Integration of large-scale genomic data sources to identify novel genetic loci for congenital heart disease

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Background: Congenital heart disease (CHD) is among the most prevalent birth defects in humans affecting an estimated 8 per 1000 live births. Both small nucleotide variants (SNVs) and copy number variants (CNVs) have been found to affect CHD risk. Yet, the identification of the genetic causes of CHD (majority of the cases are non-syndromic) remains quite challenging.

Purpose: To integrate data on both classes of variation, SNVs and CNVs, associated with non-syndromic CHD cases as a better means for identification of candidate genes predisposing to CHD.

Methods: Here, we have updated a previously published CHD case CNV list and generated a control CNV list using: a) the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER), b) the International Standards for Cytogenomic Arrays (ISCA) database, c) the European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations (ECARUCA) database, d) 1000 Genome phase 3 dataset, e) the Database of Genomic Variants (DGV) and f) published literature.

Results: Analysing deleted (DEL) and duplicated (DUP) CNVs independently resulted in unique case CNV regions not present in the controls (figure 1). Further filtering led to the identification of 54 novel candidate protein coding genes in DEL CNVs present only in the non-syndromic CHD cases but not in the controls and with high/medium impact variants in exome data from our cohort of Tetralogy of Fallot patients (TOF) (figure 1). Moreover, we have identified 50 genes in those unique case CNV regions that were previously shown to be associated with CHD of which 25 are associated with non-syndromic CHD such as GATA4, GATA6 and TBX20 for atria septal defects, JGA1 for atrioventricular septal defects, NNX2-6 for cootruncal heart malformations and ELN for supravalvar aortic stenosis.

Conclusions: We demonstrate a promising new strategy with the integration of large-scale genomic data sources to identify novel genetic loci for CHD and their contribution in heart development. This is an on-going project and our plan is to perform functional work with our strongest candidate gene for which there is evidence that knockout mouse has ventricular septal defects and hypoplastic posterior aortic valve leaflet.
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