

Genome-wide methylation profile of nasal polyps: relation to aspirin hypersensitivity in asthmatics

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Keywords

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Abstract

Background: In addition to the dysregulation of arachidonic acid metabolism in aspirin-intolerant asthma (AIA), aspirin acetylsalicylic acid (ASA) exerts effects on inflammation and immunity; however, many of these effects are unknown.

Objective: The aim of the study was to evaluate the methylation status of whole genome in blood and polyp tissues with and without aspirin hypersensitivity.

Methods: Genome-wide DNA methylation levels in nasal polyps and peripheral blood cells were examined by microarray analysis using five subjects with AIA and four subjects with aspirin-tolerant asthma (ATA).

Results: In the nasal polyps of the patients with AIA, hypermethylation was detected at 332 loci in 296 genes, while hypomethylation was detected at 158 loci in 141 genes. Gene ontologic and pathway enrichment analyses revealed that genes involved in lymphocyte proliferation, cell proliferation, leukocyte activation, cytokine biosynthesis, cytokine secretion, immune responses, inflammation, and immunoglobulin binding were hypomethylated, while genes involved in ectoderm development, hemostasis, wound healing, calcium ion binding, and oxidoreductase activity were hypermethylated. In the arachidonate pathway, *PGDS*, *ALOX5AP*, and *LTB4R* were hypomethylated, whereas *PTGES* was hypermethylated.

Conclusion: The nasal polyps of patients with AIA have characteristic methylation patterns affecting 337 genes. The genes and pathways identified in this study may be associated with the presence of aspirin hypersensitivity in asthmatics and are therefore attractive targets for future research.

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Aspirin-intolerant asthma (AIA) refers to the development of bronchoconstriction in asthmatic individuals following the ingestion of aspirin or other nonsteroidal anti-inflammatory drugs. This syndrome is characterized by the 'aspirin triad,' which consists of aspirin hypersensitivity, bronchial asthma, nasal polyposis, and chronic hyperplastic eosinophilic sinusitis (1, 2). The airways of patients with AIA show signs of persistent inflammation with marked eosinophilia, epithelial

disruption, cytokine production, and the upregulation of inflammatory molecules (3). The overproduction or underproduction of critical mediators in the metabolism of arachidonic acid probably accounts for this susceptibility to acetylsalicylic acid (ASA). Variation within the genes of the arachidonate pathway is responsible for changes in the production and metabolism of these mediators. Polymorphisms in such genes as *LTC4S* (4), *ALOX5* (5), *PTGER2*

(6), *PTGER3* (7), *ACE* (8), and *CYSLTR2* (9) are known to be associated with AIA.

In addition to the arachidonate pathway, ASA inhibit the activation of the transcription factor NF- κ B (10) and the IL-4- and IL-13-induced activation of STAT6 (11). These observations suggest that ASA regulates a more complex network of biochemical and cellular events than was initially thought. To characterize this complex network, high-throughput techniques are needed to identify genes related to aspirin hypersensitivity in asthmatics. Two reports have applied microarray technology to nasal polyp tissues to examine gene expression in aspirin-intolerant asthmatics (12, 13). Their data indicate that nasal polyps have characteristic transcriptional signatures compared with normal tissues. However, no global studies of DNA methylation have been undertaken for AIA. DNA methylation at CpG sites has long been considered a key mechanism of transcriptional regulation (14). Regions of methylated DNA have been correlated with the tissue-specific expression of several genes and with active coding regions across the genome (15). Recently, transitory methylation has been demonstrated at gene regulatory regions (16). The global distribution of DNA methylation in human airway tissues is unknown, and its role in the development of AIA has not been reported.

Aspirin-intolerant asthma is characterized by extensive mucosal inflammation in the lower (asthma) and upper (rhinitis and nasal polyps) airways, and a diagnosis of nasal polyps is usually made near-simultaneously with the appearance of aspirin intolerance in patients with AIA (2). The nasal polyps of patients with AIA show similar pathological characteristics, including the infiltration of inflammatory cells into the bronchial mucosa (17, 18). This inflammatory cell infiltrate sets up an extensive network of cellular interactions, which are thought to promote nasal polyp proliferation (19, 20). Thus, nasal polyps are a good model for the study of aspirin hypersensitivity in asthma. In this study, we analyzed the genome-wide DNA methylation levels in nasal polyps from patients with AIA using microarray technology for the purpose of comparing these levels to those in patients with aspirin-tolerant asthma (ATA).

Methods

Subjects

Nine nasal polyp tissues (five AIA and four ATA) and their eight matched buffy coat samples (four AIA and four ATA) were donated by biobank at the Genome Research Center for Allergy and Respiratory Diseases, Soonchunhyang University Hospital, Bucheon, Korea. All of the subjects were Korean. All patients met the criteria for asthma in the Global Initiative for Asthma (GINA) guidelines (21). All patients had a history of dyspnea and wheezing during the previous 12 months plus one of the following: (i) >15% increase in FEV₁ or >12% increase plus 200 ml following inhalation of a short-acting bronchodilator or (ii) <10 mg/ml PC₂₀ methacholine. Twenty-four common inhalant allergens were used for skin prick tests. Atopy was defined as having a

wheal reaction either equal to or greater than histamine or 3 mm in diameter. Total IgE was measured using the CAP system (Pharmacia Diagnostics, Uppsala, Sweden). The asthmatics had experienced no exacerbation of their condition or a respiratory tract infection during the 6 weeks preceding the oral aspirin challenge (OAC). The reactions of the patients to the OAC were categorized as follows: $\geq 15\%$ decrease in FEV₁ with naso-ocular reactions (AIA) or <15% decrease in FEV₁ without naso-ocular or cutaneous reactions (ATA). An oral provocation test was performed with increasing doses of aspirin (10–450 mg of Astrix; Mayne Pharma Ltd., Melbourne, Australia) (8, 22). Briefly, the patient having history of aspirin hypersensitivity was given 30 mg and those having no history started 100 mg of aspirin orally. Symptoms, external signs (urticaria and angio-oedema), blood pressure, and FEV₁ were documented every 30 min for a period of 2 h. In the absence of any symptoms or signs suggestive of adverse reaction after 2 h, 60 or 100 mg of aspirin was administered and the same measurements were repeated every 1 h, with doses of 450 mg until the patient developed a reaction. If no reaction occurred 5 h after the final dose, the test was deemed negative. Aspirin-induced bronchospasm, as reflected by the decline (%) in FEV₁, was calculated as the prechallenge FEV₁ minus the postchallenge FEV₁ divided by the prechallenge FEV₁. Diagnoses of nasal polyps and chronic rhinosinusitis were made based on the patients' symptoms, the presence of endoscopically visible nasal polyps arising from the middle nasal meatus, and involvement of the ethmoidal and maxillary sinuses as visualized by limited CT scanning of the paranasal sinuses. The clinical characteristics of the subjects are summarized in Table 1. Peripheral venous blood was collected from each subject and centrifuged to isolate the buffy coat on the same day as polypectomy. All polyps and buffy coats were refrigerated at -20°C until needed. Consent to participate in the study was obtained in writing from all subjects. The protocols used in this study were approved by the Hospital's ethics committee.

Whole-genome DNA methylation assay and differential DNA methylation analysis

Polyp and buffy coat DNA was purified using a QIAamp DNA Blood Mini Kit (Qiagen Ltd., Crawley, UK). One microgram of genomic DNA from each sample was bisulfate-converted using an EZ DNA Methylation Kit (Zymo Research, Orange, CA, USA). The amplified DNA was hybridized to a HumanMethylation27 BeadChip (Illumina, San Diego, CA, USA), and the arrays were imaged using a BeadArray™ Reader (Illumina). Each methylation signal was used to compute a Beta value (β), which is a quantitative measure of DNA methylation ranging from 0 (no cytosines methylated) to 1 (all cytosines methylated) (23). Differential DNA methylation analysis was performed using the Methylation Module in Illumina's BEADSTUDIO software. The Illumina data were normalized using the background function. To identify differentially methylated CpG sites between the patients with AIA and ATA, the difference in mean methylation levels between the two groups was analyzed using a

Table 1 Clinical characteristics of patients with nasal polyps and peripheral blood mononuclear cell (PBMC) for DNA Methylation chip

ID	Age/gender	OAC	FEV ₁ (% predicted)	Total IgE (IU/ml)	Skin test	
ATA#1	39/F	N	99	312	Y	D.f, D.p, Fusarium
ATA#2	40/F	N	107	98	Y	D.f, D.p, Strawdust, Haydust, Cockroach mix
ATA#3	75/F	N	120	25	N	
ATA#4	43/M	N	126	226	Y	D.f, D.p, Ragweed pollen, Cat fur
AIA#1	40/M	Y	87	189	Y	D.f, D.p, Strawdust, Haydust, Mixed treslings
AIA#2	53/F	Y	90	30.2	N	
AIA#3	32/M	Y	101	12.3	N	
AIA#4	44/F	Y	79	196	N	Fusarium, Cockroach mix
AIA#5	51/F	Y	102	52.2	N	

ATA, aspirin-tolerant asthma; AIA, aspirin-induced asthma; OAC, oral aspirin challenge; N, no response; Y, response; FEV₁, forced expiratory volume in 1 s; ND, not done.

t-test. DeltaBeta ($|\Delta\beta|$) was calculated as β for the AIA group minus that for the ATA group. Statistical significance was applied to loci having a $|\Delta\beta| \geq 0.50$ and $P < 0.01$.

Heatmap analysis, gene ontologic analysis, and functional pathway prediction

A heatmap of the differentially methylated CpG sites was created using BEADSTUDIO 3.0 (Illumina Inc., San Diego, CA, USA). Gene ontologic enrichment of the DNA methylation profile was performed using Gene Ontology Tree Machine (GOTM; <http://bioinfo.vanderbilt.edu/webgestalt/>), which is based on a hypergeometric test showing over-represented gene ontology categories ($P < 0.01$) (24). To confirm the significance of our results, the *P*-value was also calculated using binomial distribution (BINOMDIST) on the basis of the over-representation of certain gene ontologic categories among the hypermethylated and hypomethylated genes compared to all of the genes on the chip. The online program Pathway-Express (Onto-Tools, Wayne State University, Detroit, MI, USA; <http://vortex.cs.wayne.edu/Projects.html>) (25) was used to explore the most biologically relevant pathways impacted by an input list of genes. Specific biologic pathways were defined using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (Kanehisa Laboratories, Kyoto, Japan; <http://www.genome.jp/kegg/pathway.html>). Pathway-Express selects pathways based on an impact analysis that considers not only conventional statistical analysis, but also other biologic factors, including the expression levels of input genes, their type and position in a given pathway, and protein-protein interactions. In our pathway analysis, we used methylation level as the input data instead of gene expression level (fold change). Corrected *P*-values < 0.05 were used as an empirical cutoff for retrieving altered pathways (25).

Results

Comparison of DNA methylation between AIA and ATA

DNA methylation levels were measured with Illumina's genome-wide methylation assay chip (Methylation27[®] Illumina Inc., San Diego, CA, USA, 27 K CpG sites) using nine nasal polyp tissues (five patients with AIA and four patients with

ATA) and eight buffy coats from the blood of the same subjects (four patients with AIA and four patients with ATA). Methylation of the X chromosome was not considered in our analysis. As shown in Fig. 1B, the methylation levels in the four sample groups showed a similar pattern: a bimodal distribution with the highest peak on the left end of the *X*-axis (average $\beta = 0-0.1$) and a second peak on the right end (average $\beta = 0.8-1.0$). About 60% of the loci had an average β of 0–0.1, whereas 20% of the loci had an average β of 0.8–1.0.

DeltaBeta ($|\Delta\beta|$) was calculated as the average β for the AIA group minus that for the ATA group. The DNA methylation levels in the polyps of the patients with AIA and ATA were quite different. A volcano plot of the $|\Delta\beta|$ values for each locus from the nasal polyp tissues is shown in Fig. 1A-1. The values ranged from 0.72 to -0.69 . We also examined the difference in methylation between the buffy coat genomic DNA samples from the same subjects. The DNA methylation profiles were similar between the two groups, with a narrow range of -0.2 to 0.2 for $|\Delta\beta|$ (Fig. 1A-2). As expected, no correlation with $|\Delta\beta|$ was found between the nasal polyps and buffy coats.

To identify the loci showing AIA-specific changes in methylation, we applied the following criteria: $P \leq 0.01$ and $|\Delta\beta| \geq 0.50$. A total of 332 loci in 296 genes had a significant increase in methylation among the patients with AIA compared to the patients with ATA using the nasal polyp tissue samples, while 158 loci in 141 genes showed a significant decrease (Fig. 1C). Heatmapping of the β values for the 490 loci revealed distinct DNA methylation profiles for the nasal polyp tissues between the AIA and ATA groups, while showing similar profiles for the buffy coats. Among these loci ($n = 490$), 104 were located within CpG islands, while 386 were outside of CpG islands. A total of 273 loci were identified within a promoter region (2 kb from the transcription start site), while 217 loci were in the gene body (Table S1).

Ontology of the differently methylated genes in the AIA and ATA groups

To examine the biologic functions associated with the genes having significantly hypomethylated and hypermethylated

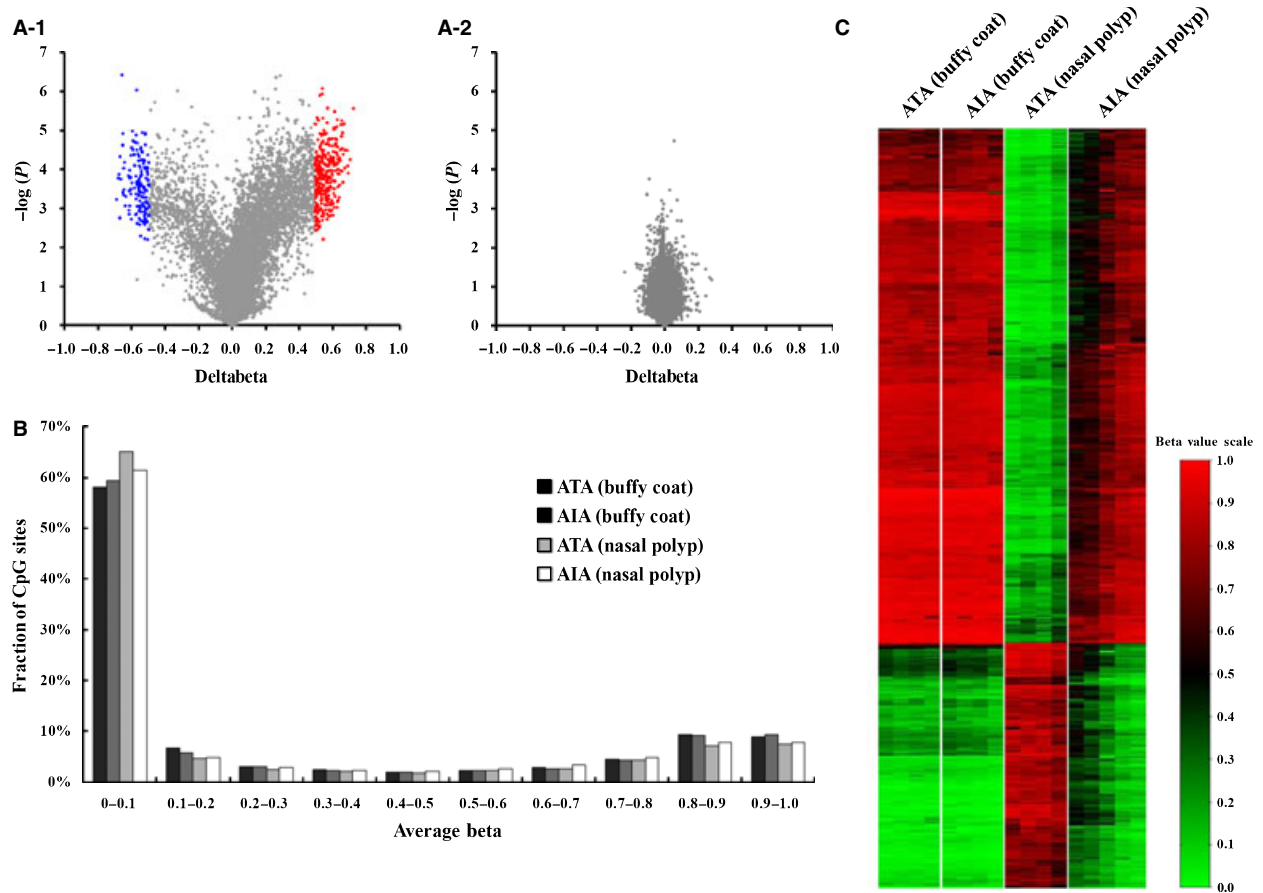


Figure 1 Summary of DNA methylation data. (A) Volcano plot of differential methylation level between aspirin-intolerant asthma (AIA) and aspirin-tolerant asthma (ATA) in nasal polyp tissues (A-1) and buffy coat samples (A-2). Red dots: $\Delta\text{beta} \geq 0.5$ and P -value ≤ 0.01 , blue dots: $\Delta\text{beta} \leq -0.5$ and P -value ≤ 0.01 , gray dots: $-0.5 \leq \Delta\text{beta} \leq 0.5$ and P -value > 0.01 . Δbeta : difference of

