Cardiovascular Research (2011) **89**, 692–700
doi:10.1093/cvr/cvq381

SPOTLIGHT REVIEW

Monogenic atrial fibrillation as pathophysiological paradigms

Saagar Mahida[1], Steven A. Lubitz[1], Michiel Rienstra[1,2], David J. Milan[1,3], and Patrick T. Ellinor[1,3]*

[1]Cardiovascular Research Center, Massachusetts General Hospital, Charlestown, MA, USA; [2]University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; and [3]Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA 02114, USA

Received 3 August 2010; revised 10 November 2010; accepted 25 November 2010; online publish-ahead-of-print 30 November 2010

Abstract Atrial fibrillation (AF) is the most common cardiac rhythm abnormality and represents a major burden, both to patients and to health-care systems. In recent years, increasing evidence from population-based studies has demonstrated that AF is a heritable condition. Although familial forms of AF have been recognized for many years, they represent a rare subtype of the arrhythmia. However, despite their limited prevalence, the identification of mutations in monogenic AF kindreds has provided valuable insights into the molecular pathways underlying the arrhythmia and a framework for investigating AF encountered in the general population. In contrast to these rare families, the typical forms of AF occurring in the community are likely to be multigenic and have significant environmental influences. Recently, genome-wide association studies have uncovered common sequence variants that confer increased susceptibility to the arrhythmia. In the future, the elucidation of the genetic substrate underlying both familial and more typical forms of AF will hopefully lead to the development of novel diagnostic tools as well as more targeted rhythm control strategies. In this article, we will focus on monogenic forms of AF and also provide an overview of case–control association studies for AF.

Keywords Atrial fibrillation • Mutation • Family • Genetics

This article is part of the Review Focus on: New Insights into the Molecular Basis of Atrial Fibrillation

1. Introduction

Atrial fibrillation (AF) is the most prevalent cardiac rhythm abnormality and is a major cause of morbidity and mortality.[1] Previous studies have reported a significant increase in the risk of stroke, dementia, heart failure, and mortality associated with AF.[1–6] Established risk factors for AF include impaired left ventricular function, valvular heart disease, hypertension, and advancing age.[6–9] In a minority of cases, AF occurs in the absence of these risk factors, a disease subtype referred to as lone AF.

Monogenic AF families have been recognized for many years. In 1943, Wolff[10] described a case of three brothers with AF. In the ensuing years, larger kindreds with heritable AF have been identified and studied. Investigators have used linkage analysis to identify a number of loci for familial AF.[11,12] In addition, mutations in both ion channel coding genes[13–18] and non-ion channel coding genes[19–21] have been reported. AF has also been described as a concomitant disease in patients with inherited arrhythmia syndromes such as the Brugada syndrome[22] and long QT syndrome[23,24] (LQTS) and in patients with familial cardiomyopathies such as hypertrophic cardiomyopathy and dilated cardiomyopathy (DCM).[25,26]

AF has traditionally been perceived as a predominantly sporadic condition with rare familial subtypes. However, in recent years, increasing evidence from population-based studies has emerged to suggest that the commonly occurring AF phenotype has a significant genetic component. Investigators from the Framingham Heart Study (FHS) have reported that a parental history of AF almost doubles the risk of future disease in offspring.[27] Similar findings regarding the heritability of AF were observed among Icelanders.[28] Investigators at Mayo Clinic and Massachusetts General Hospital have also reported that for individuals in whom a first-degree relative is diagnosed with lone AF, the risk of developing AF is significantly higher than that of the general population.[29,30]

In contrast to monogenic forms of AF, in which rare genetic mutations with high penetrance are responsible for the condition, the more common AF phenotype is likely to be caused by common

* Corresponding author. Tel: +1 617 724 8729; fax: +1 617 726 3852, Email: pellinor@partners.org

genetic polymorphisms interacting with various environmental factors. In early case–control studies comparing cohorts of AF to controls, AF risk has been associated with polymorphisms in a variety of different genes.[31–40] However, in many such studies, the results have not been systematically replicated and sample sizes have been relatively small. More recently, genome-wide association studies (GWAS) have identified common genetic variants or single-nucleotide polymorphisms (SNPs) that confer increased susceptibility to AF and have led to significant advances in understanding the genetic basis of AF in the general population.

Despite the fact that monogenic forms of AF are relatively rare, studies in familial AF kindreds have provided valuable insights into the molecular pathways underlying the arrhythmia. The identification of single gene mutations has also provided a framework for interrogation of genetic polymorphisms that predispose to the commonly occurring AF phenotype. Eventually, the elucidation of the genetic substrate underlying the different forms of AF may lead to the development of novel approaches for diagnosis and treatment of the arrhythmia. In the following review, we will discuss monogenic forms of AF and also highlight results from case–control association studies in cohorts with non-familial AF. GWAS in AF will be discussed separately in this edition.

