RARE COPY NUMBER VARIANTS IN CONGENITAL HEART DEFECTS

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To detect copy number variants (CNVs) in patients with congenital heart defects (CHD) and identify potential novel candidate genes involved in CHD pathogenesis. CHD are the most common congenital anomalies. Etiology of CHD can be genetic (chromosomal abnormalities, rare single gene disorders) or environmental, but it is mostly multifactorial. Copy number variants (CNVs) are important causes of genetic syndromes associated with CHD. Chromosomal microarray (CMA) is used as the first test to detect the CNVs in this category of patients.

We have evaluated 260 subjects with CHD in the period between Jan 2016 and Sep 2019 using CMA. In the majority of cases additional features such as facial dysmorphism, intellectual disability/developmental delays (ID/DD) or extracardiac anomalies (ECA) (190/260; 73.1%) were present; the remainder had isolated CHD. CMA analysis was performed using Agilent SurePrint G3 Unrestricted CGH ISCA v2 Human Genome, 8x60 K oligonucleotide microarray format according to the manufacturers’ instructions (Agilent Technologies, USA).

Copy number variants were detected in 71 (71/260, 27.3%) patients; 53 of them (53/71, 74.6%) were classified as pathogenic and 18 (18/71, 25.4%) as variants of unknown clinical significance (VUS). Pathogenic CNVs were predominately deletions (36), followed by duplications (9) and complex rearrangements (8). CNVs were discovered in 4 patients with isolated CHD (4/70, 5.7%) and 67 patients with additional features (67/190; 35.3%). The most frequent pathogenic CNV was 22q11.2 deletion (DiGeorge syndrome), followed by other well-known syndromes (Williams, 5p deletion etc.). Beside these, we detected CNV clusters in loci that have previously been associated with CHD in literature (such as 15q11.2, 8p23.1, 1q43 etc.). We also observed rare CNVs in loci that have not yet been recognized as important in CHD pathogenesis (i.e. Yp11.2, 17q24, 15q24.3 etc.) Identification of rare CNVs is important for clarification of CHD pathogenesis. Potential novel candidate genes in these loci warrant further research.

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