N_Shore
cg07199257	-0.248	0	-0.076	0.177	15	*CRABP1*	3'UTR	
cg24739326	-0.206	0	-0.069	0.196	19	*CHST8*	5'UTR	Island
cg11846905	0.207	0	0.073	0.208	12	*NTS*		
cg08230105	0.208	0	-0.071	0.215	17	*RP11-392O1.4*		
cg24736380	0.191	0	0.07	0.221	10	*PFKP*	Body	N_Shore
cg05653887	-0.226	0	-0.058	0.273	22	*CELSR1*	Body	N_Shelf
cg00740870	-0.244	0	-0.061	0.29	14	*PLEKHH1*	Body	
cg22329021	-0.205	0	-0.061	0.305	4	*RP11-1398P2.1*		S_Shelf
cg20730619	0.248	0	0.055	0.323	5	*SLC12A7*	Body	S_Shore
cg14159342	-0.235	0	-0.055	0.331	1	*TP73*	Body	S_Shore
cg14868994	-0.236	0	-0.052	0.334	2	*LINC01833*		Island
cg11586330	-0.199	0	-0.054	0.345	12	*LHX5*	3'UTR	Island
cg11414821	-0.226	0	-0.051	0.355	6	*KIAA1949*	Body;1stExon	N_Shore
cg16825643	0.261	0	0.048	0.367	16	*FAM38A*	Body	N_Shore
cg01120851	0.222	0	-0.056	0.368	1	*KLHL21*	Body	N_Shore

cg00530448	-0.212	0	-0.052	0.386	11	*NELL1*	Body	Island
cg22824651	-0.212	0	-0.045	0.39	12	*RPSAP52*		Island
cg03059112	-0.22	0	0.048	0.416	12	*FKBP11*	1stExon	Island
cg02122376	-0.223	0	-0.041	0.423	5	*G3BP1*	TSS1500	Island
cg11970192	-0.203	0	-0.04	0.444	15	*C15orf37,ST20*	Body;5'UTR	Island
cg06988995	-0.244	0	-0.038	0.491	10	*CSGALNACT2*	TSS200	Island
cg02838492	-0.211	0	-0.038	0.498	9	*KIF12*	1stExon;5'UTR	Island
cg01193064	-0.222	0	-0.036	0.525	21	*CBS*	5'UTR	Island
cg13246264	-0.193	0	-0.034	0.527	3	*LRCH3*	TSS1500	N_Shore
cg15161177	-0.197	0	0.034	0.554	12	*TIMELESS*	TSS1500	S_Shore
cg12527440	0.237	0	0.03	0.555	19	*ZSWIM4*	Body	S_Shore
cg10777851	-0.277	0	-0.037	0.563	3	*CD200*	TSS200	N_Shore
cg06513695	-0.222	0	-0.034	0.574	22	*RFPL1S*		Island
cg09457121	0.199	0	-0.031	0.576	2	*OBSL1*	Body	Island
cg03827835	0.217	0	-0.027	0.593	5	*C5orf66*		S_Shore
cg10527525	-0.243	0	-0.032	0.595	7	*AUTS2*	Body	S_Shore
cg04115418	-0.246	0	-0.027	0.608	20	*STMN3*	Body	Island
cg06730718	-0.212	0	-0.036	0.619	16	*PAPD5*	TSS1500	
cg17125699	-0.222	0	-0.027	0.629	17	*WSCD1*		N_Shore
cg18478319	-0.228	0	-0.026	0.652	13	*SLC15A1*	TSS200	S_Shore
cg09367367	-0.233	0	0.028	0.654	12	*RPL6*	TSS200	S_Shore
cg11154384	-0.237	0	0.026	0.654	15	*C15orf61*	Body	S_Shore
cg21722639	0.216	0	0.023	0.672	11	*TOLLIP*	Body	S_Shore
cg16622920	-0.228	0	-0.023	0.683	6	*HCG16*		Island
cg16287252	-0.229	0	-0.023	0.704	12	*GLT1D1*	Body	
cg11346837	-0.227	0	0.022	0.713	3	*RP11-649A16.1*		Island
cg20983032	-0.198	0	-0.018	0.737	19	*ATF5*		
cg26816426	0.217	0	-0.019	0.75	8	*JPH1*	Body	Island
cg05033322	-0.226	0	0.018	0.772	11	*ATM*	TSS1500;1stExon	Island

cg09386054	-0.23	0	0.014	0.813	14	*RP11-1082A3.1*		
cg20171559	-0.229	0	-0.015	0.825	7	*HOXA1*		N_Shore
cg18448991	-0.227	0	0.012	0.836	20	*MIR941-3*	TSS2005'UTR	Island
cg15371806	-0.251	0	-0.009	0.881	6	*KIF25*	TSS1500	
cg18244483	-0.192	0	-0.008	0.884	4	*LINC02173*		
cg11990770	0.259	0	0.007	0.909	10	*CFAP46*		N_Shore
cg21144922	0.18	0	-0.005	0.941	1	*C1orf59*	TSS200	Island
cg27224718	-0.224	0	-0.004	0.942	8	*ZFAT*	Body	
cg15001132	-0.233	0	-0.004	0.949	13	*NUPL1*	5'UTR	Island
cg04233664	-0.213	0	-0.003	0.966	10	*CTBP2*	5'UTR	Island
cg27232494	0.202	0	-0.002	0.978	17	*TOM1L2*	Body	
cg12264049	-0.246	0	-0.001	0.979	4	*MED28*	Body	Island
cg06239131	0.224	0	-0.001	0.99	1	*LOC115110*	Body	
cg25404454	0.194	0.001	0.133	0.002	4	*GAB1*	Body	
cg05770947	0.2	0.001	0.137	0.011	12	*SLC2A13*	Body	
cg09614565	-0.201	0.001	-0.132	0.023	3	*IL17RD*	TSS200	S_Shore
cg07629844	-0.199	0.001	-0.089	0.091	1	*CAPN2*	TSS200;Body	Island
cg03296761	-0.188	0.001	0.076	0.186	22	*MTPÊ18.00*	Body	S_Shore
cg10324701	0.226	0.001	0.063	0.273	12	*RP11-897M7.1*		S_Shore
cg10200608	-0.177	0.001	-0.058	0.323	5	*KIAA0141*	TSS1500	N_Shore
cg07660473	0.205	0.001	-0.057	0.347	16	*BEAN*	5'UTR	
cg20241375	-0.191	0.001	0.049	0.36	4	*ZNF732*		N_Shelf
cg10346242	-0.209	0.001	-0.034	0.508	12	*ARF3*	TSS1500	S_Shore
cg07926996	-0.229	0.001	0.029	0.612	2	*PREPL*	1stExon	N_Shore
cg08111661	-0.192	0.001	0.026	0.613	12	*CACNA1C*	Body	N_Shore
cg21868063	-0.194	0.001	0.022	0.701	17	*MGAT5B*	Body;1stExon	S_Shelf
cg01165752	0.208	0.001	-0.019	0.733	16	*HMGN2P41*		
cg26408861	0.169	0.001	0.014	0.795	1	*LHX4*	Body	
cg14597726	0.208	0.001	-0.01	0.865	13	*LINC00358*		

cg18694780	-0.188	0.002	-0.123	0.019	2	*CXCR7*	TSS1500	S_Shore
cg22979546	0.184	0.002	0.091	0.132	15	*HERC2*	Body	
cg06365057	-0.216	0.002	-0.074	0.164	10	*C10orf72*	TSS200	Island
cg16980245	0.193	0.002	-0.06	0.219	15	*SNORD115-42*	TSS200	
cg09884451	-0.184	0.002	0.033	0.563	4	*ZFYVE28*	Body	Island
cg19805217	0.18	0.003	-0.09	0.112	10	*RP11-428G2.1*		
cg23121394	-0.156	0.003	-0.081	0.197	6	*C6orf123*	Body	Island
cg22027725	0.17	0.003	0.055	0.241	11	*SLC37A2*		
cg25989745	0.202	0.003	0.058	0.32	9	*TYRP1*	TSS200	
cg21042248	-0.188	0.003	0.016	0.782	19	*MGC2752*	Body	N_Shore
cg27424226	0.179	0.004	-0.062	0.281	22	*H1F0*	1stExon;5'UTR	Island
cg26310551	-0.191	0.004	0.03	0.613	14	*LTB4R2*	Body	Island
cg26647291	0.143	0.004	0.015	0.799	11	*ESRRA*	Body	N_Shelf
cg23844910	0.193	0.005	0.042	0.442	1	*RP11-90C4.1*		
cg02532113	0.17	0.006	0.119	0.041	6	*RP5-991C6.2*		
cg18733820	0.19	0.007	-0.069	0.227	17	*PSMD12*	TSS200	Island
cg15096549	0.172	0.007	0.054	0.29	11	*RP11-680E19.1*		
cg01679206	-0.154	0.017	0.031	0.613	7	*WBSCR27*	Body	N_Shelf
cg14563196	-0.149	0.024	-0.009	0.88	1	*GBP4*	1stExon;5'UTR	
cg02458483	-0.127	0.031	-0.053	0.377	1	*KIAA1522*	TSS1500	N_Shore
cg13181604	-0.126	0.046	0.002	0.971	14	*NEDD8,GMPR2*	Body;	N_Shore
cg00141391	0.126	0.021			8			
cg00526274	0.189	0.001			5	*CTNNA1*	Body	
cg01199509	-0.218	0			1	*SRGAP2C*	Body	
cg01329939	0.181	0.004			12	*ANO2*	Body	
cg01492536	-0.279	0			17			
cg02086971	-0.218	0			16	*NSMCE1*	Body	
cg03080605	0.208	0			1			
cg03220054	0.176	0			2	*LAPTM4A*	TSS1500	S_Shore

cg03335248	-0.208	0.001	2			
cg03808748	0.208	0	3			
cg04021692	-0.212	0	9	*KIF12*	TSS200	Island
cg04214626	-0.207	0	11			N_Shore
cg04349509	-0.249	0	1			
cg04445379	0.224	0	5			
cg04531165	0.211	0.001	14	*EML5*	Body	
cg04725937	0.251	0	2	*ACTG2*	TSS1500	
cg04742865	0.201	0	18			
cg04830702	0.235	0	17	*AKAP1*	5'UTR	
cg04852236	0.19	0.001	2	*IL1R1*	5'UTR	
cg05001024	0.189	0.001	4	*ABCA11P,ZNF721*	Body	
cg05195455	0.155	0.005	12	*CPSF6*	3'UTR	
cg06005684	0.236	0	1			
cg06082013	-0.222	0	18	*TCF4*	TSS200	
cg06198596	-0.259	0	17	*SPECC1*	TSS1500	N_Shore
cg06330158	-0.212	0	14	*GPHN*	TSS200	N_Shore
cg06591620	-0.23	0	3	*ZNF148*	TSS1500	S_Shore
cg07068547	-0.177	0.003	16	*TFAP4*	Body	N_Shore
cg07236381	-0.225	0	5	*AFF4*	1stExon;5'UTR	Island
cg07250429	0.242	0	15	*RORA*	Body	
cg07741172	0.186	0	21	*TSPEAR-AS2*	TSS200	
cg09378610	0.213	0	15			
cg09704765	0.226	0	8	*NCALD*	5'UTR	
cg09728232	0.245	0	9			
cg10289292	0.169	0.001	15			N_Shore
cg10597549	0.259	0	1	*CDK18*	5'UTR	
cg10729726	0.098	0.035	1	*CACNA1S*	Body	
cg10771019	0.167	0.006	16	*GSE1*	5'UTR	S_Shelf

cg10852829	-0.219	0.001	7	*CCDC126*	5'UTR	S_Shore
cg11177277	-0.172	0.003	4	*PALLD*	5'UTR	S_Shelf
cg11270792	-0.245	0	1			
cg11805806	-0.203	0	12			
cg12022883	-0.217	0	7	*BMPER*	Body	
cg12026805	-0.206	0	1			
cg12305405	0.232	0	7	*LAT2*	3'UTR	
cg12777182	0.212	0.002	6			
cg12952987	0.162	0.004	4	*SORCS2*	Body	
cg13201279	-0.283	0	1	*KCNK2*	5'UTR;1stExon	
cg13225210	-0.129	0.024	1	*TMEM39B*	Body	S_Shelf
cg13371260	-0.215	0	1	*BCAN*	1stExon	Island
cg14614346	-0.204	0	4	*FAM198B*	Body	
cg14744604	0.214	0.001	14	*ITPK1*	Body	
cg14811849	-0.232	0	8			
cg14980188	-0.205	0.002	17	*NARF*	5'UTR	
cg15241587	-0.191	0	20	*LINC01522*	Body	
cg15303182	0.217	0	17	*ZBTB4;ZBTB4*	Body	N_Shore
cg16464301	0.185	0.002	12	*LOC101927653*	Body	
cg16473632	-0.238	0	17	*SDK2*	Body	
cg16556211	0.237	0	4			
cg16673168	-0.229	0	11	*PAFAH1B2*	TSS1500	N_Shore
cg18074323	0.226	0	16	*EDC4*	Body	N_Shelf
cg18749178	-0.197	0.001	1			
cg19198400	-0.23	0	5	*TSLP*	TSS200	N_Shelf
cg19292908	0.176	0.004	22	*PRAME*	5'UTR	N_Shore
cg19358359	-0.215	0	17	*MPP2*	TSS1500	S_Shore
cg19389227	-0.122	0.035	13			
cg20079855	0.216	0	3			

cg20422386	-0.198	0.002	1			
cg20595382	-0.191	0	8			
cg20603632	0.218	0	12	*AACS*	Body	S_Shore
cg20996735	-0.207	0	6	*PXT1,KCTD20*	TSS1500	S_Shore
cg21812071	-0.23	0	12			
cg22842768	-0.276	0	1			
cg23976120	0.222	0	2	*ATP6V1B1*	Body	
cg24409590	-0.209	0	16	*GPT2*	1stExon	S_Shore
cg24869879	-0.228	0	2			
cg25279605	0.235	0	2	*GPR17*	TSS1500	
cg26604499	-0.219	0	16	*DHODH*	Body	
cg26906383	0.187	0.001	2	*LTBP1*	Body	
cg27575609	-0.23	0	1			

Supplement Table S8 (A): Association of DNAm in males with neighboring gene expression (n=55)

coefficient	Pvalue	CpGs	Genes
1	0	cg19987540	*AKR1E2*
0.996115	5.14E-11	cg25121621	*COPRS*
1.340203	1.48E-09	cg25121621	*PAGR1*
0.785081	7.66E-09	cg25121621	*GDPD3*
0.5177	1.16E-08	cg25121621	*TBX6*
0.650241	1.85E-08	cg25121621	*LTN1*
0.626171	2.66E-08	cg25121621	*HIRIP3*
0.882073	4.30E-08	cg25121621	*ASCC2*
0.493743	2.54E-07	cg25121621	*TRIM31*
0.538803	6.39E-07	cg14080518	*ATP5A1*
0.641589	1.71E-06	cg25121621	*TRIM40*
0.583802	1.82E-06	cg25121621	*DOC2A*
0.337716	5.21E-06	cg25121621	*SLC7A1*

-0.50334	5.88E-06	cg20250341	*BRI3BP*
0.578815	6.13E-06	cg25121621	*CDIPT*
0.785116	1.09E-05	cg19288752	*CELA1*
0.439368	1.68E-05	cg25121621	*TMTC1*
-0.57209	1.95E-05	cg14080518	*PAIP1*
0.538247	2.49E-05	cg25121621	*SVIL*
1.272328	6.43E-05	cg16781287	*CEP192*
0.438529	7.32E-05	cg19288752	*FAM21A*
0.602809	8.70E-05	cg25121621	*MTUS2*
0.815957	0.000143	cg01098234	*ARRDC1*
0.242793	0.000178	cg02776315	*AGRN*
-0.33121	0.000199	cg25121621	*TAOK2*
-0.5935	0.000207	cg25121621	*DCTN6*
0.917735	0.000211	cg25121621	*FKBP14*
-0.64462	0.000226	cg14080518	*UBR1*
0.605009	0.000229	cg25121621	*CORO1A*
-0.62517	0.00026	cg14080518	*STK4*
0.887041	0.000294	cg01098234	*TUBB4B*
0.42375	0.000301	cg19288752	*MBD2*
528.6448	0.000383	cg20250341	*AACS*
0.403133	0.000451	cg19288752	*SLC4A8*
0.443992	0.000484	cg25121621	*RPP21*
-0.28898	0.000579	cg13331559	*EXTL3*
-0.5668	0.000682	cg20250341	*SNX4*
-0.45488	0.00074	cg10855395	*COPZ2*
0.89677	0.000782	cg01098234	*RAB33B*
0.997896	0.00091	cg16781287	*GPRC5D*
0.869628	0.00094	cg01098234	*BRAF*
1.602771	0.000943	cg16781287	*FAM9C*
0.793746	0.001149	cg19288752	*FRMD6*
0.717724	0.001269	cg25121621	*UTP6*

0.630309	0.001381	cg25121621	*NEFH*
-0.5262	0.001418	cg14080518	*CRIP3*
-0.83913	0.001524	cg16781287	*TASP1*
0.42902	0.00155	cg20250341	*RNF139*
-0.30703	0.001578	cg14080518	*ERMAP*
-0.55492	0.001868	cg13139542	*SPCS3*
0.427514	0.002089	cg19288752	*MAGED1*
-0.66027	0.002174	cg14080518	*GTPBP2*
0.391773	0.002292	cg14080518	*TTC17*
-0.73045	0.002297	cg13139542	*PRR7*
0.65202	0.002335	cg16781287	*BEND7*
-0.30084	0.002373	cg02776315	*ABCA7*
0.183425	0.002587	cg01098234	*ANAPC2*
0.537924	0.002664	cg25121621	*SUZ12*
1.247242	0.002742	cg01098234	*NAA15*
0.413378	0.00277	cg25121621	*MTURN*
-0.56374	0.002887	cg20250341	*DHX37*
0.679635	0.002959	cg25121621	*KLHL14*
0.487107	0.002982	cg01098234	*EHMT1*
-0.40538	0.003152	cg13331559	*APOBR*
0.401101	0.00324	cg04214710	*IGF2BP*
0.295691	0.003483	cg14093886	*KIF24*
0.751987	0.003498	cg12938020	*SYDE2*
0.268249	0.003659	cg17725477	*HEBP1*
-0.49154	0.003685	cg13331559	*BLMH*
0.852727	0.003747	cg01098234	*RNF208*
0.364633	0.003801	cg14080518	*SLC2A1*
-0.34452	0.004048	cg19987540	*PFN1*
0.998641	0.004708	cg16781287	*SEPHS1*
0.882772	0.00475	cg01098234	*HARS*
0.340392	0.004848	cg19288752	*SCN8A*

-1.24097	0.005144	cg16781287	*CCDC3*
0.345648	0.005293	cg19288752	*DMXL2*
0.380788	0.005533	cg18073883	*SND1*
-0.1295	0.005664	cg13425962	*ALPK2*
-0.4264	0.005721	cg19987540	*CYTL1*
0.428863	0.005754	cg19288752	*RRP9*
-0.33256	0.006106	cg20250341	*STT3A*
-0.44478	0.006165	cg25165501	*TRIM46*
0.53543	0.006591	cg01098234	*RAB19*
0.357756	0.007255	cg02776315	*SOX8*
0.209231	0.007265	cg19288752	*CLDND2*
-0.33711	0.00731	cg13331559	*EFCAB5*
-0.42895	0.007343	cg14080518	*SCUBE1*
-0.47048	0.007352	cg10855395	*TBKBP1*
0.347298	0.007894	cg02776315	*METRN*
-0.19127	0.008537	cg14080518	*POLR1C*
-0.63711	0.008584	cg16781287	*NACC1*
-0.60162	0.008749	cg20250341	*NDUFB9*
-0.67467	0.009725	cg19987540	*CHRNE*
0.514161	0.009915	cg02776315	*RAD52*
-0.20839	0.00997	cg13425962	*CES1P1*
-0.31282	0.010098	cg08991599	*RSRC1*
0.57813	0.010116	cg26453588	*PPM1L*
0.572835	0.010313	cg20318748	*NDRG2*
-0.64087	0.010511	cg20250341	*HDDC2*
0.25589	0.010696	cg14789960	*AKAP6*
0.047156	0.011362	cg10475970	*ANAPC1*
0.254495	0.011385	cg19288752	*POLI*
0.385937	0.011681	cg15909600	*AURKB*
0.552847	0.012115	cg01098234	*TPRN*
0.477949	0.012362	cg02776315	*TMEM18*

-0.5421	0.012484	cg19987540	*CSMD1*
0.336494	0.012486	cg01098234	*DPH7*
-0.00025	0.012491	cg00067274	*LMF2*
0.530026	0.012613	cg14789960	*EPC1*
0.599867	0.013038	cg01098234	*NDUFC1*
-0.89414	0.013386	cg16781287	*RAD23A*
0.497856	0.013421	cg01098234	*LRRC26*
0.223545	0.013463	cg25121621	*TRIM26*
0.420948	0.013578	cg02776315	*DGKQ*
0.79402	0.013647	cg01098234	*DND1*
0.737128	0.014377	cg22647738	*FANCA*
0.334207	0.015483	cg01098234	*EXD3*
0.393301	0.015623	cg25121621	*CABP7*
-0.38712	0.016093	cg19987540	*ANKS3*
0.576546	0.016292	cg14080518	*TFF3*
-0.38324	0.016891	cg10855395	*IPP*
0.432617	0.018096	cg04432599	*MMP11*
0.498346	0.018959	cg26453588	*PEA15*
-0.00024	0.019777	cg00067274	*ADM2*
-0.59227	0.020477	cg10855395	*CD3E*
0.458692	0.020494	cg16781287	*STX10*
-0.29961	0.020659	cg19987540	*NAGPA*
-0.65401	0.021202	cg25693132	*COG7*
0.727259	0.021258	cg14789960	*RFPL2*
0.079302	0.021465	cg03488284	*USP19*
0.447974	0.021581	cg20318748	*ZNF219*
-0.53372	0.021684	cg18073883	*MCM2*
0.254412	0.021934	cg00800038	*NINJ2*
0.309977	0.021946	cg15909600	*TRMT44*
0.564316	0.022872	cg18073883	*GOLGA1*
-0.31266	0.023042	cg19987540	*RBAK*

-0.45076	0.023151	cg19987540	*UBALD1*
-0.52309	0.023389	cg14080518	*STK17A*
-0.26807	0.023407	cg00800038	*RHOT2*
0.407399	0.023756	cg14789960	*TAP2*
0.389338	0.024784	cg04432599	*TCEB3*
0.237727	0.024804	cg02776315	*FGF22*
-0.35807	0.025946	cg02730843	*GPCPD1*
-0.48064	0.026195	cg14080518	*BMS1*
0.446589	0.026554	cg20318748	*SLC7A4*
-0.39689	0.026804	cg14093886	*SCAND1*
0.221929	0.027024	cg02776315	*GET4*
0.428555	0.027637	cg19288752	*GALNT6*
-0.22292	0.027647	cg00800038	*VPS53*
0.097624	0.027845	cg13425962	*RDH5*
0.479274	0.027869	cg26453588	*SLAMF6*
-0.38288	0.02787	cg19987540	*KCNA6*
0.229501	0.027941	cg02776315	*TTLL10*
0.331949	0.027972	cg18073883	*UROS*
-0.5773	0.028276	cg18073883	*ADAM12*
-0.16179	0.028383	cg13331559	*NPIPB8*
0.387407	0.028662	cg00800038	*LRRC56*
-0.18441	0.028735	cg13331559	*ZCWPW2*
-0.11931	0.028826	cg10475970	*DGAT1*
0.59678	0.029015	cg12938020	*SH2D6*
-0.78222	0.029929	cg25693132	*NAPB*
0.193826	0.030099	cg19288752	*BIN2*
-0.25688	0.030803	cg00800038	*EXOC3*
-0.66686	0.030823	cg25165501	*CLK2*
0.302514	0.030945	cg19288752	*CTU1*
0.438057	0.031029	cg02776315	*NXN*
-0.60374	0.031495	cg25693132	*DCTN5*

0.484591	0.031706	cg20318748	*ZNF431*
0.771171	0.032635	cg13139542	*LMAN2*
0.634944	0.032789	cg18073883	*FANK1*
-0.19642	0.03293	cg00892999	*BMP6*
0.315769	0.033176	cg04432599	*NR1D2*
0.362926	0.033236	cg18073883	*ARPC5L*
-0.24915	0.033622	cg19987540	*GALNT8*
-0.43003	0.033804	cg25165501	*THBS3*
0.436408	0.034581	cg26453588	*KPNA4*
0.295863	0.034992	cg02776315	*TYMS*
0.370741	0.035296	cg04432599	*FUCA1*
-0.45322	0.035595	cg19987540	*STK32B*
-0.21071	0.035794	cg14080518	*TOMM34*
0.191872	0.037001	cg14093886	*MMP28*
0.556817	0.037249	cg26453588	*BAZ2B*
0.711634	0.038235	cg16781287	*CALR*
-0.38714	0.038448	cg19987540	*PLD2*
0.263068	0.038683	cg04214710	*IRF2*
-0.27658	0.038754	cg10855395	*PRKCE*
-0.18926	0.038915	cg13331559	*LINGO2*
-0.38876	0.039009	cg14080518	*BIK*
-0.43759	0.03921	cg20250341	*UBC*
0.274812	0.040803	cg02776315	*JMJD8*
0.258628	0.040827	cg14080518	*MAOB*
-0.16603	0.041301	cg19558503	*ING5*
0.488836	0.041377	cg04432599	*ZNF726*
0.292591	0.043332	cg04432599	*ID3*
0.000144	0.043898	cg00067274	*KCNC3*
-1.22358	0.044569	cg25165501	*ASH1L*
0.254268	0.044898	cg15909600	*TUB*
-0.14895	0.045202	cg03921529	*MAP2K1*

-0.31274	0.045203	cg02730843	*LONP1*
-0.52293	0.045223	cg20250341	*RC3H2*
-0.30468	0.045359	cg10855395	*CKM*
0.42769	0.045372	cg19288752	*TFCP2*
0.214434	0.045972	cg02776315	*POLR2E*
0.318333	0.046357	cg04432599	*RPL11*
-0.25261	0.047957	cg19987540	*DPP9*
0.304856	0.048018	cg01098234	*NELFB*
-0.21861	0.048196	cg01098234	*WDR55*
0.638561	0.048626	cg12938020	*ZNF592*
-0.10228	0.048834	cg19558503	*BOK*
-0.13858	0.0489	cg19558503	*STK25*
-0.23964	0.048916	cg07452560	*HERC1*
0.280873	0.049226	cg18073883	*PODXL2*

Supplement Table S8 (B): Association of DNAm in females with neighboring gene expression (n=85)

coefficient	Pvalue	CpGs	Gene
1	0	cg22708914	*ALDH2*
-1.84314	3.01E-26	cg04720635	*CCDC7*
-0.92871	5.38E-10	cg04720635	*TP53INP2*
-0.68515	2.16E-09	cg04720635	*MAK16*
-1.36396	3.74E-09	cg04720635	*AQP3*
-0.40136	3.79E-08	cg04720635	*N4BP2L2*
-0.52683	2.73E-07	cg04720635	*SYNGAP1*
-0.49397	5.44E-07	cg04720635	*ANKRD27*
-0.72536	7.25E-07	cg04720635	*TMEM54*
0.840336	9.75E-07	cg04720635	*NCOA6*
-1.34463	1.60E-06	cg04720635	*RP9*
-0.65131	3.54E-06	cg02838492	*PI4K2A*
-0.42676	4.16E-06	cg04720635	*RFFL*
-0.50344	5.66E-06	cg04720635	*TDRD12*

