Supplemental material

Material and Methods

Behavioural data

Quality control of Life Events Questionnaire

The Life Events Questionnaire was used to assess life events experienced by individuals in the IMAGEN cohort. Participants rated their feelings towards the event (i.e. on a 5-point rating scale ranging from very unhappy [1], unhappy [2], neutral [3], happy [4], to very happy [5]) and the frequency with which the event had happened. Negative stressful life events from the Life Events Questionnaire were defined based on the quality ratings of adolescents who had experienced the event as previously described in Loth et al (1). Items were included into the negative stressful life events scale if they met the following criteria: a) were rated on average as negative as assessed by the feelings ratings in those participants who have experienced the event, b) were not phrased in an ambivalent way (e.g. "Got or gave a sexually transmitted disease" or "Broke up with a boyfriend/girlfriend") and c) did not show low item endorsement (i.e. "Stole something valuable" was not endorsed in 95.2% of the sample; "Brother or Sister moved out" was not endorsed in 81.8%; "Family had money problems" was not endorsed by 70.3%, "Parent abused alcohol" was not endorsed by 92.7%). Based on these criteria, we classified 14 out of 39 items as assessing negative stressful life events (SLE) in an unambiguous phrasing in the contemporary adolescents.

Substance use

The European School Survey Project on Alcohol and Drugs (ESPAD)(2,3) was used to assess the frequency of smoking in the lifetime (On how many occasions during your lifetime have you smoked cigarettes?), frequency of alcohol use in the lifetime (On how many occasions

in your whole lifetime have you had any alcoholic beverage to drink?), and frequency of binge drinking in the lifetime (How many times in your whole lifetime have you had five or more drinks in a row?) in the IMAGEN sample. Subjects provided a self-report based on a scale from 0 to 6, (1 = 1–2 times; 3 = 6–9 times; 6 = 40+ times).

Omics data

DNA extraction and methylation data preparation

DNA purification was performed by the Centre National de Génotypage in Paris. DNA was extracted from whole-blood samples (~10mL) collected at the age of 14 and preserved in BD Vacutainer EDTA tubes (Becton, Dickinson and Company) using the Gentra Puregene Blood Kit (QIAGEN) according to the manufacturer's instructions. DNA methylation of first wave n=708 individuals was assessed at the SNP & SEQ Technology platform, Uppsala University. The second wave n=600 of methylation data samples were processed at the Life & Brain Centre, Bonn University and Basel University following the same protocol. DNA (500 ng) from each sample was treated with sodium bisulfite using the EZ-96 DNA methylation kit (Zymo Research, Irvine, CA, USA). DNA methylation was quantified using the Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc.) run on an Illumina HiScan System (Illumina) using the manufacturers' standard protocol. Signal intensities for each probe were extracted using Illumina GenomeStudio software.

Genetic data

Genotype information was collected for 582,982 markers using DNA extracted from whole blood as previously described and the Illumina HumanHap610 Genotyping BeadChip. Single nucleotide polymorphisms with call rates of <98%, minor allele frequency <1% or deviation from the Hardy-Weinberg equilibrium ($p \leq 1 \times 10\text{-}4$) were excluded from the analyses. Individuals with an ambiguous sex code, excessive missing genotypes (failure rate >2%), and

outlying heterozygosity (heterozygosity rate 3 standard deviations from the mean) were also excluded. Identity-by-state similarity was used to estimate cryptic relatedness for individual using PLINK software. Closely related individuals with identity-by-descent (IBD > 0.1875) were eliminated from the subsequent analysis. Population was examined by principal component analysis (PCA) using EIGENSTRAT software. The four HapMap populations were used as reference groups in the PCA and individuals with divergent ancestry (from CEU) were also excluded. A subset of the exploration sample (n = 175) was not included in the analyses for SNPs rs2233632 and rs2233621 as they did not pass quality control.

Pyrosequencing

Technical validation for randomly selected subsample (n=94) was performed using pyrosequencing and run at the Centre for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden. Genomic DNA (500ng) was treated with sodium bisulfite using the EZ-96 DNA methylation Gold MagPrep kit (Zymo Research, Irvine, CA, USA). Bisulfite-converted DNA samples were used as templates for PCR reactions amplifying the hSPDEF regions containing the differentially methylated regions identified by Illumina bead array analysis. The assays were either provided by QIAGEN (hSPDEF cg16527629) or designed using Methprimer(4) (hSPDEF cg01395541) (see supplementary table 1 for primer sequences). The Pyromark PCR kit (QIAGEN) was used for amplification according to the manufacturer's protocol and conditions listed in the table. The PCR products were sequenced by Pyrosequencing on a PSQ96 (Pyrosequencing) using PyroMark Gold Q96 reagents (QIAGEN) according to the manufacturer's recommendations. The results were analysed using the PyromarkQ96 software (QIAGEN). To exclude PCR bias, standard curves for both assays were run off DNA standards (QIAGEN) with known methylation content.

Table S1

Gene name	Interrogated position	Forward primer (5'-3')	Reverse primer (5'-3')	Annea-ling T	Sequencing primer (5'-3')	Sequence analysed
SPDEF	cg01395541	TTTTTATGTAGATTTGTTATATAGTGG	CAAATACTTAATAATAAATACCTCTATCCT	56°C	GTAGATTTGTTATATAGTGG	CGGTGAGGAAGGACTCCTAGCTCGCTTTCCCAGGCC**C**GTAATCG
SPDEF	cg16527629	Hs_CG01395541_02_PM		58°C		GCCA**C**GCAGGA

SUPPLEMENTARY Table S1. Primer sequences for *SPDEF*.

Gene expression data

Quality control (QC)

Total RNA was extracted from whole blood cells collected at the age of 14 using the PAXgene Blood RNA Kit (QIAGEN Inc., Valencia, CA). Following quality control of the total RNA extracted, labelled complementary RNA (cRNA) was generated using the Illumina® TotalPrep™ RNA Amplification kit (Applied Biosystems/Ambion, Austin, TX). Complementary RNA was purified and quantified using a Qubit® 2.0 Fluorometer (Invitrogen, Paisly, UK). The size distributions of cRNA were determined through Bioanalyzer (Agilent Technologies, Santa Clara, CA) using the Eukaryotic mRNA Assay with smear analysis. Gene expression profiling was performed using Illumina HumanHT-12 v4 Expression BeadChips (Illumina Inc., San Diego, CA).

Pre-processing

Expression data was normalized using the loess method (5) and log-transformed to correct for systematic effects arsing for variations in the extraction and hybridisation process. Outliers were also screened for using R.

Methylation data processing

Illumina 450K microarray quality control (QC)

The qcReport function in the Bioconductor minfi package was used to identify failed samples with abnormal beta distribution, bisulfite conversion, probe extension, or hybridization, etc. Gender information was predicted for each sample based on methylation data using the getSex function in the minfi package, and one sample with gender discrepancy was removed. In order to evaluate potential batch effects, principal component analysis (PCA) was performed and first 4 PCs were evaluated against experimental batches, imaging centers, arrays and plates. We observed that the first PC was significantly associated with experimental batches and, thus, was adjusted in the following DMR analysis.

Differential cell counts estimation

Cell counts for the 6 major cell types in blood (Granulocytes, B cells, CD4+ T cells, CD8+ T cells, monocytes and NK cells) for each individual were estimated using the estimateCellCounts function in minfi(6), which gives sample-specific estimates of cell proportions based on reference information on cell-specific methylation signatures(7).

Methylation acquisition waves

Methylation data was processed in two waves, and while both waves were quantile normalized together, the acquisition wave information was still found to be the primary resource underlying the structure of methylation data, and therefore analyses involving both waves of methylation data were always corrected for the effects of acquisition wave.

Phenotype-associated DMRs identification

We performed our differentially methylation region analysis using the bump hunter package in R (8,9) with adjustment for gender, experimental batches (recruitment centre and acquisition wave) and the first two principle components of estimated differential cell counts. Regions that have a family-wise error rate (FWER) less than 0.05 with 1000 resamples and contain at least 2 probes were identified as phenotype-associated differentially methylated regions.

Methylation-Expression quantitative trait loci (methyl-eQTL) analyses

Methyl-eQTL analysis was performed on 34,833 gene expression probes and *SPDEF* methylation data generated on the Infinium HumanMethylation450 BeadChip. We ran a linear model adjusted for gender, recruitment site and genotype. DAVID was used to determine enrichment of biological processes and disease classes in the gene list generated from the methyl-eQTL analysis with $p<0.01$. Enrichment for specific biological functions and disease classes was determined using a modified Fisher's test at a significance level of $p<0.05$. A p-value that is equal or smaller than 0.05 to be considered strongly enriched in the annotation categories (10).

Blood-brain Methylation

The Blood Brain DNA Methylation Comparison Tool was used to investigate the correlation between DNA methylation in the blood and in four brain regions (prefrontal cortex, entorhinal cortex, superior temporal gyrus and cerebellum), using matched samples obtained from 71–75 individuals who were assessed using the Infinium HumanMethylation450 BeadChip. Pearson's correlation coefficients obtaining a P-value $\leq$ 0.05 were considered statistically significant.

Causal network analysis between stress, methylation and lifetime binge drinking

To infer causal flow between frequency of negative stressful life events, methylation and lifetime binge drinking, the Network Edge Orienting (NEO) multi-edge simulation was conducted in R (11). An absolute correlation threshold of 0.01 was used to determine dependent pairs and allow for multi-edge Local SEM-based Edge Orienting (LEO) scores to be calculated.

Neuroimaging data

MRI pre-processing

T1 images were segmented into grey matter and white matter by using the Computational Anatomy Toolbox (CAT) 12 toolbox (http://dbm.neuro.uni-jena.de/cat/). These segmented tissues were then normalized to the age 14 TPM from TOM8 by using an affine transformation (12). The realigned tissues were input into DARTEL software to create the customized 14-year-old DARTEL templates (13). After which CAT12 was used to normalize the segmented grey matter, estimate the modulated voxel-wise grey matter volume and estimate the corresponding total intra cranial volume for each subject. Finally, we applied the Brainnetome atlas to the normalized grey matter data to generate the volume of each brain region (14). Since regions in the subcortical nuclei are small, the subregions of the amygdala, hippocampus, basal ganglia and thalamus were merged respectively.

Results

Associations between negative stressful negative life events frequencies and substance use

Gender was controlled for in all analyses because ANOVA showed that frequency of negative stressful life events in the last year was significantly (r^2=0.007, p=0.004) higher in girls (2.91±1.86) compared to boys (2.68±1.68).

Bump hunting analyses on the frequency of negative stressful life events

Bump hunting analysis identified a statistically significant (p (family-wise error corrected) =0.021, bump hunter's regression coefficient=-0.07) covering exons 15 and 16 in the HOOK2 as shown in Figure S1.

The differentially methylated region located within the HOOK2 gene harboured 4 CpG sites, of which 2 contained SNPs that were located at the probe binding site (cg04657146 and cg11738485, rs897804 and rs35337531 respectively). Such SNPs could result in a false DNA methylation signal due to hybridization of the wrong probe or no/minimal extension at the target CpG site. As such methylation data from the HOOK2 gene was considered to be unreliable and we decided to focus our analyses on SPDEF.

Technical Validation – Pyrosequencing

A total of 94 individuals were randomly selected for pyrosequencing, while representing the genotype frequencies of rs2233632 and rs223361. There was a high correlation in the methylation data obtained with the pyrosequencing and the Illumina450K chip for both CpG sites in SPDEF, cg01395541 and cg16527629 ($r=0.85$, $p=2.21\times10^{-37}$ and $r=0.82$ and $p=6.77\times10^{-24}$, df=93, respectively).

