

## Solving syndromic congenital heart defects using WES in a Trio or Index-only approach

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### Introduction

Congenital heart defects (CHD) are a major cause of infant morbidity and mortality. Reaching an etiological diagnosis is important for prognosis and counselling on recurrence risks. Gene identification for CHD still represents a major challenge, especially since the genetics of CHD is heterogeneous. Syndromic CHD is defined as CHD with the presence of dysmorphism, additional major malformations and/or ID. Our aim is to evaluate the use of NGS in the detection of causal mutations of syndromic CHD in sporadic cases.

### Methods

Exome sequencing using a trio approach (parents and child) was compared to an index-only analysis, filtering was done against in-house exomes. Data analysis was done using commercial and in-house developed software (Genomics Core/UZ Leuven). According to Ensembl only exonic, exonic/splicing 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. Splicing site changes occurring at less than 5 positions were considered as possible candidates.

### Results

Initially, exome sequencing was done in 9 trio's. In 4 a pathogenic mutation was detected in respectively MEIS2 (c.998\_1000del:p.Arg333del), DYRK1A (c.C1282T:p.R428X), EFTUD2 (c.671delG:p.G224fs) and SALL1 (c.1998\_1999del:p.666\_667del). We analyzed exomes of 4 additional index-only cases. As WES data of parents were not available, inherited variants could not be filtered out, and we experienced seriously limitations in the filtering process. Only one case was diagnosed after identifying a causal nonsense mutation in ANKRD11, (c.7189C>T, p.Gln2397\* causing KBG syndrome).

### Conclusions

Trio analysis has a higher yield than index only analysis in syndromic CHD, due to an increased efficiency in filtering. A gene-first approach also leads to broadening the clinical spectrum of known syndromic genes. For example, MEIS2 has been previously suggested as a candidate gene for cleft palate, CHD and ID. In our patient with a MEIS2 deletion a more severe phenotype was seen than previously described in literature. This is most probably due to dominant-negative mechanisms. In addition, as others have demonstrated before, WES is an excellent means to identify new genes important in the development of cardiopathies.