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The Genetic Factors in the Development of Atrial Fibrillation

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ABSTRACT

Context: Atrial Fibrillation (AF) is the most prevalent arrhythmia in human populations with a growing world-wide burden. The present review aimed to determine the genetic factors in the development of AF.

Evidence Acquisition: The present study included the studies, which probed into the genetic factors of AF. The searches were done in PubMed, Scopus, Web of Science, Embase, and Google Scholar databases. The review highlighted two main directions of AF genetic studies; i.e., rare mutations in structural genes, including potassium and sodium channels, connexins, and transcription factors genes, and genome-wide association studies of significant common variants. The main focus was on the most important loci confirmed by numerous studies with both rare and common variants.

Results: Research on the genetic basis of AF has remained a hot topic due to its growing worldwide burden. Recent advances in genome-wide studies have provided the ground for gaining insight on minor genetic factors with cumulative effects, which are distributed more widely than previously known rare mutations.

Conclusions: Far more potential candidate genes and/or regulatory sequences have been already discovered, and there are much more to be explored in the near future. This will potentially result in a better understanding of AF and other arrhythmic conditions as well as their impacts on human health, and will provide new ways to improve diagnostics and treatment strategies.

1. Context

Atrial Fibrillation (AF) is the most common heart arrhythmia with a wide range of symptoms and severities (1). Several clinical cohort observations (such as Framingham Heart Study, Rotterdam Study, etc.) conducted in different countries have revealed the general epidemiological properties of AF (2, 3). Accordingly, the most important risk factors of AF have been reported to be age, cardiovascular disorders, diabetes mellitus, smoking, and alcohol consumption. On the other hand, AF itself has been associated with stroke (4) and dementia (5), not only via shared risk factors, but also as an independent contributing agent.

Although structural heart disorders are the usual prerequisite for AF manifestation, about 30% of the cases are being observed in the absence of such conditions (6). These cases are usually referred to as a lone AF. However, some authors have highlighted the role of genetic mutations in the development of AF and different approaches for imaging (7). Moreover, modern methods for imaging and testing can help determine the exact ethology of heart disorders, making the term 'lone or idiopathic AF' incorrect. Such cases are supposed to have a strict genetic determination. The properties of lone AF are familial inheritance and early onset. Indeed, there have been numerous observations of AF hereditability in families. The first description of familial AF was made in 1943 (8). Since then, the occurrence of familial AF was confirmed as a risk factor by a number of studies (9). It has also been demonstrated that the prevalence of risk factors associated with the development of AF was linked to racial and ethnic differences (10). The key landmark of history of studies on this problem is an invention and development of Genome-Wide Association Study (GWAS) methodology (11). Before this, the primary approach to determining the genetic variants was a linkage analysis in the families

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affected by AF following the sequencing of the supposed candidate genes. Most of these genes appeared to code the cardiac potassium and sodium ion channels directly involved in the mechanistic models of AF development (8). This approach facilitated the detection of rare variants with allele frequencies under 0.5% and large gain-of-function or loss-of-function effects (12). In fact, the GWAS-based study predominantly focused on full-genome screening for the association between thousands of known Single-Nucleotide Polymorphisms (SNP) with the phenotypes of interest (13). Unlike the previous approach, it helped find the common variants; i.e., polymorphisms widely distributed in populations and having small effects on phenotype development (12). According to the impacts caused by rare and common variants in disease development, two concepts of AF were defined. The first one was common AF as a mostly polygenic and multifactorial condition, while the second one was familial AF with preliminary monogenic heritability of rare variants with large effects and common variants with only minor modifying effects (Table 1). Between these concepts, there were cases with unclear heritability, which remained unclassified due to the complex interactions between the known and not yet discovered rare and common variants (14).

The present review aims to highlight and analyze the key points of the genetics of AF.

2. Evidence Acquisition

The present study included the studies, which probed into the genetic factors of AF. Not claiming to provide exhaustive description of all available genetic data, the study was focused on the most important aspects. The searches were done in PubMed, Scopus, Web of Science, Embase, and Google Scholar databases using a combination of free text and MeSH terms.

3. Results

3.1. Loci with Rare Genetic Variants Associated with AF

Roberts and Gollob classified all cases of lone AF into six subtypes according the underlying physiological models: 1) enhanced atrial action potential repolarization, 2) delayed atrial action potential repolarization, 3) conduction velocity heterogeneity, 4) cellular hyper-excitability, 5) hormonal modulation of atrial electrophysiology, and 6) cholinergic AF (8, 15). Except for the last one, the genetic basis of which has remained unclear, rare genetic variants related to all these subtypes have been studied since 2003 when the first mutation causing familial AF was described (16). Developmental genes were found to exert an impact on heart development, which could cause AF by altering cardiac structures and functioning. This is typical for rare variants, in which observable mutations are unique in each particular family. Hence, discoveries cannot usually be generalized to all AF cases. However, they can be an important source of knowledge about molecular mechanisms of cardiac physiology.

