Gene by Prenatal Alcohol Exposure Interaction Effects on Growth and Cognition in Mother-Child Dyads in a South African Birth Cohort

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Introduction

- Fetal Alcohol Spectrum Disorders (FASD), resulting from prenatal alcohol exposure (PAE), are a leading preventable cause of neurodevelopmental delay.
- Despite the wide range of symptoms in FASD children, the genetic contributions from both mother and child to FASD are not well understood.
- This study uses single-marker and gene-level analyses on data from mother-child dyads in two Cape Town birth cohorts to identify genetic markers and loci associated with FASD, addressing a region with one of the highest FASD prevalence rates globally.

Methods

- Illumina MegaEX genotype data from mother-child dyads were preprocessed to remove genetic outliers and outliers in confounding factors.
- Gene-environment interactions (alcohol consumption during pregnancy) on FASD outcomes, including fetal alcohol syndrome (FAS)/partial FAS diagnosis, working memory, recognition discrimination, and height, were examined using two approaches: single-marker analysis using Mixed Model Association and gene-based analysis using GCTA based on single-marker summary statistics.
- Covariates included maternal age, socioeconomic status, choline supplementation, and prenatal cigarette exposure.
- The Transmission Disequilibrium Test (TDT) was performed using Haplin R package to identify genetic haplotypes with evidence of gene-exposure interactions when transmitted from mother to child.

Results

Table 1. Top suggestive hits obtained from Single-marker analyses using GEMMA in child and mother

Chr	SNP ID	SNP Position	p-value (unadjusted)	Functional Annotation	Gene Annotation	Group
Recognition Memory						
14	14:85971029-T-C	85971029	*4.16E-06*	Intergenic	*LINC00911;FLRT2*	Child
14	JHU_14.85862075	85862076	*5.91E-06*	ncRNA_Intronic	*LINC00911*	Child
1	JHU_1.103225558	103225559	*4.51E-06*	Intergenic	*OLFM3;COL11A1*	Mother
1	JHU_1.103289573	103289574	*4.51E-06*	Intergenic	*OLFM3;COL11A1*	Mother
Reduced Child height						
3	JHU_3.148010020	148010021	*4.85E-06*	ncRNA_Intronic	*LINC02428*	Child
3	rs10866075	65937976	*5.03E-06*	Intronic	*FABP6*	Child
Working Memory						
21	JHU_21.37893531	37893532	*2.96E-06*	Intronic	*C21orf59-TCP10L*	Child
21	Rs2833924	33965444	*8.79E-08*	Intronic	*TAMM41*	Child
4	exm421046	119948059	*7.72E-07*	exonic	*SYNPO2*	Mother
12	JHU_12.82072378	82072379	*2.98E-06*	Intronic	*PPFIA2*	Mother

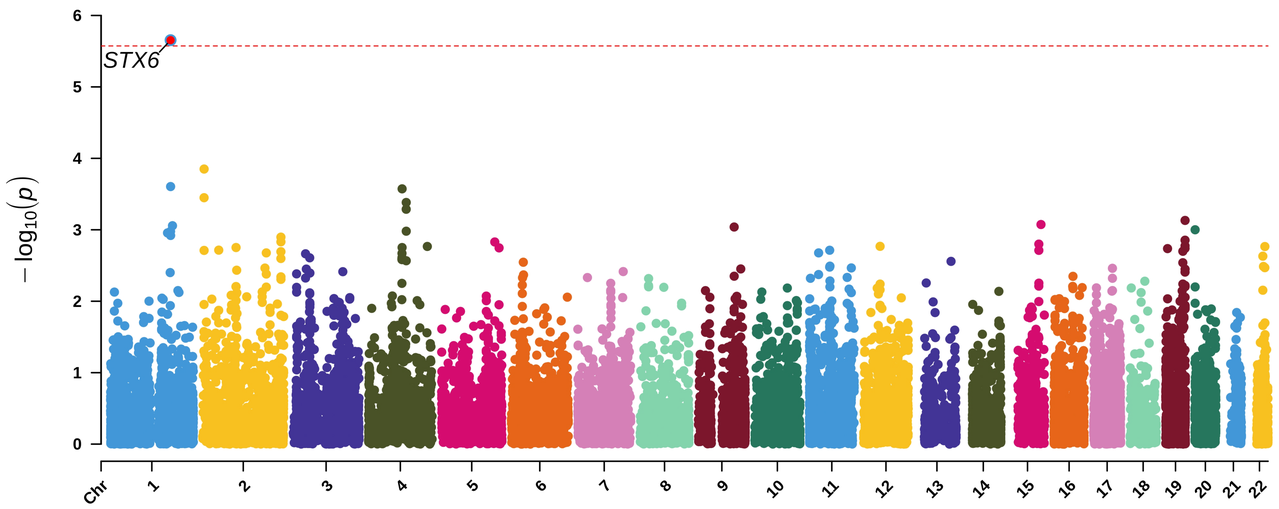
Table 2. List of genes that are significantly associated with multiple FASD outcomes in both child and mother

Gene	FASD Outcomes having statistically significant association with the gene in both mother and child
GLRX3	Recognition Memory, Working Memory
IL36B	Recognition Memory, Working Memory
DERL3	Recognition Memory, Working Memory
AQP7	Recognition Memory, Working Memory
DTX3L	Reduced Child Height, Working Memory
LIPC	Recognition Memory, Reduced Child Height
ENSG00000288643	Recognition Memory, Reduced Child Height
POLR2M	Recognition Memory, Reduced Child Height

Table 3. Comparison of Gene-based analysis with TDT analysis on multiple FASD outcomes

Phenotype	Gene	Haplin GxE p-value	Haplotype	Haplin p-value	Haplin Adjusted p-value	Child GCTA p-value	Mother GCTA p-value
Working Memory	*GLRX3*	3.138E-2	ALT: T-g-G-a (1.9%), Ref:T-A-G-a (23.5%)	7.731E-07	4.5E-2	2.41E-2	2.72E-05
Height-for-age z-score	*MED30*	1E-2	ALT: G-a-t-g (2.5%), Ref: t-G-t-T (32%)	8.115E-10	4.55E-3	4.47E-2	1.75E-2

Figure 1. Manhattan Plot of Gene-Based Analyses for Child Genotype-by-Alcohol Exposure Interaction Effects on Height-for-Age Z-Scores



Conclusions

- This study identifies GLRX3 and MED30 as novel genetic markers that when transmitted from mother to fetus, have significant interaction effects with alcohol on child neurodevelopmental outcomes.
- Additionally, genome-wide gene-based analyses identified child genotype-alcohol exposure interaction effects for STX6 on child height reductions.
- Our findings emphasize the role of gene-environment interactions in FASD, specifically how maternal and child genetic factors may alter fetal vulnerability to alcohol exposure. The use of TDT analysis allowed for a more precise evaluation of the risk of genetic transmission within mother-child dyads, making it an invaluable tool for understanding genetic influences in FASD.

Acknowledgement

- This research was supported by NIH/NIA R56-AG069118, U01-AG081817, and R01-AA027916.

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