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Exome Sequencing in Syndromic Patients with Congenital Heart Disease performing Trio Analysis

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Introduction:Congenital heart defects (CHD) are a major cause of infant morbidity and mortality. Reaching an etiological diagnosis in patients with a syndromic heart defect is important, not only to gain insight into their pathogenesis and genetic counseling on recurrence risks, but especially with regard to providing information on the future prospective, based on knowledge of the natural course of the disorder.
In syndromic cases, an exact etiological diagnosis can be reached in an estimated 50-60%, following careful clinical evaluation, complemented by various genetic tests, including array-CGH. With the advent of exome sequencing, it is now feasible to perform a trio analysis, i.e. sequencing of the coding parts of the genes in both parents and the child, where only the child is affected, in order to identify a candidate gene.
For syndromic cases, we hypothesize that these patients have a thus far not recognized monogenic condition, responsible for both the intelligence deficit and the heart defect. Since the vast majority of syndromes featuring CHD are dominant, it is likely that at least in a subset of these, a de novo dominant mutation is present.
Methods:In-solution capture (Nimblegen target enrichment system) and sequencing will be done on the Illumina HiSeq2000 platform (Genomics Core KULeuven/ UZLeuven). Data analysis will be done using commercial and in-house developed software. Afterward, the variants will be annotated by Annovar to allow filtering of all found variants in order to identify potential causal mutations.
Results and Conclusion: Preliminary results on the exome sequencing of five sets of trio's, with the child presenting with congenital heart disease, dysmorphic features and mental retardation, will be discussed.