The correlations between the genotypes at rs2233631 and rs2233632 with the methylation levels obtained from pyrosequencing were also significant (for cg01395541: $r=-0.932$, $p=2.39\times10^{-42}$, df=93; for cg16527629: $r=-0.81$, $p=1.45\times10^{-22}$, df=93). The mean level of methylation assessed with pyrosequencing for rs2233632 and rs2233631 are shown in the table below:

Table S2

SNP	G homozygotes	Heterozygotes	A homozygotes

rs2233632	M = 0.786; SD = 0.011 (n = 11)	M = 0.478; SD = 0.022 (n = 38)	M = 0.100; SD = 0.010 (n = 44)
rs2233631	M = 0.822; SD = 0.019 (n = 11)	M = 0.834; SD = 0.025 (n = 38)	M = 0.286; SD = 0.048 (n = 44)

Causal Analysis - NEO

Using a Network Edge Orienting (NEO) analysis, we found that genotype causes methylation and methylation causes binge drinking, and there is a high probability that stress causes binge drinking (see Supplementary Figure S2). This suggests independent causal relationships of frequency of negative stressful like events and cg01395541 methylation on binge drinking.

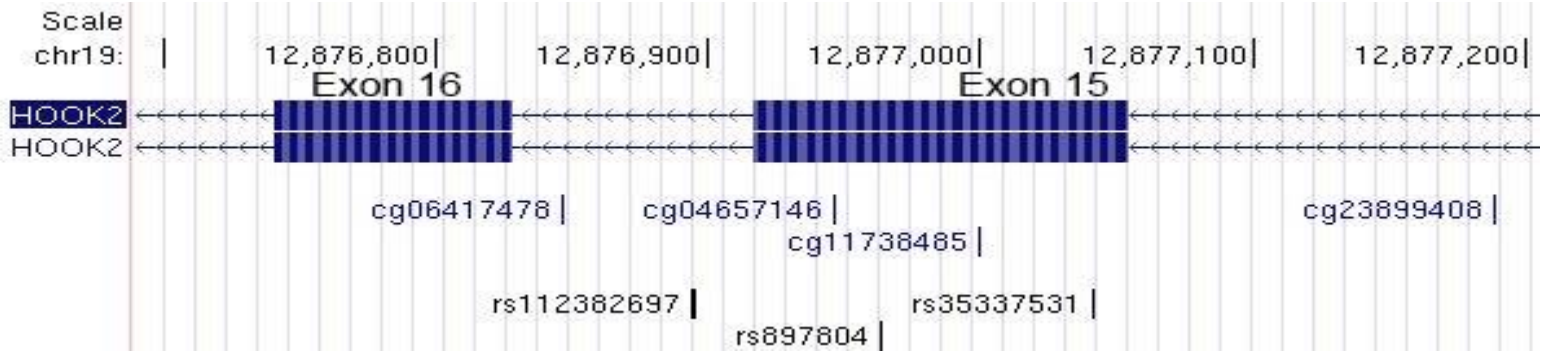


Figure S1: SNPs rs897804 and rs 3533753 within the differentially methylated region in HOOK2. Derived from Santa Cruz genome browser, build GRCh37/hg19.

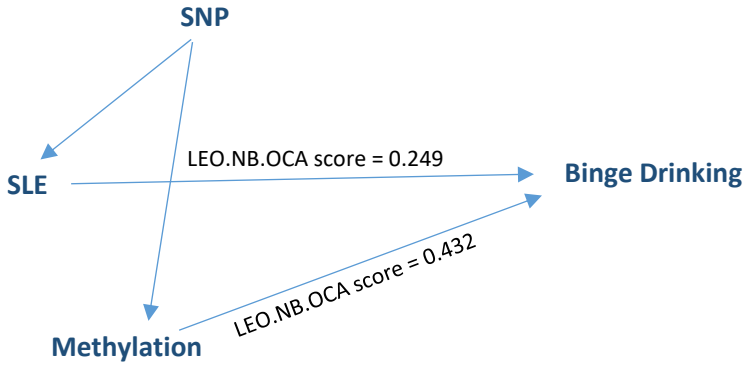


Figure S2: Network Edge Orienting. Multi-edge simulation between frequency of negative stressful life events, cg01395541 methylation and lifetime binge drinking.

Methylation-eQTL Analyses

SUPPLEMENTARY Table S2. Genes associated with methylation levels at cg01395541 for SNP genotypes GG and GA.

gene	Symbol	Definition	beta	t-stat	p-value
1743987	TRPM2	Homo sapiens transient receptor potential cation channel, subfamily M, member 2 (TRPM2), transcript variant S, mRNA.	1.649668	4.017731	7.65341E-05
1812995	CTSL1	Homo sapiens cathepsin L1 (CTSL1), transcript variant 1, mRNA.	-2.8885	-3.99542	8.36576E-05
1680273	MYOCD	Homo sapiens myocardin (MYOCD), mRNA.	-1.60027	-3.95384	9.86532E-05
3201163	LOC100131311	PREDICTED: Homo sapiens hypothetical LOC100131311 (LOC100131311), mRNA.	-2.27214	-3.94507	0.000102126
2370365	RFC4	Homo sapiens replication factor C (activator 1) 4, 37kDa (RFC4), transcript variant 1, mRNA.	-2.07146	-3.69597	0.000265957
1749376	TMEM201	Homo sapiens transmembrane protein 201 (TMEM201), mRNA.	1.771161	3.676228	0.000286312
1665748	DCC	Homo sapiens deleted in colorectal carcinoma (DCC), mRNA.	1.477759	3.641921	0.000325212
3239298	OTUD7B	Homo sapiens OTU domain containing 7B (OTUD7B), mRNA.	2.035493	3.603685	0.000374408
1709346	CLTB	Homo sapiens clathrin, light chain (Lcb) (CLTB), transcript variant 2, mRNA.	-1.70291	-3.58986	0.000393852
1749466	VAT1L	Homo sapiens vesicle amine transport protein 1 homolog (T. californica)-like (VAT1L), mRNA.	1.554227	3.505792	0.000534119

1740917	SCNN1B	Homo sapiens sodium channel, nonvoltage-gated 1, beta (SCNN1B), mRNA.	2.307899	3.478083	0.000589794
2413622	RFX4	Homo sapiens regulatory factor X, 4 (influences HLA class II expression) (RFX4), transcript variant 2, mRNA.	1.795565	3.446956	0.000658793
2158713	IL1F9	Homo sapiens interleukin 1 family, member 9 (IL1F9), mRNA.	1.844837	3.426813	0.000707393
1797526	LOC400120	Homo sapiens hypothetical LOC400120 (LOC400120), mRNA.	1.735356	3.415807	0.000735344
1675616	C12orf54	Homo sapiens chromosome 12 open reading frame 54 (C12orf54), mRNA.	1.653544	3.399992	0.000777317
2285952	PCDH11X	Homo sapiens protocadherin 11 X-linked (PCDH11X), transcript variant b, mRNA.	-1.46559	-3.38984	0.00080543
1718971	TTC7B	Homo sapiens tetratricopeptide repeat domain 7B (TTC7B), mRNA.	2.862728	3.386103	0.000816012
1794505	SHFM1	Homo sapiens split hand/foot malformation (ectrodactyly) type 1 (SHFM1), mRNA.	-1.70207	-3.37399	0.00085123
3250201	CNBP	Homo sapiens CCHC-type zinc finger, nucleic acid binding protein (CNBP), transcript variant 4, mRNA.	1.65587	3.35909	0.000896469
1697000	KIAA0258	PREDICTED: Homo sapiens KIAA0258, transcript variant 3 (KIAA0258), mRNA.	1.446655	3.354938	0.000909472
1730363	STAU1	Homo sapiens staufen, RNA binding protein, homolog 1 (Drosophila) (STAU1), transcript variant T3, mRNA.	-1.45741	-3.33543	0.000972962
1889229		BX107795 Soares breast 3NbHBst Homo sapiens cDNA clone IMAGp998G11259, mRNA sequence	-1.68721	-3.33007	0.000991094
1689814	DUSP13	Homo sapiens dual specificity phosphatase 13 (DUSP13), transcript variant 6, mRNA.	1.446816	3.329048	0.000994602
1803408	KRT18	Homo sapiens keratin 18 (KRT18), transcript variant 1, mRNA.	-1.53672	-3.2849	0.001157084
3310995	MIR578	Homo sapiens microRNA 578 (MIR578), microRNA.	-1.78181	-3.25469	0.00128214
1908872		ny42b04.s1 NCI_CGAP_Pr12 Homo sapiens cDNA clone	-1.45798	-3.25042	0.001300794

		IMAGE:1274383, mRNA sequence			
1753766	LOC388743	PREDICTED: Homo sapiens similar to calpain 8, transcript variant 5 (LOC388743), mRNA.	-1.5287	-3.24853	0.001309119
1775965	PPP4R4	Homo sapiens protein phosphatase 4, regulatory subunit 4 (PPP4R4), transcript variant 1, mRNA.	-1.62718	-3.24287	0.001334395
1770537	NGFRAP1	Homo sapiens nerve growth factor receptor (TNFRSF16) associated protein 1 (NGFRAP1), transcript variant 3, mRNA.	1.613563	3.226811	0.001408552
3201840	LOC100131818	PREDICTED: Homo sapiens similar to hCG1644435 (LOC100131818), mRNA.	1.478965	3.226365	0.001410663
3245255	LOC100133629	PREDICTED: Homo sapiens hypothetical protein LOC100133629 (LOC100133629), mRNA.	-1.61884	-3.21652	0.001458057
1806059	SPRR2B	Homo sapiens small proline-rich protein 2B (SPRR2B), mRNA.	1.278203	3.215741	0.001461882
3239588	LOC100133178	PREDICTED: Homo sapiens hypothetical protein LOC100133178 (LOC100133178), mRNA.	-1.36111	-3.21054	0.001487554
1663081	LOC440925	Homo sapiens hypothetical gene supported by AK123485 (LOC440925), mRNA.	-1.27277	-3.20524	0.001514195
1771537	LOC643920	PREDICTED: Homo sapiens region containing similar to Williams Beuren syndrome chromosome region 19; hypothetical LOC441257, transcript variant 2 (LOC643920), mRNA.	-1.70093	-3.18676	0.001610482
2293631	MGAT5B	Homo sapiens mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl-glucosaminyltransferase, isozyme B (MGAT5B), transcript variant 2, mRNA.	-1.45193	-3.18603	0.001614402
1654496	LOC646168	PREDICTED: Homo sapiens hypothetical protein LOC646167, transcript variant 1 (LOC646168), mRNA.	1.470276	3.184319	0.001623623
1791605	LOC729786	PREDICTED: Homo sapiens similar to golgi autoantigen, golgin subfamily a, 8A (LOC729786), mRNA.	-1.61452	-3.16236	0.001746344
1810532	CAV3	Homo sapiens caveolin 3 (CAV3), transcript variant 1, mRNA.	-2.09529	-3.15164	0.001809273

