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The role of common genetic variants in atrial fibrillation

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Abstract This review focuses on the genetic basis of atrial fibrillation (AF) and the role of variants in the susceptibility of developing the disease. AF is the most common cardiac arrhythmia affecting 1–2% of the general population. Studies in the last decade have demonstrated that AF, and in particular lone AF, has a substantial genetic component. A number of genome-wide association studies (GWAS) have indicated that common genetic variants, more precisely the so called single-nucleotide polymorphisms (SNPs) are associated with AF. Presently more than 10 genomic regions have been identified using this approach. Highly penetrant variants in lone AF have also been described in a number of cases. Furthermore, familial AF, although rare, have been recognized for many years.Variants associated with AF have been identified in more than 40 genes, including cardiac gap junction proteins, ion channels and beta subunits. The evidence for some of these findings is not as strong as the evidence for the common variants. All in all, it is a complex picture, as both gain- and loss of function variants have been identified in a number of the genes. This review will focus on the common variants associated with AF.The pathophysiological mechanisms responsible for AF are still far from completely understood, and it is assumed that this arrhythmia represents a complex interplay of genetic predispositions, arrhythmogenic contributors such as electrolytes and inflammatory stimuli as well as contributions from concomitant cardiac and non-cardiac diseases.

Keywords: Atrial fibrillation; Lone AF; GWAS; Common variants

Introduction

Atrial fibrillation (AF) is a common supraventricular tachycardia affecting 1–2% in the general population and on an electrocardiogram it is presented without distinct P waves and with irregular ventricular response. Clinical manifestations are palpitations, dyspnea, and fatigue, although asymptotic patients are common. AF is divided into five types: first-diagnosed, paroxysmal, persistent, long-standing persistent and permanent [1].

AF is associated with several cardiac risk factors, such as increasing age, hypertension, diabetes mellitus, ischemic heart disease and structural heart diseases [1]. However, many patients present with the arrhythmia without these predisposing factors and are diagnosed before the age of 60. These patients are diagnosed with *lone AF*, which comprises 10–20% of all AF patients, although the definition of this entity is not strict [1].

Numerous studies have shown a significant genomic component of AF and in particular lone AF [2]. Oyen et al. showed that an individual's risk of developing lone AF was increased with early age of onset and the number of affected relatives, especially if these were close relatives [3]. In a Danish twin study of 2164 twin pairs it was shown that monozygosity was associated with an increased susceptibility to AF for twins with AF-diagnosed co-twins [4].

This review discusses the genetic basis of lone AF and the role of common genetic variants in the development of the disease.

Methods

The review is based on a literature search carried out in PubMed, the MeSH database, and Google Scholar. A systematic search was performed to identify all studies published prior to April 2016, which investigated the genetic basis of atrial fibrillation. Searching with the query

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(("Atrial fibrillation" [MeSH]) OR (atrial fibrillation)) AND (("Genetics" [MeSH]) OR (genetic*)) AND (("Mutation" [MeSH]) OR (mutation*) OR ("Polymorphism, single nucleotide" [MeSH]) OR (polymorphism, single nucleotide) OR (monogenic*) OR (GWAS)) yielded 793 articles in PubMed. We searched the Human Gene Mutation Database (HGMD), where we identified 18 additionally articles of use. Only articles concerning the genetic basis of atrial fibrillation were included in this review. Small studies concerning common variants in genes not associated with AF elsewhere were excluded, unless these studies had been replicated in other independent populations or in cases where convincing electrophysiological studies were presented. This was done due to a high risk of false positive associations. The reference list and related articles of each relevant publication were also examined to identify additional studies appropriate for inclusion in this literature study.

Results

GWAS identified variants

Genome-wide association studies (GWAS) have in recent years identified more than 10 common variants associated with AF. These variants are called single nucleotide polymorphisms (SNPs). By studying the frequency of SNPs across the entire genome in individuals, GWAS illustrate whether genomic loci are more or less prevalent in cases compared with controls. Thousands of individuals are included in association studies to examine the correlation between genotype and phenotype. The reasoning for GWAS is the theory of "common variant, common disease", proposing that common diseases are related to variants present in more than 1–5% of the general population. The findings are based on haplotype-tagging, thus a marker for the involved haplotype, and therefore the findings most likely do not report the causal gene or variant [2].

