

**Developmental Associations Linking Childhood Trauma and Early Cannabis Use
to Adolescent DNA Methylation and Psychotic-Like Experiences – Online
Supplementary Material**

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1. Additional Methods

1.1. DNAm preprocessing and quality control

Quality control (QC) procedures were systematically applied to raw DNA methylation data generated using the Illumina HumanMethylation450 BeadChip (450k). QC procedures were applied at both the sample and probe level. Samples were excluded based on sex mismatch, poor signal intensity, and low overall quality (i.e., > 10% of probes had a detection p-value > 0.01 or a bead count < 3). Probes were excluded if they had detection p-value > 0.01 in > 10% of samples, bead count < 3 in > 10% of sample, or overlapped known single nucleotide polymorphisms. The present study was restricted to participant with DNA methylation measured at age 15-17 years.

1.2. DNAm Principal Component Analysis (mPCs)

To capture latent sources of biological and technical variation in the DNAm data, principal component analysis (PCA) was performed on genome-wide methylation levels measured at age 15-17 years. PCA was conducted on a random subset of 50,000 CpG sites selected from the genome-wide dataset. Methylation β -values were transformed to M-values using the logit transformation. CpGs with more than 1% missingness were excluded and remaining missing values (< 1% of the data matrix) were imputed using the mean methylation level for each CpG. CpGs with zero variance were removed prior to analysis. PCA was performed using the *prcomp* function in R, with centring and scaling applied across CpGs. The first five components (mPC1-mPC5) were retained as covariates in all models.

1.3. Smoking score derivation and validation

To account for tobacco exposure in epigenetic analyses, we derived a DNA methylation-based smoking indicator using methylation levels at cg05575921 within the aryl-hydrocarbon receptor repressor (AHRR) gene. This CpG site is one of the most robust and consistently replicated methylation markers of cigarette smoking identified in large EWAS studies.

To evaluate whether cg05575921 methylation behaved as expected in this cohort, we examined its association with self-reported nicotine dependence assessed at age 17 using the Fagerström Test for Nicotine Dependence. Valid questionnaire data were available for a subsample of 286 participants. Higher nicotine dependence was associated with lower methylation at cg05575921 ($\beta = -0.0099$ per unit increase in Fagerström score, SE = 0.0020, $p = 1.15 \times 10^{-6}$; $R^2 = 0.08$). Spearman's rank correlation confirmed a moderate inverse association ($\rho = -0.27$, $p = 2.7 \times 10^{-6}$; **Figure S1**). Consistent with this, participants with Fagerström scores greater than zero showed lower mean methylation compared to those scoring zero (mean difference ≈ -0.041 , $p < 0.001$).

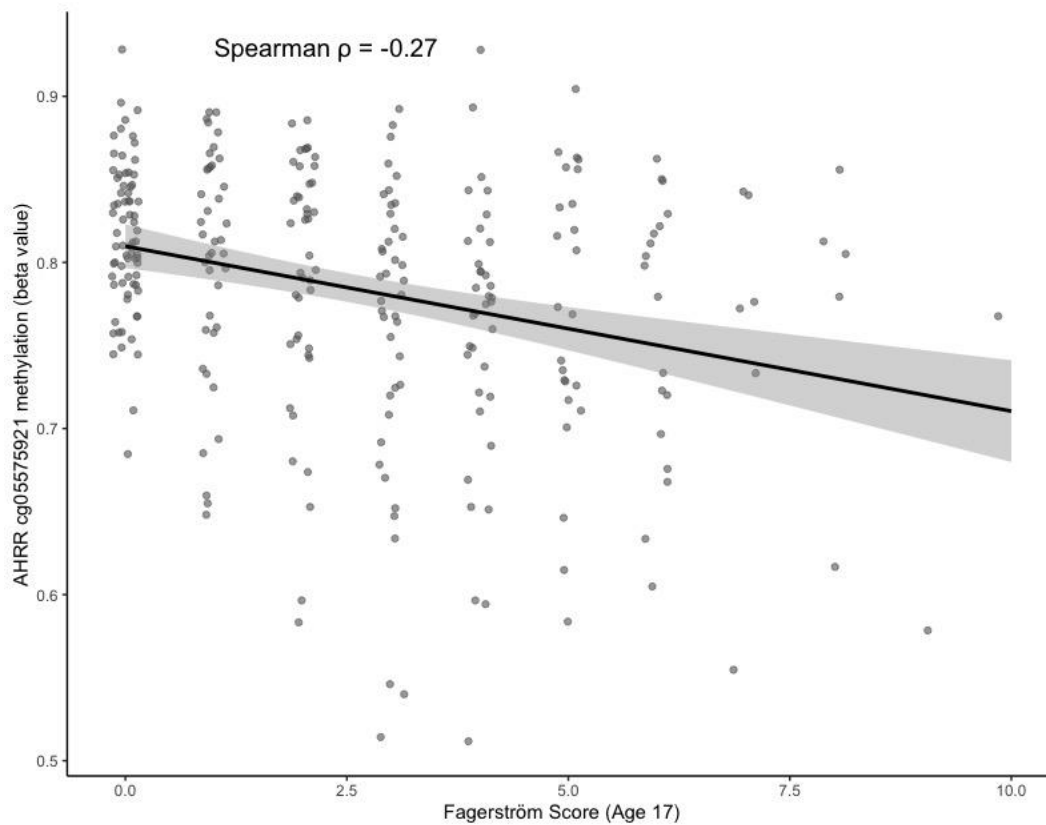


Figure S1. Association between AHRR methylation and nicotine dependence at age 17.

Scatter plot of cg05575921 (AHRR) methylation β values against Fagerström Test for Nicotine Dependence scores at age 17 among participants with available data ($N = 286$). The solid line represents the fitted linear regression with 95% CI.

These findings support the use of cg05575921 methylation as a DNAm-based indicator of smoking exposure in subsequent analyses.

1.4. Cannabis frequency imputation

Cannabis use frequency at age 15.5 years was derived as a three-level ordinal variable (0 = never, 1 = occasional, 2 = frequent) based on self-reported lifetime use and frequency measures. Occasional use corresponded to lower-frequency categories, whereas frequent use reflected higher-frequency categories among users. Missing values in cannabis frequency were imputed using multiple imputation by chained equations (MICE). The imputation model used an ordinal logistic regression approach and included earlier cannabis-related variables, sex, smoking score, trauma exposure, and psychotic-like experiences (PLEs) as predictors. A total of 20 imputed datasets were generated with 20 iterations per chain. Imputed values were extracted from the completed datasets and used in downstream analyses.

2. Supplementary Results: Phenotypic Associations

Table S1. Phenotypic associations with psychotic-like experiences at age 18

Exposure / term	Outcome	N	OR	95% CI	P-value
<i>Cumulative trauma score (0–17 years)</i>	PLEs at age 18	1457	1.59	1.38 to 1.84	2.73×10 ⁻¹⁰
<i>Occasional cannabis use vs never</i>	PLEs at age 18	1457	1.14	0.68 to 1.91	0.6061
<i>Frequent cannabis use vs never</i>	PLEs at age 18	1457	2.94	1.21 to 7.14	0.0168
<i>Trauma × occasional cannabis use</i>	PLEs at age 18	1457	1.04	0.71 to 1.51	0.8396
<i>Trauma × frequent cannabis use</i>	PLEs at age 18	1457	1.50	0.63 to 3.59	0.3626

Models adjusted for sex, age, and maternal education.

3. EWAS diagnostics

3.1. Path A Diagnostics

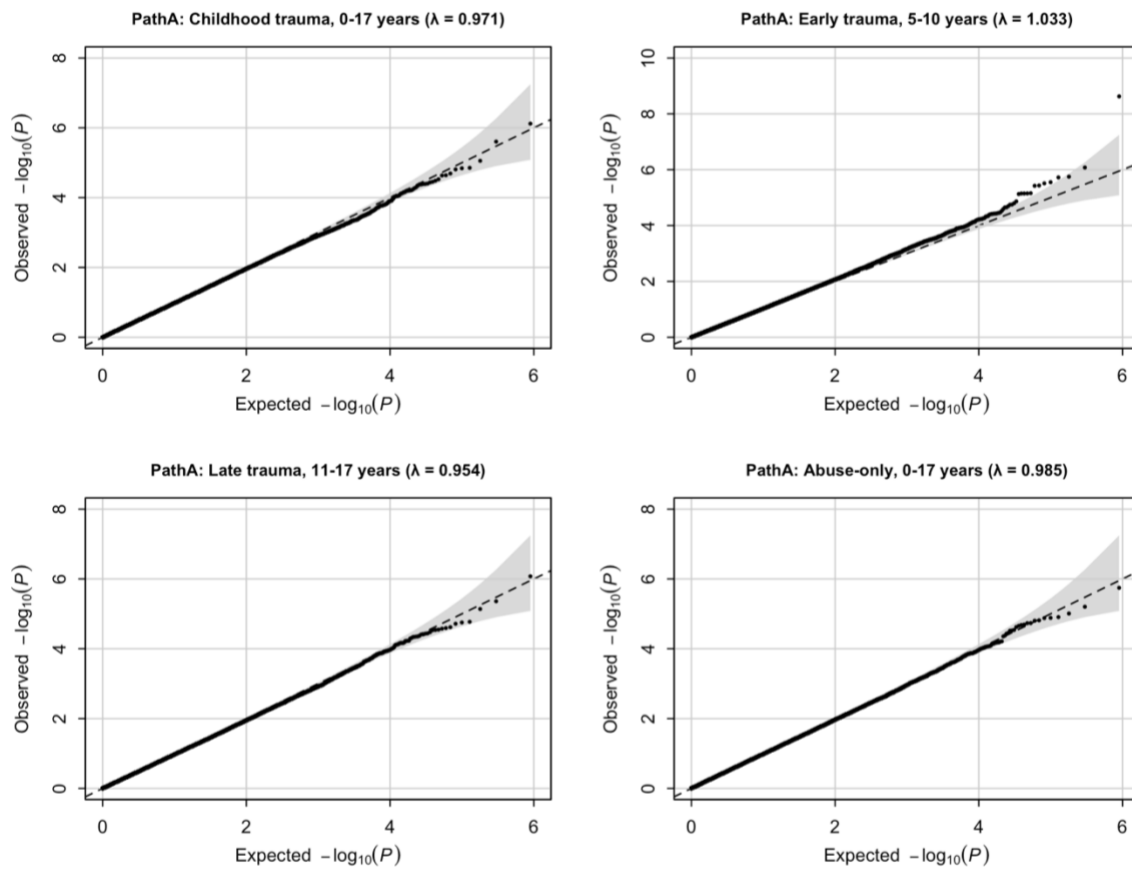


Figure S2. QQ plots for EWAS analyses of childhood trauma and DNAm (Path A).

The dashed line indicates the null expectation and the shaded region the 95% confidence envelope. Genomic inflation factors (λ) are reported in each panel.

3.2. Path B Diagnostics

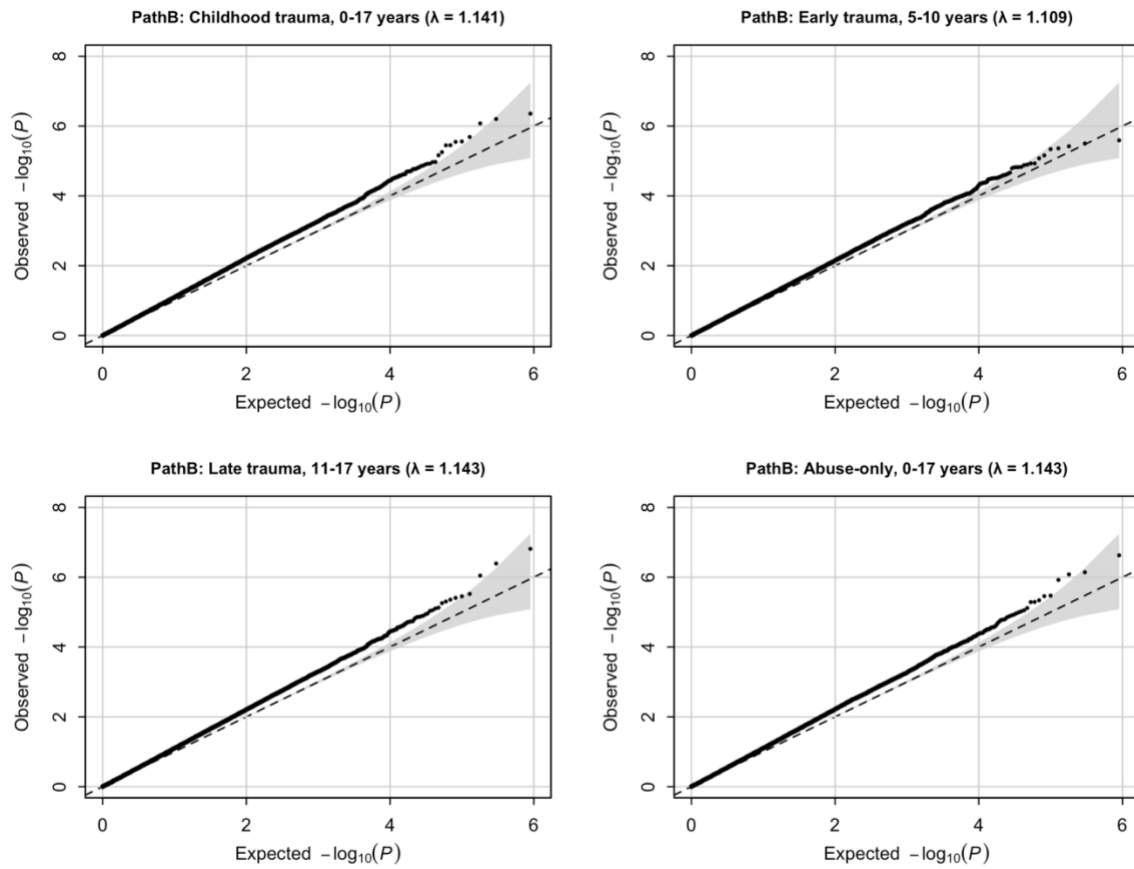


Figure S3. QQ plots for EWAS analyses of DNAm and PLEs (Path B).

The dashed line indicates the null expectation and the shaded region the 95% confidence envelope. Genomic inflation factors (λ) are reported in each panel.

4. Epigenome-wide Association Results

EWAS results are presented separately for Path A and Path B across the four childhood trauma definitions. For each analysis, top CpG associations are reported in supplementary tables.

4.1. Path A – Associations between childhood trauma and DNAm

Table S2. Top CpG sites associated with childhood trauma in EWAS association analyses

CpG	chr	pos	gene	cpg_island_relation	effect	SE	P	exposure
cg08423269	chr3	157827682	RSRC1	N_Shore	0.0254	0.0051	7.598E-07	Childhood trauma, 0-17 years
cg00284390	chr16	84492635	ATP2C2	OpenSea	-0.0451	0.0095	2.482E-06	Childhood trauma, 0-17 years
cg03667641	chr7	1046346	C7orf50	Island	0.0195	0.0044	8.808E-06	Childhood trauma, 0-17 years
cg00816008	chr16	82203996	MPHOSPH6	Island	-0.0242	0.0056	1.400E-05	Childhood trauma, 0-17 years
cg12442369	chr19	12167216	ZNF878	S_Shelf	0.0230	0.0053	1.441E-05	Childhood trauma, 0-17 years
cg16853982	chr1	236849389	ACTN2	N_Shore	-0.0344	0.0079	1.553E-05	Childhood trauma, 0-17 years
cg11527220	chr17	49041451	SPAG9	OpenSea	-0.0224	0.0052	2.037E-05	Childhood trauma, 0-17 years
cg09392615	chr15	33023237	GREM1	OpenSea	0.0253	0.0060	2.284E-05	Childhood trauma, 0-17 years
cg02770794	chrX	39872204		Island	-0.0485	0.0114	2.320E-05	Childhood trauma, 0-17 years
cg24317979	chr2	87302855	LOC285074	Island	0.0180	0.0043	2.975E-05	Childhood trauma, 0-17 years
cg27235829	chr1	158390759	OR10K2	OpenSea	-0.0227	0.0054	3.271E-05	Childhood trauma, 0-17 years
cg16550477	chrX	8769499	FAM9A	Island	0.0782	0.0188	3.513E-05	Childhood trauma, 0-17 years
cg16906595	chr11	67798128	NDUFS8	Island	0.0247	0.0060	3.659E-05	Childhood trauma, 0-17 years
cg21982660	chr20	17922310	SNX5	OpenSea	-0.0245	0.0059	3.954E-05	Childhood trauma, 0-17 years
cg00907272	chr10	74086782		OpenSea	-0.0496	0.0120	4.047E-05	Childhood trauma, 0-17 years
cg08158862	chr1	200012526	NR5A2	S_Shore	-0.0442	0.0107	4.058E-05	Childhood trauma, 0-17 years
cg26583088	chr17	40322250	KCNH4	OpenSea	-0.0595	0.0145	4.192E-05	Childhood trauma, 0-17 years
cg22025233	chr7	1022904	CYP2W1	N_Shore	0.0281	0.0068	4.201E-05	Childhood trauma, 0-17 years
cg24402667	chr17	36612623	ARHGAP23	S_Shelf	0.0383	0.0094	4.561E-05	Childhood trauma, 0-17 years

cg16255307	chr3	185271383	LIPH	OpenSea	-0.0609	0.0101	2.363E-09	Early trauma, 5-10 years
cg15057061	chr3	181437299	SOX2OT	Island	0.0544	0.0110	8.348E-07	Early trauma, 5-10 years
cg13401681	chrX	16141609	GRPR	OpenSea	0.0390	0.0081	1.780E-06	Early trauma, 5-10 years
cg04317047	chr5	148808388	MIR143; LOC728264	OpenSea	-0.0751	0.0157	1.889E-06	Early trauma, 5-10 years
cg06386482	chr6	47624117	GPR111	OpenSea	0.1664	0.0354	2.802E-06	Early trauma, 5-10 years
cg02552572	chr16	56597746	MT4	OpenSea	-0.0490	0.0105	3.081E-06	Early trauma, 5-10 years
cg11527220	chr17	49041451	SPAG9	OpenSea	-0.0346	0.0074	3.679E-06	Early trauma, 5-10 years
cg05491661	chr12	56893671		OpenSea	0.0469	0.0101	3.767E-06	Early trauma, 5-10 years
cg10523820	chr11	66314211	ACTN3; ZDHHC24	Island	-0.0893	0.0198	6.938E-06	Early trauma, 5-10 years
cg02908285	chr3	30951484		OpenSea	0.0367	0.0081	7.094E-06	Early trauma, 5-10 years
cg09159389	chr1	146644318	PRKAB2	Island	-0.0282	0.0063	7.124E-06	Early trauma, 5-10 years
cg25607225	chr2	88803870		OpenSea	-0.0569	0.0126	7.138E-06	Early trauma, 5-10 years
cg25110782	chr12	57624371	SHMT2	S_Shore	-0.0253	0.0056	7.437E-06	Early trauma, 5-10 years
cg10486655	chr16	68624584		OpenSea	0.0522	0.0120	1.364E-05	Early trauma, 5-10 years
cg22504094	chr19	2115196	AP3D1	N_Shore	-0.0563	0.0130	1.590E-05	Early trauma, 5-10 years
cg22155281	chr4	118007206	TRAM1L1	S_Shore	0.0430	0.0100	1.764E-05	Early trauma, 5-10 years
cg13220569	chr12	5155343	KCNA5	S_Shore	-0.0407	0.0094	1.787E-05	Early trauma, 5-10 years
cg08252971	chr4	41218767		Island	0.0395	0.0092	2.010E-05	Early trauma, 5-10 years
cg14698154	chr5	96747223		OpenSea	-0.0400	0.0094	2.234E-05	Early trauma, 5-10 years
cg18331412	chr5	135364986	TGFBI	Island	0.0480	0.0113	2.243E-05	Early trauma, 5-10 years
cg05823589	chr5	863749		N_Shore	0.0615	0.0146	2.562E-05	Early trauma, 5-10 years
cg27588515	chr5	115167455	ATG12	OpenSea	0.0247	0.0059	2.965E-05	Early trauma, 5-10 years
cg09019916	chr2	109335672	RANBP2	N_Shore	-0.0572	0.0137	3.338E-05	Early trauma, 5-10 years
cg24282422	chr3	125239067	SNX4	Island	-0.0236	0.0057	3.519E-05	Early trauma, 5-10 years
cg03743462	chr2	240118958	HDAC4	OpenSea	-0.0758	0.0183	3.585E-05	Early trauma, 5-10 years
cg00284390	chr16	84492635	ATP2C2	OpenSea	-0.0561	0.0136	3.700E-05	Early trauma, 5-10 years
cg05893029	chr8	88760082		OpenSea	-0.0351	0.0085	3.738E-05	Early trauma, 5-10 years
cg03070194	chr1	110210684	GSTM2	Island	-0.0408	0.0099	3.749E-05	Early trauma, 5-10 years
cg23906067	chr6	31939112	STK19; DOM3Z	N_Shore	-0.0337	0.0081	3.794E-05	Early trauma, 5-10 years