0.587489	5.95E-06	cg04720635	*CEP89*
-0.56815	6.98E-06	cg04720635	*SMU1*
-0.39016	8.00E-06	cg04720635	*TARS*
-0.74814	1.28E-05	cg04720635	*GALNT1*
-1.18491	1.32E-05	cg02838492	*UBTD1*
-0.50754	1.88E-05	cg04720635	*MAP1LC3A*
0.390379	2.61E-05	cg06636625	*ABCF2*
-0.73341	3.17E-05	cg26580576	*DTX3*
-1.17144	4.50E-05	cg26580576	*REST*
0.471511	6.23E-05	cg01193064	*TRA2A*
0.325603	6.43E-05	cg04720635	*SYN3*
-0.73195	7.03E-05	cg24739326	*CDK5R1*
-0.6377	9.52E-05	cg26580576	*ARHGAP9*
-0.27891	0.000105	cg04720635	*B4GALT1*
-0.59596	0.000168	cg04720635	*RGS9BP*
-0.4995	0.000184	cg04720635	*B3GALT4*
-0.98188	0.000188	cg26580576	*KATNB1*
-1.42817	0.000214	cg26580576	*TUBD1*
0.387642	0.000222	cg16622920	*HOMER3*
-0.56075	0.000226	cg02838492	*IGF1R*
-0.71616	0.000247	cg02838492	*GJC3*
-0.44391	0.000258	cg09890200	*PGRMC1*
-0.90366	0.00034	cg26580576	*HEATR6*
0.499198	0.000388	cg16622920	*HAUS6*
-0.83463	0.000405	cg04115418	*C1orf159*
-0.6294	0.000425	cg04720635	*HPCA*
-0.40185	0.000509	cg04720635	*TMEM132E*
-0.81834	0.000511	cg09890200	*CCDC93*
-1.10276	0.00053	cg18694780	*NUTM2D*
0.214764	0.000533	cg04115418	*ACAP3*
-1.19829	0.00067	cg26580576	*NAA30*

-0.35857	0.0007	cg09890200	*SLC25A43*
-2.32443	0.000743	cg26580576	*ZNF17*
-0.36431	0.00076	cg04720635	*NUDT19*
-0.29356	0.000765	cg04720635	*HIPK3*
-0.22082	0.00081	cg10777851	*DGKQ*
-0.86713	0.000843	cg02838492	*NIPAL2*
-0.76008	0.001028	cg06988995	*TMEM126A*
0.344271	0.001087	cg01193064	*RAB36*
0.497102	0.001109	cg01193064	*PSMB11*
0.47927	0.001175	cg01193064	*BCL2L2*
-0.29947	0.001209	cg04720635	*CCT6B*
0.524536	0.001219	cg16622920	*ESCO1*
-1.46571	0.001224	cg26580576	*IGFBP7*
0.357738	0.001232	cg19807836	*CAB39L*
-0.57216	0.001248	cg26580576	*R3HDM2*
-0.66003	0.001273	cg26580576	*DENND6A*
0.442483	0.00133	cg20730619	*GLIPR1L2*
0.484364	0.001412	cg16622920	*SLC25A1*
0.507496	0.001453	cg01193064	*OTUD1*
-0.64229	0.001456	cg26580576	*SLMAP*
0.750972	0.001457	cg12527440	*ERAL1*
0.521893	0.001645	cg20730619	*PTPN9*
1.062825	0.001757	cg20171559	*NEDD4*
-0.37826	0.001844	cg22979546	*SLC43A3*
0.432398	0.001878	cg01193064	*SLC25A37*
0.532884	0.001954	cg14291650	*MYLK3*
-0.31981	0.00199	cg11846905	*PTCD3*
-0.52043	0.00225	cg26580576	*MBD6*
-1.70586	0.002321	cg26580576	*VMP1*
-0.29847	0.002378	cg10777851	*CLPTM1L*
-0.54449	0.00244	cg22824651	*IL17C*

-1.11884	0.002509	cg06513695	*ATF5*
1.559744	0.002608	cg02532113	*UQCRFS1*
-1.03303	0.002614	cg20171559	*CCDC106*
0.279936	0.002645	cg01193064	*KLHL29*
0.164094	0.002679	cg04080041	*PDXDC2P*
-1.2443	0.00274	cg02838492	*UNC50*
-0.44512	0.002848	cg24736380	*FASN*
0.308826	0.002929	cg01193064	*TCEA3*
-0.47778	0.00293	cg22824651	*PABPN1L*
-0.38477	0.002956	cg22824651	*NAA35*
0.438542	0.002959	cg16622920	*SNRPD1*
-0.65678	0.003099	cg26580576	*DDIT3*
0.339495	0.003119	cg20730619	*TBC1D4*
-0.49274	0.003204	cg04720635	*RP9P*
-0.31834	0.003246	cg11846905	*C9orf64*
-0.24168	0.003342	cg10777851	*MED16*
-0.60305	0.003388	cg06513695	*ATP9A*
-0.6217	0.003442	cg06513695	*BRD1*
0.489472	0.003583	cg14159342	*SERP2*
-0.88264	0.003615	cg26580576	*KIF5A*
-0.29281	0.003706	cg04720635	*SOD1*
-0.41132	0.003728	cg23796713	*ZUFSP*
-0.3268	0.003748	cg02838492	*STK3*
0.656275	0.00376	cg20730619	*TMC8*
-0.42671	0.003772	cg06513695	*HDC*
0.450003	0.003813	cg18244483	*NBPF20*
-0.38308	0.003843	cg22824651	*MRPL46*
0.853802	0.003888	cg20730619	*UCHL3*
-0.73198	0.004092	cg06513695	*TRABD*
0.328563	0.004385	cg14291650	*SLC19A1*
-0.27819	0.004539	cg24736380	*GNAQ*

-0.3281	0.004655	cg22979546	*HESX1*
-0.63368	0.004909	cg06513695	*BCDIN3D*
0.596475	0.00494	cg16622920	*SUGP1*
0.519597	0.005093	cg01193064	*HERC2P2*
0.312492	0.005229	cg14291650	*SLC38A2*
0.42554	0.005231	cg09890200	*PEBP1*
0.286408	0.005348	cg14291650	*TMIE*
0.271596	0.005396	cg19807836	*RPS11*
0.874766	0.005586	cg11586330	*MSANTD4*
-0.34482	0.005678	cg11846905	*ARHGAP24*
0.779407	0.005798	cg02532113	*PRKD1*
0.500254	0.005901	cg16622920	*CXADR*
-0.34291	0.005972	cg06365057	*RNF14*
0.193811	0.006071	cg04080041	*FADD*
-1.74059	0.006124	cg26580576	*ZNF548*
-0.35474	0.006241	cg17339484	*AIF1*
-0.26228	0.006512	cg24739326	*GTF2E2*
-0.21227	0.006598	cg10777851	*KLHL17*
-1.05141	0.006651	cg26580576	*GAPT*
-0.15791	0.006657	cg10777851	*SLC26A1*
-0.417	0.006828	cg24739326	*GARS*
0.354519	0.006921	cg16622920	*TMEM161A*
-0.3704	0.007079	cg22824651	*SNCG*
-0.34678	0.007099	cg02838492	*STK24*
-0.65541	0.007165	cg04115418	*GNPTG*
-1.01026	0.007177	cg26580576	*TSPAN31*
0.435034	0.007227	cg04720635	*CSTF3*
-0.37978	0.007279	cg18694780	*ATAD1*
-0.21775	0.007311	cg24739326	*LBH*
0.55388	0.007314	cg14291650	*UQCRH*
0.443712	0.007405	cg01193064	*MMP14*

-0.22834	0.007466	cg04720635	*LTBP1*
0.426858	0.007768	cg21330703	*RCBTB1*
0.346618	0.008035	cg01193064	*PLK1*
0.567631	0.008237	cg19807836	*IFRD2*
0.230177	0.008309	cg19807836	*ADCY7*
-0.32496	0.008372	cg10527525	*TIFA*
-0.98879	0.008403	cg26580576	*PTRH2*
-0.50138	0.008747	cg04720635	*YARS*
0.262436	0.008779	cg20730619	*PARM1*
-0.78379	0.008962	cg24736380	*CD36*
0.351979	0.009015	cg20730619	*ANXA1*
0.25268	0.009051	cg22979546	*AASDH*
0.136669	0.00911	cg16287252	*CD248*
-0.23592	0.009138	cg11846905	*KIF27*
0.286993	0.009251	cg16622920	*DDX49*
0.926577	0.009323	cg20730619	*YWHAG*
0.294573	0.009556	cg01193064	*NDUFAB1*
0.270142	0.009596	cg15761799	*MUL1*
0.284098	0.009649	cg14159342	*MYO1G*
0.386604	0.00967	cg00740870	*ERCC4*
-0.78523	0.009706	cg06513695	*C3orf18*
0.296552	0.009882	cg16622920	*SLC24A3*
0.354824	0.009925	cg16622920	*ARL5B*
-0.41919	0.009992	cg22979546	*APPL1*
0.515561	0.009997	cg20730619	*TK1*
-0.23875	0.010015	cg11846905	*ST3GAL5*
-0.40974	0.010069	cg22979546	*PRIM1*
0.388256	0.010585	cg18393722	*C15orf54*
0.255224	0.010737	cg15001132	*ACOT7*
0.849561	0.010923	cg02532113	*INO80E*
0.882336	0.010977	cg02532113	*MEP1B*

0.49741	0.011148	cg06589109	*ACOT7*
-0.3992	0.011219	cg24739326	*TM9SF4*
-0.43074	0.011441	cg06513695	*HYAL2*
-0.76754	0.011551	cg04720635	*ZBTB9*
-0.84437	0.01174	cg18694780	*GAS1*
0.106386	0.011782	cg04080041	*RUFY2*
-0.16269	0.012005	cg10777851	*TMED11P*
-1.05891	0.012135	cg22824651	*ZCCHC6*
0.558831	0.012209	cg20730619	*SNX33*
0.080169	0.012228	cg23844910	*DNAJC5*
2.036127	0.012293	cg26580576	*ZNF543*
-0.20701	0.012656	cg07629844	*CIB2*
-0.29832	0.012752	cg24739326	*GOLGA8H*
-0.48265	0.01323	cg22824651	*EIF2AK3*
0.000145	0.013346	cg00530448	*KIF13B*
0.397468	0.013361	cg01193064	*RPS2P32*
-0.35522	0.01337	cg10527525	*NAA50*
0.507878	0.013482	cg20730619	*COMMD6*
-0.35376	0.013506	cg22824651	*PIEZO1*
-0.19946	0.013591	cg11586330	*AASDHPPT*
0.316756	0.013825	cg19807836	*CYB561D2*
-0.25488	0.013958	cg22979546	*RDH16*
1.162678	0.014149	cg25404454	*STMN3*
0.282004	0.014359	cg19807836	*POLE2*
0.284202	0.014402	cg16622920	*MIB1*
0.207257	0.014481	cg14159342	*PDXK*
-0.35555	0.015142	cg09890200	*SPAG17*
-0.21177	0.015546	cg04720635	*RPS18*
0.357776	0.01566	cg04080041	*GMCL1*
0.231827	0.015675	cg24739326	*KATNAL1*
0.528471	0.015908	cg11970192	*DUS4L*

0.473624	0.015927	cg01193064	*CCDC126*
-0.40131	0.01611	cg26580576	*CLTC*
-0.50761	0.016725	cg04720635	*DNAJA1*
0.211879	0.017003	cg14291650	*C18orf32*
-0.37462	0.017316	cg06988995	*TMSB10*
-0.47355	0.017695	cg26580576	*RPS6KB1*
0.243977	0.018166	cg01193064	*CEBPE*
-0.54173	0.018314	cg15096549	*GTF3C3*
0.244578	0.018432	cg16622920	*SYT17*
-0.72355	0.018504	cg07823273	*TUBBP5*
-0.42304	0.01873	cg02838492	*MARVELD1*
-0.66386	0.018852	cg18694780	*EML5*
0.429423	0.018974	cg11970192	*RIC8B*
0.355851	0.019306	cg12527440	*JAM2*
-0.63529	0.01966	cg18844144	*ZFYVE26*
0.430239	0.01983	cg15371806	*TCP10L*
0.42571	0.020194	cg17125699	*SYNPO2*
0.244179	0.020501	cg14714391	*CENPQ*
-0.41325	0.020707	cg24736380	*GNA14*
-0.27218	0.021039	cg11846905	*FRMD3*
0.067367	0.021085	cg04080041	*AARS*
-0.36601	0.02135	cg06988995	*KIAA0513*
0.144738	0.021364	cg16287252	*KPNA2*
-0.36341	0.02168	cg22979546	*PLLP*
-0.21095	0.02172	cg10527525	*ATP6V1A*
0.331229	0.022103	cg12527440	*PLAA*
-0.39757	0.022127	cg22824651	*CDT1*
-0.32309	0.022162	cg25989745	*ANKDD1A*
0.503301	0.022531	cg06513695	*MAPKAPK3*
-0.26218	0.022626	cg06365057	*GRK7*
-0.31824	0.022791	cg24736380	*RFNG*

-0.48466	0.023118	cg04720635	*AQP7*
0.556316	0.023135	cg24739326	*TTLL9*
0.097188	0.023432	cg04080041	*ANXA4*
-0.32046	0.023822	cg18694780	*GBP1*
0.309236	0.023873	cg14291650	*CDPF1*
0.583916	0.024018	cg20730619	*GLIPR1*
-0.37544	0.024153	cg24736380	*RASGRF2*
-0.34104	0.024263	cg10527525	*CKAP2L*
-0.20731	0.024281	cg10527525	*PPM1J*
0.297208	0.024402	cg20730619	*S100Z*
-0.47992	0.025638	cg22979546	*ARHGEF3*
-0.27157	0.025704	cg04466022	*ABCB7*
0.054705	0.025749	cg23844910	*SPIN4*
-0.30899	0.025774	cg22824651	*GALNS*
-0.2054	0.026081	cg24736380	*DCXR*
0.278054	0.026191	cg00740870	*TCEANC*
0.459454	0.02707	cg01193064	*IGF2BP3*
0.763397	0.027459	cg17339484	*ELP4*
0.181952	0.027482	cg16622920	*KCNH8*
-0.23177	0.027639	cg06365057	*ARAP3*
0.275103	0.027736	cg14159342	*KLHL28*
0.318215	0.028031	cg00740870	*OFD1*
0.2985	0.028234	cg14291650	*DYM*
0.515631	0.028356	cg06589109	*FAM64A*
-0.62757	0.028442	cg06513695	*KLHDC1*
0.131312	0.028974	cg06730718	*ACADSB*
-0.50837	0.029047	cg02838492	*TSPAN5*
-0.41087	0.029084	cg09890200	*TAOK3*
0.226585	0.02913	cg14291650	*HARBI1*
1.134213	0.029582	cg02532113	*IFITM4P*
0.605944	0.029618	cg22979546	*VAPB*

0.11545	0.029721	cg04080041	*ERH*
-0.24855	0.029733	cg24739326	*SEC14L2*
-0.4458	0.029763	cg06513695	*CACNA2D2*
0.3558	0.029835	cg14291650	*F2*
-0.17705	0.030132	cg10777851	*IDI1*
0.133393	0.030451	cg16287252	*TMEM248*
0.66018	0.030784	cg17339484	*PISD*
-0.33286	0.031262	cg22329021	*MRPL54*
0.248693	0.031427	cg16825643	*RNF219*
0.372488	0.031516	cg19807836	*HEATR3*
0.622309	0.031651	cg04115418	*PUSL1*
-0.19055	0.032105	cg07629844	*FUBP1*
-0.29996	0.032403	cg11846905	*CA2*
0.483288	0.032738	cg15371806	*FER1L4*
0.343301	0.032914	cg12527440	*PDSS1*
0.222466	0.032919	cg01193064	*MSRB2*
-0.1293	0.032966	cg04720635	*BRCA2*
-0.21429	0.033323	cg04720635	*CCR4*
0.301528	0.033563	cg20730619	*KRR1*
-0.18065	0.033692	cg10777851	*AURKAIP1*
0.174985	0.033845	cg11990770	*TMEM40*
0.132406	0.033999	cg14291650	*C16orf87*
-0.54628	0.034012	cg06513695	*NCKAP5L*
0.088573	0.034018	cg23844910	*TLN2*
-0.18379	0.034299	cg07629844	*JMY*
-0.25089	0.034503	cg22979546	*CPNE2*
-0.33433	0.034506	cg22824651	*TMTC3*
0.309315	0.034636	cg16622920	*MAP3K15*
-0.61869	0.034637	cg18694780	*GBP3*
0.367129	0.03533	cg19807836	*HYAL1*
0.428049	0.035466	cg20730619	*MRPL19*

0.64903	0.035714	cg20730619	*TTLL5*
-0.64208	0.03603	cg26647291	*PIGU*
0.257782	0.036266	cg04115418	*PSMF1*
-0.32239	0.036387	cg25989745	*CDC42EP2*
0.248115	0.036505	cg00740870	*ESF1*
-0.63924	0.036878	cg24736380	*ASPSCR1*
0.310499	0.036992	cg01193064	*PPP1R3E*
-0.41863	0.037003	cg06513695	*SIGLEC16*
0.272192	0.037044	cg18844144	*FAM19A1*
0.182417	0.037271	cg14291650	*NSUN4*
0.179698	0.037551	cg20983032	*ADAMTS1*
0.204681	0.037617	cg16287252	*RIN1*
-0.43731	0.037659	cg16622920	*SMG1*
-0.57993	0.03775	cg11990770	*ZNF563*
-0.15316	0.037823	cg10777851	*GTPBP4*
-0.3919	0.03795	cg22979546	*SERPING1*
-0.09677	0.038003	cg15001132	*ALOX12P2*
0.330104	0.038189	cg17125699	*C4orf3*
-0.31301	0.038307	cg24739326	*PDRG1*
-0.22763	0.038468	cg16622920	*PLIN2*
-0.27749	0.038721	cg09890200	*DDX6*
0.397485	0.038899	cg20730619	*C17orf99*
-0.38125	0.039205	cg04017131	*ZNF703*
0.163569	0.039313	cg11990770	*APOLD1*
-0.18756	0.03943	cg04017131	*ELFN2*
-0.31338	0.039651	cg11990770	*MKRN2*
0.257323	0.040243	cg12527440	*CDK8*
-0.04838	0.040667	cg04017131	*ACTR5*
0.22413	0.04124	cg04720635	*LIG3*
-0.22538	0.041313	cg22979546	*RTN4RL2*
0.66399	0.041416	cg25404454	*KHDRBS2*

-0.28947	0.041685	cg11990770	*PSMG2*
-0.26993	0.042036	cg02122376	*ANKRD16*
0.169541	0.04225	cg23844910	*WDR74*
0.258433	0.042287	cg14291650	*FAAH*
0.22371	0.042408	cg22979546	*BAZ2A*
0.155575	0.042809	cg15761799	*ACSM1*
0.215838	0.043236	cg14159342	*TMEM42*
-0.3948	0.043269	cg15096549	*HECW2*
-0.16838	0.043416	cg16622920	*SH2D4A*
-0.2305	0.043676	cg10777851	*SBNO2*
-0.12924	0.043964	cg19807836	*ALG12*
-0.37991	0.044097	cg10777851	*NOC2L*
-0.17697	0.044195	cg10527525	*C4orf32*
-0.43414	0.044216	cg11990770	*ARHGAP44*
0.319814	0.044277	cg16622920	*DGCR2*
-0.21387	0.044428	cg24739326	*SF3A1*
-0.24885	0.044611	cg18244483	*RHPN1*
-0.25582	0.04472	cg22824651	*CBFA2T3*
0.248456	0.044733	cg04080041	*EXOSC6*
0.130623	0.044908	cg04017131	*FBXO10*
-0.39309	0.04535	cg15761799	*UBXN10*
0.333617	0.046207	cg14291650	*TTC38*
-0.29081	0.046928	cg25989745	*EHBP1L1*
-0.21767	0.046981	cg24739326	*IPO8*
-0.52642	0.047215	cg26580576	*DCTN2*
0.116341	0.047747	cg07629844	*ACSBG1*
-0.39334	0.047986	cg02122376	*TRIM22*
0.222503	0.048405	cg14159342	*IGSF23*
1.356835	0.048449	cg02532113	*ZFP57*
-0.15664	0.048789	cg10777851	*GRIN3B*
-0.16528	0.048829	cg10527525	*DTX1*

-0.9938	0.049796	cg11990770	*MANSC1*
0.320261	0.049835	cg02054358	*PYGB*

Supplement Table S9 (A): Statistically significant GO terms and its biological processes from pathway enrichment analysis in each pathway for males, for the identified CpGs.

GO term	Biological Processes	N#	Raw p value
GO:0045116	protein neddylation	16	0.002
GO:0033622	integrin activation	21	0.004
GO:0045956	positive regulation of calcium ion-dependent exocytosis	19	0.004
GO:1905078	positive regulation of interleukin-17 secretion	2	0.004
GO:0008049	male courtship behavior	1	0.004
GO:0042407	cristae formation	31	0.005
GO:0006393	termination of mitochondrial transcription	2	0.006
GO:1904235	regulation of substrate-dependent cell migration, cell attachment to substrate	1	0.006
GO:1904237	positive regulation of substrate-dependent cell migration, cell attachment to substrate	1	0.006
GO:0002636	positive regulation of germinal center formation	3	0.007
GO:1902631	negative regulation of membrane hyperpolarization	1	0.007
GO:0015828	tyrosine transport	1	0.008
GO:0007007	inner mitochondrial membrane organization	41	0.008
GO:2001202	negative regulation of transforming growth factor-beta secretion	2	0.008
GO:0031296	B cell costimulation	3	0.009
GO:0006887	exocytosis	892	0.009
GO:0099093	calcium export from the mitochondrion	2	0.011
GO:1902630	regulation of membrane hyperpolarization	3	0.011
GO:2001201	regulation of transforming growth factor-beta secretion	3	0.012
GO:0006726	eye pigment biosynthetic process	3	0.012
GO:0042441	eye pigment metabolic process	3	0.012
GO:0043324	pigment metabolic process involved in developmental pigmentation	3	0.012
GO:0043474	pigment metabolic process involved in pigmentation	3	0.012

GO:2000435	negative regulation of protein neddylation	3	0.012
GO:0055085	transmembrane transport	1565	0.012
GO:0021935	cerebellar granule cell precursor tangential migration	2	0.012
GO:0045055	regulated exocytosis	785	0.012
GO:0051562	negative regulation of mitochondrial calcium ion concentration	4	0.013
GO:0060743	epithelial cell maturation involved in prostate gland development	3	0.013
GO:1905407	regulation of creatine transmembrane transporter activity	2	0.013
GO:1905408	negative regulation of creatine transmembrane transporter activity	2	0.013
GO:0046903	secretion	1639	0.014
GO:1905076	regulation of interleukin-17 secretion	5	0.014
GO:0051048	negative regulation of secretion	235	0.014
GO:0006931	substrate-dependent cell migration, cell attachment to substrate	4	0.015
GO:2000434	regulation of protein neddylation	4	0.015
GO:1904381	Golgi apparatus mannose trimming	3	0.015
GO:0071470	cellular response to osmotic stress	40	0.015
GO:0010701	positive regulation of norepinephrine secretion	4	0.017
GO:0023016	signal transduction by trans-phosphorylation	3	0.017
GO:0021934	hindbrain tangential cell migration	3	0.018
GO:0007619	courtship behavior	3	0.018
GO:0038165	oncostatin-M-mediated signaling pathway	4	0.018
GO:0038044	transforming growth factor-beta secretion	5	0.018
GO:1900069	regulation of cellular hyperosmotic salinity response	4	0.018
GO:1901000	regulation of response to salt stress	4	0.018
GO:2001268	negative regulation of cysteine-type endopeptidase activity involved in apoptotic signaling pathway	6	0.018
GO:0017158	regulation of calcium ion-dependent exocytosis	43	0.020
GO:0035987	endodermal cell differentiation	45	0.020
GO:0071526	semaphorin-plexin signaling pathway	40	0.022
GO:0072615	interleukin-17 secretion	7	0.022
GO:0036438	maintenance of lens transparency	4	0.022

GO:0007341	penetration of zona pellucida	8	0.022
GO:0038146	chemokine (C-X-C motif) ligand 12 signaling pathway	4	0.023
GO:2000649	regulation of sodium ion transmembrane transporter activity	51	0.023
GO:1903532	positive regulation of secretion by cell	398	0.023
GO:2000671	regulation of motor neuron apoptotic process	5	0.024
GO:0043615	astrocyte cell migration	7	0.024
GO:0001706	endoderm formation	50	0.024
GO:0007161	calcium-independent cell-matrix adhesion	4	0.025
GO:1903307	positive regulation of regulated secretory pathway	52	0.025
GO:0006689	ganglioside catabolic process	6	0.025
GO:0090188	negative regulation of pancreatic juice secretion	5	0.026
GO:2000697	negative regulation of epithelial cell differentiation involved in kidney development	5	0.027
GO:0050433	regulation of catecholamine secretion	62	0.028
GO:0090186	regulation of pancreatic juice secretion	6	0.028
GO:0036089	cleavage furrow formation	7	0.029
GO:0046888	negative regulation of hormone secretion	63	0.029
GO:0071475	cellular hyperosmotic salinity response	7	0.030
GO:1900454	positive regulation of long-term synaptic depression	6	0.030
GO:0051047	positive regulation of secretion	423	0.030
GO:0050432	catecholamine secretion	64	0.030
GO:0007605	sensory perception of sound	143	0.031
GO:1902305	regulation of sodium ion transmembrane transport	61	0.033
GO:0097049	motor neuron apoptotic process	7	0.034
GO:0050707	regulation of cytokine secretion	204	0.035
GO:0008360	regulation of cell shape	150	0.035
GO:0048069	eye pigmentation	8	0.035
GO:0060155	platelet dense granule organization	8	0.035
GO:0060526	prostate glandular acinus morphogenesis	6	0.036
GO:0060527	prostate epithelial cord arborization involved in prostate glandular acinus morphogenesis	6	0.036

GO:0060179	male mating behavior	8	0.036
GO:1901166	neural crest cell migration involved in autonomic nervous system development	6	0.037
GO:1903305	regulation of regulated secretory pathway	158	0.037
GO:0021957	corticospinal tract morphogenesis	7	0.038
GO:1990542	mitochondrial transmembrane transport	88	0.038
GO:0032413	negative regulation of ion transmembrane transporter activity	76	0.039
GO:0002634	regulation of germinal center formation	9	0.040
GO:0032940	secretion by cell	1509	0.041
GO:0042340	keratan sulfate catabolic process	12	0.041
GO:0017156	calcium-ion regulated exocytosis	65	0.041
GO:0071476	cellular hypotonic response	8	0.042
GO:0060159	regulation of dopamine receptor signaling pathway	11	0.043
GO:1901660	calcium ion export	11	0.043
GO:0015849	organic acid transport	330	0.043
GO:0051937	catecholamine transport	77	0.044
GO:0001867	complement activation, lectin pathway	13	0.044
GO:0050954	sensory perception of mechanical stimulus	162	0.044
GO:0106049	regulation of cellular response to osmotic stress	10	0.045
GO:0060992	response to fungicide	11	0.045
GO:0007270	neuron-neuron synaptic transmission	8	0.045
GO:0015801	aromatic amino acid transport	10	0.046
GO:0018026	peptidyl-lysine monomethylation	10	0.046
GO:0042538	hyperosmotic salinity response	12	0.046
GO:0046479	glycosphingolipid catabolic process	14	0.048
GO:0030150	protein import into mitochondrial matrix	17	0.048
GO:0140352	export from cell	1553	0.049
GO:0099527	postsynapse to nucleus signaling pathway	9	0.049
GO:0030157	pancreatic juice secretion	12	0.050
GO:1903531	negative regulation of secretion by cell	209	0.050

Note: #N: Number of genes involved in the respective pathways

Supplement Table S9 (B): Statistically significant GO terms and its biological processes from pathway enrichment analysis in each pathway for females, for the identified CpGs.