DNA methylation level (subtracting the DNA methylation level of ATA from AIA). $-\log(P)$: log-transformed t -test P -values. (B) Distribution of the DNA methylation level of AIA and ATA in buffy coat and nasal polyp. Average Beta: DNA methylation level (0–1). (C) Heatmap of 490 differentially methylated CpGs between AIA and ATA in buffy coat and nasal polyp.

loci, we analyzed the gene ontologic categories of 141 hypomethylated and 296 hypermethylated genes using GOTM (<http://bioinfo.vanderbilt.edu/gotm/>) (24). The genes on Illumina's methylation assay chip were used as a reference list. The genes with hypomethylated or hypermethylated loci were included in distinct gene ontologic categories (Tables 2 and S2). The genes with hypomethylated loci were included in the cell surface receptor-linked signal transduction, lymphocyte proliferation, leukocyte activation, cytokine biosynthesis/secretion, immune response, cellular defense response, inflammatory response, physiologic response to wounding, and immunoglobulin binding categories, while the genes with hypermethylated loci were included in the ectoderm development, hemostasis, wound healing, calcium ion binding, and oxidoreductase activity categories. In addition, genes showing hypomethylation and hypermethylation were found to encode cell membrane components.

To investigate the potential functional role of these differentially methylated genes in AIA, pathway enrichment analyses were performed using Pathway-Express, (24) which processes

an input list of genes to identify KEGG pathways. In our analysis, we used methylation level as the input data instead of gene expression level (fold change). We found that eleven altered pathways – asthma, natural killer cell-mediated cytotoxicity, cell communication, T-cell receptor signaling pathway, cytokine–cytokine receptor interaction, cell adhesion molecules, hematopoietic cell lineage, leukocyte transendothelial migration, allograft rejection, Jak-STAT signaling, and regulation of the actin cytoskeleton – were dominantly associated with differential methylation in the nasal polyp tissues of the patients with AIA (corrected $P < 0.05$) (Table 3). Five additional pathways – phosphatidylinositol signaling, melanoma, adherence junction, tight junction, and antigen processing and presentation—were also revealed through impact analysis and the consideration of gene position in a pathway (corrected gamma $P < 0.05$) (Table 3). Among the genes involved in arachidonic acid metabolism, four [those encoding prostaglandin-D synthase (*PGDS*), prostaglandin E synthase (*PTGES*), arachidonate 5-lipoxygenase-activating protein (*ALOX5AP*), and leukotriene B4 receptor (*LTB4R*)] were dif-

Table 2 Gene ontology analysis of genes with different methylation states in nasal polyp tissues

Methylation states	Category	Gene ontology category	Observed gene number	Expected gene number	Ratio of enrichment	Significance of enrichment
Hypomethylation	Biologic process	Cell surface receptor-linked signal transduction	28	10.9	2.6	1.8E-06
		Lymphocyte proliferation	3	0.2	13.6	0.001
		Regulation of cell proliferation	9	3.0	3.0	0.003
		Regulation of I-kappaB kinase/NF-kappaB cascade	4	0.8	5.2	0.007
		Cell motility	10	2.3	4.4	8.8E-05
		Leukocyte activation	5	1.0	5.3	0.003
		Cytokine biosynthesis	4	0.4	10.8	0.0005
		Cytokine secretion	2	0.1	18.2	0.005
		Immune response	29	4.7	6.1	7.5E-16
		Humoral immune response	9	1.5	6.1	1.5E-05
		Cellular defense response	5	0.6	8.1	0.0004
		Inflammatory response	8	2.4	3.4	0.002
		Antimicrobial humoral response	6	0.8	7.1	0.0002
		Physiologic response to wounding	9	3.2	2.9	0.004
	Molecular function	Immunoglobulin binding	4	0.1	28.6	9.3E-06
	Cellular component	Membrane part	64	35.7	1.8	9.0E-09
		Plasma membrane	38	16.9	2.3	3.5E-07
		Intrinsic to membrane	62	33.4	1.9	4.9E-09
		Plasma membrane part	30	14.2	2.1	3.5E-05
		Integral to membrane	62	33.3	1.9	4.3E-09
		Intrinsic to plasma membrane	27	12.0	2.3	3.0E-05
		Integrin complex	3	0.3	9.1	0.004
Hypermethylation	Biologic process	Ectoderm development	11	2.0	5.6	3.5E-06
		Hemostasis	6	1.7	3.5	0.007
		Wound healing	6	1.8	3.3	0.009
	Molecular function	Calcium ion binding	24	14.3	1.7	0.009
		Oxidoreductase activity acting on paired donors with incorporation or reduction of molecular oxygen reduced flavin or flavoprotein as one donor and incorporation of one atom of oxygen	4	0.7	6.1	0.004
	Cellular component	Membrane part	81	64.8	1.3	0.008
		Intrinsic to membrane	77	60.6	1.3	0.007
		Vesicular fraction	7	2.2	3.1	0.007
		Integral to membrane	77	60.4	1.3	0.006
		Intrinsic to plasma membrane	33	21.7	1.5	0.009
		Laminin-5 complex	2	0.0	50.0	0.0004

P-values of enrichment significance below 0.01 were shown.

ferentially methylated between the patients with AIA and ATA. *PGDS*, *ALOX5AP*, and *LTB4R* were hypomethylated, while *PTGES* was hypermethylated (Table S3).

Discussion

In the present study, the methylation levels in the four sample groups had an average β of 0–0.1 for 60% of the loci on the entire epigenome. This suggests that greater than 50% of the genes were ready to express a functional

product in the nasal polyps and peripheral blood of the study subjects. Continually expressed genes, including housekeeping genes, may be included in this group (Table S4). The second peak, representing about 10% of the loci, was at the right end (average $\beta = 0.8$ –1.0). These genes may be densely packed in nucleosomes. The methylation levels in the four sample groups showed a similar pattern. These data indicate that global gene expression may not differ between AIA and ATA according to the samples studied.

Table 3 Biologic pathways altered by differential DNA methylation in nasal polyp tissues

Pathway name	Pathway gene number	Number of input genes in pathway	Number of pathway genes on chip	Genes (hypomethylated/hypermethylated)	Corrected <i>P</i> -value	Impact factor	Corrected gamma <i>P</i> -value
Asthma	30	5	25	FCER1G, HLA-DPA1, IL10, RNASE3/MS4A2	0.001	7.8	0.004
Natural killer cell-mediated cytotoxicity	131	11	116	CD244, CD48, FCER1G, IFNGR2, ITGAL, ITGB2, LCP2, PIK3CG, TYROBP/CSF2, ICAM2	0.001	8.7	0.002
Cell communication	138	10	124	GJB6/COL3A1, GJB5, KRT15, KRT24, KRT4, KRT5, KRT8, LAMB3, LAMC2	0.006	6.0	0.02
T-cell receptor signaling pathway	93	8	87	CD28, GRAP2, IL10, LCP2, PIK3CG/CBLC, CSF2, PAK6	0.007	6.7	0.009
Cytokine-cytokine receptor interaction	259	15	237	CCL23, IFNGR2, IL10, IL2RA, TNFSF4, TNFSF8/CSF2, CX3CL1, CXCL13, GDF5, IL20RA, IL22RA1, IL5RA, TGFB3, TNFRSF17	0.009	6.1	0.02
Cell adhesion molecules	133	9	118	CD28, CD86, HLA-DPA1, ITGAL, ITGAM, ITGB2, PECAM1/CDH1, ICAM2	0.01	5.7	0.02
Hematopoietic cell lineage	88	7	81	CD33, CD37, FCGR1A, IL2RA, ITGAM/CSF2, IL5RA	0.01	5.0	0.04
Leukocyte transendothelial migration	116	8	104	ITGAL, ITGAM, ITGB2, NCF2, PECAM1, PIK3CG/MYL5, MYL7	0.02	6.2	0.01
Allograft rejection	38	4	32	CD28, CD86, HLA-DPA1, IL10/-	0.02	4.7	0.05
Jak-STAT signaling pathway	153	9	136	IFNGR2, IL10, IL2RA, PIK3CG/CBLC, CSF2, IL20RA, IL22RA1, IL5RA	0.03	5.3	0.03
Regulation of actin cytoskeleton	211	11	188	ITGAL, ITGAM, ITGB2, NCKAP1L, PIK3CG/CHRM1, FGF1, ITGB6, MYL5, MYL7, PAK6	0.04	4.9	0.04
Phosphatidylinositol signaling system	77	4	68	PIK3CG/CALML3, PI4KB, PIB5PA	0.17	7.9	0.003
Melanoma	71	3	68	PIK3CG/CDH1, FGF1	0.37	4.7	0.05
Adherens junction	75	2	72	-/CDH1, PVRL4	0.67	13.9	1.4E-05
Tight junction	135	3	122	-/EPB41L1, MYL5, MYL7	0.75	5.5	0.03
Antigen processing and presentation	88	1	73	HLA-DPA1/-	0.91	79.1	3.6E-33

Pathways listed are all pathways altered by differential DNA methylation, determined by Pathway-Express corrected *P*-value or corrected gamma *P*-value (<0.05). Corrected *P*-value was obtained using the classical statistics, and corrected gamma *P*-value was calculated using the impact analysis (25).

When we compared the average β for each locus, 332 loci in 296 genes showed significant increases in methylation, while 158 loci in 141 genes showed relative decreases for the nasal polyp tissues of the patients with AIA compared with those of the patients with ATA. However, there was no significant difference in buffy coat genomic DNA methylation between the two groups. These data suggest that the phenotypic differences in AIA and ATA may originate from differences in gene regulation in target organs (upper and lower airways) specific – gene regulation.

Notably, the hypomethylated genes were involved in lymphocyte proliferation, cell proliferation, leukocyte activation, cytokine biosynthesis, cytokine secretion, immune responses, inflammation, and immunoglobulin binding. Changes in these genes' expression by hypomethylation may lead to cellular overgrowth and extensive inflammation in the respiratory tract, as has been documented (1). In addition to the enhanced inflammatory cell recruitment, delayed programmed cell death (apoptosis) may account for the increased accumulation of inflammatory cells in nasal polyp tissue (26).

In the present study, we did not examine mRNA expression in the nasal polyps of the subjects. In a genome-wide gene expression profile of AIA polyps, mRNA expression of *ALOX5AP*, *LCP2*, *LST1*, *NCF2*, and *TYROBP* was elevated in the nasal polyps of patients with AIA (12). In the present study, the methylation levels of these genes were significantly decreased. Thus, the increase in mRNA expression may originate from hypomethylation of these genes.

We found that four genes in the arachidonate pathway were differentially methylated between the patients with AIA and ATA. *PGDS*, *ALOX5AP*, and *LTB4R* were hypomethylated, while *PTGES* was hypermethylated. PGES synthesizes prostaglandin E₂ (PGE₂) from prostaglandin H₂. Considering the hypermethylation of prostaglandin E synthase in AIA ($|\Delta\beta| = 0.56$, $P = 0.006$), inflammation-induced PGE₂ synthesis via *PGES* may be impaired in AIA because of hypermethylation of the gene. Another interesting finding is the hypomethylation of *PGDS*. Recently, Yoshimura et al. (27) reported that the concentration of PGD₂ was significantly increased in the nasal polyps of patients with ATA, whereas the concentration of PGE₂ was maximally decreased in that group. The changes in PGD₂ and PGE₂ may be attributed to differences in the methylation levels of these genes as observed in our study. *ALOX5AP* encodes arachidonate 5-lipoxygenase-activating protein, which is an essential regulator of the biosynthesis of the leukotriene B₄ (28). These eicosanoids function on cells that express LTB₄ receptors (LTB₄R and LTB₄R2). In the present study, hypomethylation was found on *LTB4R*. A nasal polyp study demonstrated that the percentage of CD45⁺ leukocytes expressing LTB₄R did not differ significantly between the two groups (29). The discrepancy between our methylation data and the protein expression of LTB₄R requires further analysis regarding the role of methylation in the regulation of gene expression. Taken together, aspirin hypersensitivity contributed by alterations in *PGDS*, *PTGES*, *ALOX5AP*, and *LTB4R* may be attributed to differences in the methylation of each gene.

Among the differentially methylated genes in the other pathways, *IL10*, *CD28*, and *PIK3CG* on T-cell receptor signaling were hypomethylated (Table 3). In allergic disease, IL-10 inhibits the production of proinflammatory cytokines from T cells directly and indirectly through the inhibition of CD28-presenting functions in asthmatics (30). Other interleukins and interleukin receptor genes were also differentially methylated. *IL2RA* was hypomethylated, while *IL5RA*, *IL20RA*, and *IL22RA1* were hypermethylated (Table 2). *IL5RA* are known to be associated with asthma and eosinophilia in asthmatics (31). In the anti-inflammatory mechanism of aspirin, ITGB2 is known to mediate the binding of T lymphocytes to activated endothelia, leading to a reduction in T-cell recruitment to inflammatory sites (32). *ITGB2* and other integrin-related genes, including *ITGAL* and *ITGAM*, were hypomethylated in the present study. These data suggest the possible association of immune-, inflammatory-, and adhesion-related genes with aspirin hypersensitivity in asthma.

Because the pattern of CpG island methylation is generally cell line specific, sampled nasal polyps should not differ

in their cellular composition between the groups. Previous studies comparing pathologic findings demonstrated that the histological appearance of polyps removed from aspirin-intolerant patients does not seem to differ from those of aspirin-tolerant patients (3, 17, 18). Although we did not perform differential count of the infiltrating cells and component ones in the nasal polyp, the extent of cellular infiltration was same between the two groups on hematoxylin and eosin stain (data not shown). However, recent immunohistochemical studies of nasal polyp showed different expression of adhesion molecules, cytokines, chemokines, and inflammatory mediators and their receptors (18, 20, 29, 33). Thus, we consider that the difference of methylation pattern may be associated with stages of cell differentiation or activation, but not with the cellular composition of the polyps.

