

Assessing genetic risk in a familial case of Ebstein's Anomaly

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Background: Ebstein's anomaly is a complex congenital heart defect (CHD) of the tricuspid valve that has significant morbidity and mortality. Faulty delamination of valve leaflets during cardiogenesis results in apical displacement of valve and atrialization of the right ventricle. Many reported cases are of sporadic origin, however several familial cases have been described. Two genes have been hypothesized to be associated with Ebstein's anomaly: myosin heavy chain 7 (*MYH7*) and transcription factor *NKX2.5* (Vermeer 2013; Benson 1999). Our study describes a multigenerational family affected with Ebstein's anomaly, likely related to a novel mutation. Upon clinical presentation, the proband was diagnosed with Ebstein's anomaly at 20 weeks gestation, and a sibling had undergone surgical closure of an atrial septal defect. We are investigating sequence variants shared in common among family members to determine the genetic cause of this phenotype. This demonstrates the importance of genetic characterization as an excellent partner in leading to more comprehensive diagnoses in clinical cases.

Methods: Compilation of family history data and electronic medical record reviews were used to create a chart of the family pedigree. Clinical echocardiography determined phenotypic status and blood samples were drawn from available family members (n=11). Genomic DNA from the peripheral blood of the proband was extracted and exome sequenced with respect to the human reference genome, GRCh37. Mutations were detected, annotated, and filtered using computational tools and databases. Filtering criteria included population frequency <1% and predicted deleterious effect of mutation. Candidate genes were prioritized by cardiac tissue expression and known association with cardiac or muscle development. Mutations meeting these criteria will be sequenced individually using Sanger sequencing in the 11 family members to determine pattern of inheritance.

Results: The disease follows an autosomal dominant inheritance pattern as affected individuals occur in subsequent generations equally between both sexes. Echocardiography of 11 descendants from consanguineous parents revealed seven family members with varying degrees of severity of Ebstein's Anomaly. Associated anomalies included atrial septal defects (ASD) and left ventricular non-compaction (LVNC). Initial Sanger sequencing of the parents of the proband, were negative for mutations residing in the coding regions of both the *MYH7* and the *NKX2.5* genes, thus requiring further investigation of novel mutations manifesting as this phenotype. Exome sequencing of the proband revealed 1259 variants, 153 of which are known to be involved in heart development, many of which have been associated with CHD's. A candidate gene list containing 30 possible mutations has resulted from list prioritization. Further sequencing of multiple family members may more strongly reveal associations between variation in normal gene sequence and disease phenotype.

Conclusions: This study describes a familial instance of Ebstein's Anomaly with seven affected and four unaffected relatives. Exome sequencing of the proband reveals mutations in many candidate genes that may lead to the disease phenotype. Further sequencing of select candidate genes from all family members will be performed in order to solidify that each variant is present in all affected individuals. Finding an association between genotype and phenotype, allows us to better diagnose disease, provide more accurate counseling for the family, and gain further understanding of human cardiac development.

1. Vermeer et al. *American Journal of Medical Genetics* 163(3):178-184

2. Benson et al. *J Clin Invest* 104:1567-1573