GO term	Biological Processes	N#	Raw p value
GO:0014834	skeletal muscle satellite cell maintenance involved in skeletal muscle regeneration	4	0.001
GO:0035264	multicellular organism growth	146	0.001
GO:0001678	cellular glucose homeostasis	151	0.002
GO:0089718	amino acid import across plasma membrane	23	0.002
GO:0071499	cellular response to laminar fluid shear stress	8	0.002
GO:0035902	response to immobilization stress	27	0.003
GO:0043090	amino acid import	26	0.003
GO:1904491	protein localization to ciliary transition zone	8	0.003
GO:0060563	neuroepithelial cell differentiation	53	0.003
GO:0046324	regulation of glucose import	60	0.003
GO:0001542	ovulation from ovarian follicle	9	0.003
GO:1990668	vesicle fusion with endoplasmic reticulum-Golgi intermediate compartment (ERGIC) membrane	6	0.003
GO:0046466	membrane lipid catabolic process	34	0.004
GO:0046323	glucose import	68	0.005
GO:2000785	regulation of autophagosome assembly	35	0.005
GO:0070914	UV-damage excision repair	13	0.005
GO:0042491	inner ear auditory receptor cell differentiation	32	0.006
GO:1904425	negative regulation of GTP binding	2	0.006
GO:0009650	UV protection	13	0.007
GO:0010827	regulation of glucose transmembrane transport	78	0.007
GO:0046326	positive regulation of glucose import	38	0.008
GO:0033388	putrescine biosynthetic process from arginine	1	0.008
GO:0033389	putrescine biosynthetic process from arginine, using agmatinase	1	0.008
GO:0007292	female gamete generation	133	0.008

GO:0044088	regulation of vacuole organization	42	0.008
GO:0098712	L-glutamate import across plasma membrane	13	0.008
GO:0045779	negative regulation of bone resorption	13	0.009
GO:0019377	glycolipid catabolic process	16	0.009
GO:0006004	fucose metabolic process	16	0.009
GO:0120222	regulation of blastocyst development	1	0.009
GO:1904073	regulation of trophectodermal cell proliferation	1	0.009
GO:1904075	positive regulation of trophectodermal cell proliferation	1	0.009
GO:0042668	auditory receptor cell fate determination	1	0.010
GO:0045609	positive regulation of inner ear auditory receptor cell differentiation	1	0.010
GO:0045633	positive regulation of mechanoreceptor differentiation	1	0.010
GO:2000982	positive regulation of inner ear receptor cell differentiation	1	0.010
GO:0002065	columnar/cuboidal epithelial cell differentiation	112	0.010
GO:0051938	L-glutamate import	14	0.010
GO:0010828	positive regulation of glucose transmembrane transport	44	0.011
GO:0035315	hair cell differentiation	40	0.011
GO:0032812	positive regulation of epinephrine secretion	2	0.011
GO:0050435	amyloid-beta metabolic process	47	0.011
GO:0033342	negative regulation of collagen binding	1	0.012
GO:0016052	carbohydrate catabolic process	196	0.012
GO:1901255	nucleotide-excision repair involved in interstrand cross-link repair	2	0.012
GO:0051691	cellular oligosaccharide metabolic process	2	0.012
GO:0051692	cellular oligosaccharide catabolic process	2	0.012
GO:0046851	negative regulation of bone remodeling	15	0.012
GO:0034616	response to laminar fluid shear stress	15	0.012
GO:0010560	positive regulation of glycoprotein biosynthetic process	20	0.013
GO:0002537	nitric oxide production involved in inflammatory response	2	0.013
GO:0006112	energy reserve metabolic process	86	0.013
GO:1903435	positive regulation of constitutive secretory pathway	1	0.014

GO:0002542	Factor XII activation	2	0.014
GO:0008643	carbohydrate transport	148	0.014
GO:0030728	ovulation	20	0.014
GO:0033140	negative regulation of peptidyl-serine phosphorylation of STAT protein	2	0.015
GO:0060766	negative regulation of androgen receptor signaling pathway	15	0.015
GO:0001505	regulation of neurotransmitter levels	353	0.015
GO:0042593	glucose homeostasis	237	0.015
GO:0034063	stress granule assembly	19	0.015
GO:0033500	carbohydrate homeostasis	238	0.015
GO:0030316	osteoclast differentiation	97	0.016
GO:0071333	cellular response to glucose stimulus	132	0.016
GO:0034755	iron ion transmembrane transport	20	0.016
GO:0045167	asymmetric protein localization involved in cell fate determination	1	0.016
GO:0002038	positive regulation of L-glutamate import across plasma membrane	2	0.016
GO:1903428	positive regulation of reactive oxygen species biosynthetic process	54	0.017
GO:0071331	cellular response to hexose stimulus	134	0.017
GO:0006293	nucleotide-excision repair, preincision complex stabilization	20	0.017
GO:0006295	nucleotide-excision repair, DNA incision, 3'-to lesion	20	0.017
GO:0071326	cellular response to monosaccharide stimulus	135	0.017
GO:0006525	arginine metabolic process	20	0.017
GO:1902631	negative regulation of membrane hyperpolarization	1	0.017
GO:1903020	positive regulation of glycoprotein metabolic process	24	0.018
GO:0001834	trophectodermal cell proliferation	2	0.018
GO:0039502	suppression by virus of host type I interferon-mediated signaling pathway	1	0.018
GO:0039503	suppression by virus of host innate immune response	1	0.018
GO:0039514	suppression by virus of host JAK-STAT cascade	1	0.018
GO:0039562	suppression by virus of host STAT activity	1	0.018
GO:0039563	suppression by virus of host STAT1 activity	1	0.018
GO:0039564	suppression by virus of host STAT2 activity	1	0.018

GO:0044414	suppression of host defenses by symbiont	1	0.018
GO:0052029	suppression by symbiont of host signal transduction pathway	1	0.018
GO:0052031	modulation by symbiont of host defense response	1	0.018
GO:0052167	modulation by symbiont of host innate immune response	1	0.018
GO:0052170	suppression by symbiont of host innate immune response	1	0.018
GO:0052553	modulation by symbiont of host immune response	1	0.018
GO:0052562	suppression by symbiont of host immune response	1	0.018
GO:0052572	response to host immune response	1	0.018
GO:0075109	modulation by symbiont of host receptor-mediated signal transduction	1	0.018
GO:0075111	suppression by symbiont of host receptor-mediated signal transduction	1	0.018
GO:0075112	modulation by symbiont of host transmembrane receptor-mediated signal transduction	1	0.018
GO:0075114	suppression by symbiont of host transmembrane receptor-mediated signal transduction	1	0.018
GO:0075528	modulation by virus of host immune response	1	0.018
GO:0043316	cytotoxic T cell degranulation	3	0.018
GO:0010506	regulation of autophagy	325	0.018
GO:0044026	DNA hypermethylation	2	0.019
GO:1902475	L-alpha-amino acid transmembrane transport	53	0.019
GO:0060370	susceptibility to T cell mediated cytotoxicity	2	0.019
GO:0071498	cellular response to fluid shear stress	21	0.019
GO:0002018	renin-angiotensin regulation of aldosterone production	4	0.019
GO:0097055	agmatine biosynthetic process	2	0.019
GO:0032625	interleukin-21 production	1	0.020
GO:0072619	interleukin-21 secretion	1	0.020
GO:1902913	positive regulation of neuroepithelial cell differentiation	2	0.020
GO:0040032	post-embryonic body morphogenesis	1	0.020
GO:0071409	cellular response to cycloheximide	3	0.020
GO:0045670	regulation of osteoclast differentiation	64	0.020
GO:0006091	generation of precursor metabolites and energy	517	0.020
GO:0042667	auditory receptor cell fate specification	2	0.020

GO:0033341	regulation of collagen binding	2	0.020
GO:0071467	cellular response to pH	23	0.020
GO:0071322	cellular response to carbohydrate stimulus	143	0.021
GO:0097532	stress response to acid chemical	3	0.021
GO:0097533	cellular stress response to acid chemical	3	0.021
GO:1904659	glucose transmembrane transport	108	0.021
GO:0070911	global genome nucleotide-excision repair	25	0.021
GO:0051919	positive regulation of fibrinolysis	4	0.021
GO:1903433	regulation of constitutive secretory pathway	2	0.022
GO:0034104	negative regulation of tissue remodeling	20	0.022
GO:0002254	kinin cascade	3	0.022
GO:0002353	plasma kallikrein-kinin cascade	3	0.022
GO:0060283	negative regulation of oocyte development	4	0.023
GO:1905880	negative regulation of oogenesis	4	0.023
GO:0045821	positive regulation of glycolytic process	23	0.023
GO:0008645	hexose transmembrane transport	112	0.023
GO:0045671	negative regulation of osteoclast differentiation	27	0.023
GO:0014036	neural crest cell fate specification	2	0.024
GO:0001582	detection of chemical stimulus involved in sensory perception of sweet taste	2	0.024
GO:0002541	activation of plasma proteins involved in acute inflammatory response	3	0.025
GO:0015749	monosaccharide transmembrane transport	114	0.025
GO:0009441	glycolate metabolic process	3	0.025
GO:0048791	calcium ion-regulated exocytosis of neurotransmitter	21	0.025
GO:0015813	L-glutamate transmembrane transport	23	0.025
GO:0014737	positive regulation of muscle atrophy	2	0.025
GO:0098968	neurotransmitter receptor transport postsynaptic membrane to endosome	2	0.026
GO:0061789	dense core granule priming	3	0.026
GO:0060113	inner ear receptor cell differentiation	56	0.026
GO:0006096	glycolytic process	112	0.026

GO:0034219	carbohydrate transmembrane transport	116	0.026
GO:0001544	initiation of primordial ovarian follicle growth	2	0.027
GO:0046903	secretion	1639	0.027
GO:0006757	ATP generation from ADP	113	0.027
GO:1990145	maintenance of translational fidelity	2	0.027
GO:0061819	telomeric DNA-containing double minutes formation	3	0.027
GO:1905764	regulation of protection from non-homologous end joining at telomere	3	0.027
GO:1905765	negative regulation of protection from non-homologous end joining at telomere	3	0.027
GO:0000710	meiotic mismatch repair	3	0.027
GO:0043153	entrainment of circadian clock by photoperiod	21	0.027
GO:0009605	response to external stimulus	2669	0.028
GO:0061470	T follicular helper cell differentiation	4	0.028
GO:0006914	autophagy	492	0.028
GO:0061919	process utilizing autophagic mechanism	492	0.028
GO:1904431	positive regulation of t-circle formation	4	0.029
GO:1902630	regulation of membrane hyperpolarization	3	0.029
GO:0002761	regulation of myeloid leukocyte differentiation	117	0.029
GO:1903409	reactive oxygen species biosynthetic process	119	0.029
GO:0008594	photoreceptor cell morphogenesis	3	0.030
GO:0071386	cellular response to corticosterone stimulus	3	0.030
GO:0044501	modulation of signal transduction in other organism	2	0.030
GO:0052027	modulation by symbiont of host signal transduction pathway	2	0.030
GO:1904891	positive regulation of excitatory synapse assembly	3	0.031
GO:0046898	response to cycloheximide	4	0.031
GO:0042698	ovulation cycle	69	0.031
GO:1905384	regulation of protein localization to presynapse	2	0.031
GO:1905386	positive regulation of protein localization to presynapse	2	0.031
GO:0050729	positive regulation of inflammatory response	152	0.032
GO:0046834	lipid phosphorylation	64	0.032

GO:1903861	positive regulation of dendrite extension	22	0.032
GO:0039506	modulation by virus of host molecular function	2	0.032
GO:0039507	suppression by virus of host molecular function	2	0.032
GO:0052055	modulation by symbiont of host molecular function	2	0.032
GO:0052056	negative regulation by symbiont of host molecular function	2	0.032
GO:1990834	response to odorant	4	0.032
GO:0010157	response to chlorate	2	0.033
GO:0006826	iron ion transport	75	0.033
GO:0070253	somatostatin secretion	4	0.033
GO:0050727	regulation of inflammatory response	368	0.033
GO:0042490	mechanoreceptor differentiation	61	0.033
GO:0015807	L-amino acid transport	67	0.033
GO:0031347	regulation of defense response	685	0.034
GO:0046031	ADP metabolic process	121	0.034
GO:0032849	positive regulation of cellular pH reduction	4	0.034
GO:0005975	carbohydrate metabolic process	610	0.034
GO:0000720	pyrimidine dimer repair by nucleotide-excision repair	4	0.035
GO:0035166	post-embryonic hemopoiesis	3	0.035
GO:0010508	positive regulation of autophagy	119	0.035
GO:0009648	photoperiodism	25	0.035
GO:1905460	negative regulation of vascular associated smooth muscle cell apoptotic process	7	0.035
GO:0032940	secretion by cell	1509	0.036
GO:2000828	regulation of parathyroid hormone secretion	2	0.036
GO:0060765	regulation of androgen receptor signaling pathway	26	0.036
GO:0009743	response to carbohydrate	229	0.036
GO:1903859	regulation of dendrite extension	24	0.037
GO:0006836	neurotransmitter transport	268	0.037
GO:0098706	iron ion import across cell outer membrane	3	0.037
GO:1990785	response to water-immersion restraint stress	4	0.037

GO:2001025	positive regulation of response to drug	33	0.037
GO:0033137	negative regulation of peptidyl-serine phosphorylation	27	0.038
GO:0006517	protein deglycosylation	29	0.038
GO:1903530	regulation of secretion by cell	749	0.038
GO:0015800	acidic amino acid transport	66	0.039
GO:0071787	endoplasmic reticulum tubular network formation	4	0.039
GO:1901300	positive regulation of hydrogen peroxide-mediated programmed cell death	5	0.039
GO:0046942	carboxylic acid transport	328	0.039
GO:1990809	endoplasmic reticulum tubular network membrane organization	4	0.039
GO:0006526	arginine biosynthetic process	5	0.039
GO:0097638	L-arginine import across plasma membrane	4	0.039
GO:0006110	regulation of glycolytic process	77	0.039
GO:0048147	negative regulation of fibroblast proliferation	30	0.040
GO:0006165	nucleoside diphosphate phosphorylation	131	0.040
GO:0030683	mitigation of host immune response by virus	3	0.040
GO:0010260	animal organ senescence	3	0.041
GO:0009649	entrainment of circadian clock	27	0.041
GO:0015849	organic acid transport	330	0.041
GO:0034644	cellular response to UV	81	0.041
GO:0070093	negative regulation of glucagon secretion	5	0.041
GO:0060066	oviduct development	3	0.042
GO:0044821	meiotic telomere tethering at nuclear periphery	5	0.042
GO:0070197	meiotic attachment of telomere to nuclear envelope	5	0.042
GO:0097240	chromosome attachment to the nuclear envelope	5	0.042
GO:0046939	nucleotide phosphorylation	133	0.042
GO:1904505	regulation of telomere maintenance in response to DNA damage	4	0.043
GO:1904506	negative regulation of telomere maintenance in response to DNA damage	4	0.043
GO:0005977	glycogen metabolic process	73	0.043
GO:0006073	cellular glucan metabolic process	74	0.043

GO:0044042	glucan metabolic process	74	0.043
GO:0002860	positive regulation of natural killer cell mediated cytotoxicity directed against tumor cell target	6	0.043
GO:0014034	neural crest cell fate commitment	4	0.043
GO:0021747	cochlear nucleus development	3	0.044
GO:0006855	drug transmembrane transport	76	0.044
GO:0014707	branchiomeric skeletal muscle development	3	0.044
GO:0021817	nucleokinesis involved in cell motility in cerebral cortex radial glia guided migration	3	0.044
GO:0048866	stem cell fate specification	4	0.045
GO:0014045	establishment of endothelial blood-brain barrier	4	0.045
GO:0022009	central nervous system vasculogenesis	4	0.045
GO:0043578	nuclear matrix organization	3	0.045
GO:0090292	nuclear matrix anchoring at nuclear membrane	3	0.045
GO:0008295	spermidine biosynthetic process	4	0.046
GO:0070777	D-aspartate transport	4	0.046
GO:0070779	D-aspartate import across plasma membrane	4	0.046
GO:0048477	oogenesis	85	0.046
GO:0031646	positive regulation of nervous system process	63	0.046
GO:0045341	MHC class I biosynthetic process	5	0.046
GO:0045343	regulation of MHC class I biosynthetic process	5	0.046
GO:0045345	positive regulation of MHC class I biosynthetic process	5	0.046
GO:0002036	regulation of L-glutamate import across plasma membrane	5	0.046
GO:0051954	positive regulation of amine transport	35	0.046
GO:0140352	export from cell	1553	0.047
GO:0006296	nucleotide-excision repair, DNA incision, 5'-to lesion	36	0.047
GO:0042733	embryonic digit morphogenesis	61	0.047
GO:0009135	purine nucleoside diphosphate metabolic process	133	0.047
GO:0009179	purine ribonucleoside diphosphate metabolic process	133	0.047
GO:0031133	regulation of axon diameter	5	0.047
GO:0006880	intracellular sequestering of iron ion	5	0.047

GO:0014735	regulation of muscle atrophy	4	0.047
GO:0045054	constitutive secretory pathway	4	0.047
GO:1902116	negative regulation of organelle assembly	36	0.048
GO:0033572	transferrin transport	36	0.048
GO:0009744	response to sucrose	6	0.049
GO:0034285	response to disaccharide	6	0.049
GO:0002420	natural killer cell mediated cytotoxicity directed against tumor cell target	8	0.049
GO:0002858	regulation of natural killer cell mediated cytotoxicity directed against tumor cell target	8	0.049
GO:1901162	primary amino compound biosynthetic process	5	0.049
GO:0015711	organic anion transport	491	0.049
GO:0009185	ribonucleoside diphosphate metabolic process	135	0.049
GO:0099011	neuronal dense core vesicle exocytosis	6	0.049
GO:0099525	presynaptic dense core vesicle exocytosis	6	0.049
GO:0006643	membrane lipid metabolic process	203	0.049
GO:0001958	endochondral ossification	27	0.050
GO:0036075	replacement ossification	27	0.050
GO:0035931	mineralocorticoid secretion	6	0.050
GO:0035932	aldosterone secretion	6	0.050
GO:2000855	regulation of mineralocorticoid secretion	6	0.050
GO:2000858	regulation of aldosterone secretion	6	0.050
GO:0097577	sequestering of iron ion	6	0.050
GO:0010559	regulation of glycoprotein biosynthetic process	40	0.050

Note: #N: Number of genes involved in the respective pathways

Supplement Table S10(A): Association of DNAm in newborn with pre-adolescent Ast_Rh at 405 CpGs that are sex specific. Males are the reference group.

CpGs	IOWBC interaction Estimate	IOWBC RAW Pvalue	IOWBC fdr pvalue	ALSPAC Interaction Estimates	ALSPAC main estimate	ALSPAC RAW Pvalue	CHR	Gene	Gene location	CpG Island

cg24818434	-2.55	6E-06	0.0007	-0.35	0.09	0.6476	1	*SLC25A44*	5'UTR	Island
cg09095892	-1.32	1E-05	0.0007	0.81	-0.64	0.0357	10			Island
cg08617683	-1.94	1E-05	0.0007	0.73	-0.18	0.0642	12	*FBRSL1*	Body	
cg05000348	-2.44	9E-06	0.0007	0.86	-0.18	0.3167	11	*CDK2AP2*	TSS1500	Island
cg01538301	3.79	1E-05	0.0007	0.23	-0.83	0.8014	14			
cg04206337	-2.46	3E-05	0.0008	0.84	-0.05	0.2912	1	*SNORA16A*	Body	N_Shore
cg21349849	2.91	2E-05	0.0008	0.40	-0.29	0.3993	8	*STK3*		
cg05396987	-2.29	3E-05	0.0008	-0.41	0.33	0.5156	4	*TMEM155*	1stExon	Island
cg21476203	2.64	2E-05	0.0008	0.27	-0.18	0.6335	8	*SCRIB*	Body;Body	S_Shore
cg06791670	-2.14	3E-05	0.0008	-0.14	0.32	0.8508	19	*HAUS5*	Body	Island
cg27635422	-2.47	3E-05	0.0008	0.05	0.01	0.9375	6	*TAPBP*	3'UTR	S_Shore
cg27635422	-2.47	3E-05	0.0008	0.05	0.01	0.9375	6	*TAPBP*	3'UTR	S_Shore
cg00980784	-3.17	3E-05	0.0008	0.03	0.05	0.9683	17	*ABI3, GN*	TSS200	
cgunit	-2.77	3E-05	0.0008							
cg12292402	-1.91	4E-05	0.0008	1.75	-0.47	0.0221	13	*HSPH1*	TSS1500	Island
cg26615794	2.94	4E-05	0.0008	0.74	0.00	0.3316	1	*RGS16*		S_Shelf
cg22081558	-2.48	4E-05	0.0008	-0.13	0.20	0.8484	11			Island
cg04019843	3.16	4E-05	0.0009	1.31	-0.06	0.1190	1	*RPS6KC1*		
cg15421520	2.88	5E-05	0.0009	-0.66	0.88	0.5206	14	*C14orf18*	1stExon;5'UTR	
cg03740167	-2.43	6E-05	0.0009	-0.46	0.70	0.4706	10			Island
cg00315816	2.45	6E-05	0.0009	0.37	-0.61	0.6006	7	*PRKAG2*	5'UTR;Body	
cg00823229	-2.05	7E-05	0.0010	0.47	-0.06	0.5187	12	*PFKM*	1stExon	Island
cg17618092	-2.12	8E-05	0.0010	0.35	-0.08	0.6191	11	*RBM14*	1stExon	Island
cg19874450	-2.70	8E-05	0.0010	-0.23	0.01	0.6729	17	*GGNBP2*	1stExon;5'UTR	Island
cg23973524	3.19	1E-04	0.0011	0.80	-0.70	0.2431	19	*CRTC1*	Body;Body	Island
cg18787783	3.90	1E-04	0.0011	1.49	-0.01	0.1753	12	*MMP19*	TSS1500	
cg15943437	-1.88	1E-04	0.0011	0.08	0.43	0.8936	11	*MRPL21*	5'UTR	N_Shore
cg21834204	-2.82	1E-04	0.0012	1.44	-0.50	0.0952	12	*MTERFD3*	TSS1500	S_Shore
cg14591123	-2.21	1E-04	0.0012	0.74	-1.07	0.2914	3	*VILL*	Body	Island

cg13539395	-3.25	1E-04	0.0012	-0.45	0.44	0.3265	19	*CFD*	TSS200	N_Shore
cg12661452	-1.97	1E-04	0.0012	0.62	0.05	0.4560	12	*AACS*	1stExon	Island
cg20852846	-2.14	1E-04	0.0012	-0.49	-0.11	0.4819	19	*ZFR2*	Body	Island
cg16073958	1.38	1E-04	0.0012	0.30	-0.63	0.5138	8			
cg17081157	-2.05	1E-04	0.0012	0.32	-0.25	0.6544	6	*SESN1*	TSS1500	Island
cg14101302	-1.93	1E-04	0.0012	0.41	-0.34	0.5671	6	*RIMS1*	TSS200	S_Shore
cg16013246	-2.27	1E-04	0.0012	0.14	-0.43	0.7946	1	*SNHG3-RC*	Body	
cg20630567	-1.86	1E-04	0.0012	-0.04	0.42	0.9560	2	*CCDC115*	5'UTR	Island
cg20736492	-1.53	2E-04	0.0013	0.38	-0.30	0.3158	12			
cg09888026	-3.36	2E-04	0.0013	-0.90	0.36	0.3690	17	*TMEM105*	5'UTR	
cg15847685	-3.04	2E-04	0.0013	-0.88	-0.23	0.3214	4			
cg07965714	-1.74	2E-04	0.0013	0.86	-0.63	0.3736	9	*XPA*	TSS200	S_Shore
cg19367136	-1.70	2E-04	0.0014	0.21	0.43	0.7014	1	*FUCA1*	TSS1500	S_Shore
cg18478353	3.05	2E-04	0.0014	1.18	-0.66	0.2627	21	*SLC37A1*	Body	N_Shelf
cg19954739	-1.87	2E-04	0.0015	0.11	-0.19	0.8645	9	*ZMYND19*	TSS1500	Island
cg13213118	-1.98	3E-04	0.0017	0.80	0.29	0.2798	12			
cg04575467	-2.30	3E-04	0.0017	0.41	0.10	0.5561	8			Island
cg14099990	-1.77	3E-04	0.0018	0.35	0.11	0.5299	13	*NBEA*	Body	
cg02461806	-2.07	3E-04	0.0018	0.33	-0.51	0.6794	17	*ZZEF1*	TSS200	Island
cg21656600	-1.79	3E-04	0.0018	0.16	-0.02	0.7860	12	*PPP1CC*	TSS1500	Island
cg01540571	-1.81	3E-04	0.0018	0.09	0.16	0.8970	1	*AGMAT*	Body	Island
cg24343755	-1.67	3E-04	0.0020	-0.21	0.20	0.7177	10	*PDSS1*	Body	Island
cg10179363	3.16	4E-04	0.0020	0.48	-0.17	0.4991	15	*ANPEP*	5'UTR	
cg07642705	-1.62	3E-04	0.0020	-0.09	0.11	0.8741	16	*SNHG9, R*	TSS200	Island
cg05440435	-1.82	4E-04	0.0020	-0.15	0.36	0.7806	16	*CA7*	TSS200;Body	Island
cg13420923	-1.91	4E-04	0.0020	0.02	0.16	0.9688	10	*DCLRE1A*	TSS1500	Island
cg23683674	-2.18	4E-04	0.0020	-0.51	0.33	0.4030	11	*ARHGEF17*	1stExon	Island
cg14724918	-1.75	4E-04	0.0021	-0.15	0.61	0.8324	5	*SEC24A*	TSS1500	Island
cg07538364	1.86	4E-04	0.0022	0.51	-0.33	0.2858	8	*SLC7A2*	Body	