3.2. Rare Variants in Cardiac Ion Channel genes

The cardiac tissue contains ion channels responsible for specific calcium and potassium currents, which delay membrane repolarization after an action potential. It plays a crucial role in maintaining the rhythm of automated heart activity. Therefore, mutations affecting the activity of ion channel proteins can be a probable cause of various arrhythmic conditions, including AF. Depending on their functional effects, mutations in the cardiac channel genes can lead to different results, including enhanced repolarization and shorter AP cycle in the case of gain-of-function, or delayed repolarization and prolonged AP in the case of loss-of-function mutations (15).

The first mutation associated with AF was found in the KCNQ1 gene in a Chinese family affected by heritable AF (16). The product of this gene is an α-subunit of a voltage-gated potassium channel. Co-expression with the KCNE gene family is required for the formation of ion pore. These channels are responsible for the slow component of the delayed rectifier potassium current, which assists the prolongation of the repolarization phase of action potential in cardiac myocytes. KCNQ1 protein consists of six transmembrane domains (S1-S6), pore loop between S5 and S6, and intracellular N- and C- termini. S4 domain has been described as containing a voltage sensor (15, 17, 18). Chen et al. discovered the point mutation S140G (A to G substitution at nucleotide 418) in S1 with a gain-of-function effect on KCNQ1/KCNE1, KCNQ1/KCNE2, and KCNQ1/KCNE3 channels. A similar effect was described for de novo substitution G to A in position 421 (V141M) in a pediatric patient with AF and short QT syndrome in utero (19). The same substitution was further revealed in three independent cases (20). Mutation leading to S209P substitution was found in highly conserved S3 region (21). Unlike these gain-of-function mutations, Q147R was discovered to have an effect depending on conjugation with the particular KCNE

Table 1. Comparison of the Rare and Common Genetic Variants

	Rare Variants	Common Variants
Abundance	Very low Mostly unique mutations, not observed in populations	Wide range: from low to high Usual polymorphisms in human populations
Location	Exons, regulatory regions	Mostly non-coding regions (UTR, introns, inter-gene intervals), regulatory regions, rarely exons
Inheritance mode	Mendelian	Complex polymeric and/or multifactorial
Effect size	Strong	Small
Caused disorders	Rare heritable conditions	Common diseases with or without reported heritability
Discovery approach	Familial genealogy study, linkage analysis, candidate gene sequencing	Genome-wide association study

protein; gain of function with KCNE2, loss of function with KCNE1, and no effects with KCNE3 or KCNE4 (22). R231C mutation in S4 was the first to show a relationship between AF with loss of function and long QT syndrome (23). Afterwards, a new substitution in the same position of R231H was discovered independently in five families (24). Four new mutations with potential loss-of-function effects were also described by Steffensen et al. as follows: G to A at 136 (A46T), C to T at 583 (R195W), C to T at 905 (A302V), and G to A at 2009 (R670K) (25). Rare variants associated with AF were also found in other potassium channel genes. Several mutations of KCNE genes closely related functionally to KCNQ1 were described, as well. For instance, transition of C to T in position 79 of KCNE2 gene leading to R27C substitution was found in a Chinese family (26). In addition, two mutations in KCNE1 and one mutation in the KCNE3 gene were found by screening of the cohort of Danish and Norwegian AF patients: G to T in position 74 (G25V) and G to A in position 179 (G60D) of KCNE1 and G to A in position 39 (V17M) of the KCNE3 gene (27, 28). Moreover, two mutations were identified in the KCNE5 gene as follows: T to C transition in position 97 leading to P33S substitution (described earlier in relation to the long QT syndrome) and T to C transition in position 193 (L65F) (29). Other potassium channel genes with described rare variants associated with AF are KCNA5, KCND3, KCNH2, KCNJ2, and KCNJ8 (30, 31).

Another important factor in AF development is the malfunction of sodium ion channels. Numerous studies have indicated the essential role of mutations in the SCN5A gene, which codes the α-subunit of the Nav1.5 sodium channel. Mutations in this gene were previously known to be associated with ventricular fibrillation (32), dilated cardiomyopathy (33), congenital sick sinus syndrome (34), and some other heart pathologies. Olson et al., for the first time, described three mutations in the families affected by AF or atrial flutter along with other conditions known to be related to mutations in the SCN5A gene; i.e., C to T substitution in position 659 (T220I), G to C substitution in position 4783 (D1595H), and C to T substitution in position 2440 (R814W) (33). Darbar et al. discovered eight mutations in the families affected by AF (M138I, E428K, H445D, N470K, E655K, T1131I, R1826C, and V1951M) as well as 11 rare variants previously reported to be associated with Brugada syndrome, long QT syndrome, and sudden infant cardiac death syndrome (35). Several mutations were also described by different authors: T to C at 5624 (M1875T) (36), C to A at 5958 (N1986K) (37), and K1493R (first described gain-of-function effect on sodium channel; affected cardiac cellular excitability, lowering cardiac AP threshold) (38). The series of mutations previously revealed in association with LQTS were found to be prevalent in the cohort of AF patients (39). Ziyadeh-Isleem et al. described unique frame-shift mutation R1860Gfs*12 (deletion of A at the position 5578), which resulted in the truncated SCN5A protein and a complex condition with AF and sick sinus syndrome (40).