In summary, the present study confirms the existence of AIA-associated methylation in nasal polyp tissues. In an attempt to determine which genes have the greatest impact, we performed bioinformatic analyses using our highly reproducible microarray data. Our DNA methylation profiles served as a robust discriminator between AIA and ATA. In this respect, the nasal polyp profiles suggest potential susceptibility genes and pathways involved in aspirin hypersensitivity in asthmatics. Functional studies will be valuable in identifying key genes or pathways that can serve as biomarkers or therapeutic targets.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article at www.wileyonlinelibrary.com:

Table S1. DNA methylation level of differentially methylated CpGs.

Table S2. Gene ontology analysis of genes with different methylation states in nasal polyp tissues.

Table S3. DNA methylation level of CpGs in genes of arachidonic acid metabolism.

Table S4. DNA methylation level of commonly used house-keeping genes.

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Table S1. DNA methylation level of differentially methylated CpGs

N	Illumina TargetID	Gene name	Chromosome	CpG Coordinate	Position	CpG island	Beta value of ATA (mean±SD)	Beta value of AIA (mean±SD)	DeltaBeta (AIA-ATA)	t-test (P-value)
1	cg22436411	FCGR2B	1	159898477	Promoter	No	0.91±0.03	0.22±0.17	-0.69	0.0006
2	cg12554857	PGDS	4	95483042	Gene Body	No	0.86±0.05	0.18±0.15	-0.68	0.0002
3	cg20748065	POR	7	75421357	Gene Body	Yes	0.93±0.04	0.25±0.14	-0.68	0.0001
4	cg16139316	S100A9	1	151597382	Gene Body	No	0.93±0.03	0.25±0.21	-0.67	0.002
5	cg09721047	ARHGAP25	2	68815516	Gene Body	No	0.84±0.04	0.17±0.11	-0.67	0.00005
6	cg26154999	FLJ22746	2	224974590	Gene Body	Yes	0.88±0.06	0.22±0.15	-0.67	0.0002
7	cg23953831	IGSF2	1	117345939	Promoter	No	0.76±0.05	0.10±0.06	-0.66	0.0000004
8	cg07973967	CD79B	17	59363339	Gene Body	Yes	0.85±0.06	0.20±0.11	-0.65	0.00002
9	cg15046675	CD37	19	54530589	Gene Body	No	0.87±0.02	0.22±0.14	-0.65	0.0004
10	cg03634982	MS4A4A	11	59804555	Promoter	No	0.79±0.05	0.14±0.10	-0.65	0.00001
11	cg10801369	RFFL	17	30441292	Promoter	Yes	0.87±0.04	0.22±0.16	-0.65	0.0004
12	cg08040471	C17orf62	17	78001068	Gene Body	Yes	0.82±0.03	0.17±0.11	-0.65	0.00009
13	cg13062935	MRGPRX2	11	19039090	Promoter	No	0.84±0.04	0.20±0.15	-0.65	0.0003
14	cg22088368	MGC35206	22	35734834	Promoter	No	0.85±0.08	0.21±0.13	-0.64	0.00007
15	cg09076077	FLJ33860	20	58063710	Promoter	Yes	0.92±0.02	0.28±0.17	-0.64	0.0009
16	cg17356733	IFNGR2	21	33696497	Promoter	Yes	0.87±0.07	0.23±0.18	-0.63	0.0005
17	cg07376232	AMICA1	11	117590130	Promoter	No	0.79±0.03	0.17±0.11	-0.62	0.0001
18	cg05959508	TRAF3IP3	1	207996135	Promoter	No	0.91±0.05	0.29±0.19	-0.62	0.001
19	cg19690214	PIP3-E	6	154720018	Promoter	No	0.87±0.03	0.26±0.18	-0.61	0.001
20	cg20542800	LTB4R	14	23852374	Gene Body	No	0.88±0.06	0.27±0.16	-0.61	0.0004
21	cg00661485	FOXI1	5	169465950	Gene Body	Yes	0.90±0.03	0.29±0.16	-0.61	0.0009
22	cg15691199	CEBPE	14	22659259	Promoter	No	0.83±0.12	0.22±0.12	-0.61	0.0002
23	cg12732155	LAPTM5	1	31003188	Gene Body	Yes	0.82±0.04	0.21±0.11	-0.61	0.0001
24	cg27631256	TNFSF8	9	116732566	Gene Body	Yes	0.78±0.00	0.18±0.12	-0.61	0.0003
25	cg13853198	FCER1G	1	159451716	Gene Body	No	0.80±0.05	0.19±0.15	-0.61	0.0004
26	cg12125117	GPR97	16	56258962	Promoter	No	0.85±0.12	0.24±0.12	-0.60	0.0002
27	cg26789453	TMEM116	12	110936807	Promoter	No	0.75±0.06	0.15±0.12	-0.60	0.00004

28	cg11024597	ECRG4	2	106047843	Promoter	No	0.89±0.06	0.29±0.21	-0.60	0.002
29	cg10861599	TNFSF4	1	171443146	Promoter	No	0.78±0.06	0.18±0.11	-0.60	0.00003
30	cg14916288	CCL23	17	31369249	Promoter	No	0.80±0.05	0.20±0.14	-0.60	0.0002
31	cg04915566	RUNX1	21	35343342	Gene Body	No	0.78±0.07	0.18±0.09	-0.60	0.00001
32	cg10925082	ARHGDIB	12	15005970	Promoter	No	0.72±0.05	0.13±0.10	-0.59	0.00002
33	cg00658007	C1orf36	1	209732752	Gene Body	No	0.75±0.08	0.16±0.11	-0.59	0.00003
34	cg17771150	LCP1	13	45654210	Gene Body	No	0.78±0.06	0.19±0.11	-0.58	0.00004
35	cg11283860	SLC45A1	1	8195939	Promoter	Yes	0.92±0.05	0.34±0.14	-0.58	0.0003
36	cg08779777	PIK3CG	7	106293008	Promoter	No	0.79±0.04	0.21±0.11	-0.58	0.00008
37	cg17936488	FAM78A	9	133141340	Gene Body	Yes	0.81±0.07	0.23±0.12	-0.58	0.00008
38	cg00852964	VNN1	6	133076843	Gene Body	No	0.75±0.06	0.17±0.10	-0.58	0.00002
39	cg14913610	KLRG1	12	9033608	Gene Body	No	0.89±0.03	0.31±0.18	-0.58	0.001
40	cg07525077	RNASE3	14	20429783	Gene Body	No	0.80±0.06	0.22±0.15	-0.57	0.0004
41	cg26149678	IL18BP	11	71387565	Promoter	No	0.76±0.05	0.19±0.13	-0.57	0.0002
42	cg02901679	IL10	1	205012622	Promoter	No	0.84±0.07	0.27±0.16	-0.57	0.0006
43	cg03840259	GRAP2	22	38626982	Promoter	No	0.73±0.06	0.15±0.09	-0.57	0.00001
44	cg10129493	CD33	19	56420398	Gene Body	No	0.91±0.04	0.34±0.18	-0.57	0.001
45	cg24516901	FLJ22746	2	224975045	Promoter	Yes	0.78±0.05	0.21±0.13	-0.57	0.0002
46	cg14176836	ITGAL	16	30391719	Gene Body	No	0.72±0.05	0.15±0.05	-0.57	0.0000009
47	cg01422337	CARD8	19	53444622	Gene Body	Yes	0.72±0.08	0.15±0.09	-0.57	0.00003
48	cg10307548	SOD3	4	24404928	Promoter	No	0.94±0.01	0.37±0.19	-0.57	0.002
49	cg20283107	FAM91A1	8	124858150	Promoter	No	0.83±0.05	0.26±0.17	-0.57	0.0009
50	cg16517394	TNFSF4	1	171442985	Gene Body	No	0.74±0.05	0.17±0.13	-0.57	0.0002
51	cg14324675	LST1	6	31662827	Gene Body	No	0.84±0.07	0.28±0.14	-0.57	0.0002
52	cg23352695	EVI2A	17	26672937	Promoter	No	0.78±0.07	0.21±0.10	-0.57	0.00002
53	cg21969640	GPR84	12	53043844	Gene Body	No	0.76±0.06	0.20±0.14	-0.56	0.0003
54	cg13821008	WASPIP	2	175207359	Gene Body	No	0.81±0.03	0.25±0.12	-0.56	0.0003
55	cg18908499	C1orf150	1	245778860	Promoter	Yes	0.78±0.07	0.21±0.11	-0.56	0.00004
56	cg07072643	EMR3	19	14646593	Gene Body	No	0.82±0.03	0.26±0.12	-0.56	0.0002
57	cg03569637	FAM113B	12	45895624	Promoter	No	0.77±0.03	0.21±0.11	-0.56	0.0002

58	cg02794695	SLA	8	134141793	Promoter	No	0.80±0.04	0.24±0.14	-0.56	0.0005
59	cg10044101	VNN2	6	133125982	Gene Body	No	0.81±0.05	0.25±0.14	-0.56	0.0003
60	cg18910313	P2RY11	19	10083409	Gene Body	No	0.81±0.03	0.25±0.15	-0.56	0.0009
61	cg05596756	FAM113B	12	45896487	Gene Body	No	0.81±0.08	0.25±0.11	-0.56	0.00006
62	cg15258980	ARHGAP25	2	68815101	Promoter	No	0.84±0.06	0.28±0.14	-0.56	0.0004
63	cg16927606	U2AF1L4	19	40925164	Gene Body	No	0.89±0.04	0.33±0.14	-0.56	0.0005
64	cg16509569	HEM1	12	53177901	Gene Body	No	0.83±0.05	0.28±0.14	-0.56	0.0003
65	cg27377213	PPP1R16B	20	36867217	Promoter	Yes	0.87±0.05	0.31±0.13	-0.56	0.0002
66	cg23506842	PTPN7	1	200397543	Promoter	No	0.85±0.05	0.29±0.11	-0.56	0.00005
67	cg12836863	BRCA2	13	31787023	Promoter	Yes	0.88±0.06	0.33±0.17	-0.56	0.001
68	cg17127769	LCP2	5	169657168	Gene Body	No	0.75±0.05	0.20±0.11	-0.55	0.00008
69	cg14386061	DOK2	8	21827392	Promoter	No	0.81±0.06	0.26±0.13	-0.55	0.0002
70	cg19056418	TMC8	17	73638812	Gene Body	No	0.89±0.04	0.34±0.18	-0.55	0.002
71	cg01623438	CTSZ	20	57016289	Promoter	No	0.81±0.06	0.26±0.14	-0.55	0.0003
72	cg13053608	LGP1	17	37599199	Gene Body	No	0.83±0.10	0.28±0.18	-0.55	0.0009
73	cg22377389	GJB6	13	19703679	Promoter	Yes	0.83±0.04	0.28±0.20	-0.55	0.003
74	cg18621299	EVL	14	99601344	Promoter	No	0.77±0.02	0.21±0.11	-0.55	0.0002
75	cg12879425	BRDG1	4	68107090	Gene Body	No	0.81±0.05	0.26±0.15	-0.55	0.0006
76	cg10548978	C10orf27	10	72215059	Gene Body	No	0.79±0.01	0.24±0.12	-0.55	0.0004
77	cg20287234	GPR55	2	231497709	Gene Body	Yes	0.80±0.06	0.25±0.14	-0.55	0.0002
78	cg00916635	PTPN22	1	114215835	Gene Body	No	0.82±0.05	0.27±0.14	-0.55	0.0004
79	cg05714729	GALNT1	18	31488094	Promoter	No	0.83±0.04	0.28±0.19	-0.55	0.002
80	cg22325572	CD53	1	111217704	Gene Body	No	0.75±0.05	0.20±0.12	-0.55	0.00009
81	cg05989054	GAMT	19	1353626	Promoter	Yes	0.77±0.14	0.22±0.17	-0.55	0.001
82	cg19464944	FCGR1A	1	148020624	Promoter	No	0.82±0.06	0.27±0.17	-0.55	0.0009
83	cg18881723	SLAMF1	1	158883494	Promoter	No	0.79±0.06	0.24±0.13	-0.55	0.0001
84	cg03886110	PECAM1	17	59817773	Promoter	Yes	0.86±0.05	0.31±0.17	-0.55	0.001
85	cg11939496	CD244	1	159100184	Promoter	No	0.93±0.02	0.38±0.22	-0.55	0.005
86	cg02611419	KCNK17	6	39390510	Promoter	No	0.80±0.05	0.26±0.09	-0.55	0.00003
87	cg10037005	CD37	19	54530290	Promoter	No	0.78±0.06	0.23±0.10	-0.54	0.00003
88	cg19252956	DOCK8	9	263072	Gene Body	No	0.82±0.09	0.27±0.15	-0.54	0.0004

89	cg11804789	CST7	20	24877716	Promoter	No	0.74±0.08	0.20±0.10	-0.54	0.00006
90	cg15361750	GPR77	19	52530972	Promoter	No	0.80±0.09	0.25±0.12	-0.54	0.0001
91	cg14437986	C6orf25	6	31799014	Promoter	Yes	0.80±0.09	0.25±0.12	-0.54	0.0001
92	cg01138020	MGC29671	17	4283843	Promoter	No	0.80±0.06	0.26±0.12	-0.54	0.0001
93	cg10590292	BIN2	12	50003941	Gene Body	Yes	0.88±0.04	0.34±0.14	-0.54	0.0005
94	cg14385738	PTPN22	1	114215863	Promoter	No	0.81±0.09	0.27±0.14	-0.54	0.0003
95	cg04098585	CD28	2	204279460	Gene Body	No	0.73±0.08	0.19±0.08	-0.54	0.00004
96	cg27365426	ARHGAP15	2	143602842	Promoter	No	0.69±0.04	0.15±0.09	-0.54	0.00004
97	cg03801286	KCNE1	21	34806378	Gene Body	No	0.89±0.06	0.36±0.16	-0.54	0.0007
98	cg12941931	SEMA6B	19	4510799	Promoter	Yes	0.84±0.05	0.30±0.19	-0.54	0.002
99	cg11733245	IL2RA	10	6144318	Promoter	Yes	0.85±0.05	0.31±0.15	-0.54	0.0005
100	cg14178895	C6orf105	6	11886888	Gene Body	No	0.66±0.06	0.12±0.08	-0.54	0.00001
101	cg16363586	BST2	19	17377329	Gene Body	Yes	0.71±0.08	0.18±0.11	-0.53	0.00006
102	cg24091474	TYROBP	19	41091025	Gene Body	No	0.82±0.05	0.29±0.16	-0.53	0.0008
103	cg27470554	FCGR2A	1	159741864	Gene Body	No	0.68±0.09	0.15±0.10	-0.53	0.00007
104	cg04340502	GSTA3	6	52883168	Promoter	No	0.85±0.02	0.32±0.18	-0.53	0.002
105	cg19963522	PIP3-E	6	154719488	Gene Body	No	0.70±0.08	0.17±0.17	-0.53	0.0009
106	cg23612220	TNFAIP8L2	1	149395922	Gene Body	No	0.84±0.04	0.31±0.13	-0.53	0.0004
107	cg15352829	PLD4	14	104462063	Promoter	No	0.93±0.04	0.40±0.13	-0.53	0.0003
108	cg24290574	CPA3	3	150065842	Gene Body	No	0.71±0.08	0.18±0.10	-0.53	0.00006
109	cg24167037	ITGB2	21	45165204	Gene Body	No	0.80±0.07	0.27±0.11	-0.53	0.00006
110	cg09571369	P2RY14	3	152479253	Promoter	No	0.77±0.12	0.25±0.13	-0.53	0.0005
111	cg07405796	TRIM40	6	30212531	Gene Body	No	0.80±0.04	0.28±0.16	-0.53	0.001
112	cg23756272	BCL2	18	59055398	Gene Body	Yes	0.92±0.02	0.40±0.16	-0.53	0.002
113	cg18384097	PTPN7	1	200396189	Gene Body	No	0.83±0.04	0.30±0.12	-0.52	0.0003
114	cg17607231	SP140	2	230798573	Promoter	No	0.70±0.05	0.18±0.11	-0.52	0.00009
115	cg13906813	HLA-DPA1	6	33148892	Gene Body	No	0.76±0.05	0.24±0.19	-0.52	0.002
116	cg01278291	DOK3	5	176869969	Promoter	No	0.87±0.04	0.34±0.19	-0.52	0.003
117	cg08529529	ALOX5AP	13	30207799	Gene Body	No	0.84±0.06	0.31±0.24	-0.52	0.006