cg25279644	-1.91	5E-04	0.0024	-0.10	-0.11	0.8629	4			Island
cg13696436	1.95	5E-04	0.0025	-0.53	0.64	0.2316	10	*EBF3*	Body	N_Shore
cg02998992	-2.48	5E-04	0.0025	-0.35	0.22	0.5639	17	*B9D1*	Body	Island
cg22192692	-2.07	5E-04	0.0025	-0.36	0.31	0.5161	20	*SNRPB*	TSS1500	S_Shore
cg22377767	1.32	5E-04	0.0025	-0.51	0.42	0.6223	7	*ZKSCAN5*	TSS200	N_Shore
cg24820996	-1.91	5E-04	0.0025	0.28	-0.34	0.6411	19	*UNC13A*	Body	Island
cg21322248	-2.36	6E-04	0.0026	-0.32	0.06	0.6053	15	*PSTPIP1*	Body	
cg18948488	-2.51	6E-04	0.0026	0.88	-0.17	0.2343	10	*FLJ41350*	Body	S_Shore
cg10579012	-1.04	6E-04	0.0027	-1.03	0.45	0.0091	1			
cg26054167	2.35	6E-04	0.0027	1.43	-1.01	0.2003	20	*COL20A1*	Body	Island
cg24496614	-2.41	6E-04	0.0027	-0.76	0.38	0.3163	11	*FTH1*	TSS1500	S_Shore
cg02419873	-2.89	6E-04	0.0027	0.34	-0.50	0.6466	16	*SNX29P1*		S_Shore
cg00652657	-1.66	6E-04	0.0027	0.26	-0.11	0.6575	10	*EBF3*	Body	Island
cg22041190	-1.93	6E-04	0.0027	0.15	0.02	0.8164	11	*PKNOX2*	5'UTR	S_Shore
cg21857959	-1.85	6E-04	0.0027	0.54	-0.30	0.4424	3	*MCF2L2*	3'UTR	Island
cg00707741	2.22	7E-04	0.0028	0.24	-0.63	0.7568	2	*FARP2*	TSS1500	N_Shore
cg16360777	1.30	7E-04	0.0029	0.43	0.04	0.5041	4	*AMBN*	Body	
cg16000406	3.21	7E-04	0.0029	-0.43	0.58	0.6205	19	*FUT5*	Body	Island
cg27241576	2.37	7E-04	0.0029	-0.26	0.61	0.7113	16	*CMIP*	Body	
cg00500229	-1.72	8E-04	0.0030	1.25	-0.02	0.0263	1			Island
cg11661809	-1.78	8E-04	0.0030	-0.05	0.03	0.9384	22	*PI4KA, S*	5'UTR	Island
cg03694279	-2.44	8E-04	0.0032	1.17	-0.96	0.1327	10			
cg04410091	2.43	9E-04	0.0034	1.22	-0.28	0.1022	8	*RHPN1*	Body	S_Shore
cg02457683	-1.54	9E-04	0.0034	1.21	-0.39	0.3382	1	*DCAF8*	Body	Island
cg09158314	-2.19	9E-04	0.0034	0.81	-0.49	0.4320	13	*TNFSF13B*	5'UTR	
cg23502772	-1.70	9E-04	0.0034	0.08	0.03	0.8710	5	*MGC42105*	TSS1500	Island
cg01015662	1.24	9E-04	0.0035	-0.09	0.03	0.8666	1	*PPT1*		N_Shore
cg16359663	2.41	1E-03	0.0035	-0.09	0.08	0.8836	4	*CC2D2A*	Body	
cg16629408	2.07	1E-03	0.0035	0.16	-0.06	0.7190	19	*ERCC1*	Body	N_Shelf

cg06412092	-1.62	1E-03	0.0036	0.40	-0.12	0.6891	5	*MIER3*	Body	Island
cg19653117	-2.07	1E-03	0.0036	0.75	0.19	0.2796	2	*YIPF4*	TSS200	N_Shore
cg19142181	0.34	1E-03	0.0037	0.14	-0.09	0.4893	20	*SLC17A9*	Body	Island
cg23023263	-1.64	1E-03	0.0037	0.14	0.01	0.8221	3	*ULK4*	TSS1500	S_Shore
cg18733433	1.73	1E-03	0.0039	-0.20	-0.16	0.5809	3	*MORC1*	TSS200	Island
cg26348902	-1.66	1E-03	0.0039	0.33	-0.07	0.5726	4			Island
cg05990720	-1.83	1E-03	0.0040	-0.53	0.23	0.3935	9	*C9orf72*	5'UTR	N_Shore
cg22279519	1.77	1E-03	0.0041	-1.18	0.71	0.2154	12	*NCOR2*	Body	S_Shelf
cg20176285	-1.05	1E-03	0.0041	-1.24	0.03	0.3831	2	*REEP1*	Body	Island
cg15081402	-2.14	1E-03	0.0041	0.33	-0.07	0.6260	3	*PRICKLE2*		S_Shelf
cg00763510	1.46	1E-03	0.0045	-0.26	-0.21	0.6620	14			
cg24601716	-2.11	2E-03	0.0047	0.46	-0.36	0.5286	13	*PDX1*	Body	Island
cg25739003	-1.81	2E-03	0.0047	-0.52	0.24	0.4676	11	*EEF1G*	Body	Island
cg24198840	1.92	2E-03	0.0047	0.22	-0.02	0.6612	2	*NEU2*	1stExon	
cg05800641	-0.89	2E-03	0.0051	0.12	0.00	0.7277	22	*CACNA1I*	Body	Island
cg07292251	1.32	2E-03	0.0051	-0.09	0.54	0.8589	5	*F12*	3'UTR	N_Shore
cg01798661	2.63	2E-03	0.0051	-0.33	-0.20	0.6475	13	*NEK5*	TSS1500	S_Shore
cg07555102	2.19	2E-03	0.0051	0.09	0.11	0.8742	1			N_Shelf
cg09396181	-2.18	2E-03	0.0052	0.00	-0.22	0.9939	3	*WNT7A*	TSS1500	Island
cg01461299	-1.94	2E-03	0.0052	0.37	0.10	0.5490	19	*MCOLN1*	TSS1500	N_Shore
cg03177034	1.74	2E-03	0.0056	-0.42	0.03	0.6362	2	*STK39*	Body	
cg12967050	-0.68	2E-03	0.0056	-0.28	0.19	0.6745	19	*TMEM149*	1stExon	S_Shore
cg14240353	-1.55	2E-03	0.0057	-0.23	0.36	0.6457	12	*IGF1*	Body	
cg07873926	0.96	2E-03	0.0058	0.43	-0.21	0.3579	18			Island
cg26349362	-1.71	2E-03	0.0058	0.02	-0.07	0.9767	12	*CAPS2*	1stExon	Island
cg15832329	1.29	2E-03	0.0058	-0.32	-0.18	0.6128	2	*FARP2*	5'UTR	S_Shore
cg08643007	-1.30	2E-03	0.0058	-0.87	0.66	0.3640	2	*ATF2*	1stExon	Island
cg04107037	-1.61	2E-03	0.0058	0.38	-0.07	0.4925	4	*ATOH1*	1stExon	Island
cg06216103	0.96	3E-03	0.0060	0.83	-0.92	0.1871	12	*GALNT9*	Body	Island

cg09776718	-1.17	2E-03	0.0060	-0.27	0.14	0.5018	19	*PLEKHF1*	Body	Island
cg19374731	1.75	3E-03	0.0061	0.16	0.02	0.7627	1	*MORN1*	Body	S_Shelf
cg01662869	3.09	3E-03	0.0062	0.21	-0.35	0.6378	16	*MGRN1*	Body	Island
cg01604539	-1.43	3E-03	0.0062	-0.06	0.19	0.9118	16	*TRADD*	Body	Island
cg20491695	-1.91	3E-03	0.0062	-0.49	0.29	0.4233	11			
cg10692870	-1.73	3E-03	0.0064	0.06	-0.07	0.9218	2	*FN1*	Body	Island
cg05104811	1.88	3E-03	0.0064	-0.17	0.49	0.8198	6	*PACRG*	Body	S_Shore
cg26904787	-1.60	3E-03	0.0067	0.38	-0.18	0.5808	10	*RTKN2*	1stExon;5'UTR	Island
cg05232576	1.56	3E-03	0.0068	-1.48	0.75	0.0978	20	*CPXM1*	Body	N_Shelf
cg24151841	1.27	3E-03	0.0069	0.23	-0.10	0.7114	2	*SPATS2L*	Body	
cg00169776	1.10	3E-03	0.0069	0.20	0.11	0.5648	1	*LINC0098*		
cg25266327	0.94	3E-03	0.0069	0.02	-0.25	0.9536	19	*KLF2*	5'UTR;1stExon	Island
cg23197881	-1.50	3E-03	0.0071	0.19	0.00	0.8213	12	*RAB3IP*	5'UTR	Island
cg20200460	1.36	3E-03	0.0074	0.45	-0.23	0.3340	10			
cg00374554	1.63	4E-03	0.0076	-0.25	-0.11	0.6766	5	*LINC0102*		N_Shore
cg18786125	-1.64	4E-03	0.0076	-0.35	0.87	0.5816	1	*MEGF6*	TSS1500	Island
cg27435903	2.38	4E-03	0.0077	1.31	-0.16	0.0902	17	*GSDMB*	Body	
cg25090315	1.96	4E-03	0.0079	-0.86	0.38	0.1373	14	*GPR68*	5'UTR	S_Shelf
cg03468115	2.41	4E-03	0.0079	0.57	-0.27	0.4600	10			
cg09543792	-1.36	4E-03	0.0079	-0.57	0.55	0.5681	17	*SLC16A13*	TSS200	Island
cg15365426	1.16	4E-03	0.0079	0.12	0.25	0.8471	2			
cg17821664	2.59	4E-03	0.0079	0.87	0.04	0.3330	15	*OSTBETA*	1stExon;5'UTR	
cg17724054	-1.67	4E-03	0.0080	1.98	-0.94	0.0480	5	*RPS23*	TSS200	S_Shore
cg06824318	-0.90	4E-03	0.0083	0.31	0.14	0.5266	1			N_Shore
cg05029148	-1.02	4E-03	0.0085	0.06	0.03	0.8934	8			S_Shore
cg06861115	-2.16	4E-03	0.0086	1.06	-0.75	0.1106	15			N_Shelf
cg15651099	-1.55	5E-03	0.0089	0.46	-0.23	0.4886	1	*KIRREL*	Body	Island
cg15847604	1.86	5E-03	0.0091	0.96	-0.62	0.1349	12	*ETV6*	Body	
cg04839616	1.77	5E-03	0.0093	-0.13	0.46	0.8517	16			

cg10410121	1.71	5E-03	0.0097	1.01	-0.22	0.0865	7			
cg26406994	-1.19	5E-03	0.0097	0.73	-0.03	0.2207	4	*RAP1GDS1*	Body	Island
cg17490648	1.68	5E-03	0.0097	-0.19	-0.27	0.8439	8	*PXMP3*	5'UTR	N_Shelf
cg06852255	-1.59	5E-03	0.0097	0.03	0.10	0.9684	6	*PSMB9*	TSS1500	Island
cg22588936	1.55	5E-03	0.0097	0.61	-0.57	0.1376	9	*LCN10*	Body	Island
cg27479400	-1.30	5E-03	0.0098	0.56	-0.06	0.3318	22	*SREBF2*	TSS200	Island
cg02725872	0.83	5E-03	0.0102	0.18	-0.14	0.7291	8			
cg01870679	1.70	6E-03	0.0103	-0.34	-0.12	0.5784	19	*ZNF506*	3'UTR	
cg01692279	-1.41	6E-03	0.0106	0.34	-0.67	0.7224	7			N_Shore
cg08995424	-1.42	6E-03	0.0109	0.57	-0.02	0.3411	12	*ATP5G2*	TSS1500	N_Shore
cg01426818	-1.58	6E-03	0.0109	-0.28	0.04	0.6732	17	*CBX4*		Island
cg23283875	-1.36	6E-03	0.0111	-1.11	0.75	0.1211	7	*C7orf63*	1stExon	Island
cg09791665	-1.16	6E-03	0.0112	-0.43	0.07	0.5191	19	*ZNF441*	Body	Island
cg02015280	-1.21	6E-03	0.0112	0.03	-0.10	0.9656	7	*AGBL3*	TSS200	Island
cg15101985	2.07	6E-03	0.0113	1.46	-0.34	0.0756	10	*PCDH21*	Body	
cg16010178	-1.52	6E-03	0.0113	0.64	-0.46	0.2938	17	*EPN3*	5'UTR	N_Shelf
cg22993878	2.33	6E-03	0.0113	0.61	-0.24	0.4067	2	*MYEOV2*	TSS1500	S_Shore
cg11160820	-1.46	7E-03	0.0117	-0.24	0.23	0.8272	1	*CD58*	5'UTR	Island
cg00812799	1.56	7E-03	0.0122	-0.52	-0.18	0.4107	13	*IL17D*	Body	Island
cg13963729	-1.58	7E-03	0.0125	-0.81	0.54	0.2808	19	*ARID3A*	TSS1500	Island
cg24517858	-1.11	7E-03	0.0129	1.55	-0.85	0.1085	1	*REN*	Body	
cg21634993	1.34	8E-03	0.0133	-0.73	-0.11	0.2715	4	*MGST2*	Body	Island
cg02430497	-1.44	8E-03	0.0136	0.34	-0.02	0.6095	10	*GTPBP4*	Body	Island
cg00131618	-1.06	8E-03	0.0137	0.63	-0.29	0.4148	5	*C5orf42*	5'UTR	Island
cg17508018	-1.08	8E-03	0.0142	0.90	-0.11	0.2862	19	*PLD3*	TSS200	Island
cg19862616	0.65	9E-03	0.0144	0.29	0.02	0.5066	7	*NCRNA001*	Body	Island
cg00755287	-1.98	9E-03	0.0145	0.13	0.06	0.8641	17	*KRTAP9-3*	TSS1500	
cg26417188	1.63	9E-03	0.0149	0.46	-0.39	0.3950	1	*KLF17*	TSS1500	
cg22085702	-1.56	9E-03	0.0150	-0.29	0.92	0.6500	11	*CALCA*	TSS1500	N_Shore

cg22364465	1.99	9E-03	0.0152	1.07	-0.44	0.1672	1	*PLXNA2*	Body	
cg13659360	1.27	9E-03	0.0152	0.62	-0.04	0.2657	11	*TECTA*	Body	
cg02948476	-1.15	9E-03	0.0152	0.14	0.11	0.8673	14	*GSC*	Body	Island
cg00152175	-0.93	1E-02	0.0156	0.93	-0.09	0.2495	16	*AMFR*	TSS1500	Island
cg01499522	-1.34	1E-02	0.0157	0.26	0.19	0.6387	7	*MLXIPL*	Body	N_Shore
cg05564836	1.28	1E-02	0.0157	-0.20	0.41	0.6534	15	*OCA2*	Body	Island
cg04871364	-1.27	1E-02	0.0158	-0.10	0.02	0.8265	1	*ESPN*	Body	Island
cg02266878	-1.02	1E-02	0.0161	-0.89	0.60	0.0450	16	*MSLNL*	Body	
cg06102330	-1.42	1E-02	0.0161	1.41	-0.08	0.0850	8	*MSC*	TSS1500	S_Shore
cg07614018	-1.53	1E-02	0.0164	-1.12	0.48	0.3621	19	*CRTC1*	Body	Island
cg12348202	1.06	1E-02	0.0168	0.05	-0.24	0.9125	7	*PTPRN2*	TSS1500	Island
cg03821689	1.43	1E-02	0.0170	1.18	-0.13	0.0280	11	*FXYD6*	TSS1500	S_Shore
cg14967868	1.12	1E-02	0.0172	-0.22	-0.49	0.9051	4	*SPATA4*	1stExon;5'UTR	Island
cg06902665	-1.65	1E-02	0.0177	1.42	-1.06	0.1078	19	*ONECUT3*	Body	N_Shelf
cg13590117	1.38	1E-02	0.0177	0.43	-0.02	0.3923	9	*OLFM1*		
cg10920378	-2.02	1E-02	0.0177	0.59	-0.68	0.4640	4	*RBM46*	TSS1500	N_Shore
cg20728639	-1.08	1E-02	0.0178	0.66	-0.05	0.3502	11	*ABTB2*	TSS1500	Island
cg14442841	-0.98	1E-02	0.0180	-0.43	0.46	0.3551	6	*MBOAT1*	Body	
cg08990264	-1.29	1E-02	0.0191	0.21	0.02	0.6738	8			
cg02712036	-0.69	1E-02	0.0191	-0.29	0.27	0.5843	15	*RAB27A*	5'UTR	
cg24478630	-1.04	1E-02	0.0196	0.68	-0.42	0.1757	2	*MOGS*	TSS200	S_Shore
cg01687864	-1.46	1E-02	0.0200	0.26	0.04	0.6349	7	*ING3*	Body;Body	S_Shore
cg14736210	-1.28	1E-02	0.0208	-0.44	0.59	0.3312	20	*KCNB1*	1stExon	Island
cg16358034	1.10	1E-02	0.0219	-0.50	-0.05	0.2770	5	*SNX18*	1stExon	Island
cg15584606	1.62	2E-02	0.0221	0.38	-0.66	0.6314	10	*GATA3*		
cg02691091	2.03	2E-02	0.0225	0.33	-0.39	0.6447	17	*SP2*	Body	
cg22755534	0.66	2E-02	0.0226	0.15	-0.22	0.7840	11			
cg05346295	0.98	2E-02	0.0234	0.85	-0.34	0.3404	19	*NUP62*	Body	
cg21197594	-1.44	2E-02	0.0244	1.83	-0.97	0.0387	9	*EHMT1*	Body	

cg06759374	-1.00	2E-02	0.0244	0.03	0.68	0.9576	3			Island
cg12271966	-0.98	2E-02	0.0247	0.66	0.06	0.4578	22	*PATZ1*	TSS1500	Island
cg06486582	1.46	2E-02	0.0250	-0.16	0.09	0.8209	5			
cg18481137	-1.00	2E-02	0.0282	0.53	-0.10	0.5271	3	*FOXP1*	5'UTR;5'UTR	Island
cg18232125	-1.58	2E-02	0.0282	-0.14	-0.02	0.8211	5			
cg24708694	1.25	2E-02	0.0293	-0.04	0.34	0.9272	4			
cg20383390	-0.98	2E-02	0.0297	-0.56	0.44	0.2895	1	*MAN1A2*	TSS1500	N_Shore
cg16526287	1.01	2E-02	0.0297	0.05	-0.56	0.9389	6	*DTNBP1*	Body	
cg07750914	-1.37	2E-02	0.0298	0.14	-0.05	0.9283	2	*PAPOLG*	Body	Island
cg07580479	0.99	2E-02	0.0305	-0.11	0.00	0.9042	6	*FOXO3*	Body;Body	
cg00925953	-1.35	2E-02	0.0307	0.31	-0.24	0.6172	1	*TAS1R2*	Body	
cg07475890	-0.98	2E-02	0.0307	-0.13	-0.10	0.8535	11	*PPP1R14B*	Body	Island
cg01754267	0.87	2E-02	0.0311	0.38	0.19	0.6253	12	*NDUFA4L2*	3'UTR	N_Shore
cg27230396	1.02	2E-02	0.0312	0.56	-0.05	0.3829	4	*SHROOM3*	Body	Island
cg00385142	1.53	2E-02	0.0318	0.11	-0.65	0.8759	3	*CLDND1*	Body	
cg05098096	1.12	2E-02	0.0319	0.31	-0.56	0.5215	16	*ARL6IP1*	Body	N_Shelf
cg08258650	-1.02	2E-02	0.0323	0.81	-0.25	0.1284	11	*SLC1A2*	TSS1500	S_Shore
cg11694433	-0.97	2E-02	0.0328	0.24	-0.08	0.6887	15	*USP3*	TSS200	Island
cg23619399	0.99	3E-02	0.0334	-0.06	0.19	0.9244	13			N_Shore
cg10200408	-1.22	3E-02	0.0336	-0.21	0.57	0.7977	12	*ASB8*	1stExon;5'UTR	Island
cg20477591	1.15	3E-02	0.0350	0.15	-0.42	0.7929	5	*PIK3R1*	3'UTR	
cg24976131	1.60	3E-02	0.0355	-0.41	0.23	0.5752	17	*NAGS*	3'UTR	S_Shore
cg05441854	0.49	3E-02	0.0359	-1.21	0.65	0.1484	16	*KIAA0182*	5'UTR	S_Shore
cg01266916	-0.99	3E-02	0.0368	0.54	-0.68	0.4712	20	*MMP9*	Body	Island
cg04436634	1.45	3E-02	0.0369	0.97	-0.30	0.3039	1	*OR10Z1*	TSS1500	
cg02374944	1.61	3E-02	0.0369	0.53	0.35	0.3988	15	*MAN2A2*	3'UTR	
cg20232060	-1.13	3E-02	0.0374	-1.49	0.43	0.2027	3	*RNF7*	Body	S_Shore
cg16332065	-0.88	3E-02	0.0390	0.62	0.20	0.2593	4	*GABRG1*	TSS200	
cg11817533	1.31	3E-02	0.0395	-0.09	0.05	0.8482	6			

cg26146287	-1.32	3E-02	0.0397	-1.06	0.39	0.1542	5	*CARTPT*	TSS1500	N_Shore
cg05951364	1.42	3E-02	0.0403	0.64	-0.21	0.2326	8	*DLGAP2*	5'UTR	
cg13664588	-2.00	3E-02	0.0413	-0.12	0.00	0.8891	17	*SNORD1A*	TSS1500	S_Shelf
cg00017461	-0.86	3E-02	0.0417	-0.22	-0.18	0.8572	22	*OSM*	TSS1500	
cg00003722	1.33	3E-02	0.0427	0.22	-0.36	0.8219	10			
cg17596905	-1.01	4E-02	0.0445	0.68	-0.51	0.4598	3	*CCDC50*	5'UTR	Island
cg11021321	0.86	4E-02	0.0452	0.14	0.17	0.8006	20	*GNAS*	Body	S_Shelf
cg26756083	-1.06	4E-02	0.0452	0.25	0.71	0.8239	8	*MMP16*	5'UTR	N_Shore
cg19738404	-1.21	4E-02	0.0460	-0.30	0.30	0.6539	2	*BIN1*		S_Shore
cg03533979	-0.85	4E-02	0.0481	0.17	0.06	0.6458	22	*CERK*	Body	Island
cg05876918	-1.10	4E-02	0.0492	0.91	-0.38	0.2242	12	*PIP4K2C*	1stExo	Island
cg00770837	1.70	1E-03	0.0035				2	*RGPD5*	TSS1500	S_Shore
cg00893493	-1.52	4E-03	0.0085				1	*MCOLN3*	5'UTR	N_Shore
cg00971789	1.02	6E-03	0.0113				17	*ARSG*	Body	
cg01120423	1.71	2E-03	0.0051				16	*KIAA0430*	Body	
cg01325599	-2.36	1E-02	0.0208				3			
cg01341327	1.87	9E-04	0.0033				2	*CNOT11*	Body	
cg01558754	-2.12	1E-02	0.0204				6	*KCNQ5*	Body	
cg01578625	-2.22	3E-03	0.0063				11	*CD44*	Body	
cg01786959	-1.87	2E-04	0.0014				1	*NPPA-AS1*	Body	
cg02300001	2.34	4E-05	0.0008				16			
cg02496392	1.32	4E-03	0.0077				1	*AHDC1*	5'UTR	
cg02665414	1.44	2E-02	0.0280				11			
cg02683869	-1.70	9E-03	0.0153				12			
cg02901886	2.74	6E-04	0.0027				14	*RAD51B*	Body;Body	
cg03035177	-2.21	2E-04	0.0014				3	*DGKG*	1stExon	Island
cg03123201	-2.45	4E-04	0.0020				5	*IRX1*	Body	Island
cg03490138	-1.80	4E-03	0.0081				12	*CD27*	Body;TSS1500	
cg03493480	3.30	1E-04	0.0011				8			

cg03501936	1.42	7E-03	0.0125	5	*CDHR2*	Body	
cg03618886	1.45	4E-02	0.0497	3	*GOLGA4*	TSS1500	N_Shore
cg03809583	1.79	2E-03	0.0056	12			
cg03898146	-1.28	1E-02	0.0168	20			
cg03920147	1.42	2E-02	0.0235	1			
cg04091518	-2.93	9E-05	0.0011	11	*CLMP*	Body	
cg04188137	-1.06	4E-02	0.0494	9			
cg04335891	-1.67	2E-03	0.0052	20	*CDH4*	Body	
cg04390191	-1.90	3E-03	0.0069	2	*SP110*	TSS200	
cg04397316	-1.64	2E-03	0.0051	6	*TAB2*	Body	S_Shore
cg04453170	-1.53	2E-02	0.0227	4			
cg05308867	2.02	5E-05	0.0009	2			
cg05356782	1.91	2E-03	0.0056	11	*PACS1*	Body	
cg05501127	2.24	3E-03	0.0061	1	*WASF2*	3'UTR	
cg05538745	-2.05	5E-05	0.0009	14	*PRKCH*	1stExon	Island
cg05753257	1.56	1E-03	0.0044	12			S_Shore
cg05789318	1.93	6E-03	0.0113	5			
cg06034584	-1.46	6E-03	0.0112	9	*TOPORS-A*	Body	N_Shore
cg06311780	-1.85	2E-03	0.0056	18			
cg06670685	1.07	9E-03	0.0152	9	*NUP214*	Body	
cg06703980	1.93	2E-03	0.0051	3	*CHCHD6*	Body	N_Shore
cg06771173	1.89	9E-05	0.0011	1	*ZSWIM5*	Body	
cg06949394	-2.59	2E-05	0.0008	10	*MKX*	5'UTR	Island
cg07194517	-2.88	2E-05	0.0008	9			
cg07201235	1.90	9E-05	0.0011	1	*SPOCD1*	Body	
cg07300949	1.06	3E-03	0.0065	14	*SLC8A3*	5'UTR	
cg08172212	1.51	1E-03	0.0035	2	*SPHKAP*	Body	
cg08504214	-1.57	4E-02	0.0452	19	*SBNO2*	TSS1500	
cg08533932	-1.10	9E-05	0.0011	8	*PDGFRL*	TSS200	N_Shore

cg08626295	1.83	3E-03	0.0061	22	*RANGAP1*	3'UTR	
cg08653158	1.90	1E-03	0.0041	11			
cg08890816	-2.36	3E-05	0.0008	4	*PAPSS1*	TSS1500	Island
cg09171201	1.09	4E-02	0.0481	5			
cg09314901	-1.73	9E-03	0.0146	10			
cg09584604	-1.47	4E-04	0.0021	4	*COX18*	TSS1500	S_Shore
cg09762585	1.58	3E-02	0.0337	1			N_Shore
cg09953309	1.84	2E-03	0.0058	7	*LINC0052*	Body	
cg10060082	2.60	5E-04	0.0023	14	*VTI1B*	Body	
cg10105621	2.47	2E-03	0.0047	11	*CELF1*	3'UTR	
cg10247069	1.75	3E-03	0.0075	1			
cg10428526	-2.53	3E-04	0.0017	9	*RABEPK*	TSS1500	Island
cg10518693	-0.92	4E-02	0.0466	14	*EXOC5, A*	1stExon	Island
cg10604470	-0.58	2E-02	0.0237	18	*RNF125*	TSS200	N_Shore
cg10761100	-2.30	4E-03	0.0078	17	*SLC39A11*	Body	
cg10769180	-1.26	1E-02	0.0168	3			
cg10903440	-1.75	3E-03	0.0066	13			
cg11081247	-2.17	2E-03	0.0051	1	*STPG1*	TSS1500	N_Shore
cg11121987	-1.42	1E-03	0.0044	11	*OPCML*	Body	
cg11125823	2.72	7E-05	0.0010	16	*ARHGAP17*	Body	
cg11170610	-2.35	6E-05	0.0009	1			Island
cg11327392	1.06	3E-02	0.0356	3			
cg11328665	-1.58	2E-02	0.0239	17	*9-Sep*	TSS1500	N_Shore
cg11502583	-2.27	5E-05	0.0009	3	*U2SURP*	TSS1500	N_Shore
cg11516862	1.61	7E-03	0.0119	12	*ANAPC7*	Body	
cg11590775	1.43	2E-02	0.0266	16	*RPS15A*	TSS1500	S_Shore
cg11713268	-2.35	8E-03	0.0130	13	*TBC1D4*	Body	
cg11784870	-3.04	2E-04	0.0013	22	*SYN3*	Body	
cg11904216	3.09	4E-07	0.0002	16	*C16orf46*	5'UTR	

