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Genetics of Atrial Fibrillation and Atrial Cardiomyopathy

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Abstract

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. Through epidemiological studies, AF has been recognized to have a considerable genetic component. Genome-wide association studies have associated more than 100 genes with AF. Newer research has established a link between atrial cardiomyopathy and a predisposition for AF. This association has been further supported by recent exome and genome sequencing projects which have shown a substantial genetic overlap between genetic variants implicated in AF and cardiomyopathy in general. This review focuses on the genetic overlap between AF and cardiomyopathy.

Atrial fibrillation (AF) affects more than 33 million people worldwide[1]. It has been linked to a substantial increased morbidity and mortality with a high risk of stroke, heart failure and sudden death[1,2]. It is well known that AF typically arises secondary to hypertension, ischemic and/or structural heart disease. A number of studies have demonstrated, that AF and in particular lone AF has a substantial genetic component[3,4]. An Icelandic study demonstrated large familial aggregation of AF in 5,000 Icelandic AF patients[4]. It has recently been recognized that atrial myopathy and fibrosis appear to play a driving role in the development of AF[5]. Most AF associated rare genetic variants were initially identified in genes encoding ion channels, particularly potassium and sodium channels[6,7,8]. These rare variants were shown to have gain-of-function or loss-of-function effects contributing to an altered cardiac depolarization or repolarization[8]. Mutations in non-ion channel genes were subsequently identified[9,10]. Rare variants in both ion channel and non-ion channel genes were found to be associated with AF using the candidate gene approach[11]. During the last decades, more than 100 single-nucleotide polymorphisms have been shown to contribute to the risk of AF through genome-wide association studies[12].

Recent discoveries suggest that AF could be caused by atrial cardiomyopathy[13]. Although cardiomyopathy involve a variety of phenotypes and etiologies, the most common cardiomyopathies are hypertrophic, dilated and restrictive cardiomyopathies, where the latter is less common and mostly associated with systemic disease[14].

Overall, Atrial cardiomyopathy has been defined to encompass any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations[15]. Furthermore, it has recently been recognized that fibrosis appear to play a driving role in the development of AF[5].

Table 1. Examples of the most common structural genes associated with cardiomyopathy[21,22,16, 18].

Gene	Protein	Chromosome location	Type of cardiomyopathy
TTN	Titin	Chr2	DCM
MYL4	Myosin light chain	Chr17	Atrial cardiomyopathy
MYH7	Myosin heavy chain	Chr14	HCM
MYBPC3	Myosin binding protein C	Chr11	HCM

At the genetic level, several structural genes have been found to be implicated in both AF and cardiomyopathy. Peng *et al.* found an association between rare loss-of-function variants in the *MYL4* gene and atrial cardiomyopathy. These rare variants were found to cause atrial fibrosis leading to atrial cardiomyopathy and atrial arrhythmia[16]. Furthermore, Gudbjartsson *et al.* identified a frameshift variant in *MYL4* associated with a recessive form of AF, suggesting a genetic overlap between AF and cardiomyopathy[5].

Another important structural gene, *TTN*, is strongly linked to AF and also associated with cardiomyopathy. This gene encodes a giant sarcomere protein (titin). Titin-truncating variants (TTNtv) have been shown to predispose directly to lone AF[17]. TTNtv were found to be significantly enriched within families diagnosed with AF and lone AF patients. Interestingly, TTNtv are known to occur in 15 % of dilated cardiomyopathy (DCM) cases and represent the most common genetic cause of DCM[18]. A CRISPR-Cas9 mutant zebrafish carrying a mutation in the homologue gene *ttn* in zebrafish, revealed increased amount of fibrosis, particularly in atria of the mutant fish, suggesting a predisposition for AF and in general arrhythmia and conduction disease[17]. Previous studies have demonstrated a higher degree of re-entry activity in patients with atrial fibrosis, which suggest a likely explanation for the development AF in these patients[19].

Both TTNtv and MYL4 constitutes components of the cardiac sarcomere. Titin is the giant protein that connect the thick filament to the sarcomere, whereas myosin light chains constitutes a part of the thick filament. The bands of the cardiac sarcomere are due to the overlap of thin and thick filaments. Abnormalities of the sarcomere are directly linked to causing cardiomyopathy and the majority of HCM cases are a result of these abnormal protein structures[20].

Findings of compromised sarcomere structure in both *TTN* and *MYL4* variants as well as increased atrial fibrosis in zebrafish with TTNtv suggest an essential role of structural genes in both AF and atrial cardiomyopathy. The relationship is complex, but identifying genetic subtypes of cardiomyopathy and their associations with AF might help to expand our understanding of the pathophysiology of AF and speed up the implementation of personized medicine.

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