118	cg19486673	LILRA2	19	59776830	Promoter	No	0.67±0.09	0.15±0.09	-0.52	0.00006
119	cg08223235	BCL2	18	59054814	Gene Body	Yes	0.88±0.03	0.36±0.17	-0.52	0.002
120	cg20764656	GPX2	14	64480232	Promoter	No	0.87±0.06	0.35±0.19	-0.52	0.002
121	cg11009736	MARCO	2	119416152	Promoter	No	0.73±0.10	0.21±0.14	-0.52	0.0003
122	cg18638581	HK2	2	74913110	Promoter	No	0.78±0.04	0.26±0.17	-0.52	0.002
123	cg05037688	EGFL7	9	138676375	Promoter	No	0.71±0.08	0.19±0.12	-0.52	0.00009
124	cg15337006	ITGAM	16	31178510	Promoter	No	0.89±0.06	0.37±0.16	-0.52	0.001
125	cg02266731	CPM	12	67643600	Promoter	No	0.78±0.12	0.26±0.15	-0.52	0.0007
126	cg03924115	P518	9	132758787	Gene Body	Yes	0.83±0.05	0.32±0.08	-0.52	0.00001
127	cg12643449	IFRD1	7	111849574	Promoter	No	0.73±0.03	0.21±0.08	-0.52	0.00002
128	cg09076123	NCF2	1	181826150	Gene Body	No	0.65±0.05	0.14±0.08	-0.52	0.00001
129	cg09848074	FLJ44186	7	138823150	Promoter	No	0.76±0.03	0.24±0.16	-0.52	0.002
130	cg17271365	MARCH1	4	164754202	Gene Body	No	0.84±0.04	0.33±0.16	-0.52	0.001
131	cg15374234	CD300LF	17	70220621	Gene Body	No	0.75±0.03	0.23±0.15	-0.51	0.001
132	cg20678353	FLJ35695	15	36775852	Promoter	No	0.78±0.03	0.26±0.13	-0.51	0.0005
133	cg19826026	ARHGDIB	12	15005660	Gene Body	No	0.71±0.05	0.20±0.12	-0.51	0.0002
134	cg20267005	TYROBP	19	41091889	Promoter	No	0.87±0.05	0.35±0.13	-0.51	0.0003
135	cg00899659	ZNF22	10	44815977	Gene Body	No	0.67±0.08	0.15±0.16	-0.51	0.0007
136	cg09303642	NFE2	12	52977085	Promoter	No	0.91±0.05	0.40±0.15	-0.51	0.0007
137	cg02099418	CD28	2	204279391	Promoter	No	0.79±0.15	0.28±0.18	-0.51	0.002
138	cg02082571	CLEC4A	12	8167985	Gene Body	No	0.83±0.06	0.32±0.18	-0.51	0.002
139	cg13311440	CD48	1	158948028	Gene Body	No	0.84±0.03	0.33±0.12	-0.51	0.0004
140	cg00041575	TSPAN32	11	2279317	Promoter	Yes	0.70±0.09	0.19±0.09	-0.51	0.00009
141	cg17699374	MGC35206	22	35733748	Gene Body	No	0.69±0.09	0.18±0.10	-0.51	0.0001
142	cg14654385	URP2	11	63729582	Promoter	Yes	0.90±0.06	0.39±0.16	-0.51	0.001
143	cg24777950	CTSG	14	24115961	Promoter	No	0.88±0.05	0.38±0.18	-0.51	0.002
144	cg04387658	CD86	3	123257770	Gene Body	Yes	0.88±0.05	0.37±0.11	-0.51	0.0001
145	cg25341726	IL27	16	28425832	Promoter	No	0.88±0.03	0.37±0.22	-0.50	0.006
146	cg23082877	RASIP1	19	53935239	Gene Body	No	0.83±0.07	0.33±0.11	-0.50	0.00009
147	cg17605084	HEM1	12	53177758	Promoter	No	0.70±0.07	0.20±0.10	-0.50	0.00004
148	cg14473145	CLEC14A	14	37795407	Promoter	Yes	0.75±0.05	0.25±0.11	-0.50	0.0001
149	cg05767404	C1orf150	1	245779214	Gene	No	0.73±0.10	0.23±0.16	-0.50	0.0008

150	cg26799474	CASP8	2	201807196	Body Gene Body	No	0.84±0.08	0.34±0.13	-0.50	0.0002
151	cg07349094	AFF3	2	100125446	Gene Body	Yes	0.78±0.03	0.28±0.15	-0.50	0.002
152	cg14173969	CD300C	17	70053527	Gene Body	No	0.67±0.05	0.17±0.12	-0.50	0.0002
153	cg26151675	CNR2	1	24112656	Promoter	No	0.67±0.07	0.17±0.13	-0.50	0.0002
154	cg02184413	VNN1	6	133076928	Promoter	No	0.83±0.06	0.33±0.20	-0.50	0.003
155	cg25866075	NALP12	19	59019592	Promoter	No	0.68±0.07	0.18±0.10	-0.50	0.00007
156	cg24715735	HPN	19	40223243	Promoter	Yes	0.66±0.10	0.16±0.09	-0.50	0.0003
157	cg19836199	RUNX1	21	35343811	Promoter	No	0.61±0.12	0.11±0.06	-0.50	0.001
158	cg05445326	TM4SF19	3	197549966	Promoter	No	0.95±0.03	0.46±0.14	-0.50	0.0009
159	cg27496506	TGM5	15	41346462	Promoter	No	0.13±0.05	0.63±0.10	0.50	0.00007
160	cg13439730	PRSS8	16	31054500	Gene Body	Yes	0.24±0.08	0.73±0.10	0.50	0.00008
161	cg10212621	HMGCS2	1	120113172	Promoter	No	0.14±0.03	0.63±0.14	0.50	0.001
162	cg20837735	SERPINB5	18	59295157	Promoter	Yes	0.11±0.06	0.60±0.16	0.50	0.001
163	cg03082060	LGALS8	1	234746847	Promoter	No	0.06±0.07	0.55±0.17	0.50	0.002
164	cg10735607	TMEM109	11	60437091	Promoter	Yes	0.33±0.09	0.83±0.11	0.50	0.0002
165	cg23128056	KRT15	17	36928152	Gene Body	No	0.16±0.07	0.65±0.14	0.50	0.0004
166	cg19580810	RAB25	1	154297806	Gene Body	No	0.12±0.05	0.62±0.14	0.50	0.0005
167	cg07484827	CHRNA10	11	3649733	Promoter	No	0.05±0.03	0.55±0.18	0.50	0.003
168	cg20993403	EPB41L1	20	34163743	Promoter	No	0.08±0.07	0.58±0.14	0.50	0.0003
169	cg24166628	TNNC1	3	52463110	Promoter	No	0.26±0.09	0.76±0.11	0.50	0.0002
170	cg20610181	CA9	9	35664000	Gene Body	No	0.20±0.05	0.70±0.12	0.50	0.0002
171	cg08404225	IL5RA	3	3126899	Gene Body	No	0.05±0.01	0.55±0.18	0.50	0.004
172	cg06224510	ITIH2	10	7785460	Gene Body	No	0.13±0.06	0.63±0.10	0.50	0.00005
173	cg14600885	MYOZ3	5	150020473	Promoter	No	0.06±0.03	0.56±0.14	0.50	0.001
174	cg06852652	CYP2C18	10	96432021	Promoter	No	0.22±0.08	0.72±0.10	0.50	0.00008
175	cg07412254	FLJ14816	2	120940004	Gene Body	Yes	0.11±0.04	0.60±0.07	0.50	0.000007
176	cg24272559	LOC116123	1	164839340	Promoter	No	0.19±0.01	0.69±0.14	0.50	0.001
177	cg00245878	H-plk	7	64088310	Gene Body	No	0.20±0.05	0.70±0.11	0.50	0.0001
178	cg23613317	LARP1	5	154072302	Promoter	No	0.15±0.09	0.65±0.14	0.50	0.0003
179	cg01888166	PUM2	2	20391116	Promoter	No	0.33±0.10	0.83±0.05	0.50	0.0007
180	cg19530885	SCGB3A2	5	147238325	Promoter	No	0.24±0.08	0.74±0.09	0.50	0.00006
181	cg00436282	STATH	4	70896038	Promoter	No	0.22±0.02	0.72±0.08	0.50	0.00006

182	cg07959477	CLEC1A	12	10143146	Promoter	No	0.16±0.04	0.66±0.16	0.50	0.002
183	cg17063201	HCRTR2	6	55146521	Promoter	No	0.25±0.05	0.75±0.09	0.50	0.00004
184	cg19682367	FAM79B	3	190371180	Promoter	No	0.05±0.04	0.55±0.14	0.50	0.0009
185	cg02717866	FLJ32771	11	61005463	Gene Body	No	0.35±0.02	0.85±0.08	0.50	0.00006
186	cg17795586	P2RY13	3	152530425	Promoter	No	0.18±0.05	0.68±0.10	0.50	0.00006
187	cg03003256	C6orf78	6	116956250	Promoter	No	0.13±0.06	0.63±0.14	0.50	0.0005
188	cg16377880	CYP4F3	19	15612167	Promoter	No	0.07±0.05	0.57±0.12	0.50	0.0003
189	cg08578641	DNAI1	9	34447440	Promoter	Yes	0.16±0.06	0.66±0.11	0.50	0.0001
190	cg20029201	BCL9L	11	118287023	Promoter	Yes	0.09±0.09	0.59±0.10	0.50	0.0001
191	cg20416179	C6orf71	6	150731836	Gene Body	No	0.23±0.04	0.73±0.13	0.50	0.0005
192	cg02729303	FLJ20152	5	16561920	Gene Body	No	0.07±0.03	0.57±0.17	0.50	0.002
193	cg14114267	SP3	2	174539749	Promoter	No	0.12±0.03	0.62±0.12	0.50	0.0005
194	cg26059632	SPRR2A	1	151297375	Promoter	No	0.09±0.06	0.59±0.12	0.50	0.0002
195	cg05232889	FOXP2	7	113842655	Gene Body	No	0.05±0.06	0.56±0.14	0.50	0.0005
196	cg06454226	METTL4	18	2562965	Promoter	No	0.25±0.13	0.75±0.06	0.50	0.002
197	cg17204557	FLJ14816	2	120940379	Promoter	Yes	0.20±0.09	0.70±0.10	0.50	0.00009
198	cg23645091	KRT5	12	51200676	Promoter	No	0.09±0.05	0.59±0.10	0.50	0.00006
199	cg12547930	WFDC6	20	43602167	Promoter	No	0.15±0.03	0.65±0.12	0.50	0.0004
200	cg00347729	MMP10	11	102156963	Promoter	No	0.12±0.07	0.62±0.14	0.50	0.0005
201	cg18913171	SLAMF9	1	158192040	Promoter	No	0.22±0.11	0.72±0.05	0.50	0.0008
202	cg15792367	KLK11	19	56223296	Promoter	No	0.16±0.07	0.66±0.10	0.50	0.00006
203	cg11693019	AKR1B10	7	133862160	Promoter	No	0.12±0.05	0.62±0.09	0.50	0.00004
204	cg15503752	ST6GALNAC1	17	72151326	Gene Body	No	0.07±0.03	0.57±0.17	0.50	0.002
205	cg20892287	RICS	11	128399061	Gene Body	No	0.12±0.09	0.62±0.11	0.50	0.0001
206	cg12965512	TSPAN8	12	69838603	Promoter	No	0.14±0.04	0.65±0.11	0.50	0.0002
207	cg27404050	PRODH2	19	40995720	Gene Body	No	0.07±0.02	0.57±0.15	0.50	0.001
208	cg18542098	FLJ36445	19	41191166	Gene Body	No	0.23±0.07	0.74±0.13	0.51	0.0002
209	cg23370883	MYL7	7	44147129	Gene Body	No	0.09±0.04	0.60±0.11	0.51	0.0002
210	cg27635271	SH3PX3	15	73728631	Gene Body	No	0.19±0.04	0.70±0.11	0.51	0.0002
211	cg21065959	LCE1E	1	151025379	Gene Body	No	0.22±0.07	0.72±0.10	0.51	0.00005
212	cg16176600	FRK	6	116488302	Gene Body	No	0.04±0.02	0.55±0.17	0.51	0.003
213	cg23538064	CFB	6	32021254	Promoter	No	0.09±0.05	0.59±0.17	0.51	0.002