<i>cg10345936</i>	chr5	150727812	SLC36A2	OpenSea	-0.0384	0.0093	3.836E-05	Early trauma, 5-10 years
<i>cg08584868</i>	chr8	53474887	FAM150A	N_Shelf	-0.0479	0.0116	3.925E-05	Early trauma, 5-10 years
<i>ch.2.4116732R</i>	chr2	206658319	NRP2	OpenSea	0.0344	0.0083	4.016E-05	Early trauma, 5-10 years
<i>cg02039022</i>	chr5	72112005	TNPO1	N_Shore	-0.0586	0.0143	4.201E-05	Early trauma, 5-10 years
<i>cg00259584</i>	chr2	106986308		OpenSea	-0.0419	0.0103	4.582E-05	Early trauma, 5-10 years
<i>cg22475576</i>	chr19	1252813	MIDN	N_Shore	-0.0364	0.0089	4.616E-05	Early trauma, 5-10 years
<i>cg17098965</i>	chr20	52199520	ZNF217	S_Shore	-0.0405	0.0099	4.691E-05	Early trauma, 5-10 years
<i>cg07708806</i>	chr16	8962224	CARHSP1	Island	-0.0227	0.0056	4.963E-05	Early trauma, 5-10 years
<i>cg04795788</i>	chr13	101327638	TMTC4	Island	-0.0379	0.0077	8.385E-07	Late trauma, 11-17 years
<i>cg08816194</i>	chrY	16733442	NLGN4Y	OpenSea	-0.0963	0.0208	4.355E-06	Late trauma, 11-17 years
<i>cg16902255</i>	chr1	35897100		OpenSea	0.0686	0.0152	7.254E-06	Late trauma, 11-17 years
<i>cg16906137</i>	chr15	72075886		OpenSea	-0.0495	0.0115	1.694E-05	Late trauma, 11-17 years
<i>cg17240157</i>	chr1	164816968	PBX1	OpenSea	0.0590	0.0137	1.767E-05	Late trauma, 11-17 years
<i>cg17289597</i>	chr10	72433155	ADAMTS14	S_Shore	0.0674	0.0157	1.922E-05	Late trauma, 11-17 years
<i>cg27413385</i>	chr17	7515425	FXR2	N_Shelf	-0.0386	0.0091	2.403E-05	Late trauma, 11-17 years
<i>cg14406727</i>	chr2	65577769	SPRED2	OpenSea	0.0464	0.0110	2.548E-05	Late trauma, 11-17 years
<i>cg10186400</i>	chr6	46138843	ENPP5	OpenSea	0.0455	0.0108	2.654E-05	Late trauma, 11-17 years
<i>cg16949378</i>	chr17	2276201	SGSM2	S_Shore	-0.0591	0.0141	2.834E-05	Late trauma, 11-17 years
<i>cg10713773</i>	chr13	51796714	FAM124A	Island	0.0408	0.0097	2.887E-05	Late trauma, 11-17 years
<i>cg24297509</i>	chr10	44339107		OpenSea	-0.0714	0.0170	2.941E-05	Late trauma, 11-17 years
<i>cg08819934</i>	chr8	146082699		S_Shelf	0.0482	0.0116	3.356E-05	Late trauma, 11-17 years
<i>cg02078882</i>	chr12	30911709		S_Shelf	-0.0804	0.0194	3.614E-05	Late trauma, 11-17 years
<i>cg16035633</i>	chr7	150700728	NOS3	OpenSea	-0.0611	0.0147	3.686E-05	Late trauma, 11-17 years
<i>cg21815882</i>	chr7	26241064	CBX3; HNRNPA2B1	Island	-0.0355	0.0086	3.868E-05	Late trauma, 11-17 years
<i>cg24602560</i>	chr11	788583	CEND1	N_Shore	0.0929	0.0225	3.875E-05	Late trauma, 11-17 years
<i>cg13298632</i>	chr2	242952648		Island	0.0772	0.0188	4.257E-05	Late trauma, 11-17 years
<i>cg10721834</i>	chr19	22990066		Island	0.0816	0.0199	4.445E-05	Late trauma, 11-17 years
<i>cg24153199</i>	chr14	50698328	SOS2	Island	-0.0317	0.0077	4.478E-05	Late trauma, 11-17 years
<i>cg02426836</i>	chr11	2444651	TRPM5	S_Shelf	0.0549	0.0134	4.553E-05	Late trauma, 11-17 years

<i>cg00190795</i>	chr3	195599898	TNK2	N_Shore	-0.0405	0.0099	4.607E-05	Late trauma, 11-17 years
<i>cg01838916</i>	chr5	85577056	NBPF22P	OpenSea	-0.0416	0.0102	4.906E-05	Late trauma, 11-17 years
<i>cg08423269</i>	chr3	157827682	RSRC1	N_Shore	0.0375	0.0078	1.795E-06	Abuse only, 0-17 years
<i>cg23493020</i>	chr14	65112169		OpenSea	0.0390	0.0086	6.259E-06	Abuse only, 0-17 years
<i>cg15349139</i>	chr11	1293211		Island	-0.0558	0.0126	9.771E-06	Abuse only, 0-17 years
<i>cg03699765</i>	chr10	43882723	HNRNPF	OpenSea	-0.0605	0.0138	1.236E-05	Abuse only, 0-17 years
<i>cg21982660</i>	chr20	17922310	SNX5	OpenSea	-0.0396	0.0091	1.305E-05	Abuse only, 0-17 years
<i>cg27413385</i>	chr17	7515425	FXR2	N_Shelf	-0.0360	0.0082	1.324E-05	Abuse only, 0-17 years
<i>cg08292485</i>	chr20	29993663	DEFB121	OpenSea	-0.0562	0.0130	1.535E-05	Abuse only, 0-17 years
<i>cg00578354</i>	chr20	47251399	PREX1	N_Shore	-0.0556	0.0128	1.574E-05	Abuse only, 0-17 years
<i>cg01641174</i>	chr15	91497412	RCCD1	N_Shore	-0.0273	0.0064	1.838E-05	Abuse only, 0-17 years
<i>cg00400263</i>	chr20	58514201	C20orf177; PPP1R3D	Island	-0.1140	0.0265	1.850E-05	Abuse only, 0-17 years
<i>cg11527220</i>	chr17	49041451	SPAG9	OpenSea	-0.0343	0.0080	2.030E-05	Abuse only, 0-17 years
<i>cg00816008</i>	chr16	82203996	MPHOSPH6	Island	-0.0362	0.0085	2.091E-05	Abuse only, 0-17 years
<i>cg14564144</i>	chr12	650711	B4GALNT3	OpenSea	-0.0578	0.0136	2.215E-05	Abuse only, 0-17 years
<i>cg14948030</i>	chr6	124122575		N_Shore	-0.0457	0.0108	2.379E-05	Abuse only, 0-17 years
<i>cg02426623</i>	chr12	3259078	TSPAN9	OpenSea	0.0579	0.0138	2.896E-05	Abuse only, 0-17 years
<i>cg02994237</i>	chrX	137750892	FGF13; MIR504	OpenSea	-0.0758	0.0181	2.993E-05	Abuse only, 0-17 years
<i>cg21500735</i>	chr19	44576159	ZNF284	Island	-0.0398	0.0095	3.028E-05	Abuse only, 0-17 years
<i>cg00743803</i>	chr22	48970600	FAM19A5	N_Shore	0.0468	0.0113	3.514E-05	Abuse only, 0-17 years
<i>cg04693701</i>	chr5	125934946		N_Shore	0.0362	0.0087	3.716E-05	Abuse only, 0-17 years
<i>cg13962846</i>	chr1	7973298		OpenSea	-0.0840	0.0204	4.204E-05	Abuse only, 0-17 years
<i>cg00473749</i>	chr7	63955932		OpenSea	0.0602	0.0147	4.409E-05	Abuse only, 0-17 years

Genomic locations are reported according to the hg19 reference genome. Gene annotation and CpG island context correspond to the Illumina HumanMethylation450 array annotation.

4.2 Path B – Associations between DNAm and PLEs

Table S3. Top CpG sites associated with PLEs in EWAS association analyses (adjusted for childhood trauma)

CpG	chr	pos	gene	cpg_island_relation	effect	SE	P	exposure
cg26428054	chr12	49484058	DHH	Island	-3.238	0.641	4.4E-07	Childhood trauma, 0-17 years
cg10529789	chr17	37009658	SNORA21; RPL23	Island	-2.76	0.5539	6.25E-07	Childhood trauma, 0-17 years
cg24157392	chr3	112217973	BTLA	OpenSea	2.298	0.4664	8.38E-07	Childhood trauma, 0-17 years
cg07992052	chr20	35402295	DSN1	Island	-1.949	0.4103	2.05E-06	Childhood trauma, 0-17 years
cg08528970	chr4	76640579		OpenSea	-1.523	0.3248	2.76E-06	Childhood trauma, 0-17 years
cg14663914	chr19	827739	AZU1	OpenSea	-2.193	0.4683	2.83E-06	Childhood trauma, 0-17 years
cg11182518	chr5	55117965		Island	0.8451	0.1822	3.53E-06	Childhood trauma, 0-17 years
cg01312828	chr6	41648365		N_Shelf	-1.266	0.2731	3.55E-06	Childhood trauma, 0-17 years
cg14672994	chr17	48503057	ACSF2	Island	-1.541	0.3391	5.56E-06	Childhood trauma, 0-17 years
cg21041594	chr7	65235699		Island	1.717	0.3817	6.86E-06	Childhood trauma, 0-17 years
cg00980622	chr14	75884845		OpenSea	-1.32	0.2998	1.06E-05	Childhood trauma, 0-17 years
cg25618765	chr22	20670922		N_Shelf	-1.508	0.3426	1.08E-05	Childhood trauma, 0-17 years
cg21889703	chr6	136607649	BCLAF1	N_Shelf	-2.093	0.4779	1.19E-05	Childhood trauma, 0-17 years
cg14010194	chr6	42152817	GUCA1B	OpenSea	-1.251	0.2858	1.21E-05	Childhood trauma, 0-17 years
cg00464520	chr10	118903060		S_Shelf	-1.151	0.2635	1.26E-05	Childhood trauma, 0-17 years
cg07942847	chr14	23420757	HAUS4	OpenSea	2.374	0.5455	1.35E-05	Childhood trauma, 0-17 years
cg10755512	chr3	44666543	ZNF197	Island	2.091	0.4813	1.39E-05	Childhood trauma, 0-17 years
cg08362273	chr17	46719577		Island	1.326	0.3064	0.000015	Childhood trauma, 0-17 years
cg08201736	chr15	79298769	RASGRF1	OpenSea	1.582	0.3662	1.56E-05	Childhood trauma, 0-17 years
cg05640294	chr19	38976794	RYR1	Island	-1.539	0.3575	1.67E-05	Childhood trauma, 0-17 years
cg16791444	chr17	71702669		OpenSea	-1.346	0.3128	1.69E-05	Childhood trauma, 0-17 years
cg14841628	chr1	16258280	SPEN	N_Shelf	-1.476	0.3432	1.71E-05	Childhood trauma, 0-17 years
cg16328610	chr6	83777335	DOPEY1	Island	-2.136	0.499	1.87E-05	Childhood trauma, 0-17 years
cg17276036	chr4	26492222	CCKAR	OpenSea	1.792	0.4198	1.97E-05	Childhood trauma, 0-17 years
cg19013753	chr15	75915192	SNUPN	N_Shelf	1.536	0.36	1.98E-05	Childhood trauma, 0-17 years

<i>cg08739188</i>	chr5	75377860	SV2C	N_Shore	0.987	0.2314	2E-05	Childhood trauma, 0-17 years
<i>cg03315940</i>	chr6	27569167		OpenSea	-1.544	0.3624	2.03E-05	Childhood trauma, 0-17 years
<i>cg05771369</i>	chr12	58021713	B4GALNT1	Island	0.6714	0.1588	2.36E-05	Childhood trauma, 0-17 years
<i>cg19754901</i>	chr3	87102643		S_Shore	-1.408	0.3333	2.41E-05	Childhood trauma, 0-17 years
<i>cg27524192</i>	chr1	228773464		Island	-1.482	0.351	2.42E-05	Childhood trauma, 0-17 years
<i>cg05814106</i>	chr1	2224791	SKI	S_Shelf	-1.018	0.2414	2.47E-05	Childhood trauma, 0-17 years
<i>cg10632722</i>	chr6	49833873	CRISP1	OpenSea	-1.69	0.4017	2.6E-05	Childhood trauma, 0-17 years
<i>cg19989295</i>	chr14	24641077	REC8	Island	0.9323	0.2217	2.61E-05	Childhood trauma, 0-17 years
<i>cg16588073</i>	chr1	156647247	NES	Island	-1.139	0.2708	2.62E-05	Childhood trauma, 0-17 years
<i>cg01996004</i>	chr5	180338435	BTNL8	OpenSea	-1.021	0.2439	2.83E-05	Childhood trauma, 0-17 years
<i>cg22936975</i>	chr13	61989412	PCDH20	OpenSea	1.668	0.3984	2.83E-05	Childhood trauma, 0-17 years
<i>cg00925244</i>	chr2	86148800		OpenSea	2.066	0.494	2.89E-05	Childhood trauma, 0-17 years
<i>cg10251328</i>	chr17	47074713	IGF2BP1	Island	-2.451	0.587	2.97E-05	Childhood trauma, 0-17 years
<i>cg08791347</i>	chr10	13831250	FRMD4A	OpenSea	1.085	0.2602	3.05E-05	Childhood trauma, 0-17 years
<i>cg23041896</i>	chr8	144462235	RHPN1	Island	-0.7632	0.1831	3.08E-05	Childhood trauma, 0-17 years
<i>cg05259836</i>	chr6	74290516		OpenSea	-1.379	0.3314	3.14E-05	Childhood trauma, 0-17 years
<i>cg02324227</i>	chr5	180591594		OpenSea	1.71	0.4112	3.2E-05	Childhood trauma, 0-17 years
<i>cg09043104</i>	chr8	117128288		OpenSea	-1.988	0.4794	3.39E-05	Childhood trauma, 0-17 years
<i>cg18343437</i>	chr8	142528415		Island	0.6246	0.1511	3.55E-05	Childhood trauma, 0-17 years
<i>cg23242341</i>	chr11	66113666	BRMS1; B3GNT1	N_Shore	-1.047	0.2532	3.57E-05	Childhood trauma, 0-17 years
<i>cg19414967</i>	chr8	49468296		N_Shore	1.487	0.3598	3.58E-05	Childhood trauma, 0-17 years
<i>cg23018689</i>	chr1	159173540	DARC	OpenSea	-1.728	0.4191	3.76E-05	Childhood trauma, 0-17 years
<i>cg03748603</i>	chr19	2494443		Island	-0.7823	0.1899	3.79E-05	Childhood trauma, 0-17 years
<i>cg13561817</i>	chr17	3213102	OR3A4	OpenSea	-0.9209	0.2239	3.91E-05	Childhood trauma, 0-17 years
<i>cg19052355</i>	chr2	237076306	GBX2	Island	1.492	0.3633	3.99E-05	Childhood trauma, 0-17 years
<i>cg03006175</i>	chr14	105412417	AHNAK2	OpenSea	-1.434	0.35	0.000042	Childhood trauma, 0-17 years
<i>cg04177395</i>	chr11	78496497	ODZ4	OpenSea	0.7618	0.1864	4.37E-05	Childhood trauma, 0-17 years
<i>cg09361493</i>	chr2	231715028		S_Shelf	-1.364	0.334	4.43E-05	Childhood trauma, 0-17 years
<i>cg19024989</i>	chr11	2024126		N_Shelf	-2.009	0.4921	4.46E-05	Childhood trauma, 0-17 years

cg17473656	chr4	190286944		S_Shore	-1.929	0.4741	4.73E-05	Childhood trauma, 0-17 years
cg18928900	chr6	170605493		Island	1.796	0.4417	4.77E-05	Childhood trauma, 0-17 years
cg25644556	chr7	27209582	MIR196B	Island	0.7151	0.1762	4.96E-05	Childhood trauma, 0-17 years
cg10529789	chr17	37009658	SNORA21; RPL23	Island	-2.584	0.5494	2.56E-06	Early trauma, 5-10 years
cg14672994	chr17	48503057	ACSF2	Island	-1.62	0.3475	3.15E-06	Early trauma, 5-10 years
cg11182518	chr5	55117965		Island	0.8363	0.1809	3.79E-06	Early trauma, 5-10 years
cg26428054	chr12	49484058	DHH	Island	-2.823	0.6146	4.34E-06	Early trauma, 5-10 years
cg02324227	chr5	180591594		OpenSea	1.863	0.4066	4.58E-06	Early trauma, 5-10 years
cg01312828	chr6	41648365		N_Shelf	-1.224	0.2722	6.91E-06	Early trauma, 5-10 years
cg25618765	chr22	20670922		N_Shelf	-1.486	0.3335	8.39E-06	Early trauma, 5-10 years
cg07942847	chr14	23420757	HAUS4	OpenSea	2.3	0.5248	1.17E-05	Early trauma, 5-10 years
cg08791347	chr10	13831250	FRMD4A	OpenSea	1.13	0.2578	1.17E-05	Early trauma, 5-10 years
cg18343437	chr8	142528415		Island	0.6515	0.1493	1.27E-05	Early trauma, 5-10 years
cg01996004	chr5	180338435	BTNL8	OpenSea	-1.076	0.2468	1.32E-05	Early trauma, 5-10 years
cg14663914	chr19	827739	AZU1	OpenSea	-1.922	0.4436	1.47E-05	Early trauma, 5-10 years
cg27524192	chr1	228773464		Island	-1.429	0.33	1.5E-05	Early trauma, 5-10 years
cg14010194	chr6	42152817	GUCA1B	OpenSea	-1.221	0.2822	1.5E-05	Early trauma, 5-10 years
cg25644556	chr7	27209582	MIR196B	Island	0.7503	0.1735	1.53E-05	Early trauma, 5-10 years
cg10755512	chr3	44666543	ZNF197	Island	2.066	0.4792	1.62E-05	Early trauma, 5-10 years
cg05814106	chr1	2224791	SKI	S_Shelf	-1.022	0.2406	2.15E-05	Early trauma, 5-10 years
cg18345219	chr1	43919084	HYI	Island	1.808	0.4268	2.29E-05	Early trauma, 5-10 years
cg21889703	chr6	136607649	BCLAF1	N_Shelf	-1.962	0.4647	2.43E-05	Early trauma, 5-10 years
cg05640294	chr19	38976794	RYR1	Island	-1.487	0.3532	2.53E-05	Early trauma, 5-10 years
cg03315940	chr6	27569167		OpenSea	-1.517	0.3603	2.55E-05	Early trauma, 5-10 years
cg18928900	chr6	170605493		Island	1.857	0.4425	2.7E-05	Early trauma, 5-10 years
cg05295015	chr14	38069001		Island	1.85	0.4416	2.81E-05	Early trauma, 5-10 years
cg20799816	chr18	21594185	TTC39C	Island	-1.941	0.4643	2.92E-05	Early trauma, 5-10 years
cg25616869	chr3	48443867		OpenSea	-2.005	0.4807	3.03E-05	Early trauma, 5-10 years
cg19013753	chr15	75915192	SNUPN	N_Shelf	1.381	0.3315	3.09E-05	Early trauma, 5-10 years

cg07992052	chr20	35402295	DSN1	Island	-1.689	0.4053	3.1E-05	Early trauma, 5-10 years
cg24157392	chr3	112217973	BTLA	OpenSea	1.853	0.4449	3.12E-05	Early trauma, 5-10 years
cg19754901	chr3	87102643		S_Shore	-1.356	0.3257	3.14E-05	Early trauma, 5-10 years
cg21964551	chr1	201368791	LAD1	Island	0.991	0.2382	3.17E-05	Early trauma, 5-10 years
cg25975856	chr3	19930780	EFHB	OpenSea	-0.4143	0.0997	3.25E-05	Early trauma, 5-10 years
cg03769992	chr10	50010141	WDFY4	OpenSea	1.981	0.4769	3.27E-05	Early trauma, 5-10 years
cg04177395	chr11	78496497	ODZ4	OpenSea	0.7636	0.1841	3.35E-05	Early trauma, 5-10 years
cg05259836	chr6	74290516		OpenSea	-1.376	0.3321	3.41E-05	Early trauma, 5-10 years
cg08201736	chr15	79298769	RASGRF1	OpenSea	1.454	0.3538	3.98E-05	Early trauma, 5-10 years
cg09859179	chr2	58655104		OpenSea	1.644	0.4004	4.01E-05	Early trauma, 5-10 years
cg09573795	chr4	4863874	MSX1	N_Shore	-0.9278	0.2264	4.16E-05	Early trauma, 5-10 years
cg17403875	chr14	55596356	LGALS3	Island	-2.333	0.5696	4.19E-05	Early trauma, 5-10 years
cg16791444	chr17	71702669		OpenSea	-1.263	0.3082	4.19E-05	Early trauma, 5-10 years
cg16328610	chr6	83777335	DOPEY1	Island	-1.993	0.4868	4.25E-05	Early trauma, 5-10 years
cg01581763	chr7	13821699		OpenSea	-1.463	0.3578	4.33E-05	Early trauma, 5-10 years
cg05533329	chr7	143039088	CLCN1	N_Shelf	-1.299	0.3181	4.42E-05	Early trauma, 5-10 years
cg23041896	chr8	144462235	RHPN1	Island	-0.7421	0.1818	4.48E-05	Early trauma, 5-10 years
cg26778516	chr4	8646016		Island	-1.039	0.2547	4.52E-05	Early trauma, 5-10 years
cg07417857	chr8	652403	ERICH1	S_Shore	-0.9627	0.2369	4.83E-05	Early trauma, 5-10 years
cg26428054	chr12	49484058	DHH	Island	-3.425	0.6525	1.54E-07	Late trauma, 11-17 years
cg10529789	chr17	37009658	SNORA21; RPL23	Island	-2.898	0.5719	4.05E-07	Late trauma, 11-17 years
cg11182518	chr5	55117965		Island	0.9253	0.1883	8.98E-07	Late trauma, 11-17 years
cg19013753	chr15	75915192	SNUPN	N_Shelf	1.756	0.376	3.01E-06	Late trauma, 11-17 years
cg19754901	chr3	87102643		S_Shore	-1.611	0.3475	3.53E-06	Late trauma, 11-17 years
cg07992052	chr20	35402295	DSN1	Island	-1.89	0.4093	3.9E-06	Late trauma, 11-17 years
cg21889703	chr6	136607649	BCLAF1	N_Shelf	-2.281	0.4967	4.39E-06	Late trauma, 11-17 years
cg08201736	chr15	79298769	RASGRF1	OpenSea	1.708	0.374	4.97E-06	Late trauma, 11-17 years
cg24157392	chr3	112217973	BTLA	OpenSea	2.151	0.4734	5.52E-06	Late trauma, 11-17 years
cg18848419	chr18	11850153	CHMP1B; GNAL	N_Shore	0.8026	0.1791	7.43E-06	Late trauma, 11-17 years

cg05640294	chr19	38976794	RYR1	Island	-1.621	0.3629	7.88E-06	Late trauma, 11-17 years
cg18928900	chr6	170605493		Island	2.061	0.4638	8.82E-06	Late trauma, 11-17 years
cg10755512	chr3	44666543	ZNF197	Island	2.192	0.4943	9.26E-06	Late trauma, 11-17 years
cg09686317	chr1	57111122	PRKAA2	Island	0.8533	0.194	1.09E-05	Late trauma, 11-17 years
cg08362273	chr17	46719577		Island	1.399	0.319	1.16E-05	Late trauma, 11-17 years
cg03315940	chr6	27569167		OpenSea	-1.605	0.3675	1.27E-05	Late trauma, 11-17 years
cg14663914	chr19	827739	AZU1	OpenSea	-2.086	0.4786	1.31E-05	Late trauma, 11-17 years
cg05814106	chr1	2224791	SKI	S_Shelf	-1.1	0.2528	1.36E-05	Late trauma, 11-17 years
cg14272822	chr9	98279166	PTCH1	Island	2.611	0.6005	1.38E-05	Late trauma, 11-17 years
cg16791444	chr17	71702669		OpenSea	-1.384	0.319	1.43E-05	Late trauma, 11-17 years
cg02324227	chr5	180591594		OpenSea	1.841	0.4261	1.55E-05	Late trauma, 11-17 years
cg03748603	chr19	2494443		Island	-0.8501	0.1982	0.000018	Late trauma, 11-17 years
cg08791347	chr10	13831250	FRMD4A	OpenSea	1.157	0.27	1.83E-05	Late trauma, 11-17 years
cg15542924	chr6	163959346	QKI	OpenSea	-0.7093	0.1657	1.86E-05	Late trauma, 11-17 years
cg07942847	chr14	23420757	HAUS4	OpenSea	2.344	0.5485	1.92E-05	Late trauma, 11-17 years
cg08528970	chr4	76640579		OpenSea	-1.41	0.33	1.93E-05	Late trauma, 11-17 years
cg01996004	chr5	180338435	BTNL8	OpenSea	-1.073	0.2518	2.03E-05	Late trauma, 11-17 years
cg14841628	chr1	16258280	SPEN	N_Shelf	-1.484	0.3497	2.2E-05	Late trauma, 11-17 years
cg10953498	chr11	208469	RIC8A; BET1L	Island	1.728	0.4074	2.23E-05	Late trauma, 11-17 years
cg06381135	chr10	134505548	INPP5A	Island	-1.004	0.2381	2.47E-05	Late trauma, 11-17 years
cg25618765	chr22	20670922		N_Shelf	-1.506	0.3574	2.5E-05	Late trauma, 11-17 years
cg25616869	chr3	48443867		OpenSea	-2.122	0.5035	2.51E-05	Late trauma, 11-17 years
cg13895765	chr2	66803345		Island	1.063	0.2531	2.67E-05	Late trauma, 11-17 years
cg22936975	chr13	61989412	PCDH20	OpenSea	1.731	0.4125	2.7E-05	Late trauma, 11-17 years
cg05771369	chr12	58021713	B4GALNT1	Island	0.6782	0.1617	2.75E-05	Late trauma, 11-17 years
cg16257434	chr17	73571444		S_Shelf	-0.9512	0.2269	2.76E-05	Late trauma, 11-17 years
cg11597902	chr17	75096239		OpenSea	-0.7871	0.1889	3.1E-05	Late trauma, 11-17 years
cg19052355	chr2	237076306	GBX2	Island	1.597	0.3837	3.14E-05	Late trauma, 11-17 years
cg08032924	chr16	66613096	CMTM2	Island	0.5852	0.1407	3.21E-05	Late trauma, 11-17 years

