Results of Genome-Wide Analyses on Neurodevelopmental Phenotypes at Four-Year Follow-Up following Cardiac Surgery in Infancy.

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BACKGROUND:
Adverse neurodevelopmental sequelae are reported among children who undergo early cardiac surgery to repair congenital heart defects (CHD). APOE genotype has previously been determined to contribute to the prediction of these outcomes. Understanding further genetic causes for the development of poor neurobehavioral outcomes should enhance patient risk stratification and improve both prevention and treatment strategies.

METHODS:
We performed a prospective observational study of children who underwent cardiac surgery before six months of age; this included a neurodevelopmental evaluation between their fourth and fifth birthdays. Attention and behavioral skills were assessed through parental report utilizing the Attention Deficit-Hyperactivity Disorder-IV scale preschool edition (ADHD-IV), and Child Behavior Checklist (CBCL/1.5-5), respectively. Of the seven investigated, three neurodevelopmental phenotypes met genomic quality control criteria. Linear regression was performed to determine the effect of genome-wide genetic variation on these three neurodevelopmental measures in 316 subjects.

RESULTS:
This genome-wide association study identified single nucleotide polymorphisms (SNPs) associated with three neurobehavioral phenotypes in the postoperative children ADHD-IV Impulsivity/Hyperactivity, CBCL/1.5-5 PDPs, and CBCL/1.5-5 Total Problems. The most predictive SNPs for each phenotype were: a LGALS8 intronic SNP, rs4659682, associated with ADHD-IV

Impulsivity (P=1.03×10(-6)); a PCSK5 intronic SNP, rs2261722, associated with CBCL/1.5-5 PDPs (P=1.11×10(-6)); and an intergenic SNP, rs11617488, 50 kb from FGF9, associated with CBCL/1.5-5 Total Problems (P=3.47×10(-7)). 10 SNPs (3 for ADHD-IV Impulsivity, 5 for CBCL/1.5-5 PDPs, and 2 for CBCL/1.5-5 Total Problems) had p<10(-5).

CONCLUSIONS:
No SNPs met genome-wide significance for our three neurobehavioral phenotypes; however, 10 SNPs reached a threshold for suggestive significance (p<10(-5)). Given the unique nature of this cohort, larger studies and/or replication are not possible. Studies to further investigate the mechanisms through which these newly identified genes may influence neurodevelopment dysfunction are warranted.