3241296	LOC100132515	PREDICTED: Homo sapiens similar to hCG2045429 (LOC100132515), mRNA.	-1.65081	-3.1494	0.001822711
1714445	SLC6A9	Homo sapiens solute carrier family 6 (neurotransmitter transporter, glycine), member 9 (SLC6A9), transcript variant 3, mRNA.	1.900563	3.140609	0.001876256
3206101	LOC728026	PREDICTED: Homo sapiens hypothetical LOC728026 (LOC728026), mRNA.	-1.49599	-3.13654	0.001901527
1656826	SH3RF1	Homo sapiens SH3 domain containing ring finger 1 (SH3RF1), mRNA.	1.314614	3.130085	0.001942279
1772506	ATP5I	Homo sapiens ATP synthase, H+ transporting, mitochondrial F0 complex, subunit E (ATP5I), nuclear gene encoding mitochondrial protein, mRNA.	-2.84818	-3.12686	0.00196291
2058070	NEDD8	Homo sapiens neural precursor cell expressed, developmentally down-regulated 8 (NEDD8), mRNA.	-1.77858	-3.11952	0.002010717
3218138	LOC283523	PREDICTED: Homo sapiens similar to telomeric repeat binding factor (NIMA-interacting) 1 (LOC283523), mRNA.	-1.53509	-3.11811	0.002020021
1793549	PTPN4	Homo sapiens protein tyrosine phosphatase, non-receptor type 4 (megakaryocyte) (PTPN4), mRNA.	-2.94949	-3.11741	0.002024626
2054481	PTCHD3	Homo sapiens patched domain containing 3 (PTCHD3), mRNA.	1.270555	3.096163	0.00216998
1710229	ARRDC2	Homo sapiens arrestin domain containing 2 (ARRDC2), transcript variant 2, mRNA.	2.36407	3.093165	0.002191243
1663099	UBE2B	Homo sapiens ubiquitin-conjugating enzyme E2B (RAD6 homolog) (UBE2B), mRNA.	1.695	3.083293	0.00226262
1748052	LOC643116	PREDICTED: Homo sapiens hypothetical protein LOC643116 (LOC643116), mRNA.	-1.64657	-3.08282	0.002266064
1769369	ELAVL2	Homo sapiens ELAV (embryonic lethal, abnormal vision, Drosophila)-like 2 (Hu antigen B) (ELAVL2), mRNA.	-1.21417	-3.07988	0.002287805
3307967	DEFB117	PREDICTED: Homo sapiens defensin, beta 117 (DEFB117), mRNA.	-1.47464	-3.07971	0.002289032
1814333	SERPINI1	Homo sapiens serpin peptidase inhibitor, clade I (neuroserpin), member 1 (SERPINI1), mRNA.	-1.4518	-3.07594	0.002317204

2275199	OPRM1	Homo sapiens opioid receptor, mu 1 (OPRM1), transcript variant MOR-1, mRNA.	1.431015	3.071248	0.002352623
1757757	TM6SF2	Homo sapiens transmembrane 6 superfamily member 2 (TM6SF2), mRNA.	1.301902	3.070578	0.002357723
2225061	TRIM71	Homo sapiens tripartite motif-containing 71 (TRIM71), mRNA.	-1.40463	-3.06805	0.002377028
1794056	DNAJB5	Homo sapiens DnaJ (Hsp40) homolog, subfamily B, member 5 (DNAJB5), mRNA.	1.353515	3.063003	0.002416111
2068274	CLEC9A	Homo sapiens C-type lectin domain family 9, member A (CLEC9A), mRNA.	-1.57298	-3.06279	0.002417807
3293097	LOC645715	PREDICTED: Homo sapiens misc_RNA (LOC645715), miscRNA.	-1.49137	-3.04399	0.002568595
2296697	MAP3K3	Homo sapiens mitogen-activated protein kinase kinase kinase 3 (MAP3K3), transcript variant 1, mRNA.	1.942959	3.042091	0.002584285
1759766	CTXN1	Homo sapiens cortexin 1 (CTXN1), mRNA.	1.894189	3.037794	0.002620151
1671010	ZNF267	Homo sapiens zinc finger protein 267 (ZNF267), transcript variant 498723, mRNA.	1.661559	3.031834	0.002670646
1737947	LSM5	Homo sapiens LSM5 homolog, U6 small nuclear RNA associated (S. cerevisiae) (LSM5), mRNA.	-3.91882	-3.02541	0.002726077
1779324	GZMA	Homo sapiens granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3) (GZMA), mRNA.	-6.46377	-3.02456	0.002733495
1766984	EIF5AL1	Homo sapiens eukaryotic translation initiation factor 5A-like 1 (EIF5AL1), mRNA.	-1.51781	-3.02291	0.002747923
1708983	CASC1	Homo sapiens cancer susceptibility candidate 1 (CASC1), transcript variant 3, mRNA.	1.890691	3.005372	0.002905847
1723632	PIGC	Homo sapiens phosphatidylinositol glycan anchor biosynthesis, class C (PIGC), transcript variant 1, mRNA.	-1.64098	-3.00365	0.00292176
1738268	IHPK3	Homo sapiens inositol hexaphosphate kinase 3 (IHPK3), mRNA.	1.489852	2.988393	0.003066616
2175715	KIR2DS3	Homo sapiens killer cell immunoglobulin-like receptor, two	-1.89504	-2.98832	0.00306736

		domains, short cytoplasmic tail, 3 (KIR2DS3), mRNA.			
1704252	LOC652439	PREDICTED: Homo sapiens hypothetical protein LOC652439 (LOC652439), mRNA.	1.468327	2.985085	0.003098874
3243471	CNPY2	Homo sapiens canopy 2 homolog (zebrafish) (CNPY2), mRNA.	-2.417	-2.98103	0.003138816
2342630	LPHN1	Homo sapiens latrophilin 1 (LPHN1), transcript variant 2, mRNA.	1.787771	2.976428	0.00318477
1780455	ZNF654	PREDICTED: Homo sapiens zinc finger protein 654 (ZNF654), mRNA.	-1.48571	-2.97466	0.003202558
1689086	CTSC	Homo sapiens cathepsin C (CTSC), transcript variant 2, mRNA.	-1.46796	-2.96389	0.003313043
2078995	CSRNP3	Homo sapiens cysteine-serine-rich nuclear protein 3 (CSRNP3), mRNA.	-1.22272	-2.96354	0.00331664
3308395	MIR1250	Homo sapiens microRNA 1250 (MIR1250), microRNA.	-1.3591	-2.96262	0.003326328
1763137	INVS	Homo sapiens inversin (INVS), transcript variant 1, mRNA.	1.332596	2.958722	0.003367283
1763657	CXXC4	Homo sapiens CXXC finger 4 (CXXC4), mRNA.	1.247439	2.94838	0.003478268
2343010	BOLA3	Homo sapiens bolA homolog 3 (E. coli) (BOLA3), transcript variant 1, mRNA.	-2.36832	-2.94742	0.003488779
1862737		AGENCOURT_8911223 NIH_MGC_141 Homo sapiens cDNA clone IMAGE:6386615 5, mRNA sequence	1.212896	2.925245	0.003738755
3309419	MIR1281	Homo sapiens microRNA 1281 (MIR1281), microRNA.	1.867459	2.921975	0.003776987
1679464	BNC1	Homo sapiens basonuclin 1 (BNC1), mRNA.	-1.43209	-2.92001	0.003800169
3236316	LOC729121	Homo sapiens hypothetical LOC729121 (LOC729121), non-coding RNA.	1.162075	2.919551	0.003805552
1737283	MGC39900	Homo sapiens hypothetical protein MGC39900 (MGC39900), mRNA.	-1.3459	-2.91708	0.003834818
1724265	PART1	PREDICTED: Homo sapiens prostate androgen-regulated transcript 1 (PART1), misc RNA.	-1.43012	-2.91613	0.003846246
1786759	C11orf10	Homo sapiens chromosome 11 open reading frame 10 (C11orf10), mRNA.	-2.59847	-2.91551	0.00385366
1661998	METTL6	Homo sapiens methyltransferase like 6 (METTL6), mRNA.	-1.78642	-2.91048	0.003914221

2047618	KCNE1	Homo sapiens potassium voltage-gated channel, Isk-related family, member 1 (KCNE1), mRNA.	1.446345	2.905577	0.003974113
1840742		zw78c04.r1 Soares_testis_NHT Homo sapiens cDNA clone IMAGE:782310 5, mRNA sequence	1.287105	2.901487	0.00402472
2209045	POU3F2	Homo sapiens POU class 3 homeobox 2 (POU3F2), mRNA.	-1.49591	-2.89476	0.004109202
1786697	TRIM9	Homo sapiens tripartite motif-containing 9 (TRIM9), transcript variant 2, mRNA.	1.114604	2.892491	0.004138115
2112811	RPL36A	Homo sapiens ribosomal protein L36a (RPL36A), mRNA.	-2.03244	-2.89232	0.004140332
1674659	OR56B4	Homo sapiens olfactory receptor, family 56, subfamily B, member 4 (OR56B4), mRNA.	1.165712	2.889227	0.004179969
1671489	PC	Homo sapiens pyruvate carboxylase (PC), nuclear gene encoding mitochondrial protein, transcript variant A, mRNA.	1.125687	2.889044	0.004182327
1832155		Homo sapiens cDNA FLJ37425 fis, clone BRAWH2001530	-1.45124	-2.88869	0.00418689
2342579	IL7R	Homo sapiens interleukin 7 receptor (IL7R), mRNA.	4.531305	2.885955	0.004222317
1751280	LOC651905	PREDICTED: Homo sapiens hypothetical protein LOC651905 (LOC651905), mRNA.	1.540105	2.884363	0.004243061
1806548	LOC647855	PREDICTED: Homo sapiens hypothetical LOC647855 (LOC647855), mRNA.	1.302928	2.883789	0.004250566
3307121	FLJ46836	PREDICTED: Homo sapiens FLJ46836 protein (FLJ46836), miscRNA.	1.262742	2.876217	0.004350681
1674817	C1orf115	Homo sapiens chromosome 1 open reading frame 115 (C1orf115), mRNA.	1.793624	2.873504	0.004387074
3250345	LOC283788	PREDICTED: Homo sapiens hypothetical protein LOC283788 (LOC283788), mRNA.	-2.66489	-2.87341	0.004388329
2190486	GGT3P	Homo sapiens gamma-glutamyltransferase 3 pseudogene (GGT3P), non-coding RNA.	1.443165	2.871742	0.004410846
1786658	BOLA3	Homo sapiens bolA homolog 3 (E. coli) (BOLA3), transcript variant 2, mRNA.	-2.39146	-2.87091	0.004422124
1669611	LOC645757	PREDICTED: Homo sapiens hypothetical LOC645757 (LOC645757), mRNA.	-1.49766	-2.87048	0.004427954

