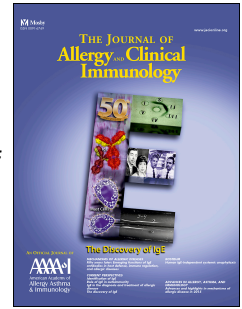


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Epigenome-wide Analysis Links *SMAD3* Methylation at Birth to Asthma in Children of Asthmatic Mothers

Avery DeVries, BS, Gabriela Wlasiuk, PhD, Susan J. Miller, MS, Anthony Bosco, PhD, Debra A. Stern, MS, I. Carla Lohman, MS, Janet Rothers, PhD, Anya C. Jones, PhD, Jessie Nicodemus-Johnson, PhD, Monica M. Vasquez, MPH, John A. Curtin, PhD, Angela Simpson, MD, PhD, Adnan Custovic, MD, PhD, Daniel J. Jackson, MD, James E. Gern, MD, Robert F. Lemanske, Jr., MD, Stefano Guerra, MD, Anne L. Wright, PhD, Carole Ober, PhD, Marilyn Halonen, PhD, Donata Vercelli, MD



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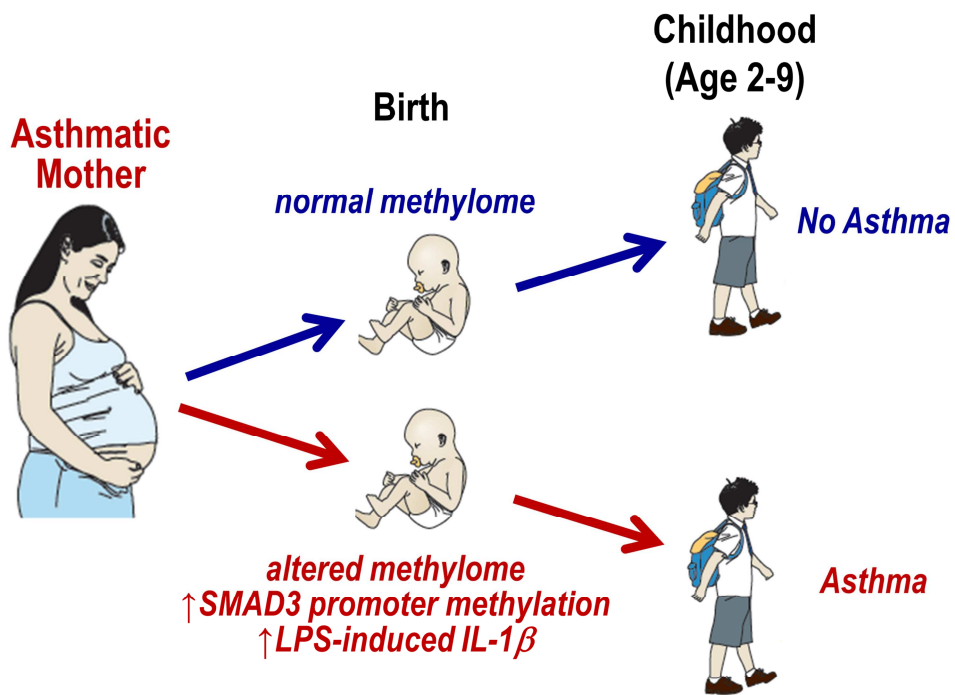
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1 **TITLE:** Epigenome-wide Analysis Links *SMAD3* Methylation at Birth to Asthma in
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3

4 Avery DeVries, BS,^{1,2} Gabriela Wlasiuk, PhD,¹ Susan J. Miller, MS,³ Anthony
5 Bosco, PhD,⁴ Debra A. Stern, MS,¹ I. Carla Lohman, MS,¹ Janet Rothers, PhD,⁵ Anya C.
6 Jones, PhD,⁴ Jessie Nicodemus-Johnson, PhD,⁶ Monica M. Vasquez, MPH,¹ John A.
7 Curtin, PhD,⁷ Angela Simpson, MD, PhD,⁷ Adnan Custovic, MD, PhD,⁷ Daniel J.
8 Jackson, MD,⁸ James E. Gern, MD,⁸ Robert F. Lemanske, Jr., MD,⁸ Stefano Guerra,
9 MD,^{1,9} Anne L. Wright, PhD,^{1,10} Carole Ober, PhD,⁶ Marilyn Halonen, PhD,^{1,11,12,13} and
10 Donata Vercelli, MD^{1,2, 12,13}

11 **AUTHOR AFFILIATIONS:**

12 ¹Arizona Respiratory Center, University of Arizona, Tucson, AZ 85724

13 ²Department of Cellular and Molecular Medicine, University of Arizona, Tucson, AZ
14 85724

15 ³Arizona Research Laboratories, University of Arizona, Tucson, AZ 85721

16 ⁴Telethon Kids Institute, University of Western Australia, Perth, Australia

17 ⁵College of Nursing, University of Arizona, Tucson, AZ 85719

18 ⁶Department of Human Genetics, University of Chicago, Chicago, IL60637

19 ⁷Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair,

20 Manchester Academic Health Science Centre, The University of Manchester and

21 University Hospital of South Manchester NHS Foundation Trust, Manchester, United

22 Kingdom

23 ⁸University of Wisconsin School of Medicine and Public Health, Department of
24 Pediatrics, Madison, WI 53792

25 ⁹CREAL, University Pompeu Fabra, Barcelona, Spain

26 ¹⁰Department of Pediatrics, University of Arizona, Tucson, AZ 85724

27 ¹¹Department of Pharmacology, University of Arizona, Tucson, AZ 85724

28 ¹²Arizona Center for the Biology of Complex Diseases, University of Arizona, Tucson,
29 AZ 85721

30 ¹³The Bio5 Institute, University of Arizona, Tucson, AZ 85721

31

32 **CORRESPONDING AUTHOR:**

33 Donata Vercelli, MD. The BIO5 Institute, Rm. 339, 1657 E. Helen Street, Tucson, AZ
34 85721. Phone: (520) 626-6387 FAX: (520) 626-6623 email: donata@email.arizona.edu

35

36 **WORD COUNT:** 4134

37

38 **KEY MESSAGES**

- 39 • The trajectory to childhood asthma begins at birth and involves epigenetic
40 modifications in innate pro-inflammatory and immunoregulatory pathways.
- 41 • Neonatal immune cells collected at birth harbor differentially methylated regions that
42 distinguish children who will and will not develop asthma by age 9.
- 43 • In three independent birth cohorts, DNA methylation at the *SMAD3* promoter was
44 selectively increased in asthmatic children of asthmatic mothers and was associated
45 with risk of childhood asthma.

46

47 **CAPSULE SUMMARY:**

48 The trajectory to childhood asthma begins at birth and involves epigenetic (DNA
49 methylation) modifications in innate pro-inflammatory and immunoregulatory pathways.

50 Maternal asthma appears to strongly influence this trajectory.

51

52 **AUTHOR CONTRIBUTIONS:** ADV and GW measured and analyzed DNA methylation.
53 SJM, AB, DAS, JR, JNJ, ACJ and MMV performed statistical and network analyses. ICL
54 generated ELISA data. JAC, AS and AC designed and provided samples from the
55 MAAS study. DJJ, JEG, and RFL designed and provided data from the COAST study.
56 ALW and MH designed and provided samples from the IIS study. CO, SG, and MH
57 contributed to data interpretation. DV designed the study, oversaw data analyses and
58 interpretation, and wrote the paper with ADV. All authors reviewed the final manuscript.

59

60

61

62 **ABSTRACT**

63 **Background** The timing and mechanisms of asthma inception remain imprecisely
64 defined. Although epigenetic mechanisms likely contribute to asthma pathogenesis, little
65 is known about their role in asthma inception.

66

67 **Objective** To assess whether the trajectory to asthma begins already at birth and
68 epigenetic mechanisms, specifically DNA methylation, contribute to asthma inception.

69

70 **Methods** We used Methylated CpG Island Recovery Assay (MIRA)-chip to survey
71 DNA methylation in cord blood mononuclear cells (CBMC) from 36 children (18 non-
72 asthmatic, 18 asthmatic by age 9) from the Infant Immune Study (IIS), an unselected
73 birth cohort closely monitored for asthma for a decade. *SMAD3* methylation in IIS
74 (n=60) and in two replication cohorts (The Manchester Asthma and Allergy Study, n=30,
75 and the Childhood Origins of ASThma Study, n=28) was analyzed by bisulfite
76 sequencing or Illumina 450K arrays. CBMC-derived IL-1 β was measured by ELISA.

77

78 **Results** Neonatal immune cells harbored 589 differentially methylated regions (DMRs)
79 that distinguished IIS children who did and did not develop asthma by age 9. In all three
80 cohorts, methylation in *SMAD3*, the most connected node within the network of asthma-
81 associated DMRs, was selectively increased in asthmatic children of asthmatic mothers
82 and was associated with childhood asthma risk. Moreover, *SMAD3* methylation in IIS
83 neonates with maternal asthma was strongly and positively associated with neonatal
84 production of IL-1 β , an innate inflammatory mediator.

85

86 **Conclusions** The trajectory to childhood asthma begins at birth and involves
87 epigenetic modifications in immunoregulatory and pro-inflammatory pathways. Maternal
88 asthma influences epigenetic mechanisms that contribute to the inception of this
89 trajectory.

90

91 **ABSTRACT WORD COUNT:** 246

92 **KEY WORDS:** epigenetics, DNA methylation, childhood asthma, *SMAD3*

93

94 **ABBREVIATIONS:**

95 CBMC: cord blood mononuclear cells

96 COAST: Childhood Origins of ASThma

97 DMR: differentially methylated region

98 GWAS: genome-wide association study

99 IIS: Infant Immune Study

100 MAAS: Manchester Asthma and Allergy Study

101 INTRODUCTION

102 Asthma is the most prevalent chronic disease of childhood (1). Epidemiological
103 evidence suggests that the disease often begins during the pre-school years even when
104 chronic symptoms appear much later in life (2). However, firm criteria to pinpoint how
105 early a child's trajectory to asthma truly begins are currently lacking. The mechanisms
106 underlying asthma inception also remain largely unknown. Subtle modifications of both
107 innate and adaptive immune responses accompany and often precede the diagnosis of
108 childhood asthma (3, 4), consistent with the notion that immune and respiratory
109 alterations at an early window of susceptibility converge to place the child on a path to
110 the disease. Genome-wide association studies (GWAS) have identified multiple genetic
111 variants that influence asthma susceptibility (5) but have accounted for only a modest
112 proportion of the total phenotypic variance, providing a compelling rationale for seeking
113 additional risk factors for asthma. In this context, epigenetic mechanisms are especially
114 worth investigating because environmental and developmental influences are essential
115 for asthma pathogenesis (1), and epigenetic processes ensure the timed unfolding of
116 developmental programs and plastic responses to environmental cues, including those
117 delivered in utero by the maternal milieu (6).

118

119 Little is known about the role of epigenetic mechanisms in childhood asthma (7). A
120 recent epigenome-wide study compared DNA methylation patterns in peripheral blood
121 mononuclear cells from 6-12 year old inner-city children with persistent atopic asthma
122 and healthy controls, and found that several immune genes involved in T cell
123 maturation, Th2 immunity and oxidative stress were hypomethylated in asthmatic

124 children (8). While these results are novel, their significance remains unclear because it
125 is difficult to determine whether epigenetic alterations concurrent with asthma are a
126 cause or a consequence of the disease. Moreover, a cross-sectional study cannot
127 provide insights into the timing and mechanisms of asthma inception. A recent
128 candidate gene study pointed to an association between *IL2* promoter methylation at
129 birth and asthma exacerbations during childhood (9), but relevant pathways were not
130 further interrogated.

131
132 In an attempt to define when the trajectory to asthma begins and which pathways are
133 involved, we performed an epigenome-wide search for DNA methylation signatures
134 associated with childhood asthma in cord blood mononuclear cells (CBMC) from
135 children enrolled in the Infant Immune Study (IIS). In this unselected birth cohort, the
136 development of asthma and immune responses was monitored at multiple times from
137 birth to age 9 (4, 10). We reasoned that the detection at birth of differentially methylated
138 regions (DMRs) associated with asthma during childhood would both support a perinatal
139 origin of the disease and highlight epigenetic mechanisms potentially contributing to
140 asthma inception. We show herein that DNA methylation signatures associated with
141 asthma during childhood were indeed present in neonatal blood immune cells, and
142 clustered in immunoregulatory and pro-inflammatory pathways. Moreover,
143 hypermethylation of the *SMAD3* promoter was selectively detected in asthmatic children
144 of asthmatic mothers and was associated with risk of childhood asthma in the IIS
145 population and in two comparable birth cohorts.

146

147 **METHODS**

148 **Study design and participants** The IIS unselected birth cohort includes 482 children
149 and was designed to assess patterns of immune maturation in early life and their impact
150 on asthma risk (4, 10). At enrollment, parents completed a respiratory health history
151 questionnaire, a cord blood sample was obtained, and their child's health was followed
152 prospectively. Childhood asthma was defined as physician-diagnosed, with symptoms
153 or medication use for asthma in the past year reported at least once on the age 2, 3, 5
154 or 9-year questionnaires.

155
156 Figure 1 shows an overview of our study design. We performed a nested case-control,
157 epigenome-wide study of DNA methylation in CBMC ($2-8 \times 10^6$ cells per sample) from a
158 discovery population of 36 children from the IIS. This population was randomly selected
159 among available samples but balanced for asthma status in the child (18 non-asthmatic,
160 18 asthmatic by age 9) and an effort was made to balance cases and controls by
161 maternal asthma (Table E1). Additional targeted analysis of DNA methylation was
162 performed in the 31 samples available from the IIS discovery population and in samples
163 from 29 additional IIS children of comparable characteristics (Table E2). The distribution
164 of cases and controls is provided in Figure 1. Availability of adequate samples was the
165 only inclusion criterion besides asthma status of the child and her/his mother. Overall,
166 the study population did not differ from the rest of the IIS population except for a greater
167 proportion of asthma and maternal asthma, as per study design (Table E1).

168
169 The results of targeted DNA methylation analysis performed in the IIS were replicated in

170 CBMC from 30 children with asthmatic mothers from the Manchester Asthma and
171 Allergy Study (MAAS) and 28 children from the Childhood Origins of ASThma (COAST)
172 study (Figure 1). The characteristics of the MAAS and COAST study populations are
173 described in Table E2. The MAAS unselected birth cohort includes 1085 children
174 monitored for asthma and allergy from birth to age 11 years. An asthma diagnosis
175 required at least one of the following criteria reported on age 5 or 8 questionnaires: 1)
176 physician diagnosis of asthma, 2) the use of asthma medications during the previous 12
177 months. Controls required a negative report on both of these criteria and no report of
178 wheezing in the previous 12 months (11). The COAST birth cohort enrolled 289
179 neonates at risk for asthma and allergy, i.e., having at least one parent with asthma
180 and/or allergies. Asthma was diagnosed at age 6 years based on the documented
181 presence of one or more of the following characteristics in the previous year: 1)
182 physician diagnosis of asthma, 2) use of physician-prescribed albuterol for coughing or
183 wheezing episodes, 3) use of a daily controller medication, 4) step-up plan including use
184 of albuterol or short-term use of inhaled corticosteroids during illness, and 5) use of
185 prednisone for asthma exacerbations (12). All three studies were approved by the
186 appropriate Institutional Review Boards. Informed consent was obtained from the
187 parents of all research participants.

188

189 **DNA methylation profiling and DMR identification** DNA methylation was profiled by
190 Methylated CpG Island Recovery Assay (MIRA)-chip (Roche-NimbleGen), as detailed in
191 the Online Repository, Methods section, and Figure E1. DNA methylation microarray

192 data from this publication were submitted to the NCBI Gene Expression Omnibus
193 (GEO) database and assigned the identifier GSE85228.

194

195 Regions that were differentially methylated between asthmatics and non-asthmatics
196 (DMRs) were identified using a Probe Sliding Window-ANOVA [Roche-NimbleGen (13)]
197 that detects maximal inter-group differences in signal intensities relative to a user-
198 defined threshold. Probability scores (P -values) are then assigned to each probe on the
199 array using a repeated measure ANOVA model. In this study, DMRs were defined by
200 region length ≥ 300 bp, magnitude (between-group mean \log_2 ratio difference) ≥ 0.2 ,
201 significance threshold (adjusted using the Benjamini-Hochberg False Discovery Rate
202 method to account for multiple testing) = 0.01, using a sliding window size = 750 bp
203 (Table E3). A positive magnitude difference indicated hypermethylation in asthmatics
204 relative to non-asthmatics. DMRs containing ≤ 5 CpG sites within a 750 bp window
205 centered on the DMR [a configuration likely to result in sub-optimal capture of
206 methylated DNA (14)] were excluded from further analyses.

207

208 Results of this analysis were technically validated by bisulfite sequencing (Online
209 Repository, Methods section and Table E4). Microarray-derived estimates of DNA
210 methylation intensity strongly correlated with DNA methylation levels measured by
211 bisulfite sequencing over the entire DNA methylation range [Spearman correlation
212 coefficient (ρ)=0.48, $P=1.2 \times 10^{-13}$] and at intermediate DNA methylation levels (8-92%,
213 $P=0.006$; Figure E2). *SMAD3* methylation estimates from bisulfite sequencing and
214 microarrays were also highly correlated ($\rho=0.46$, $P=0.009$).

215 **Functional DMR annotation** is fully described in the Online Repository, Methods
216 section. In brief, DMRs were annotated to genes based on the closest transcription start
217 site. For pathway analysis, multiple genes were allowed to be associated with a single
218 DMR (RefSeq genes +/- 5 kb).

219

220 **DNA methylation analysis in the COAST cohort** was performed using the Infinium
221 HumanMethylation450 BeadChip array (Illumina) (Online Repository, Methods section).

222

223 **Network analysis** A molecular interaction network was constructed by uploading the
224 list of DMR-containing genes into the Ingenuity Pathway Analysis software (Qiagen) and
225 using all available interaction data in the Ingenuity Systems Knowledge Base. Genes
226 with no interactions were removed from the analysis to maximize the signal-to-noise
227 ratio. The gene interaction network was then interrogated to detect enrichment for
228 biological functions, canonical pathways and upstream regulators (defined as an
229 enrichment for known targets of a given gene in a given gene list) using Ingenuity
230 Pathway Analysis tools.

231

232 **Cytokine measurements** IL-1 β concentrations were measured by ELISA (Quantikine,
233 R&D Systems) in the supernatants of LPS-stimulated IIS CBMC (n=57) also tested for
234 *SMAD3* promoter methylation.

235

236 **Statistical analyses** DMRs were detected using a Probe Sliding Window-ANOVA
237 which uses a repeated measure ANOVA model for the probes in each sliding window

238 (13). Fisher's Exact Test and one sample test of proportions were used to compare
239 proportions for categorical variables, and Student's t-test or Wilcoxon two-sample test
240 were used to compare mean levels for continuous variables. Variables with skewed
241 distributions were log-transformed prior to assessment by t-test. Two-sided *P*-values
242 less than 0.05 were considered significant. Spearman correlation was used to test for
243 association between median DNA methylation intensity (microarray) and percentage
244 DNA methylation (bisulfite sequencing). When analyzing the genomic locations of
245 DMRs and the co-localization of DMRs and DNase I hypersensitive sites, permutations
246 were performed by randomly selecting 589 independent probes (the number of DMRs)
247 and calculating the χ^2 statistic for each sampling. We recorded the number of times (out
248 of 50,000) that the permuted χ^2 statistic was larger than the observed χ^2 statistic and
249 divided by the number of permutations to get the empirical *P*-value. Linear regression
250 was used to test for an interaction between child asthma and maternal asthma
251 on *SMAD3* methylation. Pearson's χ^2 test was used to identify significant associations
252 between child and parental characteristics at birth and asthma during childhood. Meta-
253 analysis of the association between *SMAD3* CpG7 methylation and childhood asthma
254 risk in neonates born to asthmatic mothers was performed using estimates from each
255 study cohort to compute the combined estimate of risk.

256

257 **RESULTS**

258 ***Cord blood cells from IIS children harbor asthma-associated DMRs*** Our multi-step
259 study of the contribution of epigenetic mechanisms to the development of asthma in
260 early life included: 1) a discovery phase in which an epigenome-wide approach was
261 used to identify candidate regions that were differentially methylated in cord blood
262 samples from 36 IIS children (18 non-asthmatic, 18 asthmatic by age 9); 2) a targeted
263 analysis phase in which DNA methylation of the most compelling candidate region was
264 measured in CBMC from 29 IIS neonates who did, and 31 IIS neonates who did not
265 develop asthma by age 9; and 3) a final phase in which the results of the targeted
266 analysis performed in IIS were replicated in two comparable birth cohorts, MAAS and
267 COAST (Figure 1).

268
269 Relying on the longitudinal design of the IIS birth cohort, we initially searched for
270 neonatal epigenetic signatures of childhood asthma by profiling DNA methylation in
271 CBMC from a discovery cohort of 36 children (Figure 1, Figure E1 and Table E1). Five
272 hundred and eighty-nine independent regions were differentially methylated in asthmatic
273 and non-asthmatic children (Table E3). Among these, 199 were hypermethylated and
274 390 were hypomethylated at birth in children who became asthmatic.

275
276 Asthma-associated DMRs were distributed across all chromosomes but were non-
277 randomly distributed with respect to genome location ($\chi^2 = 19.49$, $df = 7$, $P = 0.007$), with
278 an overrepresentation at intergenic regions (standardized residual: 2.91) and an
279 underrepresentation at transcription start sites (standardized residual: -2.23, with

280 absolute values > 1.96 significantly contributing to the overall χ^2 test statistics) (Figure
281 E3). Of the DMRs with the most significant methylation differences, some mapped to
282 biologically plausible genes such as *ATG9A* (involved in autophagy and innate immune
283 responses (15); $-\log_{10}$ adjusted *P*-value 5.569), *OR6K6* (an olfactory receptor expressed
284 in sputum during asthma exacerbations (16); $-\log_{10}$ adjusted *P*-value 4.408), and
285 *GALNT2* (an N-acetylgalactosaminyltransferase carrying polymorphisms associated
286 with lung function (17); $-\log_{10}$ adjusted *P*-value 4.895). Moreover, several asthma-
287 associated DMRs mapped to loci (\pm 5kb from transcription start sites) identified in
288 GWAS for asthma (*RORA*, *SMAD3*) and asthma-related traits such as atopic dermatitis
289 (*FLG*), allergic rhinitis (*TMEM232*), lung function (*ANK1*, *DLEU7*, *SNRPN*, *RORA*,
290 *CFDP1*) and airflow obstruction (*SPATA13*) (<http://www.ebi.ac.uk/gwas>). Functional
291 annotation using Ingenuity Pathway Analysis linked DMR-associated genes to biological
292 processes including immune function and immune and lung development (Table E5).
293 We also mapped the locations of neonatal asthma-associated DMRs to DNase I
294 hypersensitive sites, regions of increased chromatin accessibility typically endowed with
295 regulatory activity (18). Overall, 72 asthma-associated DMRs mapped to DNase I
296 hypersensitive sites (29 monocyte-specific, 15 T cell-specific, 28 in both cell types:
297 Table E6), which represented a significant enrichment (Table E7, permutation *P*-value $<$
298 2×10^{-5} for both cell types). The co-localization of asthma-associated differential DNA
299 methylation and enhanced chromatin accessibility supports the potential biological
300 significance of asthma-associated DMRs.

301

302 ***Asthma-associated DMRs cluster in regulatory and pro-inflammatory gene***

303 ***networks*** To elucidate the functional implications of our findings and gain a pathway-
304 based view of asthma-associated methylome alterations at birth, Ingenuity Pathway
305 Analysis tools were used to construct a molecular interaction network of DMR-
306 associated genes on the basis of prior knowledge of the physical and functional
307 connections between the molecules encoded by those genes. The network included
308 146 genes organized around several nodes, the most connected of which was the
309 transcription factor *SMAD3* (Figure 2). When the network was interrogated to detect
310 enrichment for known targets of upstream regulators, *IL1B*, an innate pro-inflammatory
311 cytokine overexpressed in asthmatics (19-21), emerged as the top regulator of a gene
312 subset that included *RORA* and *RELB*, transcription factors essential for innate and
313 adaptive responses, *UBD*, an innate immunity gene regulated by the NF- κ B inhibitor
314 A20/TNFAIP3 (22), and the asthma-associated neurotrophin *BDNF* (19) (overlap
315 $P=2.26 \times 10^{-5}$, Table 1).

316

317 ***The SMAD3 promoter is significantly hypermethylated in asthmatic children of***

318 ***asthmatic mothers*** *SMAD3* is not only the most connected node in the network of
319 asthma-associated DMRs (Figure 2), but is also a well-replicated asthma-associated
320 gene from GWAS (23-25). Moreover, *SMAD3* acts as a master regulator of TGF- β
321 signaling, thereby controlling the differentiation of Treg and Th17 cells that play critical
322 and opposite roles in asthma (1, 26). Finally, the *SMAD3* DMR lies within the distal
323 promoter of the gene, a location that provides ample opportunity for DNA methylation to
324 influence *SMAD3* gene expression (Figure E4). Therefore, subsequent analyses of the

325 nexus between neonatal DNA methylation and trajectory to childhood asthma
326 specifically targeted *SMAD3*. We used bisulfite sequencing to precisely quantify
327 methylation at the *SMAD3* promoter DMR (321 bp, 8 consecutive CpG sites) in a total of
328 60 IIS neonates (31 non-asthmatics, 29 asthmatics: Figure 1). Mean *SMAD3*
329 methylation levels at birth were 41.3% (95% CI 35.5-47.5) in non-asthmatics and 47.1%
330 (95% CI 40.6-53.1) in asthmatics, a difference that did not reach statistical significance
331 ($P=0.2$ by Wilcoxon two-sample test: Figure E5). Because these results may have
332 reflected heterogeneity within the study population, we next examined the entire IIS
333 population for associations between childhood asthma and potential risk factors
334 measurable at birth in the child (sex, ethnicity, mode of delivery, total cord IgE, 17q21
335 rs8076131 genotype) and parents (maternal asthma, maternal allergy, paternal asthma,
336 paternal allergy, maternal smoking during pregnancy). As shown in Table E8, maternal
337 asthma exhibited a distinctive association with childhood asthma in IIS ($P=0.003$ by χ^2
338 test). When the relation between *SMAD3* methylation at birth and childhood asthma was
339 examined separately in children with and without maternal asthma, *SMAD3* methylation
340 was found to be significantly increased in asthmatic compared to non-asthmatic children
341 of asthmatic mothers ($P=0.005$ by Wilcoxon two-sample test). In contrast, asthmatic and
342 non-asthmatic children of non-asthmatic mothers did not differ in their *SMAD3*
343 methylation levels [P for interaction (by linear regression) = 0.001; Figure 3A].

344

345 Although associations between *SMAD3* variants [rs17228058 (25), rs744910 (23),
346 rs17294280 (24)] and asthma have been reported in GWAS, asthma-related *SMAD3*
347 methylation differences were unlikely to be influenced by *SMAD3* genotype. Indeed,

348 sequencing identified no polymorphisms within the *SMAD3* DMR (data not shown).
349 Moreover, asthma-associated *SMAD3* variants are located at least 80 kb away from the
350 *SMAD3* DMR, whereas the relationship between DNA methylation and genetic variation
351 appears to decay rapidly beyond 5 kbs (27).

352

353 ***The association between SMAD3 promoter hypermethylation and childhood***

354 ***asthma replicates in two independent birth cohorts*** The association between
355 neonatal *SMAD3* hypermethylation and childhood asthma found in IIS neonates born to
356 asthmatic mothers was assessed for replication in two birth cohorts, MAAS and COAST
357 (Table E2). Bisulfite sequencing of the *SMAD3* DMR in 30 MAAS children born to
358 asthmatic mothers revealed significantly higher DNA methylation in the asthmatic group
359 ($P=0.049$ by Wilcoxon two-sample test; Figure 3B). Comparable results were obtained
360 by assessing *SMAD3* methylation in 28 COAST neonates using the Illumina Infinium
361 HumanMethylation450 BeadChip array. Figure 3C shows that methylation at
362 cg02486855, the seventh CpG in the *SMAD3* DMR and the only *SMAD3* DMR CpG
363 interrogated on the Illumina platform, did not significantly differ between asthmatic and
364 non-asthmatic children of non-asthmatic mothers ($P=0.4$ by Wilcoxon two-sample test).
365 In contrast, significant cg02486855 hypermethylation was detected in neonates born to
366 asthmatic mothers who developed asthma during childhood, compared to neonates who
367 did not ($P=0.04$ by Wilcoxon two-sample test; Figure 3C). The data generated by
368 bisulfite sequencing and on the Illumina platform were comparable because when
369 percent methylation values for *SMAD3* CpG7 were extracted from the bisulfite
370 sequencing data for IIS and MAAS, again we found significant hypermethylation in

371 asthmatic compared to non-asthmatic children of asthmatic mothers in IIS ($P=0.004$ by
372 Wilcoxon two-sample test; Figure E6), and a difference approaching significance in
373 MAAS ($P=0.09$ by Wilcoxon two-sample test; Figure E6).

374
375 Cord blood contains a mixture of cell types with potentially distinct DNA methylation
376 profiles. The availability of COAST DNA methylation data generated on the Illumina450
377 BeadChip array allowed us to estimate cord blood cell proportions using an algorithm
378 recently developed that integrates Illumina DNA methylation data with information from
379 a cord blood reference panel (28). Figure E7 shows that cell proportions thus estimated
380 did not significantly differ between asthmatic and non-asthmatic children, regardless of
381 maternal asthma history. Most importantly, the *SMAD3* methylation differences detected
382 between asthmatic and non-asthmatic children of asthmatic mothers remained
383 significant ($P=0.04$ by Wilcoxon two-sample test) even after adjusting for CBMC
384 composition (Figure E8).

385
386 Finally, we asked whether the *SMAD3* methylation levels measured at birth in children
387 of asthmatic mothers are associated with risk for childhood asthma in our three cohorts.
388 A meta-analysis revealed that for each 10% increase in *SMAD3* CpG7 methylation
389 there is nearly a two-fold increased risk of childhood asthma (meta-analysis Odds
390 Ratio=1.95, [95%CI: 1.23, 3.10], $P=0.005$; heterogeneity $P=0.5$).

391
392 ***Maternal asthma modifies the relation between neonatal SMAD3 methylation and***
393 ***IL-1 β producing capacity*** *SMAD3* knock-out mice exhibit increased expression of *Il1b*

394 (29), which is also the top upstream regulator of genes containing asthma-associated
395 DMRs in this study and a critical pro-inflammatory mediator in human asthma (19-21).
396 Therefore, we relied again on the IIS to explore the relationship between neonatal LPS-
397 induced IL-1 β production, *SMAD3* promoter methylation and childhood asthma. The
398 distributions of *SMAD3* methylation and log IL-1 β production in non-asthmatic and
399 asthmatic children without and with a maternal history of asthma were compared by
400 dividing mean percentage *SMAD3* methylation and log IL-1 β secretion at the median,
401 thereby creating four groups (low/low, low/high, high/low and high/high). No distribution
402 differences were observed among children of non-asthmatic mothers ($P=0.79$ by
403 Fisher's Exact Test; Figure 4A). In contrast, the children of asthmatic mothers who
404 developed asthma were almost entirely found among those with high *SMAD3* promoter
405 methylation and high IL-1 β secretion ($P=0.009$ by Fisher's Exact Test; Figure 4B).
406 Moreover, asthmatic children of asthmatic mothers had higher LPS-induced IL-1 β than
407 non-asthmatic children ($P=0.03$ by Student's t test), whereas comparable IL-1 β levels
408 were measured in children without a maternal history of asthma ($P=0.65$ by Student's t
409 test; Table 2). These results suggest that a strong relationship exists between neonatal
410 *SMAD3* methylation, production of the innate cytokine IL-1 β , and childhood asthma.
411 Furthermore, our data suggest that this relationship is powerfully influenced by maternal
412 asthma.

413

414 **DISCUSSION**

415 Although asthma is the most common chronic complex disease of childhood (1), the
416 timing and mechanisms of its inception remain largely unknown. This gap in knowledge
417 severely hinders efforts aimed at preventing this disease, which no therapeutic regimen
418 can currently cure. Our study, the first epigenome-wide search for asthma-associated
419 methylome signatures at birth, sheds new light on these critical but still open questions.
420 The finding that almost 600 genomic regions were differentially methylated at birth
421 between children who did and did not develop asthma later in life strongly suggests that
422 the trajectory to asthma begins at birth if not prenatally and involves epigenetic
423 mechanisms. As importantly, data from three birth cohorts showed that *SMAD3*
424 promoter hypermethylation was associated with childhood asthma selectively in
425 neonates with a maternal history of asthma - one of the strongest, and mechanistically
426 one of the most elusive, risk factors for asthma in the child (30, 31). These findings are
427 especially noteworthy in the context of the current dearth of characteristics measurable
428 at birth that effectively predict asthma during childhood. Of note, the link between
429 epigenetic *SMAD3* dysregulation at birth and childhood asthma appeared to be
430 selective for neonates born to asthmatic mothers, a finding that suggests that
431 heterogeneity is deeply embedded in the pathogenesis of, and the trajectory to,
432 childhood asthma (1, 32). More generally, to our knowledge this is the first time that a
433 neonatal epigenetic characteristic linked to asthma during childhood is robust enough to
434 replicate across three independent birth cohorts.

435

436 Our study highlighted *SMAD3* and IL-1 β as main players in the trajectory to childhood
437 asthma. *SMAD3*, the most connected node in the network of asthma-associated DMRs,
438 is known to be critical for the regulation of both the asthma-protective Treg and the
439 asthma-promoting Th17 cell differentiation programs. Altered Treg and Th17 activities
440 have been reported in childhood asthma (1, 26) and conversely, maternal exposure to
441 asthma-protective environments such as farming has been shown to activate the Treg
442 compartment (33) and influence the expression of Th17 markers (34). On the other
443 hand, IL-1 β , which emerged as the primary upstream regulator of genes harboring
444 asthma-associated DMRs, is increasingly recognized as a key asthma mediator in both
445 children (20) and adults, especially in neutrophilic asthma (19, 21). Our data emphasize
446 the functional connection between *SMAD3* and IL-1 β . Indeed, in neonates who became
447 asthmatic by age 9, *SMAD3* promoter hypermethylation, an epigenetic configuration
448 consistent with low *SMAD3* expression, was strongly associated with high IL-
449 1 β production. This convergence is likely to destabilize the Treg program, enhance
450 inflammation, and promote Th17 differentiation (35), ultimately favoring the
451 development of asthma. While it is unclear whether these mechanisms operate pre-
452 and/or perinatally, detection of the relationship between *SMAD3* methylation and IL-1 β
453 production selectively among children of asthmatic mothers implies that the *in utero*
454 environment is critical for directing the epigenetic trajectory towards childhood asthma.
455

456 Our results should be interpreted with caution because our discovery population was
457 small, albeit longitudinally phenotyped for asthma in great detail, and environmental
458 exposures were not comprehensively assessed. Moreover, DNA methylation did not

459 distinguish between 5-methylcytosine and other cytosine modifications and was
460 assessed in mixed rather than isolated cell populations. However, our data from the
461 COAST population suggest that differential methylation by asthma status did not reflect
462 asthma-associated differences in CBMC proportions. We also acknowledge that the
463 DNA methylation differences we detected were not extreme, albeit more substantial
464 than those recently reported in other studies (8, 36). This is a recurring theme in the
465 literature (37), and systematic studies are needed to comprehensively assess how
466 relatively modest DNA methylation differences modify disease trajectories. In general,
467 the functional impact of such differences will likely depend on the regulatory properties
468 of the locus in which they reside, and the extent to which additional epigenetic
469 processes, such as post-translational histone modifications, influence those properties.

