

Next-Generation Sequencing with a 482 Gene Panel on 208 Cases of Congenital Heart Defects, Heterotaxy, Primary Ciliary Dyskinesia and Aortopathies

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Introduction: We set up a panel of 482 genes that had been involved through published studies in congenital heart defects, heterotaxy, primary ciliary dyskinesia (PCD) and aortopathies because these pathologies are largely overlapping. A series of 208 cases falling into one or several of the selected pathological groups were sequenced by Next-Generation Sequencing.

Method: DNA was enriched by hybridization on a customized set of probes (Nimblegen, Roche). Eight DNA samples by run were paired-end sequenced on a NextSeq500 (Illumina) with a mid-size flow cell. Sequences were analyzed through a pipeline designed locally. CNV were detected with DeCovA. Putative causative variants were confirmed by Sanger sequencing or qPCR and the segregation of selected variants was performed on family members.

Results: the causal mutation was found in 71% of PCD patients, in 21% of aortopathies, 47% of heterotaxy patients (and 30% of heterotaxy patients without PCD), in 39% of congenital heart defects patients and in 23% of fetuses with complex cardiac malformations. Overall, the causal mutation was found in 44% of the cohort.

Conclusion: a large panel of genes is very efficient to find the causal mutation in nearly a half of the cohort of 208 cases. These mutations fulfilled stringent criteria for pathogenicity and a positive familial segregation. These data were sufficiently strong to provide a genetic counseling including in fetus cases.