2. Susceptibility loci for AF

In 1997, Brugada *et al.*[11] described a susceptibility locus for AF in three families with autosomal dominant AF. Using linkage analysis, the locus for AF was mapped on chromosome 10q22–24; however, the causative mutation at this locus remains elusive. In 2003, a second susceptibility locus on chromosome 6q12–q16 was identified in a large family which also had autosomal dominantly inherited AF.[12] Of note, both susceptibility loci overlap with loci that have previously been reported for familial DCM.[41–43] It remains to be determined whether DCM and AF are linked in these families.

3. Monogenic mutations in AF

3.1 Ion channel mutations

The majority of mutations identified in monogenic AF families have been located in genes that encode ion channel subunits (summarized in *Table 1* and *Figure 1*). Functional analyses of these mutations have revealed either gain-of-function effects or loss-of-function effects. Interestingly, electrophysiological remodelling in patients with non-familial forms of chronic AF results in similar ion channel phenotypes.[44] These observations suggest that the different forms of AF share common underlying mechanisms. However, these mechanisms are presently not clearly understood.

There are currently two major hypotheses regarding the electrophysiological mechanisms underlying AF; the multiple wavelet hypothesis and 'mother rotor' hypothesis.[45] The mechanism of AF as proposed by the 'mother rotor' hypothesis involves stable, self-sustaining rotors that generate wavelets of activation which spread throughout the atrial myocardium.[46] Alternatively, the multiple wavelet hypothesis proposes that multiple random wavelets of activation with constantly changing re-entrant circuits underlie AF.[47] The likelihood is that different mechanisms predominate in different circumstances.[48] Alterations in ion channel function are predicted to influence one or both of the proposed mechanisms of AF.

3.1.1 Potassium channel mutations

3.1.1.1 I_{Ks} channel mutations

Chen *et al.*[13] provided the first link between ion channelopathies and AF. In a Chinese family with an autosomal dominant pattern of AF inheritance, they reported a missense mutation (S140G) located in the first transmembrane spanning domain of KCNQ1. The KCNQ1 gene encodes a pore-forming α-subunit which associates with ancillary β-subunits, to form a channel responsible for the I_{Ks} current. I_{Ks} is a delayed-rectifier potassium current which is prominent at higher heart rates and during adrenergic stimulation during the late phase of the action potential. Functionally, the S140G mutant channel was associated with a marked increase in current density suggesting a gain-of-function effect. In a subsequent study, the S140G mutation was demonstrated to cause marked slowing of I_{Ks} channel deactivation.[49]

Previous studies have also reported loss-of-function mutations in *KCNQ1* in patients with LQTS type 1.[50–54] The (S140G) *KCNQ1* gain-of-function mutation identified by Chen *et al.*[13] would therefore be expected to shorten the QT interval. Interestingly, however, in a proportion of the affected family members in the AF kindred, QT interval was prolonged rather than shortened. The molecular basis for this paradoxical observation remains unexplained. These observations highlight the fact that our understanding of cardiac repolarization in the atrium remains incomplete.

Since the original discovery by Chen *et al.*, two further mutations in the KCNQ1 gene have been described. In an unusual case of AF detected *in utero*, a valine-to-methionine mutation (V141M) adjacent to the aforementioned S140G mutation has been identified.[55] More recently, a serine-to-proline mutation (S209P) was reported in a family with an autosomal dominant pattern of inheritance of AF.[56] Both *KCNQ1* mutations displayed a gain-of-function effect with enhanced I_{Ks} current density and altered gating kinetics. The V141M mutation resulted in an expected shortening of the QT interval, whereas the S209P mutation did not alter QT interval.

Mutations in I_{Ks} channel β-subunit genes have been described in familial as well as isolated AF cases. As opposed to KCNQ1, which has six transmembrane domains, the KCNE β-subunits have only one transmembrane spanning domain. They are encoded by five genes, *KCNE1–KCNE5*.[57] In a study evaluating 28 unrelated Chinese families with lone AF, Yang *et al.*[14] identified a mutation in the KCNE2 gene which resulted in an arginine-to-cysteine substitution (R27C). More recently, an isolated non-familial case of AF with a missense (L65F) mutation has been identified after a cohort of 158 patients were screened for KCNE5 gene mutations.[58] Interaction of both mutant β-subunits (KCNE2 and KCNE5) with the KCNQ1 channel produced a gain-of-function effect with an increased I_{Ks} current.

The KCNQ1 α-subunit of the I_{Ks} channel can associate with any one of the five accessory β-subunits (KCNE1–5). Previous studies have demonstrated that each of the β-subunits causes a specific alteration in the KCNQ1 current.[59,60] On the basis of these observations, it has been proposed that alterations in the patterns of association between KCNQ1 and the β-subunits may allow modulation of the I_{Ks} current.[61] Interestingly, in normal human cardiac tissue, *KCNE4* expression is higher in the atrium as compared with the ventricle;[60] however, the precise constituents and regulation of the I_{Ks} current in the atrium vs. the ventricle remain unknown.

