Title: GWAS integrating maternal and child genetics reveals novel risk-modifying loci for fetal alcohol spectrum disorders (FASD)

Supplementary Materials

A. Sample Characteristics in Cape Town Longitudinal Cohorts (CLTC)

Table S1: Sample Characteristics of each CTLC cohort

N		CTLC 1			CTLC 2		
		Controls *M* (SD) / n (%)	Heavy drinking mothers *M* (SD) / n (%)	*p*[a]	Controls *M* (SD) / n (%)	Heavy drinking mothers *M* (SD) / n (%)	*p*[a]
		52	76		80	120	
Maternal characteristics							
Maternal age at conception (yr)		25.9 (5.4)	27.0 (6.3)	0.303	25.8 (5.2)	27.5 (6.0)	**0.031**
Parity (n live births)		2.0 (1.1)	2.3 (1.5)	0.189	1.4 (1.2)	1.7 (1.5)	0.188
Education (yr school completed)		9.7 (1.9)	7.9 (2.7)	**<0.001**	10.0 (1.7)	9.2 (1.7)	**0.002**
Socioeconomic status score [b]		22.9 (8.5)	18.9 (8.3)	**0.008**	22.8 (7.1)	20.5 (7.2)	**0.014**
Alcohol consumption	oz AA/day	0.0 (0.0)	1.0 (1.0)	**<0.001**	0.0 (0.0)	0.9 (1.1)	**<0.001**
	oz AA/drinking day	0.1 (0.3)	4.0 (2.5)	**<0.001**	0.1 (0.4)	4.3 (2.4)	**<0.001**
	Drinking days/week	0.0 (0.1)	1.5 (1.1)	**<0.001**	0.0 (0.2)	1.3 (1.0)	**<0.001**
n (%) reporting cigarette smoking		24 (46.2)	66 (86.8)	**<0.001**	53 (66.3)	102 (85.0)	**0.002**
Cigarettes/day among smokers		7.4 (8.1)	7.8 (5.4)	0.748	5.4 (3.9)	6.7 (4.2)	0.075
Child characteristics							
Weeks gestation at delivery		39.1 (1.8)	38.5 (2.7)	0.054	38.9 (2.2)	38.8 (2.0)	0.889
Preterm delivery (< 37 weeks), n (%)		6 (11.5)	17 (22.4)	0.117	12 (15.0)	15 (12.5)	0.612
Infant sex, no. female (%)		29 (55.8)	33 (43.4)	0.234	36 (45.0)	67 (55.8)	0.133
FAS or PFAS diagnosis, *n* (%)		0 (0.0)	36 (47.4)	**<0.001**	0 (0.0)	36 (30.8)	**<0.001**

FAS = fetal alcohol syndrome using Hoyme 2005 criteria [1]; PFAS = partial FAS.

[a] From comparisons of heavy exposure vs. control groups within cohort from independent samples *t*-tests for continuous variables and chi-square or Fisher's exact test for categorical variables.

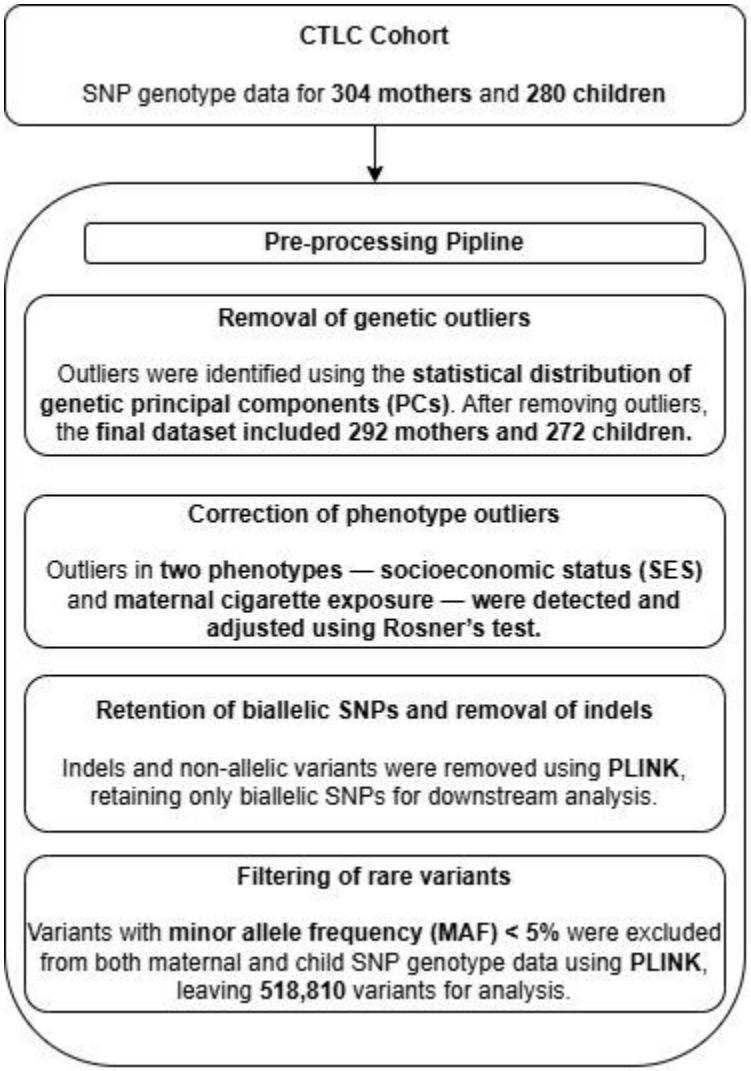
[b] Hollingshead socioeconomic score [2].