cg21041594	chr7	65235699		Island	1.617	0.3891	3.26E-05	Late trauma, 11-17 years
cg24694691	chr1	111927153	LOC441897	OpenSea	-1.558	0.3755	3.36E-05	Late trauma, 11-17 years
cg10143823	chr14	28192481		OpenSea	2.142	0.5169	0.000034	Late trauma, 11-17 years
cg26195482	chr14	104551553	ASPG	N_Shore	1.544	0.373	3.48E-05	Late trauma, 11-17 years
cg05232857	chr6	33867321		OpenSea	1.468	0.3548	3.5E-05	Late trauma, 11-17 years
cg02675083	chr1	16972917	MST1P2	N_Shore	-2.158	0.5218	3.53E-05	Late trauma, 11-17 years
cg22827724	chr6	31096189	PSORS1C1	OpenSea	-1.085	0.263	3.7E-05	Late trauma, 11-17 years
cg23041896	chr8	144462235	RHPN1	Island	-0.773	0.1875	3.73E-05	Late trauma, 11-17 years
cg18343437	chr8	142528415		Island	0.649	0.158	4.01E-05	Late trauma, 11-17 years
cg07560534	chr9	100745354	ANP32B	Island	-2.175	0.531	4.2E-05	Late trauma, 11-17 years
cg01312828	chr6	41648365		N_Shelf	-1.132	0.2778	4.59E-05	Late trauma, 11-17 years
cg08104283	chr13	113676829	MCF2L	Island	-0.9143	0.2247	4.73E-05	Late trauma, 11-17 years
cg00938816	chr17	8058149		N_Shore	-2.03	0.4992	4.77E-05	Late trauma, 11-17 years
cg04177395	chr11	78496497	ODZ4	OpenSea	0.7883	0.1939	4.78E-05	Late trauma, 11-17 years
cg17403875	chr14	55596356	LGALS3	Island	-2.37	0.5831	4.79E-05	Late trauma, 11-17 years
cg26428054	chr12	49484058	DHH	Island	-3.23	0.6249	2.36E-07	Abuse only, 0-17 years
cg10529789	chr17	37009658	SNORA21; RPL23	Island	-2.726	0.5501	7.2E-07	Abuse only, 0-17 years
cg24157392	chr3	112217973	BTLA	OpenSea	2.249	0.4563	8.29E-07	Abuse only, 0-17 years
cg14663914	chr19	827739	AZU1	OpenSea	-2.215	0.456	1.2E-06	Abuse only, 0-17 years
cg08528970	chr4	76640579		OpenSea	-1.463	0.3148	3.37E-06	Abuse only, 0-17 years
cg11182518	chr5	55117965		Island	0.845	0.1821	3.49E-06	Abuse only, 0-17 years
cg07992052	chr20	35402295	DSN1	Island	-1.861	0.4059	4.57E-06	Abuse only, 0-17 years
cg25618765	chr22	20670922		N_Shelf	-1.552	0.3404	5.11E-06	Abuse only, 0-17 years
cg14672994	chr17	48503057	ACSF2	Island	-1.547	0.3394	5.18E-06	Abuse only, 0-17 years
cg05640294	chr19	38976794	RYS1	Island	-1.572	0.3514	7.64E-06	Abuse only, 0-17 years
cg21041594	chr7	65235699		Island	1.678	0.3776	8.84E-06	Abuse only, 0-17 years
cg21889703	chr6	136607649	BCLAF1	N_Shelf	-2.098	0.4738	9.49E-06	Abuse only, 0-17 years
cg10755512	chr3	44666543	ZNF197	Island	2.096	0.4747	1.02E-05	Abuse only, 0-17 years
cg19989295	chr14	24641077	REC8	Island	0.9588	0.2179	1.09E-05	Abuse only, 0-17 years

cg01312828	chr6	41648365		N_Shelf	-1.175	0.2681	1.18E-05	Abuse only, 0-17 years
cg19754901	chr3	87102643		S_Shore	-1.434	0.3281	1.23E-05	Abuse only, 0-17 years
cg19013753	chr15	75915192	SNUPN	N_Shelf	1.56	0.3576	1.29E-05	Abuse only, 0-17 years
cg08201736	chr15	79298769	RASGRF1	OpenSea	1.548	0.3556	1.35E-05	Abuse only, 0-17 years
cg03315940	chr6	27569167		OpenSea	-1.539	0.355	1.45E-05	Abuse only, 0-17 years
cg17276036	chr4	26492222	CCKAR	OpenSea	1.787	0.4141	1.6E-05	Abuse only, 0-17 years
cg10632722	chr6	49833873	CRISP1	OpenSea	-1.712	0.3974	1.66E-05	Abuse only, 0-17 years
cg14010194	chr6	42152817	GUCA1B	OpenSea	-1.203	0.2795	1.66E-05	Abuse only, 0-17 years
cg16328610	chr6	83777335	DOPEY1	Island	-2.12	0.4933	1.73E-05	Abuse only, 0-17 years
cg27524192	chr1	228773464		Island	-1.476	0.3452	1.9E-05	Abuse only, 0-17 years
cg07942847	chr14	23420757	HAUS4	OpenSea	2.269	0.5327	2.06E-05	Abuse only, 0-17 years
cg10251328	chr17	47074713	IGF2BP1	Island	-2.454	0.5798	2.32E-05	Abuse only, 0-17 years
cg16791444	chr17	71702669		OpenSea	-1.281	0.3042	2.55E-05	Abuse only, 0-17 years
cg00980622	chr14	75884845		OpenSea	-1.226	0.2916	2.62E-05	Abuse only, 0-17 years
cg22936975	chr13	61989412	PCDH20	OpenSea	1.659	0.3954	2.73E-05	Abuse only, 0-17 years
cg16588073	chr1	156647247	NES	Island	-1.117	0.2664	2.75E-05	Abuse only, 0-17 years
cg23041896	chr8	144462235	RHPN1	Island	-0.748	0.1785	2.79E-05	Abuse only, 0-17 years
cg00464520	chr10	118903060		S_Shelf	-1.08	0.2588	3.02E-05	Abuse only, 0-17 years
cg08362273	chr17	46719577		Island	1.263	0.3031	3.07E-05	Abuse only, 0-17 years
cg05771369	chr12	58021713	B4GALNT1	Island	0.6425	0.1542	3.11E-05	Abuse only, 0-17 years
cg10953498	chr11	208469	RIC8A; BET1L	Island	1.64	0.3939	3.12E-05	Abuse only, 0-17 years
cg02324227	chr5	180591594		OpenSea	1.679	0.4046	3.34E-05	Abuse only, 0-17 years
cg05814106	chr1	2224791	SKI	S_Shelf	-0.9831	0.237	3.34E-05	Abuse only, 0-17 years
cg01996004	chr5	180338435	BTNL8	OpenSea	-0.9993	0.2413	3.46E-05	Abuse only, 0-17 years
cg18343437	chr8	142528415		Island	0.6133	0.1487	3.71E-05	Abuse only, 0-17 years
cg09859179	chr2	58655104		OpenSea	1.624	0.3949	3.91E-05	Abuse only, 0-17 years
cg05259836	chr6	74290516		OpenSea	-1.35	0.3284	3.93E-05	Abuse only, 0-17 years
cg19631585	chr1	228773514		Island	-1.809	0.4402	3.98E-05	Abuse only, 0-17 years
cg25644556	chr7	27209582	MIR196B	Island	0.7195	0.1752	4E-05	Abuse only, 0-17 years

<i>cg23018689</i>	chr1	159173540	DARC	OpenSea	-1.686	0.4109	4.07E-05	Abuse only, 0-17 years
<i>cg17403875</i>	chr14	55596356	LGALS3	Island	-2.306	0.5626	4.14E-05	Abuse only, 0-17 years
<i>cg19414967</i>	chr8	49468296		N_Shore	1.445	0.3534	4.3E-05	Abuse only, 0-17 years
<i>cg07631533</i>	chr16	13135565	SHISA9	OpenSea	1.363	0.3333	4.32E-05	Abuse only, 0-17 years
<i>cg05899741</i>	chr4	43901084		OpenSea	-1.625	0.3979	4.43E-05	Abuse only, 0-17 years
<i>cg16257434</i>	chr17	73571444		S_Shelf	-0.8814	0.2163	4.62E-05	Abuse only, 0-17 years
<i>cg19024989</i>	chr11	2024126		N_Shelf	-1.999	0.4921	4.84E-05	Abuse only, 0-17 years
<i>cg14855877</i>	chr17	12905834	ELAC2	OpenSea	-0.9195	0.2264	4.88E-05	Abuse only, 0-17 years
<i>cg02675083</i>	chr1	16972917	MST1P2	N_Shore	-2.03	0.5003	4.98E-05	Abuse only, 0-17 years

Genomic locations are reported according to the hg19 reference genome. Gene annotation and CpG island context correspond to the Illumina HumanMethylation450 array annotation.

5. Differentially methylated regions (DMR) analyses

Region-based analyses were conducted using DMRff for Path A and Path B across the four trauma definitions. Summary counts, top-ranked DMRs, and combined Manhattan-style region plots are reported below.

Table S4. Top differentially methylated regions associated with trauma exposure (Path A)

Exposure	Chromosome	Start (bp)	End (bp)	Region width (bp)	CpG sites	Gene(s)	Min CpG p-value	Region p-value	FDR (BH)
Abuse-only trauma, 0-17 years	chr6	30684837	30684905	69	4	MDC	8.1299×10^{-3}	9.1255×10^{-10}	4.3741×10^{-4}
Abuse-only trauma, 0-17 years	chr6	32164382	32164442	61	3	GPSM3; NOTCH4	8.5127×10^{-5}	7.8008×10^{-8}	0.0374
Early trauma, 5-10 years	chrX	21676344	21676593	250	4	KLHL34	2.5618×10^{-3}	6.9087×10^{-18}	3.3345×10^{-12}
Early trauma, 5-10 years	chr6	31940004	31940782	779	32	DOM3Z STK19	8.2127×10^{-3}	4.6250×10^{-13}	2.2323×10^{-7}
Early trauma, 5-10 years	chr6	31707202	31707922	721	24	MSH5	4.7171×10^{-3}	4.7856×10^{-11}	2.3098×10^{-5}
Early trauma, 5-10 years	chr1	53704012	53704033	22	2	MAGOH	1.9450×10^{-3}	1.0884×10^{-9}	5.2533×10^{-4}
Early trauma, 5-10 years	chrX	148586931	148587019	89	7	IDS	0.0195	2.8571×10^{-9}	1.3790×10^{-3}
Late trauma, 11-17 years	chr20	45338083	45338396	314	5	SLC2A10	3.7571×10^{-3}	9.9868×10^{-10}	4.7464×10^{-4}
Late trauma, 11-17 years	chrX	47483024	47483268	245	4	NA	0.0383	1.3340×10^{-8}	6.3400×10^{-3}
Childhood trauma, 0-17 years	chr19	39926698	39926862	165	5	RPS16	0.0181	5.3692×10^{-12}	2.5519×10^{-6}

Table S5. Top differentially methylated regions associated with psychotic-like experiences (Path B)

Exposure	Chromosome	Start (bp)	End (bp)	Region width (bp)	CpG sites	Gene(s)	Min CpG p-value	Region p-value	FDR (BH)
Abuse-only trauma, 0-17 years	chrX	107334809	107334922	114	3	PSMD10; ATG4A	0.0146	5.6115×10^{-11}	2.7500×10^{-5}
Abuse-only trauma, 0-17 years	chr6	153323975	153324001	27	3	MTRF1L	3.3860×10^{-3}	1.3651×10^{-10}	6.6897×10^{-5}
Abuse-only trauma, 0-17 years	chrX	70288026	70288358	333	7	SNX12	7.6132×10^{-3}	3.1251×10^{-9}	1.5315×10^{-3}
Abuse-only trauma, 0-17 years	chr3	14165888	14166327	440	3	TMEM43; CHCHD4	7.8953×10^{-4}	4.3659×10^{-8}	0.0214
Abuse-only trauma, 0-17 years	chr2	10953115	10953237	123	2	PDIA6	7.1233×10^{-4}	5.7080×10^{-8}	0.0280
Early trauma, 5-10 years	chr6	31865886	31866072	187	11	EHMT2	0.0127	2.0333×10^{-12}	9.8966×10^{-7}
Early trauma, 5-10 years	chr6	32940303	32940921	619	24	BRD2	0.0237	4.8506×10^{-10}	2.3609×10^{-4}

<i>Early trauma, 5-10 years</i>	chr6	137242316	137243249	934	4	SLC35D3	1.1282×10^{-3}	1.8288×10^{-9}	8.9014×10^{-4}
<i>Early trauma, 5-10 years</i>	chr6	153323975	153324006	32	4	MTRF1L	5.0232×10^{-3}	2.2619×10^{-9}	1.1010×10^{-3}
<i>Early trauma, 5-10 years</i>	chrX	18372612	18372696	85	2	SCML2	1.0838×10^{-3}	8.3810×10^{-9}	4.0793×10^{-3}
<i>Early trauma, 5-10 years</i>	chrX	40017092	40017469	378	3	BCOR	8.0103×10^{-3}	1.4260×10^{-8}	6.9409×10^{-3}
<i>Early trauma, 5-10 years</i>	chrX	107334809	107334815	7	2	PSMD10; ATG4A	0.0251	7.6590×10^{-8}	0.0373
<i>Late trauma, 11-17 years</i>	chr6	31865886	31866072	187	11	EHMT2	9.3044×10^{-3}	1.2309×10^{-14}	6.0354×10^{-9}
<i>Late trauma, 11-17 years</i>	chr6	30312939	30313380	442	18	RPP21	0.0209	7.6970×10^{-12}	3.7740×10^{-6}
<i>Late trauma, 11-17 years</i>	chr6	153323975	153324006	32	4	MTRF1L	1.1272×10^{-3}	5.8264×10^{-11}	2.8568×10^{-5}
<i>Late trauma, 11-17 years</i>	chr6	137242316	137243249	934	4	SLC35D3	2.1558×10^{-3}	1.0586×10^{-10}	5.1907×10^{-5}
<i>Late trauma, 11-17 years</i>	chrX	107334809	107334922	114	3	PSMD10; ATG4A	7.6447×10^{-3}	1.3799×10^{-9}	6.7660×10^{-4}
<i>Late trauma, 11-17 years</i>	chr8	23261738	23261967	230	3	LOXL2	0.0191	2.3098×10^{-9}	1.1326×10^{-3}
<i>Late trauma, 11-17 years</i>	chrX	40017092	40017469	378	3	BCOR	8.3317×10^{-3}	2.8853×10^{-8}	0.0141
<i>Late trauma, 11-17 years</i>	chr19	1479426	1480049	624	6	C19orf25	1.2018×10^{-3}	4.5483×10^{-8}	0.0223
<i>Late trauma, 11-17 years</i>	chr18	56940418	56940463	46	2	RAX	0.0104	5.2549×10^{-8}	0.0258
<i>Late trauma, 11-17 years</i>	chr2	10953115	10953237	123	2	PDIA6	4.4700×10^{-4}	5.7636×10^{-8}	0.0283
<i>Childhood trauma, 0-17 years</i>	chrX	128977498	128977653	156	3	ZDHHC9	7.0079×10^{-4}	7.2166×10^{-13}	3.5348×10^{-7}
<i>Childhood trauma, 0-17 years</i>	chr6	153323975	153324006	32	4	MTRF1L	1.7837×10^{-3}	1.3961×10^{-11}	6.8385×10^{-6}
<i>Childhood trauma, 0-17 years</i>	chrX	68047833	68048015	183	8	EFNB1	6.2569×10^{-3}	1.0970×10^{-9}	5.3731×10^{-4}
<i>Childhood trauma, 0-17 years</i>	chrX	107334809	107334922	114	3	PSMD10; ATG4A	0.0194	3.3438×10^{-9}	1.6378×10^{-3}
<i>Childhood trauma, 0-17 years</i>	chrX	70288026	70288358	333	7	SNX12	0.0105	6.4332×10^{-9}	3.1511×10^{-3}
<i>Childhood trauma, 0-17 years</i>	chr3	14165888	14166327	440	3	TMEM43; CHCHD4	5.7382×10^{-4}	2.4420×10^{-8}	0.0120
<i>Childhood trauma, 0-17 years</i>	chr2	10953115	10953237	123	2	PDIA6	8.5185×10^{-4}	5.1603×10^{-8}	0.0253

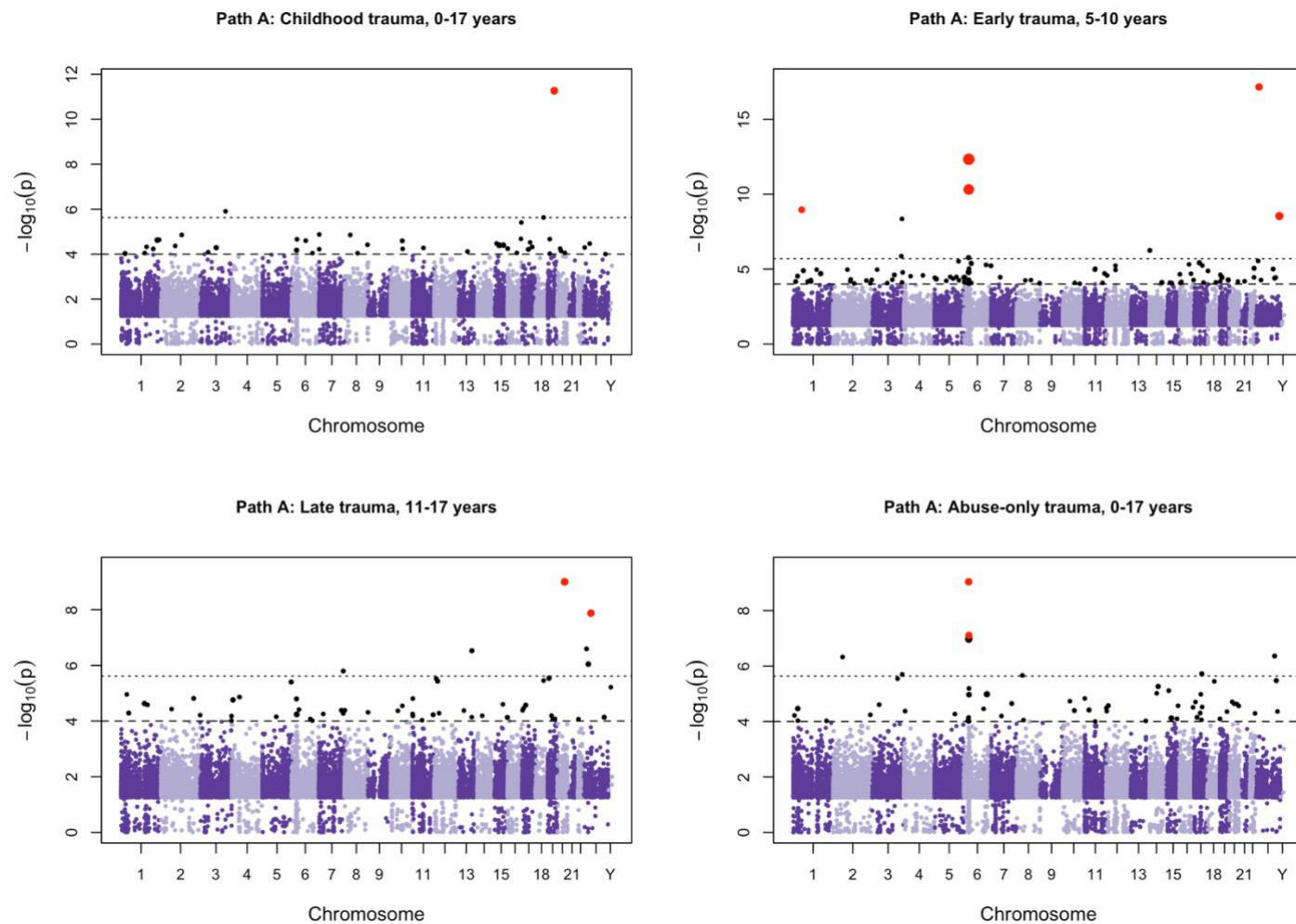


Figure S4. Differentially methylated region (DMR) analyses for Path A.

Manhattan-style plots of DMRff results for four trauma exposures. Each point represents regions plotted by genomic position and the $-\log_{10}$ -transformed region p-value. The horizontal dashed line indicates the Bonferroni-corrected significance threshold and a suggestive discovery threshold ($p < 1 \times 10^{-4}$).