Numerous publications have suggested that mutations in the genes of Nav1.5 β-subunit variants could play a role in AF pathogenesis (41). In this context, many studies have demonstrated that mutations leading to the development of AF and other heart rhythm distortions occurred in evolutionary conserved amino acid positions. This indicated the essential role of such amino acid residues in heart electrophysiology. Hence, although most discovered rare variants are unique, they provide insight into molecular mechanisms underlying heart functioning.

3.3. Rare Variants in Non-Channel Genes

Not only the correct functioning of cardiac ion channels, but also distribution of AP over the cardiac tissue is essential for heart work. All cardiac cells in atria and ventricles are connected in the functional syncytia via so-called intercalated discs or nexus (42). Apart from desmosomes and fascia adherents, there are gap junctions that provide intercellular AP transmission (43). Oligomeric connexin pores are the structural and functional basis of gap junctions (44). Connexins 40, 43, and 45 have been described as primary proteins for the heart tissue (45). Connexin 40 activity, especially relative to connexin 43, has also been identified for its importance in AF pathogenesis (46). Mutations in the GJA5 gene coding connexin 40 were first found in AF patients by Gollob et al. (P88S, M163V, G38N, and A96S). However, only the last one was confirmed to be inherited, while the others were somatic as found exclusively in the heart tissue (47). A96S transition was further confirmed in an unrelated patient (48). Missense mutations V85I, L221I, and L229M of connexin 40 were found in three unrelated families with the history of AF (49). Several publications have indicated that in many cases, connexin-driven AF resulted from polymorphisms in the regulatory regions of the connexin 40 gene rather than alterations in the structural regions (50).

Unlike mutations described above, which affected the physiological function of the heart tissue, there is a group of genetic alterations affecting the process of heart structure formation during morphogenesis. These include mutations in the genes coding transcription factors and other regulatory proteins involved in the development of the cardiac conductive system. Generally, the essential role in heart morphogenesis in all vertebrata is played by GATA4, GATA5, and GATA6 transcription factors. They are zinc finger proteins laying in the basis of the regulatory network of cardiac development (51). Abnormal expressions and structural changes of the GATA genes have been mentioned to lead to congenital heart structure defects (52). A series of mutations were found in the GATA4 (53), GATA5 (54), and GATA6 (55) genes in AF patients. The aforementioned rare variants lay in evolutionary conserved positions, which indicates their functional importance and alterations resulting in structural abnormalities leading to AF.

The Atrial Natriuretic Peptide (APN) coded by the NPPA gene is an important cardiac regulatory protein with various functions. It modulates cardiac electrophysiology indirectly by regulation of the autonomous nervous system and directly by regulation of the activity of ion channels and gap junctions. It is also known to be commonly involved in AF (56). The importance of NPPA for AF was indicated for the first time by discovery of frame-shift mutation in a family with hereditary AF (57). Abraham

et al. revealed the direct impact of mutation in the NPPA gene on increase of the potassium channel, discovering the shared phenotype of two mutations in NPPA and KCNQ1 (58). Point mutations were found in a cohort of Chinese families with AF history not only in the coding regions, but also in 3' and 5' UTR (59).

3.4. Genome-Wide Study of Common Variants Associated with AF

As mentioned previously, most rare genetic variants identified in relation to AF were described as unique genotypes in the affected families. Although the impacts of particular genes are known, specific mutation points differ. Such rare variants are described in only a limited number of AF cases, in which monogenic nature is confirmed, whereas AF is manifested as a complex multifactorial condition more frequently. A more promising approach is a search for common polymorphisms having a significant association with AF in human populations. Such researches have been successfully conducted using the GWAS methodology. The modern SNP detection technologies have allowed researchers to determine the number of polymorphisms considered sufficient for simultaneous wide genome coverage. Thus, genomic regions with higher density of SNPs with significant association with phenotypes of interest are to be studied for possible candidate genes.

