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Whole exome sequencing and whole genome sequencing improves genetic diagnosis of fetals with heterotaxy syndrome revealed by prenatal ultrasound

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Background: Heterotaxy (Htx) syndrome is an congenital disorders resulting from incorrectly establishment of left-right patterning during embryogenesis. Over 96% of patients with Htx exhibit some form of congenital heart disease (CHD),and has relatively poor survival. Multiple lines of evidence support genetic contributions to the etiology of Htx. As a specific genetic etiology is currently identifiable in only a minority of patients, there remains enormous potential for novel gene and pathway discovery.

Purpose: The aim of this study was to investigate the diagnostic yield of whole-exome sequencing (WES) and whole-genome sequencing (WGS) in fetuses with the pathogenesis of Htx, to explore candidate genes for Htx and to expand the clinical phenotype of known genetic conditions.

Method: WES and WGS were performed on specimens from 46 fetuses diagnosed with Htx and their parents. The single-nucleotide variants (SNVs) and copy-number variants (CNVs) were filtered and annotated by standard analysis process. All reported variants were classified according to he American College of Medical Genetics and Genomics guidelines.

Results: In the 46 fetuses, the detection rates of pathogenic and likely pathogenic variations were21.7% (10/46) and 10.9% (5/46) respectively. Ten pathogenic variations were identified on genes of CCDC114, DNAH11, ARMC4, STRA6, PQBP1 (hemizygote), HYDIN, RAI1 (Alagille Syndrome), ZFMP2 and Del(22q11.2) Syndrome. Five likely pathogenic variation were on DNAAF1 (Holshner syndrome), NF1, NEXN, NOTCH3 and FOXC1. Of 30 fetuses with prenatally diagnosed right atrial isomerism (RAI), the main intracardiac anomalies were atrioventricular canal (AV canal), isomerism of right atrial appendages, pulmonary stenosis or atresia (PS & PA) and right aortic arch. In 16 fetuses diagnosed left atrial isomerism (LAI) the main intracardiac anomalies were isomerism of left atrial appendages, interrupted IVC and azygos vein continuation. Of the 10 positive cases, 8 fetus were diagnosed of RAI and 2 were diagnosed of LAI by prenatal ultrasonic examination or fetal autopsy. The detection rate was 8/30 (26.7%) for RAI and 2/16 (12.5%) for LAI.

Conclusion: This study outlines the way for a substantial improvement in the diagnostic yield of prenatal genetic disorders in Htx through WES and WGS. Our experience also expanded the knowledge of the clinical phenotype of known genetic conditions. Our results indicate that the proportion of SNV in Htx of prenatal cases was significantly higher than that in patients with other congenital heart abnormalities, and the recessive inheritance occurred in a higher proportion in Htx. Our results have important implications for clinical management and genetic counseling of Htx.