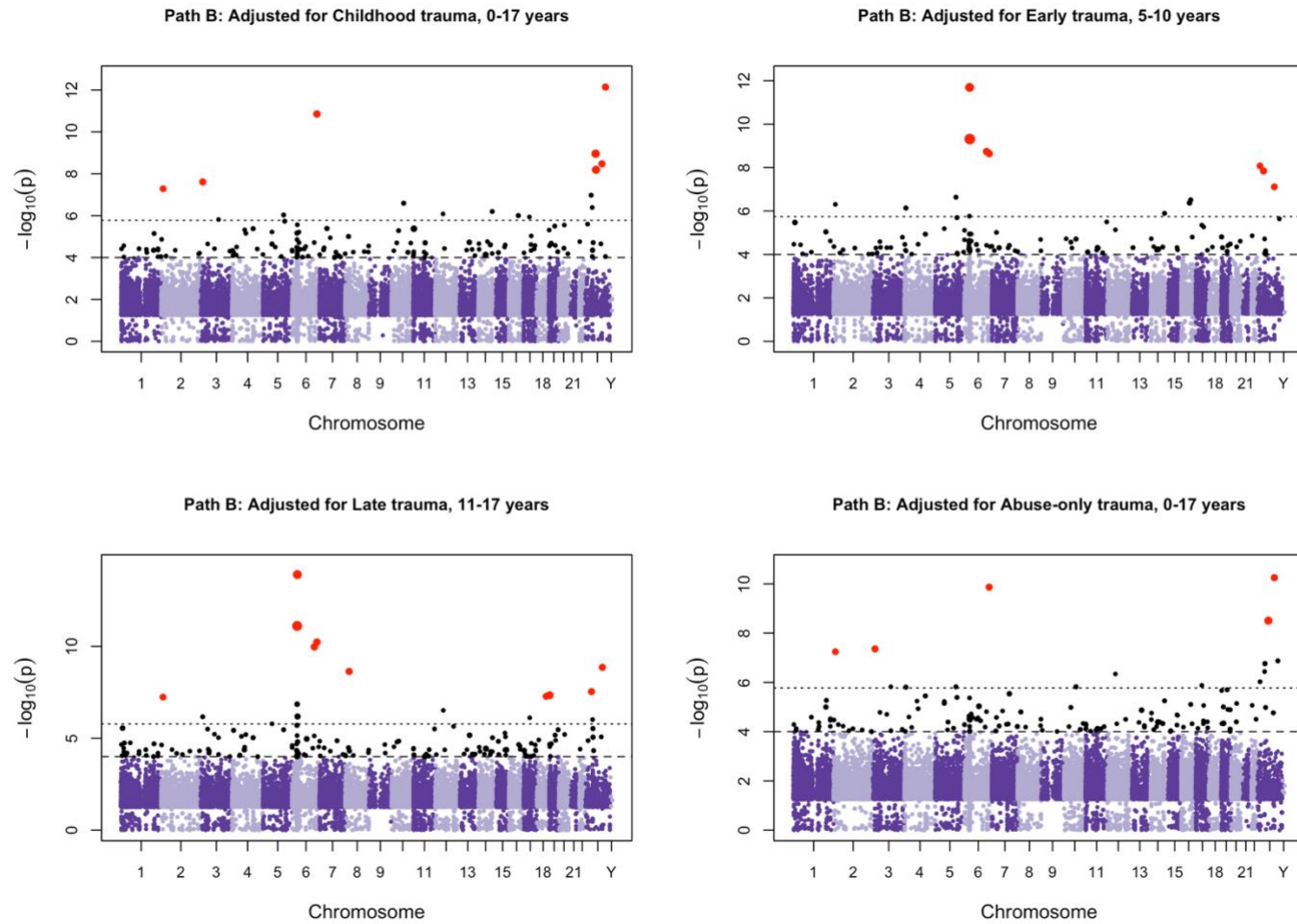


Figure S5. Differentially methylated region (DMR) analyses for Path B.

Manhattan-style plots of DMRff results for four trauma exposures. Each point represents regions plotted by genomic position and the $-\log_{10}$ -transformed region p-value. The horizontal dashed line indicates the Bonferroni-corrected significance threshold and a suggestive discovery threshold ($p < 1 \times 10^{-4}$).

6. Functional Enrichment Analyses

Table S6. Gene Ontology and KEGG pathway enrichment results for genes annotated to DMRs - Path A

Exposure	Database	Ontology	Description	N	DE	P.DE	FDR
Abuse-only trauma, 0-17 years	GO	BP	response to stress	3872	3	0.0101	1
Abuse-only trauma, 0-17 years	GO	BP	positive regulation of macromolecule metabolic process	3480	3	0.0143	1
Abuse-only trauma, 0-17 years	GO	BP	positive regulation of metabolic process	3786	3	0.0182	1
Abuse-only trauma, 0-17 years	GO	BP	regulation of gene expression	4952	3	0.0273	1
Abuse-only trauma, 0-17 years	GO	BP	positive regulation of transcription by RNA polymerase II	1208	2	0.0294	1
Abuse-only trauma, 0-17 years	GO	BP	gene expression	6365	3	0.0376	1
Abuse-only trauma, 0-17 years	GO	BP	positive regulation of DNA-templated transcription	1651	2	0.0486	1
Abuse-only trauma, 0-17 years	GO	BP	positive regulation of nucleic acid-templated transcription	1651	2	0.0486	1
Early childhood trauma, 5-10 years	GO	BP	nuclear-transcribed mRNA catabolic process	125	2	7.88E-04	1
Early childhood trauma, 5-10 years	GO	BP	mRNA catabolic process	261	2	0.00302	1
Early childhood trauma, 5-10 years	GO	BP	cellular macromolecule catabolic process	1018	3	0.00384	1
Early childhood trauma, 5-10 years	GO	BP	RNA catabolic process	312	2	0.0042	1
Early childhood trauma, 5-10 years	GO	BP	nucleobase-containing compound catabolic process	439	2	0.00766	1
Early childhood trauma, 5-10 years	GO	BP	cellular nitrogen compound catabolic process	478	2	0.00845	1
Early childhood trauma, 5-10 years	GO	BP	heterocycle catabolic process	480	2	0.00877	1
Early childhood trauma, 5-10 years	GO	BP	aromatic compound catabolic process	497	2	0.00916	1

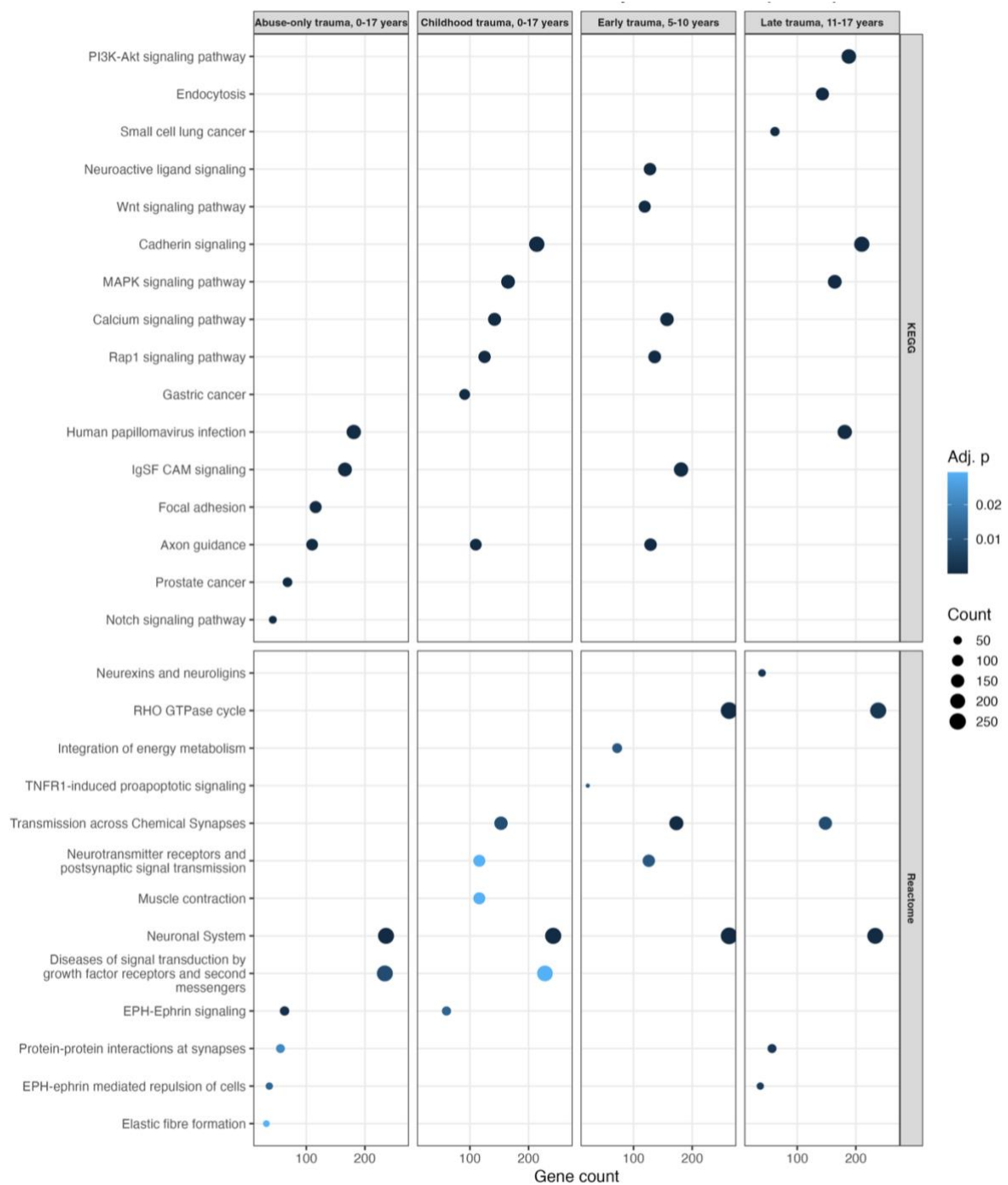


Figure S6. Functional enrichment of trauma-DMRs in Path A.

Dot plots showing the top enriched KEGG and Reactome pathways for genes mapped to DMRs identified in Path A models across the four trauma definitions. Dot sizes represent gene count and colour indicates adjusted p-value.

Table S7. *Gene Ontology and KEGG pathway enrichment results for genes annotated to DMRs - Path B*

Exposure	Database	Ontology	Description	N	DE	P.DE	FDR
Abuse-only trauma, 0-17 years	GO	MF	protein-disulfide reductase activity	34	2	7.64E-05	1
Abuse-only trauma, 0-17 years	GO	MF	disulfide oxidoreductase activity	39	2	1.05E-04	1
Abuse-only trauma, 0-17 years	GO	MF	oxidoreductase activity, acting on a sulfur group of donors	54	2	2.02E-04	1
Abuse-only trauma, 0-17 years	GO	BP	protein folding	209	2	0.00277	1
Abuse-only trauma, 0-17 years	GO	CC	endoplasmic reticulum lumen	309	2	0.00439	1
Abuse-only trauma, 0-17 years	GO	BP	protein localization	2432	4	0.00547	1
Abuse-only trauma, 0-17 years	GO	BP	cellular macromolecule localization	2442	4	0.00554	1
Abuse-only trauma, 0-17 years	GO	BP	protein maturation	327	2	0.00557	1
Early childhood trauma, 5-10 years	GO	BP	regulation of histone methylation	57	2	3.33E-04	1
Early childhood trauma, 5-10 years	GO	BP	histone lysine methylation	103	2	9.97E-04	1
Early childhood trauma, 5-10 years	GO	BP	peptidyl-lysine methylation	121	2	0.00127	1
Early childhood trauma, 5-10 years	GO	BP	histone methylation	132	2	0.00155	1
Early childhood trauma, 5-10 years	GO	BP	regulation of histone modification	141	2	0.00176	1
Early childhood trauma, 5-10 years	GO	BP	chromatin organization	631	3	0.00198	1
Early childhood trauma, 5-10 years	GO	MF	transcription factor binding	593	3	0.00205	1
Early childhood trauma, 5-10 years	GO	BP	protein alkylation	179	2	0.00261	1
Early childhood trauma, 5-10 years	KEGG	KEGG	Polycarb repressive complex	82	2	7.82E-04	0.289
Adolescent trauma, 11-17 years	GO	BP	regulation of histone methylation	57	2	6.16E-04	1
Adolescent trauma, 11-17 years	GO	BP	peptidyl-lysine modification	369	3	0.00132	1
Adolescent trauma, 11-17 years	GO	BP	histone lysine methylation	103	2	0.00215	1
Adolescent trauma, 11-17 years	GO	BP	peptidyl-lysine methylation	121	2	0.00267	1
Adolescent trauma, 11-17 years	GO	BP	histone methylation	132	2	0.00311	1

Adolescent trauma, 11-17 years	GO	BP	negative regulation of transcription by RNA polymerase II	938	4	0.00324	1
Adolescent trauma, 11-17 years	GO	BP	regulation of histone modification	141	2	0.00393	1
Adolescent trauma, 11-17 years	GO	BP	protein alkylation	179	2	0.0052	1
Childhood trauma, 0-17 years	GO	MF	protein-disulfide reductase activity	34	2	1.28E-04	1
Childhood trauma, 0-17 years	GO	MF	disulfide oxidoreductase activity	39	2	1.73E-04	1
Childhood trauma, 0-17 years	GO	BP	peptidyl-cysteine modification	49	2	2.7E-04	1
Childhood trauma, 0-17 years	GO	MF	oxidoreductase activity, acting on a sulfur group of donors	54	2	3.37E-04	1
Childhood trauma, 0-17 years	GO	BP	protein localization	2432	5	0.00275	1
Childhood trauma, 0-17 years	GO	BP	cellular macromolecule localization	2442	5	0.00279	1
Childhood trauma, 0-17 years	GO	BP	localization within membrane	664	3	0.00302	1
Childhood trauma, 0-17 years	GO	BP	protein transport	1547	4	0.00409	1



Figure S7. Functional enrichment of PLEs-DMRs in Path B.

Dot plots showing the top enriched KEGG and Reactome pathways for genes mapped to DMRs identified in Path B models across the four trauma definitions. Dot sizes represent gene count and colour indicates adjusted p-value.

7. Cannabis interaction analyses

Interaction EWAS models examining moderation by frequency of cannabis use identified several CpG sites showing evidence of trauma x cannabis interaction effects (**Figure S9**). Differentially methylated region analyses identified candidate regions associated with interaction effects across multiple trauma measures (**Table S12**).

7.1. Model diagnostics

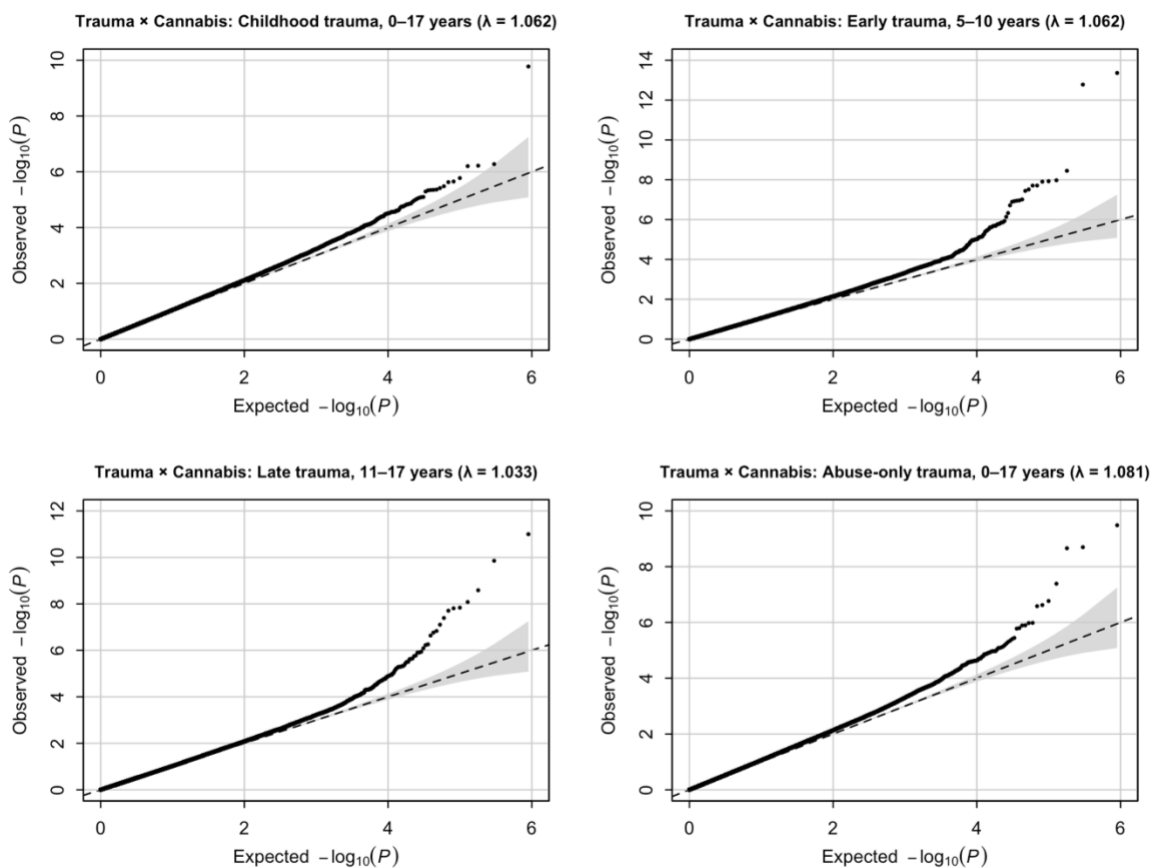


Figure S8. QQ plots for cannabis interaction analyses.

The dashed line indicates the null expectation and the shaded region the 95% confidence envelope. Genomic inflation factors (λ) are reported in each panel.

7.2. EWAS interaction results

Table S8. Top CpG sites showing suggestive evidence of interaction (cumulative childhood trauma)

CpG	Chromosome	Position (bp)	Gene(s)	Gene region	CpG island relation	Effect	SE	Statistic	P	FDR
cg20383084	chr1	26325121	PAFAH2	TSS1500	S_Shore	-0.1112	0.0173	-6.4391	1.68×10 ⁻¹⁰	7.52×10 ⁻⁰⁵
cg07840472	chr14	36278484	RALGAPA1	TSS200	Island	-0.0631	0.0125	-5.0404	5.29×10 ⁻⁰⁷	7.03×10 ⁻⁰²
cg08298794	chr2	1.98E+08			OpenSea	-0.1223	0.0244	-5.0146	6.03×10 ⁻⁰⁷	7.03×10 ⁻⁰²
cg26320410	chr3	9851826	TTLL3	TSS200	Island	0.0408	0.0082	5.0073	6.26×10 ⁻⁰⁷	7.03×10 ⁻⁰²
cg11722699	chr18	28622813	DSC3	TSS200	Island	0.0988	0.0205	4.81	1.68×10 ⁻⁰⁶	1.51×10 ⁻⁰¹
ch.X.258064R	chrX	16776121	SYAP1	Body	OpenSea	-0.1361	0.0286	-4.7521	2.23×10 ⁻⁰⁶	1.51×10 ⁻⁰¹
cg04039225	chr3	169629516	SAMD7	5'UTR; 1stExon	OpenSea	-0.0496	0.0105	-4.7411	2.36×10 ⁻⁰⁶	1.51×10 ⁻⁰¹
cg26343001	chr12	115104274			N_Shore	0.1113	0.0238	4.6708	3.31×10 ⁻⁰⁶	1.60×10 ⁻⁰¹
cg08197226	chr15	49658975	C15orf33	Body	OpenSea	0.0935	0.0202	4.6397	3.84×10 ⁻⁰⁶	1.60×10 ⁻⁰¹
cg08486065	chr19	3464875			Island	0.0607	0.0132	4.6135	4.34×10 ⁻⁰⁶	1.60×10 ⁻⁰¹
cg09035925	chr20	19915769	RIN2	Body	OpenSea	-0.095	0.0206	-4.6079	4.46×10 ⁻⁰⁶	1.60×10 ⁻⁰¹
cg18705408	chr2	20212524	MATN3	TSS200	Island	0.0798	0.0173	4.6056	4.51×10 ⁻⁰⁶	1.60×10 ⁻⁰¹
cg08511716	chr5	94621030	MCTP1	TSS1500	Island	0.0686	0.0149	4.5994	4.64×10 ⁻⁰⁶	1.60×10 ⁻⁰¹
cg24109894	chr1	36108212	PSMB2	TSS1500	S_Shore	-0.0832	0.0182	-4.5802	5.08×10 ⁻⁰⁶	1.63×10 ⁻⁰¹
cg07300574	chr12	132502636	EP400	Body	OpenSea	0.0706	0.0157	4.4835	7.98×10 ⁻⁰⁶	2.25×10 ⁻⁰¹
cg13041894	chr22	47609321			Island	-0.1316	0.0294	-4.4785	8.16×10 ⁻⁰⁶	2.25×10 ⁻⁰¹
cg24805759	chr17	77997760	TBC1D16	5'UTR	Island	0.1613	0.0361	4.4694	8.53×10 ⁻⁰⁶	2.25×10 ⁻⁰¹
cg06081306	chr17	37760830	NEUROD2	3'UTR	N_Shore	-0.0585	0.0131	-4.4547	9.11×10 ⁻⁰⁶	2.27×10 ⁻⁰¹
cg04050463	chr6	170602486			N_Shore	-0.0674	0.0152	-4.4366	9.92×10 ⁻⁰⁶	2.34×10 ⁻⁰¹
cg20163689	chr2	13088414			OpenSea	-0.0759	0.0172	-4.4186	1.07×10 ⁻⁰⁵	2.41×10 ⁻⁰¹
cg23239754	chr6	27760147			OpenSea	-0.0505	0.0115	-4.3965	1.19×10 ⁻⁰⁵	2.54×10 ⁻⁰¹
cg14252492	chr11	44332224	ALX4	TSS1500	N_Shore	-0.0829	0.019	-4.3661	1.36×10 ⁻⁰⁵	2.63×10 ⁻⁰¹
cg19103000	chr3	9851819	TTLL3	TSS200	Island	0.0375	0.0086	4.3614	1.39×10 ⁻⁰⁵	2.63×10 ⁻⁰¹
cg14602982	chr11	119599176	PVRL1	Body	Island	0.0475	0.0109	4.3509	1.46×10 ⁻⁰⁵	2.63×10 ⁻⁰¹
cg24701575	chr11	31845389			N_Shore	-0.1041	0.0239	-4.35	1.47×10 ⁻⁰⁵	2.63×10 ⁻⁰¹