Table 1 Summary of monogenic mutations associated with AF

Gene	Gene product	Family/proband characteristics	Documented familial segregation, yes/no	Functional assay performed, yes/no	Functional effect of mutation	References
KCNQ1	α-subunit of I_{Ks} channel	Chinese family with autosomal dominant AF	Yes	Yes	Gain-of-function effect with increased I_{Ks}	13
KCNQ1	α-subunit of I_{Ks} channel	Isolated case of AF detected *in utero* (Caucasian)	No	Yes	Gain-of-function effect with increased I_{Ks}	55
KCNQ1	α-subunit of I_{Ks} channel	Caucasian family with autosomal dominant AF	Yes	Yes	Gain-of-function effect with increased I_{Ks}	56
KCNE2	β-subunit of I_{Ks} channel	Two Chinese AF kindreds	Yes	Yes	Gain-of-function effect with increased I_{Ks}	14
KCNE5	β-subunit of I_{Ks} channel	Isolated non-familial case of AF (Caucasian)	No	Yes	Gain-of-function effect with increased I_{Ks}	58
KCNJ2	Kir 2.1 channel	Chinese AF kindred	Yes	Yes	Gain-of-function effect with increased I_{K1}	16
KCNA5	K_v1.5 channel	Caucasian proband with refractory AF	Yes	Yes	Loss-of-function effect with reduced I_{Kur}	17
SCN5A	Sodium channel α-subunit	Caucasian family with variable expression of AF, DCM and impaired conduction	Yes	No	Predicted to have a loss-of-function effect with reduced sodium current density	87
SCN5A	Sodium channel α-subunit	Caucasian proband with familial AF	Yes	Yes	Loss-of-function effect with hyperpolarizing shift in channel steady state inactivation	88
SCN5A	Sodium channel α-subunit	Japanese family with autosomal dominant AF	Yes	Yes	Gain-of-function effect with depolarized shift of voltage dependence of steady-state inactivation	90
SCN1B	Sodium channel β-subunit	2 isolated non-familial cases of AF (1 Caucasian, 1 black)	No	Yes	Loss-of-function effect with reduced sodium current and altered channel gating	89
SCN2B	Sodium channel β-subunit	2 isolated non-familial cases of AF (Caucasian)	Yes (in 1 of the 2 patients)	Yes	Loss-of-function effect with reduced sodium current and altered channel gating	89
NUP155	Nucleoporin	Consanguineous family from Uruguay with early-onset AF	Yes	Yes	Reduction in nuclear membrane permeability	104
GJA5	Connexin-40	4 isolated non-familial cases (3 somatic mutations, 1 germline mutation)	No	Yes	Impaired intracellular transport and intercellular electrical coupling	19
NPPA	Mutant atrial natriuretic peptide (mANP)	Caucasian family with autosomal dominant AF	Yes	Yes	Elevated levels of mutant ANP	21

Presently, information regarding alterations in the I_{Ks} current in patients with chronic AF is limited. Transcription of I_{Ks} channel subunits has been reported to be altered in patients with AF and may cause significant alterations in atrial electrical activity. However, the results from these studies have been conflicting. Brundel *et al.*[62] reported that mRNA and protein expression of *KCNE1* is reduced in AF. In contrast, Lai *et al.* reported that mRNA expression of *KCNE1* is increased in AF. The latter study also reported down-regulation of *KCNQ1* transcription.[63]

From a mechanistic perspective, the gain-of-function mutations in α- and β-subunits of the I_{Ks} channel are associated with increased repolarizing potassium currents which in effect would abbreviate the action potential duration as well as the effective refractory period in cardiomyocytes.[64] These effects are likely to create a profibrillatory substrate within the atrium.[45]

In order to further characterize the effect of alterations of I_{Ks} on arrhythmia susceptibility, investigators have attempted to use a mouse model. However, due to the fact that I_{Ks} is expressed at very low levels in the adult murine heart, it has not been possible to reproduce the effects of I_{Ks} mutations in transgenic mouse models.[65] Despite these limitations, however, investigators have reported that transgenic mice with ablation of the KCNE1 gene have spontaneous episodes of AF.[66]

3.1.1.2 I_{K1} channel mutations

In 2005, Xia *et al.*[16] reported a novel missense mutation in the KCNJ2 gene in a Chinese AF kindred. *KCNJ2* encodes the Kir2.1 channel which underlies the inward-rectifier potassium current, I_{K1}.[67,68] A valine-to-isoleucine mutation (V93I) was identified which resulted in a gain-of-function effect with increased potassium current