cg11916384	-2.40	1E-04	0.0012	7			
cg12016449	1.74	1E-02	0.0180	20	*PREX1*	Body	
cg12224382	-1.31	4E-03	0.0084	1	*GJA8*	TSS200	
cg12736742	1.58	2E-03	0.0056	13			
cg12872535	1.80	1E-02	0.0173	1			
cg13098169	1.35	4E-03	0.0081	6	*USP45*	5'UTR	N_Shelf
cg13155790	-1.58	8E-03	0.0130	15			
cg13255969	-1.38	3E-03	0.0069	9			
cg13942631	-2.30	2E-03	0.0052	10			
cg13973074	-2.00	6E-03	0.0111	1			
cg13986784	-2.57	2E-03	0.0052	3			
cg14181092	-1.54	5E-03	0.0102	5	*PPIC*	Body	Island
cg14278029	-1.35	5E-04	0.0025	1	*NFIA*	5'UTR	N_Shore
cg14293818	-1.89	9E-05	0.0011	7	*DNAJC2*	TSS200	S_Shore
cg14336545	-1.76	1E-03	0.0042	13	*ATP8A2*	ExonBnd	Island
cg14714087	-2.01	2E-03	0.0051	19			
cg14767360	-2.56	3E-04	0.0017	18	*DYM*	Body	
cg14794991	-2.14	3E-03	0.0075	10	*GRID1*	Body	
cg15051432	-1.00	2E-02	0.0291	3			
cg15260373	-1.31	4E-02	0.0487	21			
cg15418976	1.90	4E-04	0.0020	11	*PTPRJ*	Body	
cg15469038	-2.05	4E-04	0.0020	17			N_Shore
cg15556088	0.86	3E-02	0.0386	18	*TCF4*	Body	
cg15705918	2.11	2E-04	0.0015	22	*MIEF1*	5'UTR	
cg15887809	-2.18	6E-04	0.0026	6	*ARID1B*	Body	
cg15979711	1.42	2E-02	0.0314	15			
cg16181199	1.26	3E-02	0.0432	7	*ESYT2*	Body	
cg16181878	1.19	2E-02	0.0297	12			N_Shore
cg16253805	-1.70	2E-02	0.0229	16			

cg16404609	2.12	3E-03	0.0068	1	*KPNA6*	Body	
cg16423486	-2.17	2E-04	0.0013	2			N_Shore
cg16809249	-0.92	3E-03	0.0071	14			S_Shelf
cg16947819	2.75	4E-04	0.0022	10	*KIAA1462*	Body	
cg17364708	1.65	2E-03	0.0047	17	*UBE2O*	Body	
cg17698505	-2.33	1E-04	0.0012	22	*EWSR1, R*	TSS1500	S_Shore
cg17775336	1.99	2E-04	0.0014	8	*GRHL2*	Body	
cg17853121	-1.91	7E-04	0.0027	2	*CENPO*	TSS200	Island
cg17939602	-2.13	4E-03	0.0076	5			
cg18019618	-2.10	1E-03	0.0042	5	*ARHGEF28*	5'UTR	
cg18104668	-1.19	1E-03	0.0039	5	*RGMB*	TSS1500	N_Shore
cg18622049	-1.61	4E-03	0.0085	1	*RABGAP1L*	Body	
cg19382123	-4.39	2E-04	0.0014	4	*LINC0098*	TSS1500	
cg19427589	-3.40	6E-03	0.0106	17	*PLEKHM1*	Body	
cg19545865	1.02	9E-03	0.0152	16			
cg19635805	-1.90	1E-06	0.0003	10	*LRRC20*	5'UTR	
cg19637744	1.82	9E-03	0.0146	1	*OBSCN*	Body	
cg19825503	1.26	1E-02	0.0196	2	*EHBP1*	Body	
cg19958721	-1.31	1E-03	0.0039	2	*ARHGAP15*	Body	
cg19994575	2.38	6E-04	0.0027	3	*FAM19A4*	Body	
cg20040976	-1.48	2E-03	0.0047	15			
cg20397901	2.43	1E-05	0.0007	10			
cg20728881	-2.34	4E-04	0.0020	10	*ARID5B*	TSS1500	
cg20756051	2.08	6E-03	0.0113	3	*LNP1*	Body	
cg20866256	2.83	5E-05	0.0009	12			N_Shore
cg20951352	2.36	6E-04	0.0025	2			
cg21055045	-3.01	2E-03	0.0056	2	*TTC7A*	Body	
cg21202847	-2.03	5E-03	0.0093	1	*E2F2*	TSS1500	Island
cg21353284	-1.83	1E-03	0.0037	1	*GJB3*	5'UTR	S_Shore

cg21433170	-3.14	1E-02	0.0180	11	*IFITM1*	TSS1500	S_Shore
cg21459672	-3.39	1E-03	0.0035	13	*DCUN1D2*	Body	
cg21548114	-2.24	4E-04	0.0020	11	*GDPD5*	Body	
cg21568193	-1.80	2E-03	0.0048	1	*SLC9C2*	Body	
cg22471376	-1.76	2E-02	0.0266	15	*ISG20*	5'UTR	
cg22874664	-1.51	3E-02	0.0343	20			
cg23033164	1.89	2E-03	0.0059	12			
cg23059673	1.65	6E-03	0.0111	19			
cg23128484	2.11	3E-03	0.0063	2			
cg23263679	1.63	2E-03	0.0056	19	*DNAAF3*	Body	N_Shore
cg23293998	-2.07	2E-03	0.0047	1	*CACNA1E*	Body	
cg23339014	-2.89	3E-04	0.0017	14	*PRKCH*	Body	
cg23653514	1.55	1E-03	0.0037	12	*NR2C1*	Body	
cg24061073	-1.83	6E-04	0.0026	1	*CASP9*	TSS1500	S_Shore
cg24736834	0.83	3E-02	0.0430	15	*PDE8A*	TSS200	Island
cg24785373	1.27	1E-02	0.0178	2			
cg25042436	-1.99	4E-03	0.0079	11	*ZC3H12C*	Body	
cg25095420	2.72	1E-03	0.0041	22	*NEFH*	Body	S_Shelf
cg25114671	2.58	2E-03	0.0059	16	*SMPD3*	5'UTR	
cg25434113	-1.80	4E-02	0.0481	13	*C1QTNF9*	TSS1500	Island
cg25503398	-2.95	4E-06	0.0006	3	*BBX*	1stExon	N_Shore
cg25587451	2.44	2E-04	0.0013	19			
cg25665603	-1.77	7E-04	0.0027	3	*ALCAM*	TSS200	N_Shore
cg25985183	-1.82	1E-02	0.0191	10			
cg26466155	1.79	2E-03	0.0052	1	*KIF26B*	Body	
cg27127276	1.44	2E-03	0.0056	10			
cg27575100	-3.46	6E-05	0.0009	11	*LGR4*	Body	
cg27647719	-1.52	2E-02	0.0248	6	*LOC10192*	Body	

Supplement Table S10 (B): Association of DNAm in newborn with pre-adolescent Ast_Rh at 70 CpGs that are sex nonspecific. Males are the reference group.

CpGs	IOWBC Estimates	IOWBC Raw Pvalue	IOWBC fdr Pvalue	Alspac Estimate	AlSPAC pvalue	CHR	Gene	Gene Location	CpG Island
cg16616362	0.88	0.0000	0.0003	0.14	0.5021	21	*C21orf81*	TSS1500	S_Shore
cg09397375	-0.61	0.0002	0.0030	-0.16	0.7800	1	*ZNF672*	TSS1500	Island
cg11864592	1.17	0.0006	0.0053	-0.02	0.9504	15	*GOLGA6L4*		
cg10189362	1.29	0.0010	0.0055	-0.18	0.4304	2	*STEAP3*	Body	Island
cg13999210	-1.23	0.0009	0.0055	0.32	0.5323	4	*NPY2R*		
cg19766820	-0.76	0.0010	0.0055	0.10	0.7274	5			N_Shore
cg00815214	-0.55	0.0010	0.0055	0.06	0.8073	21			Island
cg04946910	0.92	0.0010	0.0055	0.06	0.8270	16	*OR1F1*		Island
cg13793782	-0.68	0.0014	0.0063	0.22	0.2755	9	*RALGDS*	Body	N_Shore
cg21100167	0.81	0.0013	0.0063	-0.13	0.6735	21	*PCBP3*	Body;Body	S_Shore
cg13627491	0.57	0.0032	0.0126	0.18	0.6581	9	*LPPR1*	5'UTR	Island
cg20977448	-0.56	0.0036	0.0126	-0.10	0.8464	5	*GRPEL2*	Body	S_Shore
cg10890016	0.58	0.0041	0.0131	-0.23	0.4355	7	*UNC84A*	Body	N_Shore
cg17574471	0.54	0.0046	0.0131	-0.15	0.5065	4	*LETM1*	Body	
cg14062152	-0.89	0.0048	0.0131	0.23	0.5913	10	*TMEM26*	Body	N_Shore
cg18845692	-0.72	0.0056	0.0136	0.40	0.2064	14	*FLRT2*	TSS1500	N_Shore
cg26806713	0.52	0.0061	0.0145	0.31	0.2330	6			N_Shore
cg08976554	0.81	0.0071	0.0164	0.19	0.4951	12	*NCOR2*	Body	N_Shelf
cg14399790	-0.51	0.0074	0.0167	-0.01	0.9740	8			N_Shore
cg13675319	0.81	0.0081	0.0178	0.22	0.3255	9			Island
cg02982198	0.56	0.0092	0.0178	0.29	0.5596	10	*ANKRD26*	Body	N_Shore
cg27357049	0.64	0.0095	0.0178	-0.10	0.7104	15	*MIR548H4*	Body	N_Shore
cg27357049	0.64	0.0095	0.0178	-0.10	0.7104	15	*MIR548H4*	Body	N_Shore
cg00105306	0.95	0.0094	0.0178	-0.07	0.8357	15	*WDR73*	Body	N_Shelf

cg14273401	-0.27	0.0084	0.0178	-0.01	0.9837	6	*TRIM31*	3'UTR	N_Shore
cg20241375	-0.79	0.0125	0.0217	-0.25	0.5185	4			N_Shelf
cg23112563	-0.46	0.0135	0.0229	0.05	0.8036	7	*LOC64200*	TSS200	Island
cg07455685	-0.64	0.0152	0.0249	0.27	0.3089	19	*PVR*	Body	Island
cg21103269	0.55	0.0163	0.0263	0.60	0.0585	6			
cg02724025	0.47	0.0176	0.0273	0.14	0.5980	16	*CDH11*	Body	Island
cg16654216	0.64	0.0191	0.0291	-0.26	0.4185	2	*SATB2*		
cg13185308	-0.81	0.0200	0.0300	0.26	0.6392	11	*ABCC8*	TSS1500	S_Shore
cg01395217	-0.81	0.0214	0.0316	-0.35	0.3267	1	*SEC22B*	Body	S_Shelf
cg19248893	0.86	0.0261	0.0367	0.58	0.0651	1	*DNAJC11*	Body	
cg12372414	-0.57	0.0381	0.0499	-0.42	0.1838	3	*KY*	3'UTR	
cg24366127	-0.51	0.0379	0.0499	0.35	0.2315	3	*BOC*	Body	
cg17133224	0.50	0.0382	0.0499	-0.38	0.2438	20	*WFDC9*	3'UTR	
cg16556156	-2.17	0.0000	0.0001			16	*CLEC16A*	Body	S_Shore
cg03106024	-1.03	0.0000	0.0003			11			
cg04078283	-1.36	0.0000	0.0007			4	*HTT*	Body	
cg26933978	1.88	0.0000	0.0007			8	*HTRA4, P*	TSS1500	N_Shore
cg04580455	0.70	0.0002	0.0023			6			
cg02017733	-1.31	0.0003	0.0034			22	*PISD, MI*	Body	
cg04672034	-1.04	0.0004	0.0037			20	*PTPN1*	5'UTR	
cg03892671	0.69	0.0009	0.0055			4	*PPA2*	Body	
cg08227938	-1.10	0.0009	0.0055			17	*DBF4B*	Body	
cg14970957	1.09	0.0014	0.0063			9	*RUSC2*	TSS1500	
cg02160496	0.82	0.0033	0.0126			1	*LOC14937*	Body	
cg06117032	-0.72	0.0036	0.0126			5	*LOC10050*	TSS200	S_Shore
cg10639871	-1.02	0.0032	0.0126			10			
cg19337057	-1.18	0.0035	0.0126			20	*CEP250*	Body	
cg00718959	0.75	0.0046	0.0131			5			
cg01479032	-1.29	0.0045	0.0131			1			

cg12220491	0.93	0.0044	0.0131	15	*ZNF106*	Body	
cg19098799	-0.92	0.0046	0.0131	2			
cg02571397	-0.83	0.0053	0.0131	11			S_Shelf
cg11609995	-0.88	0.0052	0.0131	2	*IL18R1*	5'UTR	
cg26165441	-0.79	0.0052	0.0131	4	*PIGG*	Body	
cg14760788	0.63	0.0090	0.0178	22	*EFCAB6-A*	Body	
cg21519785	0.76	0.0090	0.0178	13	*SACS*	TSS1500	
cg22638066	-0.69	0.0090	0.0178	6	*SGK1*	Body	
cg10398502	-1.10	0.0107	0.0192	13	*LINC0038*	TSS1500	
cg10408324	-1.00	0.0106	0.0192	21			
cg13601382	0.80	0.0113	0.0200	4			
cg26281383	-0.42	0.0144	0.0240	2			
cg02174096	-0.86	0.0168	0.0266	16	*LINC0030*	Body	S_Shore
cg02856340	0.44	0.0217	0.0316	1	*ZBTB40*	5'UTR	
cg04698728	-0.90	0.0251	0.0359	8			
cg01160497	0.91	0.0307	0.0425	11	*LMO1*	Body	
cg21005828	-0.63	0.0351	0.0478	22			

Supplement Table S11 (A): Association of DNAm in males with neighboring gene expression (n=55)

coefficient	Pvalue	CpGs	Gene
0.916875	4.30E-07	cg01662869	*DPYSL4*
0.827036	6.55E-07	cg01662869	*QRFP*
-1.80075	8.53E-07	cg19248893	*RGS6*
1.045963	1.56E-06	cg01662869	*JADE2*
1.924089	2.18E-06	cg01662869	*JAM3*
-0.81809	3.53E-06	cg05990720	*GNB1*
-1.14956	7.47E-06	cg19248893	*BCL7B*
-0.63891	9.09E-06	cg19248893	*ARMC7*

0.878885	1.31E-05	cg01662869	*LAMC3*
-1.47691	1.35E-05	cg02266878	*TLE2*
0.818827	2.82E-05	cg14273401	*NME8*
-0.631	3.67E-05	cg19248893	*KLF9*
-0.49871	0.000158	cg05990720	*HIC1*
-0.47902	0.000175	cg02266878	*SGTA*
1.494738	0.000233	cg01662869	*IGSF9B*
0.800258	0.000306	cg27230396	*ABHD8*
-0.40952	0.000345	cg05990720	*ATP8B3*
1.619155	0.000349	cg14273401	*MIEN1*
-1.04492	0.000437	cg02266878	*THOP1*
0.777331	0.000445	cg14273401	*RMDN2*
0.710671	0.000517	cg11661809	*METTL4*
-0.90581	0.000517	cg27230396	*MED9*
0.822986	0.000534	cg01662869	*EXOC4*
-0.48546	0.000566	cg19248893	*FCHSD2*
0.954409	0.000604	cg27230396	*CNTLN*
1.852549	0.000666	cg11661809	*CLUH*
-0.16162	0.000792	cg26146287	*AKR1E2*
-0.44096	0.000797	cg04019843	*SEC22B*
1.09255	0.000807	cg14273401	*CASC3*
-0.36014	0.000927	cg21322248	*LZTS2*
-0.47291	0.001029	cg19248893	*SMC5*
-0.72681	0.001109	cg19248893	*MRPS7*
-1.41225	0.001155	cg01538301	*MUS81*
0.943836	0.001202	cg11661809	*BRAT1*
-1.11397	0.001211	cg02982198	*TUT1*
-1.09334	0.001242	cg27230396	*MED28*
-0.71297	0.00129	cg19248893	*EXOC6B*
-0.25449	0.001297	cg05990720	*GABRD*
0.84544	0.001342	cg12967050	*RASAL3*

-0.44503	0.00141	cg02266878	*HTT*
1.082943	0.001546	cg20232060	*CES1P1*
-0.70906	0.001597	cg13963729	*SAMD8*
-0.49925	0.001684	cg05951364	*JMJD1C*
-0.47547	0.002058	cg04019843	*GYPB*
-0.48668	0.002154	cg02266878	*NOP14*
0.629126	0.002195	cg01662869	*LRGUK*
-0.24427	0.002196	cg16629408	*FNTB*
0.632839	0.002411	cg14273401	*THRA*
1.13781	0.002498	cg05396987	*SPTA1*
1.497453	0.0025	cg12967050	*TMEM27*
1.244615	0.002659	cg25266327	*CITED2*
-0.23246	0.002674	cg05990720	*CASKIN1*
-0.50168	0.002684	cg12967050	*RBM11*
0.517246	0.002733	cg01662869	*TG*
1.678386	0.002773	cg11661809	*CHST12*
0.997468	0.002802	cg20477591	*TBC1D14*
0.468938	0.002951	cg01662869	*GLB1L3*
-1.01751	0.002954	cg23973524	*DTX3*
-0.27214	0.003055	cg05990720	*NPW*
-0.79804	0.003161	cg27230396	*NR2F6*
-0.5486	0.003224	cg02266878	*CARD11*
0.841411	0.003582	cg20232060	*TMEM86B*
-0.33408	0.003754	cg04019843	*PDE4DIP*
0.152495	0.003829	cg11160820	*PCDH1*
0.48695	0.003924	cg22192692	*FAM127A*
-1.0216	0.00403	cg00315816	*FBXL16*
0.572832	0.004281	cg20232060	*TESPA1*
0.49941	0.004323	cg14273401	*OXSR1*
0.529218	0.004429	cg14273401	*SHB*
1.313691	0.004615	cg02691091	*C20orf1*

0.683974	0.004662	cg14273401	*EPHA10*
-0.33952	0.004685	cg02266878	*CSMD1*
-0.39979	0.004788	cg05990720	*NDUFS6*
0.428407	0.004813	cg22192692	*INPP5A*
-0.74014	0.004827	cg27230396	*SLC27A1*
0.44378	0.004832	cg22192692	*TG*
0.304036	0.004857	cg03468115	*INO80E*
1.067266	0.00492	cg19738404	*PTK6*
0.568628	0.004932	cg03468115	*RPP21*
-0.28982	0.005009	cg04019843	*NBPF20*
-0.42611	0.005033	cg05951364	*CCT6P1*
-0.5341	0.00523	cg02266878	*PTPRA*
-0.35257	0.00527	cg05951364	*ARL2*
0.51873	0.005412	cg01662869	*FAM127A*
0.857096	0.00543	cg12967050	*CYP4F22*
0.808963	0.005787	cg20477591	*MCPH1*
0.594884	0.006029	cg03468115	*UBL3*
-0.18189	0.006055	cg05990720	*LSP1*
0.342058	0.006379	cg05951364	*ADAMTS6*
-1.20768	0.006392	cg27230396	*LAP3*
0.457482	0.006521	cg01662869	*FIBCD1*
-0.24	0.006615	cg16629408	*CHURC1*
0.53727	0.006728	cg01426818	*PIP5K1B*
-0.18514	0.006783	cg05990720	*PGP*
0.81459	0.00707	cg03468115	*TMTC1*
-0.70461	0.007081	cg00315816	*TNFRSF1*
0.940001	0.007088	cg20477591	*PTMS*
-0.56879	0.007156	cg00315816	*PNPLA2*
-0.427	0.007239	cg04019843	*NBPF9*
0.674981	0.007287	cg11661809	*TMC2*
-0.70206	0.00732	cg13539395	*GPR153*

0.452796	0.007363	cg03468115	*C19orf1*
914.0104	0.007559	cg22081558	*AAGAB*
0.390845	0.007696	cg03468115	*COPRS*
1.796971	0.007757	cg20232060	*RSL24D1*
-0.5013	0.007902	cg02266878	*GNA15*
0.592209	0.008155	cg14273401	*ERBB2*
0.829912	0.008166	cg19874450	*MAP3K2*
-0.67031	0.008225	cg01538301	*EDA2R*
-0.97457	0.008235	cg21322248	*KAZALD1*
0.604316	0.008288	cg14273401	*CARD10*
0.895658	0.008484	cg14442841	*ADARB2*
-0.33326	0.008563	cg05990720	*KLF16*
-0.23909	0.008596	cg05990720	*TRAF7*
-0.48844	0.008779	cg02266878	*PRSS30P*
0.453102	0.008932	cg11661809	*PGP*
0.753833	0.009066	cg11661809	*MIR940*
0.646969	0.00913	cg11661809	*TRPM5*
0.638253	0.009173	cg11661809	*MYLK4*
1.465945	0.009284	cg01662869	*STK32C*
-0.50146	0.009312	cg10410121	*MRPL9*
-2.2322	0.009417	cg18787783	*GRIN3B*
-0.30927	0.009835	cg27435903	*ACTR1B*
0.527638	0.009952	cg01662869	*GLB1L2*
-0.2717	0.010023	cg21322248	*TECPR2*
-0.33398	0.010024	cg02266878	*SMCHD1*
-0.60384	0.010048	cg02266878	*DDRGK1*
-0.54279	0.010198	cg27230396	*PGLS*
0.477404	0.010219	cg14273401	*EPDR1*
0.489023	0.01044	cg01662869	*MOSPD1*
-0.42491	0.010503	cg05951364	*FRMD8*
1.072044	0.010551	cg22192692	*TXNDC15*

0.282792	0.01079	cg14273401	*RPGR*
-1.30887	0.010814	cg22081558	*RTTN*
-0.81153	0.010822	cg09791665	*GPR179*
0.918757	0.010837	cg24818434	*CERS4*
-0.22332	0.010966	cg05990720	*SYNGR3*
-0.56661	0.011023	cg27230396	*MRPL34*
-0.51295	0.011038	cg05951364	*TRIP4*
0.707645	0.011071	cg06791670	*EXOC3L2*
0.748489	0.011104	cg09543792	*GATC*
1.082027	0.011237	cg22192692	*FAM127C*
0.443105	0.011638	cg22192692	*DDX46*
1.194002	0.011676	cg09543792	*TRIAP1*
-0.60216	0.011888	cg05098096	*EPS8L2*
0.903861	0.011897	cg01395217	*TACO1*
-0.61102	0.012104	cg05951364	*CDCA5*
-0.39125	0.01218	cg13539395	*PHF13*
0.45426	0.012189	cg19248893	*JPX*
-1.24426	0.012298	cg13963729	*TBCA*
0.691221	0.012318	cg24343755	*ARID2*
-1.0212	0.012419	cg13963729	*SDAD1*
-0.63454	0.012599	cg20491695	*PRKY*
0.414925	0.012634	cg13675319	*SDF2*
0.570204	0.012743	cg03468115	*FKBP14*
0.553652	0.01281	cg01662869	*SMIM10*
-0.2827	0.012896	cg05990720	*CTSD*
-1.347	0.012987	cg02982198	*UCKL1*
-0.2511	0.013074	cg00315816	*RPLP2*
-0.4807	0.013106	cg04019843	*EPPK1*
1.697077	0.013192	cg21476203	*PLXDC2*
0.851012	0.013263	cg20477591	*RRP8*
-0.52387	0.013448	cg02266878	*EMILIN2*

0.426049	0.013512	cg03468115	*KLHL14*
0.44001	0.013547	cg00169776	*PPRC1*
-0.23101	0.01355	cg05990720	*SPSB3*
0.759456	0.013613	cg05440435	*MRPS17*
0.725944	0.013616	cg27435903	*COX5B*
0.538644	0.013696	cg09543792	*GRIK4*
-0.27694	0.013736	cg00315816	*NARFL*
-0.45043	0.013777	cg00315816	*SLC12A7*
1.093944	0.013799	cg01395217	*HAR1B*
0.659123	0.013804	cg25266327	*PTGDS*
0.235956	0.014209	cg10179363	*GPBP1L1*
-0.43889	0.014337	cg02266878	*MYLK4*
0.336036	0.014616	cg03468115	*CORO1A*
-0.40175	0.014834	cg02266878	*SLC39A3*
0.304	0.014989	cg03468115	*TBX6*
-0.56826	0.015132	cg02266878	*GNG7*
0.438001	0.015171	cg01426818	*TSPAN15*
0.000262	0.015331	cg00003722	*CCNH*
0.305861	0.015424	cg01426818	*NCOA2*
1.355311	0.015589	cg01395217	*SERPINB*
0.529508	0.016062	cg13675319	*OTOF*
0.720181	0.01619	cg19862616	*CEP164*
0.889367	0.016296	cg13659360	*MRPL40*
0.407787	0.016789	cg14273401	*TBC1D1*
-0.55679	0.016835	cg00315816	*NXN*
-0.31242	0.016852	cg00707741	*TIE1*
0.739673	0.016913	cg14442841	*PRPF8*
-0.3839	0.017005	cg00315816	*TMED11P*
0.667976	0.017572	cg09543792	*TAF2*
0.619871	0.017744	cg14442841	*SLC35E2*
-0.81184	0.017792	cg00315816	*SUN1*

-0.95372	0.017905	cg13963729	*GSAP*
0.527185	0.017992	cg09543792	*NANOS1*
-1.25458	0.01813	cg27230396	*FAM8A1*
-0.69025	0.018167	cg27230396	*CECR5*
-0.61047	0.018262	cg13963729	*CAPN5*
1.331242	0.018278	cg20232060	*FBXO34*
0.506395	0.018279	cg03468115	*DCTN6*
1.166207	0.018292	cg09543792	*DSCC1*
-0.33057	0.018368	cg04019843	*SH3RF2*
0.350908	0.018569	cg03468115	*MTUS2*
-1.32028	0.018718	cg02982198	*PTK6*
0.248229	0.018755	cg00169776	*LDB1*
0.285528	0.018874	cg20491695	*DEFA4*
-0.4989	0.019099	cg05951364	*BATF2*
0.368192	0.019308	cg02724025	*TMEM30B*
0.737372	0.019373	cg11661809	*PANK4*
-0.43217	0.019576	cg13675319	*GPATCH3*
1.221838	0.0199	cg02691091	*CAMP*
-1.23788	0.019914	cg01395217	*FTH1*
-0.42068	0.020162	cg10410121	*CGN*
-0.84011	0.020191	cg12967050	*HACL1*
-0.30398	0.020375	cg19248893	*UNC5B*
0.753671	0.020457	cg01426818	*FOXP1*
-0.43544	0.020565	cg00707741	*GCK*
-0.30189	0.020716	cg02266878	*CLDN9*
-0.56294	0.021049	cg05951364	*TM7SF2*
-0.33744	0.021074	cg00315816	*MFSD7*
-1.25789	0.021179	cg12967050	*BMX*
1.112547	0.021295	cg11661809	*TMPRSS9*
0.276217	0.021342	cg03468115	*MTURN*
-0.30127	0.021465	cg00315816	*LMF1*