cg13938035	chr9	116346435	RGS3	Body; 5'UTR	Island	-0.1121	0.0259	-4.3366	1.56×10 ⁻⁰⁵	2.69×10 ⁻⁰¹
cg23350274	chr14	68188663	RDH12	5'UTR	OpenSea	-0.0639	0.0148	-4.3254	1.64×10 ⁻⁰⁵	2.69×10 ⁻⁰¹
cg23687000	chr21	38071673	SIM2	TSS1500	Island	0.0756	0.0175	4.3117	1.74×10 ⁻⁰⁵	2.69×10 ⁻⁰¹
cg13299942	chr12	119798505	CCDC60	Body	OpenSea	-0.0314	0.0073	-4.3102	1.75×10 ⁻⁰⁵	2.69×10 ⁻⁰¹
cg23681730	chr11	35683551	TRIM44	TSS1500	N_Shore	-0.0986	0.0229	-4.3042	1.80×10 ⁻⁰⁵	2.69×10 ⁻⁰¹
cg09379485	chr19	53758297	ZNF677	TSS200	S_Shore	0.1075	0.0251	4.2859	1.95×10 ⁻⁰⁵	2.83×10 ⁻⁰¹
cg24818939	chrX	101906109	GPRASP1	TSS200	Island	0.0807	0.019	4.2534	2.25×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg21512185	chr2	39005322	GEMIN6	TSS200	OpenSea	0.0844	0.0199	4.2351	2.44×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg22090592	chr14	105174642	INF2	Body	OpenSea	0.0538	0.0127	4.2351	2.44×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg27441486	chr1	201708522	NAV1	TSS1500; Body	N_Shore	0.1043	0.0246	4.2337	2.46×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg17301223	chr8	145106438	OPLAH	Body	Island	-0.0542	0.0129	-4.2149	2.67×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg26101410	chr4	174451564	HAND2; NBLA00301	TSS200	N_Shore	-0.0842	0.02	-4.2119	2.70×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg00255699	chr1	40307257	TRIT1	3'UTR	OpenSea	-0.0661	0.0157	-4.212	2.70×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg02337166	chr17	38257303	NR1D1	TSS1500	S_Shore	-0.0532	0.0126	-4.2091	2.74×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg24946736	chr19	7542181	PEX11G	Body	Island	-0.0778	0.0185	-4.2085	2.74×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg02642223	chr17	38109030			OpenSea	-0.0356	0.0085	-4.206	2.77×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg02444695	chr6	148950185			OpenSea	-0.0627	0.0149	-4.1961	2.90×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg18500368	chr12	56509603	RPL41	TSS1500	N_Shelf	-0.0747	0.0178	-4.1893	2.98×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg20142390	chr21	40564147	BRWD1	3'UTR; Body	OpenSea	-0.0431	0.0103	-4.186	3.03×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg05736378	chr16	89283996	ZNF778	TSS200	Island	0.0476	0.0114	4.1807	3.10×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg13922935	chr15	42804870	SNAP23	Body	OpenSea	0.0462	0.011	4.1788	3.12×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg21123573	chr12	120740055	SIRT4	TSS200	OpenSea	-0.1158	0.0277	-4.1767	3.16×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg00013899	chr1	64992433	CACHD1	Body	OpenSea	0.0734	0.0176	4.1742	3.19×10 ⁻⁰⁵	2.98×10 ⁻⁰¹
cg09719477	chr11	113930430	ZBTB16	1stExon; TSS1500; 5'UTR	Island	0.0399	0.0096	4.1644	3.33×10 ⁻⁰⁵	3.01×10 ⁻⁰¹
cg01382502	chr16	22252504	EEF2K	Body	OpenSea	-0.1139	0.0274	-4.1628	3.35×10 ⁻⁰⁵	3.01×10 ⁻⁰¹
cg27514608	chr4	23892540	PPARGC1A	TSS1500	OpenSea	-0.0611	0.0147	-4.1485	3.56×10 ⁻⁰⁵	3.13×10 ⁻⁰¹
cg05923101	chr21	45876770	LRRC3	Body	Island	-0.097	0.0235	-4.1277	3.89×10 ⁻⁰⁵	3.24×10 ⁻⁰¹
cg07963147	chr3	141086820	ZBTB38	5'UTR	OpenSea	0.0941	0.0228	4.1271	3.90×10 ⁻⁰⁵	3.24×10 ⁻⁰¹
cg22524998	chr19	17877846	FCHO1	Body	S_Shore	0.0762	0.0185	4.1201	4.02×10 ⁻⁰⁵	3.24×10 ⁻⁰¹

cg17263026	chr2	121453143			OpenSea	-0.1409	0.0342	-4.1203	4.02×10 ⁻⁰⁵	3.24×10 ⁻⁰¹
cg17264818	chr2	95612985			OpenSea	0.0786	0.0191	4.1195	4.04×10 ⁻⁰⁵	3.24×10 ⁻⁰¹
cg26363272	chr2	240904871	NDUFA10	Body	OpenSea	0.1462	0.0355	4.1135	4.17×10 ⁻⁰⁵	3.28×10 ⁻⁰¹
cg05999287	chr7	116312265	MET	TSS200	Island	0.0474	0.0115	4.1041	4.31×10 ⁻⁰⁵	3.32×10 ⁻⁰¹
ch.1.117057666F	chr1	117256143			OpenSea	0.0884	0.0216	4.1005	4.37×10 ⁻⁰⁵	3.32×10 ⁻⁰¹
cg01418667	chr20	3387969	C20orf194	Body	Island	0.0403	0.0098	4.0969	4.44×10 ⁻⁰⁵	3.32×10 ⁻⁰¹
cg26924209	chr1	193074740	GLRX2	1stExon; TSS200	Island	-0.0445	0.0109	-4.0858	4.66×10 ⁻⁰⁵	3.41×10 ⁻⁰¹
cg10163222	chr19	45004637	ZNF180	TSS200	Island	0.0447	0.011	4.0799	4.77×10 ⁻⁰⁵	3.41×10 ⁻⁰¹
cg21430685	chr8	29387008			OpenSea	0.0854	0.0209	4.0791	4.79×10 ⁻⁰⁵	3.41×10 ⁻⁰¹

Genomic locations are reported according to the hg19 reference genome. Gene annotation and CpG island context correspond to the Illumina HumanMethylation450 array annotation.

Table S9. Top CpG sites showing suggestive evidence of interaction (early childhood trauma)

CpG	Chromosome	Position (bp)	Gene(s)	Gene region	CpG island relation	Effect	SE	Statistic	P	FDR
cg26320410	chr3	9851826	TTLL3	TSS200	Island	0.0825	0.0108	7.6346	4.35×10 ⁻¹⁴	1.95×10 ⁻⁰⁸
cg19103000	chr3	9851819	TTLL3	TSS200	Island	0.0848	0.0114	7.4527	1.66×10 ⁻¹³	3.74×10 ⁻⁰⁸
cg08511716	chr5	94621030	MCTP1	TSS1500	Island	0.1134	0.0191	5.9451	3.54×10 ⁻⁰⁹	5.30×10 ⁻⁰⁴
cg14252492	chr11	44332224	ALX4	TSS1500	N_Shore	-0.1438	0.025	-5.7576	1.06×10 ⁻⁰⁸	9.36×10 ⁻⁰⁴
cg25688568	chr18	6730036			Island	0.1193	0.0208	5.7386	1.18×10 ⁻⁰⁸	9.36×10 ⁻⁰⁴
cg23632875	chr10	133110244	TCERG1L	TSS1500	Island	0.1027	0.0179	5.7293	1.25×10 ⁻⁰⁸	9.36×10 ⁻⁰⁴
cg13118906	chr17	61524292	CYB561	TSS1500	Island	0.0745	0.0132	5.6516	1.95×10 ⁻⁰⁸	1.10×10 ⁻⁰³
cg13928709	chr5	176237221	UNC5A	TSS1500	Island	0.1045	0.0185	5.6505	1.96×10 ⁻⁰⁸	1.10×10 ⁻⁰³
cg02882381	chr11	69590332	FGF4	TSS200	Island	0.0732	0.0131	5.5713	3.07×10 ⁻⁰⁸	1.53×10 ⁻⁰³
cg24199112	chr11	69590328	FGF4	TSS200	Island	0.0781	0.0141	5.5429	3.60×10 ⁻⁰⁸	1.62×10 ⁻⁰³
cg14940308	chr2	73144644	EMX1	5'UTR; 1stExon	Island	0.0918	0.0171	5.3614	9.76×10 ⁻⁰⁸	3.81×10 ⁻⁰³
cg20629468	chr10	81664583			Island	0.0803	0.015	5.3413	1.09×10 ⁻⁰⁷	3.81×10 ⁻⁰³
cg24701575	chr11	31845389			N_Shore	-0.1703	0.0319	-5.3348	1.13×10 ⁻⁰⁷	3.81×10 ⁻⁰³
cg17353893	chr7	73753326	CLIP2	Body	Island	-0.1521	0.0286	-5.3248	1.19×10 ⁻⁰⁷	3.81×10 ⁻⁰³

cg22654039	chr20	11871282	BTBD3	TSS200	N_Shore	0.0731	0.0138	5.3104	1.28×10 ⁻⁰⁷	3.85×10 ⁻⁰³
cg00789545	chr14	102770909	RAGE	Body	N_Shore	-0.1159	0.0221	-5.2349	1.92×10 ⁻⁰⁷	5.40×10 ⁻⁰³
cg01728704	chr16	20818015	LOC81691; ERI2	1stExon; 5'UTR; TSS1500	Island	-0.0461	0.0091	-5.0639	4.70×10 ⁻⁰⁷	1.24×10 ⁻⁰²
cg26583481	chr10	135139100	CALY	3'UTR	Island	0.068	0.0137	4.9785	7.27×10 ⁻⁰⁷	1.81×10 ⁻⁰²
cg21798447	chr4	85504053	CDS1	TSS200	Island	0.0658	0.0135	4.882	1.18×10 ⁻⁰⁶	2.79×10 ⁻⁰²
cg08197226	chr15	49658975	C15orf33	Body	OpenSea	0.1309	0.027	4.8509	1.38×10 ⁻⁰⁶	3.03×10 ⁻⁰²
cg23866687	chr11	96026956	MAML2	Body	OpenSea	-0.2248	0.0464	-4.847	1.42×10 ⁻⁰⁶	3.03×10 ⁻⁰²
cg05126421	chr7	26726046	SKAP2	Body	OpenSea	-0.1321	0.0274	-4.8235	1.58×10 ⁻⁰⁶	3.23×10 ⁻⁰²
cg10194160	chr6	30071387	TRIM31	Body	Island	0.0723	0.015	4.812	1.67×10 ⁻⁰⁶	3.26×10 ⁻⁰²
cg26313647	chr1	8085795	ERRFI1	5'UTR	Island	0.0991	0.0206	4.7991	1.78×10 ⁻⁰⁶	3.33×10 ⁻⁰²
cg23639399	chr10	135192176	PAOX	TSS1500	Island	-0.0577	0.0121	-4.7714	2.04×10 ⁻⁰⁶	3.46×10 ⁻⁰²
cg00261781	chr2	20212517	MATN3	TSS200	Island	0.1089	0.0228	4.7709	2.04×10 ⁻⁰⁶	3.46×10 ⁻⁰²
cg18705408	chr2	20212524	MATN3	TSS200	Island	0.1109	0.0233	4.7669	2.08×10 ⁻⁰⁶	3.46×10 ⁻⁰²
cg14602982	chr11	119599176	PVRL1	Body	Island	0.0695	0.0146	4.7459	2.30×10 ⁻⁰⁶	3.68×10 ⁻⁰²
cg18899035	chr14	20811563	PARP2; RPPH1	TSS1500; Body	OpenSea	-0.1642	0.0347	-4.7341	2.44×10 ⁻⁰⁶	3.68×10 ⁻⁰²
cg06340552	chr4	142054329	RNF150	1stExon; 5'UTR	Island	0.0581	0.0123	4.7322	2.46×10 ⁻⁰⁶	3.68×10 ⁻⁰²
cg05923101	chr21	45876770	LRRC3	Body	Island	-0.1472	0.0314	-4.6937	2.97×10 ⁻⁰⁶	4.29×10 ⁻⁰²
cg20467168	chr1	76081408			Island	0.06	0.0128	4.6782	3.19×10 ⁻⁰⁶	4.48×10 ⁻⁰²
cg10943191	chr1	1850414	TMEM52	Body	Island	0.0535	0.0115	4.6548	3.57×10 ⁻⁰⁶	4.86×10 ⁻⁰²
cg11838152	chr13	102359110	ITGBL1	Body	OpenSea	-0.0823	0.0177	-4.6437	3.77×10 ⁻⁰⁶	4.97×10 ⁻⁰²
cg06695611	chr2	180726328	ZNF385B; MIR1258	TSS200; TSS1500	Island	0.067	0.0145	4.6224	4.17×10 ⁻⁰⁶	5.35×10 ⁻⁰²
cg27644733	chr16	9857216	GRIN2A	Body	OpenSea	-0.0979	0.0214	-4.5677	5.40×10 ⁻⁰⁶	6.73×10 ⁻⁰²
cg14233374	chr21	47813461	PCNT	Body	Island	0.1025	0.0225	4.5537	5.76×10 ⁻⁰⁶	6.99×10 ⁻⁰²
cg23318990	chr6	31599289	BAT2	Body	N_Shore	0.0939	0.0208	4.5107	7.04×10 ⁻⁰⁶	8.21×10 ⁻⁰²
cg07057670	chr3	185000824			Island	0.0995	0.0221	4.5036	7.28×10 ⁻⁰⁶	8.21×10 ⁻⁰²
cg09187098	chr7	1913848	MAD1L1	Body	Island	-0.0663	0.0147	-4.5019	7.33×10 ⁻⁰⁶	8.21×10 ⁻⁰²
cg09860601	chr1	1374601	VWA1	Body; 3'UTR	Island	-0.1137	0.0253	-4.4972	7.49×10 ⁻⁰⁶	8.21×10 ⁻⁰²
cg19544459	chr7	22123197			S_Shore	0.0949	0.0211	4.4903	7.74×10 ⁻⁰⁶	8.27×10 ⁻⁰²
cg07507257	chr18	21112105	NPC1	3'UTR	OpenSea	0.0907	0.0202	4.4852	7.92×10 ⁻⁰⁶	8.27×10 ⁻⁰²

cg01367666	chr16	2052269	ZNF598	Body	Island	0.0925	0.0208	4.4545	9.13×10 ⁻⁰⁶	9.24×10 ⁻⁰²
cg15654121	chr1	34630944	CSMD2	Body	Island	0.0546	0.0123	4.4433	9.61×10 ⁻⁰⁶	9.24×10 ⁻⁰²
cg01046309	chr16	18995391	TMC7	TSS1500; 1stExon	Island	0.062	0.014	4.4407	9.72×10 ⁻⁰⁶	9.24×10 ⁻⁰²
cg03650946	chr7	27154562	HOXA3	5'UTR; TSS1500; 5'UTR	N_Shore	0.1196	0.0269	4.4403	9.75×10 ⁻⁰⁶	9.24×10 ⁻⁰²
cg16890428	chr19	55866412	FAM71E2; COX6B2	3'UTR; TSS1500	S_Shore	0.0737	0.0166	4.4371	9.88×10 ⁻⁰⁶	9.24×10 ⁻⁰²
cg11281641	chr2	171674855	GAD1	5'UTR	Island	0.0718	0.0162	4.4282	1.03×10 ⁻⁰⁵	9.26×10 ⁻⁰²
cg12648600	chr6	30585819	MRPS18B; PPP1R10	Body; TSS1500	S_Shore	-0.0728	0.0165	-4.4192	1.07×10 ⁻⁰⁵	9.26×10 ⁻⁰²
cg04743859	chr11	67817488	TCIRG1	Body	OpenSea	-0.1414	0.032	-4.4173	1.08×10 ⁻⁰⁵	9.26×10 ⁻⁰²
cg03517073	chr2	239957283			OpenSea	0.1358	0.0308	4.4171	1.08×10 ⁻⁰⁵	9.26×10 ⁻⁰²
cg09964012	chr14	105036453			OpenSea	0.1353	0.0306	4.4151	1.09×10 ⁻⁰⁵	9.26×10 ⁻⁰²
ch.X.258064R	chrX	16776121	SYAP1	Body	OpenSea	-0.1692	0.0385	-4.391	1.22×10 ⁻⁰⁵	1.01×10 ⁻⁰¹
cg26229895	chr6	30301504	TRIM39	Body	OpenSea	-0.1157	0.0264	-4.3817	1.27×10 ⁻⁰⁵	1.04×10 ⁻⁰¹
cg03967192	chr2	10861604	ATP6V1C2	TSS200	Island	0.1123	0.0257	4.3692	1.35×10 ⁻⁰⁵	1.08×10 ⁻⁰¹
cg18222759	chr14	22989081			OpenSea	-0.0987	0.0227	-4.3402	1.53×10 ⁻⁰⁵	1.21×10 ⁻⁰¹
cg07389273	chr10	133020009	TCERG1L	Body	OpenSea	-0.1066	0.0247	-4.3256	1.64×10 ⁻⁰⁵	1.27×10 ⁻⁰¹
cg19780993	chr14	34529242			Island	0.1267	0.0294	4.3037	1.80×10 ⁻⁰⁵	1.37×10 ⁻⁰¹
cg12646452	chr2	144560348			OpenSea	-0.0654	0.0152	-4.2983	1.85×10 ⁻⁰⁵	1.38×10 ⁻⁰¹
cg07920148	chr11	33397821			Island	0.0878	0.0205	4.2892	1.92×10 ⁻⁰⁵	1.40×10 ⁻⁰¹
cg01691856	chr15	93215561			OpenSea	0.0879	0.0205	4.2885	1.93×10 ⁻⁰⁵	1.40×10 ⁻⁰¹
cg03965044	chr17	48712212	ABCC3	TSS200	Island	0.0761	0.0179	4.2458	2.33×10 ⁻⁰⁵	1.66×10 ⁻⁰¹
cg18083704	chr3	9851847	TTLL3	TSS200	Island	0.0759	0.0179	4.2365	2.43×10 ⁻⁰⁵	1.68×10 ⁻⁰¹
cg09379485	chr19	53758297	ZNF677	TSS200	S_Shore	0.1417	0.0334	4.2356	2.44×10 ⁻⁰⁵	1.68×10 ⁻⁰¹
cg13706365	chr10	11504219	USP6NL	3'UTR	N_Shore	-0.0968	0.023	-4.2103	2.73×10 ⁻⁰⁵	1.85×10 ⁻⁰¹
cg27514608	chr4	23892540	PPARGC1A	TSS1500	OpenSea	-0.0827	0.0197	-4.2055	2.78×10 ⁻⁰⁵	1.86×10 ⁻⁰¹
cg05654340	chr6	111197834	AMD1	5'UTR; Body	S_Shore	-0.1339	0.0319	-4.1953	2.91×10 ⁻⁰⁵	1.92×10 ⁻⁰¹
cg18468511	chr14	27067638	NOVA1	TSS1500	S_Shore	0.121	0.0289	4.1807	3.10×10 ⁻⁰⁵	2.02×10 ⁻⁰¹
cg16206511	chr12	62860399	MON2	TSS200	Island	-0.1082	0.026	-4.167	3.29×10 ⁻⁰⁵	2.09×10 ⁻⁰¹
cg12750884	chr1	11303204	MTOR	Body	OpenSea	-0.0657	0.0158	-4.1651	3.32×10 ⁻⁰⁵	2.09×10 ⁻⁰¹
cg09571420	chr7	145813008	CNTNAP2	TSS1500	N_Shore	0.0539	0.0129	4.1632	3.34×10 ⁻⁰⁵	2.09×10 ⁻⁰¹

cg13971154	chr7	128828460	SMO	TSS1500	Island	0.0538	0.013	4.1529	3.49×10^{-05}	2.10×10^{-01}
cg09357483	chr16	87904491	SLC7A5	TSS1500	S_Shore	0.3037	0.0732	4.1474	3.58×10^{-05}	2.10×10^{-01}
cg07897077	chr19	56705386	ZSCAN5B	TSS1500	N_Shelf	-0.0677	0.0163	-4.147	3.58×10^{-05}	2.10×10^{-01}
cg16176837	chr1	5919155			OpenSea	-0.1431	0.0345	-4.1461	3.60×10^{-05}	2.10×10^{-01}
cg21773322	chr8	61836533			S_Shore	0.0633	0.0153	4.1456	3.61×10^{-05}	2.10×10^{-01}
cg07963147	chr3	141086820	ZBTB38	5'UTR	OpenSea	0.1262	0.0305	4.1435	3.64×10^{-05}	2.10×10^{-01}
cg06228857	chr15	35372947			OpenSea	0.0769	0.0186	4.1396	3.70×10^{-05}	2.10×10^{-01}
cg20338300	chr2	56411534	CCDC85A	1stExon; 5'UTR	Island	0.0636	0.0155	4.1133	4.14×10^{-05}	2.30×10^{-01}
cg13042252	chr8	74005756	C8orf84	TSS1500	Island	0.096	0.0233	4.1131	4.15×10^{-05}	2.30×10^{-01}
cg13759808	chr11	64885159	ZNHIT2	1stExon; 5'UTR	Island	0.0395	0.0096	4.1078	4.24×10^{-05}	2.30×10^{-01}
cg02979703	chr8	37558858			Island	0.2028	0.0494	4.1049	4.29×10^{-05}	2.30×10^{-01}
cg21625464	chr11	314044	IFITM1	1stExon; 5'UTR	N_Shore	-0.1347	0.0328	-4.104	4.31×10^{-05}	2.30×10^{-01}
cg16027727	chr17	78586328	RPTOR	Body	OpenSea	0.0862	0.021	4.0958	4.47×10^{-05}	2.32×10^{-01}
cg05672174	chr5	150701709	SLC36A2	Body	OpenSea	-0.1312	0.032	-4.095	4.48×10^{-05}	2.32×10^{-01}
cg09809720	chr5	162886885	NUDCD2; HMMR	1stExon; TSS1500	Island	-0.0425	0.0104	-4.0947	4.49×10^{-05}	2.32×10^{-01}
cg02681842	chr8	145033310	PLEC1	Body	OpenSea	0.0906	0.0222	4.082	4.74×10^{-05}	2.39×10^{-01}
cg05075416	chr15	99500703	IGF1R	3'UTR	Island	-0.1804	0.0442	-4.0816	4.74×10^{-05}	2.39×10^{-01}

Genomic locations are reported according to the hg19 reference genome. Gene annotation and CpG island context correspond to the Illumina HumanMethylation450 array annotation.