B. Supplementary Methods

1. *Biospecimen collection/handling and DNA and RNA extraction:*
A 10 ml venous EDTA whole blood sample was obtained from each mother and child in CTLC 1 in 2009 at our diagnostic clinic. For CTLC 2, a 10 ml venous EDTA whole blood sample was obtained from mothers at a prenatal study visit (2011-2015); saliva samples were obtained with oragene-575 kits (DNAgenotek, Ottawa, Canada) from infants in the 1st year of life. For mothers or children from both cohorts missing a venous blood sample (e.g., due to missed visits or failed blood draws), saliva samples were obtained using oragene-500 kits (DNAgenotek, Ottawa, Canada). All samples were stored at -80 degrees C (within 24 hours for blood and within 1 year for saliva (per manufacturer instructions)) and shipped with continuous cold chain until processing for DNA. DNA was isolated using the Maxwell® 16 LEV Blood DNA Kit (Promega, #AS1290, Madison, WI) and stored at - 20°C until genotyping assays were performed.

   In CTLC 2, immediately following delivery, placentas were stored at 2 °C to preserve tissue integrity. Biopsies were excised from four quadrants within 2 cm of the umbilical cord insertion site, ensuring exclusion of maternal decidua, and were flash-frozen at −80 °C within 72 hours post-delivery. Whole blood samples were obtained from children in CTLC 1 at age 9 years in phlebotomy tubes with RNALater solution and from children in CTLC 2 at age 5 years in PAX gene tubes (all samples frozen at −80 °C within 24 hours). Total RNA was extracted from homogenized frozen placental tissue and blood samples using the Maxwell 16 LEV simplyRNA Tissue Kit (Promega #AS1280; Madison, WI), according to the manufacturer's protocol. RNA integrity was evaluated with an Agilent Bioanalyzer (Agilent Technologies, Santa Clara, CA). Samples with RNA integrity number (RIN) < 4 were excluded from downstream analyses to ensure high-quality transcriptomic data.

2. *Quality Control Pre-processing Pipeline:*
Supplementary Figure S1: Pre-processing pipeline for CLTC. The SNP genotype data of 304 mothers and 280 children underwent a series of quality-control and filtering steps before downstream analysis. Genetic outliers were identified based on the distribution of genetic principal components, resulting in 292 mothers and 272 children left. Phenotype outliers in socioeconomic status (SES) and maternal cigarette exposure were detected and corrected using Rosner's test. Finally, rare variants with minor allele frequency (MAF) < 5% were removed from both maternal and child genotype datasets using PLINK.



3. *Stratified Single Marker and Gene-based analysis*

Single-marker genome-wide association analyses were conducted using GEMMA [3] based on a univariate linear mixed-model framework, adjusting for cohort, relevant biological covariates, and the top three genetic principal components. Gene-based analyses were performed in GCTA [4] using the fastBAT implementation, which aggregates single-marker summary statistics within gene boundaries while accounting for linkage disequilibrium (LD). All gene-based analyses were run with the following parameters: minimum minor allele frequency (MAF) cutoff (--maf 0.05), LD r^2 threshold for variant pruning (--fastBAT-ld-cutoff 0.2), and maximum allowable allele frequency difference between GWAS summary statistics and the LD reference panel (--diff-freq 1). Stratified analyses were

performed separately for mothers and children in CTLC, enabling independent evaluation of maternal- vs. child-specific genetic contributions. For CIFASD, analyses were limited to child genotypes due to the absence of maternal genetic data, and the same model framework and parameter settings were applied. Summary statistics generated from GEMMA (single-marker) and GCTA (gene-based) analyses in CTLC (mother and child strata) and CIFASD were subsequently combined using METAL [5] under an inverse-variance weighted fixed-effects model. Meta-analysis was performed separately for each outcome—working memory, recognition discrimination, height-for-age Z-scores, and FAS/PFAS diagnoses—ensuring harmonized allele orientation, consistent variant filtering, and comparable model specifications across datasets.

C. Supplementary Tables:

Supplementary Table S2. Top results (p <10^{-5}) from single-marker gene-by-prenatal alcohol exposure interaction analyses, stratified by child vs. maternal genotype.

Working memory[a]						
Child SNP	**Position**	**Allele frequency**	**B[b]**	***p*[b]**	**Gene**	**Functional location**
rs2833924	21:33965444	0.069	-1.95	8.796E-08	C21orf59-TCP10L	intronic
rs17105769	10:92875198	0.149	-1.18	1.730E-06	LINC00502;NUDT9P1	intergenic
JHU_21.37893531	21:37893532	0.011	-3.81	2.955E-06	CLDN14	intronic
rs4755863	11:44696386	0.201	-0.98	6.792E-06	CD82;TSPAN18	intergenic
JHU_4.118805143	4:118805144	0.04	-2.06	7.684E-06	LINC02264;NDST3	intergenic
rs12090855	1:28874969	0.168	-1.07	9.059E-06	RCC1;TRNAU1AP	intergenic
Maternal SNP	**Position**	**Allele frequency**	**B[b]**	***p*[b]**	**Gene**	**Functional location**
rs17050152	4:119948059	0.099	-1.46	7.724E-07	SYNPO2[a]	exonic
JHU_12.82072378	12:82072379	0.021	-2.69	2.983E-06	PPFIA2	intronic
rs11004189	10:56025604	0.294	0.87	5.249E-06	PCDH15	intronic
rs2837409	21:41434841	0.353	-0.81	6.012E-06	DSCAM[b]	intron
rs928874	21:43422525	0.225	0.87	6.059E-06	ZBTB21[c]	intron
JHU_5.173608177	5:173608178	0.124	-1.18	6.651E-06	NSG2;LINC01411	intergenic
JHU_5.173608186	5:173608187	0.124	-1.18	6.651E-06	NSG2;LINC01411	intergenic
Recognition Memory[a]						
Child SNP	**Position**	**Allele frequency**	**B[b]**	***p*[b]**	**Gene**	**Functional location**
rs146158456	4:104299169	0.031	2.61	1.622-06	CENPE;LINC02428	intergenic

