

Exome Sequencing and Linkage Analysis as Tools in solving Syndromic Cardiopathies in Small Families

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Introduction: We present three small families with syndromic cardiopathies diagnosed in two children of each family. The parents are non-consanguineous and have a normal phenotype. In one family with three children one sibling is unaffected. An autosomal recessive hypothesis is most likely, as these are very rare and unique phenotypes.

Methods: Analysis using linkage analysis and exome sequencing was performed. Genomewide parametric linkage analysis was performed, SNP typing platform was used in a recessive model. Genotyping was done in parents and both the unaffected and affected siblings. Data analysis was done using commercial and in-house developed software. Only variants in genes from the linkage regions were retained. All homozygous calls were excluded in the parents and the unaffected sibling, reference calls were excluded in the affected siblings. 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: After variant filtering, candidate genes are identified in the linkage regions with homozygous mutations in the patients, inherited from both parents, and for which the unaffected sibling is heterozygous or reference. Results of this analysis will be presented and will be confirmed by Sanger sequencing.

Conclusions: Reaching a genetic diagnosis in rare disorders remains a challenge. Sophisticated genetic tools can be combined to aid in finding causal mutations in small families.