P4647

Next generation sequencing in 83 fetal left-sided CHDs reveals the entire genetic architecture of left-sided CHDs in fetal population

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Background: No data is available for the contribution of single gene disorders (SGDs) to left-sided congenital heart defects (LSCHDs) in the fetal population.

Purpose: The aim of this study was to explore the entire genetic architecture of LSCHDs, especially the contribution of SGDs in a cohort of fetal LSCHDs.

Methods: Low-pass whole genome sequencing (WGS) and whole exome sequencing (WES) were performed on specimens from 83 deceased fetuses with lSCHDs, including 48 HLHS, 22 CoA, 5 AS, 3 AAH, 2 AS+CoA and 1 case of AA, AS+MS, MA. Sequencing was predominantly performed in fetus-parent trios (n=63, 75.9%), or in fetus only (n=20, 24.1%).

Results: 34.9% (n=29) of the 83 fetal left-sided CHDs were identified with related genetic abnormalities. WGS analysis identified 14 (16.9%) with chromosomal abnormalities, including 6 (7.2%) aneuploidies and 8 (9.6%) pathogenic copy number variants (CNVs). WES analysis of the remaining 69 cases without chromosomal abnormalities identified 15 (15/69, 21.7%) with pathogenic/likely pathogenic variants. Of these 15 cases, KMT2D was the most frequently mutated gene (7/69, 10.1%), followed by NOTCH1 (4/69, 2.5%). Compound heterozygosity was identified in 3 genes (DNAH11, POFUT1, CRB2) that are not yet well established as CHD genes. Finally, we also observed a LOF variant in NONO (X-linked) that was maternally transmitted to an affected male case.

Conclusions: Our experience supports that SGDs contribute a significant part to the pathogenesis of fetal CHDs, WES has the potential to provide molecular diagnoses in fetal left-sided CHDs without chromosomal abnormalities. KMT2D mutations accounted for a large fraction of left-sided CHDs in fetal population. If the KMT2D mutation is detected, further diagnosis of Kabuki syndrome should be considered.

The genetic results of this cohort

Aneuploidies	Trisomy 18	4
	Turner syndrome	2
CNVs	11q terminal deletion	3
	1p36 deletion	1
	15q terminal deletion	1
	7q11.23 deletion	1
	4p terminal deletion	1
	12q complex internal duplication	1
SGDs	AD (KMT2D = 7; NOTCH1 = 4)	11
	AR (DNAH11, POFUT1, CRB2)	3
	X-recessive (NONO)	1

AD: autosomal dominant; AR: autosomal recessive.