Increased vitamin D levels at birth and in early infancy increase offspring allergy risk—evidence for involvement of epigenetic mechanisms

To the Editor:

Although a beneficial effect of vitamin D on health is widely accepted, its role in allergy development has been controversial. Both allergy-preventing and allergy-promoting effects have been reported. Thus, a deeper mechanistic understanding of how vitamin D is related to the regulation of immune reactivity and allergic inflammation is required. Vitamin D was shown to modify gene expression[1] through binding of the vitamin D receptor to vitamin D response elements. However, only 26% of the genes identified as regulated by vitamin D have a vitamin D response element in proximity to their transcription start site (TSS),[1] indicating that additional mechanisms are involved in the transcriptional control by vitamin D. As an additional mechanism, epigenetically mediated transcriptional deregulation through vitamin D–induced changes in DNA methylation was suggested.[2]

Here, we studied DNA-methylation pattern on a genomewide scale at base-pair resolution in healthy newborn children with high and low vitamin D levels to elucidate the role of vitamin D in epigenetic programming of an allergy-protective or allergy-promoting immune reactivity. Within the LINA (Lifestyle and environmental factors and their Influence on Newborns Allergy risk) mother-child cohort,[3] differential DNA methylation was assessed by using whole genome bisulfite sequencing in 6 cord blood samples comparing 3 children with high to 3 children with low 25-hydroxyvitamin D_3 (25[OH]D_3) levels. We assessed blood cell type composition on the basis of promoter methylation level from 5 lineage markers in each sample (see Methods in this article's Online Repository at www.jacionline.org). The analysis showed that the variation in high versus low vitamin D samples was in a nonsignificant range of 1% to 2% for all cell types analyzed in cord blood (see Table E2 in this article's Online Repository at www.jacionline.org). To omit differentially methylated regions (DMRs) solely caused by differences in cellular blood composition between low and high vitamin D samples, we used an additional threshold of 10% methylation difference for DMR calling. Differential methylation was validated in the entire cohort by target-specific methylation analysis. To decipher the regulatory role of 25(OH)D_3-induced DNA-methylation changes, we performed histone modification Chromatin Immuno Precipitation sequencing to segment the genome into distinct regulatory elements and linked differential DNA methylation to transcription (see this article's Online Repository). Furthermore, vitamin D levels and their link to allergic outcomes at different time points in early childhood were studied. Serum 25(OH)D_3 levels were measured in 378 newborns, 466 1-year-old children and 304 2-year-old children (see Fig E1 in this article's Online Repository at www.jacionline.org) by using high-performance liquid chromatography tandem mass spectrometry as described earlier.[4]

Median 25(OH)D_3 levels from birth until age 2 years, seasonal variation, correlations between different ages, and the impact of vitamin D supplementation are presented in Table E1 and Fig E2 (see this article's Online Repository at www.jacionline.org). As described earlier,[4,5] we found that cord blood 25(OH)D_3 level was positively associated with physician-diagnosed food allergy and atopic dermatitis until the children were 3 years old (Table I). In addition, an association was found between 25(OH)D_3 levels at age of 2 years and an enhanced risk of wheezing within the third year of life (Table I).

Next, we identified 508 significantly differentially methylated regions associated with 483 genes in children with high compared with low 25(OH)D_3 levels. Thereby, 25(OH)D_3-dependent methylation changes were predominantly associated with loss of DNA methylation (see Fig E3, *A*, and Table E3 in this article's Online Repository at www.jacionline.org), which is in line with earlier reported data.[2] Among those 508 DMRs, an intergenic DMR spanning 6 CpGs was identified, located 52,400 base pairs upstream of the TSS of group-specific component (vitamin D binding protein; Δmethylation, 17.3%; see Fig E3, *B*, and Table E3). However, validation in low versus high vitamin D cord blood samples in the entire LINA cohort using MassARRAY-based target-specific methylation analysis barely missed the significance level ($P = .063$; see Fig E5 in this article's Online Repository at www.jacionline.org). No DMRs were called for other known key regulators of vitamin D metabolism.

To further filter the 508 significant DMRs assessed by whole genome bisulfite sequencing, we used WEB-based GEne SeT AnaLysis Toolkit (WebGestalt) with all predicted target genes (see Table E3) for pathway analyses. As a preliminary result, 103 significantly affected pathways ($P < .01$) were identified (see Table E4 in this article's Online Repository at www.jacionline.org), including pathways with a potential link to immune system dysfunction or allergy development: "immune system disease," "lung disease/obstructive lung disease," and "skin and connective tissue disease." In total, 3 genes involved in all these 3 pathways were identified: thymic stromal lymphopoietin (*TSLP*), *IL17F*, and *MBL2*. *IL17F* and *MBL2* are involved in inflammation and infection, whereas for *TSLP* links have already been shown to both allergic diseases and vitamin D. *TSLP* was selected for further validation because of its known functional role in allergic diseases.

For *TSLP*, a DMR spanning 5 CpGs 113kbp upstream of the *TSLP* TSS was identified (Δmethylation, 24%; Fig E3, *C*, and Table E3). Further analysis of the region flanking this DMR revealed a broader, significantly regulated region that includes this DMR together with an annotated enhancer region located 100bp downstream (Chr5:110.292.001-110.293.600; $P = .0058$; Δmethylation, 12.2%). Although this broader region was at a remarkable distance from the *TSLP* TSS, chromatin interaction data indicate that this enhancer targets *TSLP* (Fig 1, *A*). We validated the loss of methylation in this region in relation to high cord blood 25(OH)D_3 levels by MassARRAY-based analysis in the entire LINA cohort (see Fig E4, *A*, in this article's Online Repository at www.jacionline.org). No overall correlation was found in all children or those with low 25(OH)D_3 levels. However, in children with high cord blood 25(OH)D_3 levels, the methylation level of this region correlated significantly with 25(OH)D_3 concentrations. This association was observed for 2 CpGs (Chr5:110.292.389-392) located in the *TSLP* enhancer ($P = .026$; $R = -0.236$;

TABLE I. Association between cord blood, year 1 and year 2 25(OH)D_3 levels, and atopic outcomes of the child in the months following the vitamin D measurement

		25(OH)D_3, quartiles							
		n (%)				OR (95% CI)			
	N	First	Second	Third	Fourth	Raw	*P* value	Adjusted	*P* value
Vitamin D birth → outcome month 0-36									
Atopic eczema (symptoms)	320	27 (8.4)	21 (6.6)	15 (4.7)	27 (8.4)	0.98 (0.79-1.22)	.885	1.05 (0.82-1.35)	.673
Atopic eczema (diagnosed)	305	15 (4.9)	13 (4.3)	13 (4.3)	20 (6.6)	1.17 (0.91-1.50)	.216	**1.34 (1.00-1.80)**	**.047**
Food allergy (diagnosed)	291	4 (1.4)	3 (1.0)	5 (1.7)	9 (3.1)	1.48 (0.97-2.25)	.066	**1.86 (1.08-3.20)**	**.023**
Wheezing ever	324	38 (11.7)	34 (10.5)	25 (7.7)	34 (10.5)	0.94 (0.77-1.15)	.542	0.97 (0.78-1.22)	.817
Wheezing recurrent	367	19 (5.2)	23 (6.3)	16 (4.4)	20 (5.4)	0.96 (0.77-1.20)	.701	1.07 (0.83-1.38)	.606
Vitamin D year 1 → outcome month 12-36									
Atopic eczema (symptoms)	409	25 (6.1)	17 (4.2)	30 (7.3)	19 (4.6)	0.97 (0.79-1.20)	.797	1.01 (0.98-1.04)	.690
Atopic eczema (diagnosed)	374	10 (2.7)	7 (1.9)	14 (3.7)	13 (3.5)	1.21 (0.91-1.62)	.191	1.04 (0.99-1.09)	.064
Food allergy (diagnosed)	370	3 (0.8)	5 (1.4)	5 (1.4)	7 (1.9)	1.33 (0.87-2.03)	.186	1.03 (0.97-1.09)	.291
Wheezing ever	409	25 (6.1)	37 (9.0)	33 (8.1)	30 (7.3)	1.06 (0.87-1.28)	.561	1.01 (0.99-1.04)	.312
Wheezing recurrent	408	13 (3.2)	17 (4.2)	21 (5.1)	22 (4.9)	1.25 (0.99-1.58)	.064	1.03 (0.99-1.06)	.097
Vitamin D year 2 → outcome month 24-36									
Atopic eczema (symptoms)	289	12 (4.2)	15 (5.2)	9 (3.1)	7 (2.4)	0.78 (0.58-1.05)	.101	0.92 (0.65-1.29)	.623
Atopic eczema (diagnosed)	289	4 (1.4)	5 (1.7)	7 (2.4)	6 (2.1)	1.16 (0.78-1.72)	.469	1.37 (0.87-2.14)	.168
Food allergy (diagnosed)	289	4 (1.4)	2 (0.7)	2 (0.7)	1 (0.4)	0.64 (0.34-1.22)	.170	0.95 (0.47-1.93)	.881
Wheezing ever	288	5 (1.7)	15 (5.2)	17 (5.9)	15 (5.2)	**1.35 (1.02-1.78)**	**.035**	**1.38 (1.01-1.90)**	**.044**
Wheezing recurrent	288	3 (1.0)	5 (1.7)	9 (3.1)	7 (2.4)	1.34 (0.91-1.97)	.142	1.50 (0.95-2.38)	.080

N = cases with questionnaire data and vitamin D measurement in the given combination. Odds ratios (ORs) with 95% CI and *P* value are shown either for raw data or adjusted for sex of the child, number of siblings, family history for atopy, maternal urine cotinine level (34th week of pregnancy), keeping of a cat, month of birth, and breast-feeding. Significant values are in boldface.

Fig 1, *B*) as well as for 1 further CpG (Chr5:110.292.306) located in the *TSLP* DMR ($P = .024$; $R = -0.233$; see Fig E6 in this article's Online Repository at www.jacionline.org). The methylation level of the TSLP enhancer region was stable from birth until age 3 years (Fig E4, *B* and *C*). On analyzing histone modifications in the *TSLP*-associated DMR and the adjacent enhancer, we found repressive marks (H3K9me3 and/or H3K27me3) in this region in blood cells of children with low 25(OH)D_3 levels whereas children with high 25(OH)D_3 levels were deprived of repressive histone marks. Neither the *TSLP* DMR nor the *TSLP* enhancer region has meQTL-single nucleotide polymorphisms in its neighborhood. Thus, we conclude that differences in *TSLP* methylation levels are not linked to genetic variation.

Altogether, the concomitant loss of DNA methylation and repressive chromatin marks strongly suggest a gain of expression of the target gene *TSLP*. In fact, a negative correlation between methylation in the enhancer region and *TSLP* mRNA expression was observed (Fig 1, *C*). The *TSLP* mRNA expression was significantly elevated at birth ($P = .048$) and age 1 year ($P = .003$) in the high vitamin D group (Fig 1, *D* and *E*). Finally, we found that children who suffered from wheezing symptoms later in life had significantly enhanced *TSLP* mRNA expression at age 1 year (Fig 1, *F*). Furthermore, a link between wheezing symptoms and reduced methylation at CpG Chr5:110.292.315 located in the *TSLP* DMR region could be shown (Δmethylation, 2%; $P = .045$; n = 309 controls vs n = 66 wheezing children).

TSLP plays a critical role in allergic diseases by inducing an inflammatory T_H2 response via conditioning dendritic cell maturation.[6,7] *TSLP* mRNA as well as protein levels were shown to correlate with asthma severity,[8] while treatment of patients with asthma with an anti-*TSLP* antibody reduced airway inflammation before and after allergen challenge.[9] Here, we demonstrated that high cord blood vitamin D levels were associated with epigenetic regulation of an enhancer region shown to interact with the *TSLP* promoter. Children with higher 25(OH)D_3 levels at birth showed a lower DNA-methylation level and a loss of repressive histone marks in this *TSLP* enhancer region, resulting in a higher *TSLP* mRNA expression. Furthermore, a link between enhanced *TSLP* expression and wheezing was found. Our result provides evidence that epigenetic deregulation of *TSLP* could be involved in the vitamin D–related programming for allergic diseases. However, this result does not exclude that vitamin D may act in comparable manner via other genes.

We thank Stephan Wolf and Nicole Diessl at the German Cancer Research Center (DKFZ) Genomics and Proteomics Core Facility for the excellent technical support and expertise. Furthermore, we are grateful to Marion Bähr and Monika Helf who provided support in MassARRAY validation. We cordially thank the participants of the LINA study and Beate Fink, Anne Hain, Livia Sztraka, and Melanie Nowak for their excellent technical assistance and fieldwork. We are grateful to Martin von Bergen and Ulrike Rolle-Kampczyk for providing urine cotinine concentrations.

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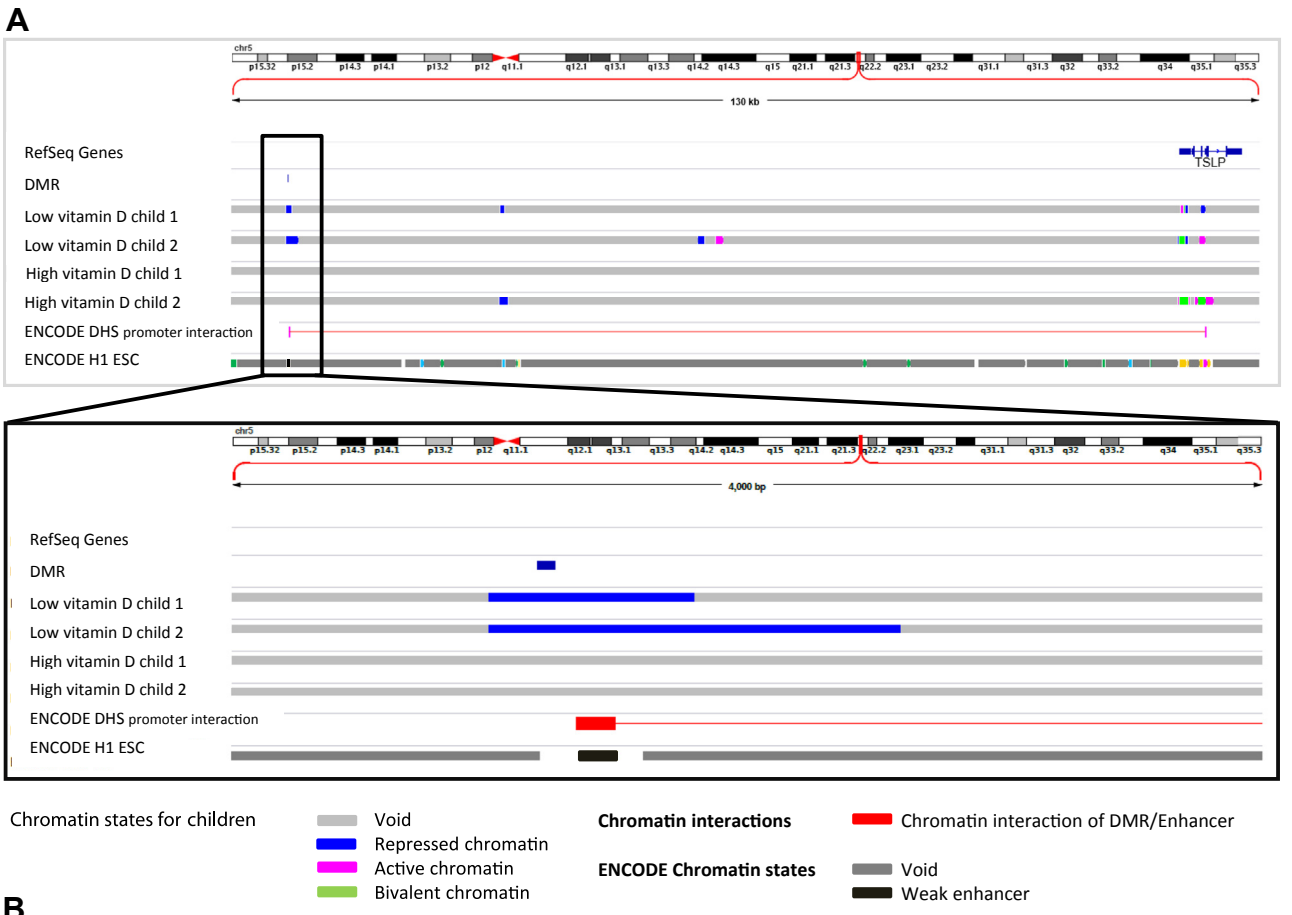
A
chr5
130 kb
RefSeq Genes
TSLP
DMR
Low vitamin D child 1
Low vitamin D child 2
High vitamin D child 1
High vitamin D child 2
ENCODE DHS promoter interaction
ENCODE H1 ESC
4,000 bp
Chromatin states for children
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Active chromatin
Bivalent chromatin
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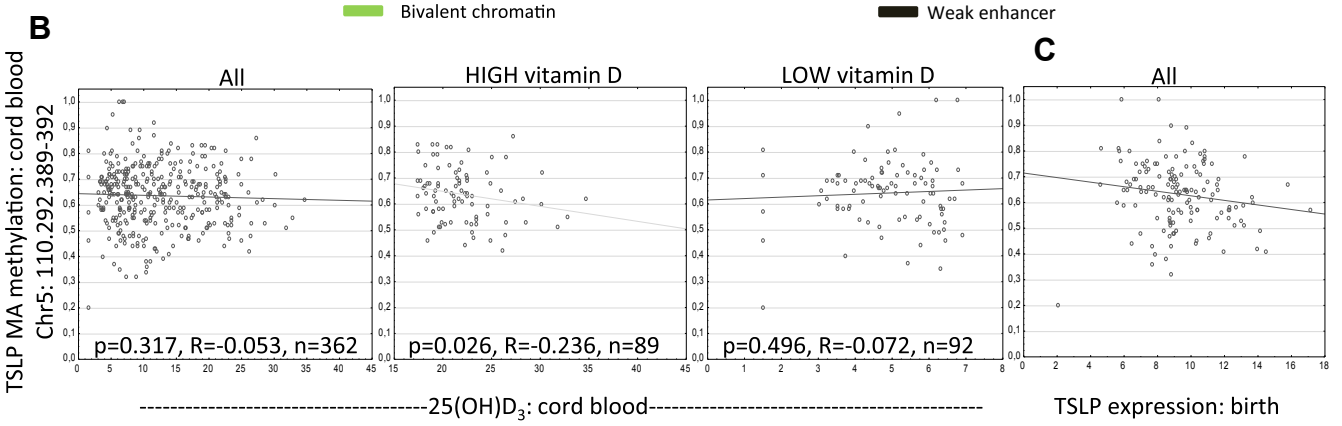
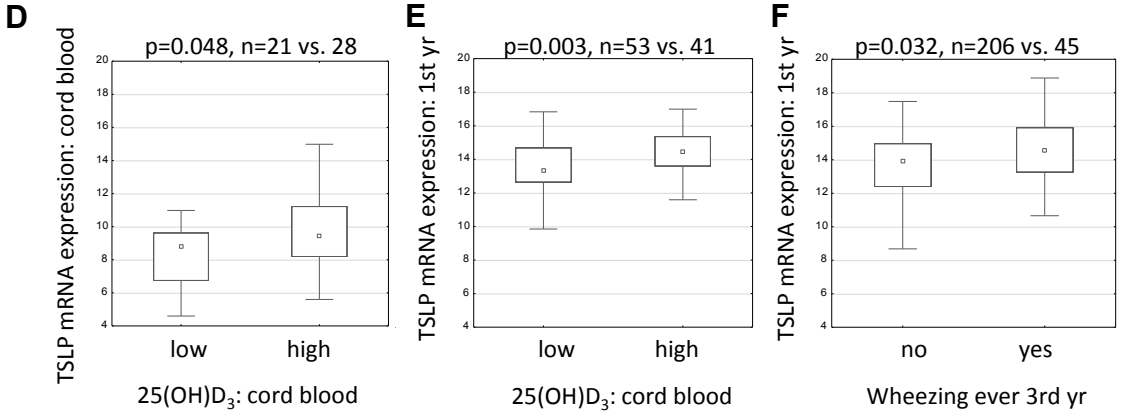
ENCODE Chromatin states
Void
Weak enhancer


B
C
All
HIGH vitamin D
LOW vitamin D
All
TSLP MA methylation: cord blood
Chr5: 110.292.389-392
p=0.317, R=-0.053, n=362
p=0.026, R=-0.236, n=89
p=0.496, R=-0.072, n=92
25(OH)D3: cord blood
TSLP expression: birth


D
E
F
p=0.048, n=21 vs. 28
p=0.003, n=53 vs. 41
p=0.032, n=206 vs. 45
TSLP mRNA expression: cord blood
TSLP mRNA expression: 1st yr
TSLP mRNA expression: 1st yr
low
high
low
high
no
yes
25(OH)D3: cord blood
25(OH)D3: cord blood
Wheezing ever 3rd yr

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This work was supported by Helmholtz institutional funding (Helmholtz Centre for Environmental Research [UFZ] and German Cancer Research Centre—[DKFZ]) and funding by the Institute of Agricultural and Nutrition Science, Martin Luther University Halle-Wittenberg. Further support came from the German Cancer Research Center–Heidelberg Center for Personalized Oncology (DKFZ-HIPO).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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Available online August 15, 2015.
http://dx.doi.org/10.1016/j.jaci.2015.06.040

Effects of lidocaine on regulatory T cells in atopic dermatitis

To the Editor:

Atopic dermatitis (AD) is a chronic and relapsing skin disease characterized by inflammation and pruritus. In our previous hospital-based study of 1008 patients with AD, we found that the proportion of patients with severe AD was 10.7%.[1] Moreover, AD is a huge economic burden for families and society in general due to the long course of relapsed disease.

Regulatory T (Treg) cells control immune homeostasis and balance immune responses during inflammation. Treg cells suppress immune responses by interacting with effector T cells or antigen-presenting cells.[2] Recent clinical research has found that parents, particularly mothers, who have a history of atopy could have babies with less stable $FOXP3^+$ Treg cells in cord blood. These babies have the onset of AD less than 1 year after birth.[3] Therefore, it is likely that the abnormal numbers of Treg cells weaken the inhibition of T_H2 lymphocytes, thus resulting in AD inflammation.