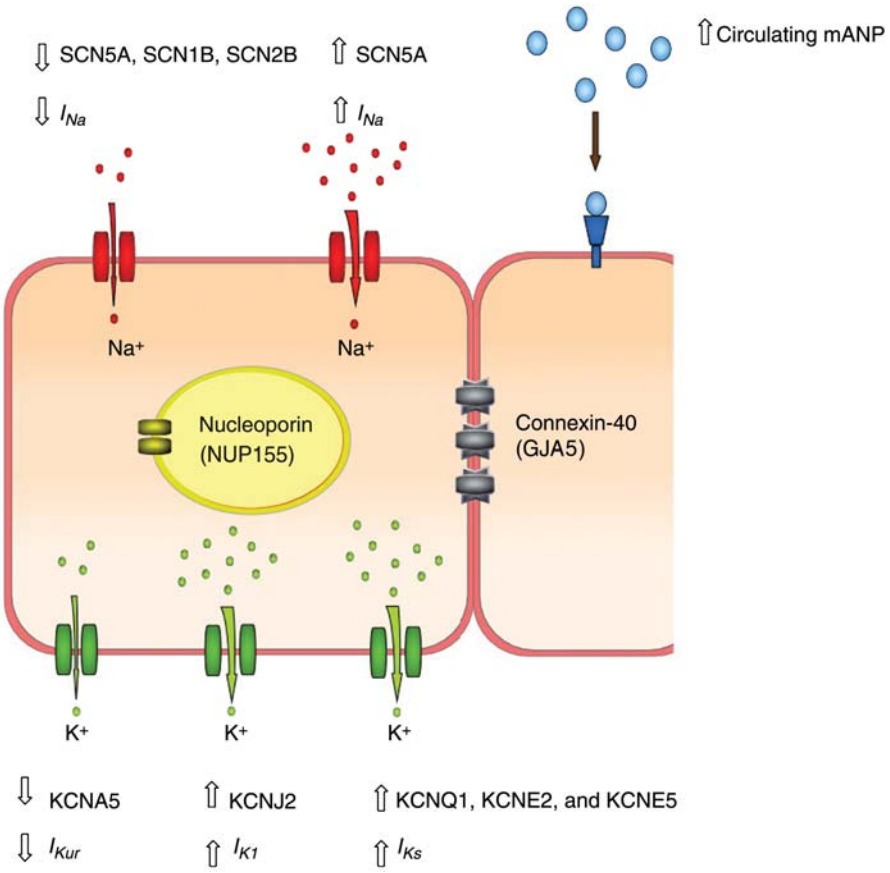

Figure 1 Pictorial image of adjacent cardiomyocytes illustrating the genes implicated in Mendelian forms of AF and the presumed mechanism of action of the mutation.

amplitudes, both in the inward and outward directions. Interestingly, loss-of-function mutations in Kir2.1 have been reported to cause the Anderson syndrome, a condition characterized by QT interval prolongation, ventricular arrhythmias, multiple bony abnormalities, and intermittent episodes of muscular weakness.[69] The gain-of-function mutation in *KCNJ2* in the AF kindred was not associated with an alteration in the QT interval. A possible explanation for the missing effect of the V93I mutation at the ventricular level is that the I_{K1} current is significantly smaller in the atrium as compared with the ventricle.[70,71]

A number of studies have reported an up-regulation of inward-rectifier current density in AF patients.[72–74] In turn, enhanced inward-rectifier currents have been demonstrated to promote AF by accelerating and stabilizing atrial rotors that maintain the arrhythmia.[75–77] Further evidence for the role of I_{K1} in the pathogenesis of AF has come from studies demonstrating chamber-specific differences in inward-rectifier current function (I_{K1} and I_{Kach}). Voigt *et al.* reported that in patients with paroxysmal AF, inward-rectifier current densities were two-fold larger in left atrial cardiomyocytes when compared with right atrial cardiomyocytes. In contrast, in patients with chronic AF, there were no differences in I_{K1} between the atria, although they did report elevated basal currents. These observations may suggest that an unequal distribution of inward-rectifier potassium currents in atria supports the transition from paroxysmal to persistent AF.[78]

3.1.1.3 I_{Kur} channel mutations

Olson *et al.*[17] identified a loss-of-function potassium channel gene mutation associated with AF. In a proband with lone AF which was refractory to conventional therapy, they reported a heterozygous nonsense mutation (E375X) in the KCNA5 gene. *KCNA5* encodes the Kv1.5 channel which underlies the ultrarapid delayed-rectifier (I_{Kur}) current. I_{Kur} is an important repolarizing current specific to the atrium.[79–81] Functional analysis of the mutant Kv1.5 channel revealed prolongation of the atrial action potential and triggered activity with stress, which would be predicted to promote initiation of AF. More recently, three further loss-of-function KCNA5 gene mutations (T527M A576V and E610K) have been reported in four families after screening a total of 120 families.[82]

In patients with chronic AF, some studies have reported reduced expression of Kv1.5 in parallel with an attenuation of the ultrarapid delayed-rectifier (I_{Kur}) current.[83,84] These observations lend further support to the hypothesis that suppression of the I_{Kur} current increases susceptibility to AF.

3.1.1.4 Candidate gene screening for potassium channel mutations in AF cohorts

Following the reports of potassium channel gene mutations in rare monogenic kindreds, a number of investigators have performed candidate gene screening to determine the prevalence of such mutations. In 2004, Ellinor *et al.*[85] screened a cohort of 141 unrelated patients with

lone AF for *KCNQ1* mutations and failed to identify any mutations. In a subsequent study, the same group screened 96 unrelated probands with familial AF for mutations in the KCNJ2 and KCNE1–5 genes and once again found no evidence of causal mutations.[86] In a study by Otway *et al.*,[18] four potassium channel genes (KCNQ1, KCNE1, KCNE2, and KCNE3) were screened for mutations in 50 AF families. Only one missense mutation in the KCNQ1 gene was identified. Functional analysis of the mutant gene product did not demonstrate altered channel kinetics, suggesting that the *KCNQ1* mutation might not be causative. Taken together, these data suggest that potassium channel mutations are not a major cause of AF in the general population.