Since its introduction in 2002 (60), despite some criticisms, GWAS showed its applicability in research on numerous quantitative traits and common human disorders, revealing the genetic components of many complex conditions (13). GWAS has been performed on large samples of individuals with phenotypes of interest and control individuals, demonstrating its efficacy and accuracy. The precision of this method depends on sample size, number of SNPs, and study design (61). Furthermore, the great improvement of GWAS is the meta-analysis of data from independent studies, which allows the increase of sample size and reduction of sampling bias associated with particular populations. It has resulted in a change in focus from single studies to international GWAS consortia (62).

The first application of GWAS to AF genetics was conducted over Icelandic, European, and Chinese populations in 2007 (63). This study revealed common polymorphisms with strong associations with AF phenotype in 4q25. The assumption of importance of this region for AF pathogenesis was supported by further studies (64). 4q25 region contains the PITX2 gene coding homeobox transcription factor PITX2c, which is known to be directly involved in heart morphogenesis (65). Model studies have also shown its role in AF and other arrhythmic conditions as a complex regulator, not only affecting the development of cardiac structures, but also directly interacting with cardiac ion channels and inter-cellular junctions (66). Moreover, numerous independent GWAS assays summarized by meta-analyses have confirmed the PITX2 locus as having the highest density of linked SNPs with strong associations with AF in 4q25 (67). The PITX2 common variants have also shown to play a key role in the clinical prognosis of AF after anti-arrhythmic treatment (68).

Apart from PITX2, several other loci have demonstrated a high density of associated polymorphisms consistently. For instance, polymorphisms in 16q22 linked with the ZFHX3 gene were first identified in five European cohorts in 2009 (69). ZFHX3 is a homeobox zinc-finger transcription factor involved in the regulation of myogenesis (70). It plays a crucial role in AF development through interaction with PITX2c and regulatory miRNA (71). KCNN3 is a potassium ion-channel gene whose impact on AF has been described primarily by common genetic variants determined by GWAS (72). These two loci along with PITX2 demonstrated the most consistent association with AF phenotype according to genome-wide studies. Other noticeable loci included CAV1, CAV2, PRRX1, SYNE2, C9orf3, WNT8A, HCN4, SYNPO2L, NEURL1, SH3PXD2A, CEP68, etc. (Table 2) (73). Further studies indicated that an increase in the study sample size helped improve the detectability of loci with lower relative effects on AF (74).

Further development of genomic technologies and the application of more complex methods help increase the data volumes and deepen and analyze them. In fact, the whole transcriptome sequencing provides the opportunity to analyze broader variation data comparing microarray methods and, at the same time, to understand the functional properties of candidate genes transcription in relation to the disorder. For instance, Roselli et al. combined whole transcriptome analysis with multi-ethnic meta-analysis of GWAS across multiple cohorts. The researchers reported the detection of a set of 42 genes loci involved in cardiac pathways with overlapping GWAS, thus connecting SNPs data to functional implications (77). Ahlberg et al. used a whole exome sequencing to broaden the spectrum of detected structural variations. Such an approach helped find the variation of sarcomeric protein titin. Followed by the functional validation of the revealed candidate mutations with CRISPR/Cas9 experiment on zebrafish, that study opened a new horizon on AF development in the context of muscular protein structure, unlike traditional electrophysiological and developmental approaches (78).

4. Conclusions

Research on the genetic basis of AF has remained a hot topic due to its growing worldwide burden. Recent advances in genome-wide studies have helped gain an insight on minor genetic factors with cumulative effects, which have been distributed more widely compared to previously known rare mutations. Such common variants can affect noticeable parts of human populations. Therefore, their studies may have diagnostic and clinical implications. In the present study, only a part of known loci with the biggest impact in cardiology and genetics was described. Far more potential candidate genes and/or regulatory sequences have been already discovered, and there are much more to be explored in the near future. This will potentially result in a better understanding of AF and other arrhythmic conditions and their impacts on human health and will provide new ways to improve diagnostics and treatment strategies.

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Table 2. The Most Significant Genes with Known rare and Common Variants Associated with Atrial Fibrillation