Lidocaine is a widely used short-acting local anesthetic and antiarrhythmic agent. Previous studies demonstrated that lidocaine attenuated bronchoconstriction in patients with severe asthma, which enabled the dosage of oral corticosteroids to be reduced or eliminated in long-term treatment.[4] Because of the similarity of allergic diseases, lidocaine was used as a treatment for AD in China. Previous studies have shown that lidocaine dose-dependently inhibits the proliferative response and release of inflammatory factors from Staphylococcal enterotoxins A- and Staphylococcal enterotoxins B–stimulated PBMCs in patients with AD, contributing to clinical remission.[5]

In vivo, we sought to explore the effect of lidocaine on Treg cells and other key cytokines in patients with AD and murine AD models. Twenty patients were administered lidocaine (3 mg/kg per day) via a slow intravenous drip for 14 days. During

FIG 1. TSLP DMR, histone marks, and mRNA expression. **A,** Location of the *TSLP* DMR in relation to the *TSLP* gene *(upper part)*. The *TSLP* DMR shows a predicted chromosomal interaction with the *TSLP* promoter *(red bar)*. Furthermore, chromatin segmentation tracks generated by ChromHMM are displayed for 2 (high cord blood 25[OH]D_3) vs 2 (low cord blood 25[OH]D_3) samples over the region relating to the DMR and *TSLP* gene *(upper part)*, and a close-up of the DMR region *(lower part)*: Repressed chromatin states are observed in samples of low 25(OH)D_3 *(blue bars)* over the DMR region, and an ECNODE-predicted weak enhancer is found nearby (WE; *black bar*, *lower part* of the Fig 1, *A*). **B,** Association between *TSLP* enhancer methylation at birth (mean of 2 CpGs at Chr5:110.292.389-392, which marks the start of the enhancer region close to the *TSLP* DMR; analyzed via MassARRAY) and cord blood 25(OH)D_3; shown for all participants *(left column)*, only for those within the high vitamin D group (25[OH]D_3 >75th percentile, *middle column*), or for those within the low vitamin D group (25[OH]D_3 <25th percentile, *right column*). **C,** Association between methylation of the *TSLP* enhancer region (2 CpGs at Chr5:110.292.389-392) and *TSLP* mRNA expression, both analyzed in cord blood. **D,** Association between cord blood *TSLP* mRNA expression and 25(OH)D_3 concentrations. **E,** Association between *TSLP* mRNA expression at year 1 (first year) and cord blood 25(OH)D_3 concentration. **F,** *TSLP* mRNA expression at year 1 (first year) in children with (yes) or without (no) wheezing symptoms ever within the third year of life (*P* values from Mann-Whitney *U* test).

Online Repository

Increased vitamin D levels at birth and in early infancy increase offspring allergy risk – evidence for involvement of epigenetic mechanisms

Short title: vitamin D, epigenetic effects and allergy risk

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METHODS

Study design and sample collection

The LINA mother-child-cohort (**L**ifestyle and environmental factors and their **I**nfluence on **N**ewborns **A**llergy risk) was established to investigate how lifestyle and environmental factors in the pre- and postnatal period influence the development of the immune system in early childhood and the risk for allergic diseases later in life (for details see [1, 2]). For this population-based study, 629 mother-child pairs (622 mothers and 629 children; 7 twins) were recruited between May 2006 and December 2008 in Leipzig, Germany (latitude 51.4 °N). Mothers suffering from immune or infectious diseases during pregnancy were excluded from the study. 606 mother-child-pairs participated in the one year follow up, 546 in the two year follow-up, and 514 in the three year follow-up investigation.

Blood samples were obtained at delivery (cord blood) and annually thereafter during scheduled clinical visits. Standardized questionnaires about family history of atopy (FHA), housing and environmental conditions (first or second hand smoke, mould, traffic, noise, pets, renovation activities, personal lifestyle, etc.), as well as atopic outcomes of the children were recorded during pregnancy and at every child's birthday. All questionnaires were self-administered by the parents. Participation in the study was voluntary and informed consent was obtained from all participants. The study was approved by the Ethics Committees of the University of Leipzig (046-2006, 160-2008, 160b/2008).

Atopic outcomes

Atopic dermatitis was recorded as a parental report of a physician-diagnosed dermatitis or of dermatitis symptoms during the last 12 months. Children were classified as having dermatitis symptoms when parents reported an intermittent itchy skin rash, which affected places other than the nappy area and lasted at least 2 weeks or appeared repeatedly in the last 12 months. Food allergy and asthma were recorded as a parental report of a physician's diagnosis. Ever wheezing

was recorded as a parental report of wheezing symptoms ('Did your child suffer from whistling / wheezy respiration during the last twelve months?'), recurrent wheezing as a repeated report of wheezing symptoms in the relevant time window.

Assessment of vitamin D

Serum 25 hydroxy-vitamin D_3 ($25(OH)D_3$) levels were measured in a LINA subgroup of 378 newborns, 466 one year old and 304 two year old children by liquid chromatography tandem mass spectrometry (HPLC-MS/MS) as also described elsewhere [3]. Analysis was performed by Agilent 1100 HPLC (Agilent Technologies, Böblingen, Germany) with an API 2000 triple quadrupol mass spectrometer (Applied Biosystems, Darmstadt, Germany) using the HPLC-MS/MS *MassChrom* Reagent Kit (Chromsystems, Munich, Germany). A high resolution analytical column was used to separate the C3-epimer of $25(OH)D_3$.

The assay detection limit was defined as 3 ng/ml for $25(OH)D_3$ of cord blood and 3.9 ng/ml for $25(OH)D_3$ of one and two year old children. Only 5 cord blood samples had $25(OH)D_3$ values below the detection limit and were included in analyses using half of the defined detection limit.

Further, the vitamin D supplementation was recorded as a parental report of vitamin D supplementation within the child's first year of life ('Did your child get vitamin D supplements during the months 1-3, 4-6 or 7-12, respectively?')

Isolation of gDNA from whole blood and bisulfite treatment

Genomic DNA was isolated from whole blood samples (peripheral blood or cord blood) using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany), as stated by the manufacturer. The DNA was chemically modified with sodium bisulfite using the EZ methylation kit (Zymo Research, Freiburg, Germany) according to the manufacturer's instructions.

Whole genome bisulfite sequencing (WGBS) Library Construction and Sequencing

Cord blood samples from three newborn children with high (>19.9ng/ml) and three newborn children with low (<7.9ng/ml) 25(OH)D_3 were selected for whole genome bisulfite sequencing.

Illumina Libraries were prepared using the TruSeq DNA Sample Prep Kit v2-Set A (Illumina Inc., San Diego, CA, USA) according to the manufacturer's instructions. Briefly, 2 µg genomic DNA in 55 µl nuclease-free water (Ambion/Life Technologies GmbH, Darmstadt, Germany) was fragmented using a Covaris S2 ultrasonicator (Covaris, Woburn, Massachusetts, USA) and the following settings: 10% duty cycle, intensity 5, 200 cycles per burst, frequency sweeping, for 6 minutes. The fragmented DNA was end-repaired, extended with an 'A' base on the 3′ end and ligated with TruSeq paired-end indexing adapters. Then, adapter-ligated fragment libraries were treated with bisulfite using the EpiTect Bisulfite Kit (Qiagen, Hilden, Germany) following the instructions in the Illumina WGBS for Methylation Analysis Guide (Part # 15021861 Rev. B). After bisulfite conversion the fragment libraries were directly amplified using KAPA HiFi Uracil+ DNA Polymerase according to the settings for TruSeq™ DNA in the technical Data Sheet (KAPA HiFi HotStart Uracil+ Ready Mix, KR0413 - version 1.12, peqlab, Erlangen, Germany). Two 50 µl PCR reactions per sample were prepared and 14 cycles of PCR performed. Amplified fragment libraries were pooled and purified with 1x Agencourt AMPure XP beads (Beckman Coulter GmbH, Krefeld, Germany). WGBS Illumina Libraries were validated using Agilent 2100 Bioanalyzer (DNA 1000 Kit, Agilent Technologies) and Qubit fluorometer (Qubit dsDNA HS Assay Kit, Invitrogen/ Life Technologies GmbH, Darmstadt, Germany).

The final libraries were clustered on the cBot (Illumina Inc., San Diego, CA, USA) using TruSeq PE Cluster Kit v3 according to the manufacturer`s instructions with a final concentration of either 9 pM or 10 pM (depending on the sample) spiked with 1% PhiX control v3 and an additional dedicated PhiX control lane. Sequencing on HiSeq2000 (101 bp paired-end) was performed using standard Illumina protocols and the 200-cycles TruSeq SBS Kit v3 (Illumina Inc., San Diego, CA, USA).

Sequence alignment and cytosine methylation estimation

We used a mapping method as described earlier [4] for reads from conventional whole-genome bisulfite sequencing. Briefly, the hg19 reference genome (37d5) was transformed *in silico* for both the top strand (C to T) and bottom strand (G to A). Before alignment, adaptor sequences were trimmed using SeqPrep (https://github.com/jstjohn/SeqPrep). Then the first read in each read pair was C-to-T converted and the 2nd read in the pair was G-to-A converted. The converted reads were aligned to a combined reference of the transformed top (C to T) and bottom (G to A) strands using BWA (bwa-0.6.1-tpx) [5] with default parameters except the quality threshold for read trimming (-q) of 20 and the Smith-Waterman for the unmapped mate disabled (-s). After alignment, reads were converted back to the original states and reads mapped to the antisense strand of the respective reference were removed. Duplicate reads were removed using Picard MarkDuplicates (http://picard.sourceforge.net/). Reads with alignment scores less than 1 were filtered before subsequent analysis. Total genome coverage was calculated using the total number of bases aligned from uniquely mapped reads over the total number of mappable bases in the genome.

At each cytosine position, reads that maintain the cytosine status were considered methylated, and the reads that have cytosine converted to thymine were considered unmethylated. Only bases with Phred-scaled quality score of ≥ 20 were considered.

Cellular composition estimation

We used the promoter methylation level from 4 lineage markers to assess the proportion of each cell type in each sample: CD14 for monocytes, CD3D and CD3G for T cells and CD19 for B cells. The rationale behind our approach was that specific promoter regions of marker genes are fully demethylated in the respective cell lineage, whereas they are fully methylated in all other cell types. For each marker gene, we first extracted all CpGs within the promoter region (TSS upstream 2 kb and downstream 500 bp) for each sample. Then we removed uninformative CpGs, which are lowly methylated (methylation level < 0.3) in all samples. For the remaining CpGs, we calculated the average methylation level (av_meth) in each sample. The proportion of the respective cell type was

148 then estimated as 1-av_meth. For granulocytes, we derived a cell type specific methylation
149 signature based on BRD4 promoter methylation from a genome wide methylation analysis. We first
150 derived the 7 CpG sites that are unmethylated in granulocytes and methylated in the other
151 hematopoietic lineages according to the methylation signature by Houseman and colleagues. For
152 each of the 7 CpG sites, we carefully inspected the methylation level around it in whole-genome
153 bisulfite sequencing data from different blood cell types. The promoter region of BRD4 is
154 unmethylated in granulocytes (granulocytic neutrophils) and methylated in B cells and
155 hematopoietic stem/progenitor cells (HSPC)
156
157 **DMR calling and annotation**
158 Using the bsseq v0.10 package [6] for R statistical software v3.0.0 we smoothed bisulfite sequencing
159 data and called candidate DMRs. Because of our high average CpG coverage we performed
160 smoothing on a small window size with minimum ns=11 CpGs and a minimum total width of 1 kb
161 (h=500), breaking the smoothing if gaps between CpGs exceeded 2 kb (maxGap=2000). We
162 calculated average raw methylation levels of each DMR and sample and performed a moderated t-
163 test as in SAM statistics (significance analysis of microarrays [7], R-package siggenes v1.36.0 [8]) to
164 assign p-values to each of the DMR. Based on the p-value (pSAM<0.1) and the level of mean
165 methylation changes (Δmethylation>0.1 in both raw and smoothed data), we filtered and ranked the
166 DMR list for downstream analyses.
167
168 One of the advantages of WGBS over e.g. 450k arrays is that we can explore regional context
169 rather than individual CpGs. Particularly with small sample sizes this is of importance, so our
170 intention was to identify differentially methylated regions (DMRs) rather than positions (DMPs).
171 DMPs are potentially more biased to genomic background because of CpG-destroying SNPs. We
172 aimed to minimize such effects by applying a smoothing approach with subsequent DMR calling as
173 previously described in the bsseq-method [9]. Of course, we do not generally question the potential
174 biological relevance of individual CpG methylation. However, to control the false positive rate, we

set a threshold of 3 CpGs, and additionally applied the moderated t-statistics (with permuation analysis) implemented in SAM-analysis to ensure constitutively differential methylation for each region. SAM p-values are lowest for regions where all samples of one group have lower methylation values than samples of group two. We found that a SAM p-value cutoff of $p<0.05$ is sufficient to obtain consistency in differential methylation.

ChIP-seq assays

Chromatin Immuno Precipitation sequencing (ChIP-seq) was performed for four histone marks for 4 children (2 children with high and 2 children with low cord blood $25(OH)D_3$ levels) where whole genome bisulfite sequencing data was available. Sample preparation was performed using standard ChIP-seq protocols. In detail, peripheral blood mononuclear cells were fixed with freshly prepared 0.4% formaldehyde in PBS for 10 min. The reaction was stopped with 125 mM glycine for 5 min. Cells were incubated in swelling buffer (25 mM HEPES, pH 7.8, 1 mM $MgCl_2$, 10 mM KCl, 0.1% NP-40, 1 mM DTT) on ice for 10 min. Then the cells were resuspended in MNase buffer (25 mM KCl, 4 mM $MgCl_2$, 1 mM $CaCl_2$, 50 mM Tris/HCl pH 7.4) and 4 U MNase per $1x10^6$ cells was added. After 15 min incubation at 37°C, MNase was stopped by adding 10x covaris buffer (100 mM Tris pH 8.0, 2 M NaCl, 10 mM EDTA, 5% N-lauroylsarcosine, 1% Na-deoxycholate, supplemented with protease inhibitors). The samples were sonicated for 15 min with a Covaris S2 system with the following parameters: burst 200, cycle 20%, intensity 8. After centrifugation the supernatant was collected and directly used for IP.

After IgG preclearance the sheared chromatin was incubated with protein G magnetic beads (Cell signaling, 9006) and with 4 µg of the following antibodies overnight: H3K4me1 (abcam, ab8895), H3K9me3 (abcam, ab8898), H3K27me3 (abcam, ab6002), H3K27ac (abcam, ab4729) and H3 (abcam, ab1791). After washes with 1x covaris buffer (10 mM Tris–HCl, pH 8.0, 200 mM NaCl, 1 mM EDTA, 0.5% N-lauroylsarcosine, 0.1% Na–deoxycholate), high-salt-buffer (50 mM Hepes pH 7.9, 500 mM NaCl, 1mM EDTA, 1% Triton X-100, 0.1% Na–deoxycholate, 0.1% SDS), lithium buffer (20 mM Tris–HCl pH 8.0, 1 mM EDTA, 250 mM LiCl, 0.5% NP-40, 0.5% Na–deoxycholate) and 10

mM Tris–HCl, chromatin was eluted from the magnetic beads (elution buffer: 50 mM Tris pH 8.0, 1 mM EDTA, 1% SDS, 50 mM $NaHCO_3$) and the crosslink was reversed overnight. After RNase A and proteinase K digestion, DNA was purified and cloned in a barcoded sequencing library for the Illumina sequencing platform. In brief, after DNA repair and A-addition NEBNext adapters (NEB, E7335) were ligated and digested with the USER enzyme. Barcodes (NEB, E7335) were introduced via PCR with a maximum of 14 cycles by the NEBNext polymerase (NEB, M0541). Size selection for mononucleosomal insert fragments was done with Ampure XP beads (Agencourt, A63880).

Peak calling for Histone modification ChIP-seq

Two active and two repressive histone marks were analyzed (H3K4me1, H3K27ac, H3K9me3, H3K27me3). Regions of the genome exhibiting significant enrichment of histone modifications were identified using SICER v1.3 [10] and MACS v 1.4.1 [11]. Reads were aligned as outlined by Feng et al. [12]. Briefly, reads were aligned to the GRCh37 human genome assembly with hs37d5 decoy sequence concatenated using the bowtie 1.0 short read aligner [13] only reporting the uniquely mapping reads in SAM format [14]. MACS was used to call peaks setting the histone modification SAM file as the treatment and the H3 SAM file as the control files, suppressing calculation of shifting model, using a fixed background lambda, and using the shift size as half the size reported by the Bioanalyzer (or 166 bp, the mean fragment size, in the absence of a reported fragment size). A threshold of $p < 1e\text{-}5$ was used to identify significant peaks. Additional peaks were called user SICER. The SAM files were sorted using samtools sort, and then converted to BED format using bedtools bamToBed [15]. SICER was used to call peaks on all histone modifications using H3 as a control, removing all duplicate reads, defining the fragment length as in MACS, 0.85 expected genome coverage, a window size of 200bp, gapping enriched windows 200bp apart, and setting the FDR cutoff to 0.05. The MACS and SICER peaks calls were merged to maximize sensitivity. Quality control statistics were calculated, as outlined by Landt et al. [16] including the fraction of read in peaks (FRiP), PCR bottleneck coefficient (PBC) using custom scripts, and the normalized and relative strand correlations (NSC/RSC) using SPP v1.046 in R v2.15.0 (http://www.R-project.org).

Pathway enrichment

Enrichment of genes related to vitamin D DMRs was determined using the latest update of the online Gene SeT AnaLysis Toolkit (WebGestalt) [17]. Predicted targets of all DMRs (see Table EIII) were used as an input and enrichment in disease related genes was calculated based on a hypergeometric test followed by a Benjamini & Hochberg multiple test adjustment. A minimum of 3 genes per disease term was required to be considered for enrichment.

MassARRAY methylation analysis

Quantitative DNA methylation analysis of the GC and TSLP gene was performed using Sequenom's MassARRAY platform (Sequenom, Hamburg, Germany). Briefly, genomic DNA from whole blood samples was chemically modified with sodium bisulfite using the EZ methylation kit (Zymo Research, Freiburg, Germany) according to the manufacturer's instructions. PCR primers were designed with an additional T7 promoter tag for *in vitro* transcription for each reverse primer, as well as a 10-mer tag on the forward primer. Bisulfite treated DNA was PCR amplified (GC: forward primer: aggaagagagAGAGTTTGTTTATTTTGGAATTG, reverse primer: cagtaatacgactcactatagggagaaggctTTTATTTATACTTCCCAAAACC, amplicon coordinates chr4:72723448-72723802; TSLP: forward primer: aggaagagagGTTTTTTTGGGTGTAGTTGTAG, reverse primer: cagtaatacgactcactatagggagaaggctATACTAAAAAACACCACCTAC, amplicon coordinates chr5:110292168-110292499) using HotStarTaq DNA Polymerase (Qiagen, Hilden, Germany) with the following cycling program: 95°C for 15 min, followed by 45 cycles of 94°C for 30 sec, 56°C for 30 sec, 72°C for 1 min and a final elongation step at 72°C for 5 min on a LightCycler 480 (Roche Applied Science, Mannheim, Germany). The PCR product was *in vitro* transcribed and cleaved by RNase A using the EpiTyper T Complete Reagent Set (Sequenom, Hamburg, Germany) and subjected to MALDI-TOF mass spectrometry analysis to determine methylation patterns as previously described [18]. DNA methylation standards (0%, 20%, 40%, 60%, 80%, and 100% methylated genomic DNA) were used to control for potential PCR bias.

RNA Extraction, cDNA Synthesis, and qPCR

Total RNA was prepared from fresh cord blood by using peqGold RNA Pure (peqlab, Erlangen, Germany) according to manufacturer's instructions. The cDNA synthesis was carried out with 5 µg of RNA by using ImProm-II™ Reverse Transcription System (Promega, Mannheim, Germany).

Gene expression was measured using the 96.96 Dynamic Array (Fluidigm, San Francisco, CA, USA). Intron-spanning primers were designed and UPL probes were selected by the Universal Probe Library Assay Design Center (http://qpcr.probefinder.com/organism.jsp, GC_for 5'-gtctgcctctgaagattgcat, -rev 5'-tggataaattgtcacagagttttactg, UPL 27; TSLP_for 5'-ccaggctattcggaaactca, -rev 5' ttgtgacacttgttccagacatt, UPL 35). A preamplification reaction was performed by pooling all primers (final concentration, 50 nM), 5 µl of cDNA and 2x PreAmp Master Mix (Applied Biosystems/Life Technologies GmbH, Darmstadt, Germany). The cycling program consisted of 95°C for 10 min, followed by 14 cycles of 95°C for 15 sec and 60°C for 4 min on a LightCycler 480 (Roche Applied Science, Mannheim, Germany). The qPCRs of 1:5 diluted with TE buffer preamplified templates were performed following manufacture's instruction for UPL (Roche Applied Science, Mannheim, Germany) assays. Briefly, for each individual assay, a 10X Assay Mix that contained 2 µM of each forward and reverse primer, 1 µM UPL probe and 0.025% Tween-20 was prepared, and 5 µl of the mix was loaded into the assay inlets of the array. Into the sample inlets, 5 µl of the following solution was dispensed: 2.5 µl of PreAmp sample in 1.1X of FastStart Universal Probe Master Mix (Roche Applied Science, Mannheim, Germany). The cycling program consisted of 2 min at 50°C, 10 min at 95°C, followed by 35 cycles of 95°C for 15 sec, 70°C for 5 sec, and 1 min at 60°C. All reactions were performed in triplicates.

Gene expression values were determined by using the $2^{-\Delta\Delta CT}$ method [19] with *GAPD* and *GUSB*, as reference genes and normalized to the lowest measured value.

Only data with raw expression values above the detection limit were included in the analyses.

Chromatin interaction datasets

We used a published dataset describing genomic interactions between distal loci based on predicted interactions obtained from DNAseI hypersensitivity assays conducted as part of the ENCODE project in 125 cell lines [20]. The predicted interactions relate distal DHS regions with gene promoters. An interaction between a genomic element and a gene was defined as any event in which the DHS overlaps with the genomic element considered. The dataset was downloaded from ftp://ftp.ebi.ac.uk/pub/databases/ensembl/encode/integration_data_jan2011/byDataType/openchrom/jan2011/dhs_gene_connectivity/

Statistical analyses

$25(OH)D_3$ levels were not normally distributed. Therefore, analyses were performed using non-parametric tests in general and presented as medians with 25^{th}-75^{th} percentile. Spearman's rank correlation test was performed to analyze metric data such as for the correlation between $25(OH)D_3$ at different time points. Seasonal distribution of $25(OH)D_3$ concentration was calculated using ANOVA. The relationship between categorical data such as infant's outcomes and metric data, such as $25(OH)D_3$ levels was addressed using the Mann-Whitney U-test. In addition, multivariate logistic regression models were used to consider possible confounding factors. Here, data are presented as odds ratios per $25(OH)D_3$ quartile with 95% confidence interval adjusted for gender, number of siblings, FHA, smoking during pregnancy (via maternal cotinine levels), breast feeding, keeping of a cat and month of birth.

All p-values <0.05 were considered to be significant. Statistical analyses were performed in STATISTICA for Windows, Version 12 (Statsoft Inc. (Europe), Hamburg, Germany).

