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# Genetic Factors in the Development of Atrial Fibrillation

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**Abstract:** Atrial fibrillation (af) is the most common tachyarrhythmia, significantly impairing patients' quality of life and work capacity. despite advancements in managing af, it remains a leading cause of stroke, heart failure, and sudden cardiac death worldwide. to meet the growing demand for effective treatment, new research is continually being conducted and published. in most cases, af is secondary, developing alongside other medical conditions. However, in at least one-third of patients, the cause of AF cannot be identified, leading to a diagnosis of idiopathic or primary AF. It is hypothesized that a significant proportion of idiopathic AF cases have a genetic basis. Even in secondary AF, a hereditary component may play a role, as not all patients with similar severity of an underlying condition develop AF. This opens possibilities for predicting, preventing, and treating this form of arrhythmia. This article reviews literature on the genetic mechanisms of atrial fibrillation, with findings that could significantly impact future treatment and prevention strategies.

**Keywords:** atrial fibrillation, hereditary atrial fibrillation.

Genetic research on atrial fibrillation (AF) focuses on two main areas:

1. Identifying genes with mutations that directly cause arrhythmia, typically inherited following Mendelian patterns.
2. Investigating polymorphisms in susceptibility or candidate genes that contribute to both primary and secondary AF [1].

AF caused by mutations in specific genes is relatively rare. More commonly, AF arises from a combination of polymorphisms in certain genes. Therefore, screening for susceptibility genes and analyzing their variations should be a primary focus in AF genetic research. Most studies on the genealogy of atrial fibrillation date back to the 1990s, describing families where multiple members exhibited AF or atrial flutter. In the 21st century, research continues to explore genes whose mutations may trigger AF, aiming to identify not only the triggers for acute AF episodes but also factors contributing to its chronicity. The limited success in AF treatment is partly due to an incomplete understanding of its molecular pathophysiology. R. Brugada et al. [4, 5] conducted clinical, electrophysiological, and genetic studies on six Spanish families with AF, diagnosing the condition in 50 of 132 relatives. Genetic analysis revealed that the gene responsible for AF was located on chromosome 10q in the 10q22-24 region, with the pathological gene locus identified between D10S1694 and D10S1786. The condition showed high penetrance. The researchers proposed β-adrenergic receptor genes (ADRB1), α-adrenergic receptor genes (ADRA2), and G-protein-coupled receptor kinase genes (GRK5), located on the same chromosome in loci 23-26, as potential candidate genes. AF exhibits genetic heterogeneity, as similar phenotypic presentations can result from mutations in different genetic loci. In addition to the AF locus on chromosome 10, P.T. Ellinor et al. [6, 18] mapped an AF gene to the proximal long arm of chromosome 6q14-16, between D6S286 and D6S1021, where AF was inherited as a Mendelian disorder. Taiwanese researchers [6, 18] identified two genes responsible for hereditary AF, encoding potassium channel proteins in cardiomyocytes. Specifically, I. Yang et al. [18] reported a substitution of arginine with cysteine at position 27 in the KCNE2 gene (chromosome 21q22.1-22.2), which encodes the β-subunit of the I(Kr) potassium channel. This mutation was found in two of 28 Chinese families with hereditary AF. Y.H. Chen et al. [6] studied four generations of a Chinese family with AF and identified a missense mutation (S140G) in the KCNQ1 gene (chromosome 11p15.5), encoding the α-subunit of the I(Ks) potassium channel. These mutations enhance the function of the respective potassium channels, shortening the action potential duration and effective refractory period in the atria, leading to AF. Belocq et al. [3] described a family where a KCNQ1 mutation caused short QT syndrome with paroxysms of both atrial and ventricular fibrillation. Conversely, mutations reducing the function of these channels are known to cause long QT syndrome with its associated arrhythmias, such as LQT1 (KCNQ1 mutation) and LQT6 (KCNE2 mutation).