3.1.2 Sodium channel mutations

Mutations in the genes encoding both the α- and β-subunits of the voltage-gated sodium channel have been reported in patients with AF.[87–91] The pore-forming α-subunit is encoded by the SCN5A gene, whereas four genes designated *SCN1B* through *SCN4B* encode the function-modifying β-subunits. In addition to AF, mutations in sodium channel genes are associated with a range of arrhythmias. *SCN5A* mutations have been reported to cause the Brugada syndrome,[92] congenital sick sinus syndrome,[93] cardiac conduction disease,[94] idiopathic ventricular fibrillation,[95] and LQTS type 3 (LQTS3).[96] *SCN1B* and *SCN3B* mutations are also associated with cardiac conduction system disease and Brugada syndrome.[97,98] As a result, patients with AF associated with sodium channel mutations often have complex, overlapping phenotypes.

In 2005, Olson *et al.*[87] reported an *SCN5A* mutation (D1275N) in a large multigenerational family. The mutation was associated with variable clinical manifestations which included AF, DCM, and abnormal cardiac conduction. On the basis of reports from other studies, the D1275N mutation is expected to cause a loss of cardiac sodium channel function.[99] In a more recent study, a cohort of 189 AF patients were screened for *SCN5A* mutations and a single missense mutation (N1986K) was identified in one AF kindred. Functional analysis of the mutation revealed a loss-of-function effect with a hyperpolarized shift of steady-state inactivation. One family member with the N1986K mutation had associated conduction system disease.[88]

Loss-of-function mutations in the SCN5A gene are also associated with Brugada syndrome.[92] The occurrence of AF in patients with Brugada syndrome appears to be relatively common. However, reports of AF and Brugada syndrome in patients with *SCN5A* mutations are rare. In a cohort of 38 patients with Brugada syndrome, Makiyama *et al.*[100] reported the occurrence of AF in 10 cases (26.3%). However, they did not identify *SCN5A* mutations in any of the patients with co-existing AF and Brugada syndrome. Similarly, in 59 Brugada syndrome patients, Bordachar *et al.*[101] reported an incidence of AF in 20%. However, only two of the Brugada syndrome patients with an *SCN5A* mutation had documented AF. The reasons why loss-of-function mutations in *SCN5A* cause AF in some cases and ventricular arrhythmic conditions in others are presently unclear.

The role of the function-modifying sodium channel β-subunits in arrhythmic cardiac diseases is less clearly defined. In a recent study of 480 AF patients, Watanabe *et al.*[89] screened the four β-subunit genes (SCN1B–SCN4B) for mutations and reported two mutations in *SCN1B* (R85H, D153N) and two mutations in *SCN2B* (R28Q, R28W). Functional analysis of the mutant β1- and β2-subunits demonstrated altered channel gating and a reduction in sodium current indicating a loss-of-function effect. Interestingly, in three of the four mutation carriers, the electrocardiogram demonstrated ST-segment elevation in the right-sided leads. The findings from this study are consistent with previous reports linking decreased sodium current with enhanced AF susceptibility.[87,88]

Makiyama *et al.*[90] recently reported a gain-of-function *SCN5A* mutation associated with AF. They identified a novel missense mutation (M1875T) in a Japanese family with autosomal dominant hereditary AF. Analysis of the mutant channel function demonstrated that the voltage dependence of steady-state inactivation was shifted in the depolarizing direction, suggesting a gain-of-function. Gain-of-function *SCN5A* mutations are also associated with LQTS3.[96] However, in contrast to LQTS3 mutations, the M1875T mutation in the AF kindred did not display persistent inward sodium currents. As a result, normal QT interval was observed in the majority of affected individuals.

AF has previously also been described as a concomitant disease in familial LQTS3. Benito *et al.*[24] described a three-generation family with LQTS3 and AF due to a gain-of-function mutation (Y1795C) in *SCN5A*. Three out of eight family members displayed early-onset paroxysmal AF. Johnson *et al.*[23] reported a mixed phenotype of LQTS and AF in one of 59 patients with genetically proven LQTS3. These findings provide further evidence of the role of gain-of-function *SCN5A* mutations in AF.

The electrophysiological mechanisms by which sodium channel mutations cause AF are not clearly understood. Increased inward sodium currents induce triggered activity and stabilize high-frequency rotors.[102,103] Yet, they also make re-entry less likely. Conversely, reduced sodium current density promotes re-entry by shortening action potential duration and shortening the atrial re-entry wavelength.[102] However, the attenuation of sodium current also destabilizes high-frequency rotors.[102] Overall, multiple effects in various experimental models make it difficult to predict a priori what the effects of alterations in sodium channel function will be.

