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Exome Sequencing Reveals Overrepresentation of Rare Variants in ErbB Pathway Genes in Patients with Left Ventricular Outflow Tract Obstruction Defects

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Introduction

Left ventricular outflow tract obstruction defects (LVOTO), such as bicuspid aortic valve, congenital aortic stenosis, coarctation of the aorta, and hypoplastic left heart, are thought to share a similar genetic basis. These defects are associated with significant heritability, yet few genes have been associated with LVOTO in humans and explain only a minority of cases.

The ErbB family receptor tyrosine kinases serve multiple functions during embryonic development, and signaling defects in these pathways are shown to lead to congenital cardiac malformations in mice. We determined the frequency of very rare variants in ErbB family genes ERBB2, ERBB3, and ERBB4 in a Finnish LVOTO patient population.

Methods

The exomes of 50 Finnish patients with LVOTO and their family members (total n=112) were sequenced at University of Washington, Center for Mendelian Genomics. Variant calling was performed with the Realtime Genomics Package (RTG version 3.4) in reference to the UCSC reference sequence (hg19). Synonymous single nucleotide polymorphisms (SNP) and variants with minor allele frequency over 0.01 in the Exome Aggregation Consortium (ExAC) database were excluded.

Results

A total of 11 probands had rare missense variants in the ErbB family receptor tyrosine kinase genes. One individual had two missense variants in the ERBB3 gene and one individual had a missense variant both in ERBB2 and ERBB3. We identified a very rare ERBB2 variant p.Arg599Cys that was present in all affected members in two unrelated families with multiple LVOTO patients in three generations. This ERBB2 variant is found only in one ExAC individual (MAF of 0.0007), and in none of the ethnically matched Finnish Sequencing Initiative Suomi population (N= 10,474). The variant is located in a highly conserved area of the ERBB2 gene. Both the CADD score (14.39) and the PolyPhen2 score (0.985) predict this variant to be pathogenic.
Functional work in endothelial cell models is currently being carried out to investigate the disease causing potential of these variants.

Conclusion

Very rare ErbB family receptor tyrosine kinase variants were overrepresented in this LVOTO cohort. A fifth of LVOTO probands had at least one potentially pathogenic variant in ERBB2, ERBB3, or ERBB4.