0.448635	0.021623	cg27435903	*RGMB*
-0.60569	0.022082	cg02266878	*TTYH3*
0.514821	0.02218	cg12967050	*CC2D2A*
0.540944	0.022183	cg18232125	*PDCD2L*
0.420639	0.022412	cg25279644	*TMEM185*
0.247024	0.022664	cg22192692	*PCBD2*
0.275855	0.023214	cg03468115	*LRRC37B*
0.728372	0.023253	cg01426818	*B3GAT2*
0.58071	0.02332	cg03468115	*PRKD1*
-0.59747	0.023343	cg02266878	*PRSS22*
-0.36329	0.023427	cg10579012	*AK3*
-0.49297	0.023548	cg02266878	*ITFG2*
-0.81681	0.024409	cg07555102	*RSF1*
-0.31872	0.024465	cg09396181	*NDUFA10*
-0.46978	0.024515	cg02266878	*PAQR4*
-0.67381	0.024601	cg23973524	*CDK4*
0.213325	0.024754	cg22192692	*ACAD8*
-0.32247	0.024812	cg22364465	*R3HDM2*
0.385618	0.024817	cg21476203	*AKAP10*
-0.27396	0.024861	cg24151841	*RBM11*
0.479016	0.025094	cg00169776	*NOLC1*
0.791425	0.025179	cg19248893	*FZD9*
0.60237	0.025241	cg19738404	*FAM161A*
0.311622	0.025364	cg00315816	*RAB40C*
0.637911	0.02549	cg07538364	*UBE2E2*
0.860927	0.025585	cg17821664	*ATP9A*
1.524991	0.026233	cg05440435	*GNAO1*
0.723389	0.026485	cg19374731	*TIGD7*
1.149834	0.026518	cg25266327	*SLC4A9*
0.461499	0.026644	cg19738404	*AR*
0.552245	0.026671	cg21322248	*ANKRD9*

-0.70669	0.0267	cg00707741	*TMEM63B*
-0.96034	0.026712	cg22588936	*FBXL8*
0.35095	0.026792	cg14724918	*EXOC2*
0.441938	0.0268	cg11661809	*CASKIN1*
0.564571	0.026925	cg12967050	*NPIPA5*
-1.13603	0.026935	cg02982198	*TM2D1*
-0.91601	0.027092	cg22588936	*OPHN1*
0.684316	0.027116	cg20232060	*LPCAT2*
-0.48855	0.027447	cg00315816	*TMEM18*
1.571906	0.027568	cg19142181	*ASB8*
0.397792	0.027685	cg24151841	*PGLYRP2*
-0.34275	0.027883	cg22364465	*DNAH12*
0.320524	0.028088	cg22192692	*GLB1L3*
-1.0727	0.028111	cg22081558	*MAP2K6*
0.651756	0.028354	cg11661809	*MLST8*
0.154699	0.028407	cg07642705	*SPRY3*
1.243103	0.028474	cg20232060	*NLRP2*
-0.37053	0.028786	cg03740167	*ADAMTS7*
0.533515	0.028803	cg11661809	*OAZ1*
-0.25838	0.028862	cg02712036	*IMMP1L*
-0.54936	0.028867	cg22081558	*MCMDC2*
0.520855	0.028884	cg05396987	*SNX9*
0.349712	0.028898	cg01604539	*PACSIN1*
-0.59897	0.02897	cg13539395	*MCPH1*
0.694685	0.028986	cg14273401	*PNMT*
0.164956	0.029134	cg26054167	*COPZ2*
-1.03614	0.029307	cg01538301	*EIF1AD*
-0.65649	0.029468	cg13539395	*MRPL51*
-0.48544	0.029577	cg23973524	*RPS6KB1*
-0.26803	0.029898	cg05990720	*HAUS3*
0.685783	0.029999	cg14240353	*GNG7*

1.25322	0.030145	cg08643007	*EEPD1*
0.232124	0.030325	cg10179363	*CBX1*
-0.28642	0.030329	cg05990720	*MSRB1*
0.751503	0.03034	cg03468115	*MPPED2*
-1.04051	0.030727	cg00385142	*CNPY4*
0.747709	0.030793	cg22192692	*FAM78A*
0.823609	0.030831	cg01538301	*CNIH2*
0.229152	0.031039	cg10179363	*SMAD7*
0.38846	0.031085	cg14273401	*MTF1*
-2.3819	0.031178	cg03821689	*NRM*
-0.37801	0.031224	cg02266878	*FAM193A*
-0.42173	0.032203	cg00315816	*CEND1*
1.078219	0.03223	cg20977448	*SSB*
0.618513	0.032558	cg19374731	*RPS7*
-0.18966	0.032799	cg16629408	*NLN*
-0.95831	0.033028	cg23973524	*RNFT1*
0.559089	0.033052	cg20477591	*PMS2CL*
-0.59327	0.033132	cg01395217	*TCFL5*
-0.60405	0.033418	cg02982198	*SNAPC1*
-0.65339	0.033545	cg00707741	*TFF3*
0.662712	0.033606	cg11661809	*TSR1*
-0.29208	0.033638	cg18787783	*ABR*
-0.36264	0.033681	cg02712036	*SLC5A2*
1.399547	0.033894	cg12967050	*KAZN*
-0.07612	0.033902	cg11160820	*AGK*
0.538616	0.033968	cg14273401	*PGAP3*
-0.57579	0.034015	cg16073958	*ANKRD29*
0.46021	0.034116	cg19374731	*CEP104*
0.799391	0.034322	cg20477591	*PRKCQ*
0.577944	0.034343	cg11661809	*TSSC4*
-0.16926	0.034685	cg16629408	*RASSF3*

-0.7171	0.034922	cg15847604	*KRT81*
0.624624	0.034989	cg05440435	*BLOC1S1*
0.701347	0.035109	cg20232060	*MTIF2*
0.649857	0.035158	cg11661809	*CCNF*
-0.75447	0.035324	cg13963729	*COMTD1*
-0.31588	0.035548	cg19248893	*TMEM104*
-0.39835	0.035811	cg02266878	*OXT*
-0.49308	0.036055	cg02266878	*RIPK1*
-0.37586	0.036101	cg05951364	*TRAPPC1*
-0.43916	0.036407	cg13539395	*DNAJC11*
0.371742	0.036963	cg12967050	*EPS8*
0.772264	0.037085	cg14273401	*ELFN2*
-1.18386	0.037336	cg09791665	*APOL6*
-0.554	0.037357	cg21322248	*CINP*
-0.88229	0.037458	cg15847685	*UBLCP1*
-0.39482	0.037585	cg02266878	*KCTD5*
0.599604	0.037601	cg01426818	*TEX261*
-1.17465	0.037604	cg13963729	*ISL2*
0.671445	0.037858	cg11661809	*GNG7*
0.85893	0.038324	cg14240353	*THOP1*
0.217516	0.038875	cg24343755	*NFE2L1*
0.248076	0.03907	cg24343755	*LRRC3*
0.34544	0.039072	cg14273401	*SH3BP1*
-0.52446	0.039218	cg23973524	*TUBD1*
1.330471	0.039502	cg00385142	*COQ3*
0.444833	0.039517	cg09791665	*RNF38*
0.663577	0.039606	cg03468115	*TRIM31*
-0.52082	0.039629	cg23973524	*HEATR6*
-0.78218	0.039722	cg03740167	*ANXA3*
0.728746	0.039801	cg09543792	*TECTA*
-0.43213	0.039843	cg00315816	*TRIP13*

-0.45046	0.040247	cg20491695	*LAG3*
-0.5346	0.040417	cg20491695	*RNF144A*
-0.71525	0.040757	cg05440435	*ORMDL2*
-0.33777	0.041836	cg05951364	*HELZ*
-0.7923	0.042265	cg25266327	*LCN10*
-0.62326	0.04231	cg22081558	*CD226*
-0.40879	0.042708	cg02712036	*CAPN14*
0.437655	0.042903	cg19738404	*COMMD1*
-0.70672	0.042967	cg02266878	*FLYWCH1*
-0.38558	0.043056	cg07555102	*AQP11*
-0.39428	0.043087	cg00315816	*IDUA*
-0.34345	0.043298	cg09888026	*ALG6*
-0.91828	0.043312	cg19874450	*ETS1*
0.51665	0.043633	cg22192692	*TBPL1*
0.360262	0.04417	cg14442841	*MAFK*
0.488877	0.044242	cg14240353	*MYLK4*
-0.35152	0.044259	cg09396181	*RGS7*
0.346271	0.044294	cg14273401	*NR1D1*
0.379147	0.044361	cg12372414	*FKBP8*
0.201452	0.044609	cg03468115	*GDPD3*
0.738691	0.044972	cg02982198	*KHDRBS2*
-0.77933	0.044978	cg13963729	*MAGT1*
0.166783	0.045229	cg18232125	*IFNGR2*
-0.43553	0.045275	cg10410121	*SNX27*
0.494864	0.045308	cg14442841	*BRSK2*
-0.24078	0.045705	cg14273401	*GRB7*
0.489728	0.045768	cg00315816	*CCDC78*
0.625124	0.045909	cg11661809	*HAUS3*
-1.35544	0.045914	cg01538301	*KPNA2*
0.325657	0.046245	cg02998992	*HSPA9*
0.175626	0.046355	cg10179363	*COPZ2*

0.305394	0.046406	cg14273401	*ANKRD54*
1.174682	0.046621	cg20176285	*LYVE1*
-0.24608	0.046669	cg05990720	*TSR1*
-0.38683	0.046863	cg05990720	*SKI*
0.406408	0.046879	cg07538364	*RPS2P32*
0.757276	0.047992	cg00315816	*PDDC1*
0.786197	0.048379	cg05440435	*MSX2P1*
-0.35317	0.048538	cg15847685	*EBF1*
-0.2949	0.048552	cg15584606	*ABR*
-0.35707	0.04864	cg00315816	*SBNO2*
0.657886	0.048678	cg20852846	*ANKRD6*
-0.44947	0.048837	cg13675319	*TBC1D19*
0.172925	0.049405	cg02724025	*PSMC5*
0.761859	0.049517	cg11661809	*LSM7*
0.227197	0.049624	cg18478353	*ANKRD26*
0.289648	0.04998	cg26054167	*PNPO*

Supplement Table S11 (B): Association of DNAm in females with neighboring gene expression (n=85)

coefficient	Pvalue	CpGs	Gene
0.933795	1.72E-11	cg01662869	*JADE2*
0.828278	2.99E-10	cg01662869	*DPYSL4*
0.556397	8.41E-08	cg01662869	*MOSPD1*
0.613822	1.66E-07	cg01662869	*GLB1L2*
0.684088	1.67E-07	cg01662869	*LAMC3*
0.867954	1.78E-07	cg09543792	*NANOS1*
0.659914	2.23E-07	cg01662869	*QRFP*
-0.92084	3.42E-07	cg18478353	*ARNTL2*
-1.15058	4.31E-07	cg02266878	*THOP1*
1.169448	7.08E-07	cg01662869	*IGSF9B*
1.382506	1.06E-06	cg01662869	*JAM3*
0.860626	2.33E-06	cg09543792	*TAF2*

-1.1085	3.64E-06	cg18478353	*GPN2*
1.433978	3.67E-06	cg01662869	*STK32C*
0.901585	3.72E-06	cg09543792	*GATC*
-0.83808	4.42E-06	cg19248893	*BCL7B*
-0.79322	5.77E-06	cg02266878	*PTPRA*
1.30047	6.10E-06	cg12967050	*RASAL3*
-1.21233	6.32E-06	cg19248893	*RGS6*
0.806838	6.71E-06	cg14273401	*CARD10*
2.561337	7.64E-06	cg12967050	*KAZN*
-0.62546	8.82E-06	cg04019843	*GYPB*
-0.70195	1.02E-05	cg05990720	*SKI*
-0.80897	1.07E-05	cg19248893	*SFXN5*
1.023046	1.18E-05	cg12967050	*NPIPA5*
0.848806	1.26E-05	cg09543792	*TECTA*
-0.82428	1.36E-05	cg19248893	*BAZ1B*
0.931676	1.38E-05	cg09543792	*DSCC1*
-1.03002	1.41E-05	cg18478353	*SLC9A1*
0.634557	1.48E-05	cg09543792	*GRIK4*
-0.74619	2.36E-05	cg18478353	*MAPRE3*
-1.38492	2.61E-05	cg02266878	*TLE2*
0.674314	2.91E-05	cg01662869	*TG*
0.910733	3.30E-05	cg12967050	*MEIS3P1*
0.925519	3.87E-05	cg09543792	*CABP1*
-0.25581	3.88E-05	cg13539395	*AGPAT5*
0.752606	3.89E-05	cg12967050	*SH3BP5*
-0.78295	4.64E-05	cg02266878	*MYLK4*
-0.73025	5.52E-05	cg18478353	*PIPOX*
-0.87476	5.70E-05	cg02266878	*KCTD5*
0.702191	6.43E-05	cg01662869	*EXOC4*
1.243577	7.07E-05	cg14273401	*TRIOBP*
-0.52545	7.13E-05	cg03740167	*ADAMTS7*

-0.23275	7.98E-05	cg05990720	*SCAMP4*
0.608641	0.0001	cg09543792	*COQ5*
-0.90795	0.000101	cg19248893	*TSIX*
0.298292	0.000103	cg19248893	*NUP85*
0.871695	0.000106	cg11661809	*BRAT1*
1.247581	0.000107	cg14273401	*HLCS*
0.910255	0.000117	cg01395217	*FADS1*
-0.70083	0.000117	cg18478353	*HOXA3*
0.456164	0.00012	cg13539395	*ACOT7*
0.852893	0.000125	cg21103269	*PNRC1*
-0.64067	0.000133	cg02266878	*HTT*
0.462665	0.00014	cg01662869	*GLB1L3*
-0.814	0.000141	cg02266878	*EMILIN2*
0.336581	0.000141	cg22192692	*AKR1B1*
0.603816	0.00015	cg01662869	*FAM127A*
0.853473	0.00015	cg14273401	*THRA*
-0.35671	0.000156	cg19248893	*ARMC7*
-0.72745	0.000193	cg02266878	*RIPK1*
1.077572	0.000198	cg02374944	*ARL10*
0.764746	0.0002	cg14273401	*EPHA10*
0.671462	0.000208	cg19862616	*COL27A1*
1.208781	0.000211	cg09543792	*TRIAP1*
0.64508	0.000216	cg09543792	*RALB*
0.745947	0.000222	cg14273401	*RMDN2*
0.461875	0.000224	cg07873926	*NRBP1*
-0.52506	0.000235	cg02266878	*SLC39A3*
-0.73347	0.000237	cg02266878	*NOP14*
1.649648	0.000284	cg14273401	*MIEN1*
-0.57048	0.00029	cg18478353	*GPATCH3*
0.645035	0.000291	cg09543792	*EIF3A*
0.465566	0.000292	cg14273401	*SNIP1*

-0.4626	0.000301	cg04019843	*SEC22B*
0.533005	0.000322	cg09543792	*SRSF9*
0.562213	0.000344	cg17821664	*ALG12*
-0.53076	0.000369	cg19248893	*KCTD2*
1.031218	0.000372	cg14273401	*PNMT*
-0.4031	0.000381	cg14273401	*LGALS1*
-0.65898	0.000392	cg02266878	*PRSS30P*
-0.38558	0.000396	cg19248893	*TMEM104*
0.821664	0.000402	cg12967050	*ANKRD28*
0.726829	0.000429	cg09543792	*RNF10*
-0.66184	0.000436	cg19248893	*CDR2L*
0.820457	0.000465	cg23683674	*MCUR1*
-0.69654	0.000478	cg13659360	*SNRPD1*
1.324977	0.000495	cg14273401	*GNL2*
0.689536	0.000498	cg12967050	*CA5BP1*
-0.65677	0.000502	cg02266878	*FKBP4*
-0.81895	0.000505	cg20477591	*LAG3*
0.549877	0.000524	cg14273401	*OXSR1*
0.779375	0.000533	cg14273401	*NME8*
0.396474	0.000549	cg01662869	*BNIP3*
-0.47663	0.000562	cg05990720	*GNB1*
0.428093	0.000574	cg01395217	*DAGLA*
-1.22895	0.000582	cg09776718	*COMMD3*
-0.67294	0.000642	cg02266878	*GNA15*
0.915412	0.000696	cg01395217	*FTSJ3*
-0.45498	0.0007	cg19248893	*KLF9*
-0.57563	0.000772	cg14273401	*GRB7*
0.472908	0.000787	cg19862616	*PAFAH1B*
-0.91883	0.000867	cg18478353	*ESCO2*
0.364562	0.000905	cg07873926	*EPHX2*
0.400155	0.000931	cg20241375	*ACAD9*

0.87238	0.00096	cg19142181	*SIAH1*
0.421222	0.001023	cg01662869	*SMIM10*
1.211253	0.001054	cg11661809	*ATP6V0C*
-1.1161	0.001062	cg20477591	*CHD4*
0.575566	0.001069	cg02266878	*NQO2*
0.865072	0.001072	cg01395217	*HAR1B*
1.00295	0.001169	cg21103269	*POLR3G*
-0.90661	0.001178	cg08976554	*MEX3A*
0.665429	0.001223	cg14273401	*NR1D1*
1.172479	0.001224	cg14273401	*LSM1*
-0.70102	0.001238	cg13659360	*UBR4*
-1.56977	0.001257	cg22588936	*E2F4*
-0.53757	0.001303	cg19248893	*TBL2*
1.258372	0.00136	cg19142181	*RNF114*
-0.27018	0.001483	cg06791670	*ALOX5*
-0.35696	0.001501	cg04019843	*SH3RF2*
-0.51798	0.001526	cg12967050	*BTD*
0.727815	0.001589	cg01395217	*MYRF*
-0.27264	0.0016	cg05990720	*MORN1*
0.36686	0.001616	cg07873926	*MOB3B*
-0.78684	0.001619	cg06216103	*LUM*
-0.80587	0.001628	cg02266878	*DDRGK1*
0.760826	0.001652	cg19142181	*LRRC59*
1.022889	0.001711	cg14273401	*GSDMA*
0.925602	0.001748	cg14273401	*BAG4*
0.773689	0.001782	cg02266878	*OR3A2*
1.079656	0.001815	cg11661809	*SKI*
1.131115	0.001816	cg11661809	*CLUH*
-0.66002	0.001923	cg20200460	*UBASH3B*
0.742505	0.001975	cg19862616	*HRK*
-1.23158	0.001976	cg02982198	*PTK6*

1.003832	0.00201	cg21103269	*UBE2J1*
0.397452	0.002061	cg01395217	*RAB3IL1*
-0.20315	0.002089	cg05990720	*CASKIN1*
0.661792	0.002118	cg05990720	*NUBP2*
0.240723	0.002128	cg19874450	*ADAM12*
-0.41791	0.002167	cg19248893	*EXOC6B*
-0.70847	0.002226	cg18478353	*PRSS16*
0.478653	0.002327	cg14273401	*SH3BP1*
-0.3454	0.002538	cg19248893	*FCHSD2*
0.547037	0.002639	cg12967050	*EFHD2*
0.441938	0.002707	cg13627491	*MED6*
-1.85397	0.002762	cg22588936	*PTPRCAP*
0.961635	0.002818	cg13539395	*FAM220A*
1.057247	0.002819	cg22588936	*C8orf46*
0.738126	0.002826	cg14273401	*DNALI1*
0.544385	0.002832	cg01395217	*TACO1*
0.629631	0.00286	cg12967050	*CYP4F22*
-0.59227	0.002871	cg19248893	*TSHZ1*
0.418905	0.002949	cg05396987	*CD1B*
0.531016	0.002986	cg21103269	*MC1R*
0.554522	0.002998	cg19142181	*SLC9A8*
1.471632	0.003008	cg19142181	*PFKM*
1.281381	0.003042	cg26806713	*PHLDA3*
-0.61922	0.003076	cg22588936	*RPS6KB2*
0.268298	0.003146	cg07873926	*LGR4*
0.867522	0.003242	cg20232060	*FBXO34*
-0.40461	0.00332	cg18478353	*MED21*
0.285188	0.003393	cg05440435	*AMFR*
0.920107	0.003393	cg23683674	*NANOS3*
0.462949	0.003437	cg10579012	*AKAP3*
1.279882	0.003475	cg23683674	*OFD1*

0.906914	0.003528	cg01662869	*TXNDC15*
-0.45627	0.003547	cg04019843	*NBPF9*
0.686131	0.003611	cg19738404	*TUT1*
0.329141	0.003654	cg22081558	*ACY3*
0.699556	0.003696	cg13664588	*GTDC1*
-0.34484	0.003784	cg05990720	*HIC1*
-0.65506	0.003807	cg13539395	*ALKBH7*
1.102307	0.003925	cg01395217	*FADS2*
0.360724	0.003959	cg01395217	*PTPRG*
-0.29444	0.004038	cg05990720	*DPH1*
0.467382	0.004086	cg09543792	*MAD2L1*
-0.37907	0.004088	cg04019843	*NBPF20*
0.935978	0.004202	cg21103269	*GBP6*
-0.49353	0.004203	cg22588936	*PLEKHG4*
-0.3131	0.004207	cg02266878	*SGTA*
0.31795	0.004313	cg26417188	*IRF2BPL*
0.367992	0.004331	cg11661809	*ABCA17P*
0.681151	0.00439	cg23683674	*NFIB*
0.391421	0.004443	cg01426818	*PHLPP2*
0.752863	0.004453	cg00315816	*GLOD4*
0.952842	0.004498	cg19142181	*PLXNB1*
-0.55547	0.004581	cg22588936	*SMAD3*
0.779026	0.004596	cg11661809	*MYT1L*
0.567278	0.004669	cg01395217	*CCDC47*
0.41099	0.004695	cg19248893	*CHIC1*
-0.55157	0.004775	cg20200460	*B3GNT4*
-0.505	0.004842	cg02266878	*OXT*
1.062986	0.004862	cg19142181	*CCDC51*
0.963836	0.004868	cg01426818	*RUFY3*
0.659539	0.004903	cg01395217	*TANC2*
0.428655	0.004929	cg01662869	*FAM78A*

0.773338	0.004942	cg19142181	*ELAC1*
-0.3984	0.004976	cg04019843	*GPAA1*
0.620773	0.005008	cg00315816	*TRIP13*
-0.40538	0.005043	cg19248893	*PPP4R2*
1.512198	0.005175	cg05440435	*DYNLL2*
0.605028	0.005223	cg01395217	*CCDC6*
-0.36529	0.005378	cg18478353	*CCDC25*
0.251542	0.005414	cg26417188	*ATP7A*
-0.84016	0.005548	cg20477591	*NCAPD2*
-0.47724	0.005702	cg20477591	*UBE2QL1*
0.363449	0.005787	cg14273401	*ANKRD54*
0.264605	0.005966	cg27435903	*RAP2A*
-0.68021	0.006052	cg15584606	*ACAP3*
-0.90311	0.006201	cg02982198	*TUT1*
0.286058	0.006312	cg05990720	*RAB26*
0.873446	0.006463	cg14273401	*NOL12*
0.394597	0.00656	cg09543792	*GRK5*
-0.71541	0.006575	cg20477591	*GAPDH*
-1.06002	0.006604	cg20200460	*TSN*
0.562877	0.006608	cg14273401	*EPDR1*
-0.78223	0.006612	cg02266878	*TSSC1*
0.390489	0.0068	cg01395217	*FADS3*
-0.29554	0.006861	cg19248893	*SMC5*
0.499616	0.007034	cg01395217	*PSMC5*
0.344656	0.007187	cg13664588	*FAM83H*
-0.77103	0.007224	cg20477591	*TNFSF9*
0.304845	0.007271	cg13627491	*KCNMB4*
0.59953	0.007357	cg14273401	*MSL1*
0.358817	0.007358	cg19738404	*MTA2*
-0.30065	0.007453	cg12372414	*ROCK1*
0.510832	0.007551	cg01395217	*RORA*

-0.23971	0.00756	cg05098096	*TTLL10*
-0.4617	0.007613	cg24496614	*GLI4*
1.065227	0.007649	cg09543792	*EMBP1*
0.893084	0.007653	cg21103269	*PM20D2*
0.219824	0.007681	cg24151841	*AKAP8L*
-0.69449	0.007768	cg20477591	*BMP2*
0.489759	0.007872	cg11661809	*MORN1*
-0.92752	0.008171	cg02691091	*DLX4*
0.42244	0.008232	cg17821664	*SOS2*
-0.28981	0.00834	cg13539395	*ACER1*
0.607249	0.008376	cg23683674	*RANBP9*
-0.60214	0.008771	cg20477591	*NOL9*
0.40756	0.008831	cg11021321	*ARPC5L*
-0.47463	0.008914	cg02266878	*CARD11*
-0.69467	0.00897	cg20477591	*DCHS1*
573.7044	0.009081	cg22081558	*AAGAB*
0.788674	0.009082	cg19374731	*SIGLEC1*
0.727753	0.009164	cg14273401	*CASC3*
0.706663	0.009214	cg01426818	*FOXP1*
0.000232	0.009302	cg00003722	*RMI1*
-0.81093	0.009308	cg06216103	*GPR68*
0.383242	0.009358	cg01395217	*PRKCH*
-0.42531	0.009447	cg02266878	*FAM193A*
1.211913	0.009514	cg01538301	*SLC24A1*
-0.59238	0.009523	cg15584606	*SLC12A7*
0.460126	0.009532	cg19862616	*CD2*
-0.48717	0.009544	cg02266878	*EBF4*
0.782505	0.009582	cg11661809	*LSM7*
0.642343	0.009608	cg12967050	*HSPA13*
1.065503	0.009609	cg05440435	*GNAO1*
0.977256	0.009628	cg05440435	*IKZF4*

-0.92652	0.009676	cg21322248	*ERP44*
0.213812	0.009705	cg07873926	*TMEM222*
1.360989	0.009831	cg01395217	*LIMD2*
0.426892	0.009854	cg01426818	*PIP5K1B*
-0.69571	0.009876	cg03821689	*BCL7C*
0.92108	0.009926	cg12967050	*CTRC*
0.328705	0.010213	cg26417188	*FBXL3*
0.495353	0.010278	cg19738404	*C3orf14*
0.320003	0.01049	cg10579012	*AJAP1*
0.528826	0.010714	cg21476203	*DGCR6L*
0.763138	0.010854	cg05440435	*MMP19*
0.46138	0.010938	cg07538364	*ARMC3*
0.971858	0.011007	cg13659360	*B9D1*
0.681868	0.011184	cg01662869	*FAM127C*
-0.32693	0.011188	cg19248893	*UNC5B*
-0.31142	0.011273	cg07555102	*AQP11*
-0.57434	0.011329	cg22588936	*SUCLG2*
0.250419	0.011589	cg13627491	*MAP3K9*
-0.27306	0.011713	cg04019843	*PDE4DIP*
0.464968	0.01175	cg26417188	*COX7B*
-0.53903	0.011789	cg02982198	*ROM1*
0.540746	0.011947	cg21103269	*LRRC8B*
0.168573	0.012021	cg19862616	*AKNA*
0.344715	0.012045	cg02266878	*PITRM1*
-1.04228	0.012097	cg22588936	*CABP4*
0.392649	0.012178	cg19738404	*PSMC5*
0.590725	0.012229	cg19248893	*RELT*
0.476069	0.012289	cg04871364	*COPG2*
0.79815	0.012349	cg25739003	*MAP2K4*
-0.4436	0.012349	cg20477591	*DNHD1*
0.242995	0.012382	cg18478353	*SFN*