Consistent with the data reported for potassium channel gene mutations, mutations in genes coding sodium channel subunits do not appear to be a common cause of AF. Chen *et al.*[31] screened a cohort of 157 lone AF patients and did not identify any *SCN5A* mutations. Similarly, we identified *SCN5A* mutations in only one kindred out of a cohort of 189 AF patients and Watanabe *et al.*[89] identified only four patients with *SCNB* mutations in a cohort of 480 patients.[88] Darbar *et al.*[91] sequenced the SCN5A gene in a cohort of 375 AF patients and discovered eight novel variants. However, segregation analysis suggested that only six of the novel *SCN5A* variants are associated with AF.

3.2 Non-ion channel mutations

3.2.1 Nucleoporin gene (NUP155) mutation

In 2004, Oberti *et al.*[104] identified a large consanguineous family from Uruguay with autosomal recessive inheritance of AF. The pattern of disease was characterized by an early onset of AF at the foetal or infantile stage with severe associated complications including cardiomyopathy, ventricular arrhythmias, and sudden death. The locus was mapped on chromosome 5p13 (arAF1).

In a subsequent study, a homozygous mutation (R391H) in a nucleoporin gene (*NUP155*) was identified.[20] *NUP155* encodes a nucleoporin which is an essential molecular component of the nuclear pore complexes (NPCs).[105] NPCs mediate exchange of macromolecules between the nucleus and the cytoplasm.[106] The mechanistic link between *NUP155* mutation and AF remains unclear. It has been proposed that a reduction in nucleocytoplasmic

transport due to NUP155 deficiency may alter expression of atrial genes which in turn may influence cellular processes such as maturation of calcium handling proteins and ion channels. These effects may ultimately alter the action potential duration and promote AF. An alternative hypothesis is that altered function of the nuclear envelope due to *NUP155* deficiency may reduce myocyte survival by blocking mitosis. Myocyte apoptosis may promote cardiac fibrosis and conduction heterogeneity which may in turn create a substrate for arrhythmia.[107] Future studies are required to further define the role of the nucleoporin in AF.

3.2.2 Connexin-40 gene (GJA5) mutations

In a study by Gollob *et al.*[19] involving a small cohort of unrelated patients with lone AF, four novel mutations were identified in the GJA5 gene. *GJA5* encodes connexin-40, a gap junction protein in the atrium which plays a critical role in mediating coordinated conduction of the action potential through cell-to-cell electrical coupling.[108] Out of 15 AF patients in the study, four patients carried missense *GJA5* mutations. Interestingly, only one of the patients had a germ-line sequence variant. The three remaining patients had tissue-specific mutations, suggesting that somatic mutations could also be involved in AF predisposition. Functional analysis of the mutant gene product revealed abnormal intracellular transport in addition to a reduction in electrical coupling between cells. It has been proposed that impaired cell–cell electrical coupling results in conduction heterogeneity, micro-re-entrant circuits, and hence AF.[19]

A number of studies have investigated connexin-40 expression in patients with chronic AF. The results from such studies have not been consistent. Some investigators have reported increased connexin-40,[109,110] others have reported decreased connexin-40,[111–114] and yet others have reported no change in the level of connexin.[115] Similarly, reports of changes in distribution of connexins in AF have been inconsistent. Some investigators have reported increased lateralization of gap junction distribution,[109,112,116] whereas others have reported increased heterogeneity.[117]

3.2.3 Atrial natriuretic peptide gene (NPPA) mutation

Hodgson-Zingman *et al.*[21] reported on a family with an autosomal dominant pattern of AF which co-segregated with a frameshift mutation in the gene encoding atrial natriuretic peptide (*NPPA*). The mutation was associated with markedly elevated levels of mutant atrial natriuretic peptide (ANP). ANP is involved in the regulation of sodium and water homeostasis and arterial blood pressure. In response to volume expansion and atrial stretch, ANP release causes natriuresis, diuresis, and vasodilator effects.[118] Previous studies have reported that when exposed to pathophysiological levels of ANP, atrial myocytes display altered electrophysiological properties.[119–122] The mutant peptide in the AF kindred was demonstrated to shorten atrial action potential duration in an animal model.[21] An alternative plausible hypothesis is that excessive ANP may cause structural atrial remodelling due to its pro-apoptotic effect.[123] Thus, at this stage, the role of ANP in the pathogenesis of AF remains speculative.

4. Polymorphisms associated with non-familial AF

Case–control association studies have been widely used for genetic analysis of a variety of complex traits including AF in the general population. Association studies involve the comparison of genotype