rs17033640	4:104352298	0.037	2.51	1.715E-06	LINC02428	ncRNA_intronic
14:85971029-T-C	14:85971029	0.017	3.64	4.156E-06	LINC00911;FLRT2	intergenic
JHU_3.193298036	3:193298037	0.017	-3.65	4.678E-06	ATP13A4-AS1;OPA1	intergenic
JHU_8.139934415	8:139934416	0.158	-1.08	4.807E-06	COL22A1;KCNK9	intergenic
rs245881	7:29186576	0.21	1.05	5.073E-06	CHN2	splicing
rs79981953	3:11846332	0.017	3.14	5.583E-06	TAMM41	intronic
JHU_14.85862075	14:85862076	0.019	3.55	5.914E-06	LINC00911	ncRNA_intronic
rs2367270	1:63775056	0.303	0.82	6.646E-06	LINC00466	ncRNA_intronic
JHU_2.227462768	2:227462769	0.015	3.64	6.720E-06	LOC646736;MIR5702	intergenic
8:106550935-T-C	8:106550935	0.023	-2.71	7.881E-06	ZFPM2	intronic
rs115050136	2:2290118	0.027	-2.42	8.063E-06	MYT1L	intronic
JHU_1.58800894	1:58800895	0.029	-2.35	8.624E-06	DAB1;OMA1	intergenic
JHU_8.32830308	8:32830309	0.015	-3.12	9.142E-06	NRG1;FUT10	intergenic
16:85945839-T-C	16:85945839	0.375	0.77	1.030E-05	IRF8	intronic
Maternal SNP	**Position**	**Allele frequency**	**B[b]**	***p*[b]**	**Gene**	**Functional location**
JHU_10.24636091	10:24636092	0.01	3.81	8.041E-07	KIAA1217	intronic
rs58700910	4:72821343	0.02	3.71	8.139E-07	GC;NPFFR2	intergenic
rs13334607	16:11501672	0.07	1.78	9.975E-07	LOC400499	intronic
JHU_11.132776282	11:132776283	0.03	2.37	1.230E-06	OPCML	intronic
rs142305106	8:19445942	0.03	2.51	1.657E-06	CSGALNACT1	intronic
rs117715715	9:17800733	0.03	3.40	1.885E-06	SH3GL2;ADAMTSL1	intergenic
JHU_5.74579976	5:74579977	0.01	3.68	1.967E-06	ANKRD31;HMGCR	intergenic
rs10088422	8:2515011	0.10	1.29	2.697E-06	LOC101927815	ncRNA_intronic
JHU_5.116289861	5:116289862	0.01	3.62	2.768E-06	LINC02214;LINC00992	intergenic
rs2118306	7:51230648	0.26	0.87	3.036E-06	COBL	intronic
JHU_5.74603566	5:74603567	0.02	3.45	3.836E-06	ANKRD31;HMGCR	intergenic
JHU_17.81069039	17:81069040	0.02	2.88	4.207E-06	METRNL;RPL23AP87	intergenic
rs78922030	11:74808060	0.02	3.40	4.356E-06	OR2AT4	upstream
JHU_1.103225558	1:103225559	0.01	3.58	4.516E-06	OLFM3;COL11A1	intergenic
JHU_1.103289573	1:103289574	0.01	3.58	4.516E-06	OLFM3;COL11A1	intergenic
rs77959025	8:128761169	0.03	2.06	4.635E-06	MYC;PVT1	intergenic
JHU_8.5494744	8:5494745	0.03	-2.23	4.902E-06	CSMD1;LOC100287015	intergenic
rs77254457	4:16116327	0.02	4.60	4.998E-06	PROM1;TAPT1	intergenic
rs144198095	1:40567480	0.02	3.38	5.121E-06	PPT1;RLF	intergenic

rs7920612	10:64155108	0.13	1.10	5.336E-06	ZNF365	intronic
rs9929426	16:65554054	0.03	2.11	5.541E-06	LINC00922	ncRNA_intronic
rs61910329	11:132894580	0.02	2.70	5.690E-06	OPCML	intronic
JHU_1.234092092	1:234092093	0.04	2.11	5.692E-06	SLC35F3	intronic
JHU_7.49100983	7:49100984	0.01	4.49	6.492E-06	CDC14C;VWC2	intergenic
JHU_5.149978080	5:149978081	0.01	3.26	6.624E-06	NDST1;SYNPO	intergenic
rs6074288	20:11354492	0.02	3.43	6.778E-06	LOC339593;LINC00687	intergenic
JHU_7.31300246	7:31300247	0.01	4.52	7.305E-06	ADCYAP1R1;NEUROD6	intergenic
JHU_10.80474090	10:80474091	0.02	4.49	7.355E-06	LINC00595;ZMIZ1-AS1	intergenic
JHU_19.28843470	19:28843471	0.01	4.53	7.661E-06	LOC101927151;LOC100420587	intergenic
rs17034520	3:3671797	0.09	1.31	7.934E-06	CRBN;LOC100130207	intergenic
JHU_19.56510897	19:56510898	0.01	-3.09	7.949E-06	NLRP5	upstream
JHU_16.58365619	16:58365620	0.04	1.95	8.122E-06	PRSS54;GINS3	intergenic
JHU_2.220589811	2:220589812	0.37	0.74	8.154E-06	SLC4A3;LINC01803	intergenic
rs7495569	15:67152143	0.19	0.89	8.164E-06	SMAD6;LINC02206	intergenic
rs115586346	4:190383444	0.01	3.66	8.288E-06	LINC02508;LINC01262	intergenic
rs186393424	4:92343724	0.01	3.43	8.401E-06	CCSER1	intronic
rs16845151	1:172903801	0.03	2.06	8.788E-06	FASLG;TNFSF18	intergenic
rs57256427	1:184227393	0.02	2.80	8.846E-06	TSEN15;C1orf21	intergenic
rs73788238	5:132284424	0.02	3.29	9.154E-06	AFF4	intronic
JHU_6.122191508	6:122191509	0.05	1.89	9.173E-06	GJA1;HSF2	intergenic
rs79991851	9:108443145	0.01	4.56	9.469E-06	TAL2;TMEM38B	intergenic
rs66491337	11:17019362	0.01	-4.52	9.690E-06	PLEKHA7	intronic
rs77422618	12:126390116	0.02	4.39	9.884E-06	TMEM132B;LINC00939	intergenic
rs116633419	5:1863141	0.02	4.33	1.013E-05	LINC02116;IRX4	intergenic
Height[c]						
Child SNP	**Position**	**Allele frequency**	**B[b]**	***p*[b]**	**Gene**	**Functional location**
rs7629412	3:10553635	0.19	-0.98	4.643E-06	ATP2B2	intronic
JHU_3.148010020	3:148010021	0.09	-1.29	4.854E-06	LINC02046	ncRNA_intronic
rs10866075	3:65937976	0.49	0.77	5.035E-06	MAGI1-IT1	ncRNA_intronic
rs17057519	5:159637815	0.15	-1.11	5.992E-06	FABP6	intronic
JHU_3.148028085	3:148028086	0.11	-1.23	6.987E-06	LINC02046	ncRNA_intronic
JHU_3.148011647	3:148011648	0.09	-1.29	7.895E-06	LINC02046	ncRNA_intronic
JHU_1.7001077	1:7001078	0.27	0.84	8.817E-06	CAMTA1	intronic

