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Gene210 - SNP Summary
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rs3903239 and Atrial Fibrillation

rs3903239 (1q23) is a SNP discovered 46kb upstream of the *PRRX1* gene (1). Recent work has shown *PRRX1* is a transcriptional co-activator that enhances the DNA affinity of serum response factor (2). This protein, in turn, regulates numerous growth and differentiation factors, including muscle creatine kinase (MCK) (2). MCK controls growth and development genes, specifically in developing mesodermal muscle such as the heart (2).

PrrX1-/- mice are embryonic lethal and have a significantly altered neonatal phenotype including microcephaly, cleft palate, and hypoplastic processes of the mandible (3). Other studies have shown this gene is involved in lung vascular development and skeletogenesis (4).

A meta-analysis GWA study correlated rs3903239 with atrial fibrillation ($p = 9.1 \times 10^{-11}$, discovery phase) in a European cohort (1). Although many studies have identified loci associated with atrial fibrillation, much of the heritability remains unexplained. Atrial fibrillation is particularly critical for clinical applications as the presence of a heart murmur can increase an individual's risk of stroke up to seven times that of normal.

Ellinor *et al* investigated a cohort of individuals (European ancestry) composed of 6,707 people with confirmed atrial fibrillation and 52,426 without (1). Six novel SNPs, including rs3903239, were discovered, and several previously known SNPs confirmed. In the meta-analysis, the authors found rs3903239 had a minor allele frequency (C) of 29.9% compared to the major allele (G), and a risk frequency of 1.14.

These results were validated in a cohort composed of 5,381 European individuals with atrial fibrillation and 10,030 individuals without (1). rs3903239 had a p-value of 2×10^{-4} and a risk frequency of 1.13 in this second cohort. Overall, the meta-analysis and validation yielded a p-value of 8.4×10^{-14} and a risk frequency of 1.14.

Drawbacks to this meta-study are the wide range of ages included and the high prevalence of potentially correlated atrial fibrillation-based traits, such as hypertension, relative body mass index, and diabetes. Thus, SNPs discovered could correlate to these secondary traits rather than the primary issue of atrial fibrillation. The authors attempt to address this by noting none of the variants associated with atrial fibrillation were "strongly associated" with systolic dysfunction in a second cohort of 12,000 European individuals ($p<1 \times 10^{-5}$) (1).

This SNP did not meet standard GWAS thresholds for a Japanese cohort composed of 843 individuals with atrial fibrillation and 3,350 without (1). However, there was atrial fibrillation-association of an alternative SNP near *PRRX1*. This SNP, rs593479 (minor allele T, major C), had an associated p-value of 2.4×10^{-3} and an odds ratio of 1.21 (1).

Currently, knowledge of the rare allele variant of either of these SNPs is not being using for treatment of atrial fibrillation symptoms or as a diagnosis for atrial fibrillation.

References:

1. Ellinor, P.T., et al., *Meta-analysis identifies six new susceptibility loci for atrial fibrillation.* Nature Genetics, 2012. **Advance Online Publication**.
2. GeneCards.org. *"Paired Related Homeobox 1".* [cited 2012 May 17]; Available from: http://www.genecards.org/cgi-bin/carddisp.pl?gene=PRRX1.
3. Martin, J.F., Bradley, A., Olson, E.N. (1995) The*paired*-like homeo box gene *MHox* is required for early event of skeletogenesis in multiple lineages. Genes & Development. 9:1237‑1249.
4. Ihida-Stansbury, K., et al., *Paired-related homeobox gene Prx1 is required for pulmonary vascular development.* Circulation research, 2004. **94**(11): p. 1507-1514.