a) Rare Variants			b) Common Variants		
Gene	Functional role of the coded protein *	References	**Gene**	Functional role of the coded protein *	References
KCNQ1	Potassium ion channels	(8-11, 13, 15)	**PITX2**	Transcription factors involved in heart morphogenesis	(52-55, 75)
KCNE1		(18)	**ZFHX3**		(54-58)
KCNE2		(16)	**PRRX1**		(54, 55)
KCNE3		(17)	**CAV1**	Caveolin proteins involved in cellular transport and regulation	(54, 55)
KCNE5		(19, 20)	**CAV2**		(54)
KCNA5		(21)	**SYNE2**	Nesprin-2 protein of nucleus envelope	(54, 55)
KCND3		(25)	**WNT8A**	Signaling protein in developmental processes	(54)
KCNH2		(24, 26)	**C9orf3**	Aminopeptidase involved in protein processing in the heart	(54, 55)
KCNJ2		(23)	**HCN4**	Non-selective cation channel gene	(54, 55)
KCNJ8		(22)	**SYNPO2L**	Regulator of the structural components of cardiac muscle cells	(54, 55)
SCN5A	Sodium ion channels	(29, 30)	**NEURL1**	Protein involved in formation of synaptic contacts	(54)
SCN1Bb		(31)	**SH3PXD2A**	Transcription factor involved in cell migration	(54)
SCN4B		(76)	**CEP68**	Component of centrosomes	(54)
GJA5	Intercellular distribution of action potential in the heart tissue	(36, 38-40)	**KCNN3**	Potassium ion channel gene	(55, 60)
GATA4	Transcription factors involved in heart development	(42, 43)			
GATA5		(44, 45)			
GATA6		(46, 47)			
NPPA	Multi-functional regulator of cardiac electrophysiology	(50)			

* According to GeneCards database: *https://www.genecards.org/*

Authors' Contribution

Study concept and design: A.P., Z.K. and T.S.; analysis and interpretation of data: Sh. T., B.T. and B. R.; drafting of the manuscript: A.P., Z.K. and I.F.; critical revision of the manuscript for important intellectual content: A. P., Z. K., and T. S.; All authors read and approved the final manuscript.

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References

1. Wyndham CR. Atrial fibrillation: the most common arrhythmia. *Tex Heart Inst J*. 2000;**27**(3):257-67.
2. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC, Jr., *et al.* Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. *Ann Epidemiol*. 2015;**25**(2):71-6, 6 e1.
3. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, *et al.* Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ*. 2018;**361**:k1453.
4. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener HC, Bernstein RA, *et al.* Uncovering Atrial Fibrillation Beyond Short-Term Monitoring in Cryptogenic Stroke Patients: Three-Year Results From the Cryptogenic Stroke and Underlying Atrial Fibrillation Trial. *Circ Arrhythm Electrophysiol*. 2016;**9**(1):e003333.
5. Manoux A, Fayosse A, Sabia S, Canonico M, Bobak M, Elbaz A, *et al.* Atrial fibrillation as a risk factor for cognitive decline and dementia. *Eur Heart J*. 2017;**38**(34):2612-8.
6. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol*. 2001;**37**(2):371-8.
7. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, *et al.* Lone atrial fibrillation: does it exist? *J Am Coll Cardiol*. 2014;**63**(17):1715-23.
8. Roberts JD, Gollob MH. A contemporary review on the genetic basis of atrial fibrillation. *Methodist Debakey Cardiovasc J*. 2014;**10**(1):18-24.
9. Marcus GM, Smith LM, Vittinghoff E, Tseng ZH, Badhwar N, Lee BK, *et al.* A first-degree family history in lone atrial fibrillation patients. *Heart Rhythm*. 2008;**5**(6):826-30.
10. Ugowe FE, Jackson LR, 2nd, Thomas KL. Racial and ethnic differences in the prevalence, management, and outcomes in patients with atrial fibrillation: A systematic review. *Heart Rhythm*. 2018;**15**(9):1337-45.
11. Bapat A, Anderson CD, Ellinor PT, Lubitz SA. Genomic basis of atrial fibrillation. *Heart*. 2018;**104**(3):201-6.
12. Hayashi K, Tada H, Yamagishi M. The genetics of atrial fibrillation. *Curr Opin Cardiol*. 2017;**32**(1):10-6.
13. Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, *et al.* 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am J Hum Genet*. 2017;**101**(1):5-22.
14. Sinner MF, Ellinor PT, Meitinger T, Benjamin EJ, Kaab S. Genome-wide association studies of atrial fibrillation: past, present, and future. *Cardiovasc Res*. 2011;**89**(4):701-9.
15. Roberts JD, Gollob MH. Impact of genetic discoveries on the classification of lone atrial fibrillation. *J Am Coll Cardiol*.