JHU_13.69171696	13:69171697	0.02	-3.04	9.427E-06	LINC00364;LINC00550	intergenic
Maternal SNP	**Position**	**Allele frequency**	**B[b]**	***p*[b]**	**Gene**	**Functional location**
rs115951928	16:82997358	0.10	-1.34	8.461E-07	LOC101928417	ncRNA_intronic
rs11762282	7:3152116	0.04	1.94	1.519E-06	CARD11;LOC100129603	intergenic
JHU_6.103709506	6:103709507	0.02	-2.81	3.150E-06	GRIK2;HACE1	intergenic
rs7021714	9:124364349	0.30	0.78	5.559E-06	DAB2IP	intronic

[a]Z-scores were calculated within each cohort for working memory and recognition memory scores on the California Verbal Learning Test-Children's version (Pearson Clinical Assessments, USA) administered at age 10 years for CTLC 1 and on the Wide Range Assessment of Memory and Learning, 2nd Edition (Pearson Clinical Assessments, USA) administered at age 7 years for CTLC 2. Missing for 24 children.

[b]Values are unstandardized regression coefficients and associated p-values for gene-by-prenatal alcohol exposure (yes vs. no) adjusting for cohort, maternal age at conception, and Hollingshead socioeconomic status score (37) from INSERT METHOD.

[c]Age- and sex-specific Z-scores were calculated using CDC reference norms.

Supplementary Table S3. Top results (p <10^{-4}) from gene-based analyses, stratified by child vs. mother genotype.

Working Memory									
Child Gene	**Chr**	**Start**	**End**	**No.SNPs**	**SNP_start**	**SNP_end**	**TopSNP**	**TopSNP_Pvalue**	**P_fastBAT**
SYNJ1	21	34001069	34100351	24	rs2833916	rs11910504	rs2833924	8.90E-09	4.37E-05
SYS1-DBNDD2	20	43991840	44039250	34	exm1544474	JHU_20.44080776	JHU_20.44075785	6.73E-05	4.56E-05
RARA	17	38465432	38513895	7	rs76584199	17:38545824-CA	17:38482263-A-C	0.000204848	6.47E-05
TP53TG5	20	44001197	44036529	29	rs6104118	JHU_20.44080776	JHU_20.44075785	6.73E-05	0.00006925
GJD3	17	38516904	38520989	6	17:38482263-A-C	17:38545824-CA	17:38482263-A-C	0.000204848	7.36E-05
EPGN	4	75174187	75182506	15	rs16850798	rs2168889	rs2125398	1.25E-05	8.76E-05
CFAP298	21	33964389	33984913	22	rs2833876	rs10470165	rs2833924	8.90E-09	9.98E-05
Mother Gene	**Chr**	**Start**	**End**	**No.SNPs**	**SNP_start**	**SNP_end**	**TopSNP**	**TopSNP_Pvalue**	**P_fastBAT**
GLRX3	10	131934655	131982785	38	rs752847	rs11017147	rs752847	0.000716219	0.000027152
Recognition Memory									
Child Gene	**Chr**	**Start**	**End**	**No.SNPs**	**SNP_start**	**SNP_end**	**TopSNP**	**TopSNP_Pvalue**	**P_fastBAT**
FOXD3	1	63788238	63790799	20	JHU_1.63748131	rs10889417	rs2367270	2.48E-06	4.66E-06
TMEM37	2	120187477	120196080	21	rs6759748	rs10193449	rs11123523	0.00206776	0.000022371
SCTR	2	120197419	120282877	40	rs9308776	JHU_2.120324824	rs11123523	0.00206776	3.05E-05
Mother Gene	**Chr**	**Start**	**End**	**No.SNPs**	**SNP_start**	**SNP_end**	**TopSNP**	**TopSNP_Pvalue**	**P_fastBAT**

IQGAP3	1	156495197	156542396	24	rs74116853	rs2365714	rs10159180	0.000123681	1.71E-05
Reduced Child Height									
Child Gene	**Chr**	**Start**	**End**	**No.SNPs**	**SNP_start**	**SNP_end**	**TopSNP**	**TopSNP_Pvalue**	**P_fastBAT**
STX6	1	180941848	180992257	34	rs12735084	rs12144382	rs12240122	9.84E-06	2.22E-06
Mother Gene	**Chr**	**Start**	**End**	**No.SNPs**	**SNP_start**	**SNP_end**	**TopSNP**	**TopSNP_Pvalue**	**P_fastBAT**
NFIC	19	3314401	3469215	78	rs12461208	JHU_19.3513202	rs10412720	2.48E-04	5.52E-05
TRIM37	17	57059999	57184282	11	JHU_17.57033522	rs7502947	rs16943326	9.64E-05	7.24E-05
FASD Diagnosed									
Child Gene	**Chr**	**Start**	**End**	**No.SNPs**	**SNP_start**	**SNP_end**	**TopSNP**	**TopSNP_Pvalue**	**P_fastBAT**
ENSG00000269242	19	12754645	12759211	11	rs2861405	exm1431347	rs2861405	0.000281537	4.01E-05
MAN2B1	19	12757325	12777556	12	rs2861405	rs722572	rs2861405	0.000281537	4.64E-05
WFDC11	20	44277202	44298909	6	exm1544910	rs6065861	rs2072973	5.69E-05	5.00E-05
ZNF490	19	12686914	12750912	18	rs6511824	exm1431323	rs2861405	0.000281537	0.000072566

Supplementary Table S4. Top results (p <10^{-5}) from single-marker analyses in CIFASD dataset.