1730937	SLC39A13	Homo sapiens solute carrier family 39 (zinc transporter), member 13 (SLC39A13), mRNA.	1.379143	2.870024	0.004434157
2356331	PCDHGA10	Homo sapiens protocadherin gamma subfamily A, 10 (PCDHGA10), transcript variant 2, mRNA.	1.372113	2.867623	0.004466908
3309001	MIR1-2	Homo sapiens microRNA 1-2 (MIR1-2), microRNA.	1.414402	2.866687	0.004479728
1655783	ATP1B3	PREDICTED: Homo sapiens ATPase, Na+/K+ transporting, beta 3 polypeptide, transcript variant 1 (ATP1B3), mRNA.	1.495792	2.863212	0.004527644
1662061	LOC645635	PREDICTED: Homo sapiens hypothetical protein LOC645635 (LOC645635), mRNA.	1.423356	2.86168	0.004548926
1761945	FGFBP2	Homo sapiens fibroblast growth factor binding protein 2 (FGFBP2), mRNA.	-5.56396	-2.85961	0.004577818
1652287	NOG	Homo sapiens noggin (NOG), mRNA.	1.324347	2.853581	0.00466291
1800642	RELN	Homo sapiens reelin (RELN), transcript variant 2, mRNA.	1.159319	2.852704	0.004675409
2317348	APTX	Homo sapiens aprataxin (APTX), transcript variant 2, mRNA.	-1.2606	-2.85191	0.004686739
1814952	FLCN	Homo sapiens folliculin (FLCN), transcript variant 2, mRNA.	-1.38727	-2.8517	0.004689727
3279987	LOC442232	PREDICTED: Homo sapiens misc_RNA (LOC442232), miscRNA.	-1.54352	-2.85026	0.004710365
2073184	S1PR5	Homo sapiens sphingosine-1-phosphate receptor 5 (S1PR5), mRNA.	-4.17417	-2.84695	0.004758144
2278518	NFATC2IP	Homo sapiens nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2 interacting protein (NFATC2IP), mRNA.	-1.31304	-2.84525	0.00478282
3278608	LOC139431	PREDICTED: Homo sapiens similar to hCG1799751 (LOC139431), mRNA.	-1.30437	-2.84275	0.004819418
1680794	LOC643570	PREDICTED: Homo sapiens hypothetical protein LOC643570 (LOC643570), mRNA.	1.509165	2.840768	0.004848552
1669350	LOC729197	PREDICTED: Homo sapiens similar to Dynamin-1 (D100) (Dynamin, brain) (B-dynamin) (LOC729197), mRNA.	-1.39655	-2.83785	0.00489176

3309694	SNORD69	Homo sapiens small nucleolar RNA, C/D box 69 (SNORD69), small nucleolar RNA.	-1.47855	-2.83715	0.004902209
1754077	EYA2	Homo sapiens eyes absent homolog 2 (Drosophila) (EYA2), transcript variant 2, mRNA.	1.092626	2.833994	0.004949401
1710408	LGR4	Homo sapiens leucine-rich repeat-containing G protein-coupled receptor 4 (LGR4), mRNA.	-1.15642	-2.82906	0.005024026
3308728	MIR635	Homo sapiens microRNA 635 (MIR635), microRNA.	1.921407	2.82852	0.005032284
2094631	TRIM60	Homo sapiens tripartite motif-containing 60 (TRIM60), mRNA.	1.214425	2.827831	0.0050428
3256004	LOC100130003	PREDICTED: Homo sapiens misc_RNA (LOC100130003), miscRNA.	-4.38637	-2.82541	0.005079899
2259633	MLL5	Homo sapiens myeloid/lymphoid or mixed-lineage leukemia 5 (trithorax homolog, Drosophila) (MLL5), transcript variant 1, mRNA.	2.649472	2.824545	0.005093252
2285585	C13orf23	Homo sapiens chromosome 13 open reading frame 23 (C13orf23), transcript variant 1, mRNA.	1.483559	2.823231	0.005113548
1675057	DRD2	Homo sapiens dopamine receptor D2 (DRD2), transcript variant 2, mRNA.	-1.34496	-2.82295	0.005117871
1656715	THSD7A	Homo sapiens thrombospondin, type I, domain containing 7A (THSD7A), mRNA.	1.277524	2.819703	0.005168429
1803671	SSX1	PREDICTED: Homo sapiens synovial sarcoma, X breakpoint 1 (SSX1), mRNA.	-1.56593	-2.81657	0.005217596
1739641	MTMR3	Homo sapiens myotubularin related protein 3 (MTMR3), transcript variant 3, mRNA.	2.698469	2.810433	0.005315181
1797988	KLRD1	Homo sapiens killer cell lectin-like receptor subfamily D, member 1 (KLRD1), transcript variant 1, mRNA.	-4.0996	-2.80571	0.005391443
3260618	LOC100128086	PREDICTED: Homo sapiens misc_RNA (LOC100128086), miscRNA.	-1.70663	-2.80547	0.005395334
1821997		wn53g02.x1 NCI_CGAP_Lu19 Homo sapiens cDNA clone IMAGE:2449202 3, mRNA sequence	1.423032	2.804304	0.005414277

1771822	ARL6	Homo sapiens ADP-ribosylation factor-like 6 (ARL6), transcript variant 2, mRNA.	-1.22771	-2.79281	0.005604655
2110281	UFC1	Homo sapiens ubiquitin-fold modifier conjugating enzyme 1 (UFC1), mRNA.	-2.89756	-2.79255	0.005609094
1709131	LOC649422	PREDICTED: Homo sapiens hypothetical protein LOC649422 (LOC649422), mRNA.	1.684834	2.789247	0.005664866
3242856	BEND3	Homo sapiens BEN domain containing 3 (BEND3), mRNA.	1.663913	2.778183	0.00585567
1781182	RAB43	Homo sapiens RAB43, member RAS oncogene family (RAB43), mRNA.	1.357762	2.767873	0.006038692
1672658	OR6B2	Homo sapiens olfactory receptor, family 6, subfamily B, member 2 (OR6B2), mRNA.	-1.09246	-2.76784	0.006039244
1810712	ARHGEF12	Homo sapiens Rho guanine nucleotide exchange factor (GEF) 12 (ARHGEF12), mRNA.	-1.38938	-2.76408	0.006107277
2108699	IL2RA	Homo sapiens interleukin 2 receptor, alpha (IL2RA), mRNA.	-1.3782	-2.76374	0.006113578
1772092	LOC152586	PREDICTED: Homo sapiens similar to RIKEN cDNA 4933434I20 (LOC152586), mRNA.	1.816249	2.760334	0.006175796
2285141	USP48	Homo sapiens ubiquitin specific peptidase 48 (USP48), transcript variant 1, mRNA.	2.3107	2.759562	0.006189994
1709322	LOC651249	PREDICTED: Homo sapiens similar to ribosomal protein L34 (LOC651249), mRNA.	-1.75972	-2.7595	0.006191148
2172547	TRIM74	Homo sapiens tripartite motif-containing 74 (TRIM74), mRNA.	1.200444	2.757443	0.006229099
1784294	CPA4	Homo sapiens carboxypeptidase A4 (CPA4), mRNA.	-1.25153	-2.7552	0.006270848
1734696	FRG1	Homo sapiens FSHD region gene 1 (FRG1), mRNA.	-4.67111	-2.75506	0.006273274
1660315	SPN	Homo sapiens sialophorin (SPN), transcript variant 2, mRNA.	1.297858	2.753137	0.00630929
1694382	LOC642608	PREDICTED: Homo sapiens hypothetical protein LOC642608 (LOC642608), mRNA.	-1.51161	-2.74852	0.006396351
2097421	MRPL51	Homo sapiens mitochondrial ribosomal protein L51 (MRPL51), nuclear gene encoding mitochondrial protein, mRNA.	-4.57587	-2.74641	0.006436342
2395856	TMEM218	Homo sapiens transmembrane protein 218 (TMEM218), mRNA.	-1.55753	-2.74439	0.006475017

3240883	SNORA11C	Homo sapiens small nucleolar RNA, H/ACA box 11C (retrotransposed) (SNORA11C), small nucleolar RNA.	1.470533	2.741103	0.006538362
2360202	PPP2R2B	Homo sapiens protein phosphatase 2 (formerly 2A), regulatory subunit B, beta isoform (PPP2R2B), transcript variant 4, mRNA.	-1.31711	-2.73667	0.006624621
2070102	SLC5A2	Homo sapiens solute carrier family 5 (sodium/glucose cotransporter), member 2 (SLC5A2), mRNA.	-1.14324	-2.73443	0.006668688
3253850	LOC100129250	PREDICTED: Homo sapiens similar to hCG1811779 (LOC100129250), mRNA.	-1.61852	-2.73077	0.006740961
1787140	LOC644341	PREDICTED: Homo sapiens hypothetical protein LOC644341 (LOC644341), mRNA.	-1.53952	-2.73055	0.006745329
1661616	FSHR	Homo sapiens follicle stimulating hormone receptor (FSHR), transcript variant 1, mRNA.	-1.29619	-2.73032	0.006749888
1753773	ANAPC11	Homo sapiens anaphase promoting complex subunit 11 (ANAPC11), transcript variant 1, mRNA.	1.320119	2.723684	0.006883261
1790810	HCN4	Homo sapiens hyperpolarization activated cyclic nucleotide-gated potassium channel 4 (HCN4), mRNA.	1.625887	2.723449	0.006888014
3181406	DHX40P	Homo sapiens DEAH (Asp-Glu-Ala-His) box polypeptide 40 pseudogene (DHX40P), non-coding RNA.	-1.2487	-2.72318	0.006893477
3235308	LOC100133580	PREDICTED: Homo sapiens hypothetical LOC100133580 (LOC100133580), mRNA.	-1.24005	-2.72135	0.006930769
2367818	CD40	Homo sapiens CD40 molecule, TNF receptor superfamily member 5 (CD40), transcript variant 2, mRNA.	-1.34507	-2.71755	0.007008669
1700888	ENPP1	Homo sapiens ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), mRNA.	1.179718	2.717095	0.007017941
1665824	C6orf218	Homo sapiens chromosome 6 open reading frame 218 (C6orf218), mRNA.	1.378763	2.714363	0.007074488
1808661	TOMM5	Homo sapiens translocase of outer mitochondrial membrane 5 homolog (yeast) (TOMM5), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.	-3.0739	-2.71288	0.007105338

2183728	INTU	Homo sapiens inturned planar cell polarity effector homolog (Drosophila) (INTU), mRNA.	-1.35139	-2.71205	0.007122724
3310316	MIR1324	Homo sapiens microRNA 1324 (MIR1324), microRNA.	-1.34197	-2.71142	0.007135838
1696921	LATS1	Homo sapiens LATS, large tumor suppressor, homolog 1 (Drosophila) (LATS1), mRNA.	-1.38315	-2.70618	0.007246293
3242654	LOC100134654	PREDICTED: Homo sapiens hypothetical protein LOC100134654 (LOC100134654), mRNA.	1.377005	2.705514	0.00726046
1825182		ym06b01.s1 Soares infant brain 1NIB Homo sapiens cDNA clone IMAGE:47119 3, mRNA sequence	-1.25607	-2.70519	0.007267459
3181379	LOC100130734	PREDICTED: Homo sapiens hypothetical protein LOC100130734 (LOC100130734), mRNA.	1.394079	2.703789	0.007297223
2294086	STMN1	Homo sapiens stathmin 1 (STMN1), transcript variant 2, mRNA.	-0.97209	-2.70342	0.00730515
1666967	BRP44L	Homo sapiens brain protein 44-like (BRP44L), mRNA.	-1.61671	-2.69955	0.007388358
1714424	PTCD3	Homo sapiens Pentatricopeptide repeat domain 3 (PTCD3), mRNA.	1.393067	2.699436	0.007390744
1658477	C12orf64	Homo sapiens chromosome 12 open reading frame 64 (C12orf64), mRNA.	1.286899	2.698629	0.007408207
1676749	C3orf15	Homo sapiens chromosome 3 open reading frame 15 (C3orf15), mRNA.	-1.30725	-2.69443	0.00749953
2120965	NPAT	Homo sapiens nuclear protein, ataxia-telangiectasia locus (NPAT), mRNA.	2.458876	2.692517	0.007541624
1726603	ATP5I	Homo sapiens ATP synthase, H+ transporting, mitochondrial F0 complex, subunit E (ATP5I), nuclear gene encoding mitochondrial protein, mRNA.	-4.07344	-2.69211	0.007550578
1773352	CCL5	Homo sapiens chemokine (C-C motif) ligand 5 (CCL5), mRNA.	-3.60232	-2.69098	0.007575606
1693560	HMGA1	Homo sapiens high mobility group AT-hook 1 (HMGA1), transcript variant 4, mRNA.	1.257295	2.690912	0.007577023
1709004	LOC440092	PREDICTED: Homo sapiens hypothetical LOC440092 (LOC440092), mRNA.	1.864614	2.688745	0.007625032