Table 2 Summary of results from association studies in AF cohorts

Gene	Polymorphism	Cases	Controls	Ethnicity	Comment	*P*-value	Odds ratio	References
KCNE1 minK	38G	331	441	Caucasian		0.004	1.73	32
KCNE1 minK	38G	108	108	Asian		0.024	1.80	34
KCNE5	97T	158	96	Caucasian		0.007	0.52	35
KCNH2	K897T	1207	2475	Caucasian		0.00033	1.25	33
GNB3	C825T	291	292	Caucasian		0.02	0.46	36
eNOS	2786C	331	441	Caucasian		0.01	1.50	32
eNOS	G894T	51	289	Caucasian	HF patients	0.001	3.2	127
SCN5A	H558R	157	314	Caucasian		0.002	1.6	31
GJA5	−44AA/+71GG	173	232	Asian		<0.006	1.514	37
AGT	M235T	250	250	Asian		<0.001	2.5	39
AGT	G-6A	250	250	Asian		0.005	3.3	39
AGT	G-217A	250	250	Asian		0.002	2.0	39
AGT	T174M	968	8267	Caucasian		0.05	1.2	126
AGT	20C/C	968	8267	Caucasian		0.01	1.5	126
ACE	D/D	51	289	Caucasian	HF patients	0.016	1.5	127
ACE	D/D	404	520	Caucasian		<0.001	1.89	128
MMP2	C1306T	196	873	Asian		1.26×10^{-2}	8.1	129
IL10	A-592C	196	873	Asian		3.7×10^{-3}	0.32	129
IL6	G-174C	26	84	Caucasian	Post-operative AF (after CABG)	<0.001	3.25	130
SLN	C-65G	147	92	Caucasian		0.011	1.98	124

ACE, angiotensin-converting enzyme; AGT, angiotensinogen; CABG, coronary artery bypass graft surgery; eNOS, endothelial nitric oxide synthase 3; GNB3, guanine nucleotide-binding protein; GJA5, connexin 40; HF, heart failure; IL6, interleukin 6; IL10, interleukin 10; MMP, matrix metalloproteinase; SLN, sarcolipin gene.

frequencies for candidate genes between a diseased population and a population of healthy controls. In recent years, association studies in AF cohorts have identified a variety of polymorphisms that may influence susceptibility to the arrhythmia. Examples include polymorphisms in the cardiac potassium channel subunit genes,[32–35] sodium channel genes,[31] genes that regulate ion channel function,[36,124] gap junction protein genes,[37] genes encoding circulating hormones,[125–128] and genes encoding inflammatory mediators.[129,130]

Interestingly, some of the association studies have identified genetic polymorphisms that are predicted to cause functional alterations in the same ion channels as those implicated in monogenic forms of AF. Examples include polymorphisms in *KCNE1* and *KCNE5*, which encode α- and β-subunits of the I_{Ks} channel respectively, and *SCN5A*, which encodes the α-subunit of the I_{Na} channel.[31,32,35,131] In addition, one of the reported polymorphisms encodes the β_3-subunit of a heterotrimeric G protein (*GNB3*) which has been linked with an increased inward-rectifier current (I_{K1}).[36,132] These results suggest that the same molecular mechanisms may underlie familial and sporadic forms of AF. It should be noted however that the majority of the association studies in AF cohorts have been limited by relatively small sample sizes, inconsistent replication, and a low pre-test probability of the polymorphism actually causing AF. The results from the studies are summarized in *Table 2*.

5. Summary

In summary, studies involving familial AF kindred have reported several monogenic mutations. The majority of the mutations have been identified in genes encoding ion channels, although some studies have also uncovered mutations in non-ion channel coding genes. Based on available evidence, these rare mutations appear to provide little explanation for the heritability of AF in the general population. However, the identification of these mutations has provided valuable insights into the molecular pathways underlying AF and has also provided a framework for investigating the genetic basis of common forms of the arrhythmia.

The genetic basis of non-familial AF is presently largely unknown. In recent years, GWAS have led to significant advances in our understanding of the genetic basis of complex traits. A recent GWAS for AF has led to the identification of novel variants that appear to confer increased susceptibility to the arrhythmia.[40] However, most of the SNPs are located outside the commonly known genes; therefore, the molecular mechanisms underlying their association with AF remains unclear.[40]

Current attempts to interpret GWAS signals are based on the assumption that common sequence variants are responsible for common traits. However, an interesting alternative hypothesis is that the genetic control of complex traits is due to rare mutations that are either not represented in current GWAS or that cause the observed associations through 'synthetic' associations.[133,134] This possibility challenges the currently held belief that monogenic mutations are restricted to AF families and rare isolated AF cases. In the future, the use of next-generation sequencing technology to sequence the entire exome or genome may uncover numerous private monogenic mutations that might account for some of the unexplained GWAS signals. In this context, studies in AF families will be of increasing relevance because demonstrating transmission of these private mutations will be essential for proving causality.

Ultimately, the identification of the genes and pathways underlying the familial and more common forms of AF should give us new insights into the development of novel diagnostic tests and targeted therapies for the arrhythmia.

Conflict of interest: none declared.

Funding

This work was supported by a grant from the Netherlands Organization of Scientific Research to M.R. (Rubicon Grant 825.09.020), grants from the National Institutes of Health to S.A.L. (T32 HL007575), D.J.M. (R21HL096009 and R21DA026982), and P.T.E. (R01HL104156, R21DA027021, R01HL092577, and K24HL105780).