	Chr	SNP	bp	A1	A2	Freq	b	se	p	Gene.refGene	Func.refGene
FASD Diagnosed	6	rs117411227	162493955	A	C	0.038307	0.412107	0.077977	1.26E-07	PRKN	intronic
	6	rs117503335	162487291	A	G	0.038307	0.412107	0.077977	1.26E-07	PRKN	intronic
	6	rs117898110	32503750	T	C	0.008065	0.900472	0.175428	2.85E-07	HLA-DRB5;HLA-DRB6	intergenic
	6	rs116982244	162493064	T	C	0.048387	0.339245	0.06927	9.71E-07	PRKN	intronic
Reduced Child Height	2	rs10211032	117323073	G	A	0.545455	0.376339	0.078265	0.000002	DPP10;DDX18	intergenic
	2	rs4849503	117318913	C	A	0.54397	0.374808	0.077954	0.000002	DPP10;DDX18	intergenic
	2	rs6542329	117313119	T	C	0.348601	-0.36963	0.078528	0.000003	DPP10;DDX18	intergenic
	2	rs4849504	117319906	A	G	0.542607	0.361885	0.077719	0.000003	DPP10;DDX18	intergenic
	2	rs4848424	117303977	T	C	0.355499	-0.363897	0.078702	0.000004	DPP10;DDX18	intergenic
	2	rs11899224	117321055	T	C	0.350254	-0.360021	0.07816	0.000004	DPP10;DDX18	intergenic
	2	rs4849497	117310394	T	C	0.33794	-0.363166	0.079461	0.000005	DPP10;DDX18	intergenic
Working Memory	15	rs1023924	73438622	C	T	0.33419	5.4527	1.21379	0.000007	NEO1	intronic
	5	rs1482371	113096508	G	A	0.345758	-5.34338	1.20019	0.000009	YTHDC2;KCNN2	intergenic

Supplementary Table S5. Top results (p <10^{-4}) from gene-based analyses in CIFASD dataset.

	Gene	Chr	Start	End	No.SNPs	SNP_start	SNP_end	TopSNP	TopSNP_Pvalue	P_fastBAT
FASD Diagnosed	MIR2278	9	97572243	97572339	141	rs12337706	rs4744386	rs7019720	8.03E-06	2.25E-05
	SNORD102	13	27829200	27829272	44	rs4454823	rs9507870	rs9507870	1.43E-05	4.85E-05
	TMEM67	8	94767071	94831460	49	rs2976365	rs4236814	rs3133974	6.60E-06	5.97E-05
	SIGLEC16	19	50472911	50479076	70	rs3786665	rs2278410	rs55914901	2.06E-05	6.66E-05
	RBM12B	8	94743730	94753224	32	rs10104450	rs3134028	rs3133974	6.60E-06	8.23E-05
	RBM12B-AS1	8	94752338	94753047	32	rs10104450	rs3134028	rs3133974	6.60E-06	8.23E-05
Reduced Height	SKOR1	15	68112041	68126174	62	rs3784713	rs338364	rs4306451	2.29E-05	2.49E-05
	LOC100506834	9	89563612	89616948	127	rs11141592	rs7870591	rs10780806	2.45E-05	4.76E-05
Recognition Discrimination	PUS7	7	105096959	105162685	39	rs4266584	rs818628	rs2392749	3.23E-05	8.77E-05
Working Memory	RAPH1	2	204298404	204400058	77	rs4234075	rs17478098	rs76829926	5.00E-05	4.88E-05
	SELE	1	169691780	169703220	102	rs12045330	rs10919240	rs4656704	0.000274407	5.96E-05

Supplementary Table S6. Regional enrichment of nominally significant haplotypes in genotype data surrounding haplotypes identified as significant in imputed data. (A) Total number of nominally significant haplotypes identified within the specified genomic proximity windows surrounding significant imputed haplotypes in the CTLC genotype dataset. (B) List of nominally significant haplotypes from genotype data located within these enriched regions, including haplotype structure, effect estimates, confidence intervals, nominal p-values, and adjusted p-values.

(A)

Haplotype	Proximity (mb)	# Nominally Significant Haplotype in CTLC Genotype Data
Chr 1 (C-A-G-A)	1	14
Chr 9 (C-c-g-c)	1	6
Chr 16 (C-A-C-G)	10	22