470
471 Gene expression analyses are often used to complement epigenetic studies, but
472 samples for such analyses were not collected at birth in our study populations. On the
473 other hand, samples for cytokine protein assessments were available and proved
474 essential to integrate our epigenetic findings. Finally, our search for asthma-associated
475 differential methylation returned almost 600 regions, only some of which mapped to
476 genes involved in immunoregulation and inflammation. DMRs that reside in functionally
477 interesting genes but lack a link to immune regulation or inflammation may also
478 contribute to asthma pathogenesis, albeit through different mechanisms. With these
479 caveats, we propose that in a proportion of children with childhood-onset asthma, a
480 distinctive methylome is in place already at birth, particularly within innate
481 immunoregulatory and pro-inflammatory pathways, and promotes a trajectory that may

482 ultimately lead to clinical disease. Some of the epigenetic mechanisms that contribute to
483 the inception of this trajectory are strongly influenced by the milieu associated with
484 maternal asthma. A scenario in which epigenetic modifications at an early window of
485 susceptibility promote a long-term developmental trajectory to asthma is consistent with
486 the emerging paradigm that chronic non-communicable diseases have their origins in
487 early life through an epigenetic calibration of set points for later responsiveness and
488 function (38, 39).

489

490

491

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511

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- 621

622 **FIGURE LEGENDS**

623 **Figure 1.** *Overview of study design.* IIS: Infant Immune Study, MAAS: Manchester
624 Asthma and Allergy Study, COAST: Child Origins of ASThma study. NN: Non-asthmatic
625 child with a Non-asthmatic mother, NA: Non-asthmatic child with an Asthmatic mother,
626 AN: Asthmatic child with a Non-asthmatic mother, AA: Asthmatic child with an Asthmatic
627 mother.

628
629 **Figure 2.** *Molecular interaction network of asthma-associated DMRs.* The network was
630 constructed using all available interaction data in the Ingenuity Systems Knowledge
631 Base. The most highly connected gene (*SMAD3*, 17 connections) is highlighted in
632 black. Targets of *IL1B*, the top upstream regulator of network genes, are highlighted in
633 gray. Types of interactive molecules are defined in the Legend.

634
635 **Figure 3.** *Effects of maternal asthma on the association between neonatal SMAD3*
636 *methylation and childhood asthma in IIS (panel A), MAAS (panel B) and COAST (panel*
637 *C).* *SMAD3* methylation In IIS and MAAS was assessed by bisulfite sequencing and
638 expressed as mean percent DNA methylation across 8 consecutive CpG sites in the
639 *SMAD3* DMR. In COAST, percent *SMAD3* methylation at cg02486855, the seventh
640 CpG in the *SMAD3* DMR, was assessed by the Infinium HumanMethylation450
641 BeadChip array. N: non-asthmatic, A: asthmatic. *P*-values by Wilcoxon two-sample test.
642 The results presented in panel A were unaffected after adjusting for ethnicity.

643

644 **Figure 4.** *Effects of maternal asthma on the relation between neonatal SMAD3*
645 *methylation and IL-1 β protein production.* The distributions of SMAD3 methylation and
646 log IL-1 β producing capacity in non-asthmatic and asthmatic children without and with a
647 maternal history of asthma were compared by dividing mean percentage SMAD3
648 methylation and log IL-1 β secretion at the median, thereby creating four groups
649 (low/low, low/high, high/low and high/high). Distributions for asthmatics and non-
650 asthmatics were compared across all four quadrants (panel A) or focusing the analysis
651 on the high/high and low/low quadrants (panel B) (*P* by Fisher's Exact Test). N: non-
652 asthmatic, A: asthmatic.
653

654 **Table 1.** *Upstream regulators of genes containing asthma-associated DMRs*

Upstream Regulator	Molecule Type	Overlap P^*	Target molecules in dataset
IL1B	cytokine	2.26E-05	ACAN, BDNF, CFTR, COL10A1, CXCL10, CYP7A1, FGFR3, GNAS, LDHA, NCOA2, NEUROD1, PFKP, RELB, RORA, SCX, SNCA, UBD
HSPG2	enzyme	8.60E-05	ACAN, COL10A1, FGFR3
BDNF	growth factor	1.43E-04	BDNF, DUSP6, NRXN1, PRKCZ, PTBP1, RPL35A, SLC17A8, TMEM45A, TTC3
SNCA	enzyme	1.56E-04	BDNF, CFL1, DNMI, SNCA, SYN3
PRMT5	enzyme	3.51E-04	CXCL10, CYP7A1, FASN

655 ^{*}Enrichment for known targets of a given gene in a given gene list. The Table shows the top hits provided by this analysis.

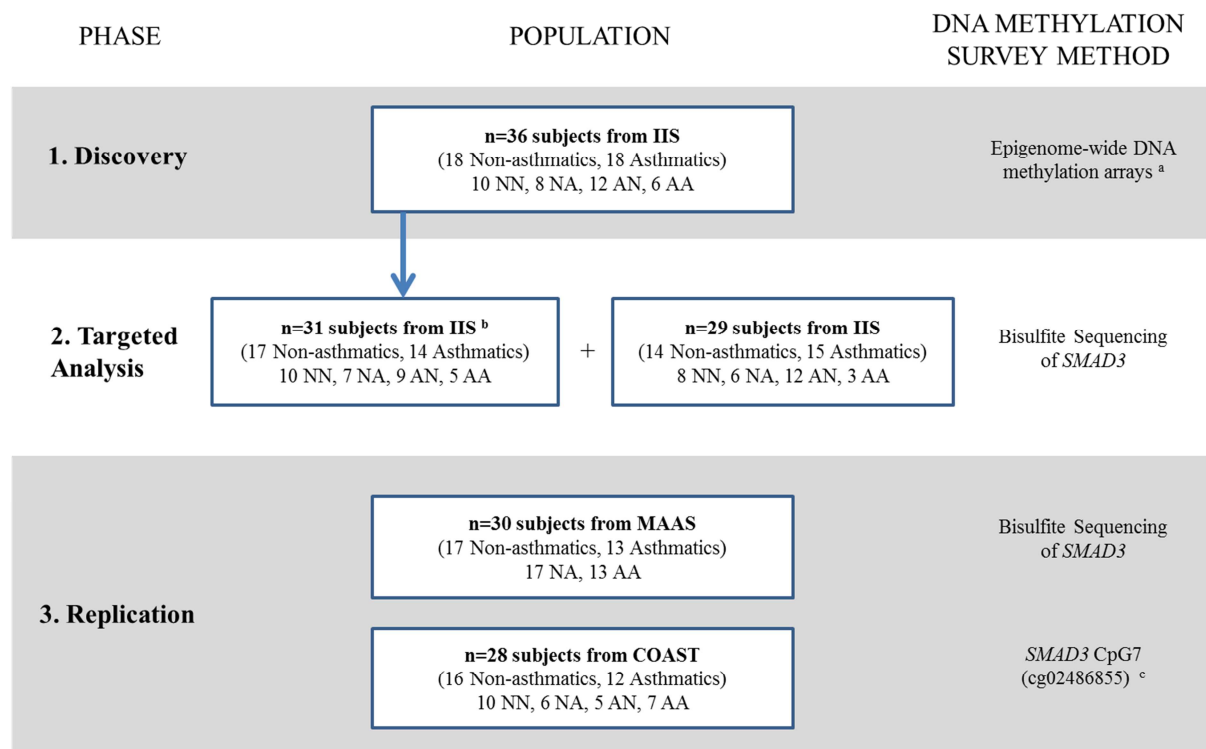
656

Table 2. LPS-stimulated CBMC-production of IL-1 β in IIS children with or without a history of maternal asthma.

	Children with Asthmatic Mothers		Children with Non-asthmatic Mothers	
	Asthmatic* (n=7)	Non-asthmatic (n=12)	Asthmatic* (n=19)	Non-asthmatic (n=16)
Geometric Mean (ng/ml)	16.5	6.0	6.7	7.7
95% CI (ng/ml)	6.9-39.4	4.8-7.6	4.1-10.9	4.7-12.5
P^{\dagger}	0.03		0.65	

* Physician-diagnosed with symptoms or medication use for asthma in the past year reported at least once on the age 2, 3, 5 or 9-year questionnaires

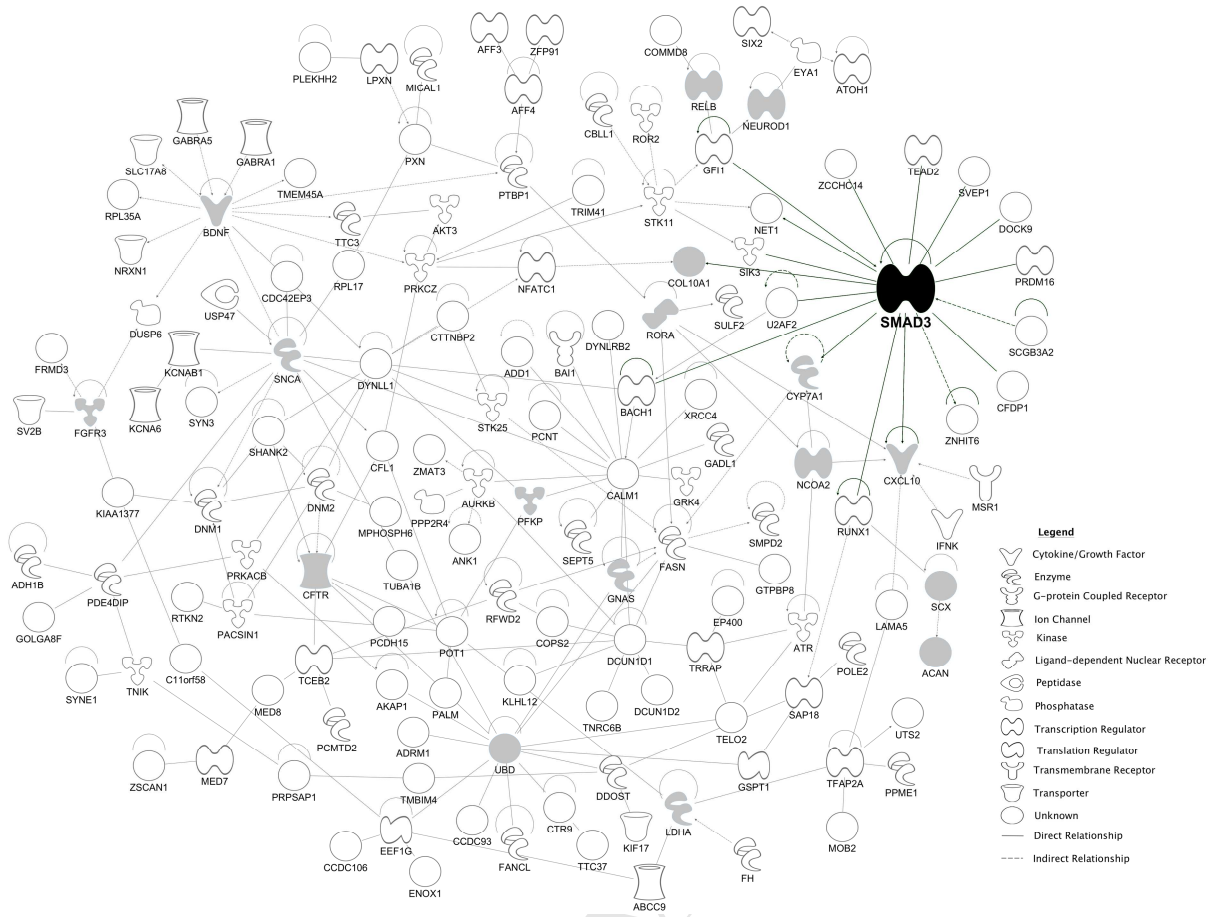
\dagger by Student's t-test after log₁₀ transformation.

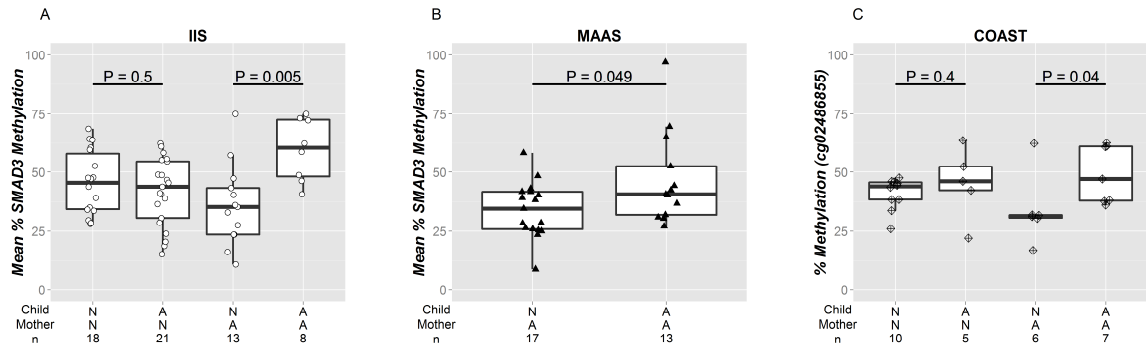


^aHuman DNA Methylation 2.1M Deluxe Promoter arrays (Roche NimbleGen).

^bAll those available from the discovery population.

^cHumanMethylation450 BeadChip arrays (Illumina).





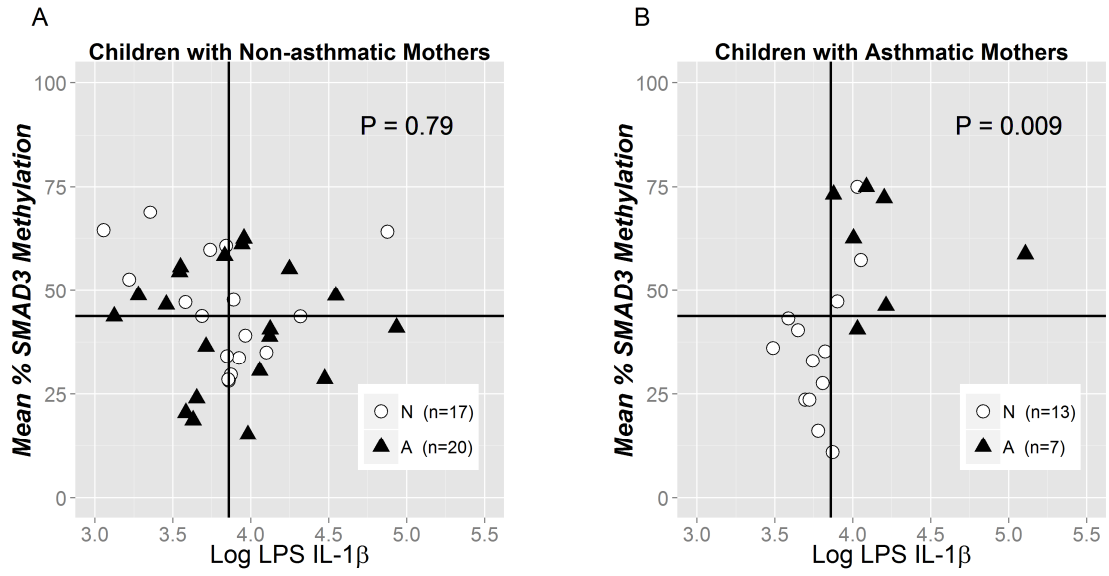


Table E1. Characteristics of IIS study subjects.

	% (n/N)							
	Asthma, ages 2 to 9*	Maternal asthma [†]	Paternal asthma [†]	Maternal atopy [‡]	Paternal atopy [‡]	Female child	Household smoking at birth	Caucasian child
Discovery Cohort, N=36	50.0 (18/36)	38.9 (14/36)	17.1 (6/35)	80.0 (28/35)	82.4 (28/34)	58.3 (21/36)	14.7 (5/34)	75.0 (27/36)
Additional Subjects included in the Targeted Analysis, N=29	51.7 (15/29)	31.0 (9/29)	8.0 (2/25)	64.3 (18/28)	75.9 (20/26)	58.6 (17/29)	17.9 (5/28)	51.7 (15/29)
Remaining IIS subjects, N=417	12.1 (44/365)	16.7 (67/402)	16.5 (60/364)	66.2 (251/379)	77.6 (264/340)	50.4 (210/417)	24.5 (101/412)	56.8 (237/417)
P value [§]	<0.001	0.002	0.623	0.238	0.874	0.492	0.363	0.082

* Physician-diagnosed with symptoms or medication use for asthma in the past year reported at least once on the age 2, 3, 5 or 9-year questionnaires

[†] Physician-diagnosed asthma ever, as assessed by questionnaire.

[‡] Positive skin test response to any of 17 local aeroallergens shortly after the child's birth.

[§] by Fisher's Exact test.

Table E2. Characteristics of non-asthmatic and asthmatic children in the IIS, MAAS and COAST study populations.

	% (n/N)					
	Maternal asthma [†]	Paternal asthma [†]	Maternal atopy ^{**}	Paternal atopy ^{**}	Female child	Household smoking at birth
Discovery Cohort (IIS)						
No Asthma (N=18)	44.4 (8/18)	11.1 (2/18)	76.5 (13/17)	94.1 (16/17)	66.7 (12/18)	11.1 (2/18)
Asthma* (N=18)	33.3 (6/18)	23.5 (4/17)	83.3 (15/18)	70.6 (12/17)	50.0 (9/18)	18.8 (3/16)
<i>P</i> value [†]	N/A ^{††}	0.4	0.69	0.18	0.5	0.65
Targeted Analysis (IIS)[‡]						
No Asthma (N=31)	41.9 (13/31)	6.5 (2/31)	70.0 (21/30)	80.0 (24/30)	64.5 (20/31)	12.9 (4/31)
Asthma* (N=29)	27.6 (8/29)	16.7 (4/24)	75.0 (21/28)	80.0 (20/25)	44.8 (13/29)	19.2 (5/26)
<i>P</i> value [†]	N/A ^{††}	0.39	0.77	>0.99	0.19	0.72
Replication Cohort 1 (MAAS)						
No Asthma (N=17)	100 (17/17)	17.6 (3/17)	100 (17/17)	100 (17/17)	64.7 (11/17)	17.6 (3/17)
Asthma [§] (N=13)	100 (13/13)	15.4 (2/13)	100 (13/13)	92.3 (12/13)	46.2 (6/13)	7.7 (1/13)
<i>P</i> value [†]	-	>0.99	-	0.43	0.46	0.61
Replication Cohort 2 (COAST)						
No Asthma (N=16)	37.5 (6/16)	25.0 (4/16)	100 (16/16)	84.6 (11/13)	50.0 (8/16)	31.3 (5/16)
Asthma [¶] (N=12)	58.3 (7/12)	25.0 (3/12)	90.9 (10/11)	81.8 (9/11)	41.7 (5/12)	41.7 (5/12)
<i>P</i> value [†]	0.45	>0.99	0.41	>0.99	0.72	0.7

* Physician-diagnosed with symptoms or medication use for asthma in the past year reported at least once on the age 2, 3, 5 or 9-year questionnaires

[†] by Fisher's Exact test comparing characteristics of asthmatic and non-asthmatic children separately in each cohort.

[‡] Includes 31 individuals from the IIS Discovery Cohort (17 non-asthmatics, 14 asthmatics).

[§] At least one of the following criteria reported on age 5 or 8 questionnaires: (1) physician diagnosis of asthma, (2) the use of asthma medications during the previous 12 months.

[¶] At least one of the following criteria reported at age 6 years : (1) physician diagnosis of asthma, (2) use of albuterol for coughing or wheezing episodes (prescribed by physician), (3) use of a daily controller medication, (4) step-up plan including use of albuterol or short-term use of inhaled corticosteroids during illness, and (5) use of prednisone for asthma exacerbation

[†] Physician-diagnosed asthma ever, as assessed by questionnaire.

^{**} Positive skin test response and/or allergen-specific IgE response to local aeroallergens as described previously [E8-E10].

^{††} Not applicable - maternal asthma was included as selection criteria.

Table E3. Complete list of annotated asthma-associated DMRs (n=589) in IIS children** Identified by a 750 bp within-probe sliding window ANOVA (size ≥ 300 bp, magnitude difference ≥ 0.2 , BH-adjusted p value < 0.01)

† Within a 750 bp window centered on the DMR

DMR ID	Chr.	Start	End	Size (bp)	Magnitude difference	-log ₁₀ BH-adjusted P-value	No. CpG [†]	Location based on closest TSS	Closest TSS				Overlapping Refseq Genes (± 5 kb)
									Distance	PromoterID	Entrez ID	Gene Name	
D1	1	28029	28475	446	-0.242	2.518	7	intron (NR_024540, intron 1 of 10)	1118	NR_024540	653635	WASH7P	WASH7P
D2	1	619416	620291	875	-0.262	3.171	5	Intergenic	2181	NM_001005277	81399	OR4F16	OR4F29, OR4F16, OR4F3
D3	1	2078616	2079016	400	-0.303	4.435	9	intron (NM_001033581, intron 4 of 14)	42661	NM_001033582	5590	PRKCZ	PRKCZ
D4	1	3195396	3195771	375	0.392	2.944	42	intron (NM_199454, intron 3 of 16)	151044	NR_036215	100422968	MIR4251	PRDM16
D5	1	3446116	3446641	525	0.235	2.985	26	intron (NM_001409, intron 4 of 36)	30976	NR_030277	693135	MIR551A	MEGF6
D6	1	7916430	7916782	352	0.212	2.184	24	Intergenic	-3055	NM_021995	10911	UTS2	UTS2
D7	1	11790134	11790509	375	0.235	2.192	18	Intergenic	-5821	NM_001040196	57085	AGTRAP	intergenic
D8	1	13008095	13008420	325	-0.25	2.28	6	promoter-TSS (NM_001010889)	-851	NM_001010889	440561	PRAMEF6	PRAMEF6
D9	1	13636362	13636756	394	-0.222	3.797	5	Intergenic	-5414	NM_001010890	343070	PRAMEF9	intergenic
D10	1	13640855	13641175	320	-0.24	2.247	8	promoter-TSS (NM_001098376).2	-958	NM_001010890	343070	PRAMEF9	PRAMEF9, PRAMEF15
D11	1	16924065	16924409	344	-0.295	2.516	9	intron (NM_017940, intron 2 of 28)	15745	NM_017940	55672	NBPF1	NBPF1
D12	1	20985704	20986119	415	-0.237	3.06	10	intron (NM_005216, intron 2 of 10)	2126	NM_005216	1650	DDOST	KIF17, DDOST
D13	1	24826914	24827289	375	0.201	2.798	17	intron (NR_045408, intron 1 of 2)	-1740	NM_001251984	11123	RCAN3	RCAN3, RCAN3AS
D14	1	26579075	26579576	501	-0.236	2.374	11	intron (NM_022778, intron 3 of 13)	18632	NM_022778	64793	CEP85	CEP85
D15	1	26947080	26947575	495	0.252	2.84	79	Intergenic	66294	NR_031740	100302190	MIR1976	intergenic
D16	1	28259405	28259738	333	0.368	2.468	10	Intergenic	-1933	NM_014474	27293	SMPDL3B	SMPDL3B
D17	1	43857017	43857397	380	-0.33	2.88	17	intron (NM_015284, intron 1 of 70)	1651	NM_015284	23334	SZT2	MED8, SZT2
D18	1	45082683	45083278	595	0.227	3.334	63	intron (NM_018150, intron 3 of 14)	57119	NM_024587	79639	TMEM53	RNF220
D19	1	45251683	45252108	425	0.29	2.246	45	exon (NM_153274, exon 4 of 9)	1531	NM_153274	266675	BEST4	BEST4
D20	1	49511297	49511617	320	-0.215	2.486	7	exon (NM_032785, exon 5 of 14)	-268910	NM_024603	79656	BEND5	AGBL4
D21	1	67521434	67521924	490	-0.241	3.141	7	Intergenic	-1599	NM_015139	23169	SLC35D1	SLC35D1
D22	1	84607359	84607754	395	-0.211	3.061	5	intron (NM_207578, intron 1 of 8)	-2396	NM_182948	5567	PRKACB	PRKACB
D23	1	86171241	86171769	528	-0.24	3.097	5	intron (NM_001170670, intron 5 of 10)	2611	NM_001170670	54680	ZNHIT6	ZNHIT6
D24	1	92947121	92947521	400	0.219	3.137	33	intron (NM_001127215, intron 3 of 6)	2035	NM_001127215	2672	GF11	GF11
D25	1	118468419	118468991	572	-0.238	3.024	5	intron (NM_001135589, intron 1 of 12)	3597	NM_017686	54834	GDAP2	GDAP2, WDR3
D26	1	144929866	144930438	572	-0.235	4.134	6	intron (NM_001198832, intron 8 of 45)	1880	NM_001002811	9659	PDE4DIP	PDE4DIP
D27	1	145045538	145045941	403	-0.225	2.309	6	intron (NM_022359, intron 1 of 6)	-5747	NM_001198832	9659	PDE4DIP	PDE4DIP
D28	1	146549619	146551474	1855	0.35	4.28	51	Intergenic	-35947	NR_024442	728989	LOC728989	intergenic
D29	1	147958520	147959033	513	-0.24	2.486	6	Intergenic	-3357	NM_178230	164022	PPIAL4A	PPIAL4A, PPIAL4B
D30	1	147960243	147960598	355	-0.204	2.94	6	Intergenic	-5001	NM_178230	164022	PPIAL4A	PPIAL4A, PPIAL4B
D31	1	148579506	148579826	320	-0.228	2.553	5	exon (NM_173638, exon 6 of 19)	2309	NM_001102663	728936	NBPF16	NBPF15, NBPF16
D32	1	151740167	151740662	495	0.261	2.244	7	intron (NM_001134939, intron 2 of 4)	1283	NM_016178	51686	OAZ3	OAZ3, MRPL9, TDRKH
D33	1	152298811	152299501	690	-0.247	3.425	7	Intergenic	-1477	NM_002016	2312	FLG	FLG
D34	1	152390374	152390914	540	0.294	3.65	17	Intergenic	-3894	NM_016190	49860	CRNN	CRNN
D35	1	153091540	153091916	376	-0.244	2.689	7	Intergenic	-5739	NM_001014450	6705	SPRR2F	intergenic
D36	1	154195857	154196175	318	-0.239	3.163	6	intron (NM_014847, intron 1 of 26)	2691	NM_014847	9898	UBAP2L	C1orf43, UBAP2L
D37	1	158547123	158547491	368	-0.242	3.735	5	Intergenic	2382	NM_001004477	128367	OR10X1	OR10X1
D38	1	158688854	158689379	525	-0.246	2.698	8	Intergenic	-1211	NM_001005327	391114	OR6K3	OR6K3
D39	1	158717724	158718039	315	-0.219	2.694	12	Intergenic	-6725	NM_001005184	128371	OR6K6	intergenic
D40	1	158720911	158721216	305	-0.239	4.408	7	Intergenic	-3543	NM_001005184	128371	OR6K6	OR6K6
D41	1	176155727	176156214	487	-0.269	2.627	9	intron (NM_001001740, intron 1 of 18)	20400	NM_001001740	64326	RFWD2	RFWD2
D42	1	197870276	197870876	600	-0.24	3.868	5	Intergenic	-1106	NM_001024594	388722	C1orf53	C1orf53
D43	1	200375870	200376180	310	-0.255	2.681	10	3' UTR (NM_012482, exon 2 of 2)	3141	NM_012482	23528	ZNF281	ZNF281
D44	1	202859572	202859942	370	-0.227	3.315	8	TTS (NM_021633)	-1372	NM_002871	5877	RABIF	KLHL12, RABIF
D45	1	203061380	203062267	887	-0.258	3.342	6	Intergenic	-6657	NM_002479	4656	MYOG	intergenic
D46	1	210128503	210128888	385	-0.226	2.617	5	intron (NR_027459, intron 3 of 8)	17176	NR_027459	255928	SYT14	SYT14

D47	1	211313605	211313938	333	-0.207	2.267	6	Intergenic	-6314	NM_172362	3756	KCNH1	intergenic
D48	1	215176873	215177243	370	-0.248	2.335	10	Intergenic	-1827	NM_001017424	3776	KCNK2	KCNK2
D49	1	220954769	220955083	314	-0.232	2.752	5	intron (NM_017898, intron 6 of 7)	-5113	NM_022746	64757	MARC1	MARC2, MARC1
D50	1	221921025	221921335	310	-0.223	2.848	8	Intergenic	-5664	NM_144729	11221	DUSP10	intergenic
D51	1	230197990	230198665	675	-0.256	4.895	8	Intergenic	-4629	NM_004481	2590	GALNT2	GALNT2
D52	1	241686365	241686955	590	-0.278	3.059	5	Intergenic	-3575	NM_000143	2271	FH	FH
D53	1	241697860	241698284	424	-0.239	2.567	6	intron (NM_003679, intron 1 of 14)	2638	NM_003679	8564	KMO	KMO
D54	1	243791053	243791537	484	-0.281	3.665	8	intron (NM_001206729, intron 6 of 13)	215289	NM_181690	10000	AKT3	AKT3
D55	1	247667137	247667637	500	-0.252	3.435	8	Intergenic	13017	NM_001004698	441932	OR2W5	intergenic
D56	1	247879633	247880233	600	-0.246	4.246	5	Intergenic	-3876	NM_001005286	343169	OR6F1	OR6F1
D57	10	3160852	3161157	305	0.214	2.316	34	exon (NM_002627, exon 15 of 22)	-22789	NR_038284	100507034	LOC100507034	PFKP
D58	10	4864339	4864829	490	-0.239	3.19	6	Intergenic	-3785	NR_073127	83592	AKR1E2	AKR1E2
D59	10	5133284	5133669	385	-0.249	3.383	6	intron (NM_001253908, intron 1 of 8)	-3092	NM_001253909	8644	AKRIC3	AKRIC3
D60	10	5486603	5487098	495	-0.248	3.182	8	intron (NM_001047160, intron 3 of 11)	-1664	NM_005863	10276	NET1	NET1
D61	10	14051467	14051957	490	0.219	3.582	24	intron (NM_018027, intron 2 of 24)	321154	NM_018027	55691	FRMD4A	FRMD4A
D62	10	23215392	23216377	985	-0.234	3.33	9	Intergenic	-1070	NM_173081	219681	ARMC3	ARMC3
D63	10	42672545	42673015	470	0.215	2.812	87	Intergenic	190713	NR_024380	441666	LOC441666	intergenic
D64	10	55581713	55582248	535	-0.214	2.725	9	exon (NM_001142763, exon 35 of 35)	979071	NM_001142765	65217	PCDH15	PCDH15
D65	10	55888543	55888948	405	-0.209	2.901	6	intron (NM_001142773, intron 14 of 31)	672306	NM_001142765	65217	PCDH15	PCDH15
D66	10	55965520	55966047	527	-0.22	3.146	7	intron (NM_001142773, intron 9 of 31)	595268	NM_001142765	65217	PCDH15	PCDH15
D67	10	64016217	64016642	425	-0.236	2.975	5	intron (NM_145307, intron 2 of 11)	12037	NM_145307	219790	RTKN2	RTKN2
D68	10	71809023	71809403	380	-0.222	2.581	6	Intergenic	-3144	NM_018649	55506	H2AFY2	H2AFY2
D69	10	71890257	71890767	510	-0.241	2.58	7	intron (NM_001198696, intron 1 of 8)	2178	NM_001198696	84883	AIFM2	AIFM2
D70	10	85892270	85892660	390	-0.361	2.955	5	Intergenic	-6720	NM_014394	27069	GHITM	intergenic
D71	10	92454928	92455240	312	-0.233	2.279	5	Intergenic	162587	NM_019860	3363	HTR7	intergenic
D72	10	105344175	105344485	310	0.217	4.101	102	exon (NM_004210, exon 4 of 6)	90595	NM_004210	9148	NEURL	NEURL
D73	10	115422789	115423260	471	-0.231	2.22	8	intron (NM_001261463, intron 2 of 41)	805	NM_001261463	4892	NRAP	NRAP
D74	10	118931854	118932254	400	-0.249	2.776	11	Intergenic	-4769	NR_037436	100500893	MIR3663	MIR3663
D75	10	134067135	134067437	302	0.225	2.708	28	intron (NM_173575, intron 1 of 11)	54191	NM_173575	282974	STK32C	STK32C
D76	10	134149160	134149565	405	0.22	2.878	12	intron (NM_001143758, intron 2 of 7)	-1249	NR_026559	80313	LRRC27	LRRC27
D77	10	135012691	135013061	370	0.223	4.265	39	intron (NM_152643, intron 14 of 29)	-30902	NM_003577	8433	UTF1	KNDC1
D78	10	135254566	135255051	485	0.217	2.17	32	Intergenic	-12624	NR_002934	619207	LOC619207	intergenic
D79	11	1763722	1764047	325	0.347	3.015	7	intron (NM_001170820, intron 2 of 2)	7940	NM_001170820	402778	IFTM10	MOB2, IFTM10
D80	11	2011138	2011549	411	0.229	2.662	27	promoter-TSS (NR_024471)	-193	NR_024471	100133545	MRPL23-AS1	H19, MRPL23-AS1
D81	11	2068424	2069844	1420	-0.255	2.68	7	Intergenic	-50069	NR_002196	283120	H19	intergenic
D82	11	2076419	2077319	900	-0.248	2.312	5	Intergenic	-57804	NR_002196	283120	H19	intergenic
D83	11	2085620	2086550	930	-0.281	2.757	6	Intergenic	-67020	NR_002196	283120	H19	intergenic
D84	11	4393525	4393903	378	0.367	2.369	8	Intergenic	-4098	NM_001005161	143496	OR52B4	OR52B4
D85	11	4903522	4904022	500	-0.247	2.942	11	exon (NM_001004759, exon 1 of 1)	723	NM_001004759	401665	OR51T1	OR51T1
D86	11	5019521	5019823	302	-0.246	3.34	7	promoter-TSS (NM_001004755)	-541	NM_001004755	119682	OR51L1	OR51L1
D87	11	5111850	5112255	405	-0.244	3.076	6	Intergenic	-31195	NM_001005164	119678	OR52E2	intergenic
D88	11	5443751	5444151	400	-0.22	3.878	15	exon (NM_001004757, exon 1 of 1)	610	NM_001004757	390061	OR51Q1	OR51B5, OR51Q1
D89	11	5743837	5744146	309	-0.218	3.131	5	Intergenic	-13687	NM_001005180	387748	OR56B1	intergenic
D90	11	5880266	5880641	375	-0.232	3.537	9	Intergenic	-1521	NM_001005168	390079	OR52E8	OR52E8
D91	11	6050754	6051134	380	-0.213	2.367	5	Intergenic	-1973	NM_001001917	120796	OR56A1	OR56A1
D92	11	6052435	6052881	446	-0.227	3.186	9	Intergenic	-3687	NM_001001917	120796	OR56A1	OR56A1
D93	11	6912947	6913457	510	-0.248	3.407	8	exon (NM_003700, exon 1 of 1)	529	NM_003700	120776	OR2D2	OR2D2
D94	11	10773833	10774303	470	-0.247	2.895	9	intron (NM_014633, intron 1 of 24)	1257	NM_014633	9646	CTR9	CTR9
D95	11	11857771	11858301	530	-0.246	3.331	7	Intergenic	-4934	NM_017944	55031	USP47	USP47
D96	11	16760509	16760879	370	0.225	2.505	31	intron (NM_014267, intron 1 of 4)	546	NM_014267	10944	C11orf58	C11orf58
D97	11	18410042	18410442	400	0.23	2.733	13	Intergenic	-5694	NM_001165416	3939	LDHA	intergenic