2010;**55**(8):705-12.
16. Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY*, et al.* KCNQ1 gain-of-function mutation in familial atrial fibrillation. *Science*. 2003;**299**(5604):251-4.
17. Abbott GW. Biology of the KCNQ1 potassium channel. *New Journal of Science*. 2014;**2014**.
18. Jespersen T, Grunnet M, Olesen SP. The KCNQ1 potassium channel: from gene to physiological function. *Physiology (Bethesda)*. 2005;**20**:408-16.
19. Hong K, Piper DR, Diaz-Valdecantos A, Brugada J, Oliva A, Burashnikov E*, et al.* De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. *Cardiovasc Res*. 2005;**68**(3):433-40.
20. Sarquella-Brugada G, Campuzano O, Iglesias A, Grueso J, Bradley DJ, Kerst G*, et al.* Short QT and atrial fibrillation: A KCNQ1 mutation-specific disease. Late follow-up in three unrelated children. *HeartRhythm Case Rep*. 2015;**1**(4):193-7.
21. Das S, Makino S, Melman YF, Shea MA, Goyal SB, Rosenzweig A*, et al.* Mutation in the S3 segment of KCNQ1 results in familial lone atrial fibrillation. *Heart Rhythm*. 2009;**6**(8):1146-53.
22. Lundby A, Ravn LS, Svendsen JH, Olesen SP, Schmitt N. KCNQ1 mutation Q147R is associated with atrial fibrillation and prolonged QT interval. *Heart Rhythm*. 2007;**4**(12):1532-41.
23. Bartos DC, Duchatelet S, Burgess DE, Klug D, Denjoy I, Peat R*, et al.* R231C mutation in KCNQ1 causes long QT syndrome type 1 and familial atrial fibrillation. *Heart Rhythm*. 2011;**8**(1):48-55.
24. Bartos DC, Anderson JB, Bastiaenen R, Johnson JN, Gollob MH, Tester DJ*, et al.* A KCNQ1 mutation causes a high penetrance for familial atrial fibrillation. *J Cardiovasc Electrophysiol*. 2013;**24**(5):562-9.
25. Steffensen AB, Refsgaard L, Andersen MN, Vallet C, Mujezinovic A, Haunso S*, et al.* IKs Gain- and Loss-of-Function in Early-Onset Lone Atrial Fibrillation. *J Cardiovasc Electrophysiol*. 2015;**26**(7):715-23.
26. Yang Y, Xia M, Jin Q, Bendahhou S, Shi J, Chen Y*, et al.* Identification of a KCNE2 gain-of-function mutation in patients with familial atrial fibrillation. *Am J Hum Genet*. 2004;**75**(5):899-905.
27. Lundby A, Ravn LS, Svendsen JH, Hauns S, Olesen SP, Schmitt N. KCNE3 mutation V17M identified in a patient with lone atrial fibrillation. *Cell Physiol Biochem*. 2008;**21**(1-3):47-54.
28. Olesen MS, Bentzen BH, Nielsen JB, Steffensen AB, David JP, Jabbari J*, et al.* Mutations in the potassium channel subunit KCNE1 are associated with early-onset familial atrial fibrillation. *BMC Med Genet*. 2012;**13**:24.
29. Hofman-Bang J, Jespersen T, Grunnet M, Larsen LA, Andersen PS, Kanters JK*, et al.* Does KCNE5 play a role in long QT syndrome? *Clin Chim Acta*. 2004;**345**(1-2):49-53.
30. Deo M, Ruan Y, Pandit SV, Shah K, Berenfeld O, Blaufox A*, et al.* KCNJ2 mutation in short QT syndrome 3 results in atrial fibrillation and ventricular proarrhythmia. *Proc Natl Acad Sci U S A*. 2013;**110**(11):4291-6.
31. Olesen MS, Refsgaard L, Holst AG, Larsen AP, Grubb S, Haunso S*, et al.* A novel KCND3 gain-of-function mutation associated with early-onset of persistent lone atrial fibrillation. *Cardiovasc Res*. 2013;**98**(3):488-95.
32. Akai J, Makita N, Sakurada H, Shirai N, Ueda K, Kitabatake A*, et al.* A novel SCN5A mutation associated with idiopathic ventricular fibrillation without typical ECG findings of Brugada syndrome. *FEBS Lett*. 2000;**479**(1-2):29-34.
33. Olson TM, Michels VV, Ballew JD, Reyna SP, Karst ML, Herron KJ*, et al.* Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. *JAMA*. 2005;**293**(4):447-54.
34. Benson DW, Wang DW, Dyment M, Knilans TK, Fish FA, Strieper MJ*, et al.* Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). *J Clin Invest*. 2003;**112**(7):1019-28.
35. Darbar D, Kannankeril PJ, Donahue BS, Kucera G, Stubblefield T, Haines JL*, et al.* Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. *Circulation*. 2008;**117**(15):1927-35.
36. Makiyama T, Akao M, Shizuta S, Doi T, Nishiyama K, Oka Y*, et al.* A novel SCN5A gain-of-function mutation M1875T associated with familial atrial fibrillation. *J Am Coll Cardiol*. 2008;**52**(16):1326-34.
37. Ellinor PT, Nam EG, Shea MA, Milan DJ, Ruskin JN, MacRae CA. Cardiac sodium channel mutation in atrial fibrillation. *Heart Rhythm*. 2008;**5**(1):99-105.