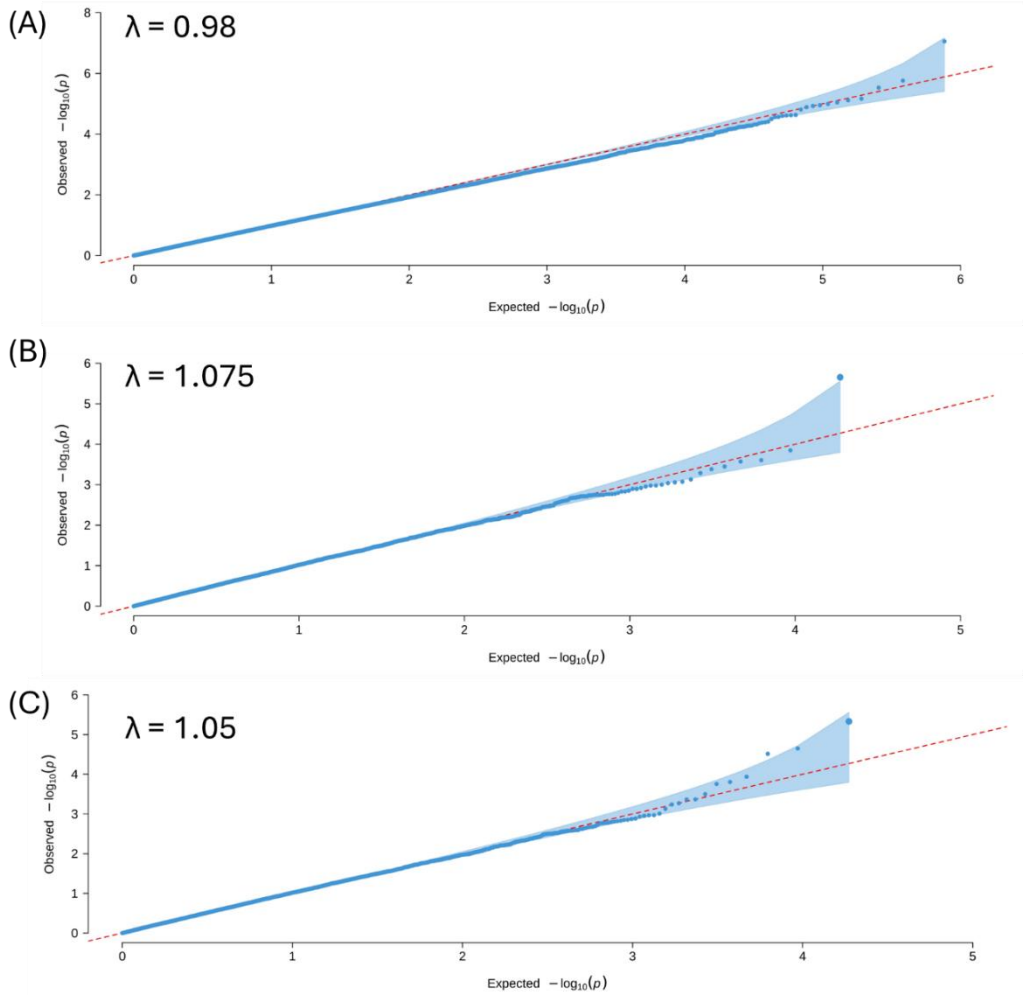
(B)

marker	chr	haplotypes	est.name	est.	lower	upper	p.value	p.adj
rs17218614-rs10114641-rs10978480-rs980616	9	a-T-C-c (16.5%), ref: G-T-t-A (39.2%)	RRc8	1.995615	1.017382	3.800281	0.042759	0.922336
rs17218614-rs10114641-rs10978480-rs980616	9	a-T-C-c (16.5%), ref: G-T-t-A (39.2%)	RRcdd8	3.98248	1.035066	14.44213	0.042759	0.922336

