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Genomics in Atrial Fibrillation: A Brief Review

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Genomics in Atrial Fibrillation

Atrial fibrillation (AF) carries a significant burden in the form of morbidity, mortality, and cost to the healthcare system. According to the Center for Disease Control, AF is the most common cardiac arrhythmia in the United States with an incidence of 2.26 million people in 2010 that is expected to increase to 12 million people by 2050 [1]. The mortality rate from AF as a primary or secondary cause of death is increasing, as is the cost burden to the healthcare system [1]. It is estimated that in the year 2005, the cost to the U.S. healthcare system for treating AF was \$6.65 billion [1]. European population studies show a prevalence of AF of 5.5%, with an incidence of 9.9 per 1000 person years [2]. The Rotterdam study showed that a 55-year-old European man had a 24.8% lifetime risk of developing AF [2]. In a 2010 Global Burden of Disease study the worldwide incidence of AF was estimated at 33.5 million people [3]. In this same study, the worldwide mortality rate from AF was found to have doubled from 1990 to 2010 [3]. Morbidity and mortality associated with AF arise from risk of thromboembolic stroke, tachycardia mediated cardiomyopathy, and from the treatment of the disease itself. Although the exact mechanism of AF is not known, what has been known for many years is that there is a probable genetic association for this disease. This is based on the fact that a strong family history of AF increases risk of one developing the disease [4]. Genetics in AF is an exciting area of research with implications that we could one day predict who will develop AF, choose therapy targeted to specific genotypes, and eventually prevent this disease in patients who are genetically predisposed to develop AF.

One of the initial genome wide association studies (GWAS) in AF was in an Icelandic population that found two variants on the 4q25 gene associated with AF. In this study, genome wide association was performed on 550 patients with AF and 4,476 controls in an Icelandic population. Of the 316,515 single-nucleotide polymorphisms (SNPs) that met the quality criteria, two located on chromosome 4q25 where found to have a significant association with AF when compared to healthy control subjects who did not carry these alleles. The two alleles on chromosome 4q25, rs2200733 and rs10033464, have a population allelic frequency of 12.05% and 8.53% respectively. This analysis was replicated in an additional group of Icelandic patients, as well as a population from Sweden, the United States, and Hong Kong [4].

Other genome wide association studies have identified SNPs at additional loci that are associated with AF. In the CHARGE-AF consortium 5,558 patients with AF and 41,178 controls, again demonstrated was the association with SNPs on the 4q25 locus; however, a new locus on the 16q22 gene was also found to have genome wide significant association with AF [5]. This was replicated by a study in an Icelandic population [6]. In a GWAS looking at 1335

patients with early-onset AF and 12,844 controls a SNP on chromosome 1q21 was found to have genome wide significant association with AF [7].

One group performed a GWAS looking at the heritability of the PR interval, as prolongation of the PR interval has been shown to carry increased risk of developing AF. There were nine loci that reached genome wide significant associations with PR interval, five of which were significant for an association with AF [8].

Showing association between SNPs on these three gene loci 4q25, 16q22, and 1q21 is promising; however, the mechanism of these associations or how we can therapeutically manipulate them is unclear. One area of promising research is in the PITX2 gene, which is located near the 4q25 gene [9]. PITX2c is the primary isoform of the PITX2 transcription factor that is expressed in the cardiac myocytes. PITX2c is thought to be involved in development of the left atrium, the conduction system, as well as the myocardial sheath surrounding the pulmonary veins [10]. Yang et al. published a study of a Chinese population looking for the prevalence of PITX2c mutations in familial AF. 152 patients with familial AF and 200 controls were enrolled for GWAS. Two mutations on the PITX2c gene were found in the group with familial AF. Interestingly, these mutations were not observed in the control group [10]. This was reproduced by two more recent studies that found heterozygous missense mutations on the PITX2c gene in a patient with familial AF as well as a patient lone AF that were not detected in healthy controls [11,12]. The association with the mutation of the PITX2c gene and AF could be explained by the role of the PITX2c gene in developing the myocardial sleeve of the pulmonary veins, which are a known and targeted source of initiation of AF. In an animal study, PITX2c knockout mice developed normal pulmonary veins that were lacking the myocardial sleeve [13]. Further associating this gene locus with underlying mechanisms of AF was a human study that showed significantly decreased PITX2c expression in patients with AF, suggesting that a loss of function of this gene predisposes to AF [14].

Despite the recent revelations in the genetics of AF, these discoveries have not yet translated into changing clinical practice. There is still much to be learned about how genes play a role in the development of the disease and offer opportunity for intervention. It is possible that through current and future discoveries of genes related to AF, and their transcription byproducts that we will one day come to understand the exact pathophysiologic mechanism of the disease. The genetic associations of AF offer the opportunity for future therapies such as gene-targeted therapy, pharmacogenetic therapy, as well as early detection, and hopefully one day prevention of this problematic disease.

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