Table S10. Top CpG sites showing suggestive evidence of interaction (late childhood trauma)

CpG	Chromosome	Position (bp)	Gene(s)	Gene region	CpG island relation	Effect	SE	Statistic	P	FDR
cg26320410	chr3	9851826	TTLL3	TSS200	Island	0.091	0.0133	6.8678	1.01×10^{-11}	4.52×10^{-06}
cg19103000	chr3	9851819	TTLL3	TSS200	Island	0.0907	0.014	6.4683	1.40×10^{-10}	3.15×10^{-05}
cg09719477	chr11	113930430	ZBTB16	1stExon; TSS1500; 5'UTR	Island	0.0936	0.0156	5.9971	2.61×10^{-09}	3.90×10^{-04}
cg02936752	chr19	54963326	LENG8	Body	S_Shelf	0.0946	0.0163	5.7995	8.34×10^{-09}	9.36×10^{-04}
cg02882381	chr11	69590332	FGF4	TSS200	Island	0.0917	0.0161	5.7025	1.46×10^{-08}	1.16×10^{-03}
cg20383084	chr1	26325121	PAFAH2	TSS1500	S_Shore	-0.1619	0.0285	-5.6912	1.56×10^{-08}	1.16×10^{-03}

cg02507480	chr7	112032146			Island	-0.1187	0.021	-5.6515	1.97×10 ⁻⁰⁸	1.27×10 ⁻⁰³
cg25934863	chr15	101419506	ALDH1A3	TSS1500	Island	0.1216	0.022	5.521	4.06×10 ⁻⁰⁸	2.28×10 ⁻⁰³
cg23239754	chr6	27760147			OpenSea	-0.1012	0.0187	-5.4008	7.88×10 ⁻⁰⁸	3.93×10 ⁻⁰³
cg26915774	chr2	162094867			Island	0.1302	0.0246	5.2851	1.47×10 ⁻⁰⁷	6.61×10 ⁻⁰³
cg21847751	chr2	232379328	C2orf52	TSS1500	Island	-0.1155	0.022	-5.2559	1.72×10 ⁻⁰⁷	7.03×10 ⁻⁰³
cg21123573	chr12	120740055	SIRT4	TSS200	OpenSea	-0.2338	0.0449	-5.2012	2.31×10 ⁻⁰⁷	8.64×10 ⁻⁰³
cg24199112	chr11	69590328	FGF4	TSS200	Island	0.0869	0.0173	5.0319	5.55×10 ⁻⁰⁷	1.91×10 ⁻⁰²
cg10208370	chr4	90758469	SNCA	TSS1500; 5'UTR; TSS200	Island	0.1412	0.0281	5.0176	5.96×10 ⁻⁰⁷	1.91×10 ⁻⁰²
cg01357429	chr7	27285563	EVX1	Body	Island	0.0839	0.0169	4.9557	8.16×10 ⁻⁰⁷	2.44×10 ⁻⁰²
cg14602982	chr11	119599176	PVRL1	Body	Island	0.0873	0.0179	4.8875	1.15×10 ⁻⁰⁶	3.12×10 ⁻⁰²
cg23010344	chr1	228871301	RHOU	1stExon; 5'UTR	Island	0.0861	0.0177	4.871	1.25×10 ⁻⁰⁶	3.12×10 ⁻⁰²
cg00530638	chr5	98108543	RGMB	Body	N_Shore	-0.1961	0.0403	-4.8703	1.25×10 ⁻⁰⁶	3.12×10 ⁻⁰²
cg20142390	chr21	40564147	BRWD1	3'UTR; Body	OpenSea	-0.0811	0.0169	-4.812	1.67×10 ⁻⁰⁶	3.94×10 ⁻⁰²
cg05633605	chr5	55530180	ANKRD55	TSS1500	OpenSea	-0.1121	0.0234	-4.7993	1.78×10 ⁻⁰⁶	3.99×10 ⁻⁰²
cg17572445	chr13	98893146	FARP1	Body	OpenSea	-0.172	0.0362	-4.7526	2.23×10 ⁻⁰⁶	4.68×10 ⁻⁰²
cg02242344	chr2	85640943			N_Shore	0.1257	0.0265	4.7437	2.34×10 ⁻⁰⁶	4.68×10 ⁻⁰²
cg26286805	chr14	51411267	PYGL	TSS200	Island	0.0759	0.016	4.7376	2.40×10 ⁻⁰⁶	4.68×10 ⁻⁰²
cg26665891	chr1	204159832	KISS1	Body	Island	0.0883	0.0189	4.6841	3.11×10 ⁻⁰⁶	5.63×10 ⁻⁰²
cg18705408	chr2	20212524	MATN3	TSS200	Island	0.1331	0.0284	4.6824	3.13×10 ⁻⁰⁶	5.63×10 ⁻⁰²
cg21875802	chr2	45231382			Island	0.0958	0.0206	4.6619	3.45×10 ⁻⁰⁶	5.97×10 ⁻⁰²
cg05143332	chr7	109218838			OpenSea	-0.1031	0.0223	-4.6227	4.16×10 ⁻⁰⁶	6.92×10 ⁻⁰²
cg02924619	chr14	65007171	HSPA2	TSS200	Island	-0.0822	0.0179	-4.598	4.68×10 ⁻⁰⁶	7.12×10 ⁻⁰²
cg20566450	chr5	31854651	PDZD2	Body	N_Shore	-0.1433	0.0312	-4.5941	4.77×10 ⁻⁰⁶	7.12×10 ⁻⁰²
cg04543008	chr11	71955332	PHOX2A	TSS200	Island	0.0964	0.021	4.5835	5.02×10 ⁻⁰⁶	7.12×10 ⁻⁰²
cg10080155	chr22	45405904	PHF21B	TSS1500; TSS200	Island	0.0555	0.0121	4.5806	5.08×10 ⁻⁰⁶	7.12×10 ⁻⁰²
cg06340552	chr4	142054329	RNF150	1stExon; 5'UTR	Island	0.0688	0.015	4.5773	5.16×10 ⁻⁰⁶	7.12×10 ⁻⁰²
cg22654039	chr20	11871282	BTBD3	TSS200	N_Shore	0.0777	0.017	4.5744	5.23×10 ⁻⁰⁶	7.12×10 ⁻⁰²
cg07112562	chr10	16741619	RSU1;RSU1	Body	OpenSea	0.1066	0.0234	4.5548	5.73×10 ⁻⁰⁶	7.57×10 ⁻⁰²
cg18286127	chr10	120070743	C10orf84	Body	OpenSea	-0.1124	0.0247	-4.5434	6.05×10 ⁻⁰⁶	7.76×10 ⁻⁰²

cg08511716	chr5	94621030	MCTP1	TSS1500	Island	0.1111	0.0246	4.5183	6.80×10^{-06}	8.48×10^{-02}
cg08324796	chrX	48979771	GPKOW	Body	N_Shore	-0.2265	0.0504	-4.4888	7.79×10^{-06}	9.46×10^{-02}
cg15846718	chr6	75953307	COX7A2	Body	OpenSea	-0.1428	0.0321	-4.45	9.34×10^{-06}	1.10×10^{-01}
cg15654121	chr1	34630944	CSMD2	Body	Island	0.0671	0.0151	4.4431	9.62×10^{-06}	1.11×10^{-01}
cg03933495	chr16	3493614	NAT15; ZNF597	TSS200	S_Shore	-0.1176	0.0267	-4.4111	1.11×10^{-05}	1.22×10^{-01}
cg14492800	chr5	37839923	GDNF	TSS200	Island	0.1229	0.0279	4.4107	1.12×10^{-05}	1.22×10^{-01}
cg06695611	chr2	180726328	ZNF385B; MIR1258	TSS200; TSS1500	Island	0.0784	0.0178	4.4025	1.16×10^{-05}	1.24×10^{-01}
cg22058122	chr18	6414958	L3MBTL4	TSS200	S_Shore	0.1088	0.0248	4.3912	1.22×10^{-05}	1.26×10^{-01}
cg13118906	chr17	61524292	CYB561	TSS1500	Island	0.0714	0.0163	4.3877	1.24×10^{-05}	1.26×10^{-01}
cg19591206	chr3	133748809	SLCO2A1	1stExon; 5'UTR	Island	0.1037	0.0237	4.3786	1.29×10^{-05}	1.27×10^{-01}
cg13324546	chr8	23564031	NKX2-6	TSS200	Island	0.1406	0.0321	4.3766	1.30×10^{-05}	1.27×10^{-01}
cg09518742	chr11	119020115	ABCG4	TSS200; 5'UTR	Island	0.0509	0.0117	4.3617	1.39×10^{-05}	1.33×10^{-01}
cg15993083	chr12	4381788	CCND2	TSS1500	Island	0.0796	0.0183	4.3546	1.44×10^{-05}	1.34×10^{-01}
cg10498524	chr2	178937663	PDE11A	Body; TSS200	Island	0.1146	0.0265	4.3255	1.64×10^{-05}	1.47×10^{-01}
cg12252090	chr8	49833279	SNAI2	Body	N_Shelf	-0.1496	0.0346	-4.3221	1.66×10^{-05}	1.47×10^{-01}
cg01418667	chr20	3387969	C20orf194	Body	Island	0.0696	0.0161	4.3214	1.67×10^{-05}	1.47×10^{-01}
cg15424477	chr13	113428288	ATP11A	Body	N_Shore	-0.1643	0.0381	-4.3131	1.73×10^{-05}	1.49×10^{-01}
cg15087347	chr12	41086227	CNTN1	TSS200	N_Shore	0.1014	0.0236	4.301	1.83×10^{-05}	1.55×10^{-01}
cg10624122	chr7	19158747	TWIST1	TSS1500	S_Shore	-0.0816	0.019	-4.2888	1.93×10^{-05}	1.58×10^{-01}
cg14059988	chr7	127669170	SND1; LRRC4	Body	N_Shore	-0.1133	0.0264	-4.2884	1.93×10^{-05}	1.58×10^{-01}
cg01116059	chr5	121647630	SNCAIP	TSS200	Island	0.1031	0.0241	4.2825	1.98×10^{-05}	1.59×10^{-01}
cg02022224	chr17	39967428	SC65	Body	Island	0.0543	0.0127	4.2728	2.07×10^{-05}	1.63×10^{-01}
cg06967120	chr10	25464259	LOC100128811; GPR158	Body; TSS200	Island	0.2031	0.0476	4.2658	2.14×10^{-05}	1.65×10^{-01}
cg03006716	chr7	98741357	SMURF1	1stExon	Island	0.0505	0.0118	4.26	2.19×10^{-05}	1.67×10^{-01}
cg22871668	chr6	133562492	EYA4	TSS200	Island	0.1099	0.0258	4.2516	2.27×10^{-05}	1.70×10^{-01}
cg12956507	chr3	193854670	HES1	Body	Island	0.0929	0.0219	4.2443	2.35×10^{-05}	1.73×10^{-01}
cg16674467	chr3	46854311			S_Shore	-0.0936	0.0221	-4.2395	2.40×10^{-05}	1.74×10^{-01}
cg20713035	chr5	14410284	TRIO	Body	OpenSea	-0.0987	0.0234	-4.2207	2.60×10^{-05}	1.83×10^{-01}
cg07810961	chr5	139927271	EIF4EBP3; ANKHD1	1stExon; 5'UTR; Body	Island	0.0645	0.0153	4.2202	2.61×10^{-05}	1.83×10^{-01}

cg00402812	chr1	109633307	TMEM167B	TSS200	Island	-0.0864	0.0206	-4.1971	2.89×10 ⁻⁰⁵	2.00×10 ⁻⁰¹
cg26829088	chr19	3626949	C19orf29	TSS200	Island	-0.0849	0.0202	-4.1912	2.96×10 ⁻⁰⁵	2.02×10 ⁻⁰¹
cg13904562	chr12	48690974			OpenSea	-0.1538	0.0367	-4.1848	3.04×10 ⁻⁰⁵	2.02×10 ⁻⁰¹
cg20467168	chr1	76081408			Island	0.0657	0.0157	4.1843	3.05×10 ⁻⁰⁵	2.02×10 ⁻⁰¹
cg27608102	chr17	39680504	KRT19	Body	N_Shelf	-0.1934	0.0463	-4.1795	3.12×10 ⁻⁰⁵	2.03×10 ⁻⁰¹
cg04153241	chr12	133562589	ZNF26	TSS1500	N_Shore	-0.2099	0.0504	-4.161	3.38×10 ⁻⁰⁵	2.17×10 ⁻⁰¹
cg26999902	chr19	6108921	RFX2; RFX2	5'UTR	Island	0.0998	0.024	4.1566	3.44×10 ⁻⁰⁵	2.18×10 ⁻⁰¹
cg14448830	chr9	79627216			N_Shore	0.0929	0.0224	4.1479	3.57×10 ⁻⁰⁵	2.23×10 ⁻⁰¹
cg22979807	chr19	55837197	TMEM150B	TSS1500	OpenSea	0.1457	0.0353	4.1275	3.90×10 ⁻⁰⁵	2.37×10 ⁻⁰¹
cg15491911	chr6	167764620			Island	0.0605	0.0147	4.1256	3.93×10 ⁻⁰⁵	2.37×10 ⁻⁰¹
cg24946736	chr19	7542181	PEX11G	Body	Island	-0.1245	0.0302	-4.1239	3.96×10 ⁻⁰⁵	2.37×10 ⁻⁰¹
cg06836497	chr1	29063467	YTHDF2	5'UTR; 1stExon	Island	0.0452	0.011	4.1187	4.05×10 ⁻⁰⁵	2.39×10 ⁻⁰¹
cg03155112	chr7	47556928	TNS3	5'UTR	OpenSea	-0.1432	0.0349	-4.1019	4.37×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg13733797	chr8	121824218	SNTB1	5'UTR; 1stExon	Island	-0.0563	0.0137	-4.0983	4.42×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg11722699	chr18	28622813	DSC3	TSS200	Island	0.1379	0.0337	4.0959	4.47×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg16259904	chr10	134146220	LRRC27	5'UTR	S_Shore	-0.258	0.0631	-4.0923	4.53×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg15775218	chr2	3286338	TSSC1	Body	Island	-0.2308	0.0565	-4.0854	4.67×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg13653153	chr9	130885858	PTGES2	Body	N_Shelf	0.1025	0.0251	4.0816	4.75×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg06664872	chr5	96519548	RIOK2	TSS1500	Island	-0.0853	0.0209	-4.0801	4.78×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg13579574	chr15	75975227	CSPG4	Body	Island	-0.0761	0.0187	-4.0789	4.80×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg13928709	chr5	176237221	UNC5A	TSS1500	Island	0.093	0.0228	4.0759	4.86×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg11664500	chr6	133562479	EYA4	TSS200	Island	0.0789	0.0194	4.0752	4.88×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg12980477	chr6	27156454			OpenSea	-0.0768	0.0189	-4.0735	4.91×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg08189989	chr2	105459164			Island	0.0642	0.0158	4.073	4.92×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg04754916	chr19	10381498	ICAM1	TSS200	Island	0.0605	0.0148	4.0716	4.95×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg25815683	chr6	28742918			OpenSea	-0.0828	0.0203	-4.0714	4.96×10 ⁻⁰⁵	2.44×10 ⁻⁰¹
cg00192031	chr7	47620790			N_Shore	-0.0808	0.0199	-4.0701	4.98×10 ⁻⁰⁵	2.44×10 ⁻⁰¹

Genomic locations are reported according to the hg19 reference genome. Gene annotation and CpG island context correspond to the Illumina HumanMethylation450 array annotation.

Table S11. Top CpG sites showing suggestive evidence of interaction (abuse-only trauma)

CpG	Chromosome	Position (bp)	Gene(s)	Gene region	CpG island relation	Effect	SE	Statistic	P	FDR
cg26320410	chr3	9851826	TTL3	TSS200	Island	0.0781	0.0123	6.3334	3.28×10^{-10}	1.47×10^{-04}
cg20383084	chr1	26325121	PAFAH2	TSS1500	S_Shore	-0.1589	0.0263	-6.04	2.00×10^{-09}	3.28×10^{-04}
cg04852989	chr22	19974685	ARVCF	Body	Island	-0.1317	0.0219	-6.025	2.19×10^{-09}	3.28×10^{-04}
cg02882381	chr11	69590332	FGF4	TSS200	Island	0.0824	0.0149	5.5196	4.08×10^{-08}	4.58×10^{-03}
cg24199112	chr11	69590328	FGF4	TSS200	Island	0.0843	0.016	5.2575	1.70×10^{-07}	1.53×10^{-02}
cg19103000	chr3	9851819	TTL3	TSS200	Island	0.0677	0.013	5.1943	2.38×10^{-07}	1.68×10^{-02}
cg01357429	chr7	27285563	EVX1	Body	Island	0.081	0.0157	5.1763	2.61×10^{-07}	1.68×10^{-02}
cg14602982	chr11	119599176	PVRL1	Body	Island	0.0814	0.0166	4.9077	1.04×10^{-06}	5.23×10^{-02}
cg08197226	chr15	49658975	C15orf33	Body	OpenSea	0.1502	0.0306	4.9043	1.05×10^{-06}	5.23×10^{-02}
cg10668926	chr13	28527255			N_Shore	0.0786	0.0162	4.8673	1.27×10^{-06}	5.23×10^{-02}
cg16315582	chr11	104839349	CASP4	TSS200	OpenSea	-0.1133	0.0233	-4.8649	1.28×10^{-06}	5.23×10^{-02}
cg13118906	chr17	61524292	CYB561	TSS1500	Island	0.0726	0.0151	4.8207	1.60×10^{-06}	5.74×10^{-02}
cg08511716	chr5	94621030	MCTP1	TSS1500	Island	0.1091	0.0227	4.8125	1.66×10^{-06}	5.74×10^{-02}
cg25245636	chr17	79848873	ANAPC11	TSS1500; Body	Island	-0.0619	0.0133	-4.6538	3.59×10^{-06}	1.15×10^{-01}
cg12110327	chr10	38264581	ZNF25	5'UTR	N_Shore	-0.1157	0.025	-4.6326	3.97×10^{-06}	1.19×10^{-01}
cg18705408	chr2	20212524	MATN3	TSS200	Island	0.1213	0.0263	4.6037	4.55×10^{-06}	1.28×10^{-01}
cg10008501	chr8	9763558			Island	-0.1674	0.0365	-4.5822	5.03×10^{-06}	1.33×10^{-01}
cg04402633	chr11	2907113	CDKN1C	TSS200	N_Shore	0.0937	0.0206	4.5517	5.81×10^{-06}	1.45×10^{-01}
cg22892043	chr11	61731930	BEST1; FTH1	3'UTR	N_Shelf	-0.0852	0.0188	-4.524	6.61×10^{-06}	1.56×10^{-01}
cg08298794	chr2	198243396			OpenSea	-0.1671	0.0371	-4.499	7.42×10^{-06}	1.61×10^{-01}
cg20163689	chr2	13088414			OpenSea	-0.1171	0.0261	-4.4877	7.83×10^{-06}	1.61×10^{-01}
cg00789545	chr14	102770909	RAGE	Body	N_Shore	-0.1138	0.0254	-4.4784	8.17×10^{-06}	1.61×10^{-01}
cg23346227	chr12	57024964	BAZ2A	Body	S_Shore	0.1033	0.0231	4.477	8.22×10^{-06}	1.61×10^{-01}
cg04528961	chr2	32289715	SPAST	Body	S_Shore	-0.1014	0.0228	-4.4484	9.38×10^{-06}	1.73×10^{-01}
cg00926285	chr3	122398533	PARP14	TSS1500	N_Shore	-0.1461	0.0331	-4.4209	1.06×10^{-05}	1.73×10^{-01}
cg20629468	chr10	81664583			Island	0.0759	0.0172	4.4204	1.07×10^{-05}	1.73×10^{-01}
cg18555073	chr15	45002662	B2M	TSS1500	N_Shore	-0.1056	0.0239	-4.4189	1.07×10^{-05}	1.73×10^{-01}

cg18791121	chr11	7694814	CYB5R2	1stExon; 5'UTR	Island	0.0676	0.0153	4.4175	1.08×10^{-05}	1.73×10^{-01}
cg00261781	chr2	20212517	MATN3	TSS200	Island	0.1148	0.026	4.4105	1.12×10^{-05}	1.73×10^{-01}
cg01392544	chr10	18429760	CACNB2	1stExon; 5'UTR	Island	0.0874	0.0199	4.3979	1.18×10^{-05}	1.75×10^{-01}
cg05127380	chr11	63953685	STIP1	1stExon; 5'UTR	Island	-0.0657	0.015	-4.3901	1.22×10^{-05}	1.75×10^{-01}
cg03110787	chr19	6217641	MLLT1	Body	S_Shelf	-0.1162	0.0265	-4.3862	1.24×10^{-05}	1.75×10^{-01}
cg05869491	chr6	209763			OpenSea	-0.1351	0.0309	-4.3737	1.32×10^{-05}	1.75×10^{-01}
cg27608102	chr17	39680504	KRT19	Body	N_Shelf	-0.1871	0.0429	-4.3665	1.36×10^{-05}	1.75×10^{-01}
cg10937890	chr2	170440953	PPIG	1stExon; 5'UTR	Island	-0.0583	0.0134	-4.3617	1.39×10^{-05}	1.75×10^{-01}
cg18440523	chr21	42690652	FAM3B	Body	S_Shore	-0.1148	0.0263	-4.3598	1.40×10^{-05}	1.75×10^{-01}
cg06527052	chr1	109633875	TMEM167B	Body	S_Shore	-0.0933	0.0215	-4.3301	1.60×10^{-05}	1.94×10^{-01}
cg21306775	chr18	74402010			OpenSea	-0.1386	0.0321	-4.3191	1.68×10^{-05}	1.98×10^{-01}
cg08364607	chr11	64677562	ATG2A	Body	OpenSea	-0.1477	0.0342	-4.314	1.72×10^{-05}	1.98×10^{-01}
cg20467168	chr1	76081408			Island	0.0625	0.0146	4.2864	1.95×10^{-05}	2.03×10^{-01}
cg04700861	chr10	13865934	FRMD4A	Body	OpenSea	-0.0771	0.018	-4.2848	1.96×10^{-05}	2.03×10^{-01}
cg05903046	chr12	50629130	LIMA1; MIR1293	Body; TSS1500	OpenSea	-0.0895	0.0209	-4.2816	1.99×10^{-05}	2.03×10^{-01}
cg12657380	chr1	9795590	CLSTN1	Body	OpenSea	0.1443	0.0337	4.2783	2.02×10^{-05}	2.03×10^{-01}
cg25813235	chr6	33397883	SYNGAP1	Body	S_Shore	-0.075	0.0176	-4.2561	2.23×10^{-05}	2.03×10^{-01}
cg16594913	chr12	5607455			S_Shelf	-0.0972	0.0229	-4.252	2.27×10^{-05}	2.03×10^{-01}
cg22654039	chr20	11871282	BTBD3	TSS200	N_Shore	0.0671	0.0158	4.2433	2.36×10^{-05}	2.03×10^{-01}
cg02507480	chr7	112032146			Island	-0.083	0.0196	-4.2433	2.36×10^{-05}	2.03×10^{-01}
cg05735765	chr18	32556655	MAPRE2	TSS1500	Island	-0.1131	0.0267	-4.2421	2.37×10^{-05}	2.03×10^{-01}
cg09257635	chr1	228346181	GJC2	Body	Island	0.1192	0.0281	4.2401	2.39×10^{-05}	2.03×10^{-01}
cg27564373	chrX	47050093	UBA1	TSS200	Island	-0.1356	0.032	-4.2372	2.42×10^{-05}	2.03×10^{-01}
cg04039225	chr3	169629516	SAMD7	5'UTR; 1stExon	OpenSea	-0.0675	0.0159	-4.2339	2.45×10^{-05}	2.03×10^{-01}
cg20116266	chr3	127771061	SEC61A1	TSS200	Island	-0.0467	0.011	-4.2312	2.48×10^{-05}	2.03×10^{-01}
cg10953002	chr4	74241932			OpenSea	-0.0826	0.0195	-4.2292	2.51×10^{-05}	2.03×10^{-01}
cg09586060	chr11	114099086	ZBTB16	Body	OpenSea	-0.079	0.0187	-4.2289	2.51×10^{-05}	2.03×10^{-01}
cg00004979	chr12	111885466	SH2B3	Body	OpenSea	-0.2097	0.0497	-4.2219	2.59×10^{-05}	2.03×10^{-01}
cg11351687	chr6	170863423	PSMB1; TBP	TSS1500; TSS200	Island	0.0729	0.0173	4.2194	2.62×10^{-05}	2.03×10^{-01}

cg09035925	chr20	19915769	RIN2	Body	OpenSea	-0.1323	0.0314	-4.2158	2.66×10^{-05}	2.03×10^{-01}
cg06081306	chr17	37760830	NEUROD2	3'UTR	N_Shore	-0.0842	0.02	-4.2134	2.69×10^{-05}	2.03×10^{-01}
cg23385838	chr12	1755068	WNT5B	Body	Island	0.1639	0.0389	4.2125	2.70×10^{-05}	2.03×10^{-01}
cg18426014	chr12	54582795	SMUG1	TSS200	OpenSea	-0.0756	0.018	-4.2114	2.71×10^{-05}	2.03×10^{-01}
cg18050233	chr5	42800967	CCDC152; SEPP1	3'UTR; Body	OpenSea	-0.1005	0.0239	-4.2032	2.81×10^{-05}	2.07×10^{-01}
cg02460371	chr1	150266604	MRPS21	5'UTR; 1stExon	Island	-0.069	0.0165	-4.1884	3.00×10^{-05}	2.17×10^{-01}
cg21412992	chr1	61547497	NFIA	Body; TSS1500; TSS200	N_Shore	-0.1265	0.0302	-4.1839	3.05×10^{-05}	2.18×10^{-01}
cg06340552	chr4	142054329	RNF150	1stExon; 5'UTR	Island	0.0583	0.0139	4.1778	3.14×10^{-05}	2.19×10^{-01}
cg00577629	chr8	104426828	SLC25A32; DCAF13	Body; TSS200	N_Shore	-0.0574	0.0138	-4.1705	3.24×10^{-05}	2.19×10^{-01}
cg06551997	chr17	33815451	SLFN12L	Body	S_Shore	-0.1504	0.0361	-4.1673	3.28×10^{-05}	2.19×10^{-01}
cg19286500	chr7	29652942			OpenSea	-0.0779	0.0187	-4.1626	3.35×10^{-05}	2.19×10^{-01}
cg03819713	chr6	32764987			OpenSea	-0.0811	0.0195	-4.1606	3.39×10^{-05}	2.19×10^{-01}
cg21875802	chr2	45231382			Island	0.0796	0.0192	4.1559	3.45×10^{-05}	2.19×10^{-01}
cg11722699	chr18	28622813	DSC3	TSS200	Island	0.13	0.0313	4.154	3.48×10^{-05}	2.19×10^{-01}
cg01966091	chr16	69141478	HAS3	5'UTR; 1stExon	Island	0.1463	0.0352	4.1539	3.48×10^{-05}	2.19×10^{-01}
cg08486065	chr19	3464875			Island	0.0831	0.02	4.1516	3.51×10^{-05}	2.19×10^{-01}
cg06834431	chr12	45049153	NELL2	Body	OpenSea	-0.1311	0.0317	-4.142	3.66×10^{-05}	2.25×10^{-01}
cg21174055	chr9	139097029	LHX3	TSS200	S_Shore	-0.103	0.025	-4.125	3.94×10^{-05}	2.39×10^{-01}
cg23632875	chr10	133110244	TCERG1L	TSS1500	Island	0.0858	0.0208	4.1165	4.08×10^{-05}	2.44×10^{-01}
cg08791424	chr2	208795653	PLEKHM3	Body	Island	-0.1874	0.0457	-4.0992	4.40×10^{-05}	2.60×10^{-01}
cg09512575	chr5	107008490			S_Shore	-0.1027	0.0251	-4.0961	4.46×10^{-05}	2.60×10^{-01}
cg21847751	chr2	232379328	C2orf52	TSS1500	Island	-0.0834	0.0204	-4.0931	4.52×10^{-05}	2.60×10^{-01}
cg01365762	chr6	30457827	HLA-E	Body	Island	0.1284	0.0314	4.0897	4.58×10^{-05}	2.60×10^{-01}
cg15599382	chr1	244084377			S_Shelf	-0.0958	0.0235	-4.0833	4.71×10^{-05}	2.64×10^{-01}
cg21833640	chr8	124287665	ZHX1	TSS1500	Island	-0.0559	0.0137	-4.0784	4.81×10^{-05}	2.66×10^{-01}
cg01883966	chr6	31938886	STK19; DOM3Z	TSS200; TSS1500; Body	N_Shore	-0.1263	0.031	-4.0748	4.88×10^{-05}	2.67×10^{-01}