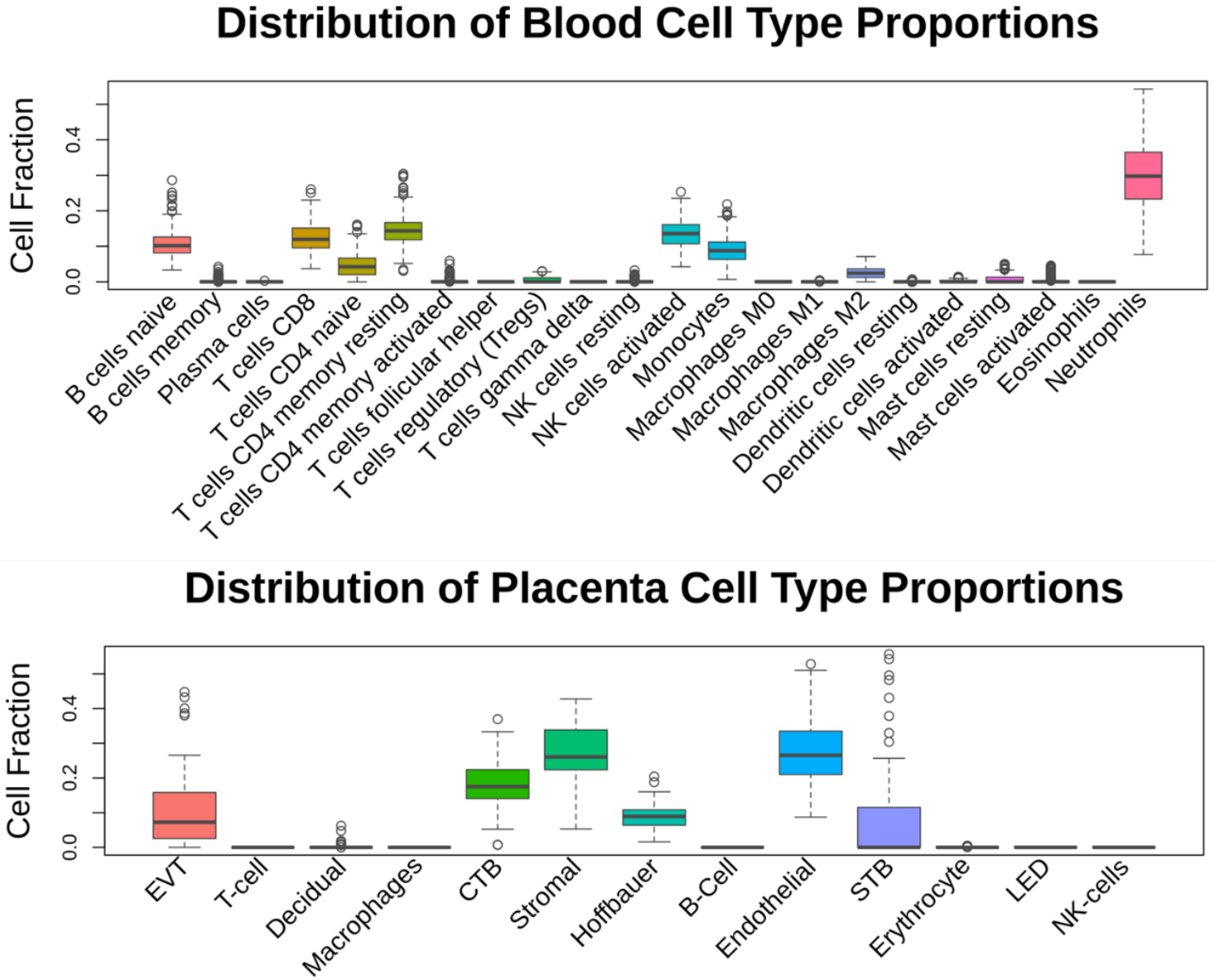
rs10114641-rs10978480-rs980616-rs4742996	9	T-C-c-A (18.1%), ref: T-t-A-g (33.8%)	RRc6	2.031751	1.021409	4.017229	0.043908	0.922986
rs10114641-rs10978480-rs980616-rs4742996	9	T-C-c-A (18.1%), ref: T-t-A-g (33.8%)	RRcdd6	4.128013	1.043276	16.13813	0.043908	0.922986
rs10978480-rs980616-rs4742996-JHU_9.109205932	9	C-c-A-A (22.2%), ref: t-A-g-A (33.6%)	RRc3	1.926845	1.006453	3.656391	0.046154	0.924153
rs10978480-rs980616-rs4742996-JHU_9.109205932	9	C-c-A-A (22.2%), ref: t-A-g-A (33.6%)	RRcdd3	3.712732	1.012948	13.36919	0.046154	0.924153
rs7189823-rs12051258-JHU_16.78491537-rs2738645	16	G-C-C-a (13.4%), ref: G-C-C-G (45.6%)	RRm1	3.3718	1.676298	6.787739	0.000638	0.820173
rs7189823-rs12051258-JHU_16.78491537-rs2738645	16	G-C-C-a (13.4%), ref: G-C-C-G (45.6%)	RRmdd1	11.36903	2.809977	46.0734	0.000638	0.820173
rs12051258-JHU_16.78491537-rs2738645-rs8054130	16	C-C-a-C (19.4%), ref: C-C-G-C (52.1%)	RRc1	0.332022	0.16086	0.693216	0.003122	0.858356
rs12051258-JHU_16.78491537-rs2738645-rs8054130	16	C-C-a-C (19.4%), ref: C-C-G-C (52.1%)	RRcdd1	0.110239	0.025876	0.480549	0.003122	0.858356
rs7189823-rs12051258-JHU_16.78491537-rs2738645	16	G-C-C-a (13.4%), ref: G-C-C-G (45.6%)	RRc1	0.315715	0.139614	0.721269	0.005685	0.883573
rs7189823-rs12051258-JHU_16.78491537-rs2738645	16	G-C-C-a (13.4%), ref: G-C-C-G (45.6%)	RRcdd1	0.099676	0.019492	0.520229	0.005685	0.883573
rs12051258-JHU_16.78491537-rs2738645-rs8054130	16	C-C-a-C (19.4%), ref: C-C-G-C (52.1%)	RRm1	2.209833	1.185437	4.006062	0.010775	0.897276
rs12051258-JHU_16.78491537-rs2738645-rs8054130	16	C-C-a-C (19.4%), ref: C-C-G-C (52.1%)	RRmdd1	4.883364	1.40526	16.04853	0.010775	0.897276
JHU_16.78491537-rs2738645-rs8054130-rs2667657	16	C-a-C-C (18.1%), ref: C-G-C-C (52.6%)	RRc1	0.396457	0.193039	0.807848	0.011207	0.898101
JHU_16.78491537-rs2738645-rs8054130-rs2667657	16	C-a-C-C (18.1%), ref: C-G-C-C (52.6%)	RRcdd1	0.157178	0.037264	0.652619	0.011207	0.898101
rs2738645-rs8054130-rs2667657-rs2738660	16	a-C-C-A (2.2%), ref: G-C-C-A (55.6%)	RRm1	5.080529	1.425398	17.65536	0.011585	0.899232
rs2738645-rs8054130-rs2667657-rs2738660	16	a-C-C-A (2.2%), ref: G-C-C-A (55.6%)	RRmdd1	25.81177	2.031759	311.7117	0.011585	0.899232
rs2738645-rs8054130-rs2667657-rs2738660	16	a-C-t-c (10.4%), ref: G-C-C-A (55.6%)	RRc6	0.301722	0.115679	0.785263	0.013882	0.903462
rs2738645-rs8054130-rs2667657-rs2738660	16	a-C-t-c (10.4%), ref: G-C-C-A (55.6%)	RRcdd6	0.091036	0.013382	0.616638	0.013882	0.903462
rs2738645-rs8054130-rs2667657-rs2738660	16	a-C-C-c (18%), ref: G-C-C-A (55.6%)	RRc3	0.388365	0.177813	0.823178	0.015324	0.905273
rs2738645-rs8054130-rs2667657-rs2738660	16	a-C-C-c (18%), ref: G-C-C-A (55.6%)	RRcdd3	0.150827	0.031618	0.677623	0.015324	0.905273
JHU_16.78491537-rs2738645-rs8054130-rs2667657	16	C-a-C-t (9.9%), ref: C-G-C-C (52.6%)	RRc6	0.320964	0.123839	0.843262	0.021193	0.911607
JHU_16.78491537-rs2738645-rs8054130-rs2667657	16	C-a-C-t (9.9%), ref: C-G-C-C (52.6%)	RRcdd6	0.103018	0.015336	0.71109	0.021193	0.911607
rs8054130-rs2667657-rs2738660-rs76035012	16	C-C-c-G (21.5%), ref: C-C-A-G (58.9%)	RRc3	0.505199	0.263297	0.941239	0.03449	0.917142
rs8054130-rs2667657-rs2738660-rs76035012	16	C-C-c-G (21.5%), ref: C-C-A-G (58.9%)	RRcdd3	0.255226	0.069325	0.885931	0.03449	0.917142
rs8054130-rs2667657-rs2738660-rs76035012	16	C-t-c-G (9.9%), ref: C-C-A-G (58.9%)	RRc4	0.38297	0.152853	0.9447	0.037867	0.918858