38. Li Q, Huang H, Liu G, Lam K, Rutberg J, Green MS*, et al.* Gain-of-function mutation of Nav1.5 in atrial fibrillation enhances cellular excitability and lowers the threshold for action potential firing. *Biochem Biophys Res Commun*. 2009;**380**(1):132-7.
39. Olesen MS, Yuan L, Liang B, Holst AG, Nielsen N, Nielsen JB*, et al.* High prevalence of long QT syndrome-associated SCN5A variants in patients with early-onset lone atrial fibrillation. *Circ Cardiovasc Genet*. 2012;**5**(4):450-9.
40. Ziyadeh-Isleem A, Clatot J, Duchatelet S, Gandjbakhch E, Denjoy I, Hidden-Lucet F*, et al.* A truncating SCN5A mutation combined with genetic variability causes sick sinus syndrome and early atrial fibrillation. *Heart Rhythm*. 2014;**11**(6):1015-23.
41. Li RG, Wang Q, Xu YJ, Zhang M, Qu XK, Liu X*, et al.* Mutations of the SCN4B-encoded sodium channel beta4 subunit in familial atrial fibrillation. *Int J Mol Med*. 2013;**32**(1):144-50.
42. Nozdrachev AD. *Human and animal physiology. Book II: Physiology of visceral systems.* Moscow: High school; 1991.
43. Shimada T, Kawazato H, Yasuda A, Ono N, Sueda K. Cytoarchitecture and intercalated disks of the working myocardium and the conduction system in the mammalian heart. *Anat Rec A Discov Mol Cell Evol Biol*. 2004;**280**(2):940-51.
44. Laird DW. Life cycle of connexins in health and disease. *Biochem J*. 2006;**394**(Pt 3):527-43.
45. Teunissen BE, Bierhuizen MF. Transcriptional control of myocardial connexins. *Cardiovasc Res*. 2004;**62**(2):246-55.
46. Gemel J, Levy AE, Simon AR, Bennett KB, Ai X, Akhter S*, et al.* Connexin40 abnormalities and atrial fibrillation in the human heart. *J Mol Cell Cardiol*. 2014;**76**:159-68.
47. Gollob MH, Jones DL, Krahn AD, Danis L, Gong XQ, Shao Q*, et al.* Somatic mutations in the connexin 40 gene (GJA5) in atrial fibrillation. *N Engl J Med*. 2006;**354**(25):2677-88.
48. Christophersen IE, Holmegard HN, Jabbari J, Sajadieh A, Haunso S, Tveit A*, et al.* Rare variants in GJA5 are associated with early-onset lone atrial fibrillation. *Can J Cardiol*. 2013;**29**(1):111-6.
49. Yang YQ, Liu X, Zhang XL, Wang XH, Tan HW, Shi HF*, et al.* Novel connexin40 missense mutations in patients with familial atrial fibrillation. *Europace*. 2010;**12**(10):1421-7.
50. Juang JM, Chern YR, Tsai CT, Chiang FT, Lin JL, Hwang JJ*, et al.* The association of human connexin 40 genetic polymorphisms with atrial fibrillation. *Int J Cardiol*. 2007;**116**(1):107-12.
51. Peterkin T, Gibson A, Loose M, Patient R. The roles of GATA-4, -5 and -6 in vertebrate heart development. *Semin Cell Dev Biol*. 2005;**16**(1):83-94.
52. Nemer M. Genetic insights into normal and abnormal heart development. *Cardiovasc Pathol*. 2008;**17**(1):48-54.
53. Yang YQ, Wang MY, Zhang XL, Tan HW, Shi HF, Jiang WF*, et al.* GATA4 loss-of-function mutations in familial atrial fibrillation. *Clin Chim Acta*. 2011;**412**(19-20):1825-30.
54. Wang XH, Huang CX, Wang Q, Li RG, Xu YJ, Liu X*, et al.* A novel GATA5 loss-of-function mutation underlies lone atrial fibrillation. *Int J Mol Med*. 2013;**31**(1):43-50.
55. Li J, Liu WD, Yang ZL, Yang YQ. Novel GATA6 loss-of-function mutation responsible for familial atrial fibrillation. *Int J Mol Med*. 2012;**30**(4):783-90.
56. Perrin MJ, Gollob MH. The role of atrial natriuretic peptide in modulating cardiac electrophysiology. *Heart Rhythm*. 2012;**9**(4):610-5.
57. Hodgson-Zingman DM, Karst ML, Zingman LV, Heublein DM, Darbar D, Herron KJ*, et al.* Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation. *N Engl J Med*. 2008;**359**(2):158-65.
58. Abraham RL, Yang T, Blair M, Roden DM, Darbar D. Augmented potassium current is a shared phenotype for two genetic defects associated with familial atrial fibrillation. *J Mol Cell Cardiol*. 2010;**48**(1):181-90.
59. Ren X, Xu C, Zhan C, Yang Y, Shi L, Wang F*, et al.* Identification of NPPA variants associated with atrial fibrillation in a Chinese GeneID population. *Clin Chim Acta*. 2010;**411**(7-8):481-5.
60. Ozaki K, Ohnishi Y, Iida A, Sekine A, Yamada R, Tsunoda T*, et al.* Functional SNPs in the lymphotoxin-alpha gene that are associated with susceptibility to myocardial infarction. *Nat Genet*. 2002;**32**(4):650-4.
61. Pearson TA, Manolio TA. How to interpret a genome-wide association study. *JAMA*. 2008;**299**(11):1335-44.
62. Lin DY, Zeng D. Meta-analysis of genome-wide association studies: no efficiency gain in using individual participant data. *Genet*

