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Trio analysis using Next generation sequencing technology to identify de novo mutations in individuals with syndromic cardiopathy

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Introduction: Advances in genetic sequencing technology have the potential to enhance testing for genes associated with genetically heterogeneous diseases, such as congenital heart defects (CHD). Until recently, a major limitation in genetic research was genetic testing for mutations in a large number of genes simultaneously. Novel technologies such as next generation sequencing (NGS) using high-throughput massively parallel sequencing methods may circumvent this limitation. With current clinical and genetic investigation, an etiological diagnosis can be reached in 55% of cases. Nevertheless, there is a need for better diagnosis, since it is in this group that genetic counseling is frequently requested with regard to recurrence risks as well as prognosis with regard to intellectual disability. An important proportion of cases have a de novo monogenic cause, i.e. a newly occurring mutation, not present in one of the parents, and altering the function of a gene essential in embryonic development, including the heart.
Methods: Patients were included with a syndromic cardiopathy of unknown cause after extensive evaluation by an experienced clinical geneticist and with high resolution array-CGH in the patient and both parents showing no abnormal, unclassified variants. Whole exome sequencing analysis was performed. Data analysis was done using commercial and in-house developed software. Patients were filtered against 72 in-house exomes for detection of de novo mutations. Only exonic and splicing variants were included, synonymous variants were excluded. Variants occurring with a frequency of <1% in the 1000 genomes project or with an unknown frequency were included.
Results: Eight pairs of Trios were analysed. After variant filtering of the exome sequences, the gene list was manually curated using functional data and genotype-phenotype correlations. We identified a deleterious mutations in 4 cases (50%) as the most likely cause. Results were confirmed by Sanger sequencing.
Conclusions: Reaching a genetic diagnosis in individuals with a syndromic cardiopathy remains a challenge due to different factors including atypical or milder manifestations. We illustrate that using NGS technology in Trio-analysis, the identification of the underlying genetic mutation is feasible in most cases, thus also identifying new genes not previously associated with syndromic CHD.