214	cg27653134	A2ML1	12	8866576	Gene Body	No	0.09±0.02	0.59±0.13	0.51	0.0008
215	cg02377083	CCBP2	3	42826023	Gene Body	No	0.36±0.05	0.87±0.07	0.51	0.000005
216	cg24269657	F7	13	112807772	Promoter	No	0.15±0.06	0.66±0.10	0.51	0.00006
217	cg08300860	LDB3	10	88418237	Promoter	No	0.25±0.06	0.76±0.12	0.51	0.0002
218	cg05569220	FLJ44861	17	76753468	Promoter	No	0.10±0.07	0.61±0.21	0.51	0.003
219	cg17001652	CXCL13	4	78651427	Promoter	No	0.08±0.06	0.59±0.10	0.51	0.00006
220	cg27497781	CHIA	1	111634990	Promoter	No	0.09±0.04	0.60±0.09	0.51	0.00004
221	cg20804101	SLC6A13	12	242177	Gene Body	No	0.10±0.04	0.61±0.16	0.51	0.001
222	cg15154229	CPA1	7	129807247	Promoter	No	0.19±0.06	0.70±0.20	0.51	0.003
223	cg20427865	CX3CL1	16	55963854	Promoter	No	0.11±0.07	0.62±0.14	0.51	0.0003
224	cg07873488	MUC17	7	100449290	Promoter	No	0.28±0.06	0.79±0.11	0.51	0.00008
225	cg20797216	FBN3	19	8118234	Gene Body	No	0.07±0.03	0.58±0.16	0.51	0.002
226	cg21472642	CHN2	7	29199993	Promoter	Yes	0.04±0.02	0.55±0.08	0.51	0.00009
227	cg11639651	HKDC1	10	70649817	Promoter	No	0.21±0.09	0.73±0.11	0.51	0.0001
228	cg18598959	PIK4CB	1	149565290	Gene Body	No	0.29±0.06	0.80±0.09	0.51	0.00002
229	cg09871043	PKHD1	6	52060320	Gene Body	No	0.11±0.06	0.62±0.13	0.51	0.0003
230	cg27132814	C20orf79	20	18742303	Promoter	No	0.15±0.06	0.67±0.16	0.51	0.0009
231	cg25668626	OAS1	12	111827986	Promoter	No	0.14±0.06	0.65±0.13	0.51	0.0003
232	cg12385643	UGT1A6	2	234264888	Promoter	No	0.17±0.08	0.68±0.10	0.51	0.00005
233	cg16505550	PPAP2B	1	56818296	Promoter	No	0.08±0.06	0.59±0.05	0.51	0.000005
234	cg22780475	CBLC	19	49973366	Gene Body	Yes	0.21±0.06	0.72±0.12	0.51	0.0001
235	cg09494546	SLC16A4	1	110734771	Gene Body	No	0.10±0.05	0.61±0.15	0.51	0.0009
236	cg10368842	C10orf81	10	115501494	Gene Body	No	0.06±0.05	0.58±0.18	0.51	0.002
237	cg02831294	CALML3	10	5556862	Promoter	No	0.27±0.11	0.78±0.10	0.51	0.0002
238	cg03775123	ANKDD1A	15	63001128	Promoter	No	0.12±0.03	0.63±0.15	0.51	0.001
239	cg01333788	GJB5	1	34993401	Gene Body	No	0.14±0.07	0.66±0.12	0.51	0.0001
240	cg26644395	UCN3	10	5397020	Gene Body	Yes	0.15±0.04	0.67±0.11	0.52	0.0001
241	cg03399459	ANXA8	10	47217088	Gene Body	No	0.05±0.04	0.56±0.15	0.52	0.001
242	cg14802951	ADAMTS13	9	135277230	Gene Body	No	0.11±0.04	0.63±0.13	0.52	0.0004
243	cg05724065	PHKG1	7	56128022	Gene Body	No	0.07±0.03	0.59±0.09	0.52	0.00008
244	cg05135288	RHOT2	16	657708	Promoter	No	0.15±0.05	0.66±0.12	0.52	0.0002

245	cg21201572	AGR2	7	16811131	Gene Body	No	0.08±0.03	0.60±0.12	0.52	0.0004
246	cg15060813	LRFN3	19	41120148	Gene Body	No	0.21±0.05	0.73±0.11	0.52	0.00007
247	cg10574499	UNQ2446	16	66476255	Promoter	No	0.16±0.07	0.68±0.11	0.52	0.00006
248	cg00240880	WISP2	20	42776647	Promoter	No	0.15±0.07	0.67±0.12	0.52	0.0001
249	cg13530039	CHRM1	11	62446133	Promoter	No	0.16±0.04	0.68±0.20	0.52	0.003
250	cg03938043	DTL	1	210274474	Promoter	No	0.05±0.03	0.57±0.12	0.52	0.0003
251	cg10207745	C12orf36	12	13421230	Promoter	No	0.05±0.02	0.57±0.17	0.52	0.002
252	cg21012874	SNCG	10	88708373	Promoter	Yes	0.19±0.11	0.71±0.09	0.52	0.0003
253	cg04558553	UGT2B7	4	69995458	Promoter	No	0.11±0.03	0.63±0.09	0.52	0.00007
254	cg25115460	TP73	1	3596970	Gene Body	Yes	0.15±0.09	0.67±0.10	0.52	0.0001
255	cg09152089	IL22RA1	1	24342151	Gene Body	No	0.07±0.04	0.59±0.10	0.52	0.00005
256	cg03766965	SRCAP	16	30625944	Promoter	No	0.24±0.08	0.76±0.07	0.52	0.00006
257	cg22580512	NCOR2	12	123568427	Gene Body	Yes	0.17±0.07	0.69±0.10	0.52	0.00005
258	cg18121684	SERPINB13	18	59405541	Promoter	No	0.09±0.04	0.61±0.19	0.52	0.003
259	cg22214414	SYCP2	20	57940627	Promoter	No	0.31±0.05	0.84±0.05	0.52	0.000001
260	cg27285599	FLJ13841	17	78391312	Promoter	Yes	0.18±0.06	0.70±0.11	0.52	0.00008
261	cg16992787	CAPS	19	5865669	Gene Body	Yes	0.28±0.07	0.80±0.09	0.52	0.00003
262	cg16177163	PTDSS1	8	97341963	Promoter	No	0.16±0.05	0.68±0.12	0.52	0.0002
263	cg05790038	TRPV3	17	3407893	Gene Body	No	0.17±0.10	0.69±0.14	0.52	0.0003
264	cg04748010	POU6F2	7	39012738	Promoter	No	0.26±0.06	0.78±0.08	0.52	0.00001
265	cg18878432	HOXB6	17	44038408	Promoter	Yes	0.12±0.06	0.64±0.14	0.52	0.0004
266	cg11762346	HKDC1	10	70650118	Gene Body	No	0.22±0.07	0.74±0.13	0.52	0.0002
267	cg19466563	SPARCL1	4	88669530	Gene Body	No	0.15±0.07	0.68±0.13	0.53	0.0002
268	cg02105856	PIGR	1	205186407	Gene Body	No	0.12±0.02	0.64±0.08	0.53	0.00003
269	cg13904968	PCK1	20	55569418	Promoter	No	0.17±0.01	0.69±0.08	0.53	0.0001
270	cg17240454	SPDEF	6	34632256	Promoter	No	0.23±0.09	0.76±0.11	0.53	0.00009
271	cg26391080	SH2D4B	10	82287377	Promoter	No	0.32±0.09	0.85±0.07	0.53	0.0001
272	cg27446185	VTCN1	1	117555488	Promoter	No	0.11±0.05	0.64±0.14	0.53	0.0004
273	cg13300756	HAS1	19	56919850	Promoter	Yes	0.09±0.04	0.62±0.16	0.53	0.001
274	cg11584936	BNIPL	1	149276212	Gene Body	No	0.16±0.06	0.69±0.09	0.53	0.00002
275	cg08878744	LCE1B	1	151050298	Promoter	No	0.04±0.03	0.57±0.15	0.53	0.001
276	cg27383956	FLJ13265	19	45424742	Promoter	Yes	0.22±0.09	0.75±0.11	0.53	0.0001
277	cg15983538	SEMA4A	1	154390035	Gene	No	0.11±0.06	0.64±0.15	0.53	0.0006

278	cg25514304	PSEN2	1	225125732	Body Gene	No	0.26±0.07	0.79±0.13	0.53	0.0002
279	cg03752885	DAPK3	19	3920736	Body Gene	No	0.17±0.06	0.70±0.12	0.53	0.0001
280	cg22879289	NID1	1	234304366	Promoter	No	0.10±0.06	0.63±0.15	0.53	0.0005
281	cg03109701	TMEM118	12	115659141	Promoter	No	0.17±0.06	0.70±0.11	0.53	0.00005
282	cg08074477	TNS4	17	35911475	Promoter	No	0.11±0.07	0.64±0.08	0.53	0.00001
283	cg04086834	SMAP1	6	71433785	Promoter	No	0.13±0.04	0.67±0.17	0.53	0.002
284	cg20910746	BBOX1	11	27018992	Promoter	No	0.09±0.02	0.62±0.13	0.53	0.0008
285	cg13553204	CNKSR1	1	26377135	Gene Body	No	0.05±0.04	0.58±0.14	0.53	0.0008
286	cg23978557	SMPD2	6	109867512	Promoter	Yes	0.21±0.07	0.74±0.11	0.53	0.00005
287	cg25203980	CENTB5	1	1228458	Gene Body	Yes	0.20±0.07	0.73±0.13	0.53	0.0001
288	cg08815403	HSD17B13	4	88463166	Promoter	No	0.18±0.07	0.72±0.10	0.53	0.00003
289	cg14252059	TECTA	11	120478484	Promoter	No	0.06±0.02	0.59±0.13	0.54	0.0006
290	cg07471052	CDK3	17	71507840	Promoter	Yes	0.17±0.06	0.70±0.14	0.54	0.0004
291	cg01580568	LAMB3	1	207892479	Promoter	No	0.15±0.05	0.68±0.14	0.54	0.0004
292	cg08157292	PPP1R7	2	241739293	Gene Body	No	0.18±0.06	0.71±0.09	0.54	0.00002
293	cg11063110	CPA5	7	129772441	Gene Body	Yes	0.17±0.03	0.71±0.09	0.54	0.00006
294	cg19717150	HNF4A	20	42418292	Gene Body	Yes	0.14±0.06	0.67±0.10	0.54	0.00003
295	cg25112191	RORC	1	150070884	Gene Body	No	0.09±0.04	0.63±0.06	0.54	0.000001
296	cg06799664	DNAHL1	17	74078716	Gene Body	Yes	0.15±0.08	0.69±0.08	0.54	0.00004
297	cg15789095	SPOCD1	1	32054053	Gene Body	Yes	0.21±0.04	0.75±0.10	0.54	0.00006
298	cg23414387	CYP4B1	1	47037453	Gene Body	No	0.04±0.03	0.58±0.18	0.54	0.002
299	cg05245515	SLC39A2	14	20537113	Promoter	No	0.07±0.04	0.61±0.06	0.54	0.0000008
300	cg00208830	LAMC2	1	181421401	Promoter	No	0.16±0.05	0.70±0.12	0.54	0.0002
301	cg25341653	ELMO3	16	65790778	Promoter	Yes	0.29±0.12	0.83±0.11	0.54	0.0003
302	cg10324224	TTC13	1	229182620	Promoter	No	0.08±0.06	0.62±0.12	0.54	0.0001
303	cg24607535	CDH26	20	57966890	Gene Body	No	0.15±0.05	0.69±0.08	0.54	0.000005
304	cg24243265	MLZE	8	130869033	Promoter	No	0.16±0.06	0.70±0.13	0.54	0.0002
305	cg09432154	GPR87	3	152517359	Promoter	No	0.05±0.05	0.59±0.17	0.54	0.001
306	cg19815376	FLJ34503	6	114331999	Gene Body	No	0.10±0.06	0.64±0.11	0.54	0.00004
307	cg04099420	RIPK1	6	3021353	Promoter	No	0.06±0.03	0.60±0.10	0.54	0.0001

308	cg20811607	SMPD2	6	109867524	Promoter	Yes	0.20±0.08	0.74±0.12	0.54	0.0001
309	cg05820087	ATP13A4	3	194755255	Gene Body	No	0.03±0.01	0.58±0.15	0.54	0.001
310	cg07918509	ICAM2	17	59437139	Gene Body	No	0.15±0.04	0.69±0.08	0.54	0.00002
311	cg10414946	MS4A2	11	59612934	Gene Body	No	0.06±0.04	0.60±0.09	0.54	0.00004
312	cg21631754	XTP7	19	50429325	Promoter	Yes	0.38±0.17	0.92±0.05	0.54	0.006
313	cg24134767	HTR3A	11	113350848	Promoter	No	0.05±0.04	0.59±0.17	0.54	0.002
314	cg16862361	XDH	2	31491126	Promoter	No	0.07±0.04	0.62±0.11	0.54	0.0001
315	cg03421300	SFN	1	27062374	Gene Body	Yes	0.20±0.08	0.74±0.11	0.54	0.00007
316	cg05215575	FLJ25410	16	4778723	Promoter	No	0.04±0.02	0.59±0.16	0.54	0.001
317	cg25426302	PRRT1	6	32228804	Promoter	Yes	0.18±0.05	0.72±0.09	0.54	0.00001
318	cg16608652	B3GALT2	1	191422013	Gene Body	No	0.04±0.03	0.58±0.10	0.55	0.0002
319	cg22585988	PVRL4	1	159325951	Gene Body	No	0.17±0.08	0.72±0.10	0.55	0.00004
320	cg15684563	TSPAN8	12	69838455	Promoter	No	0.06±0.04	0.61±0.09	0.55	0.00003
321	cg20850981	ZNF323	6	28430082	Promoter	No	0.27±0.05	0.82±0.12	0.55	0.0002
322	cg24433189	SSTR5	16	1068690	Promoter	Yes	0.15±0.07	0.69±0.08	0.55	0.00001
323	cg18636558	SLC15A2	3	123096393	Gene Body	No	0.06±0.05	0.61±0.13	0.55	0.0003
324	cg11204562	C10orf81	10	115501143	Promoter	No	0.13±0.06	0.68±0.14	0.55	0.0004
325	cg05256043	DCT	13	93929952	Promoter	No	0.14±0.08	0.69±0.13	0.55	0.0001
326	cg20770175	COL3A1	2	189547719	Gene Body	No	0.16±0.05	0.71±0.09	0.55	0.00001
327	cg16609872	KCNQ1	11	2784940	Gene Body	Yes	0.06±0.04	0.61±0.14	0.55	0.0004
328	cg26511075	FLJ25422	5	36337193	Gene Body	No	0.30±0.11	0.85±0.07	0.55	0.0003
329	cg13689073	LARP1	5	154073453	Gene Body	No	0.06±0.03	0.61±0.15	0.55	0.0008
330	cg22506059	CARD10	22	36246103	Promoter	No	0.18±0.07	0.74±0.12	0.55	0.00008
331	cg05624196	APOD	3	196792172	Gene Body	Yes	0.15±0.04	0.70±0.08	0.56	0.00001
332	cg02657438	STON2	14	80934652	Gene Body	No	0.13±0.06	0.68±0.11	0.56	0.00005
333	cg19233472	FOXI1	5	169465330	Promoter	Yes	0.11±0.04	0.67±0.12	0.56	0.0002
334	cg23851011	S100A16	1	151852539	Promoter	No	0.08±0.03	0.63±0.16	0.56	0.001
335	cg21880903	KLB	4	39085060	Gene Body	No	0.15±0.04	0.70±0.09	0.56	0.00002
336	cg24765079	CDH1	16	67329931	Gene Body	Yes	0.07±0.06	0.63±0.15	0.56	0.0005
337	cg27324619	PIB5PA	22	29848860	Promoter	No	0.14±0.07	0.69±0.11	0.56	0.00004