0.587444	0.012409	cg23683674	*ERCC4*
-0.64131	0.012682	cg18478353	*OST4*
-0.52451	0.01286	cg04019843	*SHARPIN*
-0.63418	0.012973	cg00017461	*MAP2K2*
0.672351	0.013139	cg02374944	*ATF2*
-0.79192	0.013287	cg09776718	*LL22NC0*
-0.5865	0.013733	cg20200460	*PKIB*
-0.9669	0.013823	cg02691091	*C7orf57*
1.11326	0.013927	cg12967050	*EAF1*
-0.36083	0.013999	cg13675319	*OTOF*
-0.69142	0.01413	cg20477591	*TPP1*
-0.3891	0.01436	cg13659360	*E2F8*
-0.1711	0.014402	cg11160820	*SSBP1*
-0.39319	0.014541	cg09888026	*ALG6*
-0.19866	0.014725	cg08643007	*AGO1*
0.551306	0.014781	cg05396987	*GALNT5*
0.684691	0.014854	cg00315816	*POLR2L*
0.899116	0.015023	cg19142181	*B4GALT5*
-0.8463	0.015077	cg20200460	*TMEM155*
-0.49872	0.01508	cg00385142	*LNP1*
0.210571	0.015122	cg22755534	*ACE*
0.324081	0.015314	cg26417188	*RSF1*
0.304597	0.015528	cg17821664	*NCKAP5L*
-0.42448	0.015601	cg02266878	*NCLN*
-0.76508	0.015614	cg18478353	*HOXA4*
0.275674	0.015857	cg12967050	*CYP4F3*
0.116396	0.015883	cg26417188	*SYCE1L*
0.555058	0.016001	cg14273401	*PSMD3*
-0.22762	0.016135	cg07555102	*SYCE1L*
0.83084	0.016225	cg01662869	*JAKMIP3*
-0.56024	0.016246	cg08976554	*SLC25A4*

1.079897	0.016395	cg12967050	*NOTCH3*
0.732385	0.016524	cg00315816	*JMJD8*
0.540718	0.016572	cg01395217	*FEN1*
-0.54751	0.016755	cg02266878	*PRSS33*
-0.31241	0.016988	cg05990720	*MYT1L*
-0.98269	0.017005	cg20176285	*KRI1*
0.36622	0.017173	cg19738404	*ROM1*
-0.21304	0.017187	cg05990720	*SPSB3*
0.448935	0.017223	cg00385142	*HHIPL1*
0.313695	0.017316	cg19248893	*SLC29A3*
-0.797	0.01741	cg05440435	*MAP3K1*
0.529936	0.017422	cg20176285	*ATG4D*
0.99129	0.017531	cg23683674	*COX10*
0.296421	0.017544	cg18478353	*HOXA10*
-1.08335	0.017616	cg02691091	*C20orf1*
-0.24978	0.01785	cg05990720	*STK35*
0.613656	0.017971	cg02374944	*NOP16*
0.481676	0.017994	cg15365426	*NAA38*
-0.33236	0.018023	cg05990720	*GMDS*
-0.61144	0.018215	cg19142181	*SPATA20*
0.44438	0.018616	cg21103269	*PTEN*
0.28569	0.018683	cg13963729	*TIMP2*
-0.30218	0.018813	cg22081558	*ALDH3B1*
-0.51696	0.018951	cg20477591	*C3*
-0.43591	0.019158	cg13659360	*KCNH8*
-0.75123	0.019169	cg13539395	*GTF2F1*
0.248204	0.019469	cg07873926	*C9orf72*
0.390532	0.019579	cg12967050	*CC2D2A*
-0.44749	0.019613	cg05990720	*DOT1L*
-0.75107	0.019615	cg06216103	*FURIN*
0.374455	0.019747	cg19862616	*PCSK7*

-0.79355	0.019904	cg20477591	*FBXO39*
-0.33474	0.020055	cg11661809	*RNF4*
0.50069	0.020095	cg14273401	*LETM2*
-0.60719	0.020117	cg09776718	*BMS1P20*
0.633527	0.020461	cg12967050	*DDX1*
0.775566	0.020503	cg19142181	*SHISA5*
-0.59327	0.02055	cg20477591	*TRIP10*
0.264935	0.020609	cg19374731	*SDK1*
-1.0376	0.020699	cg22588936	*FBXL8*
0.488806	0.020738	cg20176285	*TMED1*
-0.39209	0.020742	cg13659360	*NAV2*
-1.06913	0.020824	cg16073958	*HP1BP3*
0.383414	0.020894	cg18478353	*HOXA7*
0.410918	0.020932	cg21103269	*LRRC8C*
0.342808	0.020971	cg12372414	*UPF1*
0.537857	0.020978	cg22588936	*KCTD19*
0.516425	0.020983	cg00315816	*TALDO1*
0.496734	0.021159	cg07538364	*DCTN5*
-0.46385	0.021177	cg13539395	*MRPL51*
1.388839	0.021191	cg23683674	*CD83*
-0.58837	0.021279	cg20383390	*FXYD6*
-0.41254	0.021282	cg13659360	*SUGP1*
-0.70076	0.021402	cg24496614	*RHPN1*
1.314702	0.021589	cg22588936	*RRS1*
0.39205	0.021591	cg05951364	*HELZ*
0.594872	0.021599	cg05951364	*PPP1R36*
-0.50166	0.021604	cg19142181	*CABP5*
0.338426	0.021761	cg00385142	*AGFG2*
0.510747	0.021834	cg05440435	*ERBB3*
-0.4983	0.022028	cg13659360	*PLIN2*
0.482103	0.022188	cg17821664	*CACNA2D*

-0.28115	0.022198	cg05990720	*MSRB1*
-0.56112	0.022202	cg02982198	*B3GNT2*
0.748511	0.0223	cg13539395	*LY86*
0.349034	0.022339	cg04871364	*PIK3R4*
0.430525	0.022415	cg00315816	*TMEM18*
0.323685	0.022493	cg01426818	*NAGK*
0.300388	0.022555	cg00385142	*C7orf43*
-0.2998	0.022704	cg21103269	*SPATA2L*
-0.68318	0.022726	cg09776718	*C1QA*
0.587193	0.022938	cg13664588	*GSDMD*
0.631215	0.023123	cg00315816	*DGKQ*
0.563595	0.023169	cg19142181	*UQCRC1*
-0.53031	0.023258	cg02266878	*GNG7*
0.437388	0.023267	cg11661809	*KCNQ1*
0.314907	0.023403	cg26417188	*MAGT1*
-0.68303	0.023473	cg02266878	*FLYWCH1*
0.490145	0.023611	cg19142181	*PCSK1N*
0.611066	0.023762	cg19142181	*FBN1*
-1.28343	0.023787	cg07555102	*ATP9B*
-0.43132	0.023814	cg13664588	*EPPK1*
-0.50275	0.023817	cg02691091	*MSH6*
0.467666	0.02385	cg19142181	*SPATA2*
-0.50609	0.023933	cg02266878	*ITFG2*
0.372015	0.024057	cg14273401	*MTF1*
0.338186	0.024228	cg02724025	*EEF1A2*
0.53463	0.024239	cg19142181	*SMAD4*
-0.32677	0.024306	cg02724025	*HELZ2*
-0.44216	0.024356	cg09543792	*POLQ*
0.505422	0.024425	cg01426818	*PTCD2*
-0.38632	0.024479	cg14724918	*HBQ1*
-0.78339	0.024574	cg02266878	*LPIN2*

-0.56072	0.024689	cg20477591	*THAP3*
-0.42086	0.024879	cg02691091	*ABCA13*
0.203463	0.024897	cg16616362	*ABCC6*
-0.40309	0.024926	cg07555102	*TMEM60*
0.404513	0.025204	cg10579012	*SPATA6L*
0.592243	0.025959	cg00017461	*RHOG*
0.569656	0.026513	cg19142181	*LIG1*
0.273495	0.026574	cg18786125	*ABHD17B*
0.244289	0.026575	cg19738404	*PPDPF*
0.229383	0.026626	cg09791665	*AGO4*
0.347825	0.026664	cg07538364	*MSRB2*
0.408761	0.026786	cg19738404	*FAM161A*
0.616247	0.026933	cg13539395	*GAPDH*
0.681206	0.026945	cg19862616	*IGSF3*
0.510594	0.027054	cg19142181	*RBM3*
0.429472	0.027136	cg11661809	*MYLK4*
-0.48011	0.027331	cg02982198	*INTS5*
0.386894	0.027401	cg19374731	*DFFB*
-0.28168	0.027568	cg20477591	*GRID2IP*
-0.50623	0.02763	cg15584606	*FGFRL1*
0.360182	0.027662	cg14273401	*SHB*
-0.17348	0.027695	cg05990720	*ATP8B3*
-0.44554	0.027739	cg20383390	*TNFSF8*
-0.36175	0.027756	cg21103269	*LYSMD3*
-0.29202	0.027765	cg18478353	*STK38L*
-0.66157	0.02787	cg02982198	*TTC9C*
-0.42159	0.028039	cg20477591	*MRPL51*
0.422334	0.028071	cg19142181	*FRYL*
-0.31248	0.028141	cg05990720	*RPA1*
0.395359	0.028169	cg19862616	*DSCAML1*
0.404772	0.028341	cg11661809	*EBF4*

0.315969	0.028396	cg05951364	*NEAT1*
0.291912	0.028503	cg10579012	*ALOX15*
-0.64842	0.028771	cg22588936	*DOC2GP*
1.328639	0.028938	cg05440435	*EPX*
0.520188	0.028957	cg20176285	*PINX1*
0.286946	0.029343	cg07538364	*PALB2*
0.273242	0.029367	cg27435903	*FANCC*
0.336178	0.029702	cg07538364	*RPS2P32*
0.517487	0.029834	cg11661809	*SRR*
0.888891	0.029902	cg18478353	*CAD*
0.704681	0.029921	cg05440435	*NEDD4*
-0.40845	0.03	cg02982198	*MTA2*
0.646493	0.030046	cg11661809	*GMDS*
-0.98823	0.030157	cg02691091	*KPTN*
-0.3604	0.030172	cg19248893	*FAM168A*
0.338452	0.030271	cg05396987	*RNF145*
0.392028	0.030294	cg00315816	*STUB1*
0.345043	0.030404	cg20477591	*TAPBPL*
0.254928	0.030549	cg00315816	*TMED11P*
0.343327	0.030709	cg19374731	*ATRN*
-0.31426	0.031277	cg09776718	*C1QB*
-0.52448	0.031506	cg13590117	*ARL6IP1*
0.328683	0.031534	cg21103269	*FANCA*
0.582561	0.031649	cg05951364	*DSEL*
-0.34373	0.031658	cg07538364	*PLK1*
0.405924	0.031798	cg00017461	*PIP5K1C*
0.000262	0.031876	cg00003722	*COL24A1*
0.547244	0.031894	cg19142181	*PIM2*
-0.28639	0.032071	cg02712036	*ASXL1*
0.449303	0.032302	cg21103269	*HERC3*
0.56804	0.032426	cg19142181	*SUV39H1*

-0.50492	0.032726	cg02691091	*PKD1L1*
-0.41652	0.033055	cg20477591	*LPAR5*
0.400884	0.033256	cg11661809	*TSSC4*
0.387138	0.033312	cg18478353	*HOXA5*
0.505539	0.033404	cg03468115	*FKBP14*
0.549721	0.033525	cg27435903	*TSPYL5*
-0.49947	0.033769	cg24818434	*KANK3*
0.313741	0.033785	cg19374731	*LRPAP1*
-0.79669	0.033993	cg02691091	*SLC48A1*
0.226192	0.034185	cg01426818	*MAP3K9*
-0.67949	0.034285	cg10410121	*PSMB4*
0.470954	0.034343	cg13627491	*NADSYN1*
-0.47837	0.034491	cg20477591	*ARFIP2*
-0.88484	0.034575	cg20630567	*FLI1*
-0.21488	0.034622	cg05098096	*PSMF1*
-0.41608	0.034676	cg20630567	*ACAD9*
-0.35217	0.034718	cg20477591	*MRPL17*
0.316136	0.034743	cg19738404	*COMMD1*
-0.47061	0.0352	cg09397375	*SUPT3H*
-0.36944	0.03577	cg19374731	*MEGF6*
0.262454	0.035861	cg14724918	*DECR2*
-0.17597	0.035919	cg10200408	*ABCA17P*
0.371606	0.036176	cg11661809	*TMC2*
0.722527	0.036322	cg15847604	*SFMBT1*
-0.35729	0.036375	cg07873926	*CCDC34*
0.58406	0.036447	cg05440435	*NAT14*
0.675705	0.036601	cg14273401	*ELFN2*
-0.21377	0.036657	cg05990720	*NTHL1*
0.349279	0.036853	cg19738404	*IPO11*
0.124977	0.036918	cg05990720	*POLN*
0.412857	0.037059	cg25739003	*ELOF1*

0.91686	0.037199	cg15847604	*CC2D1B*
0.294849	0.037569	cg11661809	*CASKIN1*
0.15455	0.037719	cg11021321	*SLC12A2*
0.527778	0.037957	cg14724918	*IFITM3*
0.442094	0.03797	cg10179363	*PRDX1*
0.345971	0.037989	cg19142181	*SLAIN2*
-0.44356	0.038097	cg14273401	*ORMDL3*
-0.27238	0.038369	cg21322248	*MOK*
-0.7295	0.038394	cg21476203	*PSPC1*
0.630351	0.038467	cg20232060	*LANCL2*
0.235695	0.038572	cg26417188	*RORB*
-0.19563	0.038688	cg26146287	*RCL1*
-0.3076	0.03894	cg02982198	*PTPRG*
-0.21895	0.038973	cg05990720	*HAUS3*
0.510386	0.038973	cg19738404	*TM2D1*
-0.23876	0.039157	cg14442841	*TELO2*
-0.50789	0.039241	cg07555102	*FAM47E*
0.276039	0.039378	cg19738404	*TEX2*
0.931817	0.039403	cg19142181	*NME6*
-0.41006	0.039518	cg13659360	*MAP3K15*
0.511165	0.03957	cg00315816	*RHOT2*
-0.47515	0.039801	cg23683674	*RLN3*
-0.24143	0.039881	cg05990720	*RPL3L*
0.31303	0.039885	cg01395217	*TMEM258*
0.454424	0.040204	cg11661809	*MIR940*
0.192036	0.04039	cg19374731	*ADI1*
-0.45705	0.040476	cg13539395	*L3MBTL4*
0.275523	0.040675	cg19248893	*JPX*
0.573055	0.040712	cg21103269	*FOXN3*
0.177389	0.040936	cg26417188	*PEAK1*
0.312139	0.041268	cg14273401	*TBC1D1*

-0.49406	0.041301	cg18478353	*CCDC34*
-0.21957	0.041332	cg05990720	*NDUFS6*
-0.74149	0.041545	cg20200460	*DIRC2*
0.173581	0.041634	cg16629408	*RAB15*
0.358901	0.041767	cg19738404	*AR*
0.486212	0.042021	cg23683674	*TCEANC*
-0.52955	0.042162	cg02982198	*DDX5*
-0.86428	0.042694	cg12967050	*FAM200B*
0.491014	0.042719	cg18787783	*CHID1*
-0.27658	0.04281	cg05098096	*MED16*
-0.39603	0.042872	cg19248893	*ARIH1*
-0.13891	0.042914	cg11160820	*TBC1D9*
0.78841	0.042947	cg20232060	*KIR3DL2*
-0.31469	0.043166	cg00315816	*METRN*
-1.15559	0.043457	cg20232060	*BRSK1*
-0.37308	0.04367	cg00385142	*TM9SF2*
-0.18734	0.043881	cg02712036	*MTMR10*
-0.1679	0.043999	cg05098096	*ELANE*
-0.49814	0.044019	cg21103269	*RNGTT*
-0.26019	0.044164	cg12348202	*MACROD2*
2.257363	0.044254	cg05440435	*MIER3*
-0.42819	0.044578	cg12967050	*BST1*
-0.2526	0.044691	cg05098096	*SNTG2*
-0.36977	0.044758	cg02266878	*CLDN9*
-0.21722	0.044787	cg05990720	*KLF16*
0.345218	0.044812	cg11661809	*METTL4*
-0.15365	0.044812	cg11160820	*ATP1B3*
0.341714	0.044902	cg20977448	*RANBP17*
-0.14356	0.044973	cg22081558	*AGRP*
0.293828	0.045072	cg11661809	*SNX8*
0.465994	0.04509	cg19738404	*FTSJ3*

-0.26305	0.046154	cg19248893	*SLC16A5*
-0.4844	0.046313	cg10179363	*SP2*
-0.44044	0.046571	cg02266878	*PAQR4*
0.590703	0.046603	cg01395217	*DIMT1*
1.038057	0.046633	cg09888026	*ITGB3BP*
-0.67027	0.046759	cg02982198	*BSCL2*
0.445084	0.046821	cg10579012	*CCND2*
-0.39192	0.046842	cg00385142	*GAL3ST4*
0.716386	0.046881	cg09543792	*EPB41L5*
0.514233	0.047202	cg13539395	*KLHL21*
0.234445	0.047424	cg01395217	*NFIA*
-0.27142	0.047548	cg14442841	*CRIPAK*
0.370539	0.048141	cg11661809	*TRPM5*
0.238998	0.048443	cg19374731	*DOK7*
0.24697	0.048747	cg07538364	*OXA1L*
0.747233	0.049029	cg05440435	*CHCHD2*
0.433705	0.049285	cg23683674	*RFX1*
0.558064	0.049806	cg20232060	*CES1P1*
-0.59043	0.049939	cg09776718	*BMI1*

Supplement Table S12 (A): MethQTLs identified based on association of SNPs with DNAm in males (n=306)

Dependent	Parameter	Estimate	StdErr	tValue	Probt
cg20383390	rs1009549 2	-0.10734	0.050753	-2.11	0.035248
cg24343755	rs10508720 1	0.328499	0.142266	2.31	0.021614
cg24343755	rs10508720 2	0.173538	0.054484	3.19	0.001598
cg06216103	rs10751711 1	0.559468	0.088146	6.35	<.000000001
cg06216103	rs10751711 2	0.220685	0.067784	3.26	0.001259
cg13627491	rs10819899 2	0.17396	0.070011	2.48	0.013503
cg13627491	rs10819903 1	-0.22148	0.088303	-2.51	0.012656
cg04871364	rs10864548 1	-0.26342	0.090796	-2.9	0.00399

cg06216103	rs10902512 1	0.546382	0.091213	5.99	6E-09
cg06216103	rs10902512 2	0.176893	0.069047	2.56	0.010893
cg24343755	rs11015236 2	-0.13888	0.060897	-2.28	0.023265
cg24343755	rs11015249 1	-0.28527	0.073259	-3.89	0.000121
cg24343755	rs11015249 2	-0.11335	0.052374	-2.16	0.031225
cg15847604	rs11054443 1	0.111962	0.046403	2.41	0.016424
cg15847604	rs11054443 2	0.077741	0.033723	2.31	0.021829
cg19142181	rs11086147 1	1.481875	0.240551	6.16	2E-09
cg19142181	rs11086147 2	1.211184	0.200082	6.05	4E-09
cg19248893	rs11122115 2	-0.09099	0.030955	-2.94	0.00354
cg06216103	rs11246996 1	0.580753	0.177039	3.28	0.001158
cg06216103	rs11246996 2	0.242206	0.067109	3.61	0.000359
cg06216103	rs11247000 1	0.371331	0.14846	2.5	0.012904
cg06216103	rs11247000 2	0.196931	0.067832	2.9	0.003965
cg20383390	rs1146297 2	-0.11337	0.050797	-2.23	0.026359
cg20383390	rs1146298 2	-0.10802	0.050836	-2.12	0.034411
cg26146287	rs11575893 1	-0.62074	0.150313	-4.13	4.7E-05
cg21322248	rs11639459 1	-0.32628	0.130124	-2.51	0.012683
cg21322248	rs11639459 2	-0.13683	0.036325	-3.77	0.000199
cg02724025	rs11647164 2	0.113646	0.053106	2.14	0.033154
cg02998992	rs11652712 2	0.428023	0.12835	3.33	0.000959
cg00707741	rs11682333 2	-0.0803	0.037783	-2.13	0.034364
cg04871364	rs12074379 1	0.955603	0.349143	2.74	0.006566
cg18786125	rs12080677 2	0.100514	0.046039	2.18	0.029786
cg13627491	rs12236239 1	-0.36219	0.129323	-2.8	0.005428
cg09396181	rs12492784 2	0.068696	0.032835	2.09	0.037256
cg02724025	rs12708869 2	0.113646	0.053106	2.14	0.033154
cg20383390	rs1290539 2	-0.10959	0.050825	-2.16	0.031853
cg20383390	rs1290541 2	-0.10959	0.050825	-2.16	0.031853
cg21322248	rs12912465 2	0.08542	0.035152	2.43	0.015678
cg14736210	rs13044588 1	-0.60835	0.216397	-2.81	0.005257

cg27230396	rs13121538 2	0.122612	0.059802	2.05	0.041196
cg20383390	rs1316011 2	-0.10734	0.050753	-2.11	0.035248
cg00707741	rs13388333 1	-0.11093	0.053411	-2.08	0.038653
cg00707741	rs13388333 2	-0.08652	0.037597	-2.3	0.022059
cg13627491	rs1339424 2	-0.11882	0.059916	-1.98	0.048258
cg02724025	rs1520237 2	-0.12654	0.052876	-2.39	0.017316
cg15847604	rs1547392 2	0.074214	0.033508	2.21	0.027517
cg24343755	rs1564271 1	-0.34603	0.090443	-3.83	0.000158
cg24343755	rs16927305 2	-0.1344	0.061814	-2.17	0.030462
cg10179363	rs17239917 2	0.072495	0.028527	2.54	0.011543
cg21322248	rs17465692 1	0.1224	0.048343	2.53	0.01185
cg21322248	rs17465692 2	0.080154	0.03978	2.01	0.044798
cg15847604	rs17745932 2	-0.12189	0.046507	-2.62	0.009209
cg24343755	rs1780179 1	-0.2314	0.078554	-2.95	0.003471
cg24343755	rs1780180 1	-0.23096	0.080138	-2.88	0.004233
cg24343755	rs1780196 1	0.444575	0.182203	2.44	0.01526
cg24343755	rs1780196 2	0.317385	0.054198	5.86	1.2E-08
cg18478353	rs1878069 2	-0.07696	0.029166	-2.64	0.008754
cg19248893	rs201151 2	0.067569	0.032711	2.07	0.039713
cg13627491	rs2012728 2	-0.12251	0.062103	-1.97	0.049437
cg23683674	rs2027761 2	0.106327	0.051225	2.08	0.038766
cg00707741	rs2055566 1	0.506693	0.215877	2.35	0.019562
cg19142181	rs2093045 1	0.805617	0.257458	3.13	0.001924
cg19142181	rs2093045 2	0.604156	0.197963	3.05	0.002476
cg19248893	rs2235564 1	0.10569	0.046646	2.27	0.02417
cg19248893	rs2235564 2	0.064978	0.030063	2.16	0.03145
cg26146287	rs2239670 2	0.162742	0.048614	3.35	0.000918
cg14273401	rs2240068 2	-0.22208	0.099837	-2.22	0.026857
cg19142181	rs2248900 1	1.362868	0.413597	3.3	0.0011
cg19142181	rs2248900 2	1.232939	0.174187	7.08	<.000000001
cg13627491	rs2251885 2	0.153934	0.061332	2.51	0.0126

cg14736210	rs237473	2	0.092034	0.045942	2	0.046037
cg24343755	rs2448111	1	0.342416	0.167838	2.04	0.042202
cg24343755	rs2448111	2	0.303687	0.054346	5.59	5.1E-08
cg14273401	rs2523990	2	0.278927	0.103883	2.69	0.007652
cg15847604	rs2723830	2	0.078481	0.033544	2.34	0.019954
cg18786125	rs2821050	2	0.083201	0.042103	1.98	0.049044
cg18478353	rs2839550	2	-0.07684	0.034743	-2.21	0.027738
cg18478353	rs2839557	2	-0.08825	0.029685	-2.97	0.003187
cg05951364	rs2972174	2	-0.07118	0.032909	-2.16	0.031323
cg05951364	rs2972175	2	-0.07123	0.034521	-2.06	0.039938
cg13627491	rs2993805	2	0.17396	0.070011	2.48	0.013503
cg24343755	rs3118153	1	0.34161	0.16786	2.04	0.042712
cg24343755	rs3118153	2	0.304538	0.054606	5.58	5.4E-08
cg04871364	rs34064241	1	0.953681	0.348644	2.74	0.006598
cg13963729	rs349311	1	0.780327	0.381801	2.04	0.041837
cg20977448	rs352346	1	-0.64128	0.070292	-9.12	<.000000001
cg20977448	rs352346	2	-0.30691	0.05939	-5.17	4.31E-07
cg20977448	rs352347	1	-0.64997	0.070027	-9.28	<.000000001
cg20977448	rs352347	2	-0.31976	0.059166	-5.4	1.32E-07
cg19142181	rs3729555	1	1.957778	0.226678	8.64	<.000000001
cg19142181	rs3729555	2	2.02826	0.162029	12.52	<.000000001
cg02724025	rs3760056	2	0.113646	0.053106	2.14	0.033154
cg00707741	rs3771551	2	0.13163	0.04806	2.74	0.00653
cg00707741	rs3771583	2	0.132413	0.052639	2.52	0.012404
cg15847604	rs3782137	1	0.109399	0.046414	2.36	0.019059
cg19142181	rs3810460	1	2.660948	0.181245	14.68	<.000000001
cg19142181	rs3810460	2	2.630518	0.149955	17.54	<.000000001
cg16360777	rs3924573	1	-0.21778	0.103271	-2.11	0.03578
cg09791665	rs412816	2	0.114386	0.057729	1.98	0.048446
cg24343755	rs4369307	1	0.331357	0.142085	2.33	0.02035
cg24343755	rs4369307	2	0.179586	0.053995	3.33	0.00099

cg21322248	rs4420499 1	-0.31635	0.119648	-2.64	0.008619
cg21322248	rs4420499 2	-0.11935	0.038395	-3.11	0.002058
cg09791665	rs444131 2	0.114386	0.057729	1.98	0.048446
cg05951364	rs4552929 1	0.195468	0.092009	2.12	0.034441
cg18786125	rs4648524 2	0.111049	0.040435	2.75	0.006387
cg00707741	rs4675947 2	-0.0803	0.037783	-2.13	0.034364
cg14736210	rs4809746 1	0.452865	0.217917	2.08	0.038537
cg05951364	rs4876074 1	-0.17366	0.080462	-2.16	0.031692
cg05951364	rs4876121 1	0.260136	0.111736	2.33	0.020564
cg21322248	rs4886508 1	-0.15351	0.048167	-3.19	0.001587
cg02724025	rs4967866 2	0.14469	0.057556	2.51	0.012458
cg21322248	rs5021805 1	-0.33235	0.118815	-2.8	0.005484
cg21322248	rs5021805 2	-0.13776	0.03652	-3.77	0.000195
cg09396181	rs6442414 2	0.06652	0.033417	1.99	0.047424
cg24343755	rs6482573 2	0.117113	0.052817	2.22	0.027341
cg13627491	rs649892 2	0.139856	0.061462	2.28	0.023575
cg09888026	rs6565550 1	-0.17037	0.084442	-2.02	0.044514
cg09888026	rs6565550 2	-0.07397	0.027892	-2.65	0.008419
cg02998992	rs6587074 2	0.327018	0.097489	3.35	0.000896
cg06216103	rs6598209 1	0.482705	0.200275	2.41	0.016539
cg06216103	rs6598209 2	0.160074	0.069068	2.32	0.021136
cg19248893	rs6659873 1	0.093748	0.04576	2.05	0.041356
cg19248893	rs6659873 2	0.069069	0.030193	2.29	0.022851
cg27230396	rs6849066 2	0.122612	0.059802	2.05	0.041196
cg13627491	rs7037253 2	0.188035	0.066942	2.81	0.005294
cg23683674	rs7125978 2	0.106327	0.051225	2.08	0.038766
cg09888026	rs7223219 2	-0.08267	0.026182	-3.16	0.001751
cg23683674	rs725103 2	0.102796	0.041919	2.45	0.014761
cg18478353	rs7280392 2	-0.08986	0.029839	-3.01	0.002818
cg06216103	rs7306456 1	0.626219	0.088433	7.08	<.000000001
cg06216103	rs7306456 2	0.213995	0.066478	3.22	0.001426

cg15847604	rs7310017 1	0.114072	0.046148	2.47	0.013989
cg22364465	rs7533778 1	0.592317	0.230162	2.57	0.010544
cg00707741	rs764081 1	0.186836	0.064144	2.91	0.003849
cg20977448	rs783777 1	-0.3784	0.152818	-2.48	0.013827
cg20977448	rs783777 2	-0.15207	0.060884	-2.5	0.013028
cg15847604	rs7961094 2	0.079865	0.033073	2.41	0.016335
cg06216103	rs7977641 2	0.170119	0.067813	2.51	0.012641
cg06216103	rs7977750 2	0.170119	0.067813	2.51	0.012641
cg09888026	rs8076437 2	-0.08295	0.026374	-3.15	0.001825
cg19374731	rs903914 1	0.138824	0.066049	2.1	0.036393
cg19374731	rs903914 2	0.114634	0.037419	3.06	0.002384
cg19142181	rs910934 1	1.470245	0.461154	3.19	0.001581
cg19142181	rs910934 2	1.298085	0.196167	6.62	<.000000001
cg15847604	rs974728 1	0.129442	0.046691	2.77	0.005911
cg09396181	rs9840696 1	-0.1041	0.048379	-2.15	0.032204