The first AF GWAS was performed in 2007 and identified the SNP rs2200733, located close to *PITX2* on chromosome 4q25 [5]. Three association studies investigating lone AF patients have been performed; first a study that showed two SNPs associated with lone AF: rs6843082 (*PITX2* as closest gene) and rs13376333 (*KCNN3* as closest gene) [6], later a study identifying rs2200733 in lone AF patients and the additionally SNP rs3807989 (*CAV1*) [7]. Most recent a study revealing the common variant rs6795970 in *SCN10A* has been identified [8].

All four GWAS studies and a number of association studies have identified more than 10 AF-related loci (Fig. 1 and Table 1). The pathogenicity of the variants in these loci will be discussed.

KCNN3 – rs13376333/rs6666258

The SNPs rs13376333 and rs6666258 are situated on chromosome 1q21 in the *KCNN3* gene, coding a calcium-gated potassium channel involved in atrial repolarization. The SNP rs13376333 has been associated with lone AF in a GWAS study (1335 subjects with lone AF and 12,844 controls) [6], and Yao et al. have recently investigated the relationship between the variant and development of AF [9]. Their meta-analysis proposed that rs13376333 increases the susceptibility to lone AF and AF overall by odds ratios 1.58 and 1.33, respectively. Another GWAS (6707 subjects and 52,426 controls) identified rs6666258 to be more prevalent in individuals with AF presenting a relative risk of 1.18 [10].

PRRX1 – rs3903239

The SNP rs3903239 is located on chromosome 1q24 close to *PRXX1*, responsible for a homeodomain transcription factor expressed primarily in connective tissue. The SNP was identified in a GWAS with 6707 subjects and 52,426 controls, showing a relative risk of 1.14. The gene is essential in the developing heart and studies have revealed the consequence of its impaired effect, leading to abnormalities in development of the major vessels and pulmonary vessels [10].

SCN10A – rs6795970

The SNP rs6795970 is positioned in an exon of *SCN10A* on chromosome 3p22, a gene that encodes the sodium channel $Na_V1.8$. In an association study (515 AF subjects and two control groups of 730 AF-free individuals and 6161 random subjects), the variant increases the risk of AF by odds ratios 1.33 for lone AF and 1.35 for general AF. Functional characterization of A1073 showed that the common variant of the gene increases peak current, causing a gain of function of the channel [8].

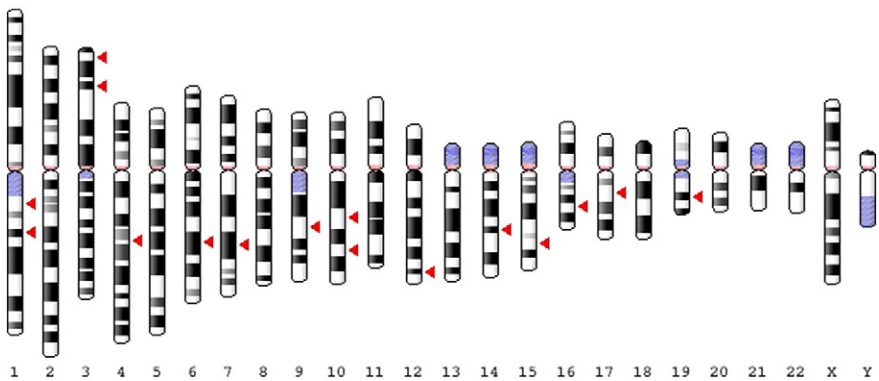

Fig. 1. Genetic atrial fibrillation loci and their chromosomes identified in GWAS. An overview of the human genome representing the different chromosomes. The arrows indicate the loci of the GWAS-identified common variants presented in Table 1.