rs8054130-rs2667657-rs2738660-rs76035012	16	C-t-c-G (9.9%), ref: C-C-A-G (58.9%)	RRcdd4	0.146666	0.023364	0.892458	0.037867	0.918858
rs4460596-rs6425374-rs12729524-JHU_1.176034842	1	T-T-t-G (21.5%), ref: T-T-G-G (44.3%)	RRc3	0.201634	0.092262	0.434659	4.74E-05	0.778215
rs4460596-rs6425374-rs12729524-JHU_1.176034842	1	T-T-t-G (21.5%), ref: T-T-G-G (44.3%)	RRcdd3	0.040656	0.008512	0.188929	4.74E-05	0.778215
rs6425374-rs12729524-JHU_1.176034842-rs79046857	1	T-t-G-C (21.8%), ref: T-G-G-C (54.4%)	RRc2	0.226315	0.105056	0.469317	0.000101	0.778215
rs6425374-rs12729524-JHU_1.176034842-rs79046857	1	T-t-G-C (21.8%), ref: T-G-G-C (54.4%)	RRcdd2	0.051219	0.011037	0.220259	0.000101	0.778215
rs10798432-rs4460596-rs6425374-rs12729524	1	A-T-T-t (22.1%), ref: A-T-T-G (29.5%)	RRc6	0.209815	0.093849	0.464907	0.000148	0.780481
rs10798432-rs4460596-rs6425374-rs12729524	1	A-T-T-t (22.1%), ref: A-T-T-G (29.5%)	RRcdd6	0.044022	0.008808	0.216138	0.000148	0.780481
rs4460596-rs6425374-rs12729524-JHU_1.176034842	1	T-T-t-G (21.5%), ref: T-T-G-G (44.3%)	RRm3	2.466702	1.292086	4.70334	0.006161	0.885294
rs4460596-rs6425374-rs12729524-JHU_1.176034842	1	T-T-t-G (21.5%), ref: T-T-G-G (44.3%)	RRmdd3	6.084618	1.669486	22.1214	0.006161	0.885294
rs10798432-rs4460596-rs6425374-rs12729524	1	A-T-T-t (22.1%), ref: A-T-T-G (29.5%)	RRm6	2.205339	1.117057	4.427386	0.023003	0.912283
rs10798432-rs4460596-rs6425374-rs12729524	1	A-T-T-t (22.1%), ref: A-T-T-G (29.5%)	RRmdd6	4.86352	1.247816	19.60174	0.023003	0.912283
rs6425374-rs12729524-JHU_1.176034842-rs79046857	1	T-t-G-C (21.8%), ref: T-G-G-C (54.4%)	RRm2	1.977826	1.083506	3.630588	0.025913	0.913206
rs6425374-rs12729524-JHU_1.176034842-rs79046857	1	T-t-G-C (21.8%), ref: T-G-G-C (54.4%)	RRmdd2	3.911797	1.173985	13.18117	0.025913	0.913206
rs4460596-rs6425374-rs12729524-JHU_1.176034842	1	c-T-G-G (10.6%), ref: T-T-G-G (44.3%)	RRm1	2.277873	1.043498	4.738002	0.033972	0.917061
rs4460596-rs6425374-rs12729524-JHU_1.176034842	1	c-T-G-G (10.6%), ref: T-T-G-G (44.3%)	RRmdd1	5.188704	1.088888	22.44867	0.033972	0.917061

Supplementary Figure S2: Quantile–quantile (QQ) plots evaluating genomic inflation for child genetic analyses. (A) Single-marker GWAS of working memory (λ = 0.98). (B) Child gene-based analysis of reduced height-for-age (λ = 1.075). (C) Child gene-based analysis of recognition memory (λ = 1.05). Across all panels, the observed –log10(p) values (blue) closely track the expected null distribution (red dashed line), indicating well-controlled type I error and no evidence of systematic bias due to population stratification, relatedness, or model misspecification.



Supplementary Figure S3: Distribution of inferred blood and placental cell-type proportions.: Boxplots show the estimated fractions of immune and stromal cell types obtained from gene expression deconvolution. *Top:* Distribution of 22 leukocyte subtypes in child whole-blood samples, illustrating variability in major lymphoid and myeloid populations (e.g., naïve/memory B cells, T-cell subsets, monocytes, macrophages, dendritic cells, neutrophils). *Bottom:* Distribution of major placental cell types, including extravillous trophoblasts (EVT), cytotrophoblasts (CTB), syncytiotrophoblasts (STB), Hofbauer cells, stromal cells, endothelial cells, and immune-cell subsets. These distributions highlight tissue-specific cellular heterogeneity and inform downstream adjustment for cell-type composition in differential gene expression analyses.



References:

[1] Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 Institute of Medicine criteria. Pediatrics 2005;115:39–47.

[2] Hollingshead AB. Four factor index of social status. Yale J Sociol 2011;8:21–51.

[3] Zhou X, Stephens M, Zhou X, Stephens M. Genome-wide efficient mixed-model analysis for association studies. Nature Genetics 2012 44:7 n.d.;44. https://doi.org/10.1038/ng.2310.

[4] Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: A Tool for Genome-wide Complex Trait Analysis. Am J Hum Genet n.d.;88. https://doi.org/10.1016/j.ajhg.2010.11.011.

[5] Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26:2190–1. https://doi.org/10.1093/bioinformatics/btq340.