Supplement Table S12 (B): MethQTLs identified based on association of SNPs with DNAm in females (n=315)

Dependent	Parameter	Estimate	Biased	StdErr	tValue	Probt
cg27230396	rs10013334 2	-0.12954	1	0.057453	-2.25	0.024843
cg13627491	rs10120384 2	-0.72009	1	0.332668	-2.16	0.031177
cg13627491	rs10156478 2	-0.16551	1	0.062701	-2.64	0.008715
cg21322248	rs1022198 2	0.058968	1	0.029163	2.02	0.044027
cg02724025	rs1040271 1	-0.20601	1	0.073517	-2.8	0.005393
cg24343755	rs10508720 1	0.301343	1	0.129533	2.33	0.020639
cg24343755	rs10508720 2	0.200818	1	0.045419	4.42	1.36E-05
cg02374944	rs1057105 1	0.578655	1	0.272534	2.12	0.034521
cg06216103	rs10751711 1	0.587038	1	0.082079	7.15	<.000000001
cg06216103	rs10751711 2	0.312146	1	0.066489	4.69	4E-06
cg22364465	rs10863698 1	0.121887	1	0.038832	3.14	0.001859
cg06216103	rs10902512 1	0.46887	1	0.086755	5.4	1.29E-07
cg06216103	rs10902512 2	0.197132	1	0.069822	2.82	0.005058

cg24343755	rs11015236 1	-0.42432	1	0.215247	-1.97	0.049573
cg24343755	rs11015249 1	-0.33466	1	0.057591	-5.81	1.5E-08
cg24343755	rs11015249 2	-0.12583	1	0.044031	-2.86	0.004552
cg24343755	rs11015253 1	-0.42885	1	0.123559	-3.47	0.000592
cg24343755	rs11015253 2	-0.11813	1	0.045566	-2.59	0.009974
cg24343755	rs11015262 1	-0.56143	1	0.163554	-3.43	0.000678
cg24343755	rs11015262 2	-0.14338	1	0.047777	-3	0.002907
cg23683674	rs1107038 1	0.445586	1	0.132259	3.37	0.000849
cg21322248	rs11072639 2	-0.13182	1	0.036563	-3.61	0.000363
cg19142181	rs11086147 1	2.311959	1	0.24966	9.26	<.000000001
cg19142181	rs11086147 2	1.58134	1	0.210926	7.5	<.000000001
cg19248893	rs11122115 2	-0.081	1	0.029443	-2.75	0.006285
cg06216103	rs11246996 1	0.523004	1	0.136279	3.84	0.00015
cg06216103	rs11246996 2	0.197637	1	0.065322	3.03	0.002688
cg06216103	rs11247000 1	0.285558	1	0.128025	2.23	0.026426
cg06216103	rs11247000 2	0.219937	1	0.06577	3.34	0.000926
cg21322248	rs11639459 1	-0.23072	1	0.092726	-2.49	0.013361
cg21322248	rs11639459 2	-0.12285	1	0.028733	-4.28	2.54E-05
cg27230396	rs11727631 2	-0.10551	1	0.047424	-2.22	0.026804
cg27230396	rs11734394 2	-0.1093	1	0.047129	-2.32	0.021032
cg18786125	rs12080677 2	0.108272	1	0.047918	2.26	0.024541
cg13659360	rs12275038 1	0.237002	1	0.1155	2.05	0.041008
cg18478353	rs12482752 2	0.072625	1	0.026006	2.79	0.005552
cg27230396	rs12501546 2	-0.13609	1	0.052645	-2.59	0.010191
cg09396181	rs12639607 1	-0.148	1	0.06699	-2.21	0.027885
cg27230396	rs12651108 1	-0.72452	1	0.281533	-2.57	0.010529
cg02374944	rs1266479 1	0.579019	1	0.272504	2.12	0.034388
cg02374944	rs1266481 1	0.579019	1	0.272504	2.12	0.034388
cg21322248	rs12912465 1	0.191172	1	0.060743	3.15	0.001808
cg00707741	rs13388333 1	-0.10112	1	0.048071	-2.1	0.036211
cg00707741	rs13388333 2	-0.07778	1	0.032991	-2.36	0.01901

cg13627491	rs1410854 2	-0.1718	1	0.062332	-2.76	0.006192
cg02724025	rs1520237 2	0.117897	1	0.055462	2.13	0.03431
cg02724025	rs1532418 1	-0.2527	1	0.087254	-2.9	0.004045
cg24343755	rs1564271 1	-0.27052	1	0.084728	-3.19	0.001553
cg22364465	rs1604364 1	-0.13016	1	0.039357	-3.31	0.001052
cg02724025	rs16968480 1	-0.17377	1	0.084762	-2.05	0.041187
cg21322248	rs16968625 2	-0.11042	1	0.043248	-2.55	0.01115
cg27230396	rs17002091 1	-0.36235	1	0.178414	-2.03	0.043109
cg27230396	rs17002091 2	-0.13215	1	0.051887	-2.55	0.011351
cg27230396	rs17002139 2	-0.12597	1	0.054902	-2.29	0.022427
cg09396181	rs17038710 1	-0.16599	1	0.06879	-2.41	0.016401
cg21322248	rs17465692 1	0.132558	1	0.041377	3.2	0.001497
cg05951364	rs17748677 1	0.208365	1	0.077692	2.68	0.00771
cg24343755	rs1780196 1	0.352862	1	0.092132	3.83	0.000155
cg24343755	rs1780196 2	0.296619	1	0.045263	6.55	<.000000001
cg23683674	rs2027761 2	0.083491	1	0.041785	2	0.046574
cg19374731	rs2055204 1	0.139013	1	0.046452	2.99	0.002987
cg02724025	rs2088285 1	-0.21163	1	0.078568	-2.69	0.00745
cg19142181	rs2093045 1	1.973028	1	0.27116	7.28	<.000000001
cg19142181	rs2093045 2	1.309237	1	0.204292	6.41	<.000000001
cg02724025	rs2195431 2	0.199969	1	0.0676	2.96	0.003332
cg13963729	rs2238577 2	-0.07973	1	0.038718	-2.06	0.040308
cg26146287	rs2239670 2	0.085961	1	0.040694	2.11	0.035451
cg19142181	rs2248900 1	1.512895	1	0.398406	3.8	0.000176
cg19142181	rs2248900 2	1.314265	1	0.207093	6.35	<.000000001
cg13627491	rs2252151 1	0.151881	1	0.075983	2	0.046487
cg02724025	rs2280396 1	-0.22419	1	0.072297	-3.1	0.002105
cg05951364	rs2301963 1	0.092896	1	0.042037	2.21	0.02784
cg24343755	rs2448111 1	0.349453	1	0.098377	3.55	0.000441
cg24343755	rs2448111 2	0.303419	1	0.044956	6.75	<.000000001
cg21322248	rs2469203 2	0.06076	1	0.029199	2.08	0.038262

cg21322248	rs2469232	2	0.06076	1	0.029199	2.08	0.038262
cg22364465	rs2478816	2	0.063383	1	0.032005	1.98	0.048532
cg22364465	rs2498024	2	0.068236	1	0.029257	2.33	0.020323
cg02724025	rs28216	1	-0.21046	1	0.075088	-2.8	0.005383
cg19374731	rs2843142	2	-0.12797	1	0.039391	-3.25	0.001285
cg19374731	rs2843146	2	-0.07298	1	0.036634	-1.99	0.047234
cg14273401	rs2844795	2	0.230071	1	0.112662	2.04	0.041979
cg05951364	rs2906590	2	-0.07388	1	0.035152	-2.1	0.036371
cg13627491	rs2993808	1	-0.26857	1	0.086701	-3.1	0.002128
cg24343755	rs3118153	1	0.343324	1	0.095124	3.61	0.000358
cg24343755	rs3118153	2	0.30198	1	0.045417	6.65	<.000000001
cg13963729	rs349311	1	-0.32797	1	0.166205	-1.97	0.049345
cg13963729	rs349312	2	-0.07198	1	0.035678	-2.02	0.044496
cg02724025	rs35188	1	-0.21198	1	0.079666	-2.66	0.008196
cg02724025	rs35195	1	-0.21198	1	0.079666	-2.66	0.008196
cg20977448	rs352346	1	-0.38123	1	0.066871	-5.7	2.8E-08
cg20977448	rs352346	2	-0.12314	1	0.057403	-2.15	0.032711
cg20977448	rs352347	1	-0.38123	1	0.066871	-5.7	2.8E-08
cg20977448	rs352347	2	-0.12314	1	0.057403	-2.15	0.032711
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cg04410091	rs3814772 2	0.100256	1	0.037312	2.69	0.007597
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cg18478353	rs8134499 2	0.077877	1	0.026112	2.98	0.003085
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cg19142181	rs910934	2	1.613536	1	0.206826	7.8	<.000000001
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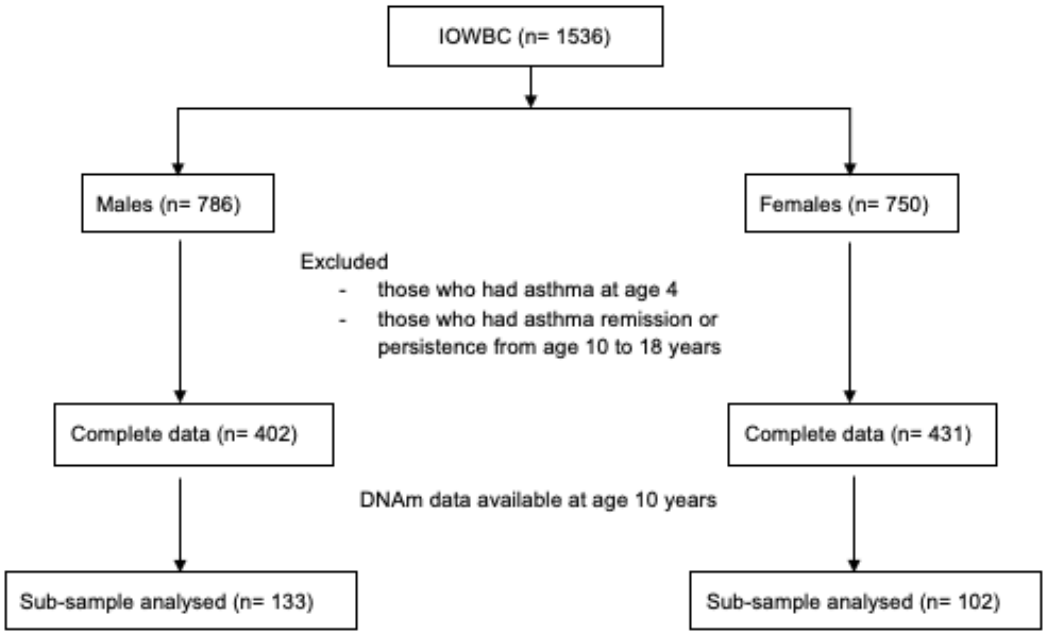
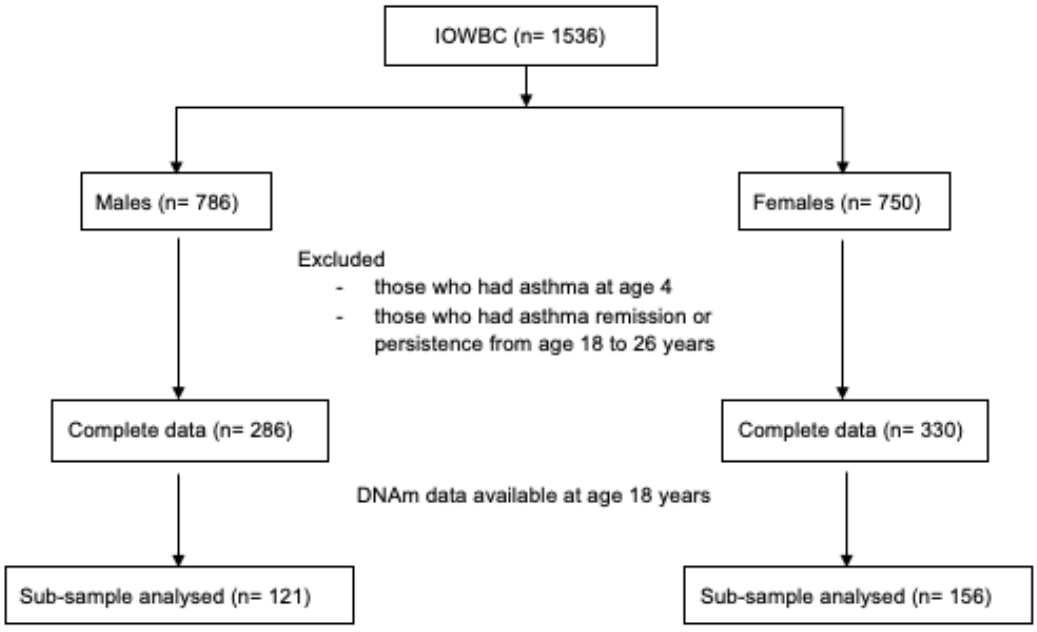
cg18478353	rs9976600	1	0.06593	1	0.032379	2.04	0.042575
cg26054167	rs6090357	2	0.218768	1	0.077774	2.81	0.005221

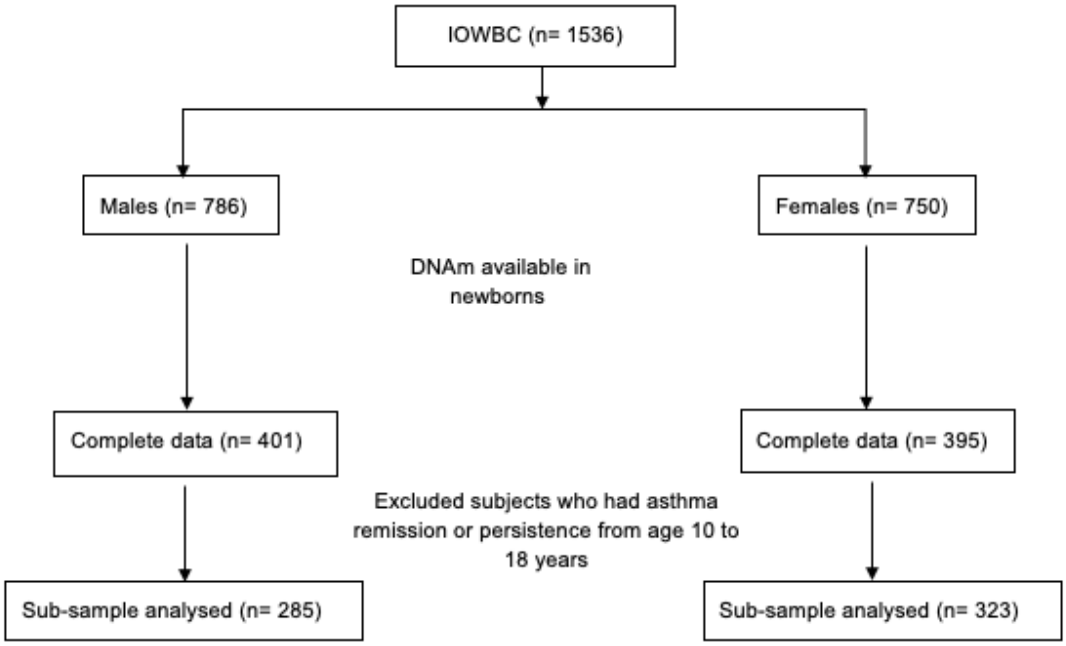
Figures



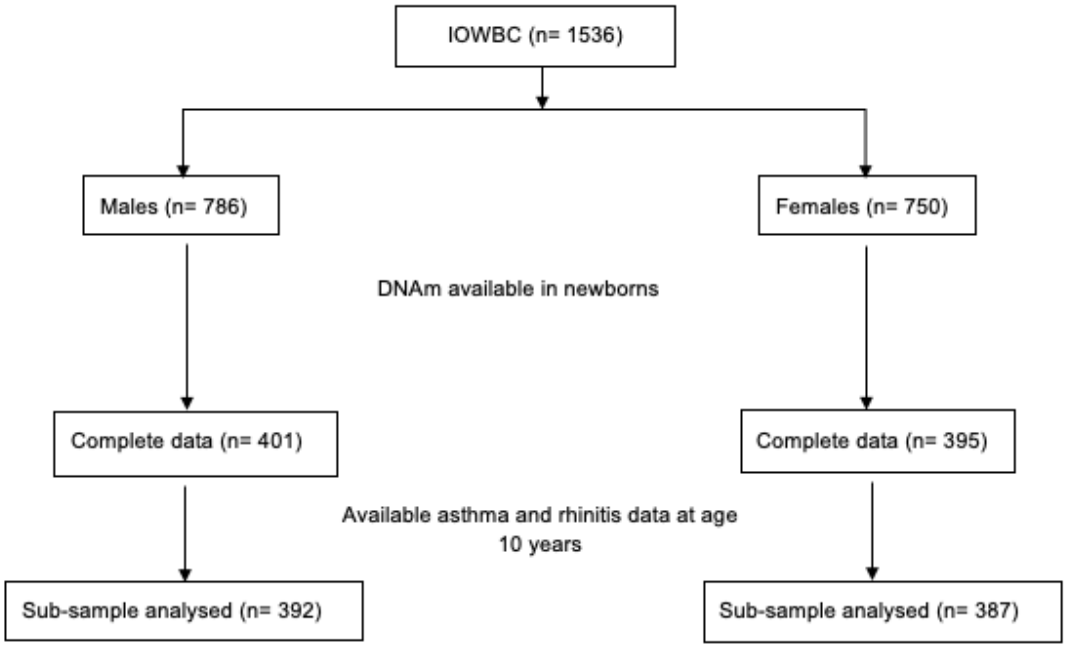
Supplement Figure S3(A): Consort diagram of Asthma acquisition subjects included in Aim 3 for 10-18 period (IOWBC).



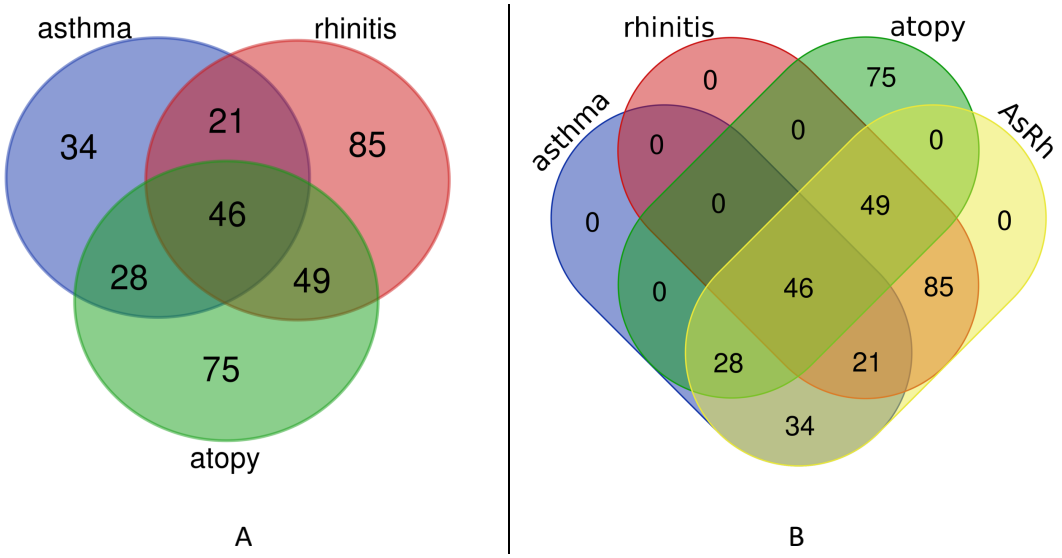
Supplement Figure S3(B): Consort diagram of Asthma acquisition subjects included in Aim 3 for 18-26 period (IOWBC).



Supplement Figure S4: Consort diagram of Asthma acquisition subjects included in Aim 4 for 10-18 period (IOWBC).



Supplement Figure S5: Consort diagram of Asthma and Rhinitis subjects included in Aim 5 at age 10 years (IOWBC).



Supplement Figure S6: Venn diagram representing not all subjects who had asthma or rhinitis also have atopy at age 10 years (IOWBC).

IRB Approvals

Sunday, October 10, 2021 at 13:06:34 Central Daylight Time

Subject: PRO-FY2021-442 - Admin Withdrawal: Not Human Subject Research
Date: Wednesday, June 30, 2021 at 9:06:51 AM Central Daylight Time
From: do-not-reply@cayuse.com
To: Aniruddha Bhadresh Rathod (abrathod), Hongmei Zhang (hzhang6)
Attachments: ATT00001.png

Institutional Review Board
Division of Research and Innovation
Office of Research Compliance
University of Memphis
315 Admin Bldg
Memphis, TN 38152-3370

June 30, 2021

PI Name: Aniruddha Rathod
Co-Investigators:
Advisor and/or Co-PI: Hongmei Zhang
Submission Type: Admin Withdrawal
Title: DNA Methylation and Asthma acquisition during and post-adolescence, an epigenome-wide longitudinal study
IRB ID: PRO-FY2021-442

From the information provided on your determination review request for “DNA Methylation and Asthma acquisition during and post-adolescence, an epigenome-wide longitudinal study”, the IRB has determined that your activity does not meet the Office of Human Subjects Research Protections definition of human subjects research and 45 CFR part 46 does not apply.

This study does not require IRB approval nor review. Your determination will be administratively withdrawn from Cayuse IRB and you will receive an email similar to this correspondence from irb@memphis.edu. This submission will be archived in Cayuse IRB.

Thanks,

IRB Administrator
Division of Research and Innovation
Office of Research Compliance
315 Administration Building
Memphis, TN 38152-3370
P: 901.678.2705

Sunday, October 10, 2021 at 13:05:48 Central Daylight Time

Subject: PRO-FY2021-443 - Admin Withdrawal: Not Human Subject Research
Date: Wednesday, June 30, 2021 at 9:05:30 AM Central Daylight Time
From: do-not-reply@cayuse.com
To: Aniruddha Bhadresh Rathod (abrathod), Hongmei Zhang (hzhang6)
Attachments: ATT00001.png

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Division of Research and Innovation
Office of Research Compliance
University of Memphis
315 Admin Bldg
Memphis, TN 38152-3370

June 30, 2021

PI Name: Aniruddha Rathod
Co-Investigators:
Advisor and/or Co-PI: Hongmei Zhang
Submission Type: Admin Withdrawal
Title: DNA Methylation at Birth is Associated with Asthma Acquisition from Pre- to Post-Adolescence Mediated by Atopy
IRB ID: PRO-FY2021-443

From the information provided on your determination review request for "DNA Methylation at Birth is Associated with Asthma Acquisition from Pre- to Post-Adolescence Mediated by Atopy", the IRB has determined that your activity does not meet the Office of Human Subjects Research Protections definition of human subjects research and 45 CFR part 46 does not apply.

This study does not require IRB approval nor review. Your determination will be administratively withdrawn from Cayuse IRB and you will receive an email similar to this correspondence from irb@memphis.edu. This submission will be archived in Cayuse IRB.

Thanks,

IRB Administrator
Division of Research and Innovation
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315 Administration Building
Memphis, TN 38152-3370

Sunday, October 10, 2021 at 13:04:14 Central Daylight Time

Subject: PRO-FY2021-480 - Admin Withdrawal: Not Human Subject Research
Date: Wednesday, June 30, 2021 at 9:04:05 AM Central Daylight Time
From: do-not-reply@cayuse.com
To: Aniruddha Bhadresh Rathod (abrathod), Hongmei Zhang (hzhang6)
Attachments: ATT00001.png

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University of Memphis
315 Admin Bldg
Memphis, TN 38152-3370

June 30, 2021

PI Name: Aniruddha Rathod
Co-Investigators:
Advisor and/or Co-PI: Hongmei Zhang
Submission Type: Admin Withdrawal
Title: Sex-specific associations of Preadolescence Asthma and Rhinitis with DNA methylation at birth
IRB ID: PRO-FY2021-480

From the information provided on your determination review request for "Sex-specific associations of Preadolescence Asthma and Rhinitis with DNA methylation at birth ", the IRB has determined that your activity does not meet the Office of Human Subjects Research Protections definition of human subjects research and 45 CFR part 46 does not apply.

This study does not require IRB approval nor review. Your determination will be administratively withdrawn from Cayuse IRB and you will receive an email similar to this correspondence from irb@memphis.edu. This submission will be archived in Cayuse IRB.

Thanks,

IRB Administrator
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Office of Research Compliance
315 Administration Building
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