Epidemiol. 2010;**34**(1):60-6.
63. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A*, et al.* Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature*. 2007;**448**(7151):353-7.
64. Olesen MS, Holst AG, Jabbari J, Nielsen JB, Christophersen IE, Sajadieh A*, et al.* Genetic loci on chromosomes 4q25, 7p31, and 12p12 are associated with onset of lone atrial fibrillation before the age of 40 years. *Can J Cardiol*. 2012;**28**(2):191-5.
65. Mommersteeg MT, Brown NA, Prall OW, de Gier-de Vries C, Harvey RP, Moorman AF*, et al.* Pitx2c and Nkx2-5 are required for the formation and identity of the pulmonary myocardium. *Circ Res*. 2007;**101**(9):902-9.
66. Syeda F, Kirchhof P, Fabritz L. PITX2-dependent gene regulation in atrial fibrillation and rhythm control. *J Physiol*. 2017;**595**(12):4019-26.
67. Low SK, Takahashi A, Ebana Y, Ozaki K, Christophersen IE, Ellinor PT*, et al.* Identification of six new genetic loci associated with atrial fibrillation in the Japanese population. *Nat Genet*. 2017;**49**(6):953-8.
68. Shoemaker MB, Bollmann A, Lubitz SA, Ueberham L, Saini H, Montgomery J*, et al.* Common genetic variants and response to atrial fibrillation ablation. *Circ Arrhythm Electrophysiol*. 2015;**8**(2):296-302.
69. Gudbjartsson DF, Holm H, Gretarsdottir S, Thorleifsson G, Walters GB, Thorgeirsson G*, et al.* A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. *Nat Genet*. 2009;**41**(8):876-8.
70. Berry FB, Miura Y, Mihara K, Kaspar P, Sakata N, Hashimoto-Tamaoki T*, et al.* Positive and negative regulation of myogenic differentiation of C2C12 cells by isoforms of the multiple homeodomain zinc finger transcription factor ATBF1. *J Biol Chem*. 2001;**276**(27):25057-65.
71. Mikhailov AT, Torrado M. Interplay between cardiac transcription factors and non-coding RNAs in predisposing to atrial fibrillation. *J Mol Med (Berl)*. 2018;**96**(7):601-10.
72. Ellinor PT, Lunetta KL, Glazer NL, Pfeufer A, Alonso A, Chung MK*, et al.* Common variants in KCNN3 are associated with lone atrial fibrillation. *Nat Genet*. 2010;**42**(3):240-4.
73. Fujii A, Ogimoto A, Nagai T, Kawakami H, Suzuki J, Inoue K*, et al.* CUMULATIVE AND INDIVIDUAL EFFECTS OF SINGLE NUCLEOTIDE POLYMORPHISMS FOR ATRIAL FIBRILLATION BY META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES IN PATIENTS WITH HEART FAILURE. *Journal of the American College of Cardiology*. 2015;**65**(10S):A473-A.
74. Nielsen JB, Thorolfsdottir RB, Fritsche LG, Zhou W, Skov MW, Graham SE*, et al.* Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nature genetics*. 2018;**50**(9):1234-9.
75. Brewer A, Pizzey J. GATA factors in vertebrate heart development and disease. *Expert reviews in molecular medicine*. 2006;**8**(22):1.
76. Olson TM, Alekseev AE, Liu XK, Park S, Zingman LV, Bienengraeber M*, et al.* Kv1. 5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation. *Human molecular genetics*. 2006;**15**(14):2185-91.
77. Roselli C, Chaffin MD, Weng L-C, Aeschbacher S, Ahlberg G, Albert CM*, et al.* Multi-ethnic genome-wide association study for atrial fibrillation. *Nature genetics*. 2018;**50**(9):1225-33.
78. 78. Ahlberg G, Refsgaard L, Lundegaard PR, Andreasen L, Ranthe MF, Linscheid N*, et al.* Rare truncating variants in the sarcomeric protein titin associate with familial and early-onset atrial fibrillation. *Nature communications*. 2018;**9**(1):1-11.