Thus, in certain cases, hereditary AF results from mutations in ion channel genes, altering the duration and shape of the myocyte action potential. These conditions are now classified as channelopathies or electrical disorders of the myocardium, characterized by arrhythmias without structural myocardial changes. Hereditary AF has been associated with other genetic conditions, including long QT syndrome, dilated cardiomyopathy, hypertrophic cardiomyopathy, and Wolff-Parkinson-White (WPW) syndrome. In 2002, E.A. Sparks et al. [14] reported a 40-year observation of nine generations of a family with hereditary cardiomyopathy, where AF was diagnosed in 106 of 325 individuals. T.M. Olson et al. [12] identified a missense mutation (D1275N) in the SCN5A sodium channel gene in patients with dilated cardiomyopathy and AF. Gruver et al. [9] found a missense mutation (arginine to histidine at position 663) in the β-myosin heavy chain gene, leading to co-inherited hypertrophic cardiomyopathy and AF. In 2008, Hodgson-Zingman et al. [10] mapped the 1p36-p35 region and identified a heterozygous frameshift mutation in the NPPA gene, encoding atrial natriuretic peptide. Patients with this mutation had elevated circulating ANP levels, and studies on an isolated heart model showed shortened action potentials, potentially contributing to AF. The researchers noted disruptions in the cGMP cycle of natriuretic peptides and sequenced the NPPA gene in a three-generation family with AF. They reported data on three generations of families (of Northern European descent), where 11 members developed AF at an average age of 40, with three cases occurring during pregnancy. In three patients, paroxysmal AF progressed to chronic, indicating progressive atrial remodeling. Five patients developed tachycardia-induced cardiomyopathy, which resolved after heart rate control. Echocardiography ruled out myocardial hypertrophy or contractile dysfunction, but seven patients showed left atrial dilatation, and four had left ventricular dilatation. In 2010, Yang T. et al. [19] identified loss-of-function mutations in the KCNA5 gene, encoding voltage-gated potassium channels. These mutations impair the function of atrium-specific potassium channels, disrupting electrical synchronization and increasing AF susceptibility. A missense mutation, Kcne1 A, in KCNE5 may be linked to non-familial acquired AF, making these channels potential therapeutic targets for familial AF. In 2012–2013, Wang X.H. et al. [11, 15, 16] studied the GATA4, GATA5, and GATA6 genes, which encode zinc-finger transcription factors critical for cardiogenesis. Functional analysis revealed that mutations in these genes significantly reduced transcriptional activity, providing new insights into the molecular mechanisms of AF pathogenesis and potential preventive and therapeutic approaches. In 2013, Shi H.F. et al. [13] investigated the gap junction alpha-5 protein (GJA5), specifically expressed in atrial myocytes and responsible for coordinated electrical activation of the atria, making it a logical candidate gene for AF. They identified four novel heterozygous GJA5 mutations in four of 310 unrelated AF patients, with a prevalence of approximately 1.29%. Genetic analysis of carrier families showed that each mutation was present in all affected family members.

In 2019, Yamada N. et al. [17] identified a heterozygous mutation in the KCNJ3 gene, encoding the acetylcholine-activated potassium channel Kir3.1, which, together with Kir3.4 (encoded by KCNJ5), forms the acetylcholine-activated potassium channel (IKACh). Cellular electrophysiological studies showed that the KCNJ3 p.N83H mutation enhances IKACh channel function by increasing basal potassium current, even without m2-muscarinic receptor (m2R) stimulation. The IKACh channel is linked to the pathophysiology of bradyarrhythmias and AF, and the mutant channel (KCNJ3 p.N83H) can be effectively inhibited by NIP-151, a selective IKACh channel blocker.

**Conclusion.** Hereditary AF may result from mutations in specific genes and is often associated with other inherited cardiac conditions, such as primary cardiomyopathies, WPW syndrome, and long or short QT syndromes. In these cases, hereditary AF is a monogenic disorder. However, in most cases, AF likely arises from a combination of polymorphisms in candidate genes. Research into the molecular mechanisms of atrial fibrillation remains highly relevant, uncovering new targets for specific therapies and genetic diagnostics.

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