RESULTS and DISCUSSION

Vitamin D levels at different ages and vitamin D supplementation

$25(OH)D_3$ at birth and at year 1 and 2 after birth were assessed in the subgroup of children from the LINA cohort with available blood samples (Figure E1). Median $25(OH)D_3$ levels in cord blood and peripheral blood of one and two year old children are shown in Table EIA. As already demonstrated for cord blood [3], $25(OH)D_3$ levels at year two followed a significant seasonal distribution ($p<0.05$, Figure E2A). In contrast, $25(OH)D_3$ levels at year one showed a season-independent trend.

Due to the general rickets prophylaxis within the first year of life (details below) absolute $25(OH)D_3$ was generally higher with minor variation due to seasonal sunlight exposure. In one year old children, only 4.9% had deficient (<20 ng/ml), 27.7% had insufficient (20 – 29.9 ng/ml) and 67.4% had optimal (>30 ng/ml) $25(OH)D_3$ levels (cut-offs according to [21]). In contrast, 39.1% of all two year old children had a deficient, 44.1% had an insufficient, and only 16.8% had an optimal $25(OH)D_3$ level.

We observed a high correlation when comparing $25(OH)D_3$ levels at birth and levels at year one ($R=0.238$, $p<0.001$) and two ($R=0.435$, $p<0.001$). Also $25(OH)D_3$ concentrations of one and two year old children ($R=0.500$, $p<0.001$) showed significant correlations (Figure E2B). These correlations remained significant when analyzed separately for those children who were supplemented with vitamin D throughout the first 12 months and after correction for month of birth (data not shown).

German pediatricians usually recommend a supplementation with vitamin D (400-500 IE/10µg/d) for rickets prevention. Of the LINA participants with $25(OH)D_3$ analyses at year one, 94.7% supplemented vitamin D at least within the first 3 months of life and 78.9% continuously during the first 12 months of life. 4.9% supplemented exclusively within the first 3 months. No supplementation with vitamin D at all during the first 12 months of life was reported for 4.2% of the study participants. Mean levels of $25(OH)D_3$ at the age of one and two in relation to their supplementation during the first year are shown in Table EIB. Taken together, only the continuous supplementation throughout

the first year resulted in significantly higher 25(OH)D_3 values at the age of one compared to those children who were never supplemented with vitamin D within the first year. Interestingly, 25(OH)D_3 levels at the age of two were not affected by the first year supplementation anymore. Independent of vitamin D supplementation, cord blood 25(OH)D_3 concentrations mostly reflecting maternal levels during pregnancy correlated significantly with levels at the age of one and two years. These correlations also remained significant after correction for month of birth.

Vitamin D levels and allergic outcomes

We next investigated the relationship between relevant outcomes and 25(OH)D_3 within the first, second and third year (Table I). In an earlier study in our cohort we already showed an association between the development of food allergy up to the age of two and high 25(OH)D_3 levels during pregnancy and in cord blood and [3]. Here, we questioned whether the allergy-promoting effects seen for vitamin D at birth remain stable beyond the second year of life and can also be reproduced for 25(OH)D_3 blood levels at later time points in infancy. Asthma was not included in our analyses due to its low prevalence until the age of three (less than 5 cases in the subgroup of children with 25(OH)D_3 measurements). Multivariate logistic regression models were calculated and adjusted for confounders known to have an influence on the development of allergic or pre-allergic diseases (gender of the child, number of siblings, family history for atopy, smoking during pregnancy (maternal cotinine levels), keeping of a cat, month of birth and breastfeeding within the first 6 months of life). 25(OH)D_3 levels at birth were positively associated with questionnaire documented food allergy (adj. OR 1.86 (95 % CI: 1.08 - 3.20) and atopic dermatitis (adj OR 1.34 (95 % CI: 1.00 - 1.80) of the child within the first three years of life (Table I). For both allergic outcomes, a promoting effect of vitamin D in the pre- or neonatal period was described also by other groups [22, 23].

Due to the general vitamin D supplementation and the consequently very high levels of 25(OH)D_3 during the first year, only some very small positive trends were observed for 25(OH)D_3 levels at year one and recurrent wheezing as well as atopic dermatitis during the years two and three. 25(OH)D_3

concentrations at year two were significantly associated with an enhanced risk of wheezing (adj OR 1.38; 95 % CI: 1.01 - 1.90) within the third year of life. Wheezing is widely recognized as an early indicator for impaired lung function and an increased risk for asthma later in life. About 22-46% of children with wheezing symptoms early in life were presented with an asthma diagnosis later on. This finding is in accordance with the earlier finding that vitamin D levels in infants were associated with an increased risk of allergic respiratory outcomes [24, 25].

Vitamin D levels and DNA methylation pattern

As reported earlier in our LINA study [3], high 25(OH)D_3 levels at birth might have an adverse rather than a protective effect on allergic outcomes. To find a potential mechanistic link that supports these so far only correlative epidemiological data, we studied the impact of 25(OH)D_3 levels at birth on epigenetic reprogramming induced by vitamin D. Therefore, we assessed differential DNA methylation by whole genome bisulfite sequencing (WGBS) in six cord blood samples comparing three children with high to three with low 25(OH)D_3. First, we analyzed the promoter methylation of five lineage markers in each sample to assess the blood cell type composition. The analysis showed that the variation according to vitamin D levels was in the range of 1-2 % for all cell types (Table EII). To omit differentially methylated regions (DMRs) solely caused by differences in cellular blood composition between low and high vitamin D samples we additionally used a threshold of 10% methylation difference for DMR calling. In total, we identified 508 significant DMRs associated with 483 genes in children with high compared to low 25(OH)D_3. Interestingly, 25(OH)D_3 dependent differential methylation was associated predominantly with loss of DNA methylation (Figure E3A and Table EIII).

Epigenetic regulation of genes involved in vitamin D metabolism

It was shown before, that adults with different vitamin D levels display modified methylation patterns in genes involved in vitamin D metabolism. In newborn children we found no significant methylation change in genes involved in vitamin D metabolism. Nevertheless, a wide intergenic DMR spanning

6 CpGs was identified located 52,400 base pairs (bp) upstream of the transcription start site (TSS) of *GC* (vitamin D binding protein; mean **Δ** methylation = 17.3%, Figure E3B, Table EIII). However, validation in low vs. high vitamin D cord blood samples in the entire LINA cohort using MassARRAY-based target-specific methylation analysis barely missed significance level (p=0.063, Figure E5A). We furthermore analyzed differential gene expression of *GC* by qPCR. Only 66 of the 387 cord blood samples showed detectable *GC* mRNA expression. Among those, only children with high cord blood 25(OH)D_3 levels showed in trend a higher GC mRNA expression (p=0.076, n=26 vs. n=14, Figure E5B). Next to *GC*, no DMRs were called for other known key regulators of vitamin D metabolism such as *DHCR7* (synthesis of pro-vitamin D_3), *CYP2R1* (synthesis of 25(OH)D_3), *CYP27B1* (synthesis of 1,25(OH)D_3), *CYP24A1* (rate limiting catabolic enzyme for 1,25-D_3) or *VDR* (vitamin D receptor).

Epigenetic regulation of genes involved in allergic inflammation

We next investigated genes that impact the early infant's immune response or allergic disease development for related DMRs. We performed an enrichment analysis in disease related genes based on the predicted target genes of the 508 DMRs and identified 103 significantly affected pathways (p<0.001, see Table EIV) including pathways with a potential link to immune system dysfunction or allergy development: "immune system disease", "obstructive lung disease" and "skin and connective tissue disease". In total, 3 genes were identified involved in all of these 3 pathways: *TSLP*, *IL17F* and *MBL2*. While *IL17F* and *MBL2* are rather involved in inflammation and infection, for *TSLP* links have already been shown both to allergic diseases and vitamin D. Due to its known functional role in the pathogenesis of allergic diseases, *TSLP* was selected for further validation. The *TSLP* DMR included 5 CpGs 113kbp upstream the *TSLP* TSS (mean **Δ**methylation 24%; see Figure E3C and Table EIII). Further analysis of the region flanking this DMR revealed a broader, significantly regulated region that includes the called DMR together with an annotated enhancer region located only 100bp downstream of this DMR (Chr.5:110.292.001-110.293.600, t-test p=0.0058, **Δ**methylation 12.2%). Although this broader region was in remarkable distance to the

TSS of *TSLP*, chromatin interaction data indicates that this enhancer targets multiple genes including *TSLP* (Figure 1A). Analyzing histone modifications in the *TSLP*-associated DMR and the adjacent enhancer we found repressive marks (H3K9me3 and/or H3K27me3) in this region in children with low cord blood 25(OH)D_3 whereas children with high cord blood 25(OH)D_3 were deprived of repressive histone marks (Figure 1A). Altogether, the concomitant loss of DNA methylation and repressive chromatin marks strongly suggest a gain of expression of the target gene *TSLP*.

First, we validated the loss of methylation in this region by targeted MassARRAY-based analysis in the entire LINA cohort. The PCR amplicon for MassARRAY was designed to cover both the called DMR and additional eight CpGs downstream, which were also significantly differentially methylated in the low vs. high vitamin D group (Figure E3C), including the enhancer region interacting with the *TSLP* promoter (Figure 1A). WGBS and MassARRAY methylation data correlated well for this region (p=0.005, R=0.497, Figure E4A). Next, we analyzed the methylation level in the extended *TSLP* DMR with respect to cord blood 25(OH)D_3 levels. No overall correlation was found in the LINA cohort or in children with low 25(OH)D_3 levels. However, in children with high cord blood 25(OH)D_3 concentrations the methylation level of this region correlated significantly with 25(OH)D_3 levels. This association was observed for 2 CpGs (Chr.5:110.292.389-392) located in the *TSLP* enhancer (p=0.026, R=-0.236, Figure 1B) as well as for one further CpG (Chr.5:110.292.306) located in the *TSLP* DMR region (p=0.024, R=-0.233, Figure E6). A lower CpG methylation level in the enhancer region was further correlated with higher *TSLP* mRNA expression (Figure 1C). For the *TSLP* enhancer region we also found a significant correlation between methylation at birth and the age of one and three (Figure E4B and C). Comparing children with low and high cord blood vitamin D levels, the *TSLP* mRNA expression was found to be significantly elevated at birth (p=0.048) and year one (p=0.003) in the high vitamin D group (Figure 1D and 1E). Finally, we found that children who suffered from wheezing symptoms later in life had significantly enhanced *TSLP* mRNA expression at age one (Figure 1F) but not at birth (data not shown). Note that for atopic dermatitis or food allergy no association to *TSLP* expression was found.

441 ***Accession Numbers***

442 Next-generation sequencing data have been deposited at the European Genome-phenome

443 Archive (EGA, http://www.ebi.ac.uk/ega/) hosted by the EBI, under accession numbers

444 EGAS00001000455.

445

Figure Legends Online Repository:

Figure E1: Cohort and sample overview. The diagram visualizes the number of children enrolled in the LINA study together with the number of available blood samples and performed analyses in total and those with 25(OH)D_3 analyses.

Figure E2: Vitamin D measurement. (A) Seasonal variation of 25(OH)D_3 levels (ng/ml) of one and two year old children. Data are presented as medians with 25th to 75th percentile. **(B)** Correlation between 25(OH)D_3 levels measured at birth, year one (1st yr) and year two (2nd yr).

Figure E3: Differentially methylated region (DMR) calling following whole genome bisulfite sequencing based on n=3 (high cord blood 25(OH)D_3; orange) vs n=3 (low cord blood 25(OH)D_3; blue) **(A)** Number of called DMRs as well as number of affected genes **(B)** DMR of *GC* (vitamin D binding protein; shaded in red); also highlighted are CpGs covered by MassARRAY primer (grey bar) **(C)** DMR of *TSLP* (thymic stromal lymphopoietin; shaded in red); also highlighted are the CpGs covered by MassARRAY validation, including the enhancer region nearby (grey bar).

Figure E4: Validation and longitudinal stability of methylation data. (A) Comparison of *TSLP* methylation data obtained by whole genome bisulfite sequencing (WGBS) and MassARRAY (MA); data are shown of CpGs within the DMR (p-values from Spearman's rank correlation test) ; each point represent of CpG of one individual **(B)** Comparison of *TSLP* methylation data obtained by MassARRAY at birth and at the age of one year (1st yr; p-values from Spearman's rank correlation test) **(C)** Comparison of *TSLP* methylation data obtained by MassARRAY at birth and at the age of three years (3rd yr; p-values from Spearman's rank correlation test)

Figure E5: *GC* and vitamin D levels at birth. (A) Association of *GC* methylation data (Chr4: 72.723.768) obtained by MassARRAY (MA) at birth is shown for low (25(OH)D_3 <25th percentile) vs

high ($25(OH)D_3$ >75th percentile) cord blood vitamin D concentrations (p-values from Mann-Whitney U-test) **(B)** Association of *GC* mRNA expression at birth is shown for low ($25(OH)D_3$ <25th percentile) vs high ($25(OH)D_3$>75th percentile) cord blood vitamin D concentrations (p-values from Mann-Whitney U-test)

Figure E6: *TSLP* methylation vs. vitamin D. Association between cord blood $25(OH)D_3$ and cord blood *TSLP* methylation analyzed via MassARRAY in the entire LINA cohort. Shown are the results for all participants (left column), only for those within the high vitamin D group ($25(OH)D_3$ >75th percentile, middle column) or for those within the low vitamin D group ($25(OH)D_3$<25th percentile, right column). Data are presented for one significant single CpG at Chr5: 110.292.306 as well as for the mean of all CpGs covering the weak enhancer region (Chr5: 110.292.389-433).

A)
B)

Table EI: (A) Analyzed 25(OH)D_3 concentrations (ng/ml and nM) in cord blood and peripheral blood at children's age of one and two years **(B)** 25(OH)D_3 concentrations (ng/ml) at children's age of one and two years in relation to their vitamin D supplementation within the first 12 months of life

	Cord blood* (n=378)	**Year ONE** (n=466)	**Year TWO** (n=304)
	ng/ml	ng/ml	ng/ml
Median year ONE	10.95	33.20	22.25
Quartiles			
1st Quartile	1.50 - 6.98	9.05 - 28.19	4.64 - 16.89
2nd Quartile	6.99 - 10.94	28.20 - 33.19	16.90 - 22.24
3rd Quartile	10.95 - 17.39	33.20 - 39.09	22.25 - 28.29
4th Quartile	17.40 - 40.10	39.10 - 65.90	28.30 - 47.20
	nM	nM	nM
Median year TWO	27.33	82.86	55.54
Quartiles			
1st Quartile	3.74 - 17.42	22.59 - 70.36	11.58 - 42.16
2nd Quartile	17.45 - 27.30	70.38 - 82.84	42.18 - 55.51
3rd Quartile	27.33 - 43.40	82.86 - 97.56	55.53 - 70.61
4th Quartile	43.43 - 100.10	97.59 - 164.48	70.63 - 117.81

	Never ever within the first 12 months	**Only within the first 3 months**	**Throughout the first 12 months**
	(n=19)	(n=22)	(n=341)
Median year ONE	24.70	26.49	34.60
Quartiles			
1st Quartile	9.05-20.39	13.10-17.99	12.10-30.19
2nd Quartile	20.40-24.69	18.00-26.48	30.20-34.59
3rd Quartile	24.70-35.79	26.49-31.49	34.60-40.39
4th Quartile	35.80-48.30	31.50-52.00	40.40-59.40
	(n=11)	(n=16)	(n=219)
Median year TWO	19.00	18.76	23.40
Quartiles			
1st Quartile	12.50-13.49	5.89-12.84	5.24-17.59
2nd Quartile	13.50-18.99	12.85-18.75	17.60-23.39
3rd Quartile	19.00-26.49	18.76-26.29	23.40-29.09
4th Quartile	26.50-38.20	26.30-38.30	29.10-47.20

*already published in Weisse et al. 2013

Table EII: Cell type distribution in cord blood estimated by methylation signature (analyzed by whole genome bisulfite sequencing) in the 3 children with high vs. 3 with low vitamin D

Cell type	Marker	High vitamin D[a]	Low vitamin D[a]	p-value[b]
Granulocytes	BRD4	0.19 (0.02)	0.20 (0.01)	0.82
Monocytes	CD14	0.21 (0.04)	0.22 (0.02)	0.82
T lymphocytes	CD3D (CD3G)	0.25 (0.02)	0.27 (0.07)	0.70
B lymphocytes	CD19	0.13 (0.02)	0.13 (0.01)	1.00

[a] estimation based on the mean (standard deviation) methylation level in the promoter region
[b] p-value was calculated by the Mann-Whitney U-test

Table EIII: DMRs. List of significant DMRs between the vitamin D high (cord blood 25(OH)D_3 concentration >75th percentile) and the vitamin D low (cord blood 25(OH)D_3 concentration <25th percentile) group at time of birth.

Provided as an external xlsx file.

Table EIV: Pathways enriched (adj. p-value <0.001) in vitamin D related DMRs identified in cord blood

Provided as an external xlsx file.

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Table EIII

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr8	59447424	59447842	15	419	0.52	0.91	-0.39	5.65E-05	-18095	NM_001007069	SDCBP	FAM110B
chr3	122365027	122365619	5	593	0.51	0.88	-0.37	2.83E-04	30798	NM_152615	PARP15	CCDC58, PARP15, PARP14
chr6	41068455	41069024	44	570	0.48	0.88	-0.40	4.52E-04	-33	NR_026938	ADCY10P1	ADCY10P1
chr17	8777563	8778036	11	474	0.52	0.84	-0.32	5.09E-04	-6806	NM_001010855	PIK3R6	NTN1
chr9	87692177	87692608	19	432	0.85	0.52	0.33	5.65E-04	407767	NM_001007097	NTRK2	NTRK2
chr20	20836961	20837633	10	673	0.80	0.21	0.59	7.35E-04	-144031	NM_020343	RALGAPA2	RALGAPA2
chr11	71278563	71278987	7	425	0.34	0.82	-0.48	9.04E-04	2166	NM_001012710	KRTAP5-10	SHANK2, KRTAP5-11
chr1	247333873	247334070	8	198	0.61	0.91	-0.30	9.61E-04	1346	NM_001243740	ZNF124	ZNF124
chr7	158958737	158958923	3	187	0.70	0.93	-0.23	1.07E-03	-21181	NM_003382	VIPR2	VIPR2
chr16	29164276	29164366	5	91	0.10	0.38	-0.27	1.13E-03	78158	NR_003369	RRN3P2	RRN3P2
chr6	110720654	110721413	33	760	0.46	0.77	-0.30	1.30E-03	15719	NM_003649	DDO	METTL24
chr5	133022998	133023357	7	360	0.49	0.74	-0.25	1.36E-03	-74955	NM_015082	FSTL4	VDAC1
chr4	185021513	185021924	9	412	0.79	0.19	0.59	1.41E-03	117395	NM_153343	ENPP6	STOX2
chr22	24201734	24201759	3	26	0.66	0.92	-0.26	1.70E-03	1706	NM_001024939	SLC2A11	MIF, SLC2A11, DERL3
chr7	100928189	100928425	6	237	0.70	0.29	0.41	1.75E-03	36786	NM_001130820	RABL5	FIS1
chr15	66965429	66966153	23	725	0.63	0.13	0.49	1.87E-03	-28883	NR_027654	SMAD6	DIS3L
chr21	44003807	44003932	3	126	0.82	0.56	0.26	1.92E-03	-69992	NM_001001571	PDE9A	UMODL1, ABCG1, TFF2, SLC37A1, PDE9A, CBS
chr6	7271578	7271705	8	128	0.41	0.80	-0.39	1.98E-03	41899	NM_003144	SSR1	SSR1, DSP
chr8	41593896	41594261	16	366	0.45	0.72	-0.26	2.04E-03	61061	NM_020475	ANK1	NKX6-3
chr1	222806819	222807081	4	263	0.25	0.52	-0.27	2.20E-03	15506	NM_198551	MIA3	TAF1A
chr12	42458146	42458288	5	143	0.87	0.56	0.31	2.26E-03	80456	NM_001099650	GXYLT1	GXYLT1
chr9	37701488	37701684	4	197	0.94	0.54	0.41	2.32E-03	50534	NM_014907	FRMPD1	FRMPD1
chr10	27643318	27644088	15	771	0.39	0.75	-0.36	2.37E-03	59594	NM_001034842	PTCHD3	PTCHD3
chr21	46789867	46789922	4	56	0.22	0.70	-0.48	2.43E-03	-35202	NM_130445	COL18A1	ADARB1

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr9	69501177	69501258	9	82	0.42	0.82	-0.40	2.49E-03	119237	NM_001098805	ANKRD20A4	ANKRD20A4
chr19	17715113	17715316	8	204	0.57	0.81	-0.24	2.54E-03	48704	NM_024656	COLGALT1	COLGALT1, FCHO1, BST2
chr19	6593268	6593400	4	133	0.87	0.63	0.24	2.60E-03	-2171	NM_001252	CD70	CD70
chr17	78301619	78301720	5	102	0.45	0.23	0.22	2.66E-03	67010	NM_020954	RNF213	RNF213
chr19	386487	386811	12	325	0.41	0.74	-0.34	2.71E-03	-10636	NM_199202	THEG	THEG
chr11	131507557	131507710	3	154	0.73	0.39	0.34	3.00E-03	267263	NM_001048209	NTM	NTM
chr20	260133	260226	9	94	0.80	0.53	0.27	3.05E-03	11239	NM_153269	C20orf96	C20orf96
chr2	228648293	228648393	4	101	0.56	0.15	0.41	3.11E-03	-30215	NM_004591	CCL20	COL4A3, TM4SF20
chr5	117822410	117822578	3	169	0.37	0.65	-0.28	3.17E-03	-487787	NR_036262	MIR1244-2	MIR1244-2
chr6	158481109	158481158	3	50	0.52	0.84	-0.32	3.22E-03	43054	NM_001178088	SYNJ2	SYNJ2, SERAC1
chr12	116806423	116806558	6	136	0.67	0.45	0.23	3.34E-03	59632	NR_039683	MIR4472-2	MIR4472-2
chr8	17533468	17534005	16	538	0.61	0.26	0.34	3.39E-03	21509	NM_020749	MTUS1	MTMR7, PDGFRL, MTUS1, FGF20, MICU3
chr7	29905630	29905752	8	123	0.37	0.63	-0.26	3.79E-03	59521	NM_001080529	WIPF3	WIPF3
chr16	58824167	58824271	6	105	0.70	0.43	0.26	3.90E-03	-55973	NM_002080	GOT2	GINS3
chr1	180886439	180886768	8	330	0.91	0.61	0.30	3.96E-03	4291	NM_020950	KIAA1614	KIAA1614
chr2	28604671	28605268	6	598	0.33	0.67	-0.34	4.01E-03	-10809	NM_005253	FOSL2	FOSL2, BRE
chr6	158478336	158478955	18	620	0.51	0.76	-0.25	4.07E-03	40566	NM_001178088	SYNJ2	SYNJ2, SNX9
chr12	96617776	96617993	4	218	0.68	0.41	0.27	4.13E-03	29678	NM_005230	ELK3	ELK3
chr14	31159970	31160286	8	317	0.76	0.53	0.23	4.18E-03	68603	NM_001257376	SCFD1	SCFD1
chr11	131451190	131451304	4	115	0.63	0.39	0.25	4.24E-03	210876	NM_001048209	NTM	NTM
chr19	59083776	59083880	6	105	0.43	0.19	0.23	4.30E-03	1114	NM_003422	MZF1	ZNF274, ZNF837, MIR4754, RPS5, ZNF446, ZBTB45, TRIM28, ZNF324B, ZNF324, PPIA, PURB, CAMK2B, ZMIZ2, NUDCD3, NPC1L1, DDX56, TMED4, OGDH,
chr7	45002624	45002930	18	307	0.51	0.80	-0.30	4.35E-03	15927	NM_033054	MYO1G	MYO1G, CCM2, NACAD, TBRG4
chr19	47552374	47552518	11	145	0.24	0.53	-0.29	4.47E-03	-564	NM_017854	TMEM160	NPAS1, SAE1

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr11	11820534	11820699	4	166	0.09	0.60	-0.51	4.58E-03	-42353	NM_017944	USP47	USP47
chr5	37806758	37806822	3	65	0.47	0.68	-0.22	4.64E-03	28803	NM_199231	GDNF	GDNF
chr14	33406198	33406446	3	249	0.53	0.76	-0.22	4.69E-03	-2137	NM_001164749	NPAS3	ARHGAP5
chr8	4238786	4238978	4	193	0.36	0.58	-0.22	4.75E-03	613446	NM_033225	CSMD1	CSMD1
chr10	49614224	49614367	3	144	0.80	0.45	0.35	4.86E-03	4609	NM_139049	MAPK8	MAPK8
chr17	29837335	29837648	10	314	0.38	0.61	-0.23	4.92E-03	-24409	NR_039877	MIR4724	OMG, EVI2B, NF1
chr17	1508049	1508608	26	560	0.17	0.67	-0.49	5.03E-03	23801	NM_152346	SLC43A2	SCARF1, PRPF8
chr4	182341916	182342191	3	276	0.31	0.54	-0.23	5.09E-03	-261752	NR_033918	LINC00290	LINC00290
chr4	2797768	2797917	5	150	0.81	0.42	0.38	5.14E-03	3093	NM_001122681	SH3BP2	TNIP2, FAM193A, ADD1
chr1	1014565	1014625	3	61	0.41	0.15	0.26	5.26E-03	-4908	NM_001205252	RNF223	RNF223, HES4, AGRN, C1orf159
chr7	150705892	150706098	15	207	0.27	0.48	-0.21	5.31E-03	15103	NM_001160110	NOS3	KCNH2, ABCB8, ZNF775, NOS3, ATG9B, SLC4A2, FASTK, AGAP3, GBX1, ABCF2, PRKAG2, REPIN1, NUB1
chr9	86109774	86109788	5	15	0.85	0.34	0.51	5.43E-03	-27124	NM_001244960	FRMD3	FRMD3
chr11	2561010	2561119	6	110	0.50	0.75	-0.25	5.60E-03	78399	NR_040711	KCNQ1	KCNQ1
chr17	64535009	64535065	3	57	0.59	0.38	0.21	5.71E-03	236111	NM_002737	PRKCA	PRKCA
chr1	109933421	109933481	6	61	0.51	0.74	-0.24	5.77E-03	2528	NM_001205228	SORT1	SORT1, CYB561D1, AMPD2
chr5	56887160	56887403	3	244	0.78	0.49	0.30	5.82E-03	-108646	NM_001017992	ACTBL2	ACTBL2
chr22	20019657	20019694	3	38	0.34	0.56	-0.22	5.88E-03	-986	NR_029706	MIR185	ARVCF
chr13	27188842	27189019	3	178	0.77	0.53	0.24	5.94E-03	57091	NM_006646	WASF3	WASF3
chr12	130766044	130766520	19	477	0.53	0.83	-0.30	5.99E-03	-56151	NM_004764	PIWIL1	PIWIL1, RIMBP2
chr22	35996505	35996666	8	162	0.48	0.28	0.20	6.05E-03	16798	NM_005368	MB	MCM5, RASD2, MB
chr1	75140186	75140777	6	592	0.64	0.86	-0.21	6.16E-03	-1060	NM_001002912	C1orf173	LRRC53
chr18	712931	713204	18	274	0.57	0.32	0.25	6.22E-03	-406	NM_001126123	ENOSF1	THOC1, YES1, C18orf56, ENOSF1, CETN1
chr7	27170152	27170891	48	740	0.16	0.48	-0.32	6.44E-03	-123	NM_002141	HOXA4	HOXA3, HOXA1, HOXA9, EVX1, TAX1BP1

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr14	88757273	88757501	7	229	0.54	0.14	0.40	6.50E-03	-20132	NM_138318	KCNK10	KCNK10
chr13	44046497	44046652	4	156	0.59	0.81	-0.22	6.56E-03	157038	NM_001127615	ENOX1	ENOX1
chr2	121864836	121864888	3	53	0.71	0.92	-0.21	6.61E-03	177916	NM_014553	TFCP2L1	TFCP2L1
chr10	5720682	5720854	4	173	0.64	0.33	0.31	6.67E-03	-6033	NM_017782	FAM208B	FAM208B
chr2	173538922	173539090	11	169	0.69	0.36	0.33	6.95E-03	-61519	NM_007023	RAPGEF4	ITGA6
chr11	122542293	122542568	10	276	0.64	0.39	0.24	7.01E-03	16033	NM_032873	UBASH3B	UBASH3B, CRTAM
chr22	48539361	48539590	5	230	0.31	0.67	-0.35	7.07E-03	-130700	NR_036172	MIR3201	MIR3201
chr22	27832002	27832115	7	114	0.55	0.32	0.23	7.12E-03	365427	NM_002430	MN1	PITPNB
chr8	97350086	97350202	3	117	0.39	0.62	-0.23	7.24E-03	75977	NM_014754	PTDSS1	PTDSS1, GDF6, MTDH
chr1	181359831	181360074	4	244	0.36	0.59	-0.23	7.29E-03	-92733	NM_001205293	CACNA1E	CACNA1E
chr2	464997	465171	6	175	0.50	0.75	-0.25	7.35E-03	-176776	NM_001002919	FAM150B	FAM150B
chr16	76673952	76674182	7	231	0.73	0.54	0.19	7.52E-03	-228766	NR_039870	MIR4719	MIR4719
chr11	60828979	60829100	3	122	0.22	0.49	-0.26	7.57E-03	-40890	NM_014207	CD5	TMEM109, VPS37C, PRPF19, TMEM132A, SLC15A3, CD6, PGA3, PGA4, PGA5, DDB1, TMEM138, TMEM216, CPSF7
chr22	30901875	30901893	3	19	0.30	0.57	-0.27	7.74E-03	-186	NM_174977	SEC14L4	SEC14L4
chr2	1597890	1597969	4	80	0.59	0.78	-0.19	7.80E-03	150361	NM_012293	PXDN	PXDN
chr11	804278	804693	20	416	0.40	0.62	-0.21	7.86E-03	764	NM_145886	PIDD	C11orf35, RASSF7, DEAF1, TMEM80, SLC25A22, PIDD, RPLP2, PDDC1, CD151, CHID1, EFCAB4A
chr2	241259651	241259915	15	265	0.47	0.67	-0.20	7.91E-03	-115332	NM_002081	GPC1	GPC1
chr3	184200026	184200158	3	133	0.60	0.84	-0.23	8.03E-03	-79495	NM_004443	EPHB3	HTR3E, EIF2B5, THPO
chr21	33957357	33957391	3	35	0.16	0.37	-0.21	8.14E-03	471	NM_144659	TCP10L	TCP10L
chr17	43333596	43333911	9	316	0.61	0.39	0.23	8.20E-03	5725	NM_152343	SPATA32	FMNL1, ARHGAP27
chr6	37504884	37504930	8	47	0.40	0.60	-0.20	8.25E-03	18291	NR_039669	MIR4462	ARMC12, BRPF3, MTCH1, FGD2, TBC1D22B, KIF6, MDGA1, ZFAND3

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr17	1870314	1870848	15	535	0.31	0.52	-0.21	8.31E-03	57597	NM_178568	RTN4RL1	WDR81, RTN4RL1
chr13	52476861	52477607	9	747	0.64	0.38	0.25	8.42E-03	41117	NM_031290	CCDC70	INTS6, DHRS12, THSD1P1
chr2	29229554	29229726	6	173	0.33	0.59	-0.27	8.54E-03	25476	NM_199280	FAM179A	PLB1, SPDYA, FAM179A, CLIP4
chr8	97350615	97350725	5	111	0.63	0.83	-0.20	8.59E-03	76503	NM_014754	PTDSS1	PTDSS1, GDF6, MTDH
chr6	33292378	33292388	4	11	0.67	0.85	-0.18	8.65E-03	-1590	NM_001141969	DAXX	CUTA, PHF1, SYNGAP1, KIFC1, TAPBP, ZBTB22
chr16	50722898	50723065	3	168	0.62	0.88	-0.26	8.71E-03	-7718	NM_001144972	SNX20	NOD2
chr16	1509853	1509993	7	141	0.66	0.43	0.24	8.82E-03	15162	NM_001287	CLCN7	UBE2I, CCDC154, LMF1, UNKL, CLCN7, CRAMP1L, NME3, MRPS34
chr15	93583958	93584221	10	264	0.71	0.48	0.23	8.88E-03	32299	NM_001166286	RGMA	CHD2
chr7	99541625	99541696	3	72	0.38	0.58	-0.20	8.93E-03	-14418	NM_181538	GJC3	CNPY4, CPSF4, ATP5J2, ZNF789, ZNF394, ZNF655, ZKSCAN1, MCM7, C7orf43, SPDYE3, PILRB, PILRA, ZCWPW1, MEPCE
chr5	117861139	117861430	4	292	0.63	0.81	-0.17	9.10E-03	-448996	NR_036262	MIR1244-2	MIR1244-2
chr17	6230128	6230178	3	51	0.34	0.69	-0.35	9.16E-03	108366	NM_014336	AIPL1	AIPL1
chr7	39781891	39782207	12	317	0.66	0.92	-0.26	9.21E-03	8882	NR_026999	LINC00265	RALA
chr16	87686376	87686940	8	565	0.27	0.60	-0.33	9.27E-03	50165	NM_001271605	JPH3	BANP
chr17	70184786	70184939	3	154	0.55	0.96	-0.41	9.33E-03	67702	NM_000346	SOX9	SOX9
chr6	170589584	170589746	10	163	0.42	0.71	-0.30	9.38E-03	10032	NM_005618	DLL1	DLL1, TCTE3, FAM120B
chr14	33979300	33979420	4	121	0.77	0.56	0.21	9.44E-03	440924	NM_022073	EGLN3	EGLN3
chr22	39162248	39162313	4	66	0.48	0.74	-0.26	9.50E-03	-10257	NM_015374	SUN2	DNAL4
chr12	68284631	68285129	4	499	0.67	0.37	0.30	9.55E-03	242368	NM_003583	DYRK2	DYRK2
chr9	100337180	100337518	11	339	0.43	0.22	0.21	9.67E-03	-58356	NM_002486	NCBP1	TMOD1, HEMGN
chr14	105636475	105636672	8	198	0.64	0.44	0.20	9.84E-03	-1413	NM_002226	JAG2	BRF1, C14orf80, ELK2BP
chr1	171111078	171111438	6	361	0.53	0.27	0.25	9.89E-03	4379	NR_002601	FMO6P	FMO3, PRRX1, FMO2, TOP1P1
chr2	71780155	71780316	8	162	0.89	0.64	0.25	1.00E-02	86404	NM_001130987	DYSF	DYSF

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr19	7004199	7004798	15	600	0.80	0.32	0.48	1.02E-02	1927	NR_024372	FLJ25758	FLJ25758
chr6	25882589	25882793	4	205	0.70	0.33	0.37	1.04E-02	-8220	NM_006632	SLC17A3	SLC17A3
chr10	11386824	11386920	8	97	0.43	0.70	-0.27	1.05E-02	179879	NM_001083591	CELF2	CELF2-AS2
chr19	34285810	34285901	9	92	0.44	0.61	-0.17	1.06E-02	-1895	NM_001129994	KCTD15	CEBPG, LSM14A, LSR, DMKN
chr1	28156779	28156787	3	9	0.47	0.70	-0.23	1.07E-02	-469	NM_014110	PPP1R8	FAM76A, SNORA44, SNORA61, SNORA16A, SNORD99, UBXN11, MED18, YTHDF2, SRSF4, XKR8, RPA2
chr14	58178926	58179072	3	147	0.72	0.49	0.23	1.09E-02	153593	NM_001206920	SLC35F4	SLC35F4
chr1	30395439	30395502	4	64	0.57	0.78	-0.21	1.09E-02	-796148	NR_034182	MATN1-AS1	MATN1-AS1
chr9	25255109	25255136	4	28	0.24	0.44	-0.20	1.10E-02	423733	NM_001004125	TUSC1	TUSC1
chr20	31921991	31922264	3	274	0.61	0.88	-0.27	1.11E-02	51187	NM_033197	BPIFB1	BPIFB1
chr2	28175847	28176205	5	359	0.50	0.78	-0.28	1.12E-02	-43208	NR_036230	MIR4263	GCKR, CCDC121, GPN1, RBKS, BRE
chr13	33281724	33281989	4	266	0.30	0.69	-0.39	1.14E-02	121293	NM_015032	PDS5B	PDS5B
chr2	98278929	98279101	4	173	0.78	0.57	0.21	1.15E-02	1546	NM_005735	ACTR1B	COX5B, ZAP70, CNGA3
chr20	25965632	25965938	20	307	0.59	0.35	0.24	1.15E-02	-24650	NR_004846	LOC100134868	LOC100134868
chr9	98266765	98266824	3	60	0.75	0.50	0.25	1.16E-02	2686	NM_001083607	PTCH1	PTCH1
chr12	45445786	45445880	4	95	0.49	0.74	-0.24	1.16E-02	-951	NM_001004329	DBX2	NELL2, ARID2
chr6	145853987	145854219	4	233	0.49	0.64	-0.16	1.17E-02	-201902	NR_038246	LOC100507557	LOC100507557
chr13	42086729	42086779	4	51	0.73	0.94	-0.21	1.18E-02	55212	NM_014059	RGCC	ELF1, CALM2P3, MORF4L1P4, NAA16, OR7E37P
chr22	49746779	49746917	7	139	0.48	0.70	-0.22	1.19E-02	304342	NR_026997	C22orf34	C22orf34
chr9	138581894	138582011	5	118	0.67	0.41	0.26	1.22E-02	9421	NM_001012415	SOHLH1	SOHLH1
chr2	5974819	5974877	3	59	0.56	0.80	-0.24	1.22E-02	-97971	NR_026832	LOC150622	LOC150622
chr3	109282059	109282093	3	35	0.47	0.27	0.20	1.23E-02	153239	NM_001145553	FLJ25363	FLJ25363
chr1	91995632	91995797	3	166	0.57	0.36	0.20	1.23E-02	29050	NM_001134420	CDC7	CDC7
chr1	25416769	25416828	3	60	0.44	0.18	0.25	1.24E-02	-125298	NM_001031680	RUNX3	TMEM50A

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr10	133890631	133890833	5	203	0.46	0.21	0.24	1.24E-02	-27581	NM_001105521	JAKMIP3	LRRC27
chr11	131514374	131514478	3	105	0.81	0.60	0.20	1.25E-02	-266286	NM_001144058	NTM	NTM
chr6	24636102	24636214	3	113	0.54	0.85	-0.31	1.25E-02	10091	NM_001168376	KIAA0319	KIAA0319
chr4	24256284	24256311	3	28	0.24	0.62	-0.38	1.27E-02	265615	NR_030299	MIR573	PPARGC1A
chr11	131504143	131504207	4	65	0.85	0.67	0.18	1.30E-02	263804	NM_001048209	NTM	NTM
chr5	110292190	110292261	5	72	0.47	0.71	-0.24	1.31E-02	-113552	NR_045089	TSLP	TSLP
chr7	15586999	15587304	14	306	0.67	0.90	-0.23	1.32E-02	14488	NM_001004320	AGMO	AGMO
chr11	114226034	114226234	6	201	0.78	0.53	0.25	1.33E-02	45138	NM_019021	C11orf71	RBM7, C11orf71
chr3	133191256	133191425	18	170	0.56	0.81	-0.26	1.33E-02	72551	NM_003571	BFSP2	BFSP2
chr17	67565717	67565765	4	49	0.36	0.58	-0.22	1.34E-02	154903	NM_002758	MAP2K6	MAP2K6
chr20	54968558	54968625	4	68	0.41	0.64	-0.22	1.35E-02	885	NM_001033522	CSTF1	CASS4, RTFDC1
chr10	110114733	110114789	8	57	0.28	0.84	-0.56	1.36E-02	-815654	NR_046928	RNU6-53	SORCS1
chr11	89787005	89787019	3	15	0.21	0.46	-0.26	1.36E-02	22738	NM_001195234	TRIM49C	TRIM49C
chr18	77306538	77306688	8	151	0.94	0.77	0.17	1.38E-02	-133188	NM_004715	CTDP1	CTDP1
chr22	49230437	49230507	3	71	0.49	0.30	0.19	1.39E-02	-32110	NR_038944	LOC100128946	LOC100128946
chr13	36699996	36700035	3	40	0.61	0.80	-0.20	1.40E-02	5498	NM_004734	DCLK1	DCLK1
chr14	24899959	24900192	15	234	0.53	0.28	0.25	1.41E-02	935	NM_015299	KHNYN	NEDD8-MDP1, NEDD8, GMPR2, DHRS1, NOP9
chr17	38618171	38618218	5	48	0.60	0.82	-0.21	1.42E-02	18519	NM_001552	IGFBP4	IGFBP4
chr22	29516494	29516650	5	157	0.86	0.64	0.22	1.42E-02	47506	NM_001039570	KREMEN1	KREMEN1, RHBDD3, EWSR1
chr15	86443455	86443482	4	28	0.40	0.61	-0.21	1.43E-02	-105280	NM_022480	KLHL25	KLHL25
chr9	123687911	123687982	3	72	0.58	0.36	0.22	1.44E-02	1226	NM_005658	TRAF1	PHF19, FBXW2, TRAF1, CNTRL
chr17	54830	55023	7	194	0.26	0.48	-0.22	1.44E-02	-23507	NM_003585	DOC2B	DOC2B
chr7	6627534	6627656	4	123	0.39	0.67	-0.27	1.46E-02	-2320	NM_024067	C7orf26	ZDHHC4
chr3	195871459	195871529	5	71	0.67	0.87	-0.19	1.46E-02	1987	NR_034088	LOC401109	TFRC, C3orf43
chr14	93475677	93475907	6	231	0.82	0.55	0.27	1.48E-02	-58005	NR_002808	ITPK1-AS1	ITPK1, SLC24A4

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr3	194014589	194014721	10	133	0.46	0.23	0.23	1.49E-02	15938	NR_024480	LOC100131551	OPA1, ATP13A3
chr22	47791280	47791504	5	225	0.23	0.43	-0.19	1.50E-02	235926	NR_033377	FLJ46257	LINC00898
chr15	41100299	41100651	14	353	0.39	0.14	0.26	1.51E-02	-799	NM_018163	DNAJC17	RMDN3, SPINT1, CHST14, RAD51
chr21	36351903	36352020	4	118	0.85	0.53	0.32	1.51E-02	59761	NR_026812	RUNX1-IT1	RUNX1-IT1
chr5	154022117	154022232	4	116	0.40	0.62	-0.22	1.52E-02	-46543	NR_036094	MIR3141	GALNT10
chr15	63686363	63686412	4	50	0.87	0.55	0.31	1.53E-02	-12313	NM_206925	CA12	CA12
chr22	47798087	47798420	13	334	0.41	0.64	-0.23	1.53E-02	229064	NR_033377	FLJ46257	LINC00898
chr19	50140058	50140226	7	169	0.45	0.73	-0.28	1.54E-02	3258	NM_006270	RRAS	RRAS
chr3	184409472	184409634	4	163	0.29	0.54	-0.25	1.55E-02	20283	NM_022149	MAGEF1	THPO
chr19	53936327	53936427	5	101	0.77	0.58	0.19	1.55E-02	1150	NR_003148	TPM3P9	ZNF765, ZNF331
chr6	52118400	52118505	7	106	0.33	0.56	-0.23	1.56E-02	-9155	NM_052872	IL17F	IL17F
chr11	61213843	61214018	5	176	0.47	0.21	0.25	1.58E-02	16334	NM_017841	SDHAF2	SDHAF2
chr1	62752642	62752776	5	135	0.40	0.71	-0.31	1.58E-02	32374	NM_181712	KANK4	USP1, NFIA, INADL, L1TD1, KANK4, DOCK7
chr5	115879282	115879555	3	274	0.46	0.71	-0.25	1.59E-02	31132	NM_020796	SEMA6A	SEMA6A
chr11	12846075	12846116	3	42	0.33	0.14	0.18	1.60E-02	150127	NM_021961	TEAD1	TEAD1
chr19	49699905	49700020	9	116	0.63	0.82	-0.19	1.61E-02	38947	NM_017636	TRPM4	C19orf73, PPFIA3, HRC, TRPM4
chr6	30783043	30783376	4	334	0.79	0.33	0.47	1.62E-02	-68651	NM_001954	DDR1	PRR3, TUBB, FLOT1, IER3, DDR1, VARS2
chr20	55487169	55487306	8	138	0.55	0.75	-0.20	1.62E-02	282880	NM_003222	TFAP2C	GCNT7, TFAP2C, SPO11, RAE1, RBM38
chr13	22459597	22459635	4	39	0.41	0.20	0.21	1.63E-02	-7317	NR_047040	LINC00424	ZDHHC20, FGF9
chr20	46888314	46888357	4	44	0.27	0.49	-0.21	1.64E-02	-100318	NR_026958	LINC00494	SULF2
chr11	850295	850405	11	111	0.30	0.52	-0.21	1.66E-02	5904	NM_001025237	TSPAN4	IRF7, EFCAB4A, CD151, POLR2L, TSPAN4, CHID1, MUC2, BRSK2
chr6	29912304	29912596	3	293	0.86	0.63	0.24	1.66E-02	2203	NM_002116	HLA-A	ABCF1, MRPS18B, HLA-B, HLA-F, GNL1, PPP1R10, GABBR1, MOG, RPL23AP1, TRIM39

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr1	157249133	157249162	3	30	0.12	0.43	-0.31	1.67E-02	-140765	NM_001145312	ETV3	ETV3, ARHGEF11
chr7	875698	875941	11	244	0.31	0.12	0.19	1.67E-02	3678	NM_001130965	SUN1	SUN1
chr11	67893375	67893383	4	9	0.35	0.65	-0.29	1.69E-02	-4521	NM_001277	CHKA	CHKA
chr20	33110710	33110944	7	235	0.50	0.74	-0.24	1.70E-02	6623	NM_014183	DYNLRB1	AHCY, DYNLRB1, PIGU, MAP1LC3A, RALY, EIF2S2, ITCH, TP53INP2, NCOA6, GGT7, ACSS2, GSS, MYH7B
chr3	184244013	184244381	7	369	0.33	0.12	0.21	1.71E-02	-35390	NM_004443	EPHB3	CLCN2, POLR2H, FAM131A, EPHB3
chr22	50050404	50050446	3	43	0.30	0.63	-0.32	1.71E-02	765	NR_026997	C22orf34	C22orf34, BRD1, ZBED4, PIM3, MLC1
chr5	178961463	178961727	10	265	0.53	0.73	-0.20	1.72E-02	-15967	NM_025158	RUFY1	RUFY1
chr16	87993408	87993547	7	140	0.31	0.57	-0.25	1.74E-02	1	NM_001173542	BANP	BANP
chr11	70310777	70311035	6	259	0.50	0.69	-0.19	1.75E-02	66294	NM_138565	CTTN	ANO1, FADD, PPFIA1, CTTN, SHANK2
chr1	91274696	91275299	5	604	0.39	0.63	-0.24	1.75E-02	-92204	NM_020063	BARHL2	BARHL2
chr19	8488926	8489102	4	177	0.55	0.34	0.21	1.76E-02	10827	NM_016496	MARCH2	MARCH2
chr1	22647188	22647528	4	341	0.55	0.77	-0.22	1.76E-02	-130986	NM_014870	ZBTB40	ZBTB40
chr12	99032661	99032723	3	63	0.68	0.94	-0.26	1.78E-02	6137	NM_153687	IKBIP	IKBIP
chr4	6687882	6688125	3	244	0.42	0.72	-0.31	1.79E-02	-7562	NM_005980	S100P	TBC1D14, TADA2B, GRPEL1
chr1	44031838	44031884	5	47	0.41	0.58	-0.17	1.79E-02	35314	NM_130440	PTPRF	C1orf50, PTPRF, SLC6A9, DMAP1, ERI3
chr1	20849144	20849250	4	107	0.59	0.43	0.16	1.80E-02	-14523	NM_024544	MUL1	PINK1
chr2	88292244	88292332	3	89	0.83	0.63	0.20	1.80E-02	-6979	NM_001024457	RGPD1	RGPD1
chr7	107028118	107028260	4	143	0.70	0.50	0.20	1.81E-02	-82313	NM_005295	GPR22	GPR22
chr1	11889726	11889822	5	97	0.94	0.76	0.19	1.81E-02	-10602	NR_037806	NPPA-AS1	NPPA-AS1
chr18	76806384	76806543	6	160	0.46	0.61	-0.15	1.83E-02	-22933	NM_198531	ATP9B	ATP9B
chr14	85426600	85426794	4	195	0.59	0.38	0.20	1.85E-02	-569791	NM_013231	FLRT2	LINC00911
chr6	4020945	4021010	4	66	0.55	0.72	-0.17	1.85E-02	-591	NM_003913	PRPF4B	RIPK1, ECI2, PSMG4, PRPF4B, SLC22A23

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr2	85534335	85534376	4	42	0.43	0.64	-0.20	1.86E-02	21063	NM_001206840	TGOLN2	TGOLN2, ELMOD3, CAPG, SH2D6, VAMP8, TMEM150A, SFTPB
chr13	108967771	108967854	3	84	0.90	0.68	0.22	1.87E-02	45836	NM_006573	TNFSF13B	TNFSF13B
chr8	85696460	85696589	3	130	0.56	0.38	0.18	1.87E-02	-322798	NM_033402	LRRCC1	LRRCC1, E2F5
chr2	224867269	224867320	5	52	0.85	0.64	0.21	1.88E-02	28900	NR_073116	SERPINE2	SERPINE2
chr6	145850951	145851495	5	545	0.39	0.58	-0.19	1.89E-02	-204782	NR_038246	LOC100507557	SHPRH
chr2	241566062	241566194	4	133	0.27	0.51	-0.25	1.89E-02	1466	NM_005301	GPR35	GPC1, ANKMY1, RNPEPL1, CAPN10, GPR35, KIF1A, AGXT, C2orf54
chr9	31808711	31808977	8	267	0.27	0.52	-0.25	1.91E-02	-575757	NM_002197	ACO1	ACO1
chr20	45402597	45402738	6	142	0.42	0.18	0.24	1.92E-02	64389	NM_030777	SLC2A10	EYA2
chr5	107996113	107996386	5	274	0.24	0.50	-0.26	1.93E-02	67712	NR_046368	HP07349	LINC01023
chr7	139967285	139967366	3	82	0.59	0.82	-0.23	1.94E-02	90265	NR_024451	LOC100134229	SLC37A3
chr17	74946229	74946334	4	106	0.55	0.78	-0.23	1.94E-02	77553	NM_198955	MGAT5B	MGAT5B
chr19	43829732	43829933	3	202	0.53	0.76	-0.23	1.96E-02	-23375	NR_026881	PRG1	IRGC
chr12	42682193	42682340	7	148	0.82	0.64	0.18	1.97E-02	37665	NM_033114	ZCRB1	ZCRB1
chr20	32034277	32034486	3	210	0.62	0.35	0.26	1.98E-02	-2684	NM_003098	SNTA1	E2F1, ZNF341
chr6	20014503	20014752	3	250	0.54	0.35	0.19	2.00E-02	177027	NM_001546	ID4	ID4
chr14	65623254	65623304	4	51	0.66	0.44	0.22	2.01E-02	-53866	NR_073137	MAX	MAX
chr11	71566779	71566841	7	63	0.57	0.81	-0.24	2.02E-02	22564	NM_001002035	DEFB108B	DEFB108B
chr9	130571967	130572304	13	338	0.16	0.49	-0.33	2.02E-02	6628	NM_001018078	FPGS	TOR2A
chr19	50872757	50872908	8	152	0.51	0.21	0.30	2.03E-02	-3902	NM_004851	NAPSA	EMC10, KCNC3, POLD1
chr5	84167832	84168096	4	265	0.45	0.66	-0.21	2.05E-02	-487353	NM_005711	EDIL3	EDIL3
chr2	144576122	144576171	3	50	0.89	0.65	0.23	2.05E-02	418759	NM_024659	GTDC1	GTDC1
chr19	49711473	49711525	4	53	0.44	0.62	-0.19	2.07E-02	50483	NM_017636	TRPM4	SNRNP70, HRC
chr4	827674	827846	6	173	0.62	0.42	0.20	2.07E-02	-7815	NM_006651	CPLX1	ABCA11P, PIGG, ATP5I, MYL5, GAK, TMEM175, IDUA, FGFRL1, CTBP1

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr7	2642210	2642274	3	65	0.45	0.61	-0.16	2.08E-02	-29361	NM_025250	TTYH3	SNX8, EIF3B, IQCE, TTYH3, AMZ1, GNA12
chr1	91257303	91257490	4	188	0.70	0.90	-0.20	2.09E-02	-74603	NM_020063	BARHL2	BARHL2
chr17	65356	65660	17	305	0.18	0.52	-0.34	2.09E-02	-34088	NM_003585	DOC2B	FAM101B
chr14	87924159	87924415	6	257	0.62	0.80	-0.18	2.10E-02	535328	NM_001201401	GALC	GALC
chr6	150894643	150894900	5	258	0.47	0.68	-0.21	2.10E-02	-26227	NM_001029884	PLEKHG1	PLEKHG1
chr10	131453308	131453576	12	269	0.40	0.62	-0.22	2.11E-02	187988	NM_002412	MGMT	MGMT
chr1	222083704	222083755	3	52	0.60	0.79	-0.19	2.13E-02	-168214	NM_144729	DUSP10	DUSP10
chr11	6907085	6907129	3	45	0.69	0.28	0.41	2.13E-02	6624	NM_003700	OR2D2	DNHD1, OR2D3, SYT9
chr9	79137985	79138094	7	110	0.64	0.45	0.19	2.14E-02	22491	NM_001097636	GCNT1	GCNT1
chr5	1559279	1559412	5	134	0.54	0.86	-0.32	2.14E-02	-35270	NM_024830	LPCAT1	LPCAT1
chr12	32261080	32261181	3	102	0.41	0.59	-0.19	2.15E-02	946	NM_001714	BICD1	AMN1, FAM60A, KIAA1551, DENND5B
chr21	46932616	46932741	6	126	0.71	0.44	0.27	2.16E-02	21863	NM_001205207	SLC19A1	ADARB1, SSR4P1
chr12	7262121	7262312	6	192	0.61	0.32	0.28	2.17E-02	-348	NM_016546	C1RL	MIR141, C1R, C12orf57, PTPN6, MIR200C, SCARNA12, LPCAT3, PEX5, C1RL, CLSTN3, MRPL51, ACRBP, ING4, ENO2, RBP5, TAPBPL, LTBR
chr9	92981695	92981860	6	166	0.59	0.77	-0.18	2.18E-02	-177997	NR_038882	LOC286370	LOC286370
chr4	20813138	20813156	7	19	0.72	0.95	-0.23	2.21E-02	39144	NM_147181	KCNIP4	PACRGL
chr12	125077706	125077923	11	218	0.55	0.26	0.29	2.23E-02	-25805	NM_001206654	NCOR2	NCOR2
chr1	7566104	7566154	4	51	0.38	0.16	0.21	2.23E-02	-265200	NM_004781	VAMP3	VAMP3
chr8	120858375	120858413	3	39	0.74	0.95	-0.21	2.24E-02	9776	NM_024094	DSCC1	DSCC1
chr15	39368005	39368162	3	158	0.27	0.70	-0.43	2.26E-02	-174801	NM_207445	C15orf54	C15orf54
chr9	45055243	45055268	3	26	0.76	0.96	-0.20	2.26E-02	65020	NR_027421	FAM27C	FAM27C
chr5	158879784	158880087	7	304	0.53	0.85	-0.32	2.27E-02	13348	NR_027110	LOC285627	LOC285627
chr19	389593	389861	9	269	0.75	0.50	0.25	2.27E-02	-13714	NM_199202	THEG	THEG

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr12	15366843	15366974	3	132	0.81	0.42	0.38	2.28E-02	7502	NM_032918	RERG	RERG
chr6	13379736	13379893	3	158	0.85	0.54	0.31	2.28E-02	28554	NM_001242630	GFOD1	TBC1D7
chr14	24527429	24527711	5	283	0.59	0.85	-0.26	2.30E-02	6364	NM_138360	LRRC16B	PCK2
chr5	83018803	83019116	6	314	0.79	0.59	0.20	2.31E-02	-2064	NM_001884	HAPLN1	VCAN
chr2	187816432	187816562	5	131	0.33	0.55	-0.22	2.32E-02	-102600	NM_182521	ZSWIM2	ZSWIM2
chr11	62692199	62692247	5	49	0.48	0.69	-0.21	2.32E-02	-3211	NM_000738	CHRM1	CHRM1, SLC3A2
chr9	5768793	5768823	3	31	0.72	0.44	0.28	2.33E-02	64273	NM_024896	ERMP1	RLN2, RLN1, KIAA1432, ERMP1
chr2	3704687	3704863	8	177	0.76	0.37	0.39	2.35E-02	-1011	NM_018436	ALLC	LOC100506054, ALLC
chr7	99067142	99067370	14	229	0.40	0.59	-0.20	2.35E-02	-3259	NM_001013258	ZNF789	ZNF394, ZKSCAN5
chr19	3999902	3999980	3	79	0.70	0.56	0.14	2.36E-02	-7808	NM_015897	PIAS4	PIAS4
chr4	186123616	186123973	7	358	0.30	0.56	-0.27	2.37E-02	1387	NM_020827	KIAA1430	ANKRD37, UFSP2, SNX25, KIAA1430, LRP2BP, SORBS2
chr10	133889348	133889623	3	276	0.75	0.52	0.23	2.37E-02	-28827	NM_001105521	JAKMIP3	JAKMIP3
chr12	124670588	124670752	6	165	0.51	0.33	0.18	2.38E-02	-103040	NM_181709	FAM101A	CCDC92, ZNF664, FAM101A, NCOR2
chr4	3485242	3485567	22	326	0.42	0.61	-0.20	2.39E-02	-866	NM_001256896	DOK7	DOK7
chr16	76321489	76321566	3	78	0.23	0.55	-0.33	2.40E-02	10352	NM_033401	CNTNAP4	CNTNAP4
chr10	621695	621794	4	100	0.58	0.80	-0.22	2.40E-02	65973	NR_049884	MIR5699	MIR5699
chr12	129267898	129268017	3	120	0.39	0.64	-0.25	2.41E-02	40583	NM_145648	SLC15A4	SLC15A4, GLT1D1, TMEM132D
chr17	4540261	4540537	5	277	0.38	0.54	-0.15	2.42E-02	4561	NM_001140	ALOX15	C17orf107, CAMTA2
chr22	39392165	39392269	4	105	0.62	0.39	0.24	2.43E-02	13813	NM_001270411	APOBEC3B	APOBEC3B
chr5	37209072	37209379	20	308	0.57	0.75	-0.18	2.43E-02	40304	NM_023073	C5orf42	OFD1P17
chr2	70778364	70778411	3	48	0.25	0.40	-0.16	2.44E-02	2759	NM_003236	TGFA	TGFA
chr12	132860284	132860365	4	82	0.22	0.48	-0.27	2.45E-02	8348	NR_024563	LOC100130238	LOC100130238
chr8	143337350	143337494	4	145	0.70	0.38	0.32	2.46E-02	57705	NR_024378	LINC00051	LINC00051
chr15	58765114	58765264	3	151	0.49	0.68	-0.19	2.48E-02	41014	NM_000236	LIPC	ADAM10

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr16	19919307	19919382	5	76	0.57	0.76	-0.19	2.49E-02	-23194	NM_016235	GPRC5B	GPRC5B
chr7	52535852	52535964	3	113	0.42	0.71	-0.29	2.50E-02	-567441	NM_182595	POM121L12	POM121L12
chr20	2084906	2084969	3	64	0.41	0.63	-0.22	2.52E-02	2410	NM_080836	STK35	NSFL1C, NOP56
chr1	10485762	10485865	8	104	0.79	0.60	0.19	2.53E-02	-4345	NM_198544	APITD1-CORT	PGD, PEX14
chr5	103560538	103560581	3	44	0.69	0.85	-0.16	2.54E-02	-662070	NM_031438	NUDT12	NUDT12
chr14	24800929	24801072	13	144	0.59	0.81	-0.22	2.56E-02	3276	NM_139247	ADCY4	MDP1, CHMP4A, TM9SF1, KHNYN, CBLN3,SDR39U1, OXA1L, MRPL52, LRP10, REM2, RBM23, AP1G2, DHRS4, PSME1, PSME2, RNF31, RABGGTA, DHRS1, LTB4R2, LTB4R, RIPK3, GMPR2, TINF2, CIDEB, CPNE6, DCAF11, NEDD8, NEDD8-MDP1
chr13	42853305	42853638	7	334	0.22	0.41	-0.20	2.56E-02	7183	NM_016248	AKAP11	AKAP11
chr4	25374405	25374574	4	170	0.66	0.41	0.25	2.57E-02	-4358	NM_013367	ANAPC4	ANAPC4
chr1	4506907	4506950	3	44	0.29	0.50	-0.21	2.58E-02	34818	NR_027088	LOC284661	LOC284661
chr10	14428428	14428623	4	196	0.83	0.54	0.29	2.59E-02	-50049	NR_031668	MIR1265	MIR1265
chr16	88286180	88286298	3	119	0.90	0.71	0.18	2.59E-02	-207640	NM_001127464	ZNF469	BANP
chr22	32272243	32272270	5	28	0.57	0.76	-0.19	2.60E-02	-68222	NM_003405	YWHAH	C22orf24, YWHAH
chr11	87776306	87776622	4	317	0.49	0.70	-0.21	2.61E-02	132171	NM_022337	RAB38	CTSC
chr12	101625514	101625693	3	180	0.07	0.24	-0.17	2.61E-02	-21588	NM_145913	SLC5A8	SLC5A8
chr6	110655377	110655780	6	404	0.76	0.57	0.19	2.63E-02	23896	NM_001123364	METTL24	METTL24
chr19	1678052	1678106	3	55	0.80	0.60	0.20	2.65E-02	-25751	NM_003200	TCF3	TCF3
chr14	97081068	97081125	8	58	0.44	0.73	-0.29	2.65E-02	112384	NM_001252006	PAPOLA	ATG2B
chr18	13136198	13136228	4	31	0.37	0.60	-0.23	2.66E-02	-82516	NM_181482	LDLRAD4	LDLRAD4
chr6	20378135	20378408	3	274	0.38	0.56	-0.19	2.67E-02	-23865	NM_001949	E2F3	E2F3
chr12	2512491	2512766	8	276	0.47	0.17	0.29	2.69E-02	133687	NR_046769	CACNA1C-IT3	FKBP4
chr6	110576693	110576778	5	86	0.15	0.31	-0.16	2.70E-02	75112	NM_015891	CDC40	GPR6

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr12	51472308	51472480	4	173	0.41	0.63	-0.22	2.71E-02	5043	NR_045072	CSRNP2	POU6F1
chr9	3528817	3528912	3	96	0.63	0.41	0.22	2.71E-02	-2882	NM_002919	RFX3	RFX3
chr11	131486482	131486615	4	134	0.20	0.53	-0.34	2.72E-02	246178	NM_001048209	NTM	NTM
chr6	4733267	4733354	4	88	0.43	0.60	-0.17	2.74E-02	26918	NR_026590	CDYL	CDYL
chr12	122377169	122377421	7	253	0.16	0.55	-0.39	2.74E-02	20832	NM_001178003	WDR66	PSMD9, WDR66, KDM2B
chr6	30777615	30777694	3	80	0.64	0.31	0.33	2.75E-02	-65328	NM_003897	IER3	TUBB, MDC1
chr1	3546974	3547081	4	108	0.71	0.49	0.22	2.75E-02	5472	NM_182752	TPRG1L	WRAP73
chr15	102021301	102021635	15	335	0.34	0.51	-0.17	2.76E-02	8719	NM_138323	PCSK6	PCSK6
chr7	137913708	137913746	3	39	0.88	0.70	0.18	2.76E-02	105223	NR_039678	MIR4468	MIR4468
chr2	52489874	52489916	6	43	0.91	0.58	0.33	2.77E-02	-1230221	NM_001135659	NRXN1	NRXN1
chr9	133776093	133776186	3	94	0.39	0.63	-0.24	2.78E-02	-6915	NM_198180	QRFP	QRFP
chr13	34368824	34368986	3	163	0.85	0.63	0.21	2.78E-02	-23301	NM_002915	RFC3	RFC3
chr22	20137361	20137629	11	269	0.30	0.48	-0.18	2.80E-02	-64	NM_001243537	LOC388849	LOC388849
chr1	6647425	6647649	6	225	0.43	0.64	-0.21	2.82E-02	7474	NM_005341	ZBTB48	CHD5, RPL22, ACOT7, ESPN, KLHL21
chr7	150003444	150003483	3	40	0.91	0.61	0.30	2.82E-02	-3395	NM_001164459	ACTR3C	ACTR3C
chr3	168093497	168093642	3	146	0.75	0.53	0.22	2.83E-02	126260	NR_021485	EGFEM1P	EGFEM1P
chr7	150923177	150923221	4	45	0.49	0.66	-0.17	2.84E-02	1118	NM_005692	ABCF2	ABCB8, CDK5, SLC4A2, FASTK, GBX1, CHPF2, SMARCD3, AGAP3, ASIC3, PRKAG2, NOS3, KMT2C, TMUB1
chr2	131752928	131753035	7	108	0.34	0.50	-0.16	2.84E-02	78758	NM_015320	ARHGEF4	ARHGEF4
chr3	149094815	149095572	17	758	0.59	0.80	-0.21	2.87E-02	374	NM_014220	TM4SF1	SIAH2, KLHL24, CPB1, GYG1, HLTF, RNF13, AGTR1, WWTR1, PFN2, CP, TM4SF18
chr10	5709176	5709400	6	225	0.50	0.31	0.19	2.87E-02	-730	NR_024581	ASB13	GDI2, FAM208B, ASB13
chr4	40056107	40056131	3	25	0.34	0.62	-0.27	2.88E-02	-2405	NM_018177	N4BP2	PDS5A
chr17	2905776	2905816	3	41	0.46	0.66	-0.20	2.88E-02	61105	NM_014566	OR1D5	TSR1
chr5	147038099	147038558	8	460	0.63	0.90	-0.27	2.89E-02	98772	NR_038902	JAKMIP2-AS1	JAKMIP2

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr6	12204553	12204752	3	200	0.13	0.46	-0.33	2.89E-02	-85876	NM_001168319	EDN1	EDN1
chr6	166719394	166719459	4	66	0.68	0.52	0.16	2.90E-02	2444	NM_175922	PRR18	PRR18
chr19	16565494	16565589	3	96	0.68	0.48	0.20	2.91E-02	17281	NM_001258374	EPS15L1	EPS15L1
chr6	43153106	43153239	4	134	0.87	0.67	0.21	2.91E-02	3251	NM_015089	CUL9	TJAP1, TAF8, PPP2R5D, MRPL2, KLC4, CUL9, ABCC10, XPO5, GTPBP2, MAD2L1BP, PTCRA, CNPY3, RPL24P4, PEX6, PTK7
chr19	13841884	13841938	4	55	0.52	0.70	-0.18	2.92E-02	-16842	NM_030818	CCDC130	CCDC130, NANOS3
chr7	27186927	27186992	9	66	0.57	0.36	0.21	2.92E-02	178	NR_038831	HOXA-AS3	HOXA3, HOXA-AS2, HOXA10, HOXA9, EVX1, HOXA7
chr3	10875538	10875901	3	364	0.24	0.41	-0.17	2.93E-02	17803	NM_014229	SLC6A11	ATP2B2
chr5	77146998	77147176	17	179	0.70	0.37	0.34	2.95E-02	-74902	NM_004607	TBCA	PDE8B, LHFPL2, WDR41
chr12	122354711	122354968	5	258	0.62	0.82	-0.20	2.95E-02	-1623	NM_144668	WDR66	BCL7A
chr15	93541699	93541783	4	85	0.82	0.63	0.19	2.96E-02	74648	NM_001166286	RGMA	RGMA
chr18	68773442	68773629	3	188	0.74	0.41	0.33	2.97E-02	472656	NR_038325	LOC100505776	LOC100505776
chr13	50108092	50108253	3	162	0.31	0.62	-0.31	2.98E-02	37645	NM_001040444	PHF11	PHF11
chr6	166511107	166511216	9	110	0.11	0.29	-0.18	2.98E-02	70995	NM_001270484	T	T
chr16	4146177	4146284	3	108	0.63	0.82	-0.19	2.99E-02	19955	NM_001116	ADCY9	ADCY9
chr2	107549313	107549428	3	116	0.71	0.88	-0.17	3.00E-02	-45808	NM_032528	ST6GAL2	ST6GAL2
chr6	28863662	28863756	9	95	0.40	0.16	0.24	3.00E-02	28059	NM_006510	TRIM27	LOC401242, TRIM27
chr11	64258267	64258564	11	298	0.79	0.57	0.22	3.01E-02	41887	NR_073177	LOC100996455	FERMT3, TRMT112, RPS6KA4, RASGRP2, SF1, MEN1
chr22	49818104	49818188	4	85	0.49	0.73	-0.24	3.01E-02	233044	NR_026997	C22orf34	C22orf34
chr3	71939699	71939900	3	202	0.49	0.68	-0.19	3.02E-02	-105443	NM_021935	PROK2	PROK2
chr2	173194581	173194769	9	189	0.76	0.52	0.24	3.03E-02	-97639	NM_000210	ITGA6	ITGA6
chr12	59862273	59862489	3	217	0.87	0.57	0.30	3.04E-02	-127440	NM_001270622	SLC16A7	SLC16A7
chr5	142473642	142474048	17	407	0.48	0.77	-0.29	3.08E-02	-225370	NR_046680	ARHGAP26-AS1	ARHGAP26-AS1

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr14	22397044	22397273	3	230	0.65	0.42	0.23	3.08E-02	263862	NM_001001912	OR4E2	OR4E2
chr18	13421460	13421659	7	200	0.49	0.66	-0.17	3.09E-02	5973	NR_040031	LOC100288122	LDLRAD4
chr1	238662532	238662727	6	196	0.50	0.79	-0.30	3.11E-02	-13313	NR_015407	LOC339535	LOC339535
chr1	17518554	17518618	3	65	0.39	0.70	-0.31	3.12E-02	-13035	NM_013358	PADI1	ATP13A2, SDHB, PADI4, ARHGEF10L
chr1	11132817	11132927	5	111	0.36	0.60	-0.23	3.15E-02	-12781	NM_003132	SRM	C1orf127, EXOSC10
chr15	80651305	80651731	5	427	0.37	0.63	-0.26	3.17E-02	-17371	NR_033833	LOC283688	LINC00927
chr1	107460427	107460473	3	47	0.58	0.78	-0.20	3.17E-02	-138817	NM_018137	PRMT6	PRMT6
chr12	109255672	109255817	5	146	0.48	0.30	0.18	3.18E-02	-4386	NM_018984	SSH1	DAO, SSH1, ISCU, ALKBH2, UNG, FOXN4
chr17	5674233	5674857	13	625	0.77	0.31	0.46	3.19E-02	-1009	NR_040000	LOC339166	LOC339166
chr9	74609653	74610077	5	425	0.49	0.72	-0.24	3.19E-02	65656	NM_001128618	C9orf57	C9orf57
chr19	45056874	45056949	4	76	0.53	0.85	-0.31	3.22E-02	3238	NR_027754	CEACAM22P	ZNF229, ZNF180, CEACAM19
chr4	95216580	95216860	6	281	0.47	0.66	-0.19	3.22E-02	42275	NM_001254949	SMARCAD1	PDLIM5
chr18	33759974	33760274	5	301	0.51	0.30	0.20	3.23E-02	-7356	NM_017947	MOCOS	MOCOS
chr7	104523955	104524128	4	174	0.34	0.51	-0.18	3.23E-02	43050	NR_027374	LHFPL3-AS2	FBXL13, ARMC10, KMT2E, PUS7
chr7	129780966	129780979	3	14	0.38	0.54	-0.16	3.24E-02	64365	NM_032842	TMEM209	NRF1, STRIP2, UBE2H, MEST, ZC3HC1
chr13	21619828	21620066	7	239	0.54	0.80	-0.26	3.25E-02	15775	NM_014572	LATS2	LATS2
chr11	122503123	122503437	6	315	0.44	0.68	-0.24	3.27E-02	-23118	NM_032873	UBASH3B	RPL31P47
chr19	57742174	57742440	14	267	0.67	0.83	-0.16	3.28E-02	-70	NM_001015879	AURKC	ZNF805, ZNF419
chr4	72723441	72723832	6	392	0.44	0.62	-0.17	3.30E-02	-52400	NM_001204306	GC	NPFFR2
chr1	120217427	120217838	5	412	0.35	0.77	-0.42	3.30E-02	-27243	NM_001080470	ZNF697	ZNF697, HSD3B1, PHGDH
chr2	231896863	231897057	4	195	0.75	0.55	0.20	3.31E-02	-5321	NM_001144994	C2orf72	C2orf72
chr5	135326365	135326643	12	279	0.33	0.57	-0.23	3.32E-02	-35781	NM_002302	LECT2	FBXL21, TGFBI
chr8	122213610	122213698	11	89	0.67	0.98	-0.31	3.33E-02	-389345	NM_021021	SNTB1	SNTB1
chr7	50546233	50546291	3	59	0.42	0.69	-0.27	3.35E-02	-28174	NM_001042762	FIGNL1	FIGNL1
chr7	137910811	137911030	4	220	0.36	0.15	0.21	3.36E-02	102417	NR_039678	MIR4468	MIR4468

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr16	87681964	87682259	21	296	0.41	0.76	-0.35	3.36E-02	45619	NM_001271605	JPH3	BANP
chr19	2639419	2639468	4	50	0.39	0.67	-0.27	3.39E-02	63302	NM_052847	GNG7	GNG7
chr8	61798550	61798744	5	195	0.47	0.22	0.25	3.40E-02	81660	NR_034003	LOC100130298	LOC100130298
chr8	26072962	26072990	3	29	0.52	0.69	-0.18	3.41E-02	-76031	NM_002717	PPP2R2A	BNIP3L
chr8	4188867	4188972	3	106	0.62	0.38	0.24	3.41E-02	663408	NM_033225	CSMD1	CSMD1
chr4	147207713	147207826	5	114	0.92	0.74	0.18	3.43E-02	110935	NM_007080	LSM6	LSM6
chr7	108019152	108019371	4	220	0.75	0.90	-0.15	3.44E-02	77579	NM_001193584	NRCAM	NRCAM
chr6	154969906	154970039	3	134	0.66	0.83	-0.17	3.44E-02	-84539	NM_014892	SCAF8	SCAF8, TIAM2
chr10	131595503	131595554	3	52	0.76	0.56	0.20	3.45E-02	46109	NR_036179	MIR4297	MIR4297
chr7	3147053	3147127	3	75	0.68	0.85	-0.17	3.47E-02	-63581	NM_032415	CARD11	CARD11
chr13	110851800	110851933	4	134	0.37	0.67	-0.30	3.48E-02	107629	NM_001845	COL4A1	CARKD, CARS2
chr2	54607872	54608087	8	216	0.42	0.61	-0.19	3.48E-02	49909	NM_001100396	C2orf73	C2orf73
chr15	60663652	60663824	5	173	0.75	0.58	0.17	3.49E-02	26447	NM_001002858	ANXA2	ANXA2, NARG2
chr1	1610304	1610570	11	267	0.53	0.72	-0.19	3.49E-02	13806	NM_001110781	SLC35E2B	SLC35E2B, CDK11A, MIB2, NADK, GNB1, PRKCZ
chr12	133360869	133361073	5	205	0.73	0.54	0.20	3.50E-02	-22520	NM_015114	ANKLE2	ANKLE2
chr17	41723952	41724018	3	67	0.40	0.59	-0.19	3.50E-02	14946	NM_013999	MEOX1	MPP3
chr15	76031648	76031680	5	33	0.24	0.38	-0.14	3.51E-02	754	NR_024595	DNM1P35	ODF3L1, FBXO22
chr13	114175964	114176059	4	96	0.91	0.73	0.18	3.53E-02	30704	NM_017905	TMCO3	TMCO3
chr1	77981049	77981421	7	373	0.37	0.12	0.24	3.54E-02	167108	NM_015534	ZZZ3	ZZZ3, USP33, ST6GALNAC5, AK5, NEXN
chr7	6616422	6616676	7	255	0.62	0.39	0.23	3.54E-02	-516	NM_018106	ZDHHC4	C7orf26, RSPH10B2, ZDHHC4, GRID2IP
chr6	148679386	148679939	7	554	0.63	0.89	-0.26	3.57E-02	15934	NM_015278	SASH1	SASH1
chr9	86098009	86098127	3	119	0.61	0.80	-0.19	3.57E-02	-15411	NM_001244960	FRMD3	FRMD3
chr12	1950457	1950505	5	49	0.67	0.45	0.21	3.58E-02	21048	NM_001039029	LRTM2	CACNA2D4, LRTM2, WNT5B

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr6	31691402	31691538	10	137	0.66	0.85	-0.20	3.59E-02	349	NM_138272	C6orf25	DDX39B, AIF1, LY6G5C, ABHD16A, LY6G6C, C6orf25, DDAH2, VARS, EHMT2, SKIV2L, AGER
chr8	28491236	28491484	7	249	0.21	0.51	-0.30	3.60E-02	-67630	NR_073469	EXTL3	EXTL3
chr6	150630398	150630512	3	115	0.45	0.66	-0.21	3.61E-02	-59573	NM_203395	IYD	IYD
chr10	107112766	107112994	5	229	0.65	0.82	-0.17	3.61E-02	712021	NM_014978	SORCS3	SORCS3
chr7	102479347	102479374	3	28	0.70	0.54	0.17	3.62E-02	-73983	NM_005824	LRRC17	NAPEPLD, S100A11P1
chr16	4042330	4042492	11	163	0.49	0.76	-0.27	3.63E-02	-112290	NM_004380	CREBBP	CREBBP
chr1	155044472	155044484	4	13	0.52	0.35	0.17	3.63E-02	-6870	NM_004952	EFNA3	ZBTB7B, DENND4B, TPM3, PYGO2, SHC1, CKS1B, LENEP, ADAM15, EFNA4, EFNA3, TRIM46, MTX1, CLK2, DAP3, GON4L, THBS3, ASH1L
chr17	80702770	80702866	4	97	0.69	0.86	-0.16	3.65E-02	-7122	NM_005993	TBCD	TBCD
chr7	556078	556262	9	185	0.27	0.49	-0.22	3.65E-02	3311	NM_002607	PDGFA	MICALL2, HEATR2
chr8	22280374	22280404	3	31	0.52	0.66	-0.14	3.67E-02	-18094	NM_005605	PPP3CC	EGR3
chr7	31296221	31296410	3	190	0.68	0.48	0.21	3.69E-02	84222	NM_022728	NEUROD6	NEUROD6, CCDC129
chr11	121633773	121633849	4	77	0.42	0.63	-0.21	3.71E-02	310899	NM_003105	SORL1	SORL1
chr7	157254674	157254791	6	118	0.71	0.49	0.22	3.72E-02	112381	NR_029689	MIR153-2	MIR153-2
chr1	27195494	27195576	4	83	0.65	0.82	-0.17	3.75E-02	5902	NM_006142	SFN	SFN
chr12	79696418	79696553	6	136	0.37	0.70	-0.33	3.75E-02	-116551	NR_031700	MIR1252	MIR1252
chr13	112508975	112509008	4	34	0.71	0.51	0.21	3.76E-02	-212921	NM_005986	SOX1	SOX1
chr15	101199052	101199157	5	106	0.59	0.34	0.25	3.77E-02	56350	NM_198243	ASB7	ASB7
chr6	95257880	95258195	5	316	0.19	0.44	-0.25	3.78E-02	-767335	NM_024641	MANEA	MANEA
chr10	104813741	104813902	8	162	0.14	0.32	-0.18	3.78E-02	135747	NM_199076	CNNM2	CNNM2, FBXW4, KCNIP2, NOLC1, PSD, FBXL15, CUEDC2, TMEM180, ACTR1A, NT5C2, PDCD11
chr15	99446210	99446219	3	10	0.47	0.22	0.25	3.80E-02	102670	NM_001102612	PGPEP1L	MEF2A

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr11	70291888	70291985	6	98	0.33	0.53	-0.20	3.80E-02	47325	NM_138565	CTTN	CTTN
chr14	55348233	55348864	8	632	0.38	0.60	-0.21	3.81E-02	-3638	NR_036194	MIR4308	MIR4308, GCH1, SOCS4
chr11	104750395	104750469	5	75	0.76	0.56	0.20	3.82E-02	18965	NR_034070	CASP12	CASP12
chr2	238224135	238224256	3	122	0.39	0.60	-0.21	3.82E-02	98654	NM_057167	COL6A3	COL6A3
chr14	66219350	66219609	3	260	0.66	0.88	-0.21	3.85E-02	340032	NR_038170	FUT8	FUT8-AS1
chr1	185460064	185460379	5	316	0.86	0.52	0.33	3.87E-02	-156051	NR_038424	LOC100288079	LOC100288079
chr6	143939283	143939333	3	51	0.49	0.66	-0.17	3.89E-02	9991	NM_014721	PHACTR2	PHACTR2
chr11	77925098	77925243	4	146	0.81	0.62	0.19	3.89E-02	25313	NM_020798	USP35	USP35
chr11	121525739	121525825	4	87	0.47	0.64	-0.17	3.90E-02	202870	NM_003105	SORL1	SORL1
chr1	235147060	235147140	3	81	0.38	0.57	-0.20	3.91E-02	144152	NR_002956	SNORA14B	TOMM20, LYST, ARID4B
chr7	149298090	149298146	5	57	0.60	0.32	0.28	3.92E-02	23763	NR_027789	ZNF767	ZNF862, ZNF767
chr15	48609972	48610061	5	90	0.76	0.51	0.25	3.93E-02	-13604	NM_001025249	DUT	DUT
chr19	45119930	45119991	4	62	0.33	0.12	0.22	3.95E-02	3021	NM_001205280	IGSF23	IGSF23
chr19	21778856	21778904	3	49	0.43	0.61	-0.18	3.96E-02	90443	NM_001001415	ZNF429	ZNF429
chr7	44807724	44808260	11	537	0.71	0.39	0.32	3.97E-02	12205	NM_174929	ZMIZ2	PPIA, ZMIZ2
chr17	35851394	35851581	7	188	0.56	0.32	0.24	3.97E-02	1537	NM_007026	DUSP14	C17orf78, ACACA, TADA2A, DDX52, GGNBP2, DUSP14
chr19	7763241	7763799	11	559	0.49	0.30	0.19	3.98E-02	845	NM_001207019	FCER2	XAB2
chr9	8432373	8432529	4	157	0.43	0.87	-0.45	3.99E-02	301495	NM_130393	PTPRD	C9orf123
chr16	77110718	77110785	4	68	0.52	0.78	-0.26	4.00E-02	-114084	NM_014940	MON1B	MON1B
chr19	7492013	7492156	4	144	0.82	0.62	0.20	4.00E-02	-12489	NM_001130955	ARHGEF18	ARHGEF18
chr1	39336826	39336914	5	89	0.59	0.29	0.30	4.02E-02	2180	NR_037632	MYCBP	NDUFS5, RRAGC
chr12	131578065	131578158	5	94	0.31	0.53	-0.23	4.06E-02	-71444	NR_026670	LOC116437	RAN, GPR133
chr1	159295508	159295564	3	57	0.46	0.88	-0.42	4.06E-02	-11087	NM_001004467	OR10J3	OR10J3
chr1	713542	713671	3	130	0.22	0.43	-0.21	4.08E-02	461	NR_033908	LOC100288069	
chr10	7348350	7348516	7	167	0.47	0.29	0.18	4.10E-02	102870	NM_001018039	SFMBT2	SFMBT2
chr14	47124258	47124346	3	89	0.77	0.53	0.24	4.11E-02	-3274	NM_080746	RPL10L	RPL10L

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr6	159571579	159571785	3	207	0.11	0.34	-0.22	4.12E-02	-18747	NM_032532	FNDC1	FNDC1
chr2	180869203	180869262	4	60	0.91	0.55	0.36	4.14E-02	2547	NM_020943	CWC22	CWC22
chr11	22097685	22097703	8	19	0.46	0.69	-0.23	4.14E-02	-117028	NM_213599	ANO5	ANO5
chr12	52773549	52773841	6	293	0.57	0.24	0.33	4.15E-02	5722	NM_033045	KRT84	KRT84
chr19	10146222	10146297	4	76	0.69	0.87	-0.19	4.16E-02	-5772	NR_027300	C3P1	C3P1
chr5	79999750	79999812	3	63	0.54	0.73	-0.20	4.17E-02	-48981	NM_000791	DHFR	DHFR
chr13	112173884	112174008	5	125	0.30	0.13	0.17	4.21E-02	200931	NM_152324	TEX29	TEX29
chr17	65908964	65909097	5	134	0.48	0.65	-0.17	4.21E-02	80734	NM_181655	C17orf58	C17orf58
chr7	26725137	26725364	3	228	0.63	0.41	0.22	4.22E-02	47761	NM_001145531	C7orf71	SNX10, C7orf71, HOXA7
chr3	129826273	129826492	5	220	0.40	0.63	-0.23	4.23E-02	3893	NR_024252	FAM86HP	FAM86HP
chr17	8897450	8897866	8	417	0.59	0.79	-0.20	4.24E-02	-27201	NM_004822	NTN1	PIK3R6
chr16	85950153	85950217	3	65	0.48	0.70	-0.22	4.26E-02	17411	NM_002163	IRF8	IRF8
chr4	172929561	172929798	3	238	0.57	0.38	0.20	4.27E-02	195105	NM_001034845	GALNTL6	GALNTL6
chr22	38808507	38808628	8	122	0.40	0.55	-0.16	4.28E-02	-13637	NR_002821	LOC400927	CBY1, FAM227A
chr1	51439347	51439664	7	318	0.82	0.63	0.19	4.28E-02	3864	NM_078626	CDKN2C	NRD1, CDKN2C, EPS15
chr1	28319916	28319960	3	45	0.38	0.19	0.20	4.30E-02	33434	NM_018053	XKR8	PPP1R8
chr5	82754756	82754941	3	186	0.75	0.94	-0.19	4.31E-02	-12644	NM_001164097	VCAN	VCAN
chr3	75040570	75040632	3	63	0.37	0.58	-0.21	4.31E-02	-223026	NR_039646	MIR4444-1	MIR4444-1
chr11	76510051	76510156	5	106	0.49	0.63	-0.14	4.32E-02	15819	NM_015516	TSKU	TSKU
chr9	5186586	5186960	5	375	0.09	0.37	-0.28	4.33E-02	-1155	NM_007179	INSL6	RLN2, RLN1, CD274
chr3	137152260	137152330	4	71	0.77	0.38	0.38	4.34E-02	-330839	NM_004189	SOX14	SOX14
chr22	37215214	37215457	6	244	0.40	0.59	-0.19	4.35E-02	181	NM_002854	PVALB	PVALB
chr16	61994171	61994223	3	53	0.40	0.67	-0.28	4.36E-02	76542	NM_001796	CDH8	CDH8
chr13	114211941	114211983	5	43	0.51	0.68	-0.17	4.36E-02	-27041	NR_026580	TFDP1	TFDP1
chr22	49992862	49993053	7	192	0.40	0.56	-0.16	4.39E-02	58232	NR_026997	C22orf34	BRD1, PIM3
chr19	56851141	56851175	3	35	0.73	0.52	0.21	4.38E-02	-28310	NR_003127	ZNF542	ZNF542

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr6	36871770	36871888	3	119	0.46	0.28	0.18	4.39E-02	18189	NM_152734	C6orf89	SRSF3
chr4	180290923	180291089	3	167	0.66	0.43	0.22	4.40E-02	1641095	NR_028342	LOC285501	LOC285501
chr13	82506702	82506968	3	267	0.56	0.80	-0.24	4.44E-02	-1591749	NM_005842	SPRY2	SPRY2
chr14	93112220	93112326	4	107	0.43	0.20	0.23	4.44E-02	102774	NM_001008530	LGMN	FBLN5, UBR7
chr15	66408308	66408548	8	241	0.46	0.69	-0.23	4.45E-02	75857	NR_036196	MIR4311	MIR4311
chr12	83783188	83783222	4	35	0.36	0.52	-0.16	4.45E-02	702271	NM_152588	TMTC2	TMTC2
chr8	22458031	22458084	4	54	0.55	0.77	-0.22	4.47E-02	944	NM_001013842	C8orf58	PPP3CC, EGR3, FAM160B2, HR, REEP4, LGI3, CCAR2, SORBS3, BIN3, PDLIM2
chr10	54831464	54831532	3	69	0.28	0.53	-0.25	4.47E-02	-300038	NM_000242	MBL2	MBL2
chr20	61660675	61660809	9	135	0.78	0.42	0.36	4.51E-02	7638	NR_028295	LINC00029	BHLHE23
chr9	136132775	136133002	9	228	0.40	0.65	-0.25	4.53E-02	17741	NM_020469	ABO	SNORD36C, SNORD36B, SNORD36A, SNORD24, RPL7A, MED22
chr16	90144573	90144787	9	215	0.38	0.56	-0.18	4.54E-02	-2342	NM_001098173	PRDM7	URAHP, AFG3L1P, PRDM7, SPATA2L
chr6	2932860	2932986	3	127	0.45	0.63	-0.18	4.55E-02	-29377	NM_004155	SERPINB9	SERPINB1, SERPINB9, SERPINB6
chr15	79092780	79092910	15	131	0.58	0.85	-0.28	4.57E-02	10928	NM_014272	ADAMTS7	IREB2, MORF4L1, CTSH
chr10	131423066	131423137	3	72	0.63	0.94	-0.31	4.57E-02	157648	NM_002412	MGMT	MGMT
chr20	31169503	31169563	3	61	0.49	0.67	-0.19	4.58E-02	3342	NM_001256798	C20orf112	DNMT3B, BCL2L1, HCK, CBFA2T2, AHCY, PLAGL2, TTLL9
chr11	10798994	10799100	3	107	0.33	0.51	-0.18	4.59E-02	24108	NR_004403	SNORD97	SNORD97
chr10	1445760	1445851	6	92	0.31	0.50	-0.19	4.62E-02	-123019	NR_033387	ADARB2-AS1	ADARB2
chr17	79041278	79041500	12	223	0.69	0.49	0.20	4.63E-02	32442	NM_006340	BAIAP2	BAIAP2, BAIAP2-AS1, SLC38A10, FSCN2
chr3	189340524	189340571	3	48	0.61	0.35	0.26	4.65E-02	-8668	NM_001114978	TP63	TP63
chr16	84516247	84516384	6	138	0.62	0.80	-0.19	4.66E-02	21972	NM_020947	TLDC1	TLDC1
chr9	136224007	136224117	7	111	0.38	0.55	-0.17	4.70E-02	641	NM_017503	SURF2	SURF2
chr18	77632917	77632966	5	50	0.49	0.27	0.22	4.69E-02	9274	NM_012283	KCNG2	KCNG2

chr	start	end	CpGs	width bp	mean meth. vitamin D high	mean meth vitamin D low	mean Diff.	p-value SAM	Distance to TSS	Nearest Promoter ID	gene name	predicted targets
chr17	20420566	20420635	3	70	0.66	0.89	-0.22	4.70E-02	-12790	NR_029393	KRT16P3	KRT16P3
chrX	730480	730578	3	99	0.45	0.63	-0.18	4.71E-02	145450	NM_006883	SHOX	SHOX
chr11	77299847	77300116	13	270	0.52	0.73	-0.21	4.71E-02	-698	NM_173039	AQP11	RSF1, USP35, PAK1
chr1	9624929	9625151	4	223	0.60	0.44	0.16	4.73E-02	-23892	NM_001130924	TMEM201	H6PD, TMEM201, CLSTN1, LZIC, UBE4B
chr6	6794070	6794211	4	142	0.54	0.35	0.19	4.73E-02	-171082	NR_026970	LY86-AS1	F13A1, CNN3P1, BTF3P7
chr1	246440564	246440677	3	114	0.47	0.65	-0.18	4.74E-02	140093	NM_022743	SMYD3	SMYD3
chr16	4181576	4181721	5	146	0.41	0.58	-0.18	4.76E-02	-15463	NM_001116	ADCY9	ADCY9
chr22	47337282	47337336	3	55	0.47	0.85	-0.38	4.77E-02	178791	NM_014346	TBC1D22A	TBC1D22A
chr7	20630907	20631261	5	355	0.74	0.89	-0.15	4.79E-02	-24161	NM_001163941	ABCB5	ABCB5
chr1	91227318	91227895	11	578	0.29	0.53	-0.24	4.79E-02	-44813	NM_020063	BARHL2	BARHL2
chr7	113728028	113728063	5	36	0.54	0.68	-0.14	4.81E-02	1681	NR_033766	FOXP2	MDFIC
chr10	76996187	76996532	5	346	0.49	0.77	-0.28	4.85E-02	-590	NM_144589	COMTD1	FUT11, SAMD8, DUSP13, ZNF503-AS2, VDAC2
chr2	5936100	5936228	3	129	0.50	0.75	-0.25	4.86E-02	103365	NM_003108	SOX11	SOX11
chr1	94057725	94057788	4	64	0.16	0.35	-0.19	4.86E-02	232	NR_034091	LOC100129046	SLC44A3
chr17	8895565	8895587	3	23	0.90	0.68	0.22	4.87E-02	-26547	NM_001142633	PIK3R5	PIK3R5
chr10	18947463	18947500	4	38	0.60	0.77	-0.16	4.88E-02	-831	NM_178815	ARL5B	NSUN6
chr17	78302774	78303046	9	273	0.75	0.59	0.16	4.90E-02	68250	NM_020954	RNF213	RNF213
chr21	16443819	16444148	6	330	0.50	0.77	-0.26	4.90E-02	-6858	NM_003489	NRIP1	NRIP1
chr8	21550152	21550249	6	98	0.46	0.23	0.23	4.91E-02	96145	NM_001495	GFRA2	DOK2, FGF17
chr8	106330023	106330057	6	35	0.26	0.42	-0.17	4.93E-02	-1107	NM_012082	ZFPM2	ZFPM2
chr20	50317508	50317573	4	66	0.23	0.43	-0.19	4.93E-02	67367	NM_006045	ATP9A	ATP9A, SALL4
chr15	74501913	74502019	3	107	0.76	0.59	0.17	4.94E-02	80	NM_001199040	STRA6	STRA6
chr1	91900932	91901284	4	353	0.48	0.75	-0.28	4.95E-02	-30682	NM_001017975	HFM1	TGFBR3
chr6	63550986	63551005	3	20	0.49	0.66	-0.16	4.97E-02	478886	NM_016571	LGSN	LGSN
chr21	23747271	23747322	3	52	0.48	0.66	-0.17	4.97E-02	276361	NR_038400	LINC00308	LINC00308
chr5	68114049	68114329	3	281	0.48	0.64	-0.16	5.00E-02	-275587	NM_001251969	SLC30A5	SLC30A5

Table EIV

Disease pathway	EntrezGene ID	Genes in pathway	Genes observed/ genes expected in pathway	p-value[#]	Adj. p-value*
HIV	5599 9150 196883 3134 5721 92140 5720 10618 146664 5578 5715 55170 5478 9582 1387 4153 5511 115 56257 29969 5901 8906 5046 129685 5058 104 5441 55048 3055 105 3106 51422 29082 79694 7535 684 5590 144423 7374 5437 4776 5528 1642	755	43/17.33	6.81e-08	1.29e-05
Disease Susceptibility	4282 65018 118 5270 2550 392636 51131 875 1960 9378 4153 114815 23569 7049 6439 1789 6653 421 1610 64478 2646 341880 4846 6499 57140 4340 2162 3784 10786 4255 23400 6390 3106 7185 185 5888 199 26281 64127 112744 11132 1719 5533 3394 63027 3283	825	46/18.94	4.46e-08	1.29e-05
Adhesion	102 3655 92140 977 10174 9378 8500 780 8578 4897 57556 83706 6464 923 8751 421 2017 9423 50863 10085 2650 2049 5058 6520 6237 266727 5777 394 1944 7525 8470 7045 56253 1832 1006 5792 1462 5754 4356 50649	647	40/14.85	2.21e-08	1.29e-05
Genetic Predisposition to Disease	4282 65018 118 5270 2550 392636 51131 875 1960 9378 4153 114815 23569 7049 6439 1789 6653 54805 421 1610 64478 2646 341880 4846 57140 2162 3784 10786 3198 4255 23400 6390 3106 7185 185 5888 199 64127 112744 11132 1719 5533 3394 63027 10891	808	45/18.55	6.45e-08	1.29e-05
Death	5599 26524 55367 2026 5272 8737 29126 598 8870 4055 1020 8626 100506742 11035 665 3784 3757 7416 1832 8772 27141 7818 7185 1869 6478 50649	343	26/7.87	1.39e-07	2.10e-05
cancer or viral infections	5599 26524 2130 4763 3655 92140 771 1875 977 8737 3400 5157 51773 29126 598 9656 23209 26038 1031 8626 406985 1789 1163 2017 9423 5058 340273 51147 1871 5727 7022 4583 6692 4221 4255 6390 5888 7535 160728 3205 25937 1869 684 9271 406933 3665 64754 2810	951	48/21.83	4.31e-07	5.43e-05
Necrosis	5599 4282 102 85480 7919 10673 8887 8737 598 8870 4055 55072 923 970 177 7039 11035 8772 7185 5608 5590 64127 3665 79155	324	24/7.44	6.28e-07	6.78e-05
Arterial Occlusive Diseases	6272 875 4205 23209 2646 177 4846 221458 10516 57674 1906 57140 2162 27433 85440 185 199 11132 9619	219	19/5.03	8.84e-07	8.35e-05
Nelson syndrome	29842 2128 245711 129303 83787 23148 54517 64005 23386 2636 2845 441272 257407 79853 29887 23660 55821 84173 29803 400966 8447 63979 10061 57140 133015 6604 7328 3757 79970 79027 3106 644150 222235 3200 5814 83637 51530	673	37/15.45	1.28e-06	0.0001
Leukemia	3204 9612 4763 6929 10673 8887 5326 3400 598 7329 3206 1387 6464 28514 923 970 64236 57167 5777 7066 9139 4221 3055 7535 3205 55363 3394 9046	452	28/10.38	2.68e-06	0.0002
Syndrome	10810 6473 4763 5190 113189 83706 4153 1075 8626 6439 2646 3425 2328 1130 1285 57167 51259 5727 8403 3784 3757 4232 4221 3198 10458 9563 23400 6390 285489 3106 51422 644150 11132 64220 60675	654	35/15.01	4.43e-06	0.0003
Neoplasms	2130 4763 3655 83605 92140 771 977 3400 5157 51773 29126 598 23209 55107 26038 1119 1031 6862 8626 406985 1789 2017 6664 340273 51147 7039 1871 5727 7022 4583 4221 4255 6390 5888 7535 160728 3205 1869 9271 406933 64754 2810	854	42/19.6	4.27e-06	0.0003
Subarachnoid Hemorrhage	1329 392636 22879 151112 3705 54872 4846 23113 1906 2162 7837 11332	104	12/2.39	5.00e-06	0.0003
Brain Diseases	3748 65018 118 2026 102 5190 2550 875 23209 1020 114815 6653 177 4846 8893 1356 2581 51259 2162 1181 4255 23400 26281 2668 2580	411	25/9.43	1.23e-05	0.0006
Central Nervous System Diseases	3748 65018 118 2026 102 5190 2550 875 23209 1020 114815 6653 177 4846 8893 1356 2581 4340 2162 1181 4255 23400 2643 26281 2668 2580	438	26/10.05	1.27e-05	0.0006
Eye Diseases	10594 10673 1261 4976 51557 392255 23746 8419 177 4846 6499 25794 10516 57167 7003 51667 8403 7045 3198 3106 1462 64127 64220	368	23/8.45	1.76e-05	0.0008

Disease pathway	EntrezGene ID	Genes in pathway	Genes observed/ genes expected in pathway	p-value[#]	Adj. p-value*
Congenital Abnormalities	6473 5190 6662 83605 875 113189 23209 80215 392255 5396 8626 26277 10253 6468 1285 57167 7039 89766 51259 5727 8403 3784 23414 3757 1832 3198 51422 547 1719 64220 2668 60675 1642	643	33/14.76	1.92e-05	0.0009
Transplantation	5272 29126 64005 83706 4153 1186 970 9423 1130 340273 7066 1906 7045 3106 199 64127	205	16/4.71	2.38e-05	0.0010
Leukemia, Myeloid	3204 9612 55870 4763 5326 3400 598 3206 1387 9577 57167 5777 9139 4221 3055 3205 55363 3394 9046	279	19/6.4	2.91e-05	0.0012
Arteriosclerosis	6272 4205 23209 2646 177 4846 221458 10516 1906 57140 2162 85440 185 199 11132 9619	214	16/4.91	4.01e-05	0.0015
Myocardial Infarction	6272 118 8673 22879 4205 151112 4153 3705 54872 177 4846 221458 1906 2162 185 144406 4151	242	17/5.56	5.11e-05	0.0017
Connective Tissue Diseases	4282 10673 875 113189 29126 7920 4153 23569 970 177 3425 10516 1285 80741 5394 7185 199 3665 6625	291	19/6.68	5.15e-05	0.0017
Heart Diseases	6473 6272 118 8673 875 4205 30819 2646 177 4846 221458 1906 2162 3784 3757 23414 1832 441911 51422 185 4776 4151	366	22/8.4	4.77e-05	0.0017
Ganglioneuroblastoma	10810 28514 2668 10611 2810	19	5/0.44	5.61e-05	0.0017
Vascular Resistance	118 6013 2017 177 4846 1906 2162 23564 185	75	9/1.72	5.53e-05	0.0017
Drug interaction with drug	5599 9612 118 2782 598 5578 5478 1387 6464 23054 970 2288 8204 5777 3757 3055 8772 5888 5590 684 4915	349	21/8.01	6.92e-05	0.0020
Leukemia, Myeloid, Acute	3204 9612 4763 6929 5326 3400 3206 1387 9577 57167 9139 55363 3205 5754 3394	208	15/4.77	0.0001	0.0022
Cell Transformation, Neoplastic	4149 2130 92140 25807 26038 1119 6464 5396 5058 7039 1871 4221 5898 3205 25937 1487	233	16/5.35	0.0001	0.0022
Neuroblastoma	10810 65018 4149 2026 102 26038 10886 9423 10277 4832 728642 10901 9201 2668 4915 203068	229	16/5.26	8.96e-05	0.0022
Multiple Endocrine Neoplasia	4763 1031 7536 4221 5792 6390	34	6/0.78	0.0001	0.0022
Musculoskeletal Diseases	4282 6473 2130 6662 10673 1293 4153 6862 23569 392255 1186 8626 23479 203859 6468 7170 57167 7039 2137 5727 10786 3106 7185 64127 8291	462	25/10.61	8.30e-05	0.0022
Diabetes Mellitus, Type 2	9826 392636 5715 4899 114815 5106 177 2646 4846 1906 57140 3784 185 81029 257019 11132 10891	254	17/5.83	9.28e-05	0.0022
Olfaction Disorders	196883 7106 64478 23400 9563 60675	33	6/0.76	9.39e-05	0.0022
Infarction	6272 118 8673 22879 4205 151112 4153 54872 177 4846 221458 1906 2162 185 144406 4151	236	16/5.42	0.0001	0.0022
H Syndrome	10810 4763 5190 875 83706 1075 8626 6439 1789 2646 3425 1130 1285 51259 5727 3784 3757 4221 3198 23400 9563 6390	394	22/9.04	0.0001	0.0022
Cerebrovascular Disorders	118 2026 875 23209 177 4846 221458 8831 57674 1906 2162 185 56413	171	13/3.93	0.0002	0.0030
De Lange Syndrome	23047 79075 3784 3757 23244	25	5/0.57	0.0002	0.0030
Leukemia, Myelogenous, Chronic, BCR-ABL Positive	3400 598 6464 5777 3055 5898 3205 3394 9046	88	9/2.02	0.0002	0.0030
Congenital diaphragmatic hernia	4205 23414 6991 53834	13	4/0.3	0.0002	0.0030
Hernia, Diaphragmatic	55805 23414 6991 64220 53834	25	5/0.57	0.0002	0.0030
Heart Failure	3270 6019 30819 4846 1906 1832 91624 51422 185 4776 10891	125	11/2.87	0.0002	0.0030

Disease pathway	EntrezGene ID	Genes in pathway	Genes observed/ genes expected in pathway	p-value[#]	Adj. p-value*
Nervous System Diseases	3748 65018 2026 102 4763 5190 83605 2550 875 1261 4976 23209 1020 114815 23746 9856 6653 2124 203859 8893 1356 2581 57167 491 4340 4255 23400 285489 26281 2643 8291 2668	694	32/15.93	0.0002	0.0030
Lymphoma, Low-Grade	84433 54625 6929 10673 8737 3400 29126 598 970 6664 605 285973 7170 5777 7535	219	15/5.03	0.0002	0.0030
Hypertrophy	6473 401082 4205 23125 4846 1906 23414 51422 185 4776 10891 3283	147	12/3,37	0.0002	0.0030
Cleft Palate	3204 56971 6662 875 1119 7049 5396 8626 421 191 10253 2049 7039 5727	200	14/4,59	0.0002	0.0030
Nervous System Neoplasms	375790 4763 6662 83605 92140 771 23209 1031 6664 5727 4221 4255 6390 6656	194	14/4.45	0.0002	0.0030
Retinoblastoma	9984 1875 4176 1031 1020 10933 5514 4174 23746 1871 51742 26512 7027 1869 9221	221	15/5.07	0.0002	0.0030
Immunologic Deficiency Syndromes	5599 3134 5721 10673 10618 5720 5715 55170 5478 83706 9582 4153 1789 1130 5441 55048 3055 3106 7535 7374 684 1642	399	22/9.16	0.0002	0.0030
von Hippel-Lindau Disease	4763 23032 112399 491 4738 6390	38	6/0.87	0.0002	0.0030
Williams Syndrome	29842 2128 245711 129303 83787 23148 54517 2636 2845 441272 257407 79853 23660 29887 55821 84173 400966 63979 133015 57140 79970 79027 644150 222235	461	24/10.58	0.0002	0.0030
Arrhythmias, Cardiac	54805 30819 54795 64785 1906 3784 3757 1832 51422 185	107	10/2.46	0.0002	0.0030
Chronic Disease	4282 5270 85480 10673 29126 4153 6439 177 4846 1285 1906 3106 3658 185 7535 112744 64127 3394	307	18/7.05	0.0003	0.0041
Parkinson Disease, Secondary	65018 23414 23400 2668 55031	26	5/0.6	0.0003	0.0041
Neoplastic Processes	10810 4149 3655 92140 977 3400 8626 406985 2017 5058 25794 51147 7022 4583 4255 5898 3205 25937 406933 302 4915 2810	411	22/9.43	0.0003	0.0041
Immune System Diseases	**4282 84433 3134 85480 6929 51131 10673 29126 83706 4153 9582 23569 923 970 177 6664 1130 605 1285 5777 4340 3106 7185 7535 199 112744 684 64127 7374 3665 3394**	**680**	**31/15.61**	**0.0003**	**0.0041**
Accelerated phase chronic myeloid leukemia	3400 4832 3205 1992	16	4/0.37	0.0004	0.0052
Albuminuria	118 55805 177 4846 1356 1906 185	60	7/1.38	0.0004	0.0052
Obstetric Labor Complications	875 4153 6013 6019 177 4846 1285 171558 7066 2162 25776 1462 64127 1719	212	14/4.87	0.0004	0.0052
Neurodegenerative Diseases	3748 65018 102 4763 4976 23209 1020 114815 23746 6653 177 2124 8893 1356 51667 23400 547 26281 2668 2580 203068	404	21/9.27	0.0005	0.0062
Carotid Artery Diseases	118 1241 177 4846 57674 185 199 56413	81	8/1.86	0.0005	0.0062
Hyperalgesia	9311 8508 1906 143425 60675	29	5/0.67	0.0005	0.0062
Pallister-Hall syndrome	6929 7407 7003 5991 85440 1487	46	6/1.06	0.0006	0.0071
Anophthalmos	7407 392255 7003 5991 85440 64220	46	6/1.06	0.0006	0.0071
Retroviridae Infections	5599 3134 5721 10618 5720 29126 5715 55170 5478 9582 4153 5058 5441 55048 3055 3106 7374 684 5437 1642	382	20/8.77	0.0006	0.0071
Optic Nerve Diseases	2026 4763 4976 7049 8317 23746 51667	64	7/1.47	0.0007	0.0076
Brain Neoplasms	375790 4763 83605 92140 771 780 1031 6664 5727 4221 4255 6656 4915	198	13/4.55	0.0007	0.0076
Retinal Diseases	10594 1261 51557 23746 177 4846 6499 25794 10516 1356 7003 51667 1871 51259 1462	247	15/5.67	0.0007	0.0076

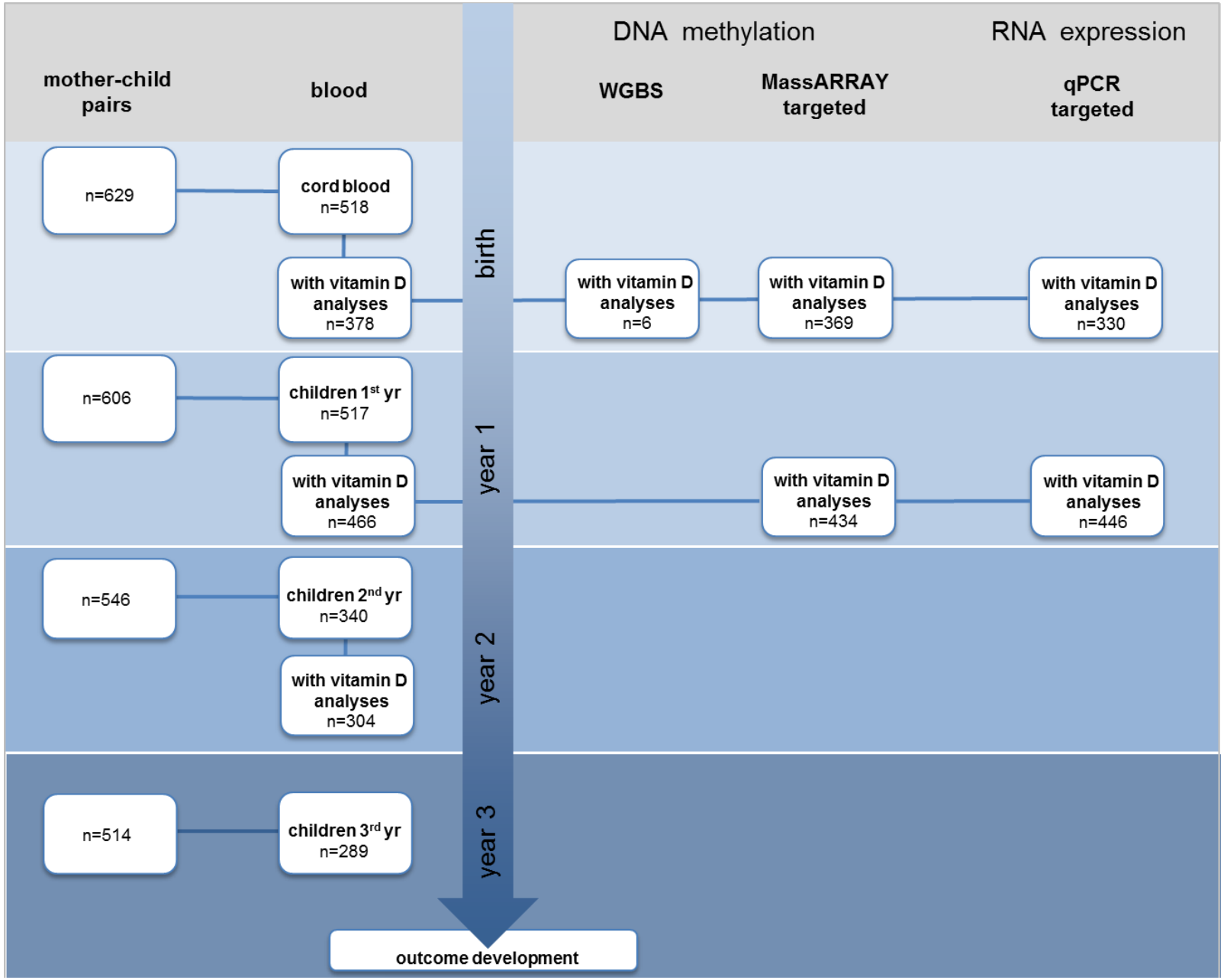
Disease pathway	EntrezGene ID	Genes in pathway	Genes observed/ genes expected in pathway	p-value[#]	Adj. p-value*
Protein Deficiency	55034 6473 84433 875 8737 83706 4153 6439 23479 3425 1130 189 83737 5777 2162 7535 8291 64788 3394	356	19/8.17	0.0007	0.0076
Osteopetrosis	83706 1186 29887 2137 29992	31	5/0.71	0.0007	0.0076
Paraganglioma	4149 4763 54949 112399 6390	31	5/0.71	0.0007	0.0076
Respiratory distress syndrome in the newborn	6662 4153 6439 79888	19	4/0.44	0.0008	0.0080
Premature Birth	875 4153 6013 6439 6019 4846 171558 7066 1906 2162 25776 64127 1719	201	13/4.61	0.0008	0.0080
Osteosarcoma	6473 2130 1875 9656 1387 8626 7398 1945 1869 53834	128	10/2.94	0.0008	0.0080
Coronary Disease	6272 118 8673 875 4205 177 2646 4846 221458 29881 1906 57140 2162 85440 185	253	15/5.81	0.0008	0.0080
Leukemia, B-Cell, Acute	3400 2665 923 64236 7535 4356	48	6/1.1	0.0008	0.0080
Schizophrenia	6536 2550 1128 1960 9378 23209 421 1610 64478 29886 266727 4340 26512 23774 285242 5533 4915 10611 7533	360	19/8.26	0.0008	0.0080
Simian acquired immune deficiency syndrome	3134 8906 5058 3055 3106 684	49	6/1.12	0.0009	0.0082
Syncope	1906 3784 3757 1832 91624 51422	49	6/1.12	0.0009	0.0082
Coronary Artery Disease	6272 118 8673 875 4205 177 2646 4846 221458 29881 1906 57140 2162 85440 185	254	15/5.83	0.0009	0.0082
Tumor Virus Infections	4149 6929 1875 29126 4153 3055 8772 3106 3665 2810	130	10/2.98	0.0009	0.0082
Atrial Fibrillation	30819 4846 2162 3784 3757 51422 185	67	7/1.54	0.0009	0.0082
Skin and Connective Tissue Diseases	**4282 3655 85480 92140 10673 875 4153 55806 23569 1075 8626 3425 10516 1285 7022 5727 1832 3106 7185 5888 199 112744 2810**	**481**	**23/11.04**	**0.0009**	**0.0082**
Cerebral Hemorrhage	118 83605 22879 151112 4846 2162	49	6/1.12	0.0009	0.0082
Lung Diseases, Obstructive	**5270 85480 4153 6439 64478 177 4846 1906 3658 112744**	**133**	**10/3.05**	**0.0010**	**0.0087**
Neurofibromatoses	4763 6662 2124 4974 6390	34	5/0.78	0.0010	0.0087
Hypertrophy, Left Ventricular	4846 1906 51422 185 4776 3283	50	6/1.15	0.0010	0.0087
Neuroectodermal Tumors	2130 2026 4763 92140 54949 5578 26038 1031 340273 51147 1871 5727 4221 4255 6390 1462 4915	313	17/7.19	0.0010	0.0087
Glioma	375790 4763 92140 771 203190 5578 1031 6664 2254 51147 5727 4255 1462	207	13/4.75	0.0011	0.0088
Endocrine System Diseases	6473 6662 51773 5715 1031 7049 389434 5106 177 2646 4846 3784 4221 8622 9563 6390 185 81029 11132 10891 60675	429	21/9.85	0.0011	0.0088
Parkinson Disease	65018 1356 84286 23400 51422 26281 6478 2668 2580 203068	134	10/3.08	0.0011	0.0088
Bipolar Disorder	2550 1960 9378 115 54805 1610 165186 64478 341880 29886 266727 57140 23774 22978 2668 5533 10611 4915	344	18/7.9	0.0011	0.0088
Neoplasm Metastasis	10810 3655 92140 977 51773 8626 822 2017 5058 25794 51147 6692 1462 9271 302 4915 2810	315	17/7.23	0.0011	0.0088
Endocrine disorder NOS	6473 6662 51773 5715 1031 7049 389434 5106 177 2646 4846 3784 4221 8622 9563 6390 185 81029 11132 10891 60675	429	21/9.85	0.0011	0.0088

Disease pathway	EntrezGene ID	Genes in pathway	Genes observed / genes expected in pathway	p-value[#]	Adj. p-value*
Endocrine disturbance NOS	6473 6662 51773 5715 1031 7049 389434 5106 177 2646 4846 3784 4221 8622 9563 6390 185 81029 11132 10891 60675	429	21/9.85	0.0011	0.0088
Cleft Lip	56971 875 1119 7049 5396 8626 191 10253 2049 7039 5727 1719	182	12/4.18	0.0011	0.0088
Neurofibroma	4763 6662 2124 4974 6390	35	5/0.8	0.0012	0.0090
Stroke NOS	118 2026 83605 8673 22879 875 151112 1020 54872 4846 221458 1906 2162 185	235	14/5.39	0.0012	0.0090
Lentivirus Infections	5599 3134 5721 10618 5720 5715 55170 5478 9582 4153 5058 5441 55048 3055 3106 7374 684 5437 1642	375	19/8.61	0.0012	0.0090
Nematode Infections	57801 10516 1906 7032 60675	35	5/0.8	0.0012	0.0090
Stroke	118 2026 83605 8673 22879 875 151112 1020 54872 4846 221458 1906 2162 185	235	14/5.39	0.0012	0.0090
Cerebral Infarction	118 2026 83605 8673 22879 875 151112 1020 54872 4846 221458 1906 2162 185	236	14/5.42	0.0012	0.0090
Rubinstein-Taybi Syndrome	1387 115 7022	10	3/0.23	0.0013	0.0095
Sexually Transmitted Diseases	5599 3134 5721 10618 5720 5715 55170 5478 9582 4153 5058 5441 55048 3055 3106 7374 684 5437 1642	377	19/8.65	0.0013	0.0095

[#] p-value from hypergeometric test

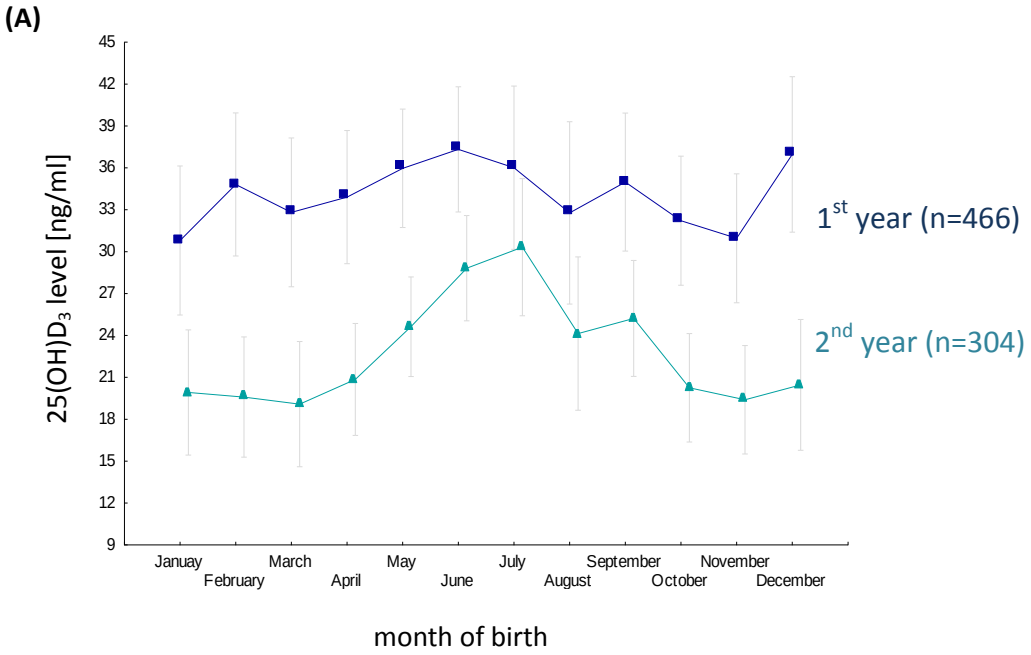
*p-value adjusted by the multiple test adjustment

Figure E1



WGBS = whole genome bisulfite sequencing; qPCR = quantitative real time PCR

Figure E2


(A)
25(OH)D3 level [ng/ml]
45
42
39
36
33
30
27
24
21
18
15
12
9
Januay
February
March
April
May
June
July
August
September
October
November
December
month of birth
1st year (n=466)
2nd year (n=304)

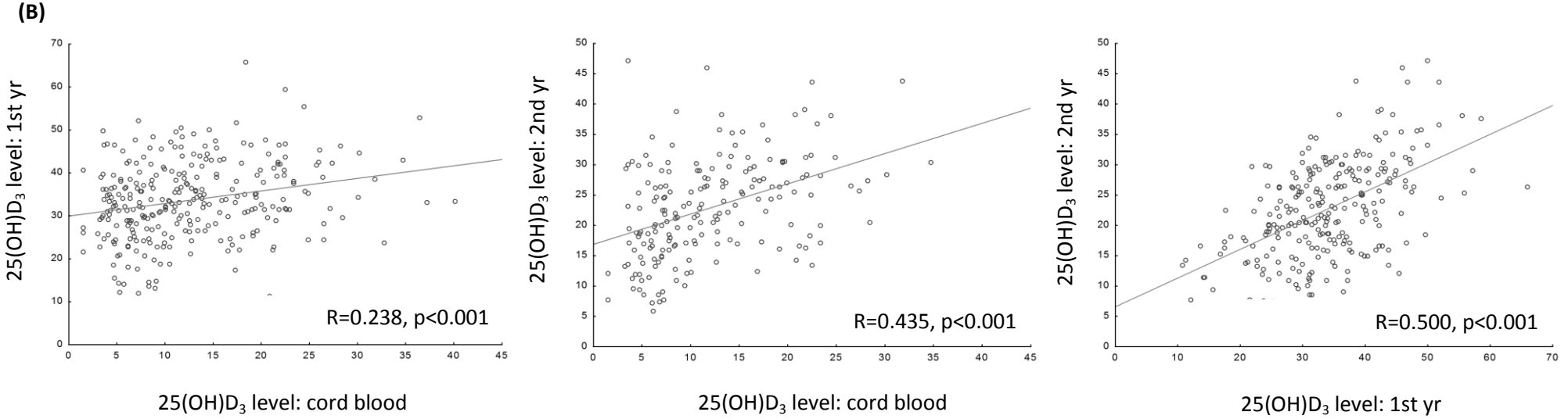
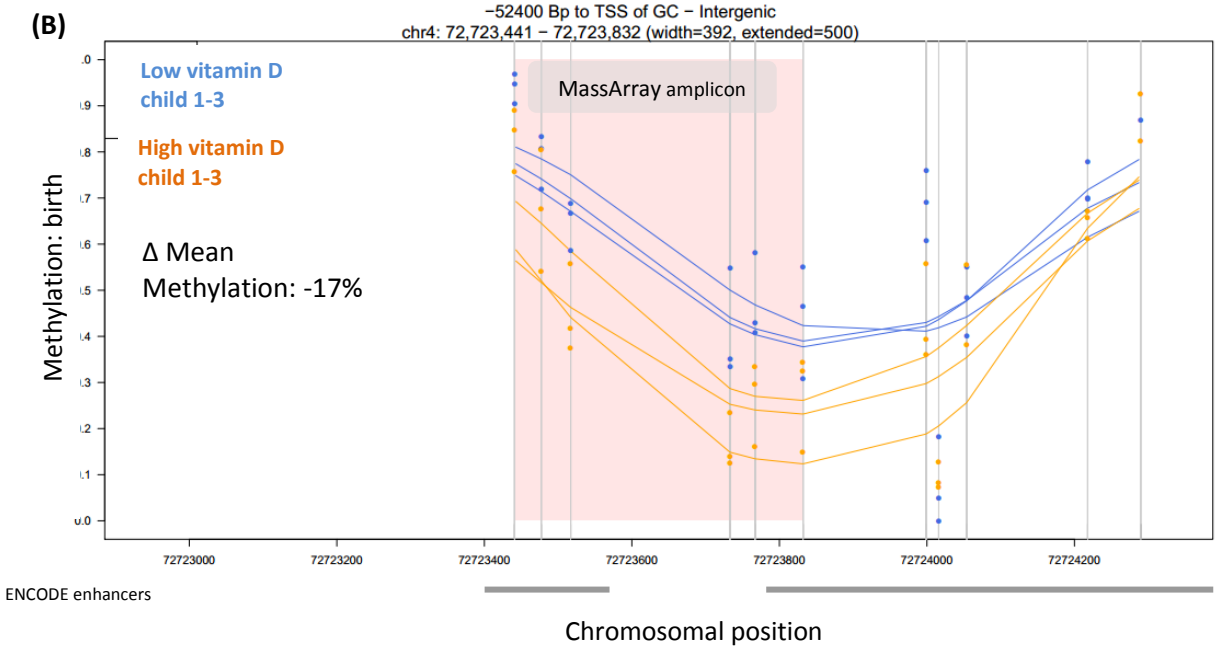

(B)
25(OH)D3 level: 1st yr
R=0.238, p<0.001
25(OH)D3 level: cord blood
25(OH)D3 level: 2nd yr
R=0.435, p<0.001
25(OH)D3 level: cord blood
25(OH)D3 level: 2nd yr
R=0.500, p<0.001
25(OH)D3 level: 1st yr

Figure E3

(A)

	Number of DMRs	Annotated genes
Total	508	483
Hypermethylated	197	190
Hypomethylated	311	293

(B)



(C)

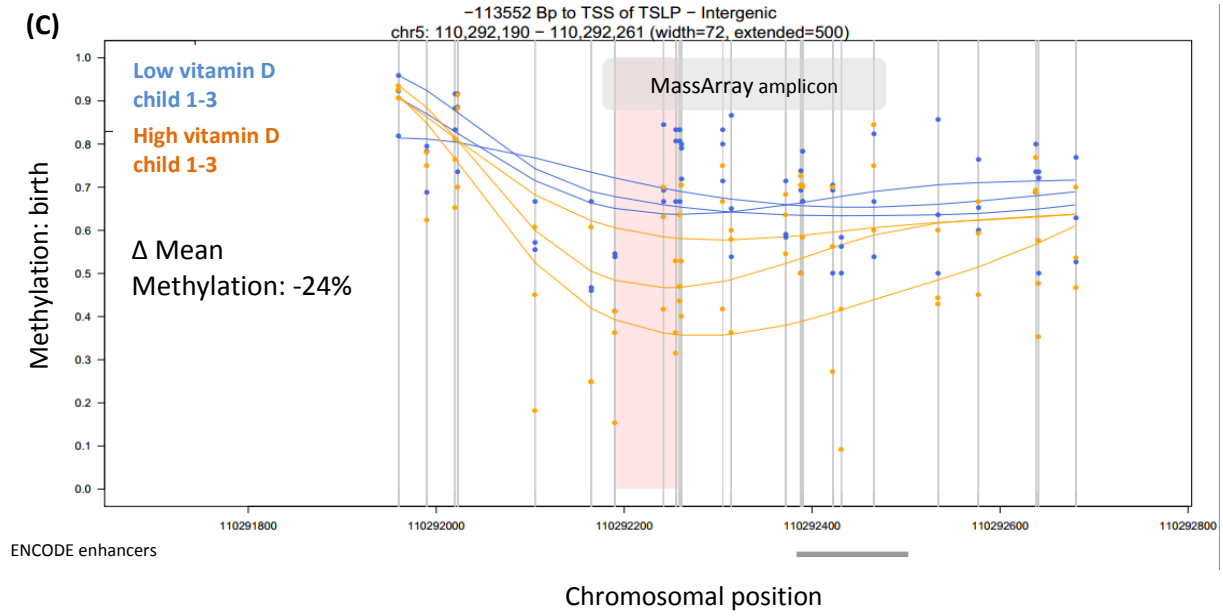
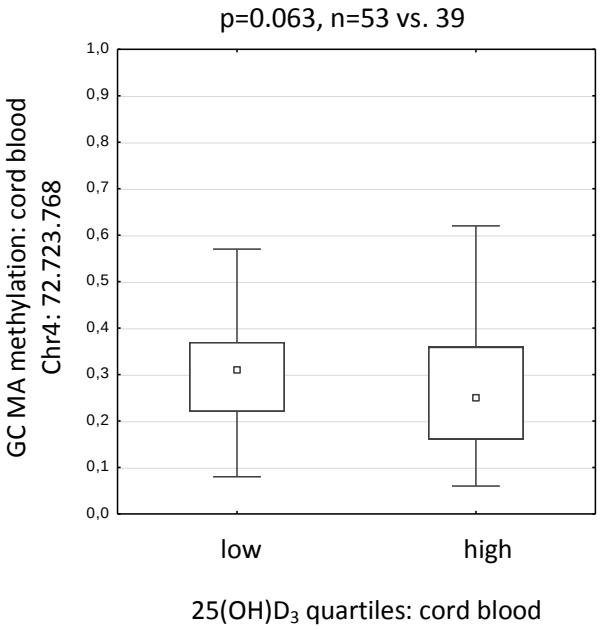


Figure E5

(A)


p=0.063, n=53 vs. 39
GC MA methylation: cord blood
Chr4: 72.723.768
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
low
high
25(OH)D3 quartiles: cord blood

(B)

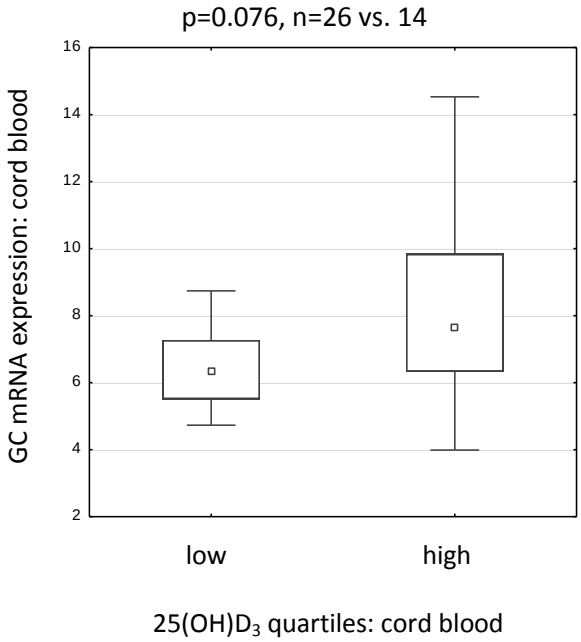
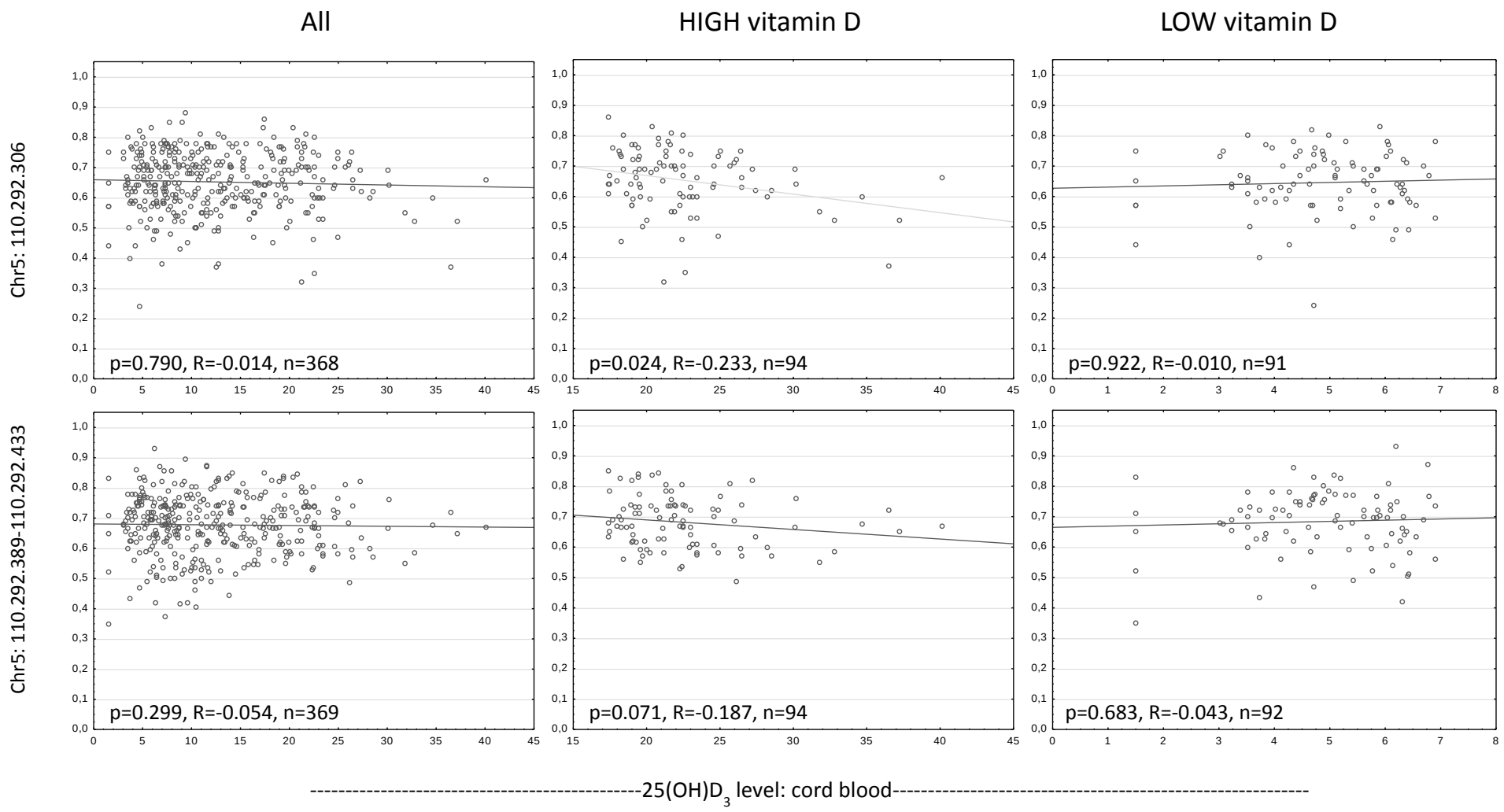

p=0.076, n=26 vs. 14
GC mRNA expression: cord blood
16
14
12
10
8
6
4
2
low
high
25(OH)D3 quartiles: cord blood

Figure E6


All
HIGH vitamin D
LOW vitamin D
Chr5: 110.292.306
Chr5: 110.292.389-110.292.433
p=0.790, R=-0.014, n=368
p=0.024, R=-0.233, n=94
p=0.922, R=-0.010, n=91
p=0.299, R=-0.054, n=369
p=0.071, R=-0.187, n=94
p=0.683, R=-0.043, n=92
----------TSLP methylationl: cord blood----------
----------25(OH)D3 level: cord blood----------