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Analysis of rare variants and CNVs in non-syndromic tetralogy of Fallot. *In: American Society of Human Genetics Annual Meeting (ASHG)*. 2015, Baltimore.

Tetralogy of Fallot (TOF) is the commonest cyanotic congenital heart disease requiring surgery in infancy. The majority of cases do not occur as part of a syndrome. We have investigated rare nucleotide variants and copy number variants (CNVs) in over 800 non-syndromic TOF cases. For nucleotide variants we filtered for variants with MAF <1% in 1000 genomes and EVS, not shared between cases and 500 UK10K individuals, not present in more than 1% of individuals in a set and not falling within a segmental duplication. Clustering of variants in transcripts and in exons was ascertained using Poisson distribution. Correcting for the difference in sample numbers in the two groups, the number of clusters when considering synonymous variants was very similar in the TOF cases and UK10K individuals. In contrast, there was an excess of clusters in TOF cases when considering truncating, predicted deleterious and non-synonymous variants. Clusters were found in genes previously associated with TOF and novel candidate genes. CNVs were called for the same TOF cases on PCA corrected SNP array intensities (Cooper et al. Hum. Mol. Genet 2014), which enabled the joint analysis of case and control data while allowing for batch effects. Penncnv and quantiSNP were used for CNV calling on the corrected data and the controls for this work were as previously reported (Soemedi et al Am. J. Hum. Genet 2012). This enabled detection of additional smaller CNVs than reported in our earlier work.