D98	11	18417431	18418016	585	0.296	2.305	47	promoter-TSS (NM_001165414)	-90	NM_001165414	3939	LDHA	LDHA
D99	11	18955777	18956247	470	0.249	2.763	25	exon (NM_147199, exon 1 of 1)	537	NM_147199	259249	MRGPRX1	MRGPRX1
D100	11	27743674	27743980	306	0.236	3.027	52	promoter-TSS (NM_170731)	-222	NM_170731	627	BDNF	BDNF
D101	11	32850713	32851213	500	0.463	3.122	23	promoter-TSS (NM_024081)	-518	NM_024081	79056	PRRG4	PRRG4
D102	11	55563441	55563931	490	-0.257	3.218	7	exon (NM_001004735, exon 1 of 1)	654	NM_001004735	219436	OR5D14	OR5D14
D103	11	57945518	57945828	310	-0.227	3.384	9	intron (NM_001005212, intron 2 of 2)	-12233	NM_001005283	219957	OR9Q2	OR9Q1
D104	11	58346012	58346628	616	0.336	2.988	67	promoter-TSS (NM_001197051)	-267	NR_024091	386607	ZFP91-CNTF	ZFP91, ZFP91-CNTF, LPXN
D105	11	62341248	62341718	470	0.301	2.707	45	promoter-TSS (NM_001404)	-23	NM_001404	1937	EEF1G	EEF1G, TUT1
D106	11	64408326	64409531	1205	-0.28	2.904	7	intron (NM_015080, intron 17 of 22)	1859	NM_138734	9379	NRXN2	NRXN2
D107	11	65629666	65630036	370	0.324	2.405	11	intron (NM_025128, intron 5 of 15)	1979	NM_025128	80198	MUS81	EFEMP2, CFL1, MUS81
D108	11	70668933	70669423	490	0.254	2.601	30	intron (NM_012309, intron 8 of 22)	49295	NR_037437	100500844	MIR3664	SHANK2
D109	11	73883801	73884108	307	-0.239	2.243	5	intron (NM_016147, intron 1 of 13)	1586	NM_016147	51400	PPME1	C2CD3, PPME1
D110	11	75139113	75139723	610	0.224	3.565	40	intron (NM_001039548, intron 2 of 5)	2256	NM_001039548	283212	KLHL35	KLHL35
D111	11	94707446	94707924	478	-0.257	2.956	14	promoter-TSS (NM_016403)	840	NM_018039	55693	KDM4D	CWC15, KDM4D
D112	11	98892394	98892774	380	-0.241	2.909	7	intron (NM_001243270, intron 1 of 23)	878	NM_014361	53942	CNTN5	CNTN5
D113	11	101789553	101790063	510	-0.252	3.742	6	intron (NM_020802, intron 1 of 10)	-2555	NM_178127	253935	ANGPTL5	KIAA1377, ANGPTL5
D114	11	103108580	103108980	400	-0.204	3.245	5	intron (NM_001377, intron 63 of 88)	128620	NM_001080463	79659	DYNC2H1	DYNC2H1
D115	11	104915738	104916253	515	0.342	2.374	6	promoter-TSS (NM_052889)	56	NM_001017534	114769	CARD16	CARD16
D116	11	114312263	114312756	493	-0.213	3.152	5	intron (NM_015523, intron 2 of 6)	2401	NM_015523	25996	REXO2	REXO2
D117	11	114550477	114551088	611	-0.227	4.063	5	intron (NM_182495, intron 2 of 5)	1582	NM_182495	120406	NXPE2	FAM55B
D118	11	116790538	116791133	595	-0.232	2.626	10	intron (NM_025164, intron 4 of 23)	-82497	NM_000039	335	APOA1	SIK3
D119	11	116874432	116874737	305	-0.221	2.133	7	intron (NM_025164, intron 1 of 23)	94409	NM_025164	23387	SIK3	SIK3
D120	11	116881940	116882310	370	-0.208	2.336	9	intron (NM_025164, intron 1 of 23)	86868	NM_025164	23387	SIK3	SIK3
D121	11	131214392	131215017	625	-0.224	2.649	11	Intergenic	-25667	NM_001048209	50863	NTM	intergenic
D122	12	1748591	1749193	602	0.264	2.657	62	exon (NM_032642, exon 4 of 5)	10480	NM_032642	81029	WNT5B	WNT5B
D123	12	4641451	4641826	375	-0.23	2.636	8	intron (NM_020374, intron 3 of 13)	5999	NM_020374	57102	C12orf4	C12orf4
D124	12	4914276	4914646	370	-0.276	2.692	8	Intergenic	-3881	NM_002235	3742	KCNA6	KCNA6
D125	12	7902903	7903288	385	-0.27	3.127	9	Intergenic	-1026	NM_203503	170482	CLEC4C	CLEC4C
D126	12	9824116	9824509	393	0.293	2.329	17	intron (NM_001197317, intron 1 of 3)	2008	NR_036693	29121	CLEC2D	CLEC2D
D127	12	11341172	11341752	580	-0.246	2.621	5	Intergenic	-1919	NM_181429	353164	TAS2R42	TAS2R42
D128	12	12814205	12814510	305	-0.213	3.753	7	exon (NM_006143, exon 4 of 4)	34764	NM_006143	2842	GPR19	GPR19
D129	12	13198821	13199316	495	0.258	3.359	10	intron (NM_020853, intron 1 of 12)	1753	NM_020853	57613	KIAA1467	KIAA1467
D130	12	21589244	21589644	400	-0.218	3.064	5	Intergenic	-1094	NM_024854	79912	PYROXD1	PYROXD1
D131	12	21995017	21995497	480	-0.212	2.906	7	exon (NM_005691, exon 27 of 38)	-67502	NM_004982	3764	KCNJ8	ABCC9
D132	12	23099370	23099760	390	-0.244	3.824	6	Intergenic	321489	NM_001039481	55500	ETNK1	intergenic
D133	12	48723063	48723393	330	0.223	3.306	47	exon (NM_181788, exon 1 of 1)	465	NM_181788	341567	H1FNT	H1FNT
D134	12	49524725	49525136	411	0.279	2.704	84	intron (NM_006082, intron 1 of 3)	374	NM_006082	10376	TUBA1B	TUBA1B
D135	12	54719022	54719422	400	0.228	2.446	22	intron (NM_016057, intron 1 of 8)	311	NM_016057	22818	COPZ1	COPZ1
D136	12	54720215	54720630	415	0.216	2.736	15	intron (NM_016057, intron 1 of 8)	1511	NM_016057	22818	COPZ1	COPZ1
D137	12	66537890	66538485	595	-0.262	2.83	6	intron (NM_016056, intron 5 of 6)	-13654	NM_032338	84298	LLPH	TMBIM4
D138	12	68653983	68654365	382	-0.248	2.909	7	Intergenic	-6893	NM_020525	50616	IL22	intergenic
D139	12	72333232	72333727	495	-0.232	5.089	5	intron (NM_173353, intron 1 of 10)	853	NM_173353	121278	TPH2	TPH2
D140	12	75699193	75699673	480	0.229	2.395	35	intron (NM_032606, intron 8 of 17)	24403	NM_032606	84698	CAPS2	CAPS2
D141	12	89743694	89744219	525	0.333	2.263	11	intron (NM_022652, intron 1 of 1)	2340	NM_001946	1848	DUSP6	DUSP6
D142	12	100748413	100748798	385	-0.262	2.749	5	Intergenic	-2252	NM_139319	246213	SLC17A8	SLC17A8
D143	12	120687466	120688076	610	0.318	3.322	9	5' UTR (NM_025157, exon 1 of 11)	193	NM_025157	5829	PXN	PXN
D144	12	120906313	120906804	491	0.296	2.919	52	intron (NM_003769, intron 1 of 3)	1000	NM_003769	8683	SRSF9	DYNLL1, SRSF9, GATC
D145	12	132394036	132394538	502	0.212	3.456	56	intron (NM_003565, intron 8 of 27)	15008	NM_003565	8408	ULK1	ULK1
D146	12	132434342	132434717	375	0.248	2.253	120	promoter-TSS (NM_015409)	64	NM_015409	57634	EP400	EP400
D147	12	133019759	133020084	325	0.211	2.465	41	Intergenic	-47236	NM_001142641	57666	FBRSL1	intergenic
D148	13	21714409	21714714	305	0.244	2.483	62	promoter-TSS (NM_005870)	-92	NM_005870	10284	SAP18	SAP18

D149	13	23752625	23753025	400	-0.224	2.8	10	Intergenic	-2235	NM_000231	6445	SGCG	SGCG
D150	13	24816697	24817088	391	-0.268	2.67	6	intron (NM_001166271, intron 2 of 12)	11685	NR_046531	100874231	SPATA13-AS1	SPATA13
D151	13	25419251	25419821	570	-0.24	3.533	7	intron (NM_031277, intron 22 of 35)	77491	NR_047595	55835	CENPJ	RNF17
D152	13	27185922	27186497	575	-0.259	3.987	7	intron (NM_006646, intron 1 of 9)	54369	NM_006646	10810	WASF3	WASF3
D153	13	30816333	30816823	490	-0.22	3.092	9	intron (NM_032116, intron 4 of 10)	64613	NM_001014380	84056	KATNAL1	KATNAL1
D154	13	36163256	36163576	320	-0.246	4.563	5	intron (NM_001204197, intron 6 of 17)	112530	NM_001204197	26960	NBEA	NBEA, MIR548F5
D155	13	43570879	43571183	304	-0.223	4.039	6	Intergenic	-4624	NM_033255	94240	EPSTI1	EPSTI1
D156	13	44200823	44201343	520	-0.218	2.651	5	intron (NM_001127615, intron 1 of 16)	2530	NM_001127615	55068	ENOX1	ENOX1
D157	13	48613616	48614502	886	0.239	2.94	24	intron (NM_018283, intron 1 of 2)	2356	NM_018283	55270	NUDT15	NUDT15
D158	13	51416034	51416534	500	-0.226	3.197	10	intron (NR_046551, intron 4 of 4)	1601	NM_198989	220107	DLEU7	DLEU7
D159	13	52376962	52377347	385	0.235	2.758	8	intron (NM_001031719, intron 1 of 7)	1144	NM_001031719	79758	DHRS12	DHRS12
D160	13	52435278	52435748	470	-0.237	3.653	6	promoter-TSS (NM_031290)	-604	NM_031290	83446	CCDC70	CCDC70
D161	13	84453945	84454255	310	0.233	3.549	32	exon (NM_052910, exon 1 of 1)	2428	NM_052910	114798	SLITRK1	SLITRK1
D162	13	88329305	88329725	420	0.232	3.138	52	exon (NM_015567, exon 2 of 2)	4645	NM_015567	26050	SLITRK5	SLITRK5
D163	13	99665699	99666374	675	-0.226	3.541	13	intron (NM_001130049, intron 1 of 32)	-35698	NM_001130050	23348	DOCK9	DOCK9
D164	13	109241531	109241931	400	-0.323	3.266	7	Intergenic	-6769	NM_015011	23026	MYO16	intergenic
D165	13	114108569	114108934	365	0.232	2.697	26	promoter-TSS (NM_138430)	-912	NM_138430	113622	ADPRHL1	ADPRHL1, DCUN1D2
D166	14	19922332	19922891	559	-0.397	3.725	8	Intergenic	97661	NM_001145442	641455	POTEM	intergenic
D167	14	50154049	50154449	400	0.22	3.201	27	intron (NM_001197330, intron 1 of 17)	849	NM_002692	5427	POLE2	POLE2
D168	14	62539883	62540493	610	-0.252	3.099	5	intron (NM_031914, intron 2 of 5)	-43887	NR_015358	646113	LINC00643	SYT16
D169	14	63786679	63787687	1008	0.29	2.727	29	Intergenic	-1590	NM_145171	122876	GPHB5	GPHB5
D170	14	89054472	89054777	305	-0.219	2.69	6	intron (NM_207660, intron 9 of 13)	-6106	NM_207662	79882	ZC3H14	ZC3H14
D171	14	101188142	101188632	490	0.236	2.441	15	Intergenic	-4815	NM_003836	8788	DLK1	DLK1
D172	14	102834884	102835300	416	-0.222	2.456	9	intron (NM_014844, intron 1 of 19)	5792	NM_014844	9895	TECPR2	TECPR2
D173	15	20717355	20717755	400	-0.238	3.581	10	Intergenic	-6122	NR_036432	283755	HERC2P3	intergenic
D174	15	22733726	22734596	870	-0.218	3.106	8	Intergenic	-2085	NM_001001413	283767	GOLGA6L1	GOLGA6L1
D175	15	23428157	23428729	572	-0.281	3.636	9	Intergenic	-6627	NR_033350	390535	GOLGA8EP	intergenic
D176	15	25200266	25200951	685	0.243	3.189	49	intron (NM_022804, intron 1 of 3)	473	NM_003097	6638	SNRPN	SNRPN, SNURF
D177	15	26108457	26108784	327	0.261	2.288	86	promoter-TSS (NM_024490)	-271	NM_024490	57194	ATP10A	ATP10A
D178	15	27138906	27139211	305	0.207	2.328	44	intron (NM_001165037, intron 6 of 10)	26785	NM_001165037	2558	GABRA5	GABRA5
D179	15	28573237	28573642	405	-0.22	3.055	8	Intergenic	-6141	NM_004667	8924	HERC2	intergenic
D180	15	28617077	28617467	390	-0.234	3.021	10	Intergenic	-6512	NR_033351	100132565	GOLGA8F	intergenic
D181	15	28620752	28621327	575	-0.327	3.143	5	Intergenic	-2745	NR_033351	100132565	GOLGA8F	GOLGA8G, GOLGA8F
D182	15	28780531	28781071	540	-0.277	2.763	5	Intergenic	-2658	NR_033353	283768	GOLGA8G	GOLGA8G, GOLGA8F
D183	15	28784414	28784814	400	-0.236	2.978	11	Intergenic	-6471	NR_033353	283768	GOLGA8G	intergenic
D184	15	28871033	28871398	365	-0.231	2.484	6	Intergenic	-28373	NR_036443	440248	HERC2P9	intergenic
D185	15	30692464	30692818	354	-0.265	2.302	7	Intergenic	-6777	NM_139320	89832	CHRFAM7A	intergenic
D186	15	36927825	36928339	514	-0.213	3.282	6	intron (NM_001130010, intron 1 of 11)	-4724	NM_032499	84529	C15orf41	C15orf41
D187	15	41786297	41786906	609	0.244	2.751	87	exon (NM_002220, exon 1 of 7)	545	NM_002220	3706	ITPKA	ITPKA
D188	15	49446102	49446407	305	-0.224	2.614	7	intron (NM_004236, intron 1 of 12)	1600	NM_001143887	9318	COPS2	COPS2, GALK2, LOC100306975
D189	15	61522646	61523248	602	-0.232	3.852	11	Intergenic	-1445	NM_134261	6095	RORA	RORA
D190	15	67356706	67357027	321	0.219	2.356	24	Intergenic	-1329	NM_005902	4088	SMAD3	SMAD3
D191	15	74377911	74378242	331	-0.24	2.374	6	Intergenic	-3185	NM_001038640	342096	GOLGA6A	GOLGA6A
D192	15	81510763	81511454	691	-0.223	2.857	6	intron (NM_001172128, intron 1 of 18)	-6532	NM_172217	3603	IL16	IL16
D193	15	82720077	82720505	428	-0.241	3.696	8	Intergenic	-1894	NM_198181	440295	GOLGA6L9	GOLGA6L9
D194	15	83025933	83026279	346	-0.258	2.322	11	intron (NR_004847, intron 1 of 4),2	2333	NR_004847	100134869	UBE2Q2P2	UBE2Q2P3
D195	15	83113821	83114336	515	0.239	2.912	51	Intergenic	15368	NM_198181	440295	GOLGA6L9	intergenic
D196	15	85775471	85775787	316	-0.297	3.13	8	Intergenic	-27111	NR_049748	642423	LOC642423	intergenic
D197	15	89348238	89348643	405	0.245	2.988	9	intron (NM_013227, intron 1 of 17)	1766	NM_013227	176	ACAN	ACAN
D198	15	91833384	91833814	430	-0.232	2.37	8	intron (NM_014848, intron 13 of 13)	190060	NM_014848	9899	SV2B	SV2B
D199	15	93614715	93615095	380	0.236	3.848	26	intron (NM_001166288, intron 2 of 3)	1484	NM_001166286	56963	RGMA	RGMA

D200	15	101332621	101332925	304	-0.22	3.219	11	Intergenic	-87236	NM_000693	220	ALDH1A3	intergenic
D201	15	102466837	102468032	1195	-0.237	3.156	10	Intergenic	-4172	NM_001004195	26682	OR4F4	OR4F4
D202	16	1559764	1560334	570	0.232	3.653	37	TTS (NM_014714)	16697	NM_016111	9894	TELO2	IFT140, TELO2
D203	16	2828985	2829665	680	0.294	2.225	22	Intergenic	-2028	NM_207013	6923	TCEB2	TCEB2, PRSS33
D204	16	6422898	6423898	1000	-0.236	3.033	8	intron (NM_001142333, intron 2 of 14)	354266	NM_018723	54715	RBFOX1	RBFOX1
D205	16	6748783	6749103	320	-0.217	2.857	10	intron (NM_001142333, intron 3 of 14)	-74867	NM_001142334	54715	RBFOX1	RBFOX1
D206	16	12009069	12009467	398	0.215	2.414	105	exon (NM_002094, exon 1 of 15)	557	NM_001130006	2935	GSPT1	GSPT1
D207	16	18443504	18443989	485	0.212	3.412	44	Intergenic	52378	NR_036142	100422956	MIR3180-2	intergenic
D208	16	20777313	20777618	305	-0.212	2.679	6	intron (NM_202000, intron 1 of 8)	2153	NM_005622	6296	ACSM3	ACSM3
D209	16	21531140	21531470	330	0.333	3.69	75	non-coding (NR_002594, exon 1 of 1)	460	NR_002594	387254	SLC7A5P2	SLC7A5P2
D210	16	22305349	22305744	395	-0.278	2.796	8	Intergenic	-3150	NM_018119	55718	POLR3E	POLR3E
D211	16	22522466	22523032	566	-0.264	2.67	8	Intergenic	-2095	NM_001135865	100132247	LOC100132247	LOC100132247
D212	16	25931053	25931743	690	-0.282	4.105	6	intron (NM_006040, intron 1 of 1)	228051	NM_006040	9951	HS3ST4	HS3ST4
D213	16	25958955	25959430	475	-0.228	2.747	10	intron (NM_006040, intron 1 of 1)	255845	NM_006040	9951	HS3ST4	HS3ST4
D214	16	26204939	26205844	905	-0.305	3.822	5	Intergenic	502044	NM_006040	9951	HS3ST4	intergenic
D215	16	26343060	26343840	780	-0.296	3.419	8	Intergenic	640103	NM_006040	9951	HS3ST4	intergenic
D216	16	31232871	31233249	378	-0.253	2.752	10	intron (NM_001008274, intron 5 of 6)	-4665	NM_152901	260434	PYDC1	PYDC1, TRIM72
D217	16	33070434	33070845	411	0.226	2.589	82	Intergenic	-134946	NM_016212	24150	TP53TG3	intergenic
D218	16	62284966	62285451	485	-0.229	3.256	5	Intergenic	-214469	NM_001796	1006	CDH8	intergenic
D219	16	62468784	62469384	600	-0.228	2.882	5	Intergenic	-398345	NM_001796	1006	CDH8	intergenic
D220	16	70208313	70208853	540	0.253	4.984	28	intron (NM_173619, intron 1 of 11)	655	NM_173619	283971	CLEC18C	CLEC18C
D221	16	71494556	71494881	325	-0.233	3.78	6	intron (NM_145911, intron 1 of 5)	1399	NM_145911	7571	ZNF23	ZNF23
D222	16	75468283	75468613	330	0.21	3.124	24	Intergenic	-1061	NM_006324	10428	CFDP1	CFDP1
D223	16	80569566	80570176	610	-0.284	3.925	6	Intergenic	-4983	NM_130897	83657	DYNLRB2	DYNLRB2
D224	16	82208779	82209277	498	-0.228	2.861	6	Intergenic	-5199	NM_005792	10200	MPHOSPH6	MPHOSPH6
D225	16	87524869	87525399	530	0.225	3.51	53	intron (NM_015144, intron 1 of 12)	326	NM_015144	23174	ZCCHC14	ZCCHC14
D226	16	90148322	90148897	575	0.306	3.78	45	Intergenic	-6271	NM_001098173	11105	PRDM7	intergenic
D227	17	2997224	2997725	501	-0.231	2.695	6	Intergenic	-1184	NM_002548	4991	OR1D2	OR1D2
D228	17	6938284	6938685	401	0.231	2.899	7	promoter-TSS (NM_201566)	-910	NM_201566	201232	SLC16A13	SLC16A13
D229	17	8114593	8114963	370	-0.218	2.58	10	promoter-TSS (NM_004217)	-834	NM_001256834	9212	AURKB	AURKB
D230	17	16555471	16555791	320	-0.217	2.296	6	intron (NM_020787, intron 1 of 5)	1536	NM_020787	57547	ZNF624	ZNF624
D231	17	19545683	19546068	385	-0.257	3.207	6	Intergenic	-6189	NM_000382	224	ALDH3A2	intergenic
D232	17	31255661	31256051	390	-0.216	2.557	18	intron (NM_001033504, intron 1 of 6)	928	NM_001033504	26022	TMEM98	TMEM98
D233	17	38277847	38278436	589	0.304	2.343	81	promoter-TSS (NM_001012241)	-649	NM_001012241	339287	MSL1	MSL1
D234	17	45062246	45062565	319	-0.297	3.934	10	Intergenic	-5791	NM_203400	388394	RPRML	intergenic
D235	17	48792207	48792602	395	-0.232	2.563	10	Intergenic	-4522	NM_016424	51747	LUC7L3	LUC7L3
D236	17	48828262	48828760	498	-0.268	3.494	10	3' UTR (NM_016424, exon 10 of 10)	16365	NR_073199	55018	LINC00483	LUC7L3
D237	17	55167220	55167595	375	-0.209	2.492	8	intron (NM_001242902, intron 2 of 11)	4272	NM_001242902	8165	AKAP1	AKAP1
D238	17	56249191	56249566	375	-0.264	2.578	7	Intergenic	2361	NM_001004707	124538	OR4D2	OR4D2
D239	17	61430940	61431347	407	-0.243	2.897	7	intron (NM_025185, intron 11 of 24)	87064	NM_001017917	1534	CYB561	TANC2
D240	17	74349827	74350512	685	0.308	2.567	62	promoter-TSS (NM_002766)	61	NM_002766	5635	PRPSAP1	PRPSAP1
D241	17	78948420	78948820	400	-0.249	3.256	9	Intergenic	-17021	NM_024591	79643	CHMP6	intergenic
D242	17	79361084	79361418	334	0.211	4.662	83	Intergenic	-12289	NM_001080519	57597	BAHCC1	intergenic
D243	17	79917839	79918309	470	0.235	3.566	107	intron (NM_178493, intron 1 of 10)	983	NM_178493	147111	NOTUM	NOTUM
D244	17	80036750	80037425	675	0.235	2.969	54	exon (NM_004104, exon 43 of 43)	-13390	NM_022156	64118	DUS1L	FASN
D245	18	22036495	22036826	331	-0.227	2.063	9	Intergenic	-3933	NM_001143828	59340	HRH4	IMPACT, HRH4
D246	18	25903262	25903737	475	-0.242	2.775	8	Intergenic	-146054	NM_001792	1000	CDH2	intergenic
D247	18	31800204	31800509	305	-0.229	2.791	7	intron (NM_001198546, intron 1 of 9)	2078	NM_001198547	8715	NOL4	NOL4
D248	18	47019290	47019788	498	-0.475	3.42	12	promoter-TSS (NM_001199345)	-604	NM_001199345	6139	RPL17	RPL17, RPL17-C18ORF32, SNORD58A, SNORD58B, SNORD58C
D249	18	56982879	56983384	505	-0.254	2.933	9	intron (NM_181654, intron 1 of 2)	2750	NM_181654	339302	CPLX4	CPLX4
D250	18	61225101	61225596	495	-0.269	3.027	5	intron (NM_080474, intron 1 of 6)	1955	NM_080474	89777	SERPINB12	SERPINB12

D251	18	61432732	61433052	320	-0.214	3.714	6	intron (NM_001040147, intron 1 of 7)	-9717	NM_001261831	8710	SERPINB7	SERPINB7
D252	18	61438138	61438548	410	-0.242	3.807	5	intron (NM_001040147, intron 1 of 7)	-4266	NM_001261831	8710	SERPINB7	SERPINB7
D253	18	66507007	66507417	410	-0.213	2.863	5	intron (NM_024781, intron 3 of 7)	41895	NM_024781	79839	CCDC102B	CCDC102B
D254	18	77196024	77196524	500	0.219	2.609	47	intron (NM_172389, intron 3 of 9)	35948	NM_172389	4772	NFATC1	NFATC1
D255	18	77791162	77791682	520	-0.224	3.233	8	Intergenic	-2924	NM_001171967	79863	RBFA	RBFA
D256	19	69351	70083	732	-0.279	3.136	7	intron (NR_033266, intron 1 of 2)	1249	NR_033266	375690	WASH5P	WASH5P
D257	19	585719	586224	505	0.286	2.474	13	Intergenic	-3922	NM_001194	610	HCN2	BSG, HCN2
D258	19	735961	736433	472	0.219	2.62	45	intron (NM_001040134, intron 7 of 7)	-14949	NM_173481	126353	C19orf21	PALM
D259	19	805752	806452	700	0.339	3.751	78	intron (NM_031990, intron 9 of 14)	1162	NR_039900	100616459	MIR4745	PTBP1, MIR4745
D260	19	1021495	1021825	330	0.241	3.03	40	promoter-TSS (NM_001033026)	-519	NM_033420	91304	C19orf6	C19orf6, CNN2
D261	19	1228365	1228945	580	0.219	4.613	101	TTS (NM_000455)	9335	NM_152769	255057	C19orf26	C19orf26, STK11
D262	19	1876344	1876934	590	0.27	2.843	46	TTS (NM_001130111)	8879	NM_001130111	81926	FAM108A1	FAM108A1
D263	19	4557006	4557331	325	0.223	3.104	37	intron (NM_032108, intron 4 of 16)	2603	NM_032108	10501	SEMA6B	SEMA6B
D264	19	5135093	5135398	305	0.261	2.284	31	intron (NM_015015, intron 14 of 22)	166121	NM_015015	23030	KDM4B	KDM4B
D265	19	10907627	10908203	576	0.226	3.466	28	intron (NM_001005360, intron 10 of 20)	16985	NR_039903	100616425	MIR4748	DNM2
D266	19	10934228	10934833	605	0.247	2.605	21	exon (NM_001190716, exon 17 of 21)	-6358	NR_029586	406976	MIR199A1	DNM2
D267	19	16051903	16052227	324	-0.241	4.468	6	Intergenic	-6389	NM_021187	57834	CYP4F11	intergenic
D268	19	17445165	17445475	310	0.207	3.571	84	promoter-TSS (NM_001195422)	318	NM_020959	57719	ANO8	GTPBP3, ANO8
D269	19	17449965	17450490	525	0.248	3.767	37	intron (NM_133644, intron 5 of 7)	1901	NM_133644	84705	GTPBP3	GTPBP3, ANO8
D270	19	18041207	18041612	405	-0.23	2.612	16	Intergenic	-2415	NM_001136203	115098	CCDC124	CCDC124
D271	19	21860585	21860955	370	0.241	2.901	37	Intergenic	-72777	NR_024523	641367	LOC641367	intergenic
D272	19	37020091	37020476	385	0.237	2.749	21	Intergenic	-1035	NM_001166036	339324	ZNF260	ZNF260
D273	19	37263404	37263994	590	0.25	3.935	53	promoter-TSS (NM_001267779)	17	NM_001267779	342892	ZNF850	ZNF850
D274	19	38084769	38085148	379	0.215	2.643	26	promoter-TSS (NM_001172226)	715	NM_016536	51276	ZNF571	ZNF540, ZNF571
D275	19	44570828	44571298	470	-0.229	3.281	11	exon (NM_013361, exon 5 of 5)	-5234	NM_001037813	342909	ZNF284	ZNF284, ZNF223
D276	19	45515333	45515643	310	0.208	3.033	56	exon (NM_006509, exon 3 of 11)	10781	NM_006509	5971	RELB	RELB
D277	19	47102132	47102507	375	-0.213	2.422	7	intron (NM_001205281, intron 1 of 3)	2138	NM_001205281	100506012	PPP5D1	LOC100506012, CALM3
D278	19	47356165	47356495	330	0.429	2.054	5	Intergenic	-2127	NM_004069	1175	AP2S1	AP2S1
D279	19	47634525	47634850	325	0.258	3.13	36	intron (NR_027280, intron 1 of 8)	572	NR_027280	10055	SAE1	SAE1
D280	19	49842935	49843245	310	0.219	3.706	49	TTS (NM_003598)	4413	NM_001774	951	CD37	CD37, TEAD2
D281	19	51572668	51572992	324	-0.218	2.753	11	Intergenic	-4463	NM_015596	26085	KLK13	KLK13
D282	19	51586807	51587137	330	0.244	2.771	18	intron (NM_022046, intron 1 of 6)	530	NM_022046	43847	KLK14	KLK14
D283	19	51774231	51774746	515	0.292	2.608	34	Intergenic	13524	NM_173635	284369	SIGLECL1	C19orf75
D284	19	54972295	54972705	410	0.217	2.484	39	TTS (NM_198988)	2394	NM_198988	94059	LENG9	LENG9, LENG8, CDC42EP5
D285	19	56163345	56163855	510	0.233	3.287	44	intron (NM_013301, intron 5 of 5)	-1816	NM_007279	11338	U2AF2	CCDC106, U2AF2
D286	19	58566138	58566541	403	0.246	2.633	27	TTS (NM_182572)	-4268	NM_003436	7694	ZNF135	ZSCAN1, ZNF135
D287	19	58874038	58874368	330	0.282	2.105	82	promoter-TSS (NM_001207009)	11	NM_001207009	162968	ZNF497	ZNF497
D288	2	557919	558444	525	0.246	3.382	43	Intergenic	119258	NM_152834	129787	TMEM18	intergenic
D289	2	10151509	10152095	586	0.248	4.112	56	Intergenic	-31880	NM_003597	8462	KLF11	intergenic
D290	2	16153858	16154233	375	0.213	2.431	32	Intergenic	-72200	NR_026766	10408	MYCNOS	intergenic
D291	2	20103745	20104076	331	-0.214	3.239	6	Intergenic	-2166	NM_001008237	130502	TTC32	TTC32
D292	2	33657519	33657949	430	-0.25	2.822	11	Intergenic	-3682	NM_170672	25780	RASGRP3	RASGRP3
D293	2	36924606	36925021	415	-0.223	3.41	8	intron (NM_053276, intron 1 of 15)	980	NM_001177969	5212	VIT	VIT
D294	2	37895804	37896174	370	-0.231	4.415	6	intron (NM_001270436, intron 1 of 1)	3353	NM_006449	10602	CDC42EP3	CDC42EP3
D295	2	42556470	42556795	325	-0.206	3.494	10	intron (NM_019063, intron 22 of 22)	31724	NM_004718	9167	COX7A2L	EML4
D296	2	43860636	43860946	310	-0.246	2.388	6	Intergenic	-3648	NM_172069	130271	PLEKHH2	PLEKHH2
D297	2	45231533	45231943	410	0.246	2.557	47	TTS (NM_016932)	4804	NM_016932	10736	SIX2	SIX2
D298	2	50577893	50578317	424	-0.239	5.112	5	intron (NM_004801, intron 17 of 21)	-3211	NM_138735	9378	NRXN1	NRXN1
D299	2	51704426	51704806	380	-0.235	3.385	5	Intergenic	-444942	NM_001135659	9378	NRXN1	intergenic
D300	2	51719209	51719714	505	-0.227	2.656	7	Intergenic	-459787	NM_001135659	9378	NRXN1	intergenic
D301	2	51950325	51950925	600	-0.24	3.499	6	Intergenic	-690951	NM_001135659	9378	NRXN1	intergenic

D302	2	54557572	54557897	325	0.242	2.761	52	promoter-TSS (NM_001100396)	-337	NM_001100396	129852	C2orf73	C2orf73
D303	2	58470499	58471103	604	-0.223	3.084	7	Intergenic	-2286	NM_018062	55120	FANCL	FANCL
D304	2	88463530	88464050	520	-0.241	3.166	11	Intergenic	-6024	NM_001244676	55258	THNSL2	intergenic
D305	2	92261990	92262507	517	0.223	3.959	48	Intergenic	133089	NR_027714	440888	ACTR3BP2	intergenic
D306	2	97910656	97911381	725	-0.256	3.637	7	exon (NM_001164315, exon 71 of 76)	-37211	NR_040097	100506123	LOC100506123	ANKRD36
D307	2	98128084	98128612	528	-0.216	2.576	9	exon (NM_025190, exon 39 of 44)	-37299	NR_040097	100506123	LOC100506123	ANKRD36B
D308	2	100760155	100760740	585	-0.229	3.542	10	Intergenic	-1410	NM_002285	3899	AFF3	AFF3
D309	2	105853033	105853408	375	0.219	3.383	28	Intergenic	-4980	NM_007227	11250	GPR45	GPR45
D310	2	107073701	107074572	871	-0.216	2.898	5	intron (NM_001144013, intron 2 of 22)	10665	NM_001144013	653489	RGPD3	RGPD3
D311	2	116065044	116065824	780	-0.265	3.61	6	intron (NM_001004360, intron 1 of 25)	145750	NM_001004360	57628	DPP10	DPP10
D312	2	118757608	118757978	370	-0.24	2.562	7	intron (NM_019044, intron 4 of 23)	13946	NM_019044	54520	CCDC93	CCDC93
D313	2	166935866	166936174	308	-0.24	2.936	5	intron (NM_001202435, intron 1 of 27)	-5871	NM_006920	6323	SCN1A	SCN1A
D314	2	174212569	174212874	305	-0.222	2.674	10	Intergenic	-6840	NM_031942	83879	CDCA7	intergenic
D315	2	182547413	182548028	615	0.313	2.648	43	Intergenic	-2328	NM_002500	4760	NEUROD1	NEUROD1
D316	2	193061133	193061508	375	-0.247	2.548	16	Intergenic	-1676	NM_016192	23671	TMEFF2	TMEFF2
D317	2	197676027	197676902	875	-0.28	4.502	6	Intergenic	-1464	NM_213608	401027	C2orf66	C2orf66
D318	2	200774538	200774963	425	-0.212	3.305	5	Intergenic	-1229	NM_153689	205327	C2orf69	C2orf69
D319	2	202564922	202565230	308	-0.216	2.53	6	TTS (NM_020919)	-1659	NM_033066	58538	MPP4	MPP4, ALS2
D320	2	219576276	219577046	770	0.376	3.481	6	intron (NM_014640, intron 1 of 19)	1093	NM_014640	9654	TTL4	TTL4
D321	2	220083145	220083530	385	0.226	5.569	68	TTS (NM_024085)	375	NM_005689	10058	ABCB6	ABCB6, ATG9A
D322	2	234987728	234988158	430	-0.238	3.205	8	Intergenic	28597	NM_006944	6694	SPP2	SPP2
D323	2	242448454	242448844	390	0.305	2.648	57	promoter-TSS (NM_006374)	-615	NM_006374	10494	STK25	STK25
D324	20	3714870	3715255	385	-0.225	2.307	13	intron (NM_052970, intron 1 of 12)	1745	NM_001197327	116835	HSPA12B	HSPA12B
D325	20	8005813	8006440	627	-0.232	2.504	8	Intergenic	-5733	NM_021156	56255	TMX4	intergenic
D326	20	18123530	18124049	519	0.387	3.142	9	TTS (NM_001164811)	921	NM_020536	57325	CSRP2BP	PET117, CSRP2BP
D327	20	23413449	23413924	475	-0.245	2.58	6	Intergenic	-6636	NM_138283	128817	CSTL1	intergenic
D328	20	36304618	36304943	325	-0.218	2.701	8	promoter-TSS (NR_040021)	-532	NR_040021	100287792	LOC100287792	LOC100287792
D329	20	46300740	46301232	492	0.274	2.918	23	exon (NM_018837, exon 11 of 21)	113822	NM_018837	55959	SULF2	SULF2
D330	20	57202945	57203330	385	0.214	4.187	10	Intergenic	-23172	NR_037943	8675	STX16	intergenic
D331	20	57416607	57417696	1089	0.221	2.865	47	non-coding (NR_002785, exon 4 of 5)	2356	NM_016592	2778	GNAS	GNAS-AS1, GNAS
D332	20	57426818	57427609	791	0.246	3.747	39	promoter-TSS (NM_080425)	-823	NM_080425	2778	GNAS	GNAS-AS1, GNAS
D333	20	60873143	60873728	585	0.308	2.481	20	Intergenic	-4592	NM_175573	11047	ADRM1	OSBPL2, ADRM1
D334	20	60888727	60889227	500	0.233	3.176	53	intron (NM_005560, intron 62 of 79)	10950	NM_007002	11047	ADRM1	LAMA5, ADRM1
D335	20	62580073	62580563	490	0.272	4.022	30	intron (NM_017859, intron 1 of 14)	2209	NM_001193379	54963	UCKL1	UCKL1, UCKL1-AS1
D336	20	62901069	62901674	605	0.256	3.883	50	intron (NM_018257, intron 5 of 5)	14323	NM_001104925	55251	PCMTD2	PCMTD2
D337	21	9437391	9438392	1001	0.22	2.906	112	Intergenic	-387941	NR_037421	100500862	MIR3648	intergenic
D338	21	9438899	9439200	301	0.232	2.728	85	Intergenic	-386783	NR_037421	100500862	MIR3648	intergenic
D339	21	15436148	15436723	575	0.238	2.246	65	Intergenic	-83670	NR_027270	391267	ANKRD20A11P	intergenic
D340	21	30674834	30675224	390	-0.231	2.512	8	intron (NM_206866, intron 1 of 4)	-2531	NR_027655	571	BACHI	BACHI
D341	21	31315685	31316187	502	-0.241	2.766	6	Intergenic	-3654	NM_175611	2897	GRIK1	GRIK1
D342	21	33961591	33961976	385	-0.212	3.328	7	Intergenic	-3938	NM_144659	140290	TCPI0L	TCPI0L
D343	21	34673773	34674168	395	0.336	2.781	5	Intergenic	-23244	NM_000629	3454	IFNAR1	IL10RB
D344	21	34756882	34757397	515	0.22	3.368	15	Intergenic	-18063	NM_005534	3460	IFNGR2	intergenic
D345	21	36262421	36263014	593	0.342	2.891	75	intron (NM_001754, intron 3 of 8)	-1730	NM_001001890	861	RUNX1	RUNX1
D346	21	38476940	38477455	515	0.262	2.595	8	intron (NM_001001894, intron 10 of 45)	21950	NM_003316	7267	TTC3	TTC3
D347	21	43236051	43236626	575	0.338	4.421	43	intron (NM_022115, intron 25 of 30)	-49089	NM_020639	54101	RIPK4	PRDM15
D348	21	47742584	47743099	515	0.22	2.457	47	5' UTR (NM_058180, exon 1 of 8)	944	NM_058180	54058	C21orf58	PCNT, C21orf58
D349	22	16190145	16190501	356	-0.256	2.229	7	Intergenic	97614	NM_001136213	23784	POTEH	intergenic
D350	22	19712690	19713420	730	0.236	3.456	61	TTS (NM_000407)	1989	NM_000407	2812	GP1BB	GP1BB, SEPT5-GP1BB, SEPT5
D351	22	21530255	21530953	698	-0.273	3.52	5	Intergenic	73299	NR_037566	400892	BCRP2	intergenic
D352	22	21531173	21531503	330	-0.254	3.05	9	Intergenic	74033	NR_037566	400892	BCRP2	intergenic

D353	22	21533789	21534104	315	-0.248	2.804	6	Intergenic	76641	NR_037566	400892	BCRP2	intergenic
D354	22	32101660	32101985	325	-0.252	2.228	15	intron (NM_173566, intron 4 of 8)	44298	NM_173566	253143	PRR14L	PRR14L
D355	22	33281882	33282357	475	0.309	2.866	12	intron (NM_133633, intron 3 of 11)	85317	NM_000362	7078	TIMP3	SYN3
D356	22	40676734	40677134	400	-0.237	2.783	7	intron (NM_001024843, intron 12 of 23)	-65570	NM_001123378	158	ADSL	TNRC6B
D357	22	44211099	44211427	328	-0.223	2.674	8	Intergenic	-3046	NM_022785	64800	EFCAB6	EFCAB6
D358	22	48730086	48730406	320	0.301	2.295	34	Intergenic	60070	NR_036172	100422916	MIR3201	intergenic
D359	3	13972732	13973102	370	-0.231	2.337	9	Intergenic	-1636	NR_036481	100132526	LOC100132526	LOC100132526
D360	3	30898339	30898963	624	-0.234	2.772	9	intron (NM_207359, intron 2 of 14)	37502	NM_207359	339896	GADL1	GADL1
D361	3	33150809	33151178	369	-0.237	2.339	6	Intergenic	-4457	NM_006371	10491	CRTAP	CRTAP
D362	3	46599590	46600220	630	0.244	4.231	21	intron (NM_024512, intron 1 of 8)	8135	NM_024512	79442	LRRC2	LRRC2
D363	3	52088932	52089632	700	0.256	2.63	28	intron (NM_001947, intron 1 of 2)	1179	NM_001947	1849	DUSP7	DUSP7
D364	3	54998632	54999035	403	-0.253	2.184	8	intron (NM_018398, intron 27 of 37)	-36761	NM_020678	57408	LRTM1	CACNA2D3
D365	3	89157491	89157806	315	-0.217	4.13	7	intron (NM_182644, intron 1 of 6)	974	NM_182644	2042	EPHA3	EPHA3
D366	3	93776193	93776560	367	-0.252	3.084	5	TTS (NM_001195643)	5455	NM_176815	200895	DHFR1	ARL13B, DHFR1
D367	3	100210474	100210790	316	-0.279	2.215	12	promoter-TSS (NM_018004)	-831	NM_018004	55076	TMEM45A	TMEM45A
D368	3	110783860	110784229	369	-0.222	2.696	6	intron (NR_045114, intron 2 of 3)	4762	NR_045114	100506555	PVRL3-AS1	PVRL3-AS1
D369	3	112712434	112712799	365	-0.225	2.678	11	intron (NM_014170, intron 2 of 5)	2816	NM_138485	29083	GTPBP8	GTPBP8
D370	3	124229077	124229577	500	-0.294	3.709	5	intron (NM_001024660, intron 33 of 59)	-74179	NM_007064	8997	KALRN	KALRN
D371	3	125685462	125685847	385	-0.227	2.448	5	Intergenic	-2374	NM_001012337	152015	ROPN1B	ROPN1B
D372	3	140662821	140663191	370	-0.208	3.367	5	intron (NM_001104647, intron 1 of 6)	2344	NM_001104647	55186	SLC25A36	SLC25A36
D373	3	142294654	142295254	600	-0.222	2.934	7	intron (NM_001184, intron 1 of 46)	2714	NM_001184	545	ATR	ATR
D374	3	155833456	155834156	700	-0.247	3.117	10	Intergenic	-4531	NM_172160	7881	KCNAB1	KCNAB1
D375	3	167046807	167047492	685	-0.258	3.062	6	intron (NM_001199202, intron 10 of 20)	50922	NM_001199202	79740	ZBBX	ZBBX
D376	3	170818668	170819189	521	-0.225	2.651	10	intron (NM_001161566, intron 19 of 29)	5620	NR_030295	693154	MIR569	TNIK
D377	3	171001952	171002338	386	-0.25	2.998	7	intron (NM_001161566, intron 2 of 29)	176052	NM_001161564	23043	TNIK	TNIK
D378	3	176746328	176746831	503	-0.225	3.055	5	intron (NM_024665, intron 14 of 15)	168469	NM_024665	79718	TBL1XR1	TBL1XR1
D379	3	178793387	178793710	323	-0.231	2.964	8	Intergenic	-3892	NM_022470	64393	ZMAT3	ZMAT3
D380	3	182699611	182700116	505	-0.26	3.195	12	Intergenic	-1537	NM_020640	54165	DCUN1D1	DCUN1D1
D381	3	183750534	183750839	305	0.423	2.914	7	promoter-TSS (NM_001163646)	67	NM_001163646	200909	HTR3D	HTR3D
D382	3	188882790	188883495	705	-0.419	4.192	6	Intergenic	-6621	NM_198485	285386	TPRG1	intergenic
D383	3	192130716	192131144	428	-0.222	2.93	5	intron (NM_004113, intron 2 of 5)	-4092	NM_021032	2257	FGF12	FGF12
D384	3	194786013	194786413	400	0.244	2.936	42	Intergenic	205682	NM_152531	152002	XXYL1	XXYL1
D385	3	195426815	195427285	470	-0.251	3.372	9	TTS (NR_030296)	778	NR_030296	693155	MIR570	MIR570
D386	3	197676983	197677483	500	0.225	2.457	27	promoter-TSS (NM_001134435)	181	NM_000996	6165	RPL35A	IQCG, RPL35A
D387	4	124613	125128	515	0.211	2.951	44	intron (NM_001039127, intron 3 of 3)	71593	NM_001039127	255403	ZNF718	ZNF718
D388	4	698291	698596	305	0.207	2.686	47	Intergenic	-1130	NM_006315	10336	PCGF3	PCGF3
D389	4	1794245	1794825	580	0.311	3.045	61	promoter-TSS (NM_000142)	-504	NM_000142	2261	FGFR3	FGFR3
D390	4	2847892	2848397	505	0.387	2.789	6	intron (NM_014190, intron 1 of 15)	2560	NM_014189	118	ADD1	ADD1
D391	4	3042964	3043339	375	0.222	2.834	46	TTS (NM_182982)	33090	NR_045414	100750326	HTT-AS1	GRK4
D392	4	3252885	3253300	415	0.247	2.512	18	intron (NM_001042690, intron 1 of 2)	2325	NM_001042690	345222	MSANTD1	MSANTD1
D393	4	10028678	10029165	487	-0.224	3.092	12	intron (NM_001001290, intron 1 of 12)	-5807	NM_020041	56606	SLC2A9	SLC2A9
D394	4	13605282	13605696	414	-0.234	2.774	7	exon (NM_148894, exon 10 of 26)	23839	NM_148894	259282	BOD1L1	BOD1L1
D395	4	41534117	41534422	305	-0.234	3.438	11	intron (NM_001112718, intron 3 of 25)	-80650	NM_001112719	22998	LIMCH1	LIMCH1
D396	4	47469443	47469844	401	-0.242	3.064	10	Intergenic	-3967	NM_017845	54951	COMMD8	COMMD8
D397	4	74489443	74490255	812	-0.248	3.603	8	Intergenic	-3501	NM_001270392	166824	RASSF6	RASSF6
D398	4	74715813	74716128	315	-0.27	2.239	7	Intergenic	-3043	NM_002620	5197	PF4V1	PF4V1
D399	4	76943285	76943650	365	-0.251	3.305	6	intron (NM_001565, intron 3 of 3)	1222	NM_001565	3627	CXCL10	ART3, CXCL10
D400	4	76993566	76994166	600	-0.293	2.692	5	intron (NM_001130017, intron 1 of 9)	-1982	NM_001179	419	ART3	ART3
D401	4	81947252	81947827	575	-0.257	4.205	6	Intergenic	-4580	NM_001201	651	BMP3	BMP3
D402	4	89051945	89052325	380	-0.243	3.563	9	intron (NM_001257386, intron 5 of 15)	27876	NM_004827	9429	ABCG2	ABCG2
D403	4	90234239	90234725	486	-0.221	2.666	10	Intergenic	-5321	NM_198281	285513	GPRIN3	intergenic

D404	4	90753936	90754556	620	-0.264	3.74	5	intron (NM_001146055, intron 2 of 5)	-3306	NR_045481	644248	LOC644248	SNCA, LOC644248
D405	4	94747689	94748179	490	-0.237	2.377	8	Intergenic	-2144	NM_005172	474	ATOH1	ATOH1
D406	4	99063393	99063723	330	-0.245	2.845	6	intron (NM_174952, intron 1 of 10)	833	NM_174952	285555	STPG2	C4orf37
D407	4	100240587	100241162	575	-0.247	3.318	5	intron (NM_000668, intron 1 of 8)	1698	NM_000668	125	ADH1B	ADH1B
D408	4	118009944	118010346	402	-0.215	2.691	5	Intergenic	-3409	NM_152402	133022	TRAM1L1	TRAM1L1
D409	4	118500576	118501373	797	-0.289	4.044	6	Intergenic	-454526	NM_004784	9348	NDST3	intergenic
D410	4	118528065	118528656	591	-0.255	2.966	6	Intergenic	-427140	NM_004784	9348	NDST3	intergenic
D411	4	118711658	118712078	420	-0.219	3.132	6	Intergenic	-243632	NM_004784	9348	NDST3	intergenic
D412	4	125591600	125591905	305	-0.204	2.606	10	exon (NM_020337, exon 4 of 5)	42135	NM_001167882	57182	ANKRD50	ANKRD50
D413	4	141296446	141296821	375	-0.244	2.371	8	intron (NM_001153663, intron 1 of 3)	1969	NM_001153663	60592	SCOC	SCOC, LOC100129858
D414	4	155418051	155418545	494	-0.266	3.062	5	Intergenic	-5368	NM_001142553	54798	DCHS2	intergenic
D415	5	84782	85252	470	0.235	3.18	58	Intergenic	-55356	NM_052909	153478	PLEKHG4B	intergenic
D416	5	2739664	2740362	698	0.278	2.224	69	Intergenic	11756	NM_033267	153572	IRX2	intergenic
D417	5	36001428	36001933	505	-0.237	2.318	6	promoter-TSS (NM_001171873)	-550	NM_001171873	133688	UGT3A1	UGT3A1
D418	5	56238259	56238654	395	-0.302	3.1	8	intron (NM_152622, intron 3 of 12)	9498	NM_152622	166968	MIER3	MIER3
D419	5	56285774	56286564	790	-0.297	3.442	6	Intergenic	-38215	NM_152622	166968	MIER3	intergenic
D420	5	65437589	65438179	590	0.297	2.621	5	Intergenic	-2162	NM_001077199	140890	SREK1	SREK1
D421	5	68974058	68975023	965	-0.328	2.898	5	intron (NR_027386, intron 3 of 5)	31732	NR_027386	653188	GUSBP3	GUSBP3
D422	5	68976563	68977313	750	-0.268	3.297	6	intron (NR_027386, intron 1 of 5)	29334	NR_027386	653188	GUSBP3	GUSBP3
D423	5	69555415	69556960	1545	-0.25	3.226	8	intron (NR_029426, intron 2 of 9)	29817	NR_029426	11039	SMA4	SMA4
D424	5	69704768	69705080	312	-0.228	3.259	5	Intergenic	-6273	NR_033417	653238	GTF2H2B	intergenic
D425	5	69849579	69850939	1360	-0.295	3.113	5	intron (NR_034021, intron 4 of 10)	891	NR_033968	100049076	GUSBP9	SMA5, GUSBP9
D426	5	69851754	69853296	1542	-0.261	3.269	8	intron (NR_034021, intron 3 of 10)	-1375	NR_033968	100049076	GUSBP9	SMA5, GUSBP9
D427	5	70555908	70557123	1215	-0.236	3.098	9	Intergenic	-1393	NR_033968	100049076	GUSBP9	GUSBP9
D428	5	75469940	75470355	415	0.214	2.427	29	intron (NM_014979, intron 2 of 12)	90842	NM_014979	22987	SV2C	SV2C
D429	5	75696649	75697349	700	-0.253	3.761	7	Intergenic	-2150	NM_006633	10788	IQGAP2	IQGAP2
D430	5	82368664	82369084	420	-0.224	2.402	10	intron (NM_174909, intron 1 of 3)	4398	NM_174909	153339	TMEM167A	TMEM167A, XRCC4
D431	5	87567189	87567564	375	-0.232	2.912	7	intron (NR_039995, intron 2 of 2)	2535	NR_039994	100505894	TMEM161B-AS1	TMEM161B-AS1, TMEM161B
D432	5	94885207	94886116	909	-0.246	3.413	8	intron (NM_014639, intron 2 of 42)	5048	NM_014639	9652	TTC37	TTC37, ARSK
D433	5	95065474	95066064	590	-0.235	2.509	6	Intergenic	-1081	NM_014899	22836	RHOBTB3	RHOBTB3
D434	5	109962533	109963128	595	-0.222	3.386	5	intron (NM_001039763, intron 6 of 13)	99620	NM_001039763	642987	TMEM232	TMEM232
D435	5	115292255	115292885	630	-0.235	3.162	6	Intergenic	-5581	NM_173800	206338	AQPEP	intergenic
D436	5	126114144	126114454	310	0.22	2.879	50	intron (NM_005573, intron 1 of 10)	1454	NM_001198557	4001	LMNB1	LMNB1
D437	5	131485248	131485818	570	-0.252	2.746	7	Intergenic	76048	NM_000758	1437	CSF2	intergenic
D438	5	132228740	132229120	380	-0.239	3.48	9	intron (NM_014423, intron 11 of 20)	19572	NM_052971	116842	LEAP2	AFF4
D439	5	140620404	140620894	490	0.237	2.935	31	non-coding (NR_001282, exon 1 of 1)	960	NR_001282	84054	PCDHB19P	PCDHB15, PCDHB18, PCDHB19P
D440	5	140719011	140719626	615	0.222	2.382	33	exon (NM_018915, exon 1 of 4)	964	NM_018915	56113	PCDHGA2	PCDHGA2, PCDHGA1, PCDHGA3
D441	5	142174675	142174985	310	-0.203	2.758	5	intron (NM_001135608, intron 1 of 22)	24538	NM_001135608	23092	ARHGAP26	ARHGAP26
D442	5	147260474	147260779	305	-0.21	3.073	6	intron (NM_054023, intron 1 of 2)	2352	NM_054023	117156	SCGB3A2	SCGB3A2
D443	5	156487454	156487819	365	-0.24	3.115	6	Intergenic	-1666	NM_001173393	26762	HAVCR1	HAVCR1
D444	5	156570589	156570894	305	0.262	3.601	27	promoter-TSS (NM_001100816)	-820	NM_004270	9443	MED7	MED7
D445	5	161270539	161271019	480	-0.235	2.684	8	Intergenic	-3418	NM_000806	2554	GABRA1	GABRA1
D446	5	175393973	175394518	545	-0.246	3.534	12	exon (NM_032361, exon 2 of 6)	1300	NM_032361	84321	THOC3	THOC3
D447	5	175488222	175488627	405	0.213	3.694	64	Intergenic	-2288	NM_001265615	202134	FAM153B	intergenic
D448	5	177303153	177303778	625	-0.259	3.5	17	intron (NR_003615, intron 1 of 5)	1203	NR_003615	728554	LOC728554	LOC728554
D449	5	180648315	180649020	705	0.228	3.595	33	TTS (NR_039781)	966	NR_039781	100616342	MIR4638	TRIM41, MIR4638
D450	5	180794543	180795188	645	-0.243	2.814	8	exon (NM_001005277, exon 1 of 1)	577	NM_001005277	26683	OR4F3	OR4F16, OR4F3, OR4F29
D451	5	180795933	180796849	916	-0.27	3.436	5	Intergenic	2103	NM_001005277	26683	OR4F3	OR4F16, OR4F3, OR4F29
D452	6	2902234	2903041	807	0.234	3.144	27	intron (NM_004155, intron 1 of 6)	909	NM_004155	5272	SERPIN9	SERPIN9
D453	6	4020994	4021489	495	0.241	2.985	35	promoter-TSS (NM_003913)	-328	NM_003913	8899	PRPF4B	PRPF4B
D454	6	10319513	10320047	534	0.261	4.52	42	Intergenic	-92771	NR_033910	100130275	LOC100130275	intergenic

D455	6	10407836	10408211	375	-0.217	3.782	7	intron (NM_003220, intron 2 of 6)	-4528	NR_033910	100130275	LOC100130275	TFAP2A, LOC100130275
D456	6	25650732	25651062	330	-0.228	2.942	5	Intergenic	-1532	NM_006998	10590	SCGN	SCGN
D457	6	25878141	25878671	530	-0.228	2.861	5	Intergenic	-3935	NM_006632	10786	SLC17A3	SLC17A3
D458	6	29530427	29530904	477	-0.243	3.013	10	Intergenic	-2963	NM_006398	10537	UBD	UBD
D459	6	33776419	33776917	498	-0.254	3.503	13	Intergenic	-4875	NM_002418	4295	MLN	MLN
D460	6	34499206	34499731	525	0.214	2.285	33	exon (NM_020804, exon 9 of 10)	16819	NM_001199583	29993	PAC SIN1	PAC SIN1
D461	6	56817935	56818330	395	-0.232	2.421	12	Intergenic	-1641	NM_152731	221336	BEND6	BEND6
D462	6	56821525	56822145	620	-0.244	3.064	6	intron (NM_152731, intron 1 of 6)	2062	NM_152731	221336	BEND6	BEND6
D463	6	70505077	70505700	623	-0.242	3.275	5	intron (NM_018368, intron 1 of 15)	1661	NM_018368	55788	LMBRD1	LMBRD1
D464	6	72589922	72590412	490	-0.221	2.539	8	Intergenic	-6239	NM_014989	22999	RIMS1	intergenic
D465	6	73733245	73733555	310	-0.208	2.377	5	intron (NM_001160130, intron 2 of 12)	-55924	NR_036244	100423005	MIR4282	KCNQ5
D466	6	99803202	99803606	404	-0.275	3.094	6	Intergenic	-5873	NM_032511	84553	FAXC	intergenic
D467	6	109767871	109768281	410	0.243	2.679	16	intron (NM_022765, intron 17 of 24)	-5702	NM_001111298	285755	PPIL6	MICAL1, SMPD2
D468	6	116450645	116450947	302	-0.228	2.24	8	intron (NM_152729, intron 6 of 11)	-3500	NM_000493	1300	COL10A1	COL10A1, NT5DC1
D469	6	132335452	132336151	699	-0.241	4.041	6	Intergenic	-63283	NM_001901	1490	CTGF	intergenic
D470	6	132534976	132535671	695	-0.236	2.755	7	Intergenic	80205	NR_038981	100507254	LOC100507254	inter
D471	6	135308670	135308980	310	-0.237	2.404	6	exon (NM_006620, exon 9 of 18)	-8255	NR_037435	100500880	MIR3662	HBS1L
D472	6	149198979	149199494	515	0.209	4.052	48	intron (NM_005715, intron 1 of 7)	86584	NR_038408	100128176	LOC100128176	UST
D473	6	151711985	151712710	725	0.327	3.029	99	intron (NM_020861, intron 1 of 2)	330	NM_020861	57621	ZBTB2	ZBTB2
D474	6	152963082	152963562	480	-0.256	3.287	11	Intergenic	-4788	NM_182961	23345	SYNE1	SYNE1
D475	6	153322336	153322841	505	-0.258	3.58	10	intron (NM_001114184, intron 1 of 5)	1337	NM_019041	54516	MTRF1L	MTRF1L
D476	6	156952081	156952556	475	0.286	2.811	39	Intergenic	-146746	NM_017519	57492	ARID1B	intergenic
D477	6	165993899	165994477	578	-0.309	3.988	6	intron (NR_045597, intron 1 of 22)	81400	NM_001130690	10846	PDE10A	PDE10A
D478	6	167410746	167411121	375	-0.282	2.362	8	TTS (NR_037504)	467	NR_037504	100500857	MIR3939	FGFR1OP, MIR3939
D479	6	167835314	167835636	323	0.228	2.937	62	Intergenic	-37477	NM_004610	6953	TCPI0	intergenic
D480	6	170147361	170147861	500	-0.233	3.02	6	intron (NM_174910, intron 1 of 3)	4027	NM_174910	6991	TCTE3	TCTE3, C6orf70
D481	6	170474407	170474907	500	0.223	2.92	46	Intergenic	97000	NR_002787	154449	LOC154449	intergenic
D482	7	6691952	6692782	830	0.232	2.675	99	Intergenic	36840	NM_017560	54753	ZNF853	intergenic
D483	7	12412350	12413319	969	-0.237	4.086	8	exon (NM_001135924, exon 10 of 29)	31018	NM_001135924	221806	VWDE	VWDE
D484	7	25025686	25026014	328	-0.211	2.216	5	Intergenic	-6090	NM_145321	26031	OSBPL3	intergenic
D485	7	26431539	26431939	400	-0.23	3.431	9	Intergenic	-11369	NR_015364	441204	LOC441204	intergenic
D486	7	27327949	27328339	390	-0.256	2.34	6	Intergenic	45980	NM_001989	2128	EVX1	intergenic
D487	7	27361924	27362322	398	-0.228	2.484	6	Intergenic	79959	NM_001989	2128	EVX1	intergenic
D488	7	27422529	27422854	325	-0.24	3.047	9	Intergenic	140527	NM_001989	2128	EVX1	intergenic
D489	7	49813357	49813987	630	0.258	2.969	87	5' UTR (NM_198570, exon 1 of 4)	415	NM_198570	375567	VWC2	VWC2
D490	7	64595524	64596163	639	-0.286	4.106	6	Intergenic	97111	NR_033416	643180	CCT6P3	intergenic
D491	7	65106699	65107337	638	-0.282	3.608	5	Intergenic	-5759	NR_027392	644619	INTS4L2	LOC441242
D492	7	89883719	89884189	470	-0.242	2.49	10	intron (NM_001160138, intron 1 of 22)	9466	NM_001160138	79846	C7orf63	C7orf63
D493	7	98610088	98610721	633	0.257	3.113	26	3' UTR (NM_003496, exon 71 of 71)	131131	NR_037403	100500819	MIR3609	TRRAP
D494	7	99479857	99480547	690	-0.218	3.402	6	Intergenic	-5546	NM_001005276	81392	OR2AE1	intergenic
D495	7	100763435	100763805	370	0.347	2.117	13	Intergenic	-6750	NM_000602	5054	SERPINE1	intergenic
D496	7	107381088	107381488	400	-0.237	2.906	5	Intergenic	-2991	NM_024814	79872	CBLL1	CBLL1
D497	7	114203667	114204037	370	-0.222	3.026	5	intron (NR_033767, intron 4 of 17)	-89548	NR_037439	100500896	MIR3666	FOXP2
D498	7	114220756	114221156	400	-0.325	2.511	6	intron (NM_148898, intron 4 of 17)	-72444	NR_037439	100500896	MIR3666	FOXP2
D499	7	114507033	114507348	315	-0.21	2.774	12	Intergenic	-55019	NM_001166346	29969	MDFIC	intergenic
D500	7	114581249	114581644	395	-0.246	2.838	6	intron (NM_001166345, intron 2 of 4)	19237	NM_001166345	29969	MDFIC	MDFIC
D501	7	114688062	114688663	601	-0.251	3.329	6	Intergenic	126153	NM_001166345	29969	MDFIC	intergenic
D502	7	114876936	114877347	411	-0.25	3.001	5	Intergenic	314932	NM_001166345	29969	MDFIC	intergenic
D503	7	116089354	116090052	698	-0.238	3.621	6	Intergenic	-49952	NM_198212	858	CAV2	intergenic
D504	7	116243038	116243352	314	-0.23	2.215	9	Intergenic	-69264	NM_000245	4233	MET	intergenic
D505	7	117009622	117010247	625	-0.234	2.344	8	intron (NM_130768, intron 10 of 12)	-46591	NR_024047	7472	WNT2	ASZ1

D506	7	117141954	117142322	368	-0.226	3.16	7	intron (NM_000492, intron 1 of 26)	22121	NM_000492	1080	CFTR	CFTR
D507	7	117442255	117442624	369	-0.239	2.793	5	intron (NM_033427, intron 3 of 22)	71122	NM_033427	83992	CTTNBP2	CTTNBP2
D508	7	117627456	117628156	700	-0.264	3.482	7	Intergenic	-114245	NM_033427	83992	CTTNBP2	intergenic
D509	7	124535340	124535945	605	-0.245	2.79	6	intron (NR_003103, intron 5 of 17)	34395	NM_001042594	25913	POT1	POT1
D510	7	126078689	126079369	680	-0.247	3.246	8	non-coding (NR_028041, exon 11 of 11)	619209	NR_030323	693177	MIR592	GRM8
D511	7	126187791	126188156	365	-0.22	2.478	8	intron (NM_000845, intron 7 of 9)	510265	NR_030323	693177	MIR592	GRM8
D512	7	126427756	126428086	330	-0.212	2.997	5	intron (NM_000845, intron 5 of 9)	270317	NR_030323	693177	MIR592	GRM8
D513	7	127175557	127175872	315	-0.219	2.893	5	Intergenic	49940	NM_024523	79571	GCC1	intergenic
D514	7	128765686	128766176	490	0.342	2.656	7	promoter-TSS (NR_002144)	-394	NR_002144	407835	LOC407835	LOC407835
D515	7	129244625	129245100	475	-0.349	4.137	8	Intergenic	-6693	NM_005011	4899	NRF1	intergenic
D516	7	129981463	129981888	425	-0.237	3.403	11	Intergenic	-2955	NM_001127442	93979	CPA5	CPA5
D517	7	130132572	130133172	600	0.24	3.01	46	intron (NM_001253900, intron 1 of 11)	973	NM_001253900	4232	MEST	MEST, MESTT1, MIR335
D518	7	143699592	143699922	330	-0.255	3.49	6	Intergenic	-1333	NM_001005281	135946	OR6B1	OR6B1
D519	7	148844069	148844499	430	0.258	2.509	61	promoter-TSS (NM_170686)	-276	NM_170686	57541	ZNF398	ZNF398
D520	7	152590887	152591292	405	0.213	2.727	30	Intergenic	134255	NR_073000	57180	ACTR3B	intergenic
D521	7	154865062	154865452	390	0.205	2.345	10	intron (NM_024012, intron 1 of 1)	-1990	NR_038945	100128264	LOC100128264	HTR5A, LOC100128264
D522	8	1048469	1048974	505	0.239	2.642	58	Intergenic	202106	NR_033895	286083	LOC286083	intergenic
D523	8	1321117	1321602	485	0.245	2.765	54	Intergenic	-70532	NR_033895	286083	LOC286083	intergenic
D524	8	1818044	1818349	305	0.205	2.931	31	intron (NM_014629, intron 7 of 28)	46047	NM_014629	9639	ARHGEF10	ARHGEF10
D525	8	6291306	6291671	365	-0.223	2.155	9	intron (NM_001172574, intron 4 of 7)	27375	NM_024596	79648	MCPH1	MCPH1
D526	8	6795035	6795435	400	-0.233	3.225	12	intron (NM_001925, intron 1 of 2)	551	NM_001925	1669	DEFA4	DEFA4
D527	8	9950169	9950699	530	-0.243	3.742	6	intron (NM_012331, intron 1 of 5)	-2632	NM_001199729	4482	MSRA	MSRA
D528	8	11246567	11246932	365	-0.233	2.128	17	intron (NR_026814, intron 2 of 6)	20838	NR_026814	83656	C8orf12	C8orf12
D529	8	12597658	12598068	410	-0.23	2.841	7	intron (NM_152271, intron 3 of 11)	-13050	NR_037492	100500870	MIR3926-1	LONRF1
D530	8	14722653	14722978	325	-0.226	2.639	8	intron (NM_139167, intron 1 of 7)	-11796	NR_029875	494332	MIR383	SGCZ
D531	8	16051096	16051461	365	-0.238	4.191	13	promoter-TSS (NM_138716)	-978	NM_138715	4481	MSR1	MSR1
D532	8	17015551	17015938	387	-0.21	3.02	9	intron (NM_016353, intron 1 of 12)	1908	NM_016353	51201	ZDHHC2	ZDHHC2
D533	8	39437313	39437713	400	-0.221	3.013	8	non-coding (NR_046245, exon 5 of 5)	-4574	NM_001190956	8749	ADAM18	ADAM18, LOC100130964
D534	8	41653347	41653672	325	-0.215	2.922	9	intron (NM_001142446, intron 1 of 42)	1631	NM_020475	286	ANK1	ANK1
D535	8	59410332	59410822	490	-0.254	3.237	6	intron (NM_000780, intron 2 of 5)	2143	NM_000780	1581	CYP7A1	CYP7A1
D536	8	71317824	71318245	421	-0.223	2.573	10	Intergenic	-2014	NM_006540	10499	NCOA2	NCOA2
D537	8	72266841	72267221	380	-0.217	3.531	7	exon (NM_172058, exon 2 of 17)	1948	NM_172058	2138	EYA1	EYA1
D538	8	79421345	79421755	410	-0.269	3.874	5	Intergenic	-6786	NM_181839	5569	PKIA	intergenic
D539	8	87876176	87876576	400	-0.221	3.206	7	Intergenic	-2300	NM_173538	168975	CNBD1	CNBD1
D540	8	92076812	92077210	398	-0.221	3.39	8	Intergenic	-5413	NM_016023	51633	OTUD6B	intergenic
D541	8	92257633	92258048	415	-0.231	2.183	9	Intergenic	-3676	NM_134266	115111	SLC26A7	SLC26A7
D542	8	94713994	94714384	390	-0.215	2.555	6	intron (NM_145269, intron 2 of 7)	1416	NM_145269	137392	FAM92A1	LINC00535, FAM92A1
D543	8	98785186	98785516	330	0.239	2.584	20	Intergenic	-2458	NM_018407	55353	LAPTM4B	LAPTM4B
D544	8	104507492	104507797	305	-0.218	2.648	8	Intergenic	-5332	NM_001100117	9699	RIMS2	intergenic
D545	8	118836458	118836773	315	-0.211	2.757	8	intron (NM_000127, intron 4 of 10)	287443	NM_000127	2131	EXT1	EXT1
D546	8	119266746	119267071	325	-0.219	2.199	10	intron (NM_001101676, intron 4 of 4)	-142850	NM_000127	2131	EXT1	SAMD12
D547	8	124214717	124215383	666	-0.242	3.702	9	promoter-TSS (NR_024479)	-67	NR_024479	100131726	LOC100131726	FAM83A, LOC100131726
D548	8	133872708	133873238	530	-0.203	2.259	9	Intergenic	-6232	NM_003235	7038	TG	intergenic
D549	8	143625560	143626165	605	0.278	2.995	61	3' UTR (NM_001702, exon 30 of 30)	69971	NM_015193	23237	ARC	BAI1
D550	8	144631520	144631835	315	0.307	2.663	23	Intergenic	-3880	NM_001166237	79792	GSDMD	GSDMD
D551	8	145317415	145317886	471	0.225	3.656	34	TTS (NM_032450)	-3867	NM_001080514	642658	SCXB	HEATR7A, SCXB, SCXA
D552	8	145460790	145461156	366	0.219	2.555	29	Intergenic	23093	NM_016458	51236	FAM203A	intergenic
D553	9	4840010	4840420	410	-0.215	2.469	6	intron (NM_005772, intron 5 of 8)	-10082	NR_029836	406894	MIR101-2	RCL1
D554	9	15508453	15508773	320	-0.217	2.892	8	intron (NM_033222, intron 2 of 15)	1674	NM_021144	11168	PSIP1	PSIP1
D555	9	27102462	27102872	410	-0.288	3.339	7	Intergenic	-6480	NM_000459	7010	TEK	intergenic
D556	9	27521612	27521917	305	0.231	2.682	13	intron (NM_024761, intron 1 of 3)	-2548	NM_020124	56832	IFNK	IFNK, MOB3B

D557	9	41958910	41959510	600	-0.259	2.416	5	non-coding (NR_003670, exon 3 of 3)	-4134	NR_015363	389741	MGC21881	KGFLP2, MGC21881
D558	9	42023436	42023746	310	-0.211	2.638	6	Intergenic	-4007	NR_003670	654466	KGFLP2	KGFLP2
D559	9	42024036	42024551	515	-0.219	2.986	11	Intergenic	-4709	NR_003670	654466	KGFLP2	KGFLP2
D560	9	42473899	42474229	330	-0.235	3.386	11	non-coding (NR_026759, exon 5 of 5).2	5475	NR_026759	100133036	FAM95B1	FAM95B1
D561	9	42699546	42700404	858	-0.268	3.182	5	Intergenic	-17259	NM_001099279	100036519	FOXD4L2	intergenic
D562	9	43089861	43090216	355	-0.226	2.494	5	TTS (NM_001012421).2	43506	NM_001012419	441425	ANKRD20A3	ANKRD20A2, ANKRD20A3
D563	9	44983637	44984636	999	-0.29	3.595	6	Intergenic	-6100	NR_027421	100132948	FAM27C	intergenic
D564	9	46682564	46683424	860	-0.224	2.727	12	Intergenic	-4563	NR_003674	387628	KGFLP1	KGFLP1
D565	9	67799758	67800627	869	-0.287	3.555	5	Intergenic	-6003	NR_027422	100133121	FAM27B	intergenic
D566	9	69217378	69217723	345	-0.205	3.019	5	intron (NM_001085457, intron 11 of 14)	-15346	NM_001085476	653404	FOXD4L6	CBWD6
D567	9	69219107	69219825	718	-0.263	3.001	5	intron (NM_001085457, intron 10 of 14)	-17262	NM_001085476	653404	FOXD4L6	CBWD6
D568	9	69424001	69424356	355	-0.234	3.472	5	3' UTR (NM_001098805, exon 15 of 15)	42197	NM_001098805	728747	ANKRD20A4	ANKRD20A4
D569	9	69787085	69787405	320	0.215	2.39	94	Intergenic	135884	NR_024443	100133920	LOC100133920	intergenic
D570	9	70195445	70196545	1100	-0.249	3.006	5	Intergenic	-17180	NM_001126334	653427	FOXD4L5	intergenic
D571	9	70446362	70447464	1102	-0.272	3.701	5	intron (NM_001024916, intron 8 of 12)	-17182	NM_001099279	100036519	FOXD4L2	CBWD3, CBWD5
D572	9	70883054	70883725	671	-0.338	4.185	5	intron (NM_201453, intron 8 of 14).2	26550	NM_201453	445571	CBWD3	CBWD3
D573	9	70899486	70899970	484	-0.237	2.684	7	intron (NM_201453, intron 10 of 14).2	-18055	NM_199135	286380	FOXD4L3	CBWD3
D574	9	71392971	71393386	415	-0.232	2.864	6	intron (NM_003558, intron 2 of 15)	-1786	NM_138333	116224	FAM122A	FAM122A, PIP5K1B
D575	9	82180820	82181195	375	-0.244	2.339	7	Intergenic	-5871	NM_007005	7091	TLE4	intergenic
D576	9	85953365	85953859	494	-0.289	3.342	6	intron (NM_174938, intron 5 of 13)	-6736	NM_001244961	257019	FRMD3	FRMD3
D577	9	94710496	94710871	375	0.221	4.192	23	intron (NM_004560, intron 1 of 8)	1761	NM_004560	4920	ROR2	ROR2
D578	9	94716003	94716619	616	-0.263	3.475	10	Intergenic	-3867	NM_004560	4920	ROR2	ROR2
D579	9	107378101	107378506	405	-0.21	3.152	5	Intergenic	2182	NM_001001956	286362	OR13C9	OR13C9
D580	9	113317535	113318035	500	-0.22	2.925	7	intron (NM_153366, intron 1 of 47)	24375	NM_153366	79987	SVEP1	SVEP1
D581	9	114373142	114373467	325	-0.228	2.003	9	intron (NR_034087, intron 1 of 2)	2529	NR_034087	652972	LRRC37A5P	LRRC37A5P
D582	9	114416816	114417321	505	-0.224	3.141	11	TTS (NR_037148)	-6783	NM_001198664	2790	GNG10	DNAJC25-GNG10, DNAJC25
D583	9	115824896	115825832	936	0.247	2.805	40	Intergenic	-6368	NM_003408	7539	ZFP37	intergenic
D584	9	124988166	124988561	395	0.217	2.634	66	intron (NM_014368, intron 4 of 9)	1502	NM_001242334	26468	LHX6	LHX6
D585	9	130980777	130981292	515	0.254	3.833	44	intron (NM_001005336, intron 3 of 21)	-14372	NM_001131015	25792	CIZ1	DNM1
D586	9	131901819	131902289	470	0.248	3.064	18	intron (NM_178000, intron 8 of 9)	28087	NM_001193397	5524	PPP2R4	PPP2R4
D587	9	132138020	132138420	400	-0.257	3.575	7	Intergenic	54925	NM_001012715	414318	C9orf106	intergenic
D588	9	139690341	139690911	570	0.299	2.646	11	promoter-TSS (NM_001039374)	-164	NM_001039374	84960	KIAA1984	KIAA1984, TMEM141
D589	9	140375158	140375528	370	0.226	2.263	30	intron (NM_152286, intron 21 of 33)	-21557	NM_001130969	26012	NELF	PNPLA7

Table E4. Primers used for bisulfite sequencing.

Amplicon coordinates (hg19)	Length (bp)	No. CpGs	Closest gene	Primers 5'-3'		Extension Temp. (C)
chr2:50,201,165-5,02,01,630	466	16	NRNX1	Forward	GAGTTTTTTTTTTAATTTTTAATGG	50
				Reverse	ATTTCCCCTCTATATTTAAC	
chr10:131,696,855-13,16,97,384	530	30	EBF3	Forward	AAATTGATTTTGGTAAAGTAG	50
				Reverse	AACACTCTACTAATAACAAC	
chr19:805,877-8,06,280	404	45	PTBP1	Forward	TTTAGTAGTTGAATTTGAGTGGT	50
				Reverse	CTACCCTAAATACCTATAAAA	
chr16:90,148,245-9,01,48,740	496	29	PRDM7	Forward	GTGAGTTAAGGTTATGTTATTGTT	53
				Reverse	AAAACTTTTTCCTCATCTTC	
chr21:43,236,140-4,32,36,400	261	16	PRDM15	Forward	GATGTTTTTGTGTAGTTTTATG	50
				Reverse	ATATTACAATCAATCCCTCC	
chr1:205,819,150-20,58,19,562	413	16	PM20D1	Forward	TAGGAGTAGTATAGTTATTAGGGTT	50
				Reverse	ATTTTACTTTTCCTCCTTTA	
chr7:114,220,317-11,42,20,913	597	10	FOXP2	Forward	TAGGAGAAGGAAATAAGATA	50
				Reverse	ACTCAACTACTAECTACCTAC	
chr6:165,994,226-16,59,94,582	357	5	PDE10A	Forward	GAAGATAAAGAAGATAGTAAG	50
				Reverse	TCTCCATAATATCACCATAA	
chr4:100,360,216-10,03,60,593	378	4	ADH7	Forward	GTTTTGGGAGGTGTTTAGTATTTTAT	53
				Reverse	ATTTCTCATATTTCTACTTCC	
chr22:22,342,517-2,23,42,893	377	5	TOP3B	Forward	GGTTTTATGTTTGTAGTGATTAAG	50
				Reverse	ATTACCTACTATTACCCTAT	
chr17:5,019,708-50,20,144	437	22	USP6	Forward	GGGGAATATTTTTGGTTTATGT	57
				Reverse	CACTTACCATCAATTTTCTCTT	
chrX:139,591,526-13,95,91,985	460	14	SOX3	Forward	TTGGTTTTTAGTTAAGATTGTGT	53
				Reverse	ACTTTTTTAAAAATACCCCC	
chrX:70,752,148-7,07,52,507	360	15	OGT	Forward	GTTGGTGGAAATGAAGTTATAATT	53
				Reverse	CAATCAATTCAAAAAATTACCTCTC	
chrX:153,363,724-15,33,63,953	230	6	MECP2	Forward	GGGTTTTGGTTTTAGAGGTTTATTTA	59
				Reverse	TCTTCCAACAAAATAACATTACC	
chrX:43,514,821-4,35,15,213	393	12	MAOA	Forward	TTTTTTGGGTATTAGTAATAGG	50
				Reverse	RCCTACCTAACACTAAAAA	
chrX:75,392,703-7,53,93,068	366	19	CXORF26	Forward	GAAGATAAGAAAGGGTATTATT	53
				Reverse	AAAAAAAAAAAAAACTCCACC	
chr15:67,356,796-6,73,57,298	503	15	SMAD3	Forward	GTAAAAATAAATAAAGGGTTTAG	54
				Reverse	ACTAAAAACACCAATAACAACCT	

Table E5: Functional annotation of asthma-associated DMRs in IIS children.

* Overrepresentation of biological functions was evaluated using Fisher's Exact Test as implemented in Ingenuity Pathway Analysis.

Category	Function	P Value*	Molecules	# Molecules
Cell Death and Survival	apoptosis	1.54E-07	AKAP1, AKT3, ATR, BACH1, BDNF, CDC42EP3, CFTR, CYP7A1, DNMI, DNM2, DUSP6, DYNLL1, EP400, EYA1, FASN, FGFR3, GF11, GNAS, IFNK, LAMA5, LDHA, MSR1, NCOA2, NEUROD1, NFATC1, POT1, PRDM16, PRKCZ, RELB, RUNX1, SMAD3, SNCA, STK11, TMBIM4, UBD, XRCC4	36
Cell Morphology	innervation of outer hair cells	1.80E-07	BDNF, FGFR3, GABRA5, GF11	4
Cellular Movement	innervation of outer hair cells	1.80E-07	BDNF, FGFR3, GABRA5, GF11	4
Nervous System Development and Function	innervation of outer hair cells	1.80E-07	BDNF, FGFR3, GABRA5, GF11	4
Cell Death and Survival	necrosis	1.75E-06	AKAP1, AKT3, ATR, BACH1, BDNF, CDC42EP3, CYP7A1, DNMI, DNM2, DUSP6, DYNLL1, EP400, FASN, FGFR3, GABRA5, GF11, GNAS, LAMA5, LDHA, MSR1, NEUROD1, NFATC1, POT1, PRKCZ, RELB, RUNX1, SMAD3, SNCA, STK11, STK25, TMBIM4, UBD, XRCC4	33
Cell Death and Survival	cell death	1.79E-06	AKAP1, AKT3, ATR, BACH1, BDNF, CALM1 (includes others), CDC42EP3, CFTR, CYP7A1, DNMI, DNM2, DUSP6, DYNLL1, EP400, EYA1, FASN, FGFR3, GABRA5, GF11, GNAS, IFNK, LAMA5, LDHA, MSR1, NCOA2, NEUROD1, NFATC1, POT1, PRDM16, PRKCZ, RELB, RUNX1, SMAD3, SNCA, STK11, STK25, TMBIM4, UBD, XRCC4	39
Organismal Survival	organismal death	3.55E-06	ABCC9, AKT3, ATR, BDNF, CFL1, CFTR, COL10A1, CXCL10, FASN, FGFR3, GABRA1, GF11, GNAS, KCNAB1, MSR1, NFATC1, RELB, RUNX1, SMAD3, SNCA, STK11, SULF2, TRRAP, UBD, XRCC4	25
Developmental Disorder	congenital anomaly of musculoskeletal system	4.25E-06	ABCC9, ACAN, COL10A1, DNM2, EYA1, FGFR3, GABRA1, GABRA5, GNAS, PCNT, SMAD3, STK25, SYNE1	13
Skeletal and Muscular Disorders	congenital anomaly of musculoskeletal system	4.25E-06	ABCC9, ACAN, COL10A1, DNM2, EYA1, FGFR3, GABRA1, GABRA5, GNAS, PCNT, SMAD3, STK25, SYNE1	13
Developmental Disorder	congenital anomaly of skeletal bone	7.18E-06	ABCC9, ACAN, COL10A1, EYA1, FGFR3, GABRA1, GABRA5, GNAS, PCNT, SMAD3	10
Skeletal and Muscular Disorders	congenital anomaly of skeletal bone	7.18E-06	ABCC9, ACAN, COL10A1, EYA1, FGFR3, GABRA1, GABRA5, GNAS, PCNT, SMAD3	10
Connective Tissue Disorders	congenital anomaly of skeletal bone	7.18E-06	ABCC9, ACAN, COL10A1, EYA1, FGFR3, GABRA1, GABRA5, GNAS, PCNT, SMAD3	10
Cell-To-Cell Signaling and Interaction	activation of cells	7.27E-06	BDNF, CFL1, CXCL10, DDOST, FGFR3, GABRA1, GF11, GNAS, IFNK, MSR1, PRKCZ, RELB, RORA, RUNX1, SMAD3, SNCA, STK11, XRCC4	18
Cellular Growth and Proliferation	proliferation of cells	1.03E-05	ABCC9, AKT3, ATR, BDNF, CALM1 (includes others), CFPD1, CFL1, CXCL10, DNM2, DUSP6, EP400, EYA1, FASN, FGFR3, GF11, GNAS, IFNK, LAMA5, LDHA, MSR1, NCOA2, NEUROD1, NFATC1, PALM, PFKP, POT1, PRDM16, PRKCZ, RELB, RORA, RTKN2, RUNX1, SMAD3, SNCA, STK11, SULF2, TNIK, TRRAP, XRCC4	39
Cellular Assembly and Organization	organization of cytoskeleton	1.12E-05	BDNF, CFL1, DNMI, DNM2, DYNLL1, EYA1, GNAS, GRK4, LAMA5, NEUROD1, PACSIN1, PALM, PCNT, PRKCZ, RELB, SNCA, STK11, SULF2, SYNE1, TNIK	20
Cellular Function and Maintenance	organization of cytoskeleton	1.12E-05	BDNF, CFL1, DNMI, DNM2, DYNLL1, EYA1, GNAS, GRK4, LAMA5, NEUROD1, PACSIN1, PALM, PCNT, PRKCZ, RELB, SNCA, STK11, SULF2, SYNE1, TNIK	20
Developmental Disorder	skeletal dysplasia	1.19E-05	ABCC9, ACAN, COL10A1, FGFR3, GNAS, PCNT	6
Skeletal and Muscular Disorders	skeletal dysplasia	1.19E-05	ABCC9, ACAN, COL10A1, FGFR3, GNAS, PCNT	6
Connective Tissue Disorders	skeletal dysplasia	1.19E-05	ABCC9, ACAN, COL10A1, FGFR3, GNAS, PCNT	6
Cell Signaling	synthesis of nitric oxide	1.26E-05	BDNF, CALM1 (includes others), CFTR, DNM2, DYNLL1, FASN, IFNK, RORA, SNCA	9
Small Molecule Biochemistry	synthesis of nitric oxide	1.26E-05	BDNF, CALM1 (includes others), CFTR, DNM2, DYNLL1, FASN, IFNK, RORA, SNCA	9
Developmental Disorder	hypoplasia of thymus gland	1.33E-05	COL10A1, GF11, RELB, RUNX1, SMAD3, XRCC4	6
Immunological Disease	hypoplasia of thymus gland	1.33E-05	COL10A1, GF11, RELB, RUNX1, SMAD3, XRCC4	6
Cellular Assembly and Organization	organization of cytoplasm	1.43E-05	BDNF, CFL1, DNMI, DNM2, DYNLL1, EYA1, GNAS, GRK4, LAMA5, NEUROD1, PACSIN1, PALM, PCNT, PRKCZ, RELB, SNCA, STK11, STK25, SULF2, SYNE1, TNIK	21
Cellular Function and Maintenance	organization of cytoplasm	1.43E-05	BDNF, CFL1, DNMI, DNM2, DYNLL1, EYA1, GNAS, GRK4, LAMA5, NEUROD1, PACSIN1, PALM, PCNT, PRKCZ, RELB, SNCA, STK11, STK25, SULF2, SYNE1, TNIK	21
Cellular Assembly and Organization	microtubule dynamics	1.82E-05	BDNF, CFL1, DNMI, DNM2, EYA1, GNAS, GRK4, LAMA5, NEUROD1, PACSIN1, PALM, PCNT, PRKCZ, RELB, SNCA, STK11, SULF2, SYNE1	18
Cellular Function and Maintenance	microtubule dynamics	1.82E-05	BDNF, CFL1, DNMI, DNM2, EYA1, GNAS, GRK4, LAMA5, NEUROD1, PACSIN1, PALM, PCNT, PRKCZ, RELB, SNCA, STK11, SULF2, SYNE1	18
Embryonic Development	size of embryonic tissue	2.31E-05	EYA1, FGFR3, LAMA5, NFATC1, STK11	5
Tissue Morphology	size of embryonic tissue	2.31E-05	EYA1, FGFR3, LAMA5, NFATC1, STK11	5
Developmental Disorder	Seckel syndrome 4	2.43E-05	ATR, PCNT	2
Hereditary Disorder	Seckel syndrome 4	2.43E-05	ATR, PCNT	2
Nervous System Development and Function	quantity of sensory neurons	2.48E-05	BDNF, EYA1, FGFR3, GF11, NEUROD1	5
Tissue Morphology	quantity of sensory neurons	2.48E-05	BDNF, EYA1, FGFR3, GF11, NEUROD1	5

Cellular Function and Maintenance	cellular homeostasis	3.07E-05	AKT3, CFTR, CXCL10, GABRA1, GABRA5, GF11, GNAS, IFNK, MSR1, NEUROD1, NFATC1, PRKCZ, RELB, RORA, RUNX1, SIK3, SMAD3, SNCA, STK11, UBD, XRCC4	21
Cellular Development	differentiation of cells	3.15E-05	BDNF, CFL1, CXCL10, EYA1, FGFR3, GF11, GNAS, IFNK, NEUROD1, NFATC1, PACSIN1, PRDM16, PRKCZ, RELB, RORA, RTKN2, RUNX1, SCGB3A2, SIX2, SMAD3, SNCA, STK11, SYNE1, TTC3, UBD, XRCC4	26
Cancer	carcinoma	3.15E-05	ADH1B, AKAP1, AKT3, CALM1 (includes others), CFTR, CXCL10, DUSP6, DYNLL1, EP400, EYA1, FASN, FGFR3, FH, FRMD3, GNAS, GSPT1, LAMA5, LDHA, MSR1, NFATC1, PFKP, POLE2, PRKCZ, RELB, RUNX1, SHANK2, SMAD3, STK11, SYNE1, TMBIM4, TNIK, TRRAP, TTC3	33
Tissue Morphology	neurodegeneration of nervous tissue	3.47E-05	BDNF, EYA1, GABRA5, GF11, SNCA	5
Neurological Disease	neurodegeneration of nervous tissue	3.47E-05	BDNF, EYA1, GABRA5, GF11, SNCA	5
Cancer	epithelial neoplasia	3.72E-05	ADH1B, AKAP1, AKT3, BDNF, CALM1 (includes others), CFTR, CXCL10, DUSP6, DYNLL1, EP400, EYA1, FASN, FGFR3, FH, FRMD3, GNAS, GSPT1, LAMA5, LDHA, MSR1, NFATC1, PFKP, POLE2, PRKCZ, RELB, RUNX1, SHANK2, SMAD3, STK11, SYNE1, TMBIM4, TNIK, TRRAP, TTC3	34
Cellular Growth and Proliferation	generation of cells	3.86E-05	BDNF, CXCL10, DYNLL1, EP400, NEUROD1, RORA, SMAD3, STK11	8
Tissue Development	generation of cells	3.86E-05	BDNF, CXCL10, DYNLL1, EP400, NEUROD1, RORA, SMAD3, STK11	8
Cell Death and Survival	cell viability	4.27E-05	ATR, BDNF, CXCL10, DNM1, DNM2, DUSP6, FGFR3, FH, GRK4, LAMA5, MSR1, NEUROD1, PRKCZ, RELB, RUNX1, SMAD3, SNCA, STK11, XRCC4	19
Developmental Disorder	kyphoscoliosis	5.12E-05	FGFR3, SMAD3, SYNE1	3
Skeletal and Muscular Disorders	kyphoscoliosis	5.12E-05	FGFR3, SMAD3, SYNE1	3
Nervous System Development and Function	differentiation of neurons	5.41E-05	BDNF, CFL1, EYA1, FGFR3, GF11, NEUROD1, PACSIN1, RUNX1, SNCA, TTC3	10
Cellular Development	differentiation of neurons	5.41E-05	BDNF, CFL1, EYA1, FGFR3, GF11, NEUROD1, PACSIN1, RUNX1, SNCA, TTC3	10
Cell Morphology	formation of cellular protrusions	6.21E-05	BDNF, CFL1, DNM1, DNM2, LAMA5, NEUROD1, PACSIN1, PALM, PCNT, RELB, SNCA, STK11, SULF2, SYNE1	14
Cellular Assembly and Organization	formation of cellular protrusions	6.21E-05	BDNF, CFL1, DNM1, DNM2, LAMA5, NEUROD1, PACSIN1, PALM, PCNT, RELB, SNCA, STK11, SULF2, SYNE1	14
Cellular Function and Maintenance	formation of cellular protrusions	6.21E-05	BDNF, CFL1, DNM1, DNM2, LAMA5, NEUROD1, PACSIN1, PALM, PCNT, RELB, SNCA, STK11, SULF2, SYNE1	14
Cell Morphology	morphology of cells	6.45E-05	BDNF, CFTR, COL10A1, CXCL10, DNM1, DNM2, EP400, FASN, FGFR3, GF11, MSR1, NCOA2, NEUROD1, PRKCZ, RELB, RORA, SIK3, SMAD3, SNCA, STK11, SULF2	21
Post-Translational Modification	phosphorylation of protein	7.05E-05	AKT3, ATR, CALM1 (includes others), CFL1, DUSP6, DYNLL1, FGFR3, GRK4, PRKCZ, SIK3, SNCA, STK11, STK25, TNIK	14
Cell Morphology	abnormal morphology of vestibular hair cells	7.26E-05	BDNF, GF11	2
Nervous System Development and Function	abnormal morphology of vestibular hair cells	7.26E-05	BDNF, GF11	2
Tissue Morphology	abnormal morphology of vestibular hair cells	7.26E-05	BDNF, GF11	2
Nervous System Development and Function	activation of hippocampus	7.26E-05	BDNF, NEUROD1	2
Cellular Movement	infiltration by myofibroblasts	7.26E-05	CXCL10, SMAD3	2
Embryonic Development	development of ear	7.33E-05	BDNF, EYA1, FGFR3, GF11, NEUROD1, SIX2	6
Tissue Development	development of ear	7.33E-05	BDNF, EYA1, FGFR3, GF11, NEUROD1, SIX2	6
Auditory and Vestibular System Development and Function	development of ear	7.33E-05	BDNF, EYA1, FGFR3, GF11, NEUROD1, SIX2	6
Organ Development	development of ear	7.33E-05	BDNF, EYA1, FGFR3, GF11, NEUROD1, SIX2	6
Organismal Development	development of ear	7.33E-05	BDNF, EYA1, FGFR3, GF11, NEUROD1, SIX2	6
Developmental Disorder	hypoplasia of organ	7.68E-05	COL10A1, EYA1, GF11, NCOA2, RELB, RUNX1, SIX2, SMAD3, XRCC4	9
Cell Death and Survival	apoptosis of tumor cell lines	8.66E-05	AKAP1, AKT3, BDNF, DNM1, DNM2, DYNLL1, FASN, FGFR3, GF11, GNAS, LAMA5, MSR1, POT1, PRKCZ, RUNX1, SMAD3, SNCA, TMBIM4	18
Neurological Disease	hearing loss	8.88E-05	BDNF, EYA1, FGFR3, GABRA5, GF11, NEUROD1	6
Auditory Disease	hearing loss	8.88E-05	BDNF, EYA1, FGFR3, GABRA5, GF11, NEUROD1	6

Cancer	Cancer	1.01E-04	ACAN, ADH1B, AKAP1, AKT3, BDNF, CALM1 (includes others), CFTR, CXCL10, DUSP6, DYNLL1, EP400, EYA1, FASN, FGFR3, FH, FRMD3, GF11, GNAS, GSPT1, LAMA5, LDHA, MSR1, NEUROD1, NFATC1, PFKP, POLE2, POT1, PRDM16, PRKCZ, RELB, RUNX1, SHANK2, SMAD3, STK11, STK25, SYNE1, TMBIM4, TNK1, TRRAP, TTC3, XRCC4	41
Cellular Function and Maintenance	T cell development	1.07E-04	GF11, IFNK, MSR1, NFATC1, PRKCZ, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	11
Cellular Development	T cell development	1.07E-04	GF11, IFNK, MSR1, NFATC1, PRKCZ, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	11
Cell-mediated Immune Response	T cell development	1.07E-04	GF11, IFNK, MSR1, NFATC1, PRKCZ, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	11
Hematological System Development and Function	T cell development	1.07E-04	GF11, IFNK, MSR1, NFATC1, PRKCZ, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	11
Hematopoiesis	T cell development	1.07E-04	GF11, IFNK, MSR1, NFATC1, PRKCZ, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	11
Lymphoid Tissue Structure and Development	T cell development	1.07E-04	GF11, IFNK, MSR1, NFATC1, PRKCZ, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	11
Cell Death and Survival	cell death of tumor cell lines	1.13E-04	AKAP1, AKT3, ATR, BDNF, DNM1, DNM2, DYNLL1, FASN, FGFR3, GF11, GNAS, LAMA5, MSR1, POT1, PRKCZ, RELB, RUNX1, SMAD3, SNCA, TMBIM4	20
Small Molecule Biochemistry	uptake of lipid	1.15E-04	BDNF, CFTR, CYP7A1, MSR1, NCOA2, PRKCZ	6
Lipid Metabolism	uptake of lipid	1.15E-04	BDNF, CFTR, CYP7A1, MSR1, NCOA2, PRKCZ	6
Molecular Transport	uptake of lipid	1.15E-04	BDNF, CFTR, CYP7A1, MSR1, NCOA2, PRKCZ	6
Digestive System Development and Function	development of digestive system	1.20E-04	BDNF, COL10A1, EYA1, FGFR3, LAMA5, NEUROD1, RELB, RUNX1, SMAD3	9
Tissue Morphology	quantity of chondrocytes	1.26E-04	FGFR3, SIK3, SMAD3	3
Connective Tissue Development and Function	quantity of chondrocytes	1.26E-04	FGFR3, SIK3, SMAD3	3
Developmental Disorder	chondrodysplasia	1.26E-04	ABCC9, ACAN, COL10A1, PCNT	4
Skeletal and Muscular Disorders	chondrodysplasia	1.26E-04	ABCC9, ACAN, COL10A1, PCNT	4
Connective Tissue Disorders	chondrodysplasia	1.26E-04	ABCC9, ACAN, COL10A1, PCNT	4
Hereditary Disorder	chondrodysplasia	1.26E-04	ABCC9, ACAN, COL10A1, PCNT	4
Cell Cycle	M phase	1.39E-04	ATR, CALM1 (includes others), CFL1, DNMI, MPHOSPH6, STK11, TRRAP	7
Dermatological Diseases and Conditions	acanthosis nigricans	1.45E-04	BDNF, FGFR3	2
Cellular Function and Maintenance	endocytosis by fibroblasts	1.45E-04	DNM1, DNM2	2
Cellular Function and Maintenance	differentiation of T lymphocytes	1.48E-04	GF11, IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	9
Cellular Development	differentiation of T lymphocytes	1.48E-04	GF11, IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	9
Cell-mediated Immune Response	differentiation of T lymphocytes	1.48E-04	GF11, IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	9
Hematological System Development and Function	differentiation of T lymphocytes	1.48E-04	GF11, IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	9
Hematopoiesis	differentiation of T lymphocytes	1.48E-04	GF11, IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	9
Lymphoid Tissue Structure and Development	differentiation of T lymphocytes	1.48E-04	GF11, IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3, STK11, XRCC4	9
Embryonic Development	development of inner ear	1.65E-04	BDNF, EYA1, FGFR3, GF11, NEUROD1	5
Tissue Development	development of inner ear	1.65E-04	BDNF, EYA1, FGFR3, GF11, NEUROD1	5
Auditory and Vestibular System Development and Function	development of inner ear	1.65E-04	BDNF, EYA1, FGFR3, GF11, NEUROD1	5
Organ Development	development of inner ear	1.65E-04	BDNF, EYA1, FGFR3, GF11, NEUROD1	5
Organismal Development	development of inner ear	1.65E-04	BDNF, EYA1, FGFR3, GF11, NEUROD1	5
Gene Expression	transactivation	1.78E-04	BDNF, DNM1, GF11, NCOA2, NEUROD1, NFATC1, PRKCZ, RELB, RORA, RUNX1, SMAD3, TRRAP	12
Small Molecule Biochemistry	concentration of lipid	1.79E-04	AKT3, BDNF, CFTR, CYP7A1, DNM2, FASN, GNAS, KCNA6, MSR1, RORA, RUNX1, SIK3, SMAD3, SNCA	14
Lipid Metabolism	concentration of lipid	1.79E-04	AKT3, BDNF, CFTR, CYP7A1, DNM2, FASN, GNAS, KCNA6, MSR1, RORA, RUNX1, SIK3, SMAD3, SNCA	14
Molecular Transport	concentration of lipid	1.79E-04	AKT3, BDNF, CFTR, CYP7A1, DNM2, FASN, GNAS, KCNA6, MSR1, RORA, RUNX1, SIK3, SMAD3, SNCA	14
Organismal Development	size of body	1.80E-04	AKT3, BDNF, CFTR, COL10A1, FGFR3, GABRA1, GF11, NCOA2, NEUROD1, RUNX1, SIK3, SMAD3, SNCA, SULF2, SYNE1	15
Cancer	testicular cancer	2.36E-04	FGFR3, GNAS, LDHA, STK11	4

Category	Phenotype	P-value	Genes	Count
Endocrine System Disorders	testicular cancer	2.36E-04	FGFR3, GNAS, LDHA, STK11	4
Reproductive System Disease	testicular cancer	2.36E-04	FGFR3, GNAS, LDHA, STK11	4
Neurological Disease	tonic-clonic seizure	2.36E-04	AKT3, GABRA1, GABRA5, NEUROD1	4
Cell-To-Cell Signaling and Interaction	delamination of cells	2.41E-04	CFL1, NEUROD1	2
Cellular Function and Maintenance	differentiation of helper T lymphocytes	2.45E-04	IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3	6
Cellular Development	differentiation of helper T lymphocytes	2.45E-04	IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3	6
Cell-mediated Immune Response	differentiation of helper T lymphocytes	2.45E-04	IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3	6
Hematological System Development and Function	differentiation of helper T lymphocytes	2.45E-04	IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3	6
Hematopoiesis	differentiation of helper T lymphocytes	2.45E-04	IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3	6
Lymphoid Tissue Structure and Development	differentiation of helper T lymphocytes	2.45E-04	IFNK, NFATC1, RELB, RORA, RUNX1, SMAD3	6
Organismal Development	abnormal morphology of distended abdomen	2.50E-04	CFTR, RELB, STK11	3
Behavior	behavior	2.50E-04	BDNF, CFTR, CYP7A1, DNMI, GABRA1, GABRA5, GFI1, KCNAB1, NCOA2, NEUROD1, PRKCZ, SHANK2, SIK3, SNCA, SYNE1	15
Molecular Transport	transport of molecule	2.51E-04	ABCC9, AKT3, BDNF, CFL1, CFTR, CYP7A1, FH, GABRA1, GABRA5, KCNA6, KCNAB1, MSR1, NEUROD1, NFATC1, PRKCZ, SIX2, SMAD3, STK11	18
Developmental Disorder	dwarfism	2.54E-04	ABCC9, ACAN, COL10A1, FGFR3, PCNT	5
Hereditary Disorder	dwarfism	2.54E-04	ABCC9, ACAN, COL10A1, FGFR3, PCNT	5
Nervous System Development and Function	development of neurons	2.76E-04	BDNF, FGFR3, GABRA5, GFI1, NEUROD1, RUNX1	6
Cellular Development	development of neurons	2.76E-04	BDNF, FGFR3, GABRA5, GFI1, NEUROD1, RUNX1	6
Tissue Development	development of neurons	2.76E-04	BDNF, FGFR3, GABRA5, GFI1, NEUROD1, RUNX1	6
Cellular Growth and Proliferation	proliferation of epithelial cells	2.78E-04	EYA1, FGFR3, LAMA5, NCOA2, NEUROD1, NFATC1, RELB, RUNX1, SMAD3	9
Cell Morphology	abnormal morphology of hair cells	2.81E-04	BDNF, FGFR3, GFI1	3
Nervous System Development and Function	abnormal morphology of hair cells	2.81E-04	BDNF, FGFR3, GFI1	3
Tissue Morphology	abnormal morphology of hair cells	2.81E-04	BDNF, FGFR3, GFI1	3
Nervous System Development and Function	synaptic transmission of hippocampal cells	2.81E-04	BDNF, PRKCZ, SNCA	3
Cell-To-Cell Signaling and Interaction	synaptic transmission of hippocampal cells	2.81E-04	BDNF, PRKCZ, SNCA	3
Cellular Development	differentiation of central nervous system cells	2.98E-04	BDNF, FGFR3, NEUROD1, PACSIN1, RUNX1	5
Developmental Disorder	Hypoplasia	3.04E-04	COL10A1, EYA1, FGFR3, GFI1, NCOA2, RELB, RUNX1, SIX2, SMAD3, XRCC4	10
Cardiovascular Disease	valvular regurgitation	3.15E-04	GABRA1, GABRA5, NFATC1	3
Lymphoid Tissue Structure and Development	morphology of lymphoid organ	3.24E-04	AKT3, COL10A1, EYA1, GFI1, MSR1, RELB, RUNX1, SMAD3, STK11	9
Organ Morphology	morphology of lymphoid organ	3.24E-04	AKT3, COL10A1, EYA1, GFI1, MSR1, RELB, RUNX1, SMAD3, STK11	9
Lymphoid Tissue Structure and Development	morphology of lymphatic system component	3.37E-04	AKT3, COL10A1, EP400, EYA1, GFI1, MSR1, RELB, RUNX1, SMAD3, STK11	10
Cellular Development	development of blood cells	3.41E-04	GFI1, IFNK, MSR1, NFATC1, PRKCZ, RELB, RORA, RTKN2, RUNX1, SMAD3, STK11, XRCC4	12
Hematological System Development and Function	development of blood cells	3.41E-04	GFI1, IFNK, MSR1, NFATC1, PRKCZ, RELB, RORA, RTKN2, RUNX1, SMAD3, STK11, XRCC4	12
Hematopoiesis	development of blood cells	3.41E-04	GFI1, IFNK, MSR1, NFATC1, PRKCZ, RELB, RORA, RTKN2, RUNX1, SMAD3, STK11, XRCC4	12

Cancer	digestive organ tumor	3.50E-04	ADH1B, AKAP1, CFTR, CXCL10, DUSP6, DYNLL1, FASN, FGFR3, FRMD3, GNAS, LDHA, POLE2, PRDM16, PRKCZ, RELB, RUNX1, SMAD3, STK11, SYNE1, TMBIM4, TNIK, TTC3	22
Gastrointestinal Disease	digestive organ tumor	3.50E-04	ADH1B, AKAP1, CFTR, CXCL10, DUSP6, DYNLL1, FASN, FGFR3, FRMD3, GNAS, LDHA, POLE2, PRDM16, PRKCZ, RELB, RUNX1, SMAD3, STK11, SYNE1, TMBIM4, TNIK, TTC3	22
Tissue Morphology	degeneration of spiral ganglion	3.52E-04	EYA1, GABRA5, GFI1	3
Neurological Disease	degeneration of spiral ganglion	3.52E-04	EYA1, GABRA5, GFI1	3
Cell Morphology	shape change of epithelial cell lines	3.52E-04	CFTR, MSR1, TNIK	3
Tissue Morphology	abnormal morphology of cartilage tissue	3.58E-04	COL10A1, EYA1, SIK3, SMAD3	4
Connective Tissue Development and Function	abnormal morphology of cartilage tissue	3.58E-04	COL10A1, EYA1, SIK3, SMAD3	4
Skeletal and Muscular System Development and Function	abnormal morphology of cartilage tissue	3.58E-04	COL10A1, EYA1, SIK3, SMAD3	4
Cell Death and Survival	degeneration of cholinergic neurons	3.60E-04	BDNF, SNCA	2
Cellular Compromise	degeneration of cholinergic neurons	3.60E-04	BDNF, SNCA	2
Cell Cycle	mitogenesis of kidney cells	3.60E-04	CXCL10, GRK4	2
Cellular Growth and Proliferation	proliferation of tumor cell lines	3.76E-04	AKT3, ATR, BDNF, FASN, FGFR3, GFI1, GNAS, LAMA5, LDHA, PFKP, PRDM16, PRKCZ, RELB, RORA, RUNX1, SMAD3, STK11, TNIK, TRRAP	19
Cellular Development	proliferation of tumor cell lines	3.76E-04	AKT3, ATR, BDNF, FASN, FGFR3, GFI1, GNAS, LAMA5, LDHA, PFKP, PRDM16, PRKCZ, RELB, RORA, RUNX1, SMAD3, STK11, TNIK, TRRAP	19
Cell Morphology	abnormal morphology of neurons	3.79E-04	BDNF, DNM1, FGFR3, GFI1, NEUROD1, SNCA, SULF2	7
Nervous System Development and Function	abnormal morphology of neurons	3.79E-04	BDNF, DNM1, FGFR3, GFI1, NEUROD1, SNCA, SULF2	7
Tissue Morphology	abnormal morphology of neurons	3.79E-04	BDNF, DNM1, FGFR3, GFI1, NEUROD1, SNCA, SULF2	7
Auditory and Vestibular System Development and Function	abnormal morphology of cochlea	3.91E-04	EYA1, FGFR3, GABRA5	3
Organ Morphology	abnormal morphology of cochlea	3.91E-04	EYA1, FGFR3, GABRA5	3
Infectious Disease	Bacterial Infection	4.27E-04	CFTR, CXCL10, GABRA1, GABRA5, MSR1, RELB, SNCA, SYNE1, UBD	9
Developmental Disorder	osteochondrodysplasia	4.33E-04	ABCC9, ACAN, PCNT	3
Skeletal and Muscular Disorders	osteochondrodysplasia	4.33E-04	ABCC9, ACAN, PCNT	3
Connective Tissue Disorders	osteochondrodysplasia	4.33E-04	ABCC9, ACAN, PCNT	3
Hereditary Disorder	osteochondrodysplasia	4.33E-04	ABCC9, ACAN, PCNT	3
Cancer	cell transformation	4.42E-04	AKT3, DYNLL1, FGFR3, LDHA, NFATC1, PRKCZ, RELB, RUNX1, STK11, TRRAP	10
Tissue Development	cartilage development	4.49E-04	ACAN, COL10A1, FGFR3, SIX2, SMAD3	5
Skeletal and Muscular System Development and Function	cartilage development	4.49E-04	ACAN, COL10A1, FGFR3, SIX2, SMAD3	5
Lymphoid Tissue Structure and Development	morphology of thymus gland	4.65E-04	AKT3, COL10A1, EYA1, GFI1, RUNX1	5
Organ Morphology	morphology of thymus gland	4.65E-04	AKT3, COL10A1, EYA1, GFI1, RUNX1	5
Cell Cycle	arrest in G1 phase of colon cancer cell lines	4.77E-04	FASN, GSPT1, STK11	3
Nervous System Development and Function	quantity of hair cells	4.77E-04	EYA1, FGFR3, GFI1	3
Tissue Morphology	quantity of hair cells	4.77E-04	EYA1, FGFR3, GFI1	3
Carbohydrate Metabolism	binding of carbohydrate	4.95E-04	CXCL10, LAMA5, PACSIN1, SULF2	4

ACCEPTED MANUSCRIPT				
Auditory and Vestibular System Development and Function	morphology of ear	4.99E-04	BDNF, EYA1, FGFR3, GABRA5, GFII	5
Organ Morphology	morphology of ear	4.99E-04	BDNF, EYA1, FGFR3, GABRA5, GFII	5
Small Molecule Biochemistry	concentration of docosahexaenoic acid	5.02E-04	CFTR, SNCA	2
Lipid Metabolism	concentration of docosahexaenoic acid	5.02E-04	CFTR, SNCA	2
Molecular Transport	concentration of docosahexaenoic acid	5.02E-04	CFTR, SNCA	2
Nervous System Development and Function	quantity of vestibular hair cells	5.02E-04	EYA1, GFII	2
Tissue Morphology	quantity of vestibular hair cells	5.02E-04	EYA1, GFII	2
Auditory and Vestibular System Development and Function	quantity of vestibular hair cells	5.02E-04	EYA1, GFII	2
Embryonic Development	kidney development	5.03E-04	BDNF, EYA1, LAMA5, SIK3, SIX2, SMAD3, SULF2	7
Tissue Development	kidney development	5.03E-04	BDNF, EYA1, LAMA5, SIK3, SIX2, SMAD3, SULF2	7
Organ Development	kidney development	5.03E-04	BDNF, EYA1, LAMA5, SIK3, SIX2, SMAD3, SULF2	7
Organismal Development	kidney development	5.03E-04	BDNF, EYA1, LAMA5, SIK3, SIX2, SMAD3, SULF2	7
Renal and Urological System Development and Function	kidney development	5.03E-04	BDNF, EYA1, LAMA5, SIK3, SIX2, SMAD3, SULF2	7
Cellular Assembly and Organization	quantity of mitochondria	5.25E-04	AKT3, DNM1, RELB	3
Embryonic Development	development of metanephric bud	5.76E-04	BDNF, EYA1, LAMA5, SIX2	4
Tissue Development	development of metanephric bud	5.76E-04	BDNF, EYA1, LAMA5, SIX2	4
Organ Development	development of metanephric bud	5.76E-04	BDNF, EYA1, LAMA5, SIX2	4
Organismal Development	development of metanephric bud	5.76E-04	BDNF, EYA1, LAMA5, SIX2	4
Renal and Urological System Development and Function	development of metanephric bud	5.76E-04	BDNF, EYA1, LAMA5, SIX2	4
Skeletal and Muscular Disorders	arthritis	5.78E-04	ACAN, BDNF, COL10A1, CXCL10, DNM1, DYNLL1, EEF1G, FASN, GABRA1, GABRA5, NCOA2, PRKCZ, SMAD3, SNCA, SYNE1	15
Connective Tissue Disorders	arthritis	5.78E-04	ACAN, BDNF, COL10A1, CXCL10, DNM1, DYNLL1, EEF1G, FASN, GABRA1, GABRA5, NCOA2, PRKCZ, SMAD3, SNCA, SYNE1	15
Inflammatory Disease	arthritis	5.78E-04	ACAN, BDNF, COL10A1, CXCL10, DNM1, DYNLL1, EEF1G, FASN, GABRA1, GABRA5, NCOA2, PRKCZ, SMAD3, SNCA, SYNE1	15
Cellular Assembly and Organization	quantity of cellular protrusions	5.91E-04	BDNF, EYA1, PACSIN1, PALM, SNCA	5
Cellular Function and Maintenance	quantity of cellular protrusions	5.91E-04	BDNF, EYA1, PACSIN1, PALM, SNCA	5
Cell Cycle	arrest in G1 phase	6.06E-04	ATR, EP400, FASN, GFII, GSPT1, RUNX1, STK11	7
Infectious Disease	infection of mammalia	6.09E-04	CFTR, CXCL10, MSR1, PRKCZ, RELB, SMAD3, SNCA, UBD	8
Cell Morphology	abnormal morphology of cells	6.15E-04	BDNF, CFTR, COL10A1, DNM1, EP400, FGFR3, GFII, NCOA2, NEUROD1, RELB, SIK3, SMAD3, SNCA, STK11, SULF2	15
Dermatological Diseases and Conditions	keratosis	6.34E-04	BDNF, CYP7A1, FGFR3, RELB	4
Cellular Function and Maintenance	receptor-mediated endocytosis	6.34E-04	DNM1, DNM2, MSR1, SYNE1	4
Skeletal and Muscular Disorders	Rheumatic Disease	6.39E-04	ACAN, BDNF, COL10A1, CXCL10, DNM1, DYNLL1, EEF1G, FASN, GABRA1, GABRA5, GFII, NCOA2, PRKCZ, SMAD3, SNCA, SYNE1	16
Connective Tissue Disorders	Rheumatic Disease	6.39E-04	ACAN, BDNF, COL10A1, CXCL10, DNM1, DYNLL1, EEF1G, FASN, GABRA1, GABRA5, GFII, NCOA2, PRKCZ, SMAD3, SNCA, SYNE1	16
Inflammatory Disease	Rheumatic Disease	6.39E-04	ACAN, BDNF, COL10A1, CXCL10, DNM1, DYNLL1, EEF1G, FASN, GABRA1, GABRA5, GFII, NCOA2, PRKCZ, SMAD3, SNCA, SYNE1	16
Tissue Development	development of connective tissue	6.43E-04	ACAN, COL10A1, FGFR3, NFATC1, RUNX1, SIX2, SMAD3	7

Cellular Assembly and Organization	accumulation of zymogen granules	6.67E-04	CFTR, NEUROD1	2
Cell-To-Cell Signaling and Interaction	activation of cerebral cortex cells	6.67E-04	BDNF, GABRA1	2
Cellular Movement	chemotaxis of hepatic stellate cells	6.67E-04	CXCL10, SMAD3	2
Connective Tissue Development and Function	chemotaxis of hepatic stellate cells	6.67E-04	CXCL10, SMAD3	2
Hepatic System Development and Function	chemotaxis of hepatic stellate cells	6.67E-04	CXCL10, SMAD3	2
Cellular Compromise	dysfunction of neurons	6.67E-04	BDNF, SNCA	2
Gastrointestinal Disease	obstruction of intestine	6.67E-04	CFTR, STK11	2
Developmental Disorder	Growth Failure	7.30E-04	BDNF, CFTR, CYP7A1, FGFR3, GF11, NEUROD1, SMAD3, STK11, SULF2, SYNE1, XRCC4	11
Nervous System Development and Function	quantity of synaptic vesicles	7.45E-04	BDNF, DNM1, SNCA	3
Cellular Assembly and Organization	quantity of synaptic vesicles	7.45E-04	BDNF, DNM1, SNCA	3
Organ Morphology	abnormal morphology of small thyroid gland	8.55E-04	EYA1, SMAD3	2
Endocrine System Development and Function	abnormal morphology of small thyroid gland	8.55E-04	EYA1, SMAD3	2
Neurological Disease	incoordination	8.55E-04	BDNF, GABRA1	2
DNA Replication, Recombination, and Repair	double-stranded DNA break repair	8.73E-04	EYA1, SMAD3, TRRAP, XRCC4	4
Auditory and Vestibular System Development and Function	morphology of inner ear	8.73E-04	BDNF, EYA1, FGFR3, GABRA5	4
Organ Morphology	morphology of inner ear	8.73E-04	BDNF, EYA1, FGFR3, GABRA5	4
Cellular Growth and Proliferation	production of lymphocytes	8.74E-04	CXCL10, RUNX1, STK11	3
Cellular Function and Maintenance	production of lymphocytes	8.74E-04	CXCL10, RUNX1, STK11	3
Hematological System Development and Function	production of lymphocytes	8.74E-04	CXCL10, RUNX1, STK11	3
Small Molecule Biochemistry	transport of cholesterol	8.74E-04	CFTR, CYP7A1, MSR1	3
Lipid Metabolism	transport of cholesterol	8.74E-04	CFTR, CYP7A1, MSR1	3
Molecular Transport	transport of cholesterol	8.74E-04	CFTR, CYP7A1, MSR1	3
Cell-To-Cell Signaling and Interaction	activation of blood cells	8.85E-04	BDNF, CXCL10, DOST, GF11, IFNK, MSR1, RELB, RORA, RUNX1, SMAD3, SNCA, STK11	12
Hematological System Development and Function	activation of blood cells	8.85E-04	BDNF, CXCL10, DOST, GF11, IFNK, MSR1, RELB, RORA, RUNX1, SMAD3, SNCA, STK11	12
Cellular Movement	cytokinesis	8.90E-04	CALM1 (includes others), CFL1, DNM1, STK11, TRRAP	5
Cell Cycle	cytokinesis	8.90E-04	CALM1 (includes others), CFL1, DNM1, STK11, TRRAP	5
Cell Morphology	branching of neurites	8.93E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2	6
Nervous System Development and Function	branching of neurites	8.93E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2	6
Cellular Assembly and Organization	branching of neurites	8.93E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2	6
Cellular Function and Maintenance	branching of neurites	8.93E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2	6
Embryonic Development	branching of neurites	8.93E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2	6
Cellular Development	branching of neurites	8.93E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2	6
Tissue Development	branching of neurites	8.93E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2	6
Tissue Morphology	quantity of cells	8.96E-04	BDNF, CFTR, COL10A1, CXCL10, DYNLL1, EYA1, FGFR3, GABRA1, GF11, MSR1, NCOA2, NEUROD1, NFATC1, PRDM16, RELB, RORA, RUNX1, SIK3, SMAD3, SNCA, STK11	21
Organ Morphology	size of brain	9.12E-04	AKT3, BDNF, NEUROD1, PRDM16	4
Skeletal and Muscular Disorders	rheumatoid arthritis	9.13E-04	ACAN, BDNF, COL10A1, CXCL10, DNM1, DYNLL1, EEF1G, GABRA1, GABRA5, NCOA2, SNCA, SYNE1	12

Connective Tissue Disorders	rheumatoid arthritis	9.13E-04	ACAN, BDNF, COL10A1, CXCL10, DNMI, DYNLL1, EEF1G, GABRA1, GABRA5, NCOA2, SNCA, SYNE1	12
Immunological Disease	rheumatoid arthritis	9.13E-04	ACAN, BDNF, COL10A1, CXCL10, DNMI, DYNLL1, EEF1G, GABRA1, GABRA5, NCOA2, SNCA, SYNE1	12
Inflammatory Disease	rheumatoid arthritis	9.13E-04	ACAN, BDNF, COL10A1, CXCL10, DNMI, DYNLL1, EEF1G, GABRA1, GABRA5, NCOA2, SNCA, SYNE1	12
Behavior	circling behavior	9.43E-04	BDNF, GF11, NEUROD1	3
Nervous System Development and Function	quantity of neuroglia	9.52E-04	BDNF, FGFR3, NEUROD1, SNCA	4
Tissue Morphology	quantity of neuroglia	9.52E-04	BDNF, FGFR3, NEUROD1, SNCA	4
Cell Morphology	neuritogenesis	9.87E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SNCA, STK11, SULF2, SYNE1	9
Nervous System Development and Function	neuritogenesis	9.87E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SNCA, STK11, SULF2, SYNE1	9
Cellular Assembly and Organization	neuritogenesis	9.87E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SNCA, STK11, SULF2, SYNE1	9
Cellular Function and Maintenance	neuritogenesis	9.87E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SNCA, STK11, SULF2, SYNE1	9
Cellular Development	neuritogenesis	9.87E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SNCA, STK11, SULF2, SYNE1	9
Tissue Development	neuritogenesis	9.87E-04	BDNF, NEUROD1, PACSIN1, PALM, RELB, SNCA, STK11, SULF2, SYNE1	9
Cell Morphology	polarization of cells	1.00E-03	CFL1, CXCL10, LAMA5, PRKCZ, STK11	5
Nervous System Development and Function	GABA-mediated receptor currents	1.07E-03	GABRA1, GABRA5	2
Cell-To-Cell Signaling and Interaction	GABA-mediated receptor currents	1.07E-03	GABRA1, GABRA5	2
Digestive System Development and Function	abnormal morphology of gall bladder	1.07E-03	CFTR, SIK3	2
Organ Morphology	abnormal morphology of gall bladder	1.07E-03	CFTR, SIK3	2
Hepatic System Development and Function	abnormal morphology of gall bladder	1.07E-03	CFTR, SIK3	2
Molecular Transport	internalization of protein	1.08E-03	CFL1, DNMI, DNM2, SIX2	4
Protein Trafficking	internalization of protein	1.08E-03	CFL1, DNMI, DNM2, SIX2	4
Cellular Growth and Proliferation	proliferation of connective tissue cells	1.11E-03	AKT3, ATR, EP400, FGFR3, LDHA, NFATC1, RELB, RUNX1, SMAD3, XRCC4	10
Cell-To-Cell Signaling and Interaction	activation of leukocytes	1.12E-03	CXCL10, DDOST, GF11, IFNK, MSR1, RELB, RORA, RUNX1, SMAD3, SNCA, STK11	11
Hematological System Development and Function	activation of leukocytes	1.12E-03	CXCL10, DDOST, GF11, IFNK, MSR1, RELB, RORA, RUNX1, SMAD3, SNCA, STK11	11
Immune Cell Trafficking	activation of leukocytes	1.12E-03	CXCL10, DDOST, GF11, IFNK, MSR1, RELB, RORA, RUNX1, SMAD3, SNCA, STK11	11
Inflammatory Response	activation of leukocytes	1.12E-03	CXCL10, DDOST, GF11, IFNK, MSR1, RELB, RORA, RUNX1, SMAD3, SNCA, STK11	11
Organismal Injury and Abnormalities	Lesion Formation	1.12E-03	ABCC9, BDNF, CFTR, CXCL10, MSR1, RUNX1, SMAD3, SNCA	8
Skeletal and Muscular Disorders	Parkinson's disease	1.14E-03	BDNF, GABRA1, GABRA5, GNAS, LDHA, SNCA	6
Neurological Disease	Parkinson's disease	1.14E-03	BDNF, GABRA1, GABRA5, GNAS, LDHA, SNCA	6
Cell Death and Survival	antiapoptosis	1.14E-03	BDNF, CFDP1, CFL1, PRKCZ, SNCA, TMBIM4	6
Cell-To-Cell Signaling and Interaction	activation of macrophages	1.16E-03	CXCL10, IFNK, MSR1, RORA, SNCA	5
Hematological System Development and Function	activation of macrophages	1.16E-03	CXCL10, IFNK, MSR1, RORA, SNCA	5
Immune Cell Trafficking	activation of macrophages	1.16E-03	CXCL10, IFNK, MSR1, RORA, SNCA	5
Inflammatory Response	activation of macrophages	1.16E-03	CXCL10, IFNK, MSR1, RORA, SNCA	5
Cellular Development	differentiation of phagocytes	1.17E-03	GF11, IFNK, NFATC1, RELB, RUNX1, UBD	6
Hematological System Development and Function	differentiation of phagocytes	1.17E-03	GF11, IFNK, NFATC1, RELB, RUNX1, UBD	6
Hematopoiesis	differentiation of phagocytes	1.17E-03	GF11, IFNK, NFATC1, RELB, RUNX1, UBD	6
Cellular Development	senescence of fibroblasts	1.17E-03	ATR, FASN, STK11	3
Connective Tissue Development and Function	senescence of fibroblasts	1.17E-03	ATR, FASN, STK11	3

Cell Cycle	senescence of fibroblasts	1.17E-03	ATR, FASN, STK11	3
Cancer	growth of tumor	1.19E-03	AKT3, DNM2, FGFR3, NEUROD1, RELB, RORA, RUNX1, TNIK	8
Cellular Development	differentiation of leukocytes	1.20E-03	GF11, IFNK, NFATC1, PRDM16, RELB, RORA, RUNX1, SMAD3, STK11, UBD, XRCC4	11
Hematological System Development and Function	differentiation of leukocytes	1.20E-03	GF11, IFNK, NFATC1, PRDM16, RELB, RORA, RUNX1, SMAD3, STK11, UBD, XRCC4	11
Hematopoiesis	differentiation of leukocytes	1.20E-03	GF11, IFNK, NFATC1, PRDM16, RELB, RORA, RUNX1, SMAD3, STK11, UBD, XRCC4	11
Cell-To-Cell Signaling and Interaction	activation of antigen presenting cells	1.22E-03	CXCL10, IFNK, MSR1, RELB, RORA, SNCA	6
Hematological System Development and Function	activation of antigen presenting cells	1.22E-03	CXCL10, IFNK, MSR1, RELB, RORA, SNCA	6
Immune Cell Trafficking	activation of antigen presenting cells	1.22E-03	CXCL10, IFNK, MSR1, RELB, RORA, SNCA	6
Inflammatory Response	activation of antigen presenting cells	1.22E-03	CXCL10, IFNK, MSR1, RELB, RORA, SNCA	6
Neurological Disease	Movement Disorders	1.29E-03	BDNF, CFTR, FGFR3, GABRA1, GABRA5, GF11, GNAS, KCNAB1, LDHA, NEUROD1, PDE4DIP, RELB, RORA, SAP18, SNCA	15
Cell Morphology	cell spreading of embryonic cell lines	1.30E-03	MSR1, TNIK	2
Embryonic Development	cell spreading of embryonic cell lines	1.30E-03	MSR1, TNIK	2
Organ Development	function of brain	1.30E-03	BDNF, RORA	2
Neurological Disease	hypophagia	1.30E-03	FASN, KCNA6	2
Nutritional Disease	hypophagia	1.30E-03	FASN, KCNA6	2
Psychological Disorders	hypophagia	1.30E-03	FASN, KCNA6	2
Cell Death and Survival	loss of neuroglia	1.30E-03	FGFR3, SNCA	2
Cell Cycle	arrest in G1 phase of tumor cell lines	1.33E-03	ATR, FASN, GF11, GSPT1, STK11	5
Cellular Development	differentiation of blood cells	1.42E-03	GF11, IFNK, NFATC1, PRDM16, RELB, RORA, RTKN2, RUNX1, SMAD3, STK11, UBD, XRCC4	12
Hematological System Development and Function	differentiation of blood cells	1.42E-03	GF11, IFNK, NFATC1, PRDM16, RELB, RORA, RTKN2, RUNX1, SMAD3, STK11, UBD, XRCC4	12
Inflammatory Response	inflammation of secretory structure	1.43E-03	CFTR, RELB, SMAD3	3
Cell Morphology	morphogenesis of neurites	1.52E-03	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2, SYNE1	7
Nervous System Development and Function	morphogenesis of neurites	1.52E-03	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2, SYNE1	7
Cellular Assembly and Organization	morphogenesis of neurites	1.52E-03	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2, SYNE1	7
Cellular Function and Maintenance	morphogenesis of neurites	1.52E-03	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2, SYNE1	7
Cellular Development	morphogenesis of neurites	1.52E-03	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2, SYNE1	7
Tissue Development	morphogenesis of neurites	1.52E-03	BDNF, NEUROD1, PACSIN1, PALM, RELB, SULF2, SYNE1	7
Developmental Disorder	biliary atresia	1.55E-03	CFTR, CYP7A1	2
Gastrointestinal Disease	biliary atresia	1.55E-03	CFTR, CYP7A1	2
Hepatic System Disease	biliary atresia	1.55E-03	CFTR, CYP7A1	2
Nervous System Development and Function	myelination of spinal cord	1.55E-03	BDNF, CXCL10	2
Tissue Development	myelination of spinal cord	1.55E-03	BDNF, CXCL10	2
Cell Death and Survival	cell viability of tumor cell lines	1.66E-03	ATR, BDNF, DNM1, DNM2, DUSP6, FGFR3, GRK4, PRKCZ, RELB, SNCA, XRCC4	11
Nervous System Development and Function	neurotransmission	1.67E-03	BDNF, CALM1 (includes others), DNM1, GABRA1, GABRA5, KCNAB1, PRKCZ, SNCA	8
Cell-To-Cell Signaling and Interaction	neurotransmission	1.67E-03	BDNF, CALM1 (includes others), DNM1, GABRA1, GABRA5, KCNAB1, PRKCZ, SNCA	8
Lymphoid Tissue Structure and Development	abnormal morphology of thymus gland	1.77E-03	COL10A1, EYA1, GF11, RUNX1	4

Organ Morphology	abnormal morphology of thymus gland	1.77E-03	COL10A1, EYA1, GF11, RUNX1	4
Cellular Assembly and Organization	stabilization of filaments	1.77E-03	CFL1, GNAS, GRK4, STK11	4
Organismal Survival	viability	1.77E-03	ACAN, GF11, RUNX1, SYNE1	4
Cancer	lymphohematopoietic cancer	1.80E-03	AKT3, CXCL10, FASN, FGFR3, GF11, GNAS, LDHA, MSR1, PRKCZ, RUNX1, STK11, TNIK, XRCC4	13
Cell Morphology	abnormal morphology of outer hair cells	1.83E-03	FGFR3, GF11	2
Nervous System Development and Function	abnormal morphology of outer hair cells	1.83E-03	FGFR3, GF11	2
Tissue Morphology	abnormal morphology of outer hair cells	1.83E-03	FGFR3, GF11	2
Cell Death and Survival	apoptosis of epithelial tissue	1.83E-03	EYA1, MSR1	2
Small Molecule Biochemistry	binding of heparin	1.83E-03	LAMA5, SULF2	2
Carbohydrate Metabolism	binding of heparin	1.83E-03	LAMA5, SULF2	2
Drug Metabolism	binding of heparin	1.83E-03	LAMA5, SULF2	2
Neurological Disease	complex partial seizure	1.83E-03	GABRA1, GABRA5	2
Cell Cycle	interphase of stem cells	1.83E-03	PRDM16, RUNX1	2
Nervous System Development and Function	long-term potentiation of hippocampal neurons	1.83E-03	BDNF, SNCA	2
Cell-To-Cell Signaling and Interaction	long-term potentiation of hippocampal neurons	1.83E-03	BDNF, SNCA	2
Nervous System Development and Function	maturation of synapse	1.83E-03	BDNF, PALM	2
Cell-To-Cell Signaling and Interaction	maturation of synapse	1.83E-03	BDNF, PALM	2
Cellular Assembly and Organization	maturation of synapse	1.83E-03	BDNF, PALM	2
Cellular Function and Maintenance	maturation of synapse	1.83E-03	BDNF, PALM	2
Tissue Development	maturation of synapse	1.83E-03	BDNF, PALM	2
Cell Cycle	mitosis of colon cancer cell lines	1.83E-03	ATR, UBD	2
Cell Death and Survival	degeneration of sensory neurons	1.84E-03	BDNF, GABRA5, GF11	3
Cellular Compromise	degeneration of sensory neurons	1.84E-03	BDNF, GABRA5, GF11	3
Cell Cycle	G1 phase	1.84E-03	ATR, EP400, FASN, GF11, GSPT1, NFATC1, RUNX1, STK11	8
Cellular Movement	migration of embryonic cells	1.90E-03	ACAN, BDNF, CFL1, LAMA5	4
Embryonic Development	migration of embryonic cells	1.90E-03	ACAN, BDNF, CFL1, LAMA5	4
Cellular Function and Maintenance	engulfment of cells	1.91E-03	CXCL10, DNM1, DNM2, MSR1, PRKCZ, RELB, SNCA	7
Cellular Movement	chemotaxis of connective tissue cells	1.95E-03	CXCL10, RELB, SMAD3	3
Cellular Function and Maintenance	movement of organelle	1.95E-03	DNM2, STK11, SYNE1	3
Neurological Disease	addiction	2.03E-03	ADH1B, GABRA1, GABRA5, SNCA	4
Psychological Disorders	addiction	2.03E-03	ADH1B, GABRA1, GABRA5, SNCA	4
Cellular Development	differentiation of antigen presenting cells	2.10E-03	GF11, IFNK, NFATC1, RELB, UBD	5
Hematological System Development and Function	differentiation of antigen presenting cells	2.10E-03	GF11, IFNK, NFATC1, RELB, UBD	5
Hematopoiesis	differentiation of antigen presenting cells	2.10E-03	GF11, IFNK, NFATC1, RELB, UBD	5
Cell-To-Cell Signaling and Interaction	excitation of cerebral cortex cells	2.13E-03	BDNF, SNCA	2
Cellular Growth and Proliferation	excitation of cerebral cortex cells	2.13E-03	BDNF, SNCA	2

Cellular Growth and Proliferation	generation of fibroblasts	2.13E-03	BDNF, EP400	2
Tissue Development	generation of fibroblasts	2.13E-03	BDNF, EP400	2
Developmental Disorder	stuttering	2.13E-03	GABRA1, GABRA5	2
Neurological Disease	stuttering	2.13E-03	GABRA1, GABRA5	2
Psychological Disorders	stuttering	2.13E-03	GABRA1, GABRA5	2
Nervous System Development and Function	synaptic transmission of hippocampal neurons	2.13E-03	BDNF, SNCA	2
Cell-To-Cell Signaling and Interaction	synaptic transmission of hippocampal neurons	2.13E-03	BDNF, SNCA	2
Gene Expression	binding of NFkB binding site	2.17E-03	CFL1, GFI1, GNAS, RELB	4
Nervous System Development and Function	generation of neurons	2.18E-03	BDNF, NEUROD1, SMAD3	3
Cellular Growth and Proliferation	generation of neurons	2.18E-03	BDNF, NEUROD1, SMAD3	3
Tissue Development	generation of neurons	2.18E-03	BDNF, NEUROD1, SMAD3	3
Tissue Development	involution	2.18E-03	CFTR, DYNLL1, SMAD3	3
Organ Morphology	involution	2.18E-03	CFTR, DYNLL1, SMAD3	3
Carbohydrate Metabolism	binding of polysaccharide	2.30E-03	CXCL10, LAMA5, SULF2	3
Cellular Movement	migration of neural crest cells	2.30E-03	ACAN, CFL1, LAMA5	3
Embryonic Development	migration of neural crest cells	2.30E-03	ACAN, CFL1, LAMA5	3
Tissue Morphology	quantity of myeloid cells	2.41E-03	BDNF, GFI1, RELB, RORA, RUNX1, SMAD3, SNCA	7
Hematological System Development and Function	quantity of myeloid cells	2.41E-03	BDNF, GFI1, RELB, RORA, RUNX1, SMAD3, SNCA	7
Cell Cycle	arrest in interphase	2.43E-03	ATR, EP400, FASN, GFI1, GSPT1, PRDM16, RUNX1, STK11	8
Cell Morphology	cell spreading of epithelial cell lines	2.45E-03	MSR1, TNIK	2
Hair and Skin Development and Function	cell spreading of epithelial cell lines	2.45E-03	MSR1, TNIK	2
Cellular Movement	chemotaxis of microglia	2.45E-03	CXCL10, SMAD3	2
Nervous System Development and Function	chemotaxis of microglia	2.45E-03	CXCL10, SMAD3	2
Hematological System Development and Function	chemotaxis of microglia	2.45E-03	CXCL10, SMAD3	2
Immune Cell Trafficking	chemotaxis of microglia	2.45E-03	CXCL10, SMAD3	2
Inflammatory Response	chemotaxis of microglia	2.45E-03	CXCL10, SMAD3	2
Cellular Assembly and Organization	formation of aggresome	2.45E-03	CFTR, UBD	2
Cellular Function and Maintenance	formation of aggresome	2.45E-03	CFTR, UBD	2
Protein Degradation	formation of aggresome	2.45E-03	CFTR, UBD	2
Protein Synthesis	formation of aggresome	2.45E-03	CFTR, UBD	2
Organ Development	function of left ventricle	2.45E-03	ABCC9, GNAS	2
Cardiovascular System Development and Function	function of left ventricle	2.45E-03	ABCC9, GNAS	2
Small Molecule Biochemistry	oxidation of NADPH	2.45E-03	CALM1 (includes others), FASN	2
DNA Replication, Recombination, and Repair	oxidation of NADPH	2.45E-03	CALM1 (includes others), FASN	2
Energy Production	oxidation of NADPH	2.45E-03	CALM1 (includes others), FASN	2
Nucleic Acid Metabolism	oxidation of NADPH	2.45E-03	CALM1 (includes others), FASN	2
Developmental Disorder	pectus excavatum	2.45E-03	GABRA1, GABRA5	2

Skeletal and Muscular Disorders	pectus excavatum	2.45E-03	GABRA1, GABRA5	2
Connective Tissue Disorders	pectus excavatum	2.45E-03	GABRA1, GABRA5	2
Nervous System Development and Function	quantity of dendrites	2.45E-03	BDNF, PACSIN1	2
Cellular Assembly and Organization	quantity of dendrites	2.45E-03	BDNF, PACSIN1	2
Cellular Function and Maintenance	quantity of dendrites	2.45E-03	BDNF, PACSIN1	2
Nervous System Development and Function	quantity of ganglion cells	2.45E-03	BDNF, NEUROD1	2
Tissue Morphology	quantity of ganglion cells	2.45E-03	BDNF, NEUROD1	2
Cellular Development	development of connective tissue cells	2.55E-03	ACAN, FGFR3, NFATC1, SMAD3	4
Tissue Development	development of connective tissue cells	2.55E-03	ACAN, FGFR3, NFATC1, SMAD3	4
Connective Tissue Development and Function	development of connective tissue cells	2.55E-03	ACAN, FGFR3, NFATC1, SMAD3	4
Cell Morphology	cell polarity formation	2.69E-03	CFL1, PRKCZ, STK11	3
Cell-To-Cell Signaling and Interaction	quantity of actin stress fibers	2.69E-03	CFL1, DNM2, PRKCZ	3
Cellular Assembly and Organization	quantity of actin stress fibers	2.69E-03	CFL1, DNM2, PRKCZ	3
Tissue Development	quantity of actin stress fibers	2.69E-03	CFL1, DNM2, PRKCZ	3
Reproductive System Development and Function	litter size	2.76E-03	AKAP1, CFTR, GABRA1, NCOA2, SULF2	5
Nervous System Development and Function	abnormal morphology of geniculate ganglion	2.79E-03	BDNF, EYA1	2
Organ Morphology	abnormal morphology of geniculate ganglion	2.79E-03	BDNF, EYA1	2
Small Molecule Biochemistry	concentration of bile salt	2.79E-03	CYP7A1, SIK3	2
Lipid Metabolism	concentration of bile salt	2.79E-03	CYP7A1, SIK3	2
Molecular Transport	concentration of bile salt	2.79E-03	CYP7A1, SIK3	2
Cellular Function and Maintenance	flux of chloride	2.79E-03	CFTR, GABRA5	2
Molecular Transport	flux of chloride	2.79E-03	CFTR, GABRA5	2
Embryonic Development	formation of neural fold	2.79E-03	CFL1, STK11	2
Tissue Development	formation of neural fold	2.79E-03	CFL1, STK11	2
Organismal Development	formation of neural fold	2.79E-03	CFL1, STK11	2
Behavior	panic-like anxiety	2.79E-03	GABRA1, GABRA5	2
Nervous System Development and Function	quantity of microglia	2.79E-03	BDNF, SNCA	2
Tissue Morphology	quantity of microglia	2.79E-03	BDNF, SNCA	2
Hematological System Development and Function	quantity of microglia	2.79E-03	BDNF, SNCA	2
Skeletal and Muscular Disorders	skelatal muscle spasticity	2.79E-03	GABRA1, GABRA5	2
Small Molecule Biochemistry	synthesis of cholesterol	2.83E-03	BDNF, CFTR, CYP7A1	3
Lipid Metabolism	synthesis of cholesterol	2.83E-03	BDNF, CFTR, CYP7A1	3
Vitamin and Mineral Metabolism	synthesis of cholesterol	2.83E-03	BDNF, CFTR, CYP7A1	3
Embryonic Development	morphology of lung	2.89E-03	CFTR, EYA1, FGFR3, NEUROD1, SYNE1	5
Tissue Development	morphology of lung	2.89E-03	CFTR, EYA1, FGFR3, NEUROD1, SYNE1	5
Organ Development	morphology of lung	2.89E-03	CFTR, EYA1, FGFR3, NEUROD1, SYNE1	5

Organismal Development	morphology of lung	2.89E-03	CFTR, EYA1, FGFR3, NEUROD1, SYNE1	5
Organ Morphology	morphology of lung	2.89E-03	CFTR, EYA1, FGFR3, NEUROD1, SYNE1	5
Respiratory System Development and Function	morphology of lung	2.89E-03	CFTR, EYA1, FGFR3, NEUROD1, SYNE1	5
Cellular Movement	homing of cells	2.91E-03	BDNF, CXCL10, DNM1, DUSP6, GNAS, PRKCZ, RELB, RUNX1, SMAD3	9
Cellular Development	development of antigen presenting cells	2.98E-03	GF11, NFATC1, RELB	3
Hematological System Development and Function	development of antigen presenting cells	2.98E-03	GF11, NFATC1, RELB	3
Hematopoiesis	development of antigen presenting cells	2.98E-03	GF11, NFATC1, RELB	3
Lymphoid Tissue Structure and Development	development of antigen presenting cells	2.98E-03	GF11, NFATC1, RELB	3
Lymphoid Tissue Structure and Development	abnormal morphology of lymphoid organ	3.00E-03	COL10A1, EYA1, GF11, RELB, RUNX1, SMAD3, STK11	7
Organ Morphology	abnormal morphology of lymphoid organ	3.00E-03	COL10A1, EYA1, GF11, RELB, RUNX1, SMAD3, STK11	7
Cell Morphology	abnormal morphology of proerythroblasts	3.15E-03	COL10A1, RELB	2
Tissue Morphology	abnormal morphology of proerythroblasts	3.15E-03	COL10A1, RELB	2
Hematological System Development and Function	abnormal morphology of proerythroblasts	3.15E-03	COL10A1, RELB	2
Hematopoiesis	abnormal morphology of proerythroblasts	3.15E-03	COL10A1, RELB	2
Cardiovascular System Development and Function	abnormal morphology of proerythroblasts	3.15E-03	COL10A1, RELB	2
Cell Cycle	arrest in cell cycle progression of cervical cancer cell lines	3.15E-03	ATR, POT1	2
Nervous System Development and Function	differentiation of granule cells	3.15E-03	BDNF, NEUROD1	2
Cellular Development	differentiation of granule cells	3.15E-03	BDNF, NEUROD1	2
Cellular Development	differentiation of myeloid dendritic cells	3.15E-03	RELB, UBD	2
Hematological System Development and Function	differentiation of myeloid dendritic cells	3.15E-03	RELB, UBD	2
Hematopoiesis	differentiation of myeloid dendritic cells	3.15E-03	RELB, UBD	2
Tissue Development	involution of thymus gland	3.15E-03	CFTR, SMAD3	2
Organ Morphology	involution of thymus gland	3.15E-03	CFTR, SMAD3	2
Nervous System Development and Function	quantity of nerve ending	3.15E-03	BDNF, SNCA	2
Cellular Assembly and Organization	quantity of nerve ending	3.15E-03	BDNF, SNCA	2
Nervous System Development and Function	recycling of synaptic vesicles	3.15E-03	DNM1, PACSIN1	2
Cellular Assembly and Organization	recycling of synaptic vesicles	3.15E-03	DNM1, PACSIN1	2
Skeletal and Muscular Disorders	torticollis	3.15E-03	BDNF, GF11	2
Skeletal and Muscular System Development and Function	morphology of axial skeleton	3.15E-03	COL10A1, FGFR3, SIK3, SMAD3, SULF2	5
Cancer	mammary tumor	3.15E-03	AKT3, CALM1 (includes others), EYA1, FASN, GNAS, GSPT1, LAMA5, MSR1, NFATC1, POLE2, RELB, RUNX1, SMAD3, SYNE1	14
Cellular Growth and Proliferation	production of cells	3.25E-03	CXCL10, FGFR3, RUNX1, STK11	4

Cellular Function and Maintenance	production of cells	3.25E-03	CXCL10, FGFR3, RUNX1, STK11	4
Cell-To-Cell Signaling and Interaction	activation of central nervous system cells	3.28E-03	BDNF, GABRA1, SNCA	3
Cell Death and Survival	cell death of motor neurons	3.28E-03	BDNF, RUNX1, SNCA	3
Cellular Development	differentiation of stem cells	3.50E-03	BDNF, GF11, NEUROD1, RUNX1, SMAD3	5
Organismal Development	morphology of body region	3.51E-03	BDNF, CFTR, COL10A1, EYA1, FGFR3, RELB, SIK3, SMAD3, STK11, SULF2	10
Nervous System Development and Function	quantity of outer hair cells	3.53E-03	FGFR3, GF11	2
Tissue Morphology	quantity of outer hair cells	3.53E-03	FGFR3, GF11	2
Auditory and Vestibular System Development and Function	quantity of outer hair cells	3.53E-03	FGFR3, GF11	2
Cellular Assembly and Organization	organization of organelle	3.53E-03	ACAN, CFL1, DNM1, PCNT, POT1, SNCA, STK25, SYNE1	8
Cancer	transformation of fibroblast cell lines	3.55E-03	AKT3, DYNLL1, FGFR3, LDHA, NFATC1, RUNX1	6
Embryonic Development	morphogenesis of metanephric bud	3.60E-03	EYA1, LAMA5, SIX2	3
Tissue Development	morphogenesis of metanephric bud	3.60E-03	EYA1, LAMA5, SIX2	3
Organ Development	morphogenesis of metanephric bud	3.60E-03	EYA1, LAMA5, SIX2	3
Organismal Development	morphogenesis of metanephric bud	3.60E-03	EYA1, LAMA5, SIX2	3
Renal and Urological System Development and Function	morphogenesis of metanephric bud	3.60E-03	EYA1, LAMA5, SIX2	3
Nervous System Development and Function	quantity of neurons	3.60E-03	BDNF, EYA1, FGFR3, GF11, NEUROD1, SNCA	6
Tissue Morphology	quantity of neurons	3.60E-03	BDNF, EYA1, FGFR3, GF11, NEUROD1, SNCA	6
Embryonic Development	morphology of limb bone	3.65E-03	COL10A1, FGFR3, SMAD3, SULF2	4
Tissue Development	morphology of limb bone	3.65E-03	COL10A1, FGFR3, SMAD3, SULF2	4
Organ Development	morphology of limb bone	3.65E-03	COL10A1, FGFR3, SMAD3, SULF2	4
Organismal Development	morphology of limb bone	3.65E-03	COL10A1, FGFR3, SMAD3, SULF2	4
Connective Tissue Development and Function	morphology of limb bone	3.65E-03	COL10A1, FGFR3, SMAD3, SULF2	4
Organ Morphology	morphology of limb bone	3.65E-03	COL10A1, FGFR3, SMAD3, SULF2	4
Skeletal and Muscular System Development and Function	morphology of limb bone	3.65E-03	COL10A1, FGFR3, SMAD3, SULF2	4
Cellular Assembly and Organization	quantity of filaments	3.65E-03	CFL1, DNM2, PRKCZ, SMAD3	4
Organ Morphology	size of bone	3.72E-03	COL10A1, MSR1, NCOA2, SIK3, SMAD3	5
Skeletal and Muscular System Development and Function	size of bone	3.72E-03	COL10A1, MSR1, NCOA2, SIK3, SMAD3	5
Nervous System Development and Function	action potential of cells	3.75E-03	BDNF, CALM1 (includes others), GABRA1, KCNAB1	4
Cell-To-Cell Signaling and Interaction	action potential of cells	3.75E-03	BDNF, CALM1 (includes others), GABRA1, KCNAB1	4
Embryonic Development	abnormal morphology of epiphyseal growth plate	3.76E-03	COL10A1, FGFR3, SMAD3	3
Tissue Morphology	abnormal morphology of epiphyseal growth plate	3.76E-03	COL10A1, FGFR3, SMAD3	3
Tissue Development	abnormal morphology of epiphyseal growth plate	3.76E-03	COL10A1, FGFR3, SMAD3	3

Organ Development	abnormal morphology of epiphyseal growth plate	3.76E-03	COL10A1, FGFR3, SMAD3	3
Organismal Development	abnormal morphology of epiphyseal growth plate	3.76E-03	COL10A1, FGFR3, SMAD3	3
Connective Tissue Development and Function	abnormal morphology of epiphyseal growth plate	3.76E-03	COL10A1, FGFR3, SMAD3	3
Organ Morphology	abnormal morphology of epiphyseal growth plate	3.76E-03	COL10A1, FGFR3, SMAD3	3
Skeletal and Muscular System Development and Function	abnormal morphology of epiphyseal growth plate	3.76E-03	COL10A1, FGFR3, SMAD3	3
Neurological Disease	dyssomnia	3.76E-03	BDNF, GABRA1, GABRA5	3
Psychological Disorders	dyssomnia	3.76E-03	BDNF, GABRA1, GABRA5	3
Cancer	hematological neoplasia	3.85E-03	AKT3, CXCL10, FASN, FGFR3, GFI1, LDHA, MSR1, PRKCZ, RUNX1, STK11, TNK1, XRCC4	12
Hematological Disease	hematological neoplasia	3.85E-03	AKT3, CXCL10, FASN, FGFR3, GFI1, LDHA, MSR1, PRKCZ, RUNX1, STK11, TNK1, XRCC4	12
Gene Expression	repression of RNA	3.88E-03	NCOA2, PRDM16, PRKCZ, RUNX1, SAP18	5
Cellular Movement	cell movement	3.93E-03	ACAN, AKT3, BDNF, CFL1, CFTR, CXCL10, DNM1, DNM2, DUSP6, FH, GNAS, LAMA5, MSR1, NEUROD1, NFATC1, PRKCZ, RELB, RUNX1, SMAD3, STK11, STK25	21
Digestive System Development and Function	abnormal morphology of duodenum	3.93E-03	CFTR, STK11	2
Organ Morphology	abnormal morphology of duodenum	3.93E-03	CFTR, STK11	2
Cell Death and Survival	cell death of spinal neuron	3.93E-03	BDNF, RUNX1	2
Dermatological Diseases and Conditions	formation of abscess	3.93E-03	CFTR, SMAD3	2
Organismal Injury and Abnormalities	formation of abscess	3.93E-03	CFTR, SMAD3	2
Developmental Disorder	scoliosis	3.93E-03	FGFR3, SIK3	2
Skeletal and Muscular Disorders	scoliosis	3.93E-03	FGFR3, SIK3	2
Neurological Disease	status epilepticus	3.93E-03	GABRA1, GABRA5	2
Small Molecule Biochemistry	synthesis of acyl-coenzyme A	3.93E-03	FASN, SNCA	2
Lipid Metabolism	synthesis of acyl-coenzyme A	3.93E-03	FASN, SNCA	2
Nucleic Acid Metabolism	synthesis of acyl-coenzyme A	3.93E-03	FASN, SNCA	2
Cardiovascular Disease	valvular regurgitation of mitral valve	3.93E-03	GABRA1, GABRA5	2
Embryonic Development	abnormal morphology of sternum	3.93E-03	SIK3, SMAD3, SULF2	3
Tissue Development	abnormal morphology of sternum	3.93E-03	SIK3, SMAD3, SULF2	3
Organ Development	abnormal morphology of sternum	3.93E-03	SIK3, SMAD3, SULF2	3
Organismal Development	abnormal morphology of sternum	3.93E-03	SIK3, SMAD3, SULF2	3
Connective Tissue Development and Function	abnormal morphology of sternum	3.93E-03	SIK3, SMAD3, SULF2	3
Organ Morphology	abnormal morphology of sternum	3.93E-03	SIK3, SMAD3, SULF2	3
Skeletal and Muscular System Development and Function	abnormal morphology of sternum	3.93E-03	SIK3, SMAD3, SULF2	3
Gastrointestinal Disease	diarrhea	3.93E-03	BDNF, CFTR, CYP7A1	3

Cancer	genital tumor	3.97E-03	EP400, FASN, FGFR3, GNAS, LAMA5, LDHA, MSR1, NEUROD1, POLE2, PRKCZ, RELB, STK11, TRRAP	13
Reproductive System Disease	genital tumor	3.97E-03	EP400, FASN, FGFR3, GNAS, LAMA5, LDHA, MSR1, NEUROD1, POLE2, PRKCZ, RELB, STK11, TRRAP	13
Cellular Growth and Proliferation	formation of cells	4.07E-03	BDNF, DNMT2, NCOA2, NEUROD1, NFATC1, PRKCZ, SMAD3	7
Cell Death and Survival	cell viability of cervical cancer cell lines	4.12E-03	ATR, DNMT1, DUSP6, GRK4, XRCC4	5
Cell Death and Survival	degeneration of dopaminergic neurons	4.35E-03	BDNF, SNCA	2
Cellular Compromise	degeneration of dopaminergic neurons	4.35E-03	BDNF, SNCA	2
Cellular Development	development of chondrocytes	4.35E-03	ACAN, FGFR3	2
Tissue Development	development of chondrocytes	4.35E-03	ACAN, FGFR3	2
Connective Tissue Development and Function	development of chondrocytes	4.35E-03	ACAN, FGFR3	2
Skeletal and Muscular System Development and Function	development of chondrocytes	4.35E-03	ACAN, FGFR3	2
Neurological Disease	myoclonic seizure	4.35E-03	GABRA1, GABRA5	2
Cell-To-Cell Signaling and Interaction	uptake of dopamine	4.35E-03	BDNF, SNCA	2
Small Molecule Biochemistry	uptake of dopamine	4.35E-03	BDNF, SNCA	2
Molecular Transport	uptake of dopamine	4.35E-03	BDNF, SNCA	2
Drug Metabolism	uptake of dopamine	4.35E-03	BDNF, SNCA	2
Cell Cycle	senescence of cells	4.37E-03	ATR, FASN, POT1, RUNX1, STK11	5
Nutritional Disease	weight gain	4.44E-03	ABCC9, BDNF, GABRA1, GABRA5, RUNX1, SMAD3	6
Neurological Disease	cognitive impairment	4.48E-03	BDNF, CXCL10, SNCA	3
Nervous System Development and Function	quantity of neurites	4.48E-03	BDNF, PACSIN1, SNCA	3
Cellular Assembly and Organization	quantity of neurites	4.48E-03	BDNF, PACSIN1, SNCA	3
Cellular Function and Maintenance	quantity of neurites	4.48E-03	BDNF, PACSIN1, SNCA	3
Cell Morphology	size of cells	4.65E-03	AKT3, BDNF, CFL1, FASN, GNAS, NCOA2, SIK3	7
Nervous System Development and Function	abnormal morphology of nervous system	4.67E-03	BDNF, NEUROD1, SULF2	3
Embryonic Development	abnormal morphology of rib	4.67E-03	FGFR3, SIK3, SMAD3	3
Tissue Development	abnormal morphology of rib	4.67E-03	FGFR3, SIK3, SMAD3	3
Organ Development	abnormal morphology of rib	4.67E-03	FGFR3, SIK3, SMAD3	3
Organismal Development	abnormal morphology of rib	4.67E-03	FGFR3, SIK3, SMAD3	3
Connective Tissue Development and Function	abnormal morphology of rib	4.67E-03	FGFR3, SIK3, SMAD3	3
Organ Morphology	abnormal morphology of rib	4.67E-03	FGFR3, SIK3, SMAD3	3
Skeletal and Muscular System Development and Function	abnormal morphology of rib	4.67E-03	FGFR3, SIK3, SMAD3	3
Cellular Movement	invasion of lung cancer cell lines	4.67E-03	AKT3, BDNF, STK11	3
Embryonic Development	lung development	4.72E-03	CFTR, EYA1, FGFR3, LAMA5, NEUROD1, SYNE1	6
Tissue Development	lung development	4.72E-03	CFTR, EYA1, FGFR3, LAMA5, NEUROD1, SYNE1	6
Organ Development	lung development	4.72E-03	CFTR, EYA1, FGFR3, LAMA5, NEUROD1, SYNE1	6
Organismal Development	lung development	4.72E-03	CFTR, EYA1, FGFR3, LAMA5, NEUROD1, SYNE1	6
Respiratory System Development and Function	lung development	4.72E-03	CFTR, EYA1, FGFR3, LAMA5, NEUROD1, SYNE1	6
Embryonic Development	abnormal morphology of basisphenoid bone	4.80E-03	EYA1, SULF2	2

Tissue Development	abnormal morphology of basisphenoid bone	4.80E-03	EYA1, SULF2	2
Organ Development	abnormal morphology of basisphenoid bone	4.80E-03	EYA1, SULF2	2
Organismal Development	abnormal morphology of basisphenoid bone	4.80E-03	EYA1, SULF2	2
Connective Tissue Development and Function	abnormal morphology of basisphenoid bone	4.80E-03	EYA1, SULF2	2
Organ Morphology	abnormal morphology of basisphenoid bone	4.80E-03	EYA1, SULF2	2
Skeletal and Muscular System Development and Function	abnormal morphology of basisphenoid bone	4.80E-03	EYA1, SULF2	2
Skeletal and Muscular System Development and Function	density of bone	4.80E-03	FGFR3, MSR1	2
Dermatological Diseases and Conditions	desquamation	4.80E-03	CYP7A1, NCOA2	2
Cellular Movement	endocytosis of synaptic vesicles	4.80E-03	DNM1, SNCA	2
Nervous System Development and Function	endocytosis of synaptic vesicles	4.80E-03	DNM1, SNCA	2
Cellular Assembly and Organization	endocytosis of synaptic vesicles	4.80E-03	DNM1, SNCA	2
Cellular Function and Maintenance	endocytosis of synaptic vesicles	4.80E-03	DNM1, SNCA	2
Cellular Function and Maintenance	function of keratinocytes	4.80E-03	RELB, SMAD3	2
Inflammatory Response	inflammation of salivary gland	4.80E-03	CFTR, RELB	2
Inflammatory Response	inflammation of stomach	4.80E-03	RELB, SMAD3	2
Cancer	breast cancer	4.87E-03	AKT3, CALM1 (includes others), EYA1, FASN, GNAS, GSPT1, LAMA5, NFATC1, POLE2, RELB, RUNX1, SMAD3, SYNE1	13
Embryonic Development	morphogenesis of embryonic tissue	4.90E-03	EYA1, LAMA5, SIX2, SMAD3	4
Tissue Development	morphogenesis of embryonic tissue	4.90E-03	EYA1, LAMA5, SIX2, SMAD3	4
Organismal Development	morphogenesis of embryonic tissue	4.90E-03	EYA1, LAMA5, SIX2, SMAD3	4

Table E6: *Overlap between asthma-associated DMRs in IIS children and DNase I HSS in monocytes and naïve T cells.*

DMRs							DNase I HSS monocytes		DNase I HSS naïve T-cells		Genes
Chr	Start	End	Size	Mag_diff	-log10 P value	CpG (750bp)	Start	End	Start	End	
1	7916430	7916782	352	0.212	2.184	24	7916580	7916730	.	.	UTS2
1	11790134	11790509	375	0.235	2.192	18	11790500	11790650	.	.	intergenic (DRAXIN-AGTRAP)
1	11790134	11790509	375	0.235	2.192	18	11790200	11790350	.	.	intergenic (DRAXIN-AGTRAP)
1	26947080	26947575	495	0.252	2.84	79	26947340	26947490	26947220	26947370	intergenic (RPS6KA1-ARID1A)
1	26947080	26947575	495	0.252	2.84	79	26947060	26947210	.	.	intergenic (RPS6KA1-ARID1A)
1	45251683	45252108	425	0.29	2.246	45	45251880	45252030	45251860	45252010	BEST4
1	118468419	118468991	572	-0.238	3.024	5	118468740	118468890	.	.	WDR3/GDAP2
2	54557572	54557897	325	0.242	2.761	52	54557880	54558030	54557880	54558030	C2orf73
2	219576276	219577046	770	0.376	3.481	6	.	.	219576240	219576390	TTL4
2	220083145	220083530	385	0.226	5.569	68	220083200	220083350	.	.	ABCB6/ATG9A
3	46599590	46600220	630	0.244	4.231	21	46599940	46600090	46599900	46600050	LRRC2
3	197676983	197677483	500	0.225	2.457	27	.	.	197677200	197677350	RPL35A/IQCG
4	124613	125128	515	0.211	2.951	44	124520	124670	125020	125170	ZNF718
4	124613	125128	515	0.211	2.951	44	124760	124910	124740	124890	ZNF718
4	3042964	3043339	375	0.222	2.834	46	3043200	3043350	.	.	GRK4
4	89051945	89052325	380	-0.243	3.563	9	89051840	89051990	.	.	ABCG2/AFF4
5	82368664	82369084	420	-0.224	2.402	10	82368860	82369010	.	.	XRCC4/TMEM167A
5	126114144	126114454	310	0.22	2.879	50	126114020	126114170	126114040	126114190	LMNB1
5	142174675	142174985	310	-0.203	2.758	5	142174960	142175110	.	.	ARHGAP26
5	156570589	156570894	305	0.262	3.601	27	156570600	156570750	156570600	156570750	MED7
5	180648315	180649020	705	0.228	3.595	33	.	.	180648420	180648570	TRIM41/MIR4638
6	2902234	2903041	807	0.234	3.144	27	2903000	2903150	.	.	SERPINB9
6	4020994	4021489	495	0.241	2.985	35	4021460	4021610	4021040	4021190	PRPF4B
6	4020994	4021489	495	0.241	2.985	35	.	.	4021400	4021550	PRPF4B
6	34499206	34499731	525	0.214	2.285	33	34499700	34499850	.	.	PACSIN1

6	151711985	151712710	725	0.327	3.029	99	151712140	151712290	151712680	151712830	ZBTB2
6	167410746	167411121	375	-0.282	2.362	8			167411080	167411230	FGFR1OP/MIR3939
7	148844069	148844499	430	0.258	2.509	61	148844320	148844470	148844180	148844330	ZNF398
8	119266746	119267071	325	-0.219	2.199	10	119266760	119266910			SAMD12
8	124214717	124215383	666	-0.242	3.702	9	124215120	124215270			LOC100131726/FAM83A
8	144631520	144631835	315	0.307	2.663	23	144631620	144631770	144631560	144631710	GSDMD
9	130980777	130981292	515	0.254	3.833	44	130981100	130981250	130981100	130981250	DNM1
10	14051467	14051957	490	0.219	3.582	24			14051580	14051730	FRMD4A
11	1763722	1764047	325	0.347	3.015	7	1763680	1763830			MOB2/IFITM10
11	16760509	16760879	370	0.225	2.505	31	16760800	16760950	16760580	16760730	C11orf58
11	16760509	16760879	370	0.225	2.505	31			16760860	16761010	C11orf58
11	18417431	18418016	585	0.296	2.305	47	18417660	18417810	18417780	18417930	LDHA
11	18417431	18418016	585	0.296	2.305	47			18417460	18417610	LDHA
11	32850713	32851213	500	0.463	3.122	23	32851200	32851350			PRRG4
11	58346012	58346628	616	0.336	2.988	67	58346380	58346530	58346380	58346530	LPXN/ZFP91/ZFP91-CNTF
11	62341248	62341718	470	0.301	2.707	45	62341400	62341550	62341400	62341550	TUT1/EEF1G
11	75139113	75139723	610	0.224	3.565	40	75139360	75139510	75139340	75139490	KLHL35
11	104915738	104916253	515	0.342	2.374	6	104916000	104916150	104916040	104916190	CARD16
11	104915738	104916253	515	0.342	2.374	6			104915740	104915890	CARD16
11	116881940	116882310	370	-0.208	2.336	9	116882020	116882170			SIK3
12	9824116	9824509	393	0.293	2.329	17			9824120	9824270	CLEC2D
12	49524725	49525136	411	0.279	2.704	84	49524600	49524750	49525100	49525250	TUBA1B
12	49524725	49525136	411	0.279	2.704	84	49525120	49525270			TUBA1B
12	54719022	54719422	400	0.228	2.446	22			54719100	54719350	COPZ1
12	89743694	89744219	525	0.333	2.263	11	89743740	89743890			DUSP6
12	132434342	132434717	375	0.248	2.253	120	132434260	132434410			EP400
13	21714409	21714714	305	0.244	2.483	62	21714540	21714690	21714460	21714610	SAP18
13	43570879	43571183	304	-0.223	4.039	6	43570780	43570930			EPSTI1
14	50154049	50154449	400	0.22	3.201	27			50154160	50154310	POLE2
15	25200266	25200951	685	0.243	3.189	49			25200240	25200390	SNRPN/SNURF
15	25200266	25200951	685	0.243	3.189	49			25200520	25200670	SNRPN/SNURF

15	26108457	26108784	327	0.261	2.288	86	26108560	26108710	26108560	26108710	ATP10A
15	41786297	41786906	609	0.244	2.751	87	41786420	41786570	.	.	ITPKA
16	12009069	12009467	398	0.215	2.414	105	12009140	12009290	.	.	GSPT1
16	21531140	21531470	330	0.333	3.69	75	21531460	21531610	21531460	21531610	SLC7A5P2
16	21531140	21531470	330	0.333	3.69	75	21531040	21531190	.	.	SLC7A5P2
16	31232871	31233249	378	-0.253	2.752	10	31233240	31233390	.	.	PYDC1/TRIM72
16	90148322	90148897	575	0.306	3.78	45	90148460	90148610	90148460	90148610	intergenic (PRDM7)
17	6938284	6938685	401	0.231	2.899	7	.	.	6938580	6938730	SLC16A13
17	38277847	38278436	589	0.304	2.343	81	38278120	38278270	.	.	MSL1
17	74349827	74350512	685	0.308	2.567	62	74350200	74350350	74349980	74350130	PRPSAP1
17	74349827	74350512	685	0.308	2.567	62	74349960	74350110	74350240	74350390	PRPSAP1
17	79361084	79361418	334	0.211	4.662	83	79361100	79361250	.	.	intergenic (LOC100130370- BAHCC1)
18	47019290	47019788	498	-0.475	3.42	12	47019720	47019870	.	.	RPL17/RPL17- C18ORF32/SNORD58 A/SNORD58B/SNOR D58C
18	77196024	77196524	500	0.219	2.609	47	.	.	77196040	77196190	NFATC1
19	1021495	1021825	330	0.241	3.03	40	1021620	1021770	1021620	1021770	CNN2/C19orf6
19	1876344	1876934	590	0.27	2.843	46	1876440	1876590	.	.	FAM108A1
19	10907627	10908203	576	0.226	3.466	28	.	.	10907800	10907950	DNM2
19	37263404	37263994	590	0.25	3.935	53	37263940	37264090	37263940	37264090	ZNF850
19	37263404	37263994	590	0.25	3.935	53	37263680	37263830	37263660	37263810	ZNF850
19	38084769	38085148	379	0.215	2.643	26	.	.	38085100	38085250	ZNF540/ZNF571
19	47634525	47634850	325	0.258	3.13	36	.	.	47634420	47634570	SAE1
19	51774231	51774746	515	0.292	2.608	34	51774480	51774630	.	.	C19orf75
19	58874038	58874368	330	0.282	2.105	82	58874200	58874350	58874200	58874350	ZNF497
20	62580073	62580563	490	0.272	4.022	30	62580520	62580670	62580460	62580610	UCKL1/UCKL1-AS1
20	62580073	62580563	490	0.272	4.022	30	62580260	62580410	62579960	62580110	UCKL1/UCKL1-AS1
21	30674834	30675224	390	-0.231	2.512	8	30674740	30674890	.	.	BACH1

21	34756882	34757397	515	0.22	3.368	15	.	.	34757220	34757370	intergenic (IFNAR1-IFNGR2)
21	36262421	36263014	593	0.342	2.891	75	36262400	36262550	.	.	RUNX1
21	47742584	47743099	515	0.22	2.457	47	47742440	47742590	.	.	PCNT/C21orf58

Table E7. Asthma-associated DMRs in IIS children and DNase I HSS

	N. of DMRs in HSS	% Total DMRs*	% HSS Covered by Array	P[†]
DNase I HSS in CD14+ Monocytes	57	9.68	4.54	2.05E-09
DNase I HSS in CD4+ Naïve T cells	43	7.3	3.4	1.79E-07

* Total number of DMRs = 589

[†] by one-sample test of proportions

Table E8: Association between child and parental risk factors at birth and asthma during childhood in IIS children.