References

1. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin North Am* 2008;**92**:17–40, ix.
2. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke* 1997;**28**:316–321.
3. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;**113**:359–364.
4. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA *et al*. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**:2920–2925.
5. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med* 1995;**98**:476–484.
6. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;**271**:840–844.
7. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med* 1982;**306**:1018–1022.
8. Kannel WB, Abbott RD, Savage DD, McNamara PM. Coronary heart disease and atrial fibrillation: the Framingham Study. *Am Heart J* 1983;**106**:389–396.
9. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP *et al*. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;**96**:2455–2461.
10. Wolff L. Familial auricular fibrillation. *N Engl J Med* 1943;**299**:396–397.
11. Brugada R, Tapscott T, Czernuszewicz GZ, Marian AJ, Iglesias A, Mont L *et al*. Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med* 1997;**336**:905–911.
12. Ellinor PT, Shin JT, Moore RK, Yoerger DM, MacRae CA. Locus for atrial fibrillation maps to chromosome 6q14–16. *Circulation* 2003;**107**:2880–2883.
13. 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**:251–254.
14. 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**:899–905.
15. Hong K, Bjerregaard P, Gussak I, Brugada R. Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. *J Cardiovasc Electrophysiol* 2005;**16**:394–396.
16. Xia M, Jin Q, Bendahhou S, He Y, Larroque MM, Chen Y *et al*. A Kir2.1 gain-of-function mutation underlies familial atrial fibrillation. *Biochem Biophys Res Commun* 2005;**332**:1012–1019.
17. 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. *Hum Mol Genet* 2006;**15**:2185–2191.
18. Otway R, Vandenberg JI, Guo G, Varghese A, Castro ML, Liu J *et al*. Stretch-sensitive KCNQ1 mutation A link between genetic and environmental factors in the pathogenesis of atrial fibrillation?. *J Am Coll Cardiol* 2007;**49**:578–586.
19. 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**:2677–2688.
20. Zhang X, Chen S, Yoo S, Chakrabarti S, Zhang T, Ke T *et al*. Mutation in nuclear pore component NUP155 leads to atrial fibrillation and early sudden cardiac death. *Cell* 2008;**135**:1017–1027.
21. 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**:158–165.
22. Morita H, Kusano-Fukushima K, Nagase S, Fujimoto Y, Hisamatsu K, Fujio H *et al*. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol* 2002;**40**:1437–1444.

23. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm* 2008;**5**: 704–709.
24. Benito B, Brugada R, Perich RM, Lizotte E, Cinca J, Mont L *et al*. A mutation in the sodium channel is responsible for the association of long QT syndrome and familial atrial fibrillation. *Heart Rhythm* 2008;**5**:1434–1440.
25. Sebillon P, Bouchier C, Bidot LD, Bonne G, Ahamed K, Charron P *et al*. Expanding the phenotype of LMNA mutations in dilated cardiomyopathy and functional consequences of these mutations. *J Med Genet* 2003;**40**:560–567.
26. Gruver EJ, Fatkin D, Dodds GA, Kisslo J, Maron BJ, Seidman JG *et al*. Familial hypertrophic cardiomyopathy and atrial fibrillation caused by Arg663His beta-cardiac myosin heavy chain mutation. *Am J Cardiol* 1999;**83**:13H–18H.
27. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ *et al*. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA* 2004; **291**:2851–2855.
28. Arnar DO, Thorvaldsson S, Manolio TA, Thorgeirsson G, Kristjansson K, Hakonarson H *et al*. Familial aggregation of atrial fibrillation in Iceland. *Eur Heart J* 2006;**27**:708–712.
29. Darbar D, Herron KJ, Ballew JD, Jahangir A, Gersh BJ, Shen WK *et al*. Familial atrial fibrillation is a genetically heterogeneous disorder. *J Am Coll Cardiol* 2003;**41**: 2185–2192.
30. Ellinor PT, Yoerger DM, Ruskin JN, MacRae CA. Familial aggregation in lone atrial fibrillation. *Hum Genet* 2005;**118**:179–184.
31. Chen LY, Ballew JD, Herron KJ, Rodeheffer RJ, Olson TM. A common polymorphism in SCN5A is associated with lone atrial fibrillation. *Clin Pharmacol Ther* 2007;**81**: 35–41.
32. Fatini C, Sticchi E, Genuardi M, Sofi F, Gensini F, Gori AM *et al*. Analysis of minK and eNOS genes as candidate loci for predisposition to non-valvular atrial fibrillation. *Eur Heart J* 2006;**27**:1712–1718.
33. Sinner MF, Pfeufer A, Akyol M, Beckmann BM, Hinterseer M, Wacker A *et al*. The non-synonymous coding IKr-channel variant KCNH2-K897T is associated with atrial fibrillation: results from a systematic candidate gene-based analysis of KCNH2 (HERG). *Eur Heart J* 2008;**29**:907–914.
34. Lai LP, Su MJ, Yeh HM, Lin JL, Chiang FT, Hwang JJ *et al*. Association of the human minK gene 38G allele with atrial fibrillation: evidence of possible genetic control on the pathogenesis of atrial fibrillation. *Am Heart J* 2002;**144**:485–490.
35. Ravn LS, Hofman-Bang J, Dixen U, Larsen SO, Jensen G, Haunso S *et al*. Relation of 97T polymorphism in KCNE5 to risk of atrial fibrillation. *Am J Cardiol* 2005;**96**:405–407.
36. Schreieck J, Dostal S, von Beckerath N, Wacker A, Flory M, Weyerbrock S *et al*. C825T polymorphism of the G-protