Title: **Major Genetic Contributors to Nonsyndromic Tetralogy of Fallot**

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Abstract

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect. Rare genetic variants have been identified as important contributors to the risk of congenital heart disease, but relatively small numbers of TOF cases have been studied. We used whole exome sequencing to assess the prevalence of unique, deleterious variants in the largest cohort of nonsyndromic TOF patients reported to date. The presence of such variants was defined by their absence in the Genome Aggregation Database and bioinformatic prediction of their deleterious effect on function. The enrichment of variants in two genes, *NOTCH1* and *FLT4*, surpassed thresholds for exome-wide significance ($P<5\times10^{-8}$) after correction for multiple comparisons (Figure 1). *NOTCH1* was most frequently found to harbour unique, deleterious variants (4.5%; 95% CI, 3.2%–6.1%). Three *NOTCH1* variants were subjected to functional evaluation, and two showed a reduction in Jagged1-induced NOTCH signalling. *FLT4* variants were found in 2.4% (95% CI, 1.6%–3.8%) of our cohort and in contrast to those found in NOTCH1 the majority of these were truncating to the protein coding sequence. They were also distinct to those FLT4 mutations known to cause the dominant condition Milroy disease, or hereditary lymphedema, highlighting a novel role for the gene in early embryonic heart development. In addition, variants in the well-established TOF gene, *TBX1* were also significantly enriched. There are potentially variants in several more genes previously not associated with TOF that we have also shown could be implicated in disease causation. Our study underlines the importance of sequencing large cohorts of CHD and other congenital disorders in order to further discover their genetic basis.

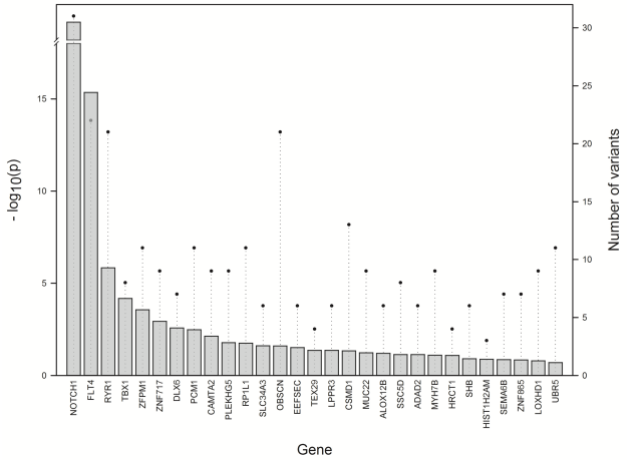


Figure 1. Top genes enriched for likely pathogenic variants in our TOF cohort order by P value. Lollipop bars represents number of variants per gene.

Recent publications

1- Page, J. D., **Monaghan, R. M.** *et al.* (2019) Whole exome sequencing reveals the major genetic contributors to non-syndromic Tetralogy of Fallot. Circulation Research 15;124(4):553-563.

2- Jin, S.C. *et al*. (2017) Contribution of rare inherited and de novo variants in 2871 congenital heart disease probands. Nature Genetics. 49:1593-160.

3- Starr, J.P. (2009) Tetralogy of Fallot: Yesterday and Today. World of Surgery. 34:658.

4- Zaidi, S. *et al*. (2013) De novo mutations in histone-modifying genes in congenital heart disease. Nature. 498:220

5- Cordell, H.J. et al. (2013) Genome-wide association study of multiple congenital heart disease phenotypes identifies a susceptibility locus for atrial septal defect at chromosome 4p16. Nature Genetics. 45:822.

Biography

Dr. Richard Monaghan has worked in cell and molecular biological research since his PhD, crossing fields such as cell signalling, mitochondrial biology, development, congenital heart disease, angiogenesis and cardiogenesis. He completed his PhD in 2012 looking at the function of a mitochondrial protein in stress signalling and ageing before moving to his current lab where he works on genetic variation in cardiovascular disease. He is currently working in the laboratory of Prof. Bernard Keavney an international expert in the genetic analyses of complex diseases in particular cardiovascular conditions.

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