338	cg02034222	DQX1	2	74606789	Gene Body	No	0.24±0.07	0.80±0.09	0.56	0.00001
339	cg02554564	NTF3	12	5473392	Promoter	Yes	0.21±0.04	0.77±0.12	0.56	0.0001
340	cg17866455	SCAND2	15	82974955	Promoter	Yes	0.21±0.05	0.77±0.09	0.56	0.00001
341	cg26672426	PTGES	9	131554403	Gene Body	Yes	0.07±0.04	0.63±0.15	0.56	0.0006
342	cg09450238	BTBD6	14	104786828	Gene Body	Yes	0.08±0.08	0.64±0.13	0.56	0.0001
343	cg08861115	IL1F9	2	113451848	Promoter	No	0.10±0.06	0.66±0.16	0.56	0.0006
344	cg03490200	A2ML1	12	8866463	Promoter	No	0.12±0.07	0.68±0.13	0.56	0.0001
345	cg04994456	RNF186	1	20014249	Gene Body	No	0.17±0.04	0.73±0.12	0.56	0.0001
346	cg09643186	GPX2	14	64479205	Gene Body	No	0.19±0.07	0.75±0.12	0.56	0.00008
347	cg10523671	SLC15A2	3	123095646	Promoter	Yes	0.18±0.05	0.74±0.15	0.56	0.0005
348	cg15485859	C1orf116	1	205273070	Promoter	No	0.09±0.06	0.66±0.13	0.56	0.0002
349	cg14430151	FLJ35725	4	8491500	Promoter	Yes	0.31±0.12	0.88±0.07	0.56	0.0005
350	cg01119135	C1orf116	1	205272148	Gene Body	No	0.10±0.06	0.67±0.15	0.56	0.0004
351	cg19910382	FABP1	2	88208676	Gene Body	No	0.24±0.09	0.80±0.06	0.56	0.00008
352	cg07197059	EFS	14	22905852	Promoter	Yes	0.09±0.05	0.65±0.13	0.56	0.0002
353	cg14918082	KCNAB3	17	7773962	Promoter	Yes	0.14±0.12	0.71±0.18	0.56	0.0008
354	cg06848073	FBXO44	1	11636127	Promoter	No	0.07±0.04	0.63±0.12	0.56	0.0002
355	cg09674867	C11orf16	11	8910782	Gene Body	No	0.08±0.02	0.65±0.16	0.56	0.001
356	cg00002426	SLMAP	3	57718583	Gene Body	Yes	0.04±0.02	0.61±0.18	0.56	0.002
357	cg08816023	FGF1	5	142045723	Gene Body	No	0.15±0.06	0.72±0.13	0.57	0.0002
358	cg04527918	UCN	2	27384674	Promoter	Yes	0.24±0.10	0.80±0.07	0.57	0.0002
359	cg01835489	KRT8	12	51585577	Promoter	No	0.11±0.06	0.68±0.14	0.57	0.0003
360	cg14481339	KCNJ1	11	128242529	Promoter	No	0.15±0.07	0.72±0.13	0.57	0.0001
361	cg07947930	PRELP	1	201711568	Gene Body	No	0.04±0.02	0.60±0.13	0.57	0.0005
362	cg06194808	MGC9712	7	1562743	Promoter	No	0.09±0.05	0.66±0.08	0.57	0.000006
363	cg17470143	DCAMKL1	13	35604433	Promoter	No	0.16±0.07	0.72±0.15	0.57	0.0003
364	cg14141399	HAS1	19	56919860	Promoter	Yes	0.08±0.03	0.65±0.18	0.57	0.002
365	cg26200585	PRX	19	45611085	Gene Body	No	0.21±0.12	0.77±0.14	0.57	0.0003
366	cg01521624	SLC13A3	20	44746345	Gene Body	No	0.28±0.06	0.84±0.06	0.57	0.000003
367	cg24691461	C20orf160	20	30062162	Gene Body	No	0.12±0.06	0.69±0.15	0.57	0.0003
368	cg21570818	FUT5	19	5821366	Gene	No	0.12±0.05	0.69±0.10	0.57	0.00002

369	cg01564343	TREML1	6	41229898	Body Gene Body	No	0.14±0.05	0.71±0.11	0.57	0.00006
370	cg18917378	BCAS1	20	52120414	Body Gene Body	No	0.09±0.04	0.66±0.14	0.57	0.0005
371	cg00075967	STRA6	15	72282407	Promoter	No	0.12±0.05	0.69±0.16	0.57	0.0007
372	cg08097973	NUMA1	11	71470699	Promoter	No	0.12±0.06	0.69±0.13	0.57	0.0002
373	cg00995152	DAB2IP	9	123536136	Gene Body	Yes	0.09±0.02	0.66±0.09	0.57	0.00008
374	cg24835159	RNF43	17	53849553	Gene Body	No	0.14±0.06	0.71±0.12	0.57	0.0001
375	cg15966757	SLC6A13	12	242520	Promoter	No	0.18±0.06	0.75±0.12	0.57	0.00008
376	cg18085435	ATP8B1	18	53551165	Promoter	Yes	0.03±0.02	0.60±0.17	0.57	0.002
377	cg06882877	PAQR6	1	154484425	Gene Body	No	0.19±0.05	0.76±0.10	0.57	0.00004
378	cg06550629	GPR133	12	130005125	Gene Body	No	0.26±0.11	0.84±0.09	0.57	0.0002
379	cg11724759	RPE65	1	68688486	Promoter	No	0.15±0.03	0.72±0.08	0.57	0.00002
380	cg01473816	ELF5	11	34491857	Gene Body	Yes	0.09±0.04	0.67±0.15	0.58	0.0006
381	cg08615333	TGFB3	14	75517166	Gene Body	No	0.14±0.05	0.72±0.13	0.58	0.0002
382	cg25370441	FLJ20184	4	106692682	Promoter	No	0.09±0.04	0.67±0.14	0.58	0.0004
383	cg26946769	MAPK4	18	46443536	Promoter	No	0.14±0.05	0.71±0.15	0.58	0.0005
384	cg00698688	SULT2B1	19	53747244	Gene Body	No	0.17±0.07	0.75±0.12	0.58	0.00008
385	cg23877385	GCNT3	15	57695944	Promoter	No	0.11±0.06	0.69±0.12	0.58	0.00008
386	cg08411049	SERPINB5	18	59295230	Gene Body	Yes	0.11±0.03	0.69±0.16	0.58	0.001
387	cg10762615	FBXW10	17	18588052	Promoter	No	0.21±0.06	0.78±0.10	0.58	0.00002
388	cg16391792	LIPC	15	56510949	Promoter	No	0.22±0.12	0.80±0.09	0.58	0.0003
389	cg23338993	UGT1A6	2	234265162	Gene Body	No	0.06±0.03	0.64±0.18	0.58	0.002
390	cg09243900	RAB25	1	154297468	Promoter	No	0.15±0.07	0.73±0.14	0.58	0.0002
391	cg17243643	RDH5	12	54400536	Gene Body	No	0.16±0.02	0.74±0.10	0.58	0.0001
392	cg20695587	TMPRSS11F	4	68678354	Promoter	No	0.10±0.04	0.68±0.10	0.58	0.00007
393	cg22438810	LCN2	9	129951613	Gene Body	No	0.08±0.04	0.66±0.09	0.58	0.00002
394	cg14851685	FLJ39501	19	15479559	Promoter	No	0.22±0.10	0.80±0.10	0.58	0.00006
395	cg21057494	CLEC3B	3	45041975	Promoter	No	0.08±0.05	0.66±0.17	0.58	0.0008
396	cg15320474	UBD	6	29635984	Promoter	No	0.07±0.04	0.65±0.13	0.58	0.0002
397	cg14992108	SNTB1	8	121894651	Promoter	No	0.06±0.04	0.64±0.17	0.58	0.001
398	cg21105318	ITGB6	2	160764766	Gene Body	No	0.07±0.06	0.66±0.11	0.58	0.00005

399	cg26960719	KCNJ16	17	65582897	Promoter	No	0.06±0.05	0.64±0.14	0.59	0.0003
400	cg27126442	FLJ20184	4	106693255	Gene Body	No	0.08±0.06	0.67±0.14	0.59	0.0003
401	cg10725344	UNQ1940	7	135084179	Promoter	Yes	0.17±0.11	0.75±0.07	0.59	0.0002
402	cg13259290	CSF2	5	131436281	Promoter	No	0.15±0.04	0.74±0.10	0.59	0.00006
403	cg18270343	JRK	8	143745007	Promoter	No	0.14±0.06	0.73±0.13	0.59	0.0001
404	cg20895028	CDH26	20	57966838	Promoter	No	0.11±0.05	0.70±0.13	0.59	0.0002
405	cg08612871	GJB5	1	34992921	Promoter	No	0.11±0.05	0.70±0.14	0.59	0.0003
406	cg18248112	KCNJ15	21	38550993	Gene Body	No	0.15±0.04	0.74±0.10	0.59	0.00006
407	cg09440340	C1orf161	1	116455938	Gene Body	No	0.06±0.04	0.65±0.18	0.59	0.002
408	cg07763768	C9orf45	9	124917744	Promoter	Yes	0.08±0.02	0.67±0.16	0.59	0.001
409	cg04245402	C19orf21	19	702241	Gene Body	Yes	0.06±0.04	0.65±0.16	0.59	0.0007
410	cg12603560	TNKS1BP1	11	56846646	Promoter	No	0.13±0.07	0.72±0.10	0.59	0.00002
411	cg21250978	PRKAR2B	7	106471777	Promoter	No	0.22±0.09	0.81±0.11	0.59	0.00005
412	cg13288195	FBXL22	15	61676764	Gene Body	No	0.17±0.10	0.77±0.10	0.59	0.00006
413	cg07705908	SPDEF	6	34631903	Gene Body	No	0.05±0.03	0.64±0.17	0.59	0.001
414	cg12927617	ORM1	9	116124423	Promoter	No	0.05±0.05	0.65±0.17	0.59	0.0008
415	cg05244766	GSTP1	11	67107075	Promoter	Yes	0.21±0.11	0.81±0.10	0.59	0.0001
416	cg19954000	FGF1	5	142045855	Promoter	No	0.04±0.02	0.64±0.14	0.59	0.0006
417	cg03846767	TP73	1	3597152	Gene Body	Yes	0.12±0.07	0.71±0.14	0.60	0.0001
418	cg25946374	IL22RA1	1	24342378	Promoter	No	0.12±0.08	0.72±0.13	0.60	0.00007
419	cg21949305	ADORA2A	22	23158655	Promoter	No	0.17±0.10	0.77±0.11	0.60	0.00007
420	cg10942056	DISP1	1	221168471	Gene Body	No	0.13±0.06	0.73±0.10	0.60	0.00002
421	cg03534410	TMEM40	3	12776112	Promoter	No	0.16±0.08	0.76±0.10	0.60	0.00002
422	cg03292149	CBLC	19	49971605	Promoter	No	0.13±0.06	0.73±0.13	0.60	0.0001
423	cg10046892	PAQR6	1	154484566	Promoter	No	0.12±0.07	0.72±0.13	0.60	0.00007
424	cg06817269	GCNT3	15	57696327	Gene Body	No	0.14±0.05	0.74±0.11	0.60	0.00005
425	cg19890739	Pfs2	16	84281040	Promoter	Yes	0.09±0.02	0.69±0.18	0.60	0.002
426	cg09970593	OPRD1	1	29012109	Gene Body	Yes	0.14±0.08	0.74±0.11	0.60	0.00004
427	cg18350391	IL32	16	3055553	Gene Body	No	0.13±0.08	0.73±0.19	0.60	0.0008
428	cg05650171	PFDN2	1	159355726	Promoter	No	0.10±0.05	0.71±0.13	0.60	0.0002
429	cg19297823	GCNT4	5	74363037	Promoter	No	0.07±0.03	0.67±0.10	0.61	0.00005
430	cg25902889	FSD1	19	4256090	Gene Body	No	0.15±0.07	0.76±0.12	0.61	0.00004

431	cg13364756	CYP3A43	7	99263129	Promoter	No	0.14±0.07	0.75±0.13	0.61	0.00008
432	cg16215361	MUC15	11	26551196	Promoter	No	0.14±0.08	0.75±0.13	0.61	0.00007
433	cg09801065	FAT2	5	150929345	Promoter	No	0.08±0.03	0.69±0.14	0.61	0.0004
434	cg03087937	MUC15	11	26550132	Gene Body	No	0.13±0.05	0.74±0.12	0.61	0.00006
435	cg17667972	KRT4	12	51494560	Gene Body	No	0.14±0.07	0.75±0.09	0.61	0.000009
436	cg05209917	CNTN6	3	1109730	Gene Body	No	0.13±0.05	0.73±0.15	0.61	0.0003
437	cg17277939	MGC13168	12	68379275	Gene Body	Yes	0.18±0.07	0.79±0.08	0.61	0.000009
438	cg03684977	GRB7	17	35147329	Promoter	No	0.10±0.02	0.71±0.11	0.61	0.0002
439	cg09548084	SLC35B3	6	8381217	Promoter	Yes	0.07±0.02	0.68±0.16	0.61	0.0009
440	cg16177830	TNFRSF17	16	11966520	Gene Body	No	0.07±0.05	0.69±0.14	0.61	0.0002
441	cg21550442	FLJ36445	19	41191679	Promoter	No	0.07±0.03	0.68±0.10	0.61	0.00007
442	cg27221338	KDELR2	7	6491550	Promoter	Yes	0.24±0.06	0.85±0.08	0.61	0.000003
443	cg21453309	FAM101A	12	123340008	Gene Body	No	0.11±0.07	0.73±0.13	0.61	0.00008
444	cg27610561	SLC2A10	20	44771191	Promoter	Yes	0.08±0.03	0.69±0.14	0.61	0.0005
445	cg03882305	TRIM50C	7	72077882	Gene Body	Yes	0.12±0.11	0.73±0.15	0.61	0.0002
446	cg15475323	FLJ36070	19	53911914	Gene Body	No	0.13±0.09	0.75±0.09	0.62	0.00002
447	cg25433648	S100A14	1	151855406	Gene Body	No	0.12±0.06	0.74±0.13	0.62	0.0001
448	cg12069042	PLXNB1	3	48441704	Gene Body	No	0.21±0.08	0.83±0.10	0.62	0.00002
449	cg11783497	IL1RN	2	113591763	Promoter	No	0.10±0.06	0.72±0.11	0.62	0.00002
450	cg17233506	HOXB1	17	43963292	Promoter	Yes	0.17±0.07	0.80±0.11	0.62	0.00003
451	cg12970084	ELF3	1	200243703	Gene Body	No	0.08±0.05	0.70±0.11	0.62	0.00004
452	cg24340657	KRT24	17	36113460	Gene Body	No	0.18±0.08	0.80±0.11	0.62	0.00002
453	cg12456510	TFF2	21	42644424	Promoter	No	0.13±0.05	0.76±0.09	0.62	0.000008
454	cg18437633	ITGB6	2	160764885	Promoter	No	0.11±0.03	0.74±0.11	0.63	0.00007
455	cg08314660	PKP3	11	384199	Promoter	Yes	0.23±0.10	0.86±0.10	0.63	0.00004
456	cg15560337	HYAL4	7	123272134	Promoter	No	0.05±0.04	0.68±0.17	0.63	0.001
457	cg25598083	ACOT2	14	73104646	Promoter	No	0.07±0.05	0.70±0.17	0.63	0.0007
458	cg05485060	CTNNAL1	9	110816600	Promoter	No	0.16±0.07	0.78±0.09	0.63	0.000005
459	cg23499956	S100A16	1	151851544	Gene Body	No	0.12±0.06	0.75±0.13	0.63	0.00007
460	cg20775254	PROM2	2	95304432	Gene Body	No	0.10±0.05	0.73±0.13	0.63	0.0001
461	cg13881341	FUT1	19	53951027	Promoter	No	0.08±0.03	0.71±0.14	0.63	0.0003