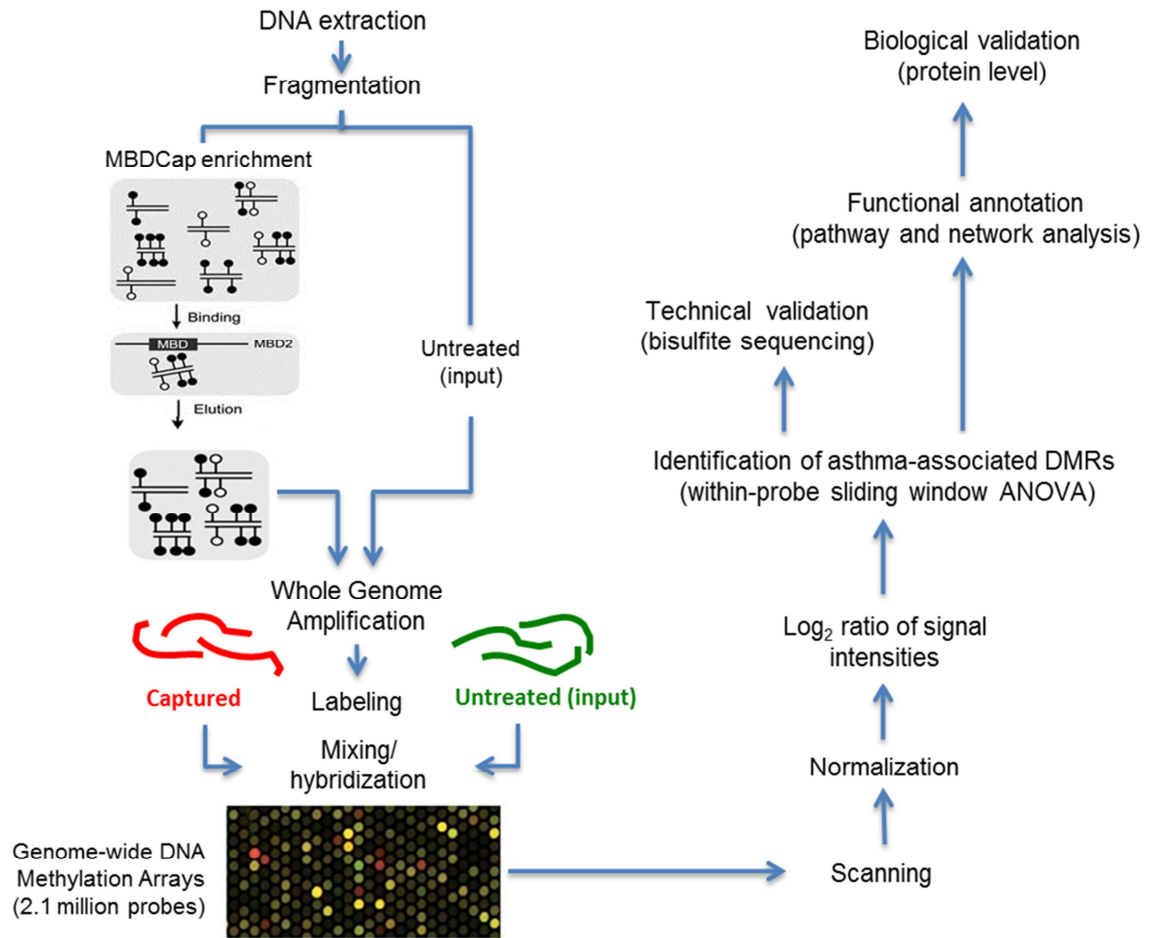
A) Child Characteristics		N	% with Asthma *	P-value †
Child sex	Male	208	20.7	--
	Female	222	15.3	0.148
Child ethnicity	Caucasian	265	16.6	--
	All others	165	20.0	0.372
Mode of delivery	Vaginal delivery	334	18.9	--
	Cesarean section	95	13.7	0.243
Total cord IgE	Undetectable	204	20.6	--
	Detectable	147	17.0	0.400
17q21 rs8076131 ‡	AA	80	21.3	--
	AG/GG	178	15.2	0.230

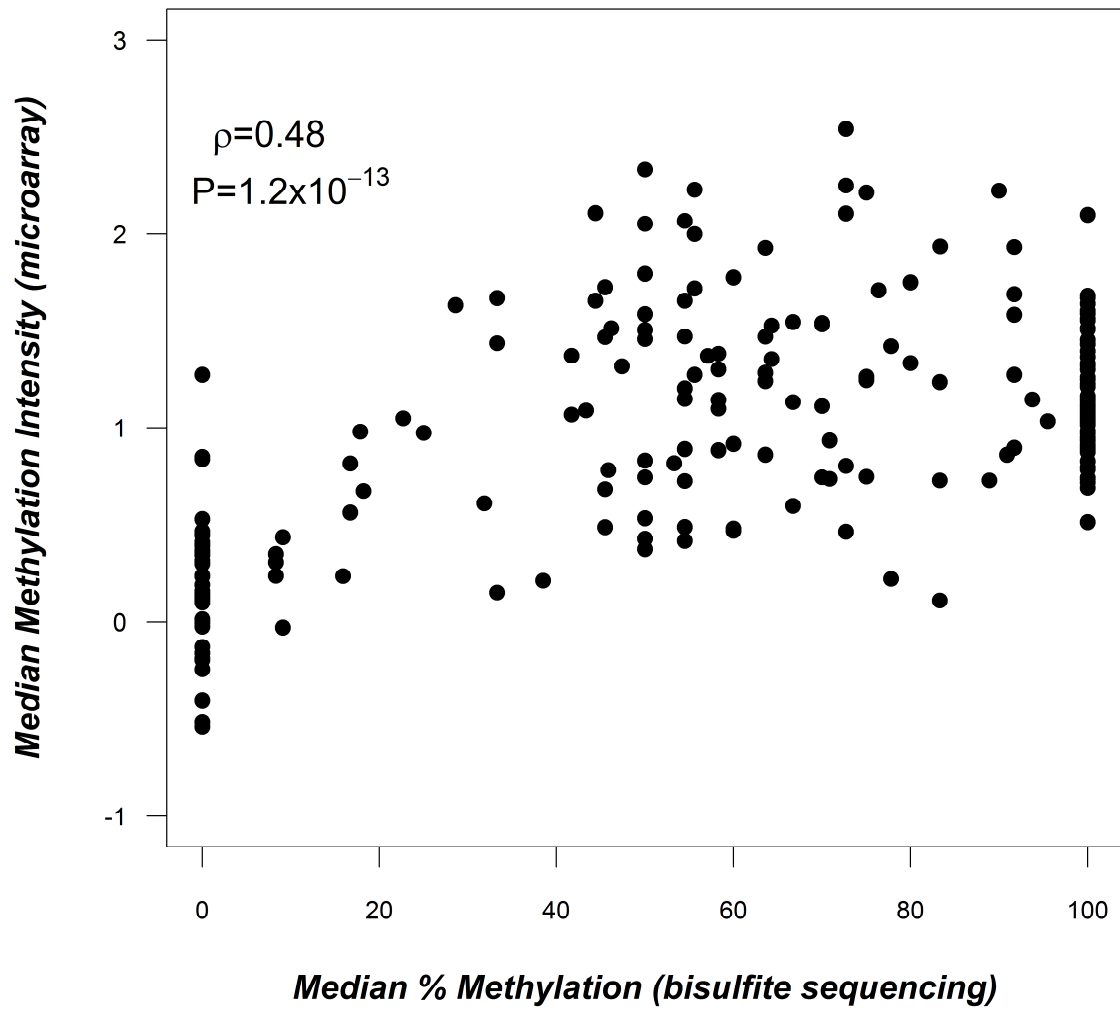
B) Parental Characteristics		N	% with Asthma *	P-value †
Maternal asthma	No	343	15.2	--
	Yes	83	28.9	0.003
Maternal allergy	No	133	17.3	--
	Yes	284	17.6	0.938
Paternal asthma	No	330	16.4	--
	Yes	63	20.6	0.409
Paternal allergy	No	82	15.9	--
	Yes	299	17.1	0.796
Maternal smoking (pregnancy)	No	411	18.3	--
	Yes	19	10.5	0.391

* Physician-diagnosed with symptoms or medication use for asthma in the past year reported at least once on the age 2, 3, 5 or 9-year questionnaires

† by Pearson's χ^2 test

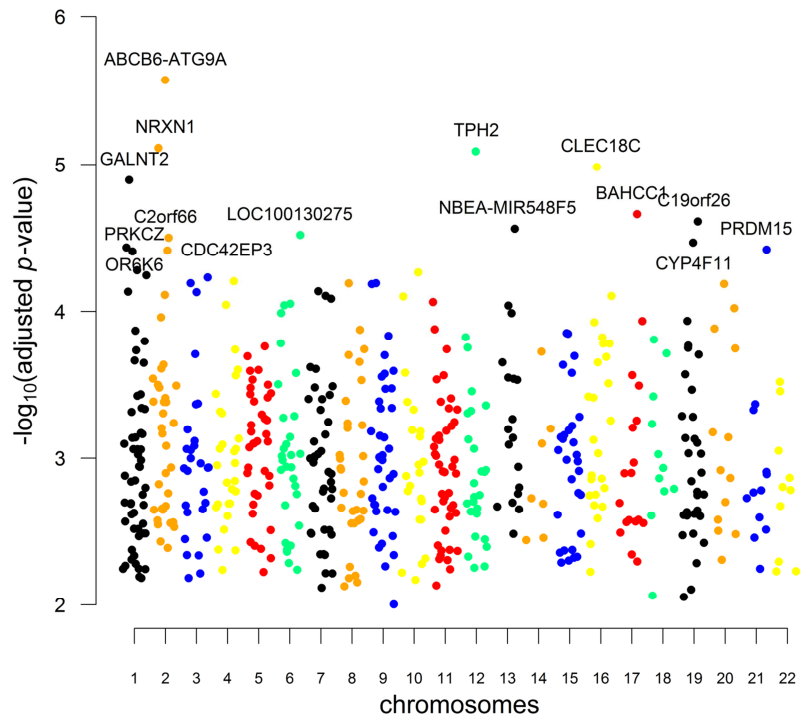
‡ Analysis limited to Caucasian children.





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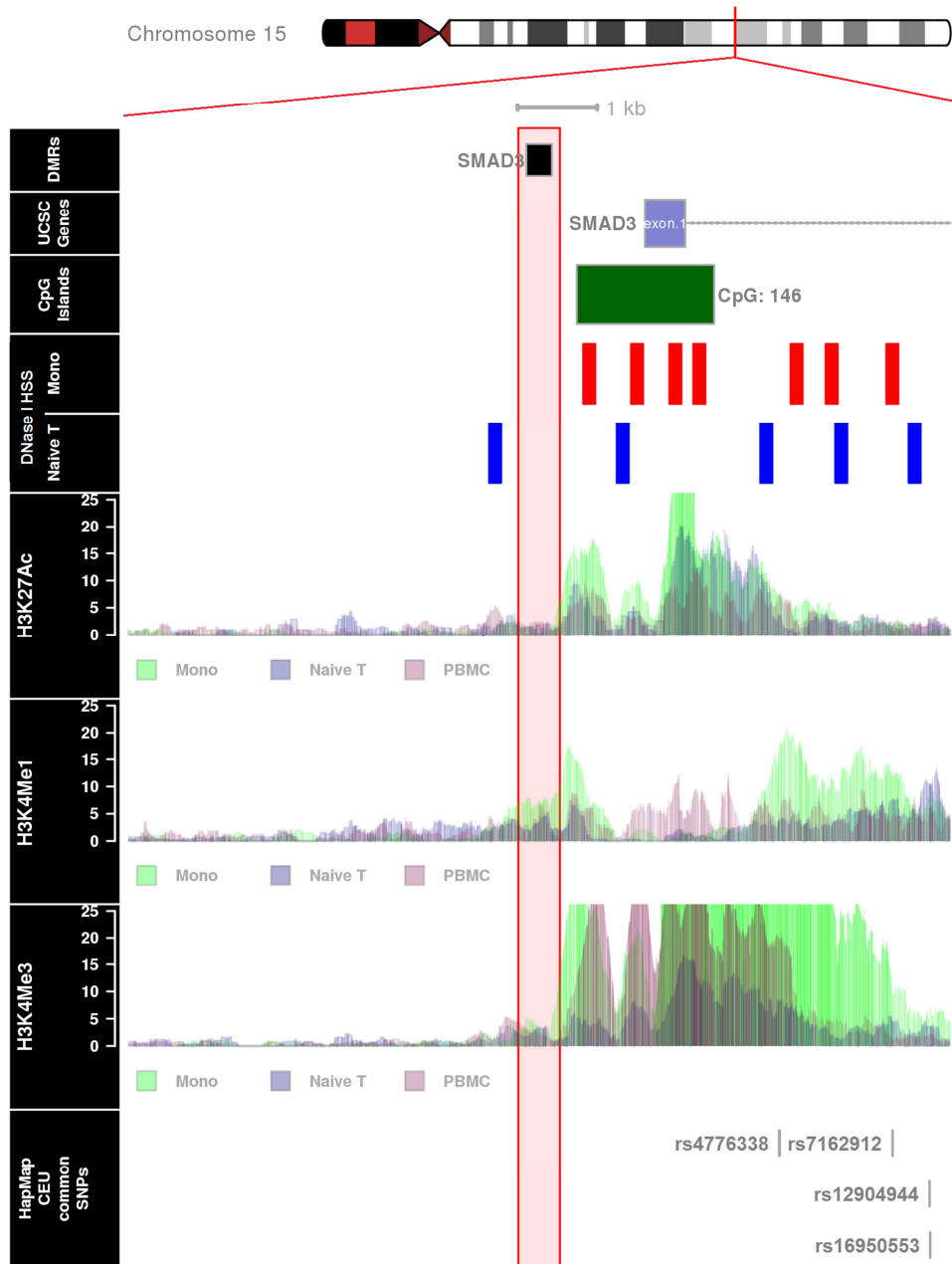


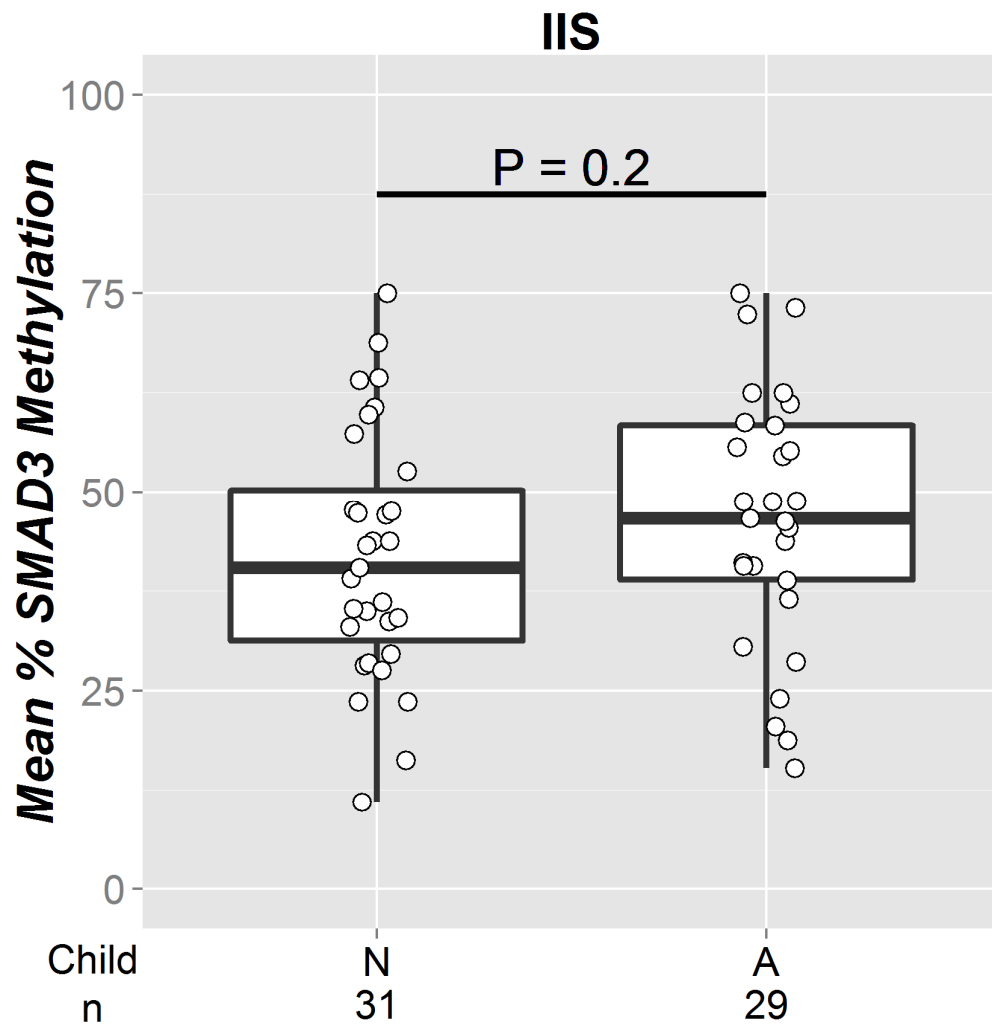
B

Genomic Location	No. of DMRs at Genomic Location*	% Total DMRs	% Genomic Location Covered by Array	Expected	Standardized Residuals
Promoter - TSS	42	7.13	10.05	59.17	-2.23
5' UTR	3	0.51	0.91	5.36	-1.02
Exon	35	5.94	4.87	28.66	1.18
Intron	235	39.9	44.8	263.88	-1.78
3' UTR	5	0.85	1.84	10.83	-1.77
TTS	20	3.4	2.57	15.16	1.24
Intergenic	242	41.09	34.08	200.71	2.91
Other	7	1.19	0.89	5.23	0.77

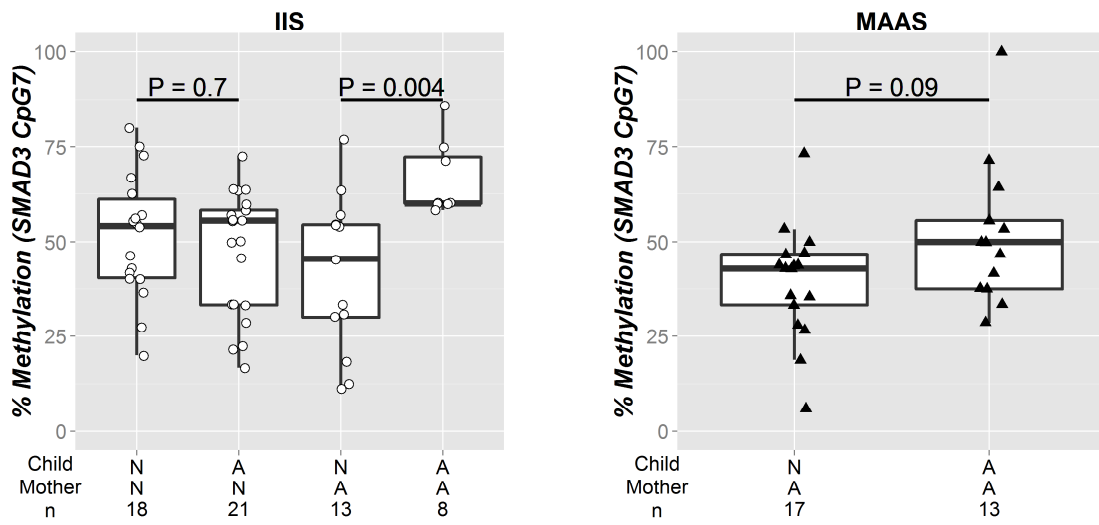
* Total number of DMRs = 589

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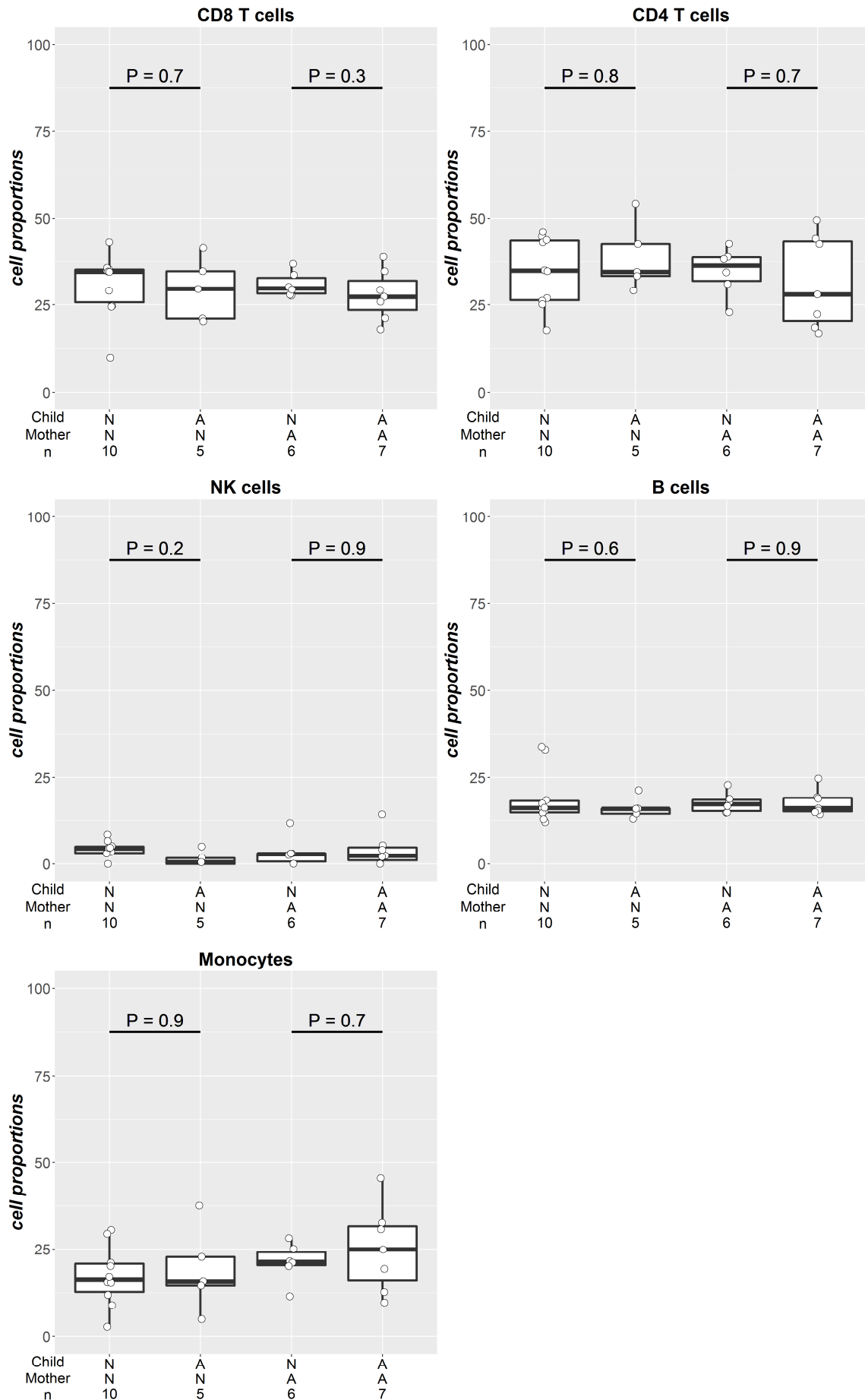


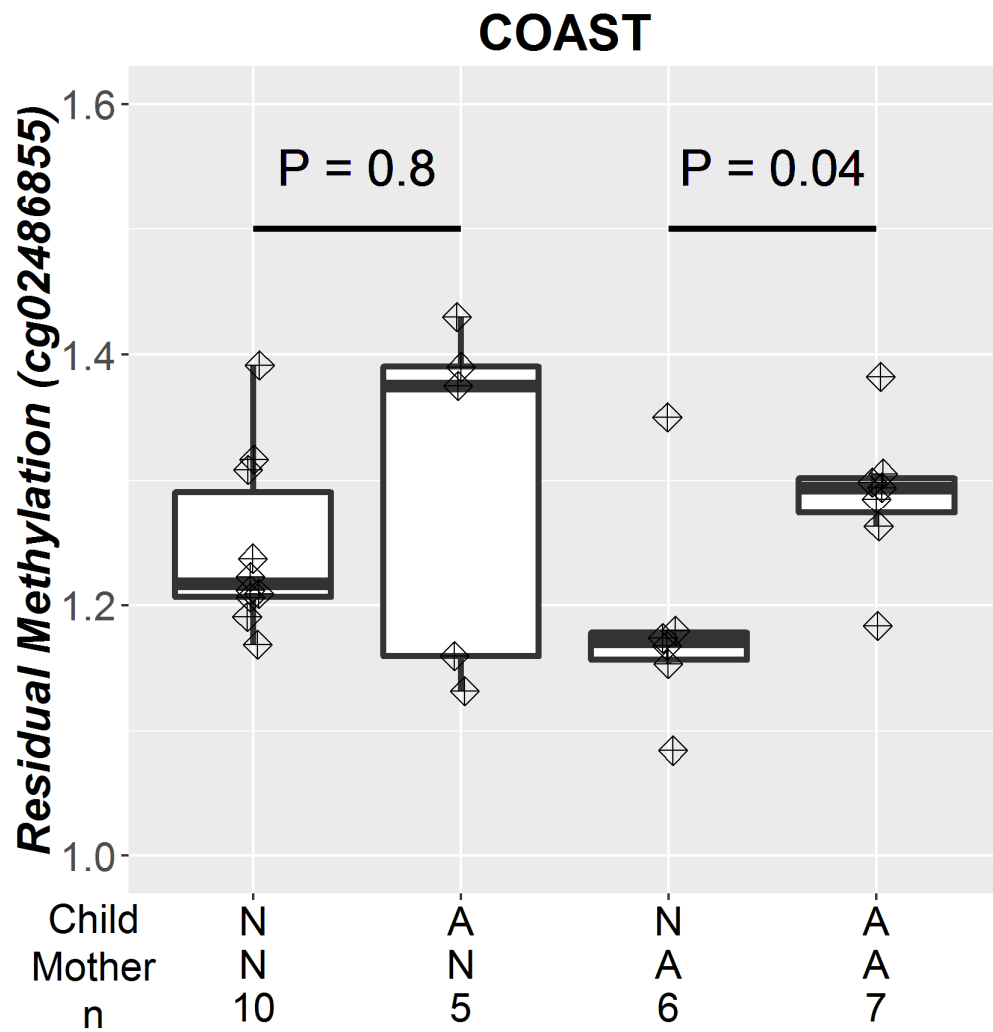


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ONLINE REPOSITORY**Epigenome-wide Analysis Links *SMAD3* Methylation at Birth to Asthma in Children of Asthmatic Mothers**

Avery DeVries, Gabriela Wlasiuk, Susan J. Miller, Anthony Bosco, Debra A. Stern, I. Carla Lohman, Janet Rothers, Anya C. Jones, Jessie Nicodemus-Johnson, Monica M. Vasquez, John A. Curtin, Angela Simpson, Adnan Custovic, Daniel J. Jackson, James E. Gern, Robert F. Lemanske, Jr., Stefano Guerra, Anne L. Wright, Carole Ober, Marilyn Halonen, and Donata Vercelli

Address correspondence to Donata Vercelli, MD, The BIO5 Institute, Rm. 339,
1657 E. Helen Street, Tucson, AZ 85721
Phone: (520) 626-6387; FAX: (520) 626-6623; email: donata@email.arizona.edu

METHODS

DNA methylation profiling by Methylated CpG Island Recovery Assay (MIRA)-chip High molecular weight genomic DNA was isolated from CBMC using the DNeasy Blood and Tissue Kit (Qiagen) and fragmented with a Bioruptor sonicator (Diagenode) to produce fragments of 200-700 bp (Figure E1). For each sample, a DNA aliquot was set aside to serve as the non-enriched, input DNA fraction.

The MethylCollector Ultra Kit (Active Motif) was then used for methyl binding protein-dependent capture (MBDCap) (E1) of methylated DNA (enriched fraction). The protocol is based on the MIRA technique (E1) and has the advantage of requiring limited amounts of DNA. For each sample, enriched and input DNA underwent one round of whole genome amplification (WGA) using the GenomePlex Whole Genome Amplification Kit (Sigma). The entire output of the MethylCollector capture (for enriched DNA) or 20 ng of input DNA were used as starting material. WGA reactions were run on 1% agarose gels (1x TBE) to assess fragment size distribution and purified with the QiaQuick PCR Purification Kit (Qiagen).

The efficiency of methylated DNA enrichment was evaluated by quantitative PCR analysis of three control regions that are typically methylated (XIST and NBR2) and unmethylated (APC) across tissues. Primers are provided with the MethylCollector Kit. WGA-input and WGA-enriched DNA (5 ng/ μ l, 5 μ l) were amplified using PerfeCTa SYBR Green FastMix ROX (Quanta BioSciences) and optimal cycling conditions. Samples were run in triplicate and their Ct values averaged. Fold-enrichment was calculated as $2^{(Ct_{WGA\ input} - Ct_{WGA\ enriched})}$. All samples met the required quality control criteria (≥ 3 -fold enrichment in XIST and NBR2, methylation depletion in APC).

WGA-input and WGA-enriched samples were labeled with Cy3 and Cy5 respectively, and co-hybridized to 2.1M Human Promoter Deluxe microarrays (Roche-NimbleGen). The arrays include 2,137,192 experimental probes [from hg18 and covering ~10 kb of each annotated human gene surrounding the transcription start site, CpG islands and regulatory regions] as well as 6726 positive, 4257 negative, 963 non-CG and 38763 random controls. Hybridization intensities were extracted separately for the Cy3 and Cy5 channels and used for subsequent processing and analysis. Labeling, hybridization, scanning and quality control were performed at Roche-NimbleGen. For each sample, the hybridization intensities of the input and enriched channels were quantile-normalized separately to remove technical noise. Probes mapping to sex chromosomes were excluded from the analysis. \log_2 ratios of enriched/input probe

intensities were then calculated from the normalized data. DNA methylation microarray data from this publication were submitted to the NCBI Gene Expression Omnibus (GEO) database and assigned the identifier GSE85228.

Technical validation of results from DNA methylation microarrays Results of genome-wide DNA methylation analysis on the NimbleGen platform were validated by bisulfite sequencing of 16 DMRs (300-600 bp) containing a total of 264 CpG sites and representative of a range of CpG densities and DNA methylation levels (Figure E2). After bisulfite conversion (EZ DNA Methylation-Gold Kit, Zymo Research), target regions were amplified with Platinum Taq DNA Polymerase High Fidelity (Invitrogen) using primers designed to amplify exclusively converted DNA (*BiSearch*, <http://bisearch.enzim.hu>) (Table E4). PCR products were run on 1% agarose gels and cloned into the pCR4-Topo vector (Invitrogen). After transformation into *E. coli* One Shot TOP10 competent cells, individual colonies were picked and analyzed. For each sample, 10-25 clones were sequenced with forward or reverse M13 primers. Sequences were edited and manually curated in *CodonCode Aligner*. Percent methylation per CpG site per clone was determined using *BISMA* (<http://biochem.jacobs-university.de/BDPC/BISMA>). Bisulfite sequencing data were summarized by the median percentage methylation across the CpG sites in each region for a total of 216 DNA methylation estimates. The corresponding estimates of microarray DNA methylation intensity were derived from the median probe signal intensities (normalized \log_2 ratios of enriched/input sample) across the same region (E2).

Functional DMR annotation DMRs were annotated using data from the hg19 version of the genome in *Homer* (Hypergeometric Optimization of Motif EnRichment, <http://biowhat.ucsd.edu/homer/>), which determines the distance to the closest transcription start site, assigns the DMR to that gene, and then determines the genomic annotation of the region occupied by the center of the DMR. DMR coordinates were also used to search for overlaps with DNase I hypersensitive sites identified by the ENCODE project (<http://www.genome.ucsc.edu/ENCODE/>) in peripheral blood CD14⁺ monocytes (RO01746) and CD4⁺ Naive T cells (Wb11970640). For all subsequent gene annotation analyses, DMR coordinates were overlapped with coordinates of RefSeq genes +/- 5 kb, allowing multiple genes to be associated with a single DMR.

DNA methylation analysis in the COAST cohort was performed using the Infinium HumanMethylation450 BeadChip array (Illumina) (E3). Probes located on the sex chromosomes and those that could not be distinguished from the background (detection *P*-value > 0.01 in 75%

of the samples) were removed. Probes were also removed if they mapped to multiple regions of the genome after bisulfite conversion or if they overlapped with the location of known SNPs (E4). This reduced the number of probes from 485,512 to 327,214. Methylation data were processed using the *minfi* R package (E5) and Infinium type I and type II probe bias was corrected using the SWAN algorithm (E6). The raw probe values were then corrected for color imbalance and background by controls normalization. The methylation level at each CpG site was reported as a β value (i.e., the fraction of signal obtained from methylated beads over the sum of methylated and unmethylated bead signals), which is interpreted as percent methylation. Principal component analysis was performed to identify chip effects and confounding variables, and the ComBat function in the *sva* R package was used to adjust for these variables.

SUPPLEMENTARY FIGURES

Figure E1. Workflow of DNA methylation profiling. Genomic DNA was fragmented by sonication and divided into two aliquots: one underwent methyl-binding protein methylation capture (MBDCap) and was enriched for methylated DNA, while the other was left untreated. The two fractions were then whole genome-amplified, fluorescently labeled [captured (enriched)=red, untreated (input)=green], mixed and hybridized to Human DNA Methylation 2.1M Deluxe Promoter Arrays (Roche NimbleGen). After scanning the arrays, the hybridization intensities for each probe were extracted separately for the red and green channels, and were quantile-normalized to remove technical noise. The difference between normalized intensities [\log_2 enriched – \log_2 input = \log_2 (enriched/input), referred to as the \log_2 ratio] was then calculated and used as a measure of methylation levels. Measurements for 16 genomic regions were validated by bisulfite sequencing. Regions differentially methylated in the asthmatic and non-asthmatic groups were detected using Roche-Nimblegen scripts that implement a probe sliding-window ANOVA. DMRs were functionally annotated using Homer and Ingenuity Pathway Analysis.

Figure E2. Correlation of bisulfite sequencing and DNA methylation microarray results. Each dot corresponds to the median normalized \log_2 ratios of enriched/input sample across probes (for microarray data) or the median percentage DNA methylation across CpG sites (for bisulfite sequencing data) for each region in each subject. The correlation between median normalized \log_2 ratios from microarray analysis and median percent DNA methylation from bisulfite sequencing was assessed by measuring the Spearman correlation coefficient (ρ).

Figure E3. Distribution of asthma-associated DMRs by chromosome and genomic location. A) Manhattan plot of asthma-associated DMRs. The x axis depicts the chromosomal location of each DMR. The y-axis shows the Benjamini Hochberg (BH)-adjusted P -values from the probe sliding window ANOVA. The minimum value of the y-axis was set at 2 because a significance threshold of 0.01 was imposed on the adjusted P -values. Genes associated with top hits are labeled. **B) Genomic location of asthma-associated DMRs.** The annotation is based on the center of the DMR, as defined by the Homer package. The genomic distribution of DMRs differed significantly from the distribution of probes across the entire array ($\chi^2= 19.49$, $df = 7$, P -value = 0.007). Fifty-thousand permutations were performed to assess whether this distribution differed from random expectations (permutation P -value = 0.008). Standardized residuals were computed for each category in order to assess which genomic locations contributed to the overall statistical significance. Absolute values > 1.96 significantly contribute to the overall χ^2 test statistics. UTR: untranslated region, TSS: transcription start site (-1kb to +100 bp), TTS: transcription termination site (-100 bp to +1kb).

Figure E4. Regulatory potential of the SMAD3 DMR. The SMAD3 DMR was mapped to the human genome (hg19/GRCh37) using University of California Santa Cruz (UCSC) Genome Browser tools. Tracks are specified on the left. UCSC genes are shown in blue. Nearby CpG islands (with identifier) are shown in green. DNase I hypersensitive sites (HSS) identified in

CD14⁺ monocytes and CD4⁺ naïve T cells are shown in red and blue, respectively. Post-translational histone modifications (H3K27Ac, H3K4Me1, and H3K4Me3) identified in CD14⁺ monocytes, CD4⁺ naïve T cells, and peripheral blood mononuclear cells (PBMC) (Roadmap Epigenomics Project) mark poised/active regulatory regions (E7). The bottom track shows common SNPs (MAF > 10%) from the HapMap CEU population, none of which are associated with asthma. The genomic region that surrounds the *SMAD3* DMR (+/- 100 bp) is highlighted in red. The figure covers 5 kb upstream and downstream of the *SMAD3* DMR.

Figure E5. Association between *SMAD3* DNA methylation at birth and childhood asthma in the IIS cohort. *SMAD3* methylation was assessed by bisulfite sequencing and expressed as mean percentage DNA methylation across 8 consecutive CpG sites in the *SMAD3* DMR. N: non-asthmatic, A: asthmatic. *P*-value by Wilcoxon two-sample test.

Figure E6. *SMAD3* CpG7 methylation in IIS and MAAS. *SMAD3* methylation was assessed by bisulfite sequencing and expressed as percent methylation at *SMAD3* CpG7 in neonates from the IIS and MAAS cohorts. N: non-asthmatic, A: asthmatic. *P*-values by Wilcoxon two-sample test.

Figure E7. Estimation of CBMC composition in the COAST cohort. Proportions of CBMC cell types were estimated using DNA methylation data generated on the Illumina HumanMethylation450 BeadChip and a cord blood reference panel (E11). N: non-asthmatic, A: asthmatic. *P*-values by Wilcoxon two-sample test.

Figure E8. Effects of maternal asthma on the association between neonatal *SMAD3* methylation and childhood asthma in COAST after adjusting for CBMC composition. Residual methylation values for *SMAD3* (cg02486855, Illumina HumanMethylation450 BeadChip) were calculated by adjusting for CBMC composition using linear regression. N: non-asthmatic, A: asthmatic. *P*-values by Wilcoxon two-sample test.

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