WHOLE EXOME SEQUENCING IN CONGENITAL HEART DISEASE REVEALS VARIANTS IN LEFT-RIGHT PATTERNING GENES PREVIOUSLY ASSOCIATED WITH HETEROTAXY SYNDROME AND PRIMARY CILIARY DYSKINESIA

Background: Heterotaxy syndrome (HTX) is a constellation of defects defined primarily by abnormal lateralization of thoracic and abdominal organs across the left-right axis of the body of either the polyspenia or asplenia type, and often involving complex congenital heart disease (CHD). Based on rare isolated cases, mutations in the same gene and even the same allele of a gene may cause either type of HTX. It is not known how genes associated with HTX are associated with other types of CHD.

Methods: Potential left right patterning defect cases were identified through a retrospective chart review of pre-surgical echocardiograms. Whole exome sequencing was performed on these samples at the Baylor-Hopkins Center for Mendelian Genomics. We stratified variants/genes into three categories: 1) loss-of-function (LOF) variants in known HTX genes; 2) homozygous or compound heterozygous mutations in genes known to cause primary ciliary dyskinesia (PCD); and 3) LOF variants in novel genes involved in left-right signaling pathways (NOTCH, NODAL and SHH). In category 3 genes, no LOF variants were found in control exome data (n=15,000).

Results: We ascertained 332 CHD cases with potential left right patterning defects. Of those cases, 32 were found to have candidate pathogenic variants in one of the three categories. For those with HTX, five cases had category 1 and five cases had category 2 variants. Twenty-two non-HTX cases included CHDs with dextrocardia, juxtaposition of the atrial appendages, transposition of the great arteries, double inlet left ventricle, and double outlet right ventricle. Of these, 15 had category 2 variants, four had category 1 variants (previously associated with HTX genes), and three had category 3 variants (involving potential novel gene associations).

Conclusion: Our results indicate that early disturbances in embryonic left-right patterning may lead to both classic HTX and a wider array of cardiac defects. In our study, only a small fraction of HTX cases bear candidate mutations in previously identified genes. Ongoing analyses include targeted re-sequencing of candidate variants within cases and direct family members to determine mode of inheritance and to validate genotypes.