462	cg26377677	FURIN	15	89213122	Gene Body	No	0.10±0.04	0.73±0.12	0.63	0.0001
463	cg13742532	CCBP2	3	42825852	Promoter	No	0.11±0.04	0.74±0.10	0.63	0.00003
464	cg18704047	PART1	5	59819425	Promoter	No	0.09±0.03	0.72±0.16	0.63	0.0006
465	cg22487322	IL20RA	6	137408015	Promoter	Yes	0.12±0.04	0.75±0.11	0.63	0.00005
466	cg01497527	ANKDD1A	15	63001218	Gene Body	No	0.14±0.07	0.77±0.14	0.63	0.0001
467	cg03670238	WISP1	8	134271552	Promoter	No	0.12±0.04	0.76±0.12	0.64	0.0001
468	cg23595927	MYL5	4	661851	Gene Body	Yes	0.08±0.04	0.72±0.16	0.64	0.0005
469	cg15464148	GPR92	12	6615318	Gene Body	No	0.11±0.10	0.75±0.10	0.64	0.00006
470	cg08772206	SH2D4B	10	82287773	Gene Body	No	0.12±0.08	0.76±0.13	0.64	0.00005
471	cg06958211	PAK6	15	38319472	Gene Body	No	0.09±0.03	0.73±0.13	0.64	0.0003
472	cg03547924	GDF5	20	33489341	Gene Body	No	0.08±0.03	0.72±0.11	0.64	0.00006
473	cg06980460	FOLH1	11	49187124	Promoter	Yes	0.07±0.04	0.71±0.12	0.64	0.0001
474	cg05654164	C1orf52	1	85498480	Promoter	No	0.09±0.04	0.73±0.11	0.65	0.00003
475	cg08775230	C11orf52	11	111294703	Promoter	No	0.10±0.06	0.74±0.10	0.65	0.000007
476	cg04806409	TFF3	21	42608574	Gene Body	No	0.13±0.08	0.78±0.11	0.65	0.00001
477	cg09473585	C3orf14	3	62280559	Gene Body	No	0.14±0.07	0.79±0.07	0.65	0.000006
478	cg07922606	HIST1H3E	6	26333368	Gene Body	Yes	0.17±0.12	0.82±0.13	0.65	0.0001
479	cg15914863	CYP2W1	7	989201	Promoter	No	0.18±0.09	0.83±0.08	0.66	0.00003
480	cg24855780	TNKS1BP1	11	56845942	Gene Body	No	0.13±0.05	0.79±0.10	0.66	0.00001
481	cg02192520	RDH5	12	54400422	Promoter	No	0.06±0.02	0.72±0.13	0.66	0.0002
482	cg10929387	ITIH4	3	52839699	Gene Body	No	0.09±0.05	0.76±0.12	0.66	0.00004
483	cg05982504	IGFALS	16	1784963	Promoter	Yes	0.19±0.08	0.86±0.09	0.67	0.000007
484	cg02633817	FXYP3	19	40298572	Promoter	No	0.08±0.03	0.75±0.11	0.67	0.00009
485	cg16752583	TRPV6	7	142293853	Promoter	No	0.09±0.08	0.76±0.13	0.67	0.00003
486	cg02067021	DNAJC5B	8	67096581	Gene Body	No	0.11±0.06	0.80±0.12	0.69	0.00003
487	cg09712066	PART1	5	59819386	Promoter	No	0.08±0.05	0.76±0.13	0.69	0.00008
488	cg00480115	FXYP3	19	40298717	Gene Body	No	0.06±0.03	0.75±0.13	0.69	0.0001
489	cg12302621	SLC28A1	15	83227915	Promoter	No	0.07±0.05	0.78±0.12	0.70	0.00006
490	cg19257550	CA9	9	35663909	Promoter	No	0.09±0.06	0.81±0.09	0.72	0.000003

Table S2. Gene ontology analysis of genes with different methylation states in nasal polyp tissues

Methylation status	Category	Gene Ontology Category	Observed genes	Observed gene number	Expected gene number	Ratio of enrichment	Significance of enrichment
Hypomethylation	Biological process	cell surface receptor linked signal transduction	CCL23, CD28, CD79B, CLEC4A, CNR2, DOK2, EMR3, EVL, FCER1G, GPR55, GPR77, GPR84, GPR97, IFNGR2, IGSF2, IL2RA, ITGAL, ITGAM, ITGB2, KLRG1, LCP2, LTB4R, MARCO, MRGPRX2, NALP12, P2RY11, P2RY14, PIK3CG	28	10.94	2.56	1.8E-06
		lymphocyte proliferation	CD28, IL10, LST1	3	0.22	13.64	0.001
		regulation of cell proliferation	BCL2, CCL23, CD28, CD33, CD86, IL10, LST1, SLAMF1, TNFSF4	9	3.02	2.98	0.003
		regulation of I-kappaB kinase/NF-kappaB cascade	BST2, CARD8, CASP8, NALP12	4	0.77	5.19	0.007
		cell motility	ARHGDIB, EGFL7, EVL, IL10, ITGAL, ITGB2, LTB4R, PECAM1, VNN1, VNN2	10	2.28	4.39	8.8E-05
		leukocyte activation	CD28, CD86, IL10, LST1, SLAMF1	5	0.95	5.26	0.003
		cytokine biosynthesis	CD28, CD86, IL10, NALP12	4	0.37	10.81	0.0005
		cytokine secretion	CARD8, NALP12	2	0.11	18.18	0.005
		immune response	ARHGDIB, BCL2, BST2, CD28, CD53, CD79B, CD86, CLEC4A, CNR2, CST7, CTSG, FCER1G, FCGR1A, FCGR2A, FCGR2B, GJB6, GRAP2, HLA-DPA1, IGSF2, IL10, IL18BP, IL2RA, ITGB2, LCP2, LILRA2, LST1, SLAMF1, TNFSF4, TNFSF8	29	4.72	6.14	7.5E-16
		humoral immune response	BCL2, BST2, CD28, CD53, CLEC4A, GRAP2, IGSF2, ITGB2, SLAMF1	9	1.47	6.12	1.5E-05
		cellular defense response	CD244, CD300C, KLRG1, NCF2, TYROBP	5	0.62	8.06	0.0004
		inflammatory response	ALOX5AP, CCL23, ITGAL, ITGB2, KLRG1, LTB4R, NALP12, S100A9	8	2.35	3.4	0.002
		antimicrobial humoral response	CD53, CLEC4A, GRAP2, IGSF2, ITGB2, SLAMF1	6	0.84	7.14	0.0002
		physiological response to wounding	ALOX5AP, CCL23, EVL, ITGAL, ITGB2, KLRG1, LTB4R, NALP12, S100A9	9	3.15	2.86	0.004
	Molecular function	immunoglobulin binding	FCER1G, FCGR1A, FCGR2A, FCGR2B	4	0.14	28.57	9.3E-06

Cellular component	membrane part	ALOX5AP, AMICA1, BCL2, BST2, C6orf105, C6orf25, CD244, CD28, CD300C, CD300LF, CD33, CD37, CD48, CD53, CD79B, CD86, CLEC14A, CLEC4A, CNR2, EMR3, EVI2A, EVL, FCER1G, FCGR1A, FCGR2A, FCGR2B, GALNT1, GJB6, GPR55, GPR77, GPR84, GPR97, HK2, HLA-DPA1, HPN, IFNGR2, IGSF2, IL2RA, ITGAL, ITGAM, ITGB2, KCNE1, KCNK17, KLRG1, LAPTM5, LILRA2, LST1, LTB4R, MARCO, MRGPRX2, MS4A4A, P2RY11, P2RY14, PECAM1, SEMA6B, SLAMF1, SLC45A1, TM4SF19, TMC8, TNFSF4, TNFSF8, TRAF3IP3, TSPAN32, TYROBP	64	35.71	1.79	9.0E-09
	plasma membrane	BST2, C6orf25, CD28, CD300C, CD33, CD37, CD48, CD53, CD79B, CD86, CLEC4A, CNR2, CPM, EVL, FCER1G, FCGR1A, FCGR2A, FCGR2B, GJB6, GPR55, HLA-DPA1, HPN, IFNGR2, IGSF2, IL2RA, ITGAL, ITGAM, ITGB2, KCNE1, LAPTM5, LTB4R, MARCO, P2RY11, PECAM1, PPP1R16B, TNFSF4, TNFSF8, TYROBP	38	16.9	2.25	3.5E-07
	intrinsic to membrane	ALOX5AP, AMICA1, BCL2, BST2, C6orf105, C6orf25, CD244, CD28, CD300C, CD300LF, CD33, CD37, CD48, CD53, CD79B, CD86, CLEC14A, CLEC4A, CNR2, EMR3, EVI2A, FCER1G, FCGR1A, FCGR2A, FCGR2B, GALNT1, GJB6, GPR55, GPR77, GPR84, GPR97, HLA-DPA1, HPN, IFNGR2, IGSF2, IL2RA, ITGAL, ITGAM, ITGB2, KCNE1, KCNK17, KLRG1, LAPTM5, LILRA2, LST1, LTB4R, MARCO, MRGPRX2, MS4A4A, P2RY11, P2RY14, PECAM1, SEMA6B, SLAMF1, SLC45A1, TM4SF19, TMC8, TNFSF4, TNFSF8, TRAF3IP3, TSPAN32, TYROBP	62	33.4	1.86	4.9E-09
	plasma membrane part	BST2, CD28, CD300C, CD33, CD37, CD48, CD53, CD79B, CLEC4A, CNR2, EVL, FCER1G, FCGR1A, GJB6, GPR55, HLA-DPA1, HPN, IFNGR2, ITGAL, ITGAM, ITGB2, KCNE1, LAPTM5, LTB4R, MARCO, P2RY11, PECAM1, TNFSF4, TNFSF8, TYROBP	30	14.2	2.11	3.5E-05

Hypermethylation	Biological process	integral to membrane	ALOX5AP, AMICA1, BCL2, BST2, C6orf105, C6orf25, CD244, CD28, CD300C, CD300LF, CD33, CD37, CD48, CD53, CD79B, CD86, CLEC14A, CLEC4A, CNR2, EMR3, EVI2A, FCER1G, FCGR1A, FCGR2A, FCGR2B, GALNT1, GJB6, GPR55, GPR77, GPR84, GPR97, HLA-DPA1, HPN, IFNGR2, IGSF2, IL2RA, ITGAL, ITGAM, ITGB2, KCNE1, KCNK17, KLRG1, LAPTM5, LILRA2, LST1, LTB4R, MARCO, MRGPRX2, MS4A4A, P2RY11, P2RY14, PECAM1, SEMA6B, SLAMF1, SLC45A1, TM4SF19, TMC8, TNFSF4, TNFSF8, TRAF3IP3, TSPAN32, TYROBP	62	33.3	1.86	4.3E-09
		intrinsic to plasma membrane	BST2, CD28, CD300C, CD33, CD37, CD48, CD53, CD79B, CLEC4A, CNR2, FCER1G, FCGR1A, GPR55, HLA-DPA1, HPN, IFNGR2, ITGAL, ITGAM, ITGB2, KCNE1, LAPTM5, LTB4R, MARCO, P2RY11, TNFSF4, TNFSF8, TYROBP	27	11.95	2.26	3.0E-05
		integrin complex	ITGAL, ITGAM, ITGB2	3	0.33	9.09	0.004
		ectoderm development	DCT, ELF3, GJB5, KRT15, KRT5, LAMB3, LAMC2, LCE1B, LCE1E, SPRR2A, TGM5	11	1.95	5.64	3.5E-06
	Molecular function	hemostasis	ADAMTS13, ADORA2A, ANXA8, F7, HNF4A, IL20RA	6	1.71	3.51	0.007
		wound healing	ADAMTS13, ADORA2A, ANXA8, F7, HNF4A, IL20RA	6	1.8	3.33	0.009
		calcium ion binding	ADAMTS13, ANXA8, CALML3, CAPS, CDH1, CDH26, CHRNA10, F7, FAT2, FBN3, FURIN, MMP10, MYL5, MYL7, NID1, RHOT2, S100A14, S100A16, SNTB1, SPARCL1, TGM5, TNNC1, TRPV3, TRPV6	24	14.3	1.68	0.009
		oxidoreductase activity acting on paired donors with incorporation or reduction of molecular oxygen reduced flavin or flavoprotein as one donor and incorporation of one atom of oxygen	CYP2C18, CYP2W1, CYP3A43, CYP4B1	4	0.66	6.06	0.004
	Cellular component	membrane part	ADORA2A, ATP13A4, ATP8B1, B3GALT2, C6orf78, CA9, CCBP2, CDH1, CDH26, CHRM1, CHRNA10, CLEC1A, CNKSR1, CX3CL1, CYP4F3, DCAMKL1, DCT, FAT2, FOLH1, FURIN, FUT1, FUT5, FXYP3, GJB5, GPR133, GPR87, GPR92, HAS1, HCRTR2, HTR3A, ICAM2, IL20RA, IL5RA, ITGB6, KCNAB3, KCNJ1, KCNJ15, KCNJ16, KCNQ1, KDELR2, KLB, LRFN3, MS4A2, MUC15, OPRD1, PAQR6, PIGR, PKHD1, PKP3, PLXNB1, PPAP2B, PROM2, PRRT1, PRSS8, PSEN2, PTDSS1, PTGES, RHOT2, SEMA4A, SLAMF9, SLC13A3, SLC15A2, SLC16A4, SLC28A1, SLC2A10, SLC35B3, SLC39A2, SLC6A13, SLMAP, SMPD2, SNTB1, SSTR5, ST6GALNAC1, STON2, TMEM109, TNFRSF17, TRPV3, TRPV6, TSPAN8, UGT1A6, UGT2B7	81	64.77	1.25	0.008

intrinsic to membrane	ADORA2A, ATP13A4, ATP8B1, B3GALT2, C6orf78, CA9, CCBP2, CDH1, CDH26, CHRM1, CHRNA10, CLEC1A, CX3CL1, CYP4F3, DCAMKL1, DCT, FAT2, FOLH1, FURIN, FUT1, FUT5, FXYD3, GJB5, GPR133, GPR87, GPR92, HAS1, HCRTR2, HTR3A, ICAM2, IL20RA, IL5RA, ITGB6, KCNAB3, KCNJ1, KCNJ15, KCNJ16, KCNQ1, KDELR2, KLB, LRFN3, MS4A2, MUC15, OPRD1, PAQR6, PIGR, PKHD1, PLXNB1, PPAP2B, PROM2, PRRT1, PRSS8, PSEN2, PTDSS1, PTGES, RHOT2, SEMA4A, SLAMF9, SLC13A3, SLC15A2, SLC16A4, SLC28A1, SLC2A10, SLC35B3, SLC39A2, SLC6A13, SLMAP, SMPD2, SSTR5, ST6GALNAC1, TMEM109, TNFRSF17, TRPV3, TRPV6, TSPAN8, UGT1A6, UGT2B7	77	60.59	1.27	0.007
vesicular fraction	CYP2C18, CYP3A43, CYP4B1, CYP4F3, DCT, UGT1A6, UGT2B7	7	2.24	3.12	0.007
integral to membrane	ADORA2A, ATP13A4, ATP8B1, B3GALT2, C6orf78, CA9, CCBP2, CDH1, CDH26, CHRM1, CHRNA10, CLEC1A, CX3CL1, CYP4F3, DCAMKL1, DCT, FAT2, FOLH1, FURIN, FUT1, FUT5, FXYD3, GJB5, GPR133, GPR87, GPR92, HAS1, HCRTR2, HTR3A, ICAM2, IL20RA, IL5RA, ITGB6, KCNAB3, KCNJ1, KCNJ15, KCNJ16, KCNQ1, KDELR2, KLB, LRFN3, MS4A2, MUC15, OPRD1, PAQR6, PIGR, PKHD1, PLXNB1, PPAP2B, PROM2, PRRT1, PRSS8, PSEN2, PTDSS1, PTGES, RHOT2, SEMA4A, SLAMF9, SLC13A3, SLC15A2, SLC16A4, SLC28A1, SLC2A10, SLC35B3, SLC39A2, SLC6A13, SLMAP, SMPD2, SSTR5, ST6GALNAC1, TMEM109, TNFRSF17, TRPV3, TRPV6, TSPAN8, UGT1A6, UGT2B7	77	60.4	1.27	0.006
intrinsic to plasma membrane	ADORA2A, ATP8B1, CCBP2, CHRM1, DCAMKL1, FOLH1, FUT1, FXYD3, HAS1, HCRTR2, HTR3A, ICAM2, IL5RA, ITGB6, KCNJ1, KCNJ15, KCNQ1, MS4A2, OPRD1, PIGR, PKHD1, PLXNB1, PSEN2, SLC15A2, SLC16A4, SLC28A1, SLC39A2, SLC6A13, SLMAP, SMPD2, SSTR5, TRPV6, TSPAN8	33	21.68	1.52	0.009
laminin-5 complex	LAMB3, LAMC2	2	0.04	50	0.0004

Table S3. DNA methylation level of CpGs in genes of arachidonic acid metabolism

N	Illumina TargetID	Gene name (synonym)	Gene product	Chromosome	CpG Coordinate	Position	CpG island	Beta value of ATA (mean±SD)	Beta value of AIA (mean±SD)	DeltaBeta (AIA-ATA)	t-test (P-value)
1	cg15201877	PTGER3 (EP3)	Prostaglandin E receptor 3	1	71285561	Gene Body	Yes	0.07±0.05	0.11±0.02	0.04	0.18
2	cg12739034	PTGER3 (EP3)	Prostaglandin E receptor 3	1	71286214	Promoter	Yes	0.02±0.01	0.03±0.01	0.01	0.31
3	cg24022301	PTGFR (FP)	Prostaglandin F receptor	1	78729158	Promoter	Yes	0.02±0.01	0.02±0.01	0.01	0.34
4	cg03495868	PTGFR (FP)	Prostaglandin F receptor	1	78729493	Gene Body	Yes	0.02±0.01	0.04±0.01	0.02	0.02
5	cg08361238	PTGFRN (FPRP)	Prostaglandin F2 receptor negative regulator	1	117253827	Promoter	Yes	0.29±0.03	0.50±0.03	0.21	0.00003
6	cg03752628	PTGFRN (FPRP)	Prostaglandin F2 receptor negative regulator	1	117255033	Gene Body	Yes	0.04±0.03	0.22±0.04	0.17	0.0001
7	cg19155599	PTGS2 (COX2)	Prostaglandin-endoperoxide synthase 2 precursor	1	184915776	Gene Body	Yes	0.04±0.01	0.04±0.02	0.00	0.96
8	cg13986130	PTGS2 (COX2)	Prostaglandin-endoperoxide synthase 2 precursor	1	184915953	Gene Body	Yes	0.00±0.01	0.00±0.00	0.00	0.59
9	cg18335243	PTGS2 (COX2)	Prostaglandin-endoperoxide synthase 2 precursor	1	184916142	Gene Body	Yes	0.01±0.01	0.00±0.00	0.00	0.35
10	cg09461185	PTGS2 (COX2)	Prostaglandin-endoperoxide synthase 2 precursor	1	184916254	Promoter	Yes	0.01±0.01	0.14±0.29	0.13	0.37
11	cg15774283	PTGS2 (COX2)	Prostaglandin-endoperoxide synthase 2 precursor	1	184916504	Gene Body	Yes	0.01±0.00	0.01±0.00	0.00	0.17
12	cg03160309	PTGS2 (COX2)	Prostaglandin-endoperoxide synthase 2 precursor	1	184916703	Promoter	Yes	0.03±0.01	0.03±0.02	0.00	0.99
13	cg07708788	SLCO2A1 (PGT)	Solute carrier organic anion transporter family; member 2A1	3	135231001	Gene Body	Yes	0.00±0.00	0.00±0.00	0.00	0.48
14	cg19591206	SLCO2A1 (PGT)	Solute carrier organic anion transporter family; member 2A1	3	135231499	Promoter	Yes	0.01±0.00	0.01±0.00	0.00	0.14
15	cg12554857*	PGDS	Prostaglandin-D synthase	4	95483042	Gene Body	No	0.86±0.05	0.18±0.15	-0.68	0.0002
16	cg08164315	PTGER4 (EP4)	Prostaglandin E receptor 4	5	40714939	Promoter	Yes	0.01±0.00	0.01±0.00	0.00	0.75
17	cg16361890	LTC4S	Leukotriene C4 synthase isoform 1	5	179153151	Promoter	No	0.09±0.02	0.12±0.06	0.03	0.36
18	cg11394785	LTC4S	Leukotriene C4 synthase isoform 1	5	179153696	Gene Body	No	0.03±0.02	0.07±0.05	0.04	0.16
19	cg14116596	TBXAS1 (TS)	Thromboxane A synthase 1	7	139175142	Promoter	No	0.71±0.11	0.50±0.11	-0.21	0.02
20	cg08876665	LTB4DH	NADP-dependent leukotriene B4 12-hydroxydehydrogenase	9	113401159	Gene Body	Yes	0.01±0.01	0.02±0.01	0.01	0.03
21	cg23964386	LTB4DH	NADP-dependent leukotriene B4 12-hydroxydehydrogenase	9	113402070	Promoter	Yes	0.04±0.02	0.20±0.04	0.17	0.0001
22	cg10493166	PTGS1 (COX1)	Prostaglandin-endoperoxide synthase 1 isoform 1 precursor	9	124172942	Promoter	Yes	0.00±0.00	0.01±0.00	0.00	0.52
23	cg12927153	PTGS1 (COX1)	Prostaglandin-endoperoxide synthase 1 isoform 1 precursor	9	124173139	Gene Body	Yes	0.00±0.00	0.00±0.00	0.00	0.12
24	cg10218959	PTGES2 (PGES2)	Prostaglandin E synthase 2 isoform 1	9	129930023	Gene Body	Yes	0.00±0.00	0.00±0.00	0.00	0.48
25	cg24730207	PTGES2 (PGES2)	Prostaglandin E synthase 2 isoform 1	9	129931564	Promoter	Yes	0.97±0.01	0.97±0.01	0.00	0.94
26	cg26672426*	PTGES (PGES)	Prostaglandin E synthase	9	131554403	Gene Body	Yes	0.07±0.04	0.63±0.15	0.56	0.0006
27	cg17683775	PTGES (PGES)	Prostaglandin E synthase	9	131555630	Promoter	No	0.78±0.07	0.59±0.04	-0.19	0.006
28	cg00563932	PTGDS (PDS)	Prostaglandin H2 D-isomerase	9	138990870	Promoter	No	0.71±0.06	0.56±0.09	-0.15	0.03
29	cg11546621	PTGDS (PDS)	Prostaglandin H2 D-isomerase	9	138991982	Gene Body	Yes	0.79±0.04	0.82±0.04	0.03	0.36
30	cg18809289	ALOX5 (5-LO)	Arachidonate 5-lipoxygenase	10	45189822	Gene Body	Yes	0.08±0.03	0.11±0.03	0.02	0.27
31	cg26240353	LTA4H	Leukotriene A4 hydrolase	12	94953402	Gene Body	Yes	0.00±0.00	0.05±0.10	0.04	0.37
32	cg08965324	LTA4H	Leukotriene A4 hydrolase	12	94953958	Promoter	Yes	0.09±0.12	0.10±0.08	0.01	0.86
33	cg08529529*	ALOX5AP (FLAP)	Arachidonate 5-lipoxygenase-activating protein	13	30207799	Gene Body	No	0.84±0.06	0.31±0.24	-0.52	0.006
34	cg18236297	CYSLTR2	Cysteinyl leukotriene receptor 2	13	48178408	Promoter	No	0.84±0.08	0.84±0.05	0.00	0.94

35	cg16886259	CYSLTR2	Cysteinyl leukotriene receptor 2	13	48179223	Gene Body	No	0.87±0.02	0.86±0.02	0.00	0.87
36	cg21418076	LTB4R2 (BLT2)	Leukotriene B4 receptor 2	14	23847718	Promoter	No	0.94±0.01	0.93±0.03	-0.01	0.60
37	cg10337819	LTB4R2 (BLT2)	Leukotriene B4 receptor 2	14	23848119	Gene Body	No	0.91±0.03	0.92±0.02	0.01	0.61
38	cg25775449	LTB4R (BLT1)	Leukotriene B4 receptor	14	23851721	Promoter	No	0.83±0.09	0.76±0.08	-0.07	0.26
39	cg20542800*	LTB4R (BLT1)	Leukotriene B4 receptor	14	23852374	Gene Body	No	0.88±0.06	0.27±0.16	-0.61	0.0004
40	cg24989962	PTGDR (DP)	Prostaglandin D2 receptor	14	51804036	Promoter	Yes	0.05±0.02	0.05±0.02	0.00	0.80
41	cg09516965	PTGDR (DP)	Prostaglandin D2 receptor	14	51804279	Gene Body	Yes	0.01±0.00	0.01±0.01	0.00	0.76
42	cg06738602	PTGER2 (EP2)	Prostaglandin E receptor 2	14	51850384	Promoter	Yes	0.04±0.01	0.04±0.03	0.00	0.89
43	cg25823578	PTGER2 (EP2)	Prostaglandin E receptor 2	14	51851062	Gene Body	Yes	0.02±0.01	0.02±0.01	0.00	0.91
44	cg09872233	ALOX15	Arachidonate 15-lipoxygenase	17	4491674	Gene Body	Yes	0.01±0.00	0.02±0.01	0.01	0.14
45	cg15843823	ALOX15	Arachidonate 15-lipoxygenase	17	4491713	Promoter	Yes	0.03±0.01	0.06±0.03	0.04	0.03
46	cg03760483	ALOX12 (LOG12)	Arachidonate 12-lipoxygenase	17	6840021	Promoter	Yes	0.24±0.08	0.45±0.03	0.21	0.01
47	cg08946332	ALOX12 (LOG12)	Arachidonate 12-lipoxygenase	17	6840612	Gene Body	Yes	0.84±0.08	0.94±0.04	0.11	0.07
48	cg12343777	ALOX15B	Arachidonate 15-lipoxygenase; second type	17	7883067	Promoter	No	0.01±0.01	0.06±0.02	0.05	0.008
49	cg15799267	ALOX15B	Arachidonate 15-lipoxygenase; second type	17	7883131	Gene Body	No	0.10±0.04	0.20±0.04	0.10	0.006
50	cg03742272	ALOX12B (12R-LOX)	Arachidonate 12-lipoxygenase; 12R type	17	7931430	Gene Body	No	0.73±0.03	0.88±0.04	0.15	0.0004
51	cg00501366	ALOX12B (12R-LOX)	Arachidonate 12-lipoxygenase; 12R type	17	7933201	Promoter	No	0.85±0.03	0.89±0.02	0.04	0.09
52	cg00184893	ALOXE3	Arachidonate lipoxygenase 3	17	7962430	Gene Body	No	0.01±0.00	0.01±0.00	0.00	0.54
53	cg10392768	ALOXE3	Arachidonate lipoxygenase 3	17	7962553	Promoter	Yes	0.01±0.00	0.01±0.00	0.00	0.56
54	cg17903316	LOXHD1	Lipoxygenase homology domains 1	18	42435658	Promoter	No	0.67±0.18	0.20±0.15	-0.46	0.006
55	cg15861540	TBXA2R (TXA2-R)	Thromboxane A2 receptor isoform 2	19	3557463	Gene Body	Yes	0.01±0.00	0.01±0.00	0.00	0.82
56	cg09998229	TBXA2R (TXA2-R)	Thromboxane A2 receptor isoform 2	19	3557757	Promoter	Yes	0.01±0.01	0.01±0.01	0.00	0.76
57	cg10468702	PTGER1 (EP1)	Prostaglandin E receptor 1	19	14446209	Gene Body	Yes	0.57±0.03	0.72±0.08	0.15	0.009
58	cg27524460	PTGER1 (EP1)	Prostaglandin E receptor 1	19	14447840	Promoter	No	0.08±0.02	0.25±0.04	0.17	0.0003
59	cg04057485	PTGIR (IP)	Prostaglandin I2 (prostacyclin) receptor	19	51819205	Gene Body	Yes	0.99±0.00	0.99±0.00	0.00	0.71
60	cg11822964	PTGIR (IP)	Prostaglandin I2 (prostacyclin) receptor	19	51821177	Promoter	Yes	0.91±0.02	0.82±0.06	-0.09	0.02
61	cg24964368	FPRL1 (ALXR)	Lipoxin A4 receptor	19	56956225	Promoter	No	0.37±0.09	0.13±0.08	-0.24	0.006
62	cg05932408	PTGIS (PGIS)	Prostaglandin I2 (prostacyclin) synthase	20	47618046	Gene Body	Yes	0.02±0.00	0.03±0.01	0.01	0.10
63	cg07612655	PTGIS (PGIS)	Prostaglandin I2 (prostacyclin) synthase	20	47618924	Promoter	No	0.37±0.06	0.26±0.07	-0.11	0.05

CYSLTR1 on X chromosome is excluded in the gene list of arachidonic acid metabolism

*Differentially methylated CpGs using the criteria of $P \leq 0.01$ and DelatBeta of ≥ 0.50

Table S4. DNA methylation level of commonly used housekeeping genes

Gene name	Gene full anem	Illumina TargetID	Chromosome	CpG Coordinate	Beta value of peripheral blood		Beta value of nasal polyps	
					ATA (mean±SD)	AIA (mean±SD)	ATA (mean±SD)	AIA (mean±SD)
ACTB	β-actin	cg23175281	7	5,536,386	0.01 ±0.00	0.01 ±0.01	0.00 ±0.00	0.01 ±0.00
		cg23261233	7	5,537,015	0.03 ±0.01	0.02 ±0.01	0.01 ±0.01	0.01 ±0.00
GAPDH	glyceraldehyde-3 phosphate dehydrogenase	cg00241355	12	6,513,890	0.02 ±0.00	0.02 ±0.00	0.01 ±0.00	0.01 ±0.00
		cg20917484	12	6,514,327	0.02 ±0.02	0.02 ±0.01	0.02 ±0.02	0.01 ±0.00
LDHA	lactate dehydrogenase A	cg01316516	11	18,372,540	0.03 ±0.01	0.02 ±0.01	0.01 ±0.00	0.01 ±0.00
		cg20429911	11	18,373,111	0.05 ±0.01	0.04 ±0.01	0.03 ±0.02	0.03 ±0.01
B2M	β-2-microglobulin	cg03355298	15	42,790,996	0.01 ±0.00	0.01 ±0.00	0.00 ±0.00	0.00 ±0.00
		cg08350173	15	42,790,970	0.02 ±0.00	0.01 ±0.00	0.01 ±0.00	0.01 ±0.00
PGAM1	phosphoglycerate mutase	cg21245135	10	99,176,506	0.01 ±0.01	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00
		cg23923462	10	99,175,996	0.03 ±0.00	0.03 ±0.00	0.03 ±0.01	0.02 ±0.01
ALDOA	aldolase A	cg01311051	16	29,972,398	0.10 ±0.12	0.04 ±0.03	0.02 ±0.02	0.01 ±0.01
TUBA1	α-tubulin	cg01693157	2	219,826,517	0.02 ±0.01	0.02 ±0.01	0.01 ±0.00	0.01 ±0.00
		cg09197965	2	219,827,423	0.02 ±0.00	0.02 ±0.01	0.01 ±0.01	0.02 ±0.00
VIM	vimentin	cg12874092	10	17,311,525	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00
PFKP	phosphofructokinase	cg08465862	10	3,099,459	0.02 ±0.00	0.02 ±0.01	0.01 ±0.00	0.01 ±0.00
		cg10247268	10	3,099,799	0.01 ±0.00	0.01 ±0.01	0.01 ±0.00	0.00 ±0.00