1708238	OR52E2	Homo sapiens olfactory receptor, family 52, subfamily E, member 2 (OR52E2), mRNA.	-1.47518	-2.68779	0.007646278
3291741	LOC255480	PREDICTED: Homo sapiens hypothetical protein LOC255480 (LOC255480), mRNA.	1.292354	2.686094	0.007684166
1914874		Homo sapiens KRTAP25-1 mRNA for keratin associated protein, complete cds	-1.4483	-2.68476	0.007714011
1781155	LYN	Homo sapiens v-yes-1 Yamaguchi sarcoma viral related oncogene homolog (LYN), mRNA.	3.35972	2.682891	0.007756151
1697751	GINS1	Homo sapiens GINS complex subunit 1 (Psf1 homolog) (GINS1), mRNA.	1.379371	2.68187	0.00777923
1659142	MDK	Homo sapiens midkine (neurite growth-promoting factor 2) (MDK), transcript variant 2, mRNA.	1.347249	2.681217	0.007794018
1793670	LOC649813	PREDICTED: Homo sapiens hypothetical protein LOC649813 (LOC649813), mRNA.	-1.25833	-2.67961	0.007830541
1726363	LOC650810	PREDICTED: Homo sapiens hypothetical protein LOC650810 (LOC650810), mRNA.	-1.0573	-2.67834	0.007859382
1723709	C9orf116	Homo sapiens chromosome 9 open reading frame 116 (C9orf116), transcript variant 2, mRNA.	-1.23739	-2.6783	0.007860407
1772719	GPN1	Homo sapiens GPN-loop GTPase 1 (GPN1), mRNA.	-1.86928	-2.67829	0.007860644
3301359	LOC728591	PREDICTED: Homo sapiens hypothetical protein LOC728591 (LOC728591), mRNA.	1.247169	2.674776	0.007941249
1667966	C1orf24	Homo sapiens chromosome 1 open reading frame 24 (C1orf24), transcript variant 2, mRNA.	4.224298	2.674344	0.007951216
2117330	NDUFB2	Homo sapiens NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa (NDUFB2), nuclear gene encoding mitochondrial protein, mRNA.	-3.78134	-2.67384	0.007962853
1791250	EDA	Homo sapiens ectodysplasin A (EDA), transcript variant 2, mRNA.	1.031798	2.672972	0.007982933
1663300	PCDH11X	Homo sapiens protocadherin 11 X-linked (PCDH11X), transcript variant d, mRNA.	-1.35953	-2.671	0.008028771
1723735	KIAA0889	Homo sapiens KIAA0889 protein (KIAA0889), mRNA.	-1.06108	-2.66896	0.008076293

1682428	C1orf59	Homo sapiens chromosome 1 open reading frame 59 (C1orf59), mRNA.	-2.35827	-2.66813	0.008095734
1787260	LCE3B	Homo sapiens late cornified envelope 3B (LCE3B), mRNA.	1.088635	2.667859	0.008102157
2312732	DPP8	Homo sapiens dipeptidyl-peptidase 8 (DPP8), transcript variant 1, mRNA.	1.619742	2.667319	0.008114834
1667417	RAB23	Homo sapiens RAB23, member RAS oncogene family (RAB23), transcript variant 1, mRNA.	-1.30641	-2.66245	0.008229953
1695108	RSPO2	Homo sapiens R-spondin 2 homolog (Xenopus laevis) (RSPO2), mRNA.	1.291668	2.661768	0.008246269
1755235	XPO6	Homo sapiens exportin 6 (XPO6), mRNA.	2.669143	2.656248	0.008378861
1683487	ZNF154	Homo sapiens zinc finger protein 154 (pHZ-92) (ZNF154), mRNA.	-1.22459	-2.65449	0.008421558
1810826	MAK10	Homo sapiens MAK10 homolog, amino-acid N-acetyltransferase subunit (S. cerevisiae) (MAK10), mRNA.	-1.18932	-2.65298	0.008458322
1811955	PRMT5	Homo sapiens protein arginine methyltransferase 5 (PRMT5), transcript variant 1, mRNA.	1.380706	2.651797	0.008487191
1724233	LOC145783	PREDICTED: Homo sapiens hypothetical protein LOC145783, transcript variant 2 (LOC145783), mRNA.	1.275588	2.649708	0.008538437
1712628	GTF2IRD1	Homo sapiens GTF2I repeat domain containing 1 (GTF2IRD1), transcript variant 1, mRNA.	-1.03907	-2.64767	0.008588608
3294074	LOC338870	PREDICTED: Homo sapiens misc_RNA (LOC338870), miscRNA.	-3.48227	-2.64579	0.008635454
3237169	FOXD4L5	Homo sapiens forkhead box D4-like 5 (FOXD4L5), mRNA.	-1.1969	-2.6429	0.008707371
1870671		yc39e06.r1 Stratagene liver (#937224) Homo sapiens cDNA clone IMAGE:83074 5, mRNA sequence	-1.15826	-2.64172	0.008737046
1848273	DNAH10	Homo sapiens dynein, axonemal, heavy chain 10 (DNAH10), transcript variant 1, mRNA.	-1.27308	-2.64154	0.008741557
1694608	C1QTNF1	Homo sapiens C1q and tumor necrosis factor related protein 1 (C1QTNF1), transcript variant 2, mRNA.	1.339911	2.639397	0.00879558

2374036	CTSL1	Homo sapiens cathepsin L1 (CTSL1), transcript variant 2, mRNA.	-2.59989	-2.63718	0.008851664
1654430	LOC731170	PREDICTED: Homo sapiens similar to eukaryotic translation elongation factor 1 alpha 2 (LOC731170), mRNA.	-1.41194	-2.63655	0.008867773
1854941		DKFZp434E0926_s1 434 (synonym: htes3) Homo sapiens cDNA clone DKFZp434E0926 3, mRNA sequence	-1.22983	-2.63254	0.008970517
3297898	LOC729769	PREDICTED: Homo sapiens similar to Ubiquinol-cytochrome c reductase hinge protein (LOC729769), mRNA.	-4.07006	-2.62886	0.009065662
1763637	KIAA0226	Homo sapiens KIAA0226 (KIAA0226), transcript variant 2, mRNA.	1.355024	2.624136	0.009188958
1869278		tj97h01.x1 NCI_CGAP_Lu24 Homo sapiens cDNA clone IMAGE:2149489 3, mRNA sequence	-2.65097	-2.62409	0.009190227
3243334	LOC645762	PREDICTED: Homo sapiens similar to TRIM5/cyclophilin A V1 fusion protein (LOC645762), mRNA.	-1.5998	-2.62303	0.009218104
1767685	SERPINB7	Homo sapiens serpin peptidase inhibitor, clade B (ovalbumin), member 7 (SERPINB7), transcript variant 1, mRNA.	1.539651	2.621477	0.009259096
3301168	LOC730052	PREDICTED: Homo sapiens misc_RNA (LOC730052), miscRNA.	-2.26522	-2.62098	0.009272233
2243553	ZNF275	Homo sapiens zinc finger protein 275 (ZNF275), mRNA.	2.632119	2.620011	0.009297954
3245591	DIO3OS	Homo sapiens DIO3 opposite strand (non-protein coding) (DIO3OS), non-coding RNA.	1.289761	2.619491	0.009311779
2200836	HSPB7	Homo sapiens heat shock 27kDa protein family, member 7 (cardiovascular) (HSPB7), mRNA.	1.235948	2.618346	0.009342297
1814650	TRAPPC4	Homo sapiens trafficking protein particle complex 4 (TRAPPC4), mRNA.	-1.96003	-2.60984	0.009571683
1838655		full-length cDNA clone CS0DI053YO09 of Placenta Cot 25-normalised of Homo sapiens (human)	1.202994	2.609767	0.009573687

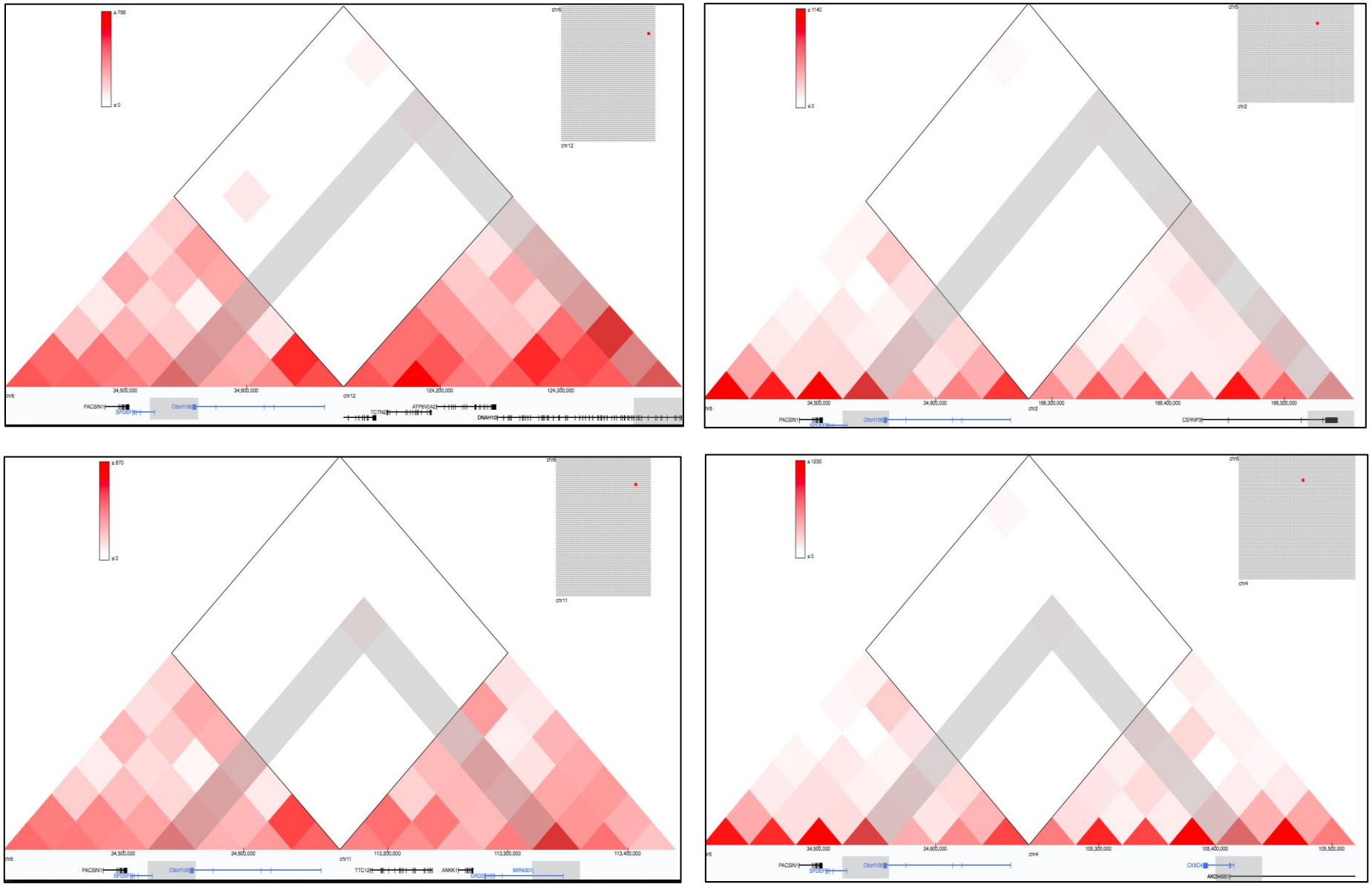
1652015	LOC647451	PREDICTED: Homo sapiens similar to heat shock protein 90Bf (LOC647451), mRNA.	1.219974	2.609516	0.009580554
1673232	LASS1	Homo sapiens LAG1 homolog, ceramide synthase 1 (LASS1), transcript variant 2, mRNA.	-1.18598	-2.60804	0.00962086
1669023	FHL5	Homo sapiens four and a half LIM domains 5 (FHL5), mRNA.	-1.0984	-2.60695	0.009650776
1766320	IL3	Homo sapiens interleukin 3 (colony-stimulating factor, multiple) (IL3), mRNA.	-1.29911	-2.60616	0.00967261
1813455	SP110	Homo sapiens SP110 nuclear body protein (SP110), transcript variant c, mRNA.	2.982809	2.60559	0.009688204
1737805	TPCN1	Homo sapiens two pore segment channel 1 (TPCN1), mRNA.	1.292254	2.604189	0.009726901
1850086		DKFZp779O1834_r1 779 (synonym: hncc1) Homo sapiens cDNA clone DKFZp779O1834 5, mRNA sequence	1.71817	2.604002	0.009732063
1705892	SH2D1A	Homo sapiens SH2 domain protein 1A, Duncan's disease (lymphoproliferative syndrome) (SH2D1A), mRNA.	-3.6569	-2.60365	0.009741798
3225329	LOC728847	PREDICTED: Homo sapiens hypothetical LOC728847 (LOC728847), mRNA.	-1.39924	-2.60137	0.00980528
3251747	UNCX	Homo sapiens UNC homeobox (UNCX), mRNA.	1.162511	2.600296	0.00983512
2369403	PALM2	Homo sapiens paralemmin 2 (PALM2), transcript variant 2, mRNA.	1.168809	2.599318	0.009862469
2143671	KPTN	Homo sapiens kaptin (actin binding protein) (KPTN), mRNA.	-1.19035	-2.59918	0.009866448
1740903	C7orf49	Homo sapiens chromosome 7 open reading frame 49 (C7orf49), mRNA.	1.181736	2.59912	0.009868027
1882041	LOC729025	PREDICTED: Homo sapiens similar to peptide/histidine transporter (LOC729025), mRNA.	-1.14133	-2.59778	0.00990552
2290338	RCAN1	Homo sapiens regulator of calcineurin 1 (RCAN1), transcript variant 1, mRNA.	1.136353	2.597277	0.009919784

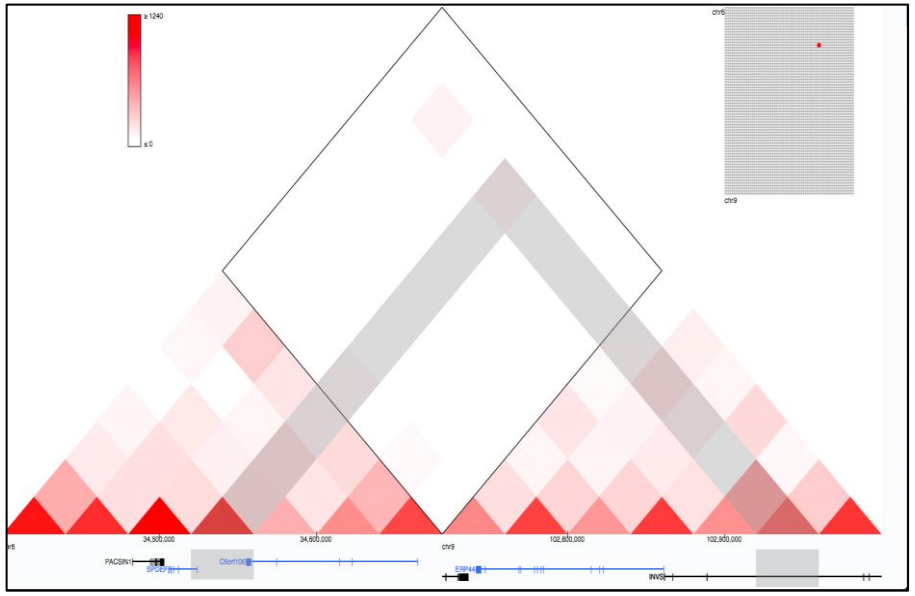
SUPPLEMENTARY Table S3. Gene networks associated with methylation at cg01395541 obtained using DAVID.

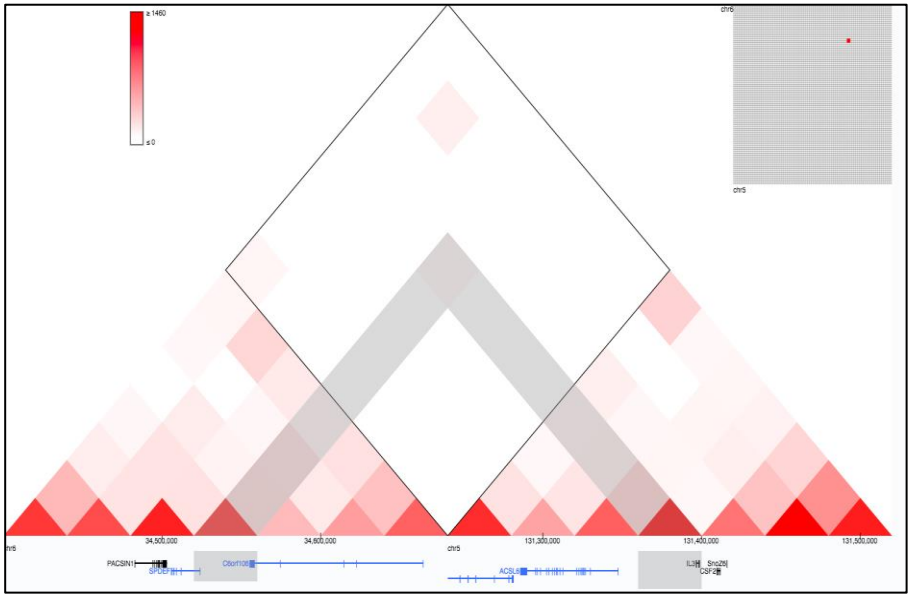
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total
GAD_DISEASE	Opioid-Related Disorders	3	1.886792	0.002347	OPRM1, MYOCD, DRD2	97	10	12971
GAD_DISEASE	Hyperparathyroidism, Secondary	6	3.773585	0.00454	OPRM1, IL3, IL2RA, KCNE1, SCNN1B, IL7R	97	146	12971
GAD_DISEASE	methamphetamine abuse	3	1.886792	0.00608	OPRM1, SLC6A9, DRD2	97	16	12971
GAD_DISEASE	Glomerulonephritis, IGA	5	3.144654	0.010424	MTMR3, ENPP1, DRD2, SERPINB7, CCL5	97	115	12971
GAD_DISEASE	Alcoholism	10	6.289308	0.012966	OPRM1, CAV3, DCC, EYA2, CSRNP3, DRD2, TMEM218, CXXC4, PPP2R2B, HMGA1	97	509	12971
GAD_DISEASE	height	6	3.773585	0.028379	NOG, LYN, MAP3K3, PALM2, SERPINI1, HMGA1	97	231	12971
GAD_DISEASE	Postoperative Nausea and Vomiting	2	1.257862	0.029281	OPRM1, DRD2	97	4	12971
GAD_DISEASE	alcohol dependence	3	1.886792	0.030523	OPRM1, DRD2, PPP2R2B	97	37	12971
GAD_DISEASE	Obesity|POF - Premature ovarian failure|POLYCYSTIC OVARIAN SYNDROME|Polycystic Ovary Syndrome|Primary Ovarian Insufficiency|Puberty, Delayed|Puberty, Precocious|Thrombophilia|Tobacco Use Disorder	6	3.773585	0.03795	OPRM1, NOG, DRD2, CCL5, CASC1, FSHR	97	250	12971
GAD_DISEASE	Bladder Cancer	9	5.660377	0.042077	OPRM1, IL3, RFC4, ENPP1, DRD2, NPAT, CD40, CCL5, IL7R	97	529	12971
GAD_DISEASE	alcohol dependency	2	1.257862	0.043601	OPRM1, DRD2	97	6	12971
GOTERM_BP_DIRECT	GO:0006955~immune response	12	7.54717	0.000561	IL3, IL2RA, ENPP1, GZMA, OTUD7B, DPP8, CTSC, CD40, CCL5, IL7R, EDA, SPN	135	421	16792
GOTERM_BP_DIRECT	GO:1900273~positive regulation of long-term synaptic	3	1.886792	0.003316	DRD2, RELN, STAU1	135	11	16792
GOTERM_BP_DIRECT	GO:0006968~cellular defense response	4	2.515723	0.013341	SH2D1A, RAB23, KIR2DS3, SPN	135	62	16792
GOTERM_BP_DIRECT	GO:0030216~keratinocyte differentiation	4	2.515723	0.022887	LCE3B, SPRR2B, LATS1, INTU	135	76	16792
GOTERM_BP_DIRECT	GO:0070668~positive regulation of mast cell proliferation	2	1.257862	0.023751	IL3, LYN	135	3	16792
GOTERM_BP_DIRECT	GO:0002027~regulation of heart rate	3	1.886792	0.0284	CAV3, DRD2, HCN4	135	33	16792
GOTERM_BP_DIRECT	GO:0002768~immune response-regulating cell surface receptor signaling pathway	2	1.257862	0.031543	LYN, CD40	135	4	16792
GOTERM_BP_DIRECT	GO:0042531~positive regulation of tyrosine phosphorylation of STAT protein	2	1.257862	0.039273	LYN, CCL5	135	5	16792
GOTERM_BP_DIRECT	GO:0051209~release of sequestered calcium ion into cytosol	3	1.886792	0.042329	DRD2, TPCN1, TRPM2	135	41	16792
GOTERM_BP_DIRECT	GO:0035335~peptidyl-tyrosine dephosphorylation	4	2.515723	0.044805	MTMR3, EYA2, DUSP13, PTPN4	135	99	16792
GOTERM_CC_DIRECT	GO:0009897~external side of plasma membrane	6	3.773585	0.02376	IL2RA, CD40, SCNN1B, IL7R, KLRD1, SPN	140	213	18224
GOTERM_CC_DIRECT	GO:0005929~cilium	5	3.144654	0.028553	DNAH10, INVS, TMEM218, ARL6, FLCN	140	151	18224
GOTERM_CC_DIRECT	GO:0060170~ciliary membrane	3	1.886792	0.049952	CLTB, DRD2, ARL6	140	47	18224
GOTERM_MF_DIRECT	GO:0005515~protein binding	80	50.31447	0.042754	OPRM1, SH3RF1, RPL36A, NOG, CLTB, XPO6, UFC1, C9ORF116, FLCN, LATS1, LGR4, SH2D1A, MYOCD, TRIM9, PRMT5, RSPO2, C7ORF49, LSM5, RAB23, KLRD1, MRPL51, BEND3, LYN, GZMA, TTC7B, APTX, CNPY2, CD40, ARL6, ARHGEF12, UBE2B, HMGA1, FSHR, KRT18, RFC4, EYA2, HSPB7, TRAPPC4, CTSC, STMN1, EDA, INTU, CAV3, PPP4R4, GPN1, DCC, CNBP, MGAT5B, ENPP1, DRD2, SLC39A13, SHFM1, TMEM218, FHL5, NEDD8, CCL5, IL7R, TPCN1, STAU1, MTMR3, RAB43, MAP3K3, DUSP13, FRG1, C1QTNF1, NPAT, KCNE1, OTUD7B, POU3F2, SCNN1B, PPP2R2B, SSX1, RFX4, PTPN4, ELAVL2, VAT1L, INVS, PTCD3, PC, DNAJB5	133	8785	16881
GOTERM_MF_DIRECT	GO:0004725~protein tyrosine phosphatase activity	4	2.515723	0.043687	MTMR3, EYA2, DUSP13, PTPN4	133	100	16881

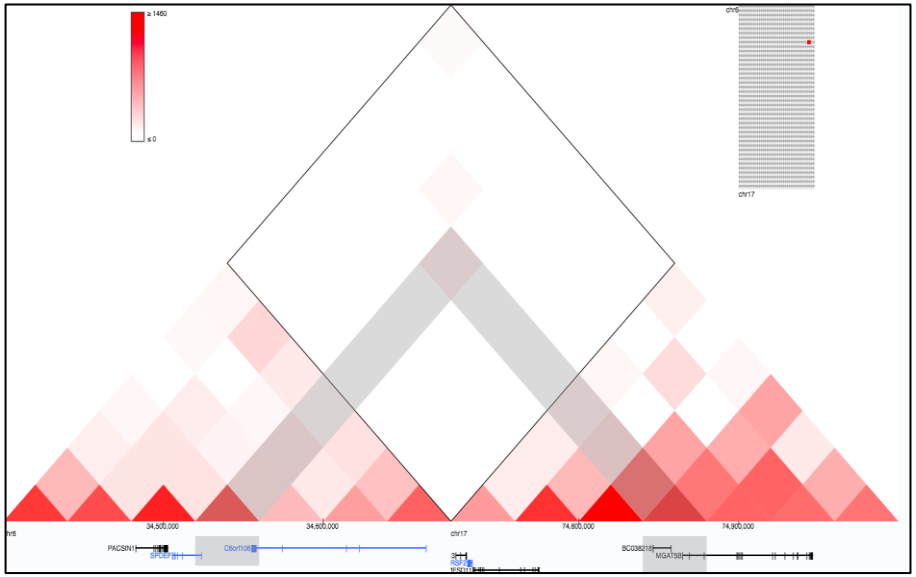
Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total
INTERPRO	IPR010414:FRG1-like	2	1.257862	0.014817	FRG1, LOC283788	139	2	18559
INTERPRO	IPR000315:Zinc finger, B-box	4	2.515723	0.023256	TRIM9, TRIM71, TRIM74, TRIM60	139	82	18559
INTERPRO	IPR017907:Zinc finger, RING-type, conserved site	5	3.144654	0.037533	SH3RF1, TRIM9, TRIM71, TRIM74, TRIM60	139	169	18559
INTERPRO	IPR002131:Glycoprotein hormone receptor	2	1.257862	0.043799	FSHR, LGR4	139	6	18559
KEGG_PATHWAY	hsa04060:Cytokine-cytokine receptor interaction	6	3.773585	0.037747	IL3, IL2RA, CD40, CCL5, IL7R, EDA	57	230	6910
SMART	SM00336:BBOX	4	2.515723	0.017071	TRIM9, TRIM71, TRIM74, TRIM60	75	74	10057
UP_KEYWORDS	Sodium transport	5	3.144654	0.009261	SLC5A2, ATP1B3, SCNN1B, HCN4, TRPM2	145	117	20581
UP_KEYWORDS	Sodium	5	3.144654	0.01129	SLC5A2, ATP1B3, SCNN1B, HCN4, TRPM2	145	124	20581
UP_KEYWORDS	Developmental protein	14	8.805031	0.015885	DCC, NOG, EYA2, INVS, GTF2IRD1, RAB23, RELN, STMN1, EDA, TRIM71, MDK, INTU, LGR4, UNCX	145	949	20581
UP_KEYWORDS	Sodium channel	3	1.886792	0.017443	SCNN1B, HCN4, TRPM2	145	29	20581
UP_KEYWORDS	Alternative splicing	88	55.34591	0.018502	OPRM1, SLC5A2, SH3RF1, CLTB, ATP1B3, XPO6, C9ORF116, FLCN, LATS1, LGR4, NFATC2IP, SH2D1A, MYOCD, TRIM9, PRMT5, RSPO2, S1PR5, LSM5, C7ORF49, DPP8, KLRD1, PCDHGA10, TMEM201, LYN, PCDH11X, METTL6, TTC7B, APTX, CNPY2, CD40, ARL6, ARHGEF12, HMGA1, ARRDC2, FSHR, TRPM2, EYA2, RFC4, GTF2IRD1, SERPINB7, HSPB7, TRAPPC4, CTSC, RELN, STMN1, EDA, INTU, TM6SF2, GPN1, PPP4R4, ZNF275, DNAH10, CNBP, MGAT5B, DRD2, SLC39A13, SP110, ANAPC11, IL7R, MDK, TRIM74, TPCN1, C12ORF54, STAU1, MTMR3, RAB43, MAP3K3, DUSP13, TOMM5, C1QTNF1, PALM2, OTUD7B, SCNN1B, PPP2R2B, CPA4, BOLA3, RFX4, RCAN1, ELAVL2, CASC1, SLC6A9, CSRNP3, INVS, PTCD3, KPTN, USP48, PC, DNAJB5	145	10587	20581
UP_KEYWORDS	Cytoplasm	44	27.67296	0.043747	PPP4R4, OPRM1, GPN1, SH3RF1, DNAH10, RPL36A, CNBP, XPO6, CXXC4, ANAPC11, FLCN, TRIM71, LATS1, STAU1, NFATC2IP, MTMR3, SH2D1A, DUSP13, FRG1, TRIM9, PRMT5, SPRR2B, RAB23, OTUD7B, C7ORF49, DPP8, PPP2R2B, LYN, PTPN4, TTC7B, APTX, ARL6, ARHGEF12, EYA2, KRT18, INVS, EIF5AL1, HSPB7, BNC1, SERPINB7, KPTN, STMN1, USP48, INTU	145	4816	20581
UP_SEQ_FEATURE	zinc finger region:RING-type	6	3.773585	0.026643	SH3RF1, TRIM9, ANAPC11, TRIM71, TRIM74, TRIM60	147	230	20063
UP_SEQ_FEATURE	splice variant	68	42.7673	0.044509	OPRM1, SH3RF1, CLTB, C9ORF116, FLCN, LATS1, NFATC2IP, SH2D1A, MYOCD, TRIM9, RSPO2, S1PR5, C7ORF49, DPP8, KLRD1, PCDHGA10, TMEM201, LYN, GZMA, PCDH11X, METTL6, TTC7B, APTX, CNPY2, CD40, ARHGEF12, ARRDC2, HMGA1, FSHR, TRPM2, EYA2, GTF2IRD1, EIF5AL1, HSPB7, RELN, EDA, INTU, PPP4R4, DNAH10, CNBP, MGAT5B, DRD2, SLC39A13, SP110, ANAPC11, IL7R, TRIM74, C12ORF54, TPCN1, STAU1, MTMR3, DUSP13, MAP3K3, PALM2, POU3F2, SCNN1B, PPP2R2B, RFX4, ELAVL2, RCAN1, CASC1, SLC6A9, INVS, CSRNP3, PTCD3, LOC728026, USP48, DNAJB5	147	7760	20063

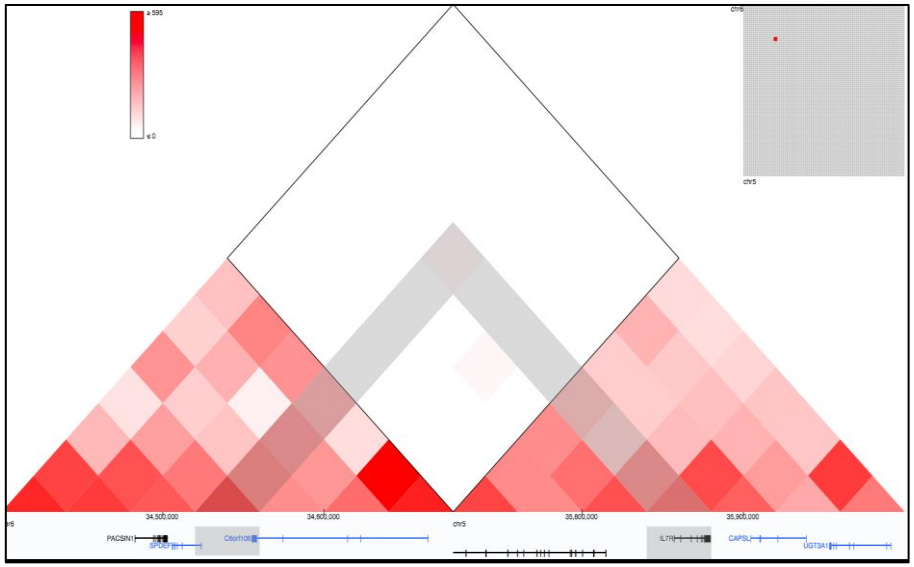
SUPPLEMENTARY Figure S3. Intra- and inter-chromosomal interactions between the *SPDEF* promoter region and *trans*-genes.

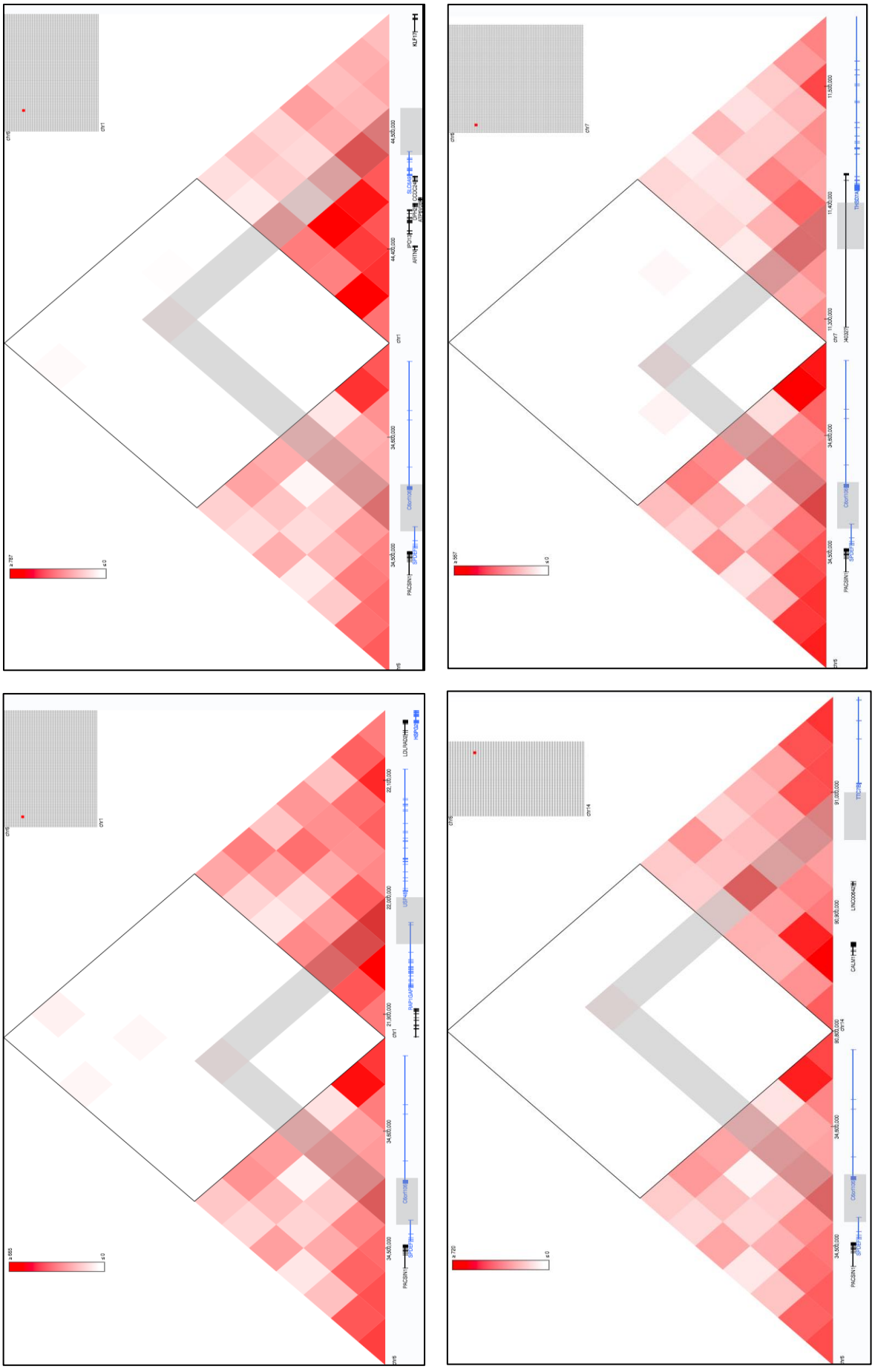



≥ 1240
≤ 0
chr9
34,500,000
34,600,000
102,800,000
102,900,000
chr9
PACSIN1
SPDEF
C6orf106
ESR1
INVS


≥ 1460
≤ 0
chr5
34,500,000
34,600,000
131,300,000
131,400,000
131,500,000
chr5
PACSIN1
SPDEF
C6orf106
ACSL6
IL3
SnoZ
CSF2


≥ 1460
≤ 0
chr17
34,500,000
34,600,000
74,800,000
74,900,000
chr17
PACSIN1
SPDEF
C6orf106
RSF1
MGAT3


≥ 595
≤ 0
chr5
34,500,000
34,600,000
35,800,000
35,900,000
chr5
PACSIN1
SPDEF
C6orf106
IL7R
CAPSL
UGT3A1



R code for Bump Hunting Analysis

```
library(minfi)
library(RColorBrewer)
setwd("/home/yun/projects/wave2")
mypar <- function(a=1,b=1,brewer.n=8,brewer.name="Dark2",...){
        par(mar=c(2.5,2.5,2,2),mgp=c(1.5,.5,0))
        par(mfrow=c(a,b),...)
        palette(brewer.pal(brewer.n,brewer.name))
        }

########## Load object
load("./rdas/object.rda")
load("./rdas/cellcount.rda")

meth <- readRDS("/home/tianye/Methylation_Both_Waves/PSC2_Beta_Recoded.rds")
pheno <- readRDS("/home/tianye/Methylation_Both_Waves/LEQ_Lifeevents.rds")
wave <- readRDS("/home/tianye/Methylation_Both_Waves/PSC2_with_Wave_Info.rds")
stopifnot(identical(colnames(meth),as.character(wave[,1])))


##remove duplicated samples
idx <- !duplicated(colnames(meth))
meth <- meth[,idx]
wave <- wave[idx,]
pheno <- pheno[match(as.character(wave[,1]),as.character(pheno[,1])),]
stopifnot(identical(as.character(pheno[,1]),as.character(wave[,1])))
pheno <- cbind(pheno,wave[,2])
colnames(pheno)[16] <- "Wave1"

fileName <- "./rdas/id_match.rda"
if (file.exists(fileName)) {
   load(fileName)
} else {fileName
        load("./rdas/beta.rda")
        beta <- beta[,beta[2,] %in% meth[2,]]
        meth <- meth[,match(beta[2,],meth[2,])]
        id_match <- matrix(ncol=2,nrow=ncol(beta))
        id_match[,1] <- colnames(beta)
        id_match[,2] <- colnames(meth)
        colnames(id_match) <- c("meth","PSC2")
        id_match <- data.frame(id_match)
        tmp <- read.delim("/home/tianye/Methylation_Both_Waves/PSC1_to_PSC2.txt",as.is=T)
        tmp <- tmp[match(as.character(id_match[,1]),as.character(tmp[,1])),]
        stopifnot(identical(as.character(id_match[,2]),as.character(tmp[,2])))
        save(id_match, file=fileName)
}

object <- object[,colnames(object) %in% id_match[,1]]
stopifnot(identical(colnames(object),as.character(id_match[,1])))
cellcount <- cellcount[rownames(cellcount) %in% id_match[,1],]
stopifnot(identical(rownames(cellcount),as.character(id_match[,1])))
```

```
pheno <- pheno[match(id_match[,2],pheno[,1]),]
stopifnot(identical(as.character(pheno[,1]),as.character(id_match[,2])))

gender <- readRDS("/home/tianye/Methylation_Both_Waves/PSC2_Data_Covariates_Complete.rds")
gender <- gender[match(pheno[,1],gender[,1]),]
pheno <-
cbind(pheno,gender[,c("Gender_Male_Recoded","Gender_Male_Predicted","Gender_Male_Combined")])

##remove samples with no gender information
idx <- pheno[,"Gender_Male_Recoded"]==1 & pheno[,"Gender_Male_Predicted"]==0 |
pheno[,"Gender_Male_Recoded"]==0 & pheno[,"Gender_Male_Predicted"]==1 |
is.na(pheno[,"Gender_Male_Combined"])
idx[is.na(idx)] <- F
object <- object[,!idx]
cellcount <- cellcount[!idx,]
pheno <- pheno[!idx,]

sex=factor(ifelse(pheno$Gender_Male_Combined==1,"M","F"),c("M","F"))
tmp <- cellcount - rowMeans(cellcount)
pc <- prcomp(tmp)

##remove sex chromosome
auIndex<-which(!seqnames(object)%in%c("chrX","chrY"))
object <- object[auIndex,]


####################################
########### bumphunting ###########
####################################
##3 cores, 100GB memory, overnight
for (i in colnames(pheno)[c(4:5,8:15)]){
        print(i)
        tt=as.numeric(pheno[,i])
        Index <- !is.na(tt) & !is.na(pheno[,2])
        design=model.matrix(~tt[Index]+pheno[Index,2]+sex[Index]+factor(pheno$Wave1)[Index]+pc$x[Index
,1]+pc$x[Index,2])
        ###need to adjust for age, if available

        fileName <- paste("./rdas/",i,"_res_adj_LEQ.rda",sep="")
        if (file.exists(fileName)) {
           load(fileName)
        } else {
                library(doParallel)
                registerDoParallel(cores=4)
                res=bumphunter(object[,Index], design, B=1000, smooth=FALSE, type="Beta", pickCutoff=T)
                save(res,file=fileName)
        }

        if(nrow(res$table)>1){
           genes=matchGenes(res$table,build="hg19")
           res$table=cbind(res$table,genes)}
        write.csv(res$table,file=paste("./tables/",i,"_bumphunter_adj_LEQ.csv",sep=""))
}
```

```
for (i in colnames(pheno)[c(6,7)]){
	print(i)
	tt=as.numeric(pheno[,i])
	Index <- !is.na(tt) & !is.na(pheno[,3])
	design=model.matrix(~tt[Index]+pheno[Index,3]+sex[Index]+factor(pheno$Wave1)[Index]+pc$x[Index
,1]+pc$x[Index,2])
	###need to adjust for age, if available

	fileName <- paste("./rdas/",i,"_res_adj_LEQ.rda",sep="")
	if (file.exists(fileName)) {
	   load(fileName)
	} else {
		library(doParallel)
		registerDoParallel(cores=4)
		res=bumphunter(object[,Index], design, B=1000, smooth=FALSE, type="Beta", pickCutoff=T)
		save(res,file=fileName)
	}

	if(nrow(res$table)>1){
	   genes=matchGenes(res$table,build="hg19")
	   res$table=cbind(res$table,genes)}
	write.csv(res$table,file=paste("./tables/",i,"_bumphunter_adj_LEQ.csv",sep=""))
}


#####################################
########### DMR plotting ###########
#####################################
tab1 <- read.csv(file="./tables/For_figure.csv",as.is=T)
tab <- GRanges(seqnames = Rle(tab1$chr), ranges = IRanges(start = tab1$start-1000, end = tab1$end+1000))
values(tab)<-cbind(as.character(tab1$name),as.character(tab1$description),tab1$distance)
pos=start(object)
b=getBeta(object)
as.fumeric<- function(x,...) as.numeric(as.factor(x,...))

pdf(file="./figs/DMRs.pdf", width=8, height=3.5)
M=min(nrow(tab1),300)
for(i in 1:2){
	mypar
	idx=subjectHits(findOverlaps(tab[i],object))
	x=pos[idx]
	bb=b[idx,]

	tmp=pheno[,tab1[i,1]]
	tt <- as.character(tmp)
	tt[tmp<3] <- "1.low"
	tt[tmp<7 & tmp>2] <- "2.middle"
	tt[tmp>6] <- "3.high"
	tt <- factor(tt)

	matplot(jitter(x),bb,col=as.fumeric(tt),ylim=c(0,1),main=paste(tab$V2[i],":",tab$V1[i]),cex=0.75,pch=1
6,xlab=paste("location on",seqnames(tab)[i]),ylab="Beta")
```

```
	tmpIndexes=split(1:ncol(bb),tt)
	for(j in seq(along=tmpIndexes)){
		bbb=rowMeans(bb[,tmpIndexes[[j]]])
		lfit=loess(bbb~x,span=0.75)
		lines(x,lfit$fitted,col=j)
	}
	legend("bottomleft",legend=levels(tt),col=seq(along=levels(tt)),lty=1)
	legend("bottomright",tab1[i,1])
}


for(i in 3:M){
	mypar
	idx=subjectHits(findOverlaps(tab[i],object))
	x=pos[idx]
	bb=b[idx,]

	tt=factor(pheno[,tab1[i,1]])

	matplot(jitter(x),bb,col=as.fumeric(tt),ylim=c(0,1),main=paste(tab$V2[i],":",tab$V1[i]),cex=0.75,pch=1
6,xlab=paste("location on",seqnames(tab)[i]),ylab="Beta")
	tmpIndexes=split(1:ncol(bb),tt)
	for(j in seq(along=tmpIndexes)){
		bbb=rowMeans(bb[,tmpIndexes[[j]]])
		lfit=loess(bbb~x,span=0.75)
		lines(x,lfit$fitted,col=j)
	}
	legend("bottomleft",legend=levels(tt),col=seq(along=levels(tt)),lty=1)
	legend("bottomright",tab1[i,1])
}

dev.off()

rm(list=ls())
q()
```

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(4) Li LC, Dahiya R. MethPrimer: designing primers for methyaltion PCRs. Bioinformatics 2002;18(11):1427-1431.

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