Genomic locations are reported according to the hg19 reference genome. Gene annotation and CpG island context correspond to the Illumina HumanMethylation450 array annotation.

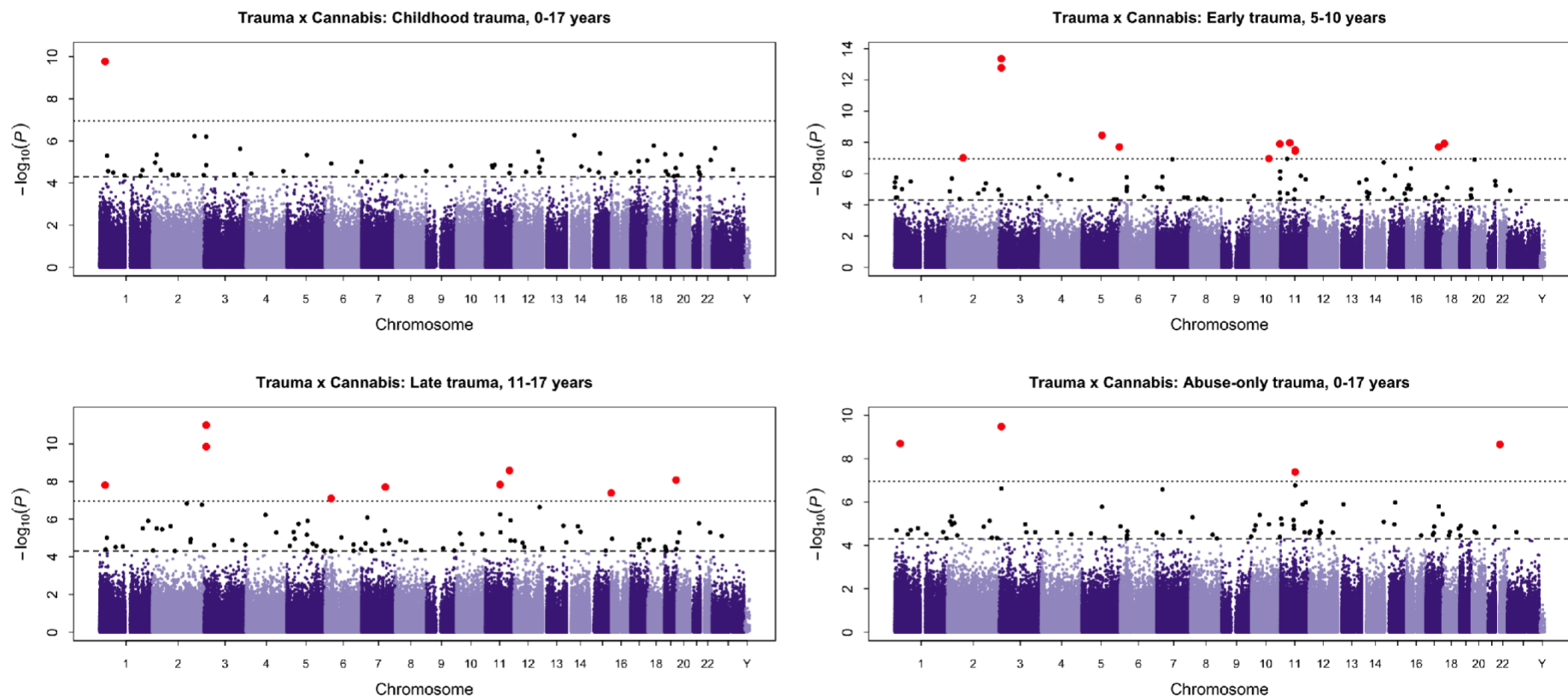


Figure S9. *Epigenome-wide interaction analysis of childhood trauma and cannabis.*

Manhattan plot showing epigenome-wide interaction results examining trauma x cannabis effects on DNAm. Each point represents a CpG site plotted according to genomic position across chromosomes and the $-\log_{10}$ -transformed p-value. The horizontal dashed line indicates a suggestive discovery threshold ($p < 5 \times 10^{-5}$), while the dotted line represents the Bonferroni-corrected threshold.

7.3. DMR interaction results

Table S12. Differentially methylated regions identified in trauma x cannabis interaction analyses

Exposure	Chromosome	Start (bp)	End (bp)	Region width (bp)	CpG sites	Gene(s)	Min CpG p-value	Region p-value	FDR (BH)
Abuse-only trauma, 0-17 years	chr3	196325238	196325552	315	3		1.6600×10 ⁻⁴	2.0000×10 ⁻¹⁴	9.7000×10 ⁻⁹
Abuse-only trauma, 0-17 years	chr11	63997961	63998032	72	3	DNAJC4	6.9900×10 ⁻³	5.3400×10 ⁻¹³	2.5900×10 ⁻⁷
Abuse-only trauma, 0-17 years	chr6	26196580	26197071	492	4	HIST1H3D	7.0700×10 ⁻⁵	3.3200×10 ⁻¹²	1.6100×10 ⁻⁶
Abuse-only trauma, 0-17 years	chrX	118986947	118987202	256	9	UPF3B	1.8500×10 ⁻³	3.6200×10 ⁻¹²	1.7600×10 ⁻⁶
Abuse-only trauma, 0-17 years	chr6	110736772	110737053	282	5	DDO	9.2300×10 ⁻³	2.1300×10 ⁻¹¹	1.0300×10 ⁻⁵
Abuse-only trauma, 0-17 years	chr6	31275643	31275807	165	8		3.7800×10 ⁻³	4.3800×10 ⁻⁹	2.1300×10 ⁻³
Abuse-only trauma, 0-17 years	chr5	94621030	94621055	26	2	MCTP1	1.6600×10 ⁻⁶	5.3700×10 ⁻⁹	2.6100×10 ⁻³
Abuse-only trauma, 0-17 years	chr11	69590328	69590332	5	2	FGF4	4.0800×10 ⁻⁸	9.9500×10 ⁻⁹	4.8300×10 ⁻³
Abuse-only trauma, 0-17 years	chr15	49658865	49658975	111	2	C15orf33	1.0500×10 ⁻⁶	1.0200×10 ⁻⁸	4.9500×10 ⁻³
Abuse-only trauma, 0-17 years	chr8	125313885	125313940	56	2		5.0100×10 ⁻³	2.0800×10 ⁻⁸	0.0101
Abuse-only trauma, 0-17 years	chr11	2292905	2293201	297	8	ASCL2	6.8500×10 ⁻⁵	2.6100×10 ⁻⁸	0.0127
Abuse-only trauma, 0-17 years	chrX	56590097	56590113	17	2	UBQLN2	1.3900×10 ⁻³	3.6400×10 ⁻⁸	0.0177
Abuse-only trauma, 0-17 years	chr2	73052964	73053217	254	2	EXOC6B	4.4800×10 ⁻³	4.0500×10 ⁻⁸	0.0197
Abuse-only trauma, 0-17 years	chr1	36108206	36108212	7	2	PSMB2	2.0900×10 ⁻⁴	4.4700×10 ⁻⁸	0.0217
Abuse-only trauma, 0-17 years	chr11	20408613	20408972	360	5	PRMT3	0.0179	5.7200×10 ⁻⁸	0.0278
Early trauma, 5-10 years	chrX	46405000	46405123	124	4	ZNF674; LOC401588	0.0154	1.0600×10 ⁻¹⁷	5.1300×10 ⁻¹²
Early trauma, 5-10 years	chr6	31275643	31275807	165	8		1.2400×10 ⁻⁴	1.4600×10 ⁻¹⁵	7.0600×10 ⁻¹⁰
Early trauma, 5-10 years	chr3	9851819	9851847	29	3	TTLL3	4.3500×10 ⁻¹⁴	4.5600×10 ⁻¹⁵	2.2000×10 ⁻⁹
Early trauma, 5-10 years	chr6	29720530	29720720	191	13		1.3400×10 ⁻³	3.6300×10 ⁻¹¹	1.7500×10 ⁻⁵
Early trauma, 5-10 years	chr5	94621030	94621055	26	2	MCTP1	3.5400×10 ⁻⁹	1.6500×10 ⁻¹⁰	7.9900×10 ⁻⁵
Early trauma, 5-10 years	chr19	51226046	51226849	804	6	CLEC11A	6.0300×10 ⁻³	2.5400×10 ⁻¹⁰	1.2300×10 ⁻⁴
Early trauma, 5-10 years	chrX	125687011	125687207	197	4	DCAF12L1	1.2300×10 ⁻³	8.3900×10 ⁻¹⁰	4.0500×10 ⁻⁴
Early trauma, 5-10 years	chr8	42234614	42234803	190	6	DKK4	9.8300×10 ⁻⁴	1.3200×10 ⁻⁹	6.3900×10 ⁻⁴
Early trauma, 5-10 years	chr5	140579296	140579644	349	5	PCDHB11	5.6400×10 ⁻⁴	1.7300×10 ⁻⁹	8.3700×10 ⁻⁴
Early trauma, 5-10 years	chr11	69590328	69590332	5	2	FGF4	3.0700×10 ⁻⁸	3.6800×10 ⁻⁹	1.7800×10 ⁻³

Early trauma, 5-10 years	chr15	66679100	66679417	318	4	MAP2K1	8.8600×10 ⁻³	5.0700×10 ⁻⁹	2.4500×10 ⁻³
Early trauma, 5-10 years	chr4	10459929	10460009	81	2	ZNF518B	2.6100×10 ⁻³	2.0500×10 ⁻⁸	9.9100×10 ⁻³
Early trauma, 5-10 years	chr21	38362727	38362754	28	3	HLCS	3.2400×10 ⁻³	2.8500×10 ⁻⁸	0.0138
Early trauma, 5-10 years	chr19	58258135	58258646	512	4	ZNF776	3.9200×10 ⁻⁴	2.9700×10 ⁻⁸	0.0143
Early trauma, 5-10 years	chr20	11871282	11871311	30	2	BTBD3	1.2800×10 ⁻⁷	3.3400×10 ⁻⁸	0.0161
Early trauma, 5-10 years	chr2	31806234	31806781	548	7	SRD5A2	8.1500×10 ⁻³	3.9300×10 ⁻⁸	0.0190
Early trauma, 5-10 years	chr2	20212517	20212524	8	2	MATN3	2.0400×10 ⁻⁶	4.6600×10 ⁻⁸	0.0225
Early trauma, 5-10 years	chr8	145106299	145106438	140	2	OPLAH	7.1700×10 ⁻⁴	6.9300×10 ⁻⁸	0.0335
Early trauma, 5-10 years	chr2	180726252	180726328	77	2	ZNF385B; MIR1258	4.1700×10 ⁻⁶	7.7900×10 ⁻⁸	0.0377
Late trauma, 11-17 years	chr12	70636487	70636659	173	8	CNOT2	0.0282	2.3800×10 ⁻¹⁴	1.1500×10 ⁻⁸
Late trauma, 11-17 years	chr5	98108198	98108543	346	2	RGMB	1.2500×10 ⁻⁶	3.1600×10 ⁻¹⁴	1.5300×10 ⁻⁸
Late trauma, 11-17 years	chr3	9851819	9851826	8	2	TTLL3	1.0100×10 ⁻¹¹	3.4500×10 ⁻¹²	1.6700×10 ⁻⁶
Late trauma, 11-17 years	chr2	54785178	54785406	229	5	SPTBN1	8.8000×10 ⁻³	1.0500×10 ⁻¹⁰	5.0900×10 ⁻⁵
Late trauma, 11-17 years	chr4	90758469	90758494	26	2	SNCA	5.9600×10 ⁻⁷	6.7300×10 ⁻¹⁰	3.2500×10 ⁻⁴
Late trauma, 11-17 years	chr8	144373356	144373369	14	3	ZNF696	3.1300×10 ⁻³	2.3700×10 ⁻⁹	1.1400×10 ⁻³
Late trauma, 11-17 years	chr11	69590328	69590332	5	2	FGF4	1.4600×10 ⁻⁸	1.0000×10 ⁻⁸	4.8300×10 ⁻³
Late trauma, 11-17 years	chr19	54963304	54963326	23	3	LENG8	8.3400×10 ⁻⁹	1.2100×10 ⁻⁸	5.8700×10 ⁻³
Late trauma, 11-17 years	chr1	26233376	26233623	248	8	STMN1	5.2600×10 ⁻³	1.3300×10 ⁻⁸	6.4500×10 ⁻³
Late trauma, 11-17 years	chr2	240171712	240171748	37	2	HDAC4	5.3800×10 ⁻³	2.1000×10 ⁻⁸	0.0101
Late trauma, 11-17 years	chr6	31275664	31276146	483	12		0.0145	2.3000×10 ⁻⁸	0.0111
Late trauma, 11-17 years	chr13	47472200	47472349	150	5	HTR2A	3.3800×10 ⁻⁴	2.7400×10 ⁻⁸	0.0132
Late trauma, 11-17 years	chr6	26196580	26196794	215	3		3.9500×10 ⁻⁴	3.7600×10 ⁻⁸	0.0182
Late trauma, 11-17 years	chr6	32064656	32064956	301	14	TNXB	0.0107	4.1100×10 ⁻⁸	0.0199
Late trauma, 11-17 years	chr22	24891129	24891158	30	4	C22orf45; UPB1	0.0134	5.2400×10 ⁻⁸	0.0253
Late trauma, 11-17 years	chr12	49297508	49297846	339	6	CCDC65	4.7700×10 ⁻³	6.1500×10 ⁻⁸	0.0297
Late trauma, 11-17 years	chr5	94621030	94621055	26	2	MCTP1	6.8000×10 ⁻⁶	7.3700×10 ⁻⁸	0.0356
Childhood trauma, 0-17 years	chr6	31275267	31276437	1171	20		2.6400×10 ⁻³	2.6900×10 ⁻¹³	1.3000×10 ⁻⁷
Childhood trauma, 0-17 years	chr4	10459929	10460237	309	3	ZNF518B	6.4900×10 ⁻⁴	4.8600×10 ⁻¹²	2.3500×10 ⁻⁶
Childhood trauma, 0-17 years	chr1	36108212	36108225	14	2	PSMB2	5.0800×10 ⁻⁶	2.9000×10 ⁻¹¹	1.4000×10 ⁻⁵

<i>Childhood trauma, 0-17 years</i>	chr6	110736772	110737053	282	5	DDO	4.9400×10 ⁻³	3.5800×10 ⁻¹¹	1.7300×10 ⁻⁵
<i>Childhood trauma, 0-17 years</i>	chrX	118986954	118987202	249	8	UPF3B	2.3400×10 ⁻³	5.3000×10 ⁻¹¹	2.5600×10 ⁻⁵
<i>Childhood trauma, 0-17 years</i>	chr7	94023308	94023557	250	3	COL1A2	9.6900×10 ⁻³	1.1600×10 ⁻¹⁰	5.6100×10 ⁻⁵
<i>Childhood trauma, 0-17 years</i>	chrX	153744384	153744612	229	5	FAM3A	0.0178	3.5100×10 ⁻¹⁰	1.7000×10 ⁻⁴
<i>Childhood trauma, 0-17 years</i>	chr2	240171712	240171748	37	2	HDAC4	2.7600×10 ⁻³	2.1700×10 ⁻⁹	1.0500×10 ⁻³
<i>Childhood trauma, 0-17 years</i>	chr2	31806234	31806767	534	6	SRD5A2	9.0900×10 ⁻³	5.1700×10 ⁻⁹	2.5000×10 ⁻³
<i>Childhood trauma, 0-17 years</i>	chr8	145106299	145106438	140	2	OPLAH	2.6700×10 ⁻⁵	7.9200×10 ⁻⁹	3.8200×10 ⁻³
<i>Childhood trauma, 0-17 years</i>	chr5	140579296	140579644	349	5	PCDHB11	7.7000×10 ⁻⁵	1.4400×10 ⁻⁸	6.9700×10 ⁻³
<i>Childhood trauma, 0-17 years</i>	chr1	26233404	26233623	220	7	STMN1	9.8800×10 ⁻⁴	1.6900×10 ⁻⁸	8.1900×10 ⁻³
<i>Childhood trauma, 0-17 years</i>	chrX	49687068	49687084	17	3	CLCN5	8.6800×10 ⁻⁴	2.1000×10 ⁻⁸	0.0102
<i>Childhood trauma, 0-17 years</i>	chrX	151999309	151999547	239	5	NSDHL; CETN2	0.0101	2.2800×10 ⁻⁸	0.0110
<i>Childhood trauma, 0-17 years</i>	chr15	49658865	49658975	111	2	C15orf33	3.8400×10 ⁻⁶	5.5300×10 ⁻⁸	0.0267
<i>Childhood trauma, 0-17 years</i>	chr2	208988863	208988967	105	3	CRYGD	5.6400×10 ⁻³	6.1200×10 ⁻⁸	0.0296
<i>Childhood trauma, 0-17 years</i>	chr3	196325238	196325552	315	3		4.6600×10 ⁻³	8.4400×10 ⁻⁸	0.0408

7.4. Functional enrichment

Table S13. Gene Ontology (GO) and KEGG pathway enrichment results for genes annotated to DMRs

Exposure	Database	Ontology	Description	N	DE	P.DE	FDR
Abuse-only trauma, 0-17 years	GO	BP	negative regulation of endocytosis	56	2	5.85E-04	1
Abuse-only trauma, 0-17 years	GO	BP	somatic stem cell population maintenance	68	2	0.00107	1
Abuse-only trauma, 0-17 years	GO	BP	stem cell population maintenance	177	2	0.00712	1
Abuse-only trauma, 0-17 years	GO	BP	maintenance of cell number	181	2	0.00745	1
Abuse-only trauma, 0-17 years	GO	BP	hormone metabolic process	240	2	0.00818	1
Abuse-only trauma, 0-17 years	GO	BP	regulation of endocytosis	213	2	0.0087	1
Abuse-only trauma, 0-17 years	GO	BP	cellular macromolecule catabolic process	1018	3	0.0301	1
Abuse-only trauma, 0-17 years	GO	BP	negative regulation of transport	478	2	0.0328	1
Abuse-only trauma, 0-17 years	KEGG	KEGG	Amyotrophic lateral sclerosis	347	2	0.0225	1
Early childhood trauma, 5-10 years	GO	MF	ligase activity, forming carbon-nitrogen bonds	48	2	0.00124	1
Early childhood trauma, 5-10 years	GO	MF	signalling receptor regulator activity	515	3	0.00737	1
Early childhood trauma, 5-10 years	GO	MF	growth factor activity	159	2	0.00819	1
Early childhood trauma, 5-10 years	GO	MF	ion binding	5867	11	0.0113	1
Early childhood trauma, 5-10 years	GO	MF	ligase activity	160	2	0.0114	1
Early childhood trauma, 5-10 years	GO	BP	pallium development	181	2	0.0145	1
Early childhood trauma, 5-10 years	GO	BP	positive regulation of ERK1 and ERK2 cascade	219	2	0.0153	1
Early childhood trauma, 5-10 years	GO	BP	skeletal system development	533	3	0.0155	1
Early childhood trauma, 5-10 years	KEGG	KEGG	Melanoma	72	2	0.00232	0.452
Early childhood trauma, 5-10 years	KEGG	KEGG	Prostate cancer	105	2	0.00505	0.623
Early childhood trauma, 5-10 years	KEGG	KEGG	Gastric cancer	149	2	0.00977	0.701
Early childhood trauma, 5-10 years	KEGG	KEGG	Breast cancer	147	2	0.00978	0.701
Adolescent trauma, 11-17 years	GO	BP	negative regulation of thrombin-activated receptor signalling pathway	3	2	8E-06	0.0916

Adolescent trauma, 11-17 years	GO	BP	regulation of thrombin-activated receptor signalling pathway	3	2	8E-06	0.0916
Adolescent trauma, 11-17 years	GO	BP	regulation of purine nucleotide metabolic process	90	3	7.99E-05	0.363
Adolescent trauma, 11-17 years	GO	BP	regulation of nucleotide metabolic process	91	3	8.09E-05	0.363
Adolescent trauma, 11-17 years	GO	BP	negative regulation of protein polymerization	78	3	8.74E-05	0.363
Adolescent trauma, 11-17 years	GO	BP	thrombin-activated receptor signalling pathway	13	2	9.76E-05	0.363
Adolescent trauma, 11-17 years	GO	BP	negative regulation of microtubule polymerization	13	2	1.11E-04	0.363
Adolescent trauma, 11-17 years	GO	BP	regulation of generation of precursor metabolites and energy	132	3	2.76E-04	0.79
Adolescent trauma, 11-17 years	KEGG	KEGG	MicroRNAs in cancer	305	3	0.00164	0.606
Adolescent trauma, 11-17 years	KEGG	KEGG	Calcium signalling pathway	250	2	0.0355	1
Adolescent trauma, 11-17 years	KEGG	KEGG	MAPK signalling pathway	298	2	0.0492	1
Childhood trauma, 0-17 years	GO	MF	steroid dehydrogenase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor	30	2	1.43E-04	1
Childhood trauma, 0-17 years	GO	MF	steroid dehydrogenase activity	34	2	1.88E-04	1
Childhood trauma, 0-17 years	GO	BP	skin development	304	3	0.00188	1
Childhood trauma, 0-17 years	GO	MF	oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor	122	2	0.00403	1
Childhood trauma, 0-17 years	GO	MF	oxidoreductase activity, acting on CH-OH group of donors	132	2	0.00454	1
Childhood trauma, 0-17 years	GO	MF	hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds	131	2	0.00517	1
Childhood trauma, 0-17 years	GO	BP	mRNA transport	127	2	0.00592	1
Childhood trauma, 0-17 years	GO	BP	skin epidermis development	121	2	0.00618	1
Childhood trauma, 0-17 years	KEGG	KEGG	Neutrophil extracellular trap formation	175	2	0.00673	1
Childhood trauma, 0-17 years	KEGG	KEGG	MicroRNAs in cancer	305	2	0.0151	1
Childhood trauma, 0-17 years	KEGG	KEGG	Metabolic pathways	1531	4	0.0382	1



Figure S10. Functional enrichment of cannabis-moderated trauma-DMRs.

Dot plots showing the top enriched KEGG and Reactome pathways for genes mapped to DMRs identified in childhood trauma x cannabis interaction models across the four trauma definitions. Dot sizes represent gene count and colour indicates adjusted p-value.

8. Mediation Analyses (DACT)

Epigenome-wide mediation analyses were conducted using the Divide-Aggregate Composite-null Test (DACT) framework to evaluate whether DNAm mediates the association between childhood trauma and PLEs. Diagnostic plots and genome-wide summaries of DACT results are presented below. These analyses are exploratory and interpreted cautiously.

8.1. DACT Model Diagnostics

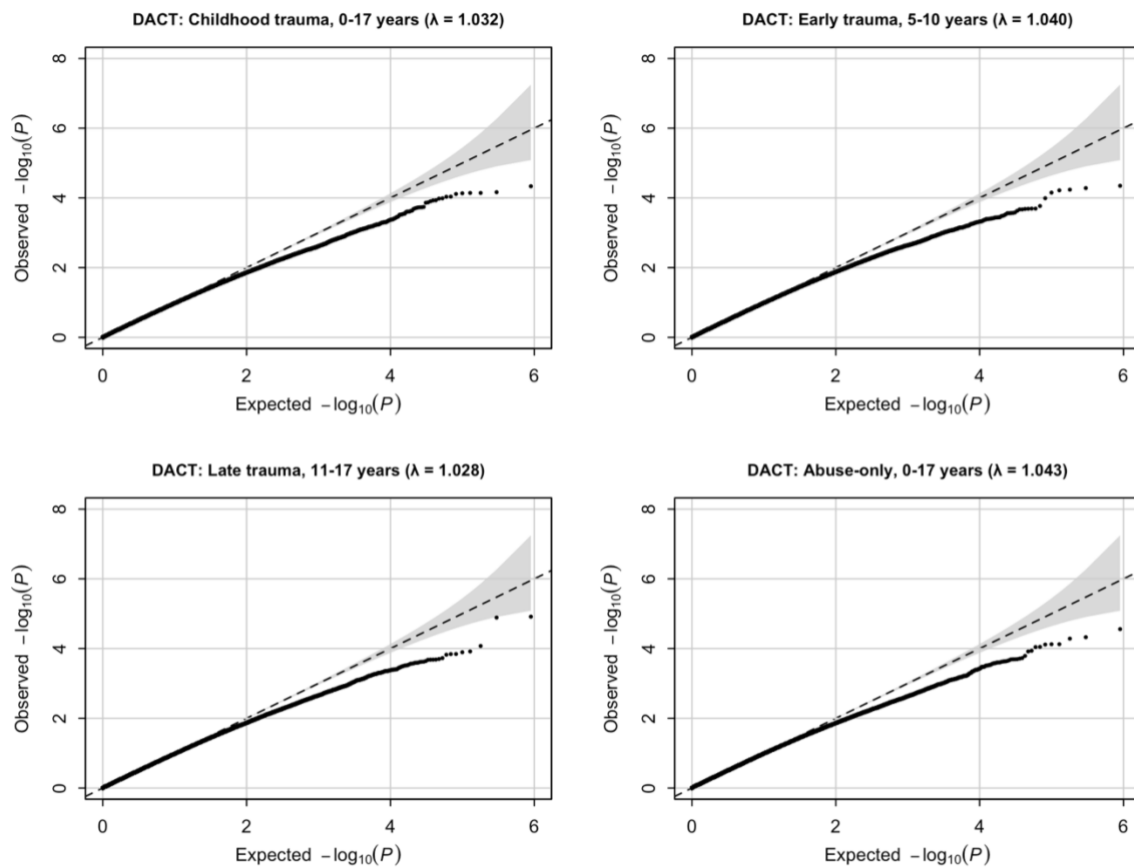


Figure S11. QQ plots for EWAS analyses using the DACT framework.

The dashed line indicates the null expectation and the shaded region the 95% confidence envelope. Genomic inflation factors (λ) are reported in each panel.

8.2. CpG-level mediation results

CpG-level mediation results from the DACT framework are summarised using Manhattan and quadrant plots (**Figures S12-S13**).

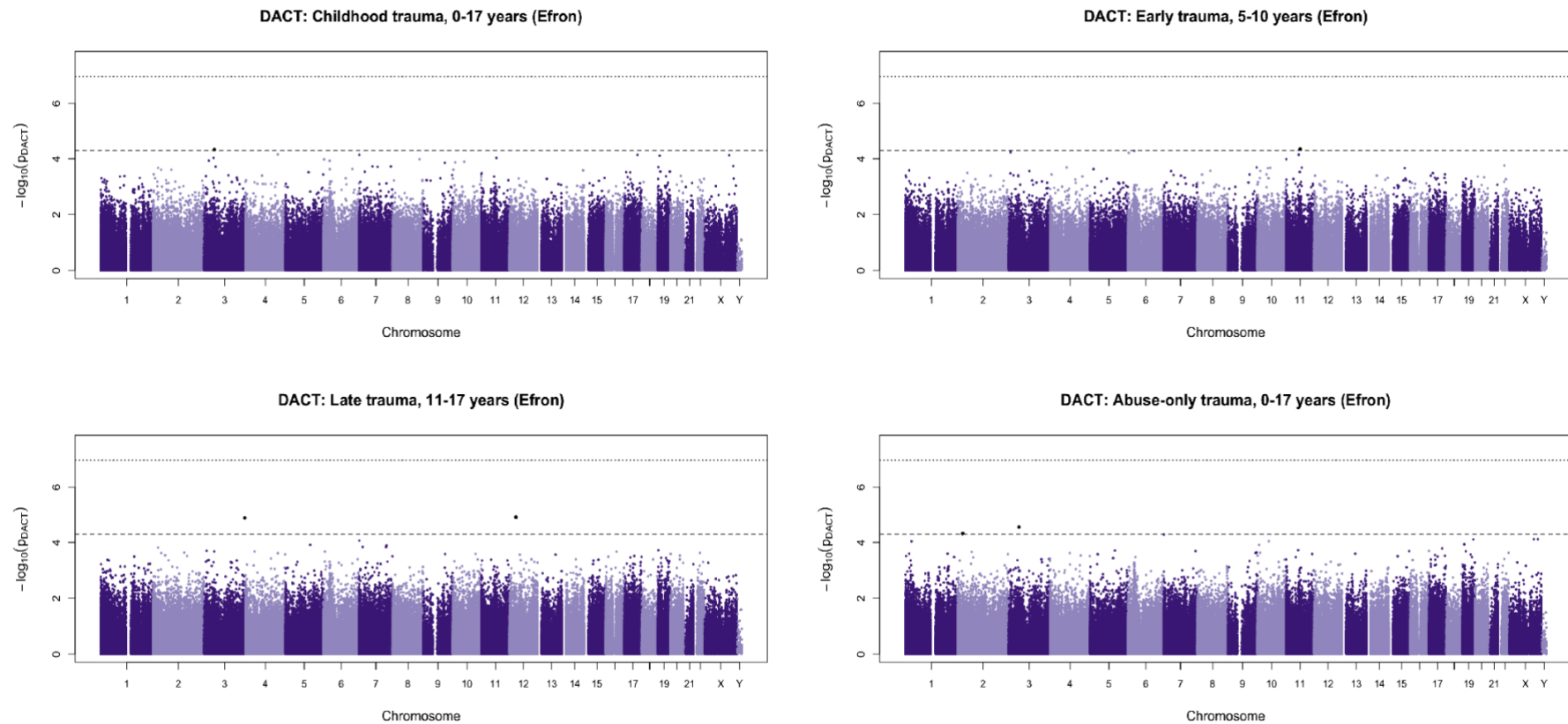


Figure S12. Epigenome-wide mediation analysis of early childhood trauma and PLEs (DACT).

Manhattan plot showing epigenome-wide mediation results from the DACT analysis examining DNAm as a mediator of the association between childhood trauma and PLEs at age 18. Each point represents a CpG site plotted according to genomic position across chromosomes and the $-\log_{10}$ -transformed DACT p-value. The horizontal dashed line indicates a suggestive discovery threshold ($p < 5 \times 10^{-5}$), while the dotted line represents the Bonferroni-corrected threshold.

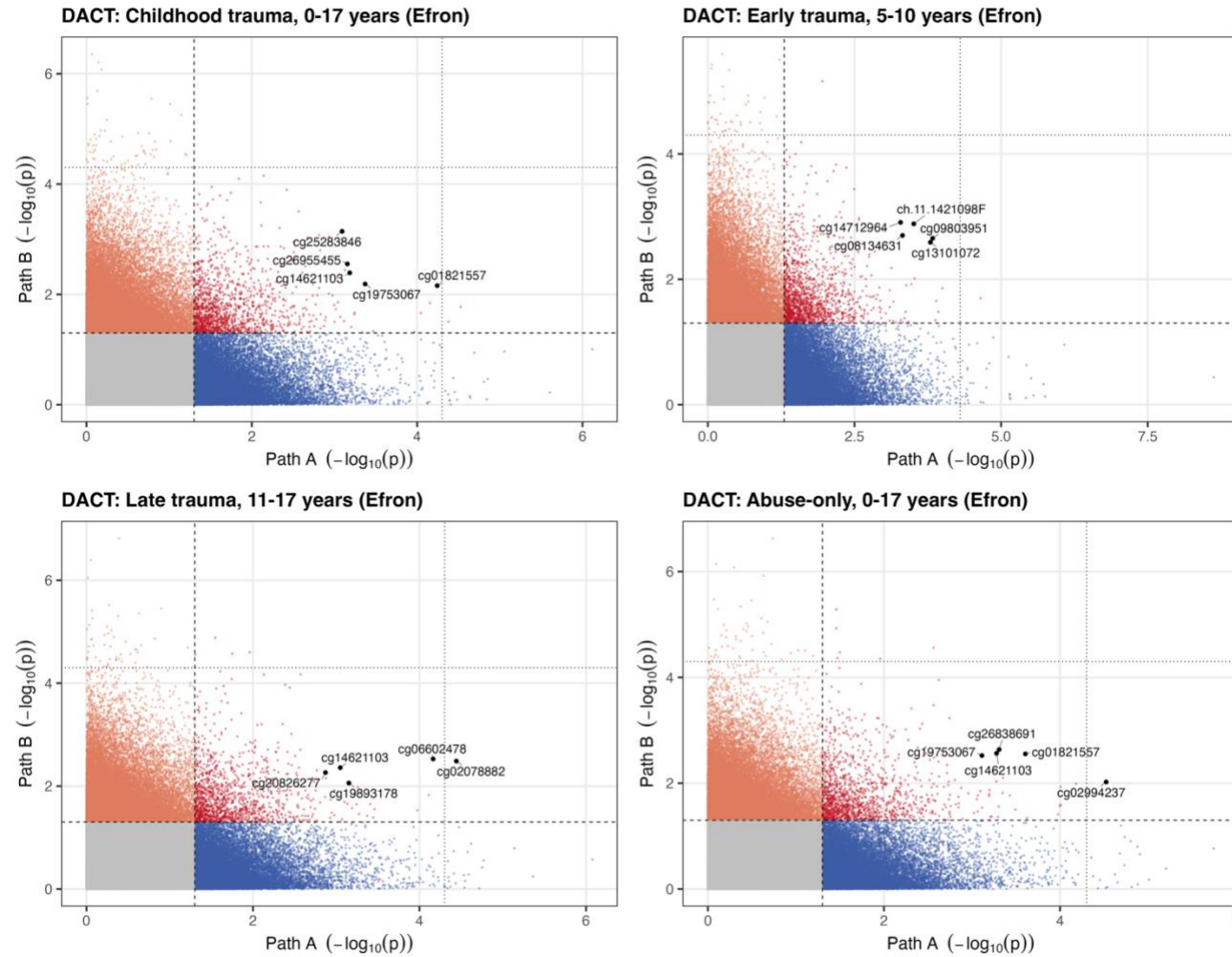


Figure S13. Quadrant plots of CpG-level associations for Path A and Path B.

Each point represents a CpG site plotted according to the $-\log_{10}$ -transformed p-values from the Path A model and the Path B model. Dashed lines indicate the nominal significance thresholds ($p = 0.05$). points are coloured according to significance pattern: both models, path A only, path B only, or neither. CpG sites showing suggestive mediation signal are highlighted and labelled.

8.3. Cannabis-moderated Mediation (DACT)

Exploratory mediation analyses were conducted using the DACT framework to assess whether DNAm mediated the association between childhood trauma and PLEs under cannabis-moderated conditions. Across models, there was little evidence supporting a mediating role of DNAm after correction for multiple testing (**Table S14**). While a small number of CpG sites showed nominal significance, these did not survive FDR correction and should be interpreted cautiously. Overall, these findings are consistent with the primary analyses, providing limited support for DNAm as a mediator of the trauma-
PLE association, even when accounting for potential modification by cannabis use.

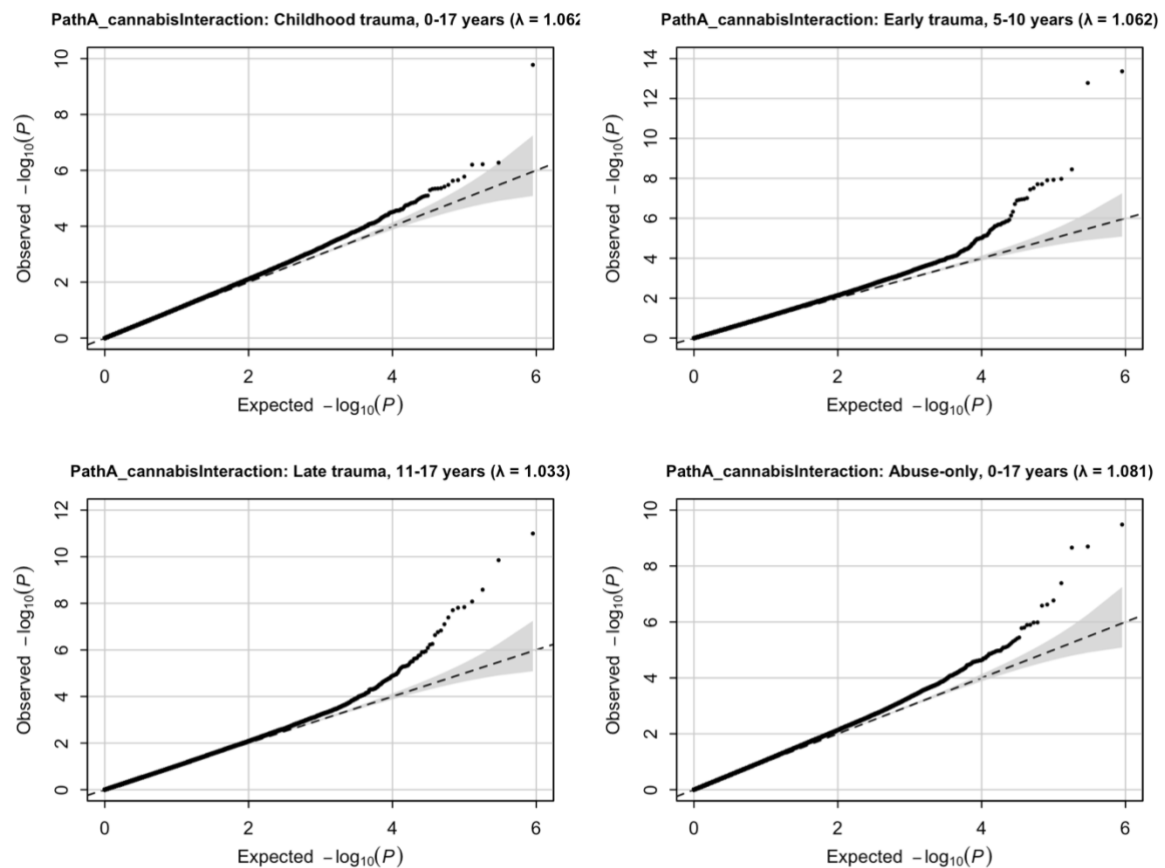


Figure S14. QQ plots for EWAS-moderated analyses using the DACT framework.

The dashed line indicates the null expectation and the shaded region the 95% confidence envelope. Genomic inflation factors (λ) are reported in each panel.

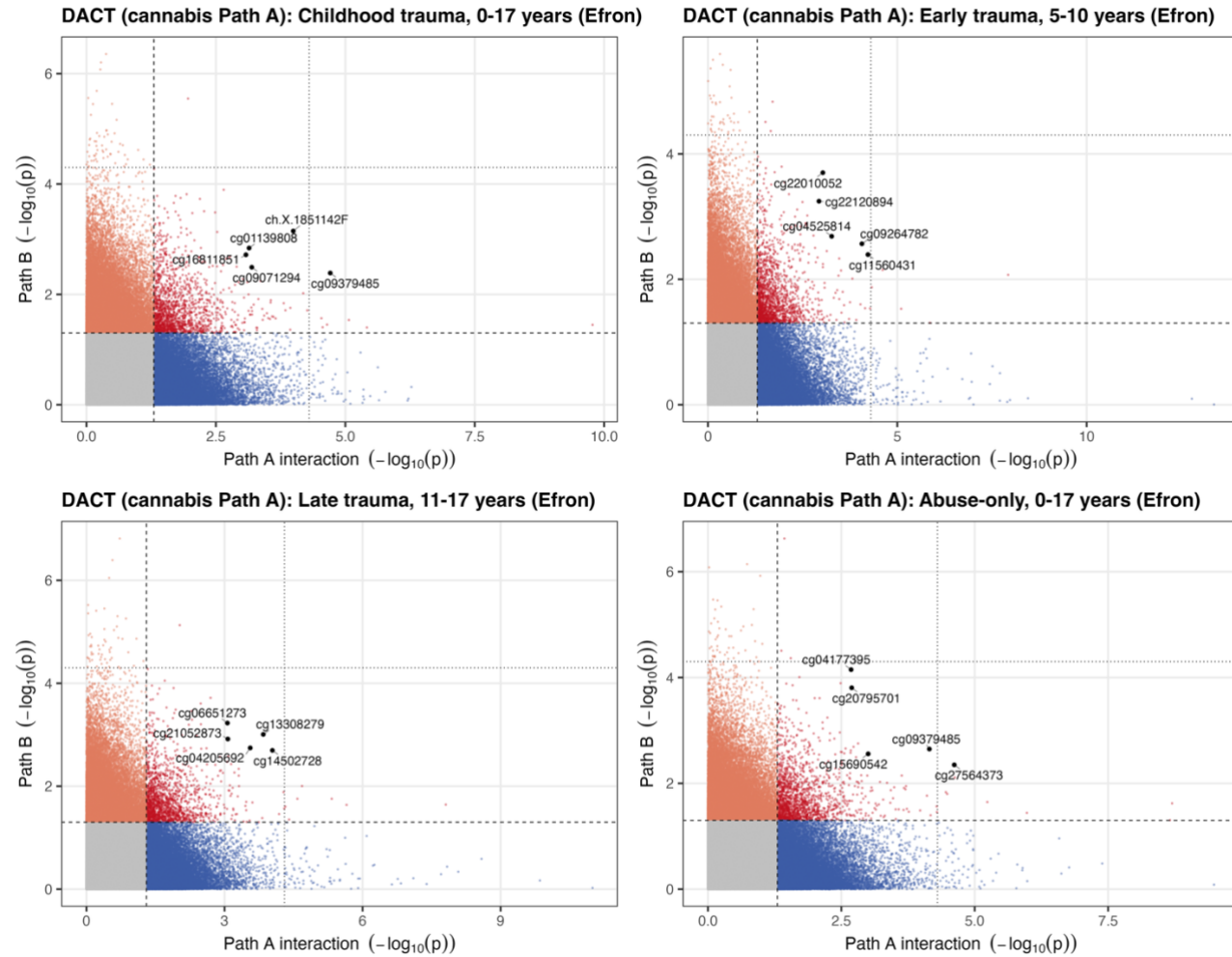


Figure S15. Quadrant plots of CpG-level associations for Cannabis-moderated Path A and Path B.

Each point represents a CpG site plotted according to the $-\log_{10}$ -transformed p-values from the Path A model and the Path B model. Dashed lines indicate the nominal significance thresholds ($p = 0.05$). points are coloured according to significance pattern: both models, path A only, path B only, or neither. CpG sites showing suggestive mediation signal are highlighted and labelled.

Table S14. Top CpG sites showing suggestive evidence of mediation

Exposure	Probe	Genomic location (hg19)	Gene	Location	Mediation effect	P-value	FDR
Childhood trauma, 0-17 years	ch.X.1851142F	X:128216049		OpenSea	-0.2173	3.5463×10^{-5}	0.9678
Late trauma, 11-17 years	cg13308279	2:197456953	HECW2	N_Shore	0.1252	3.8818×10^{-5}	0.9725

Genomic locations are reported according to the hg19 reference genome. Gene annotation and CpG island context correspond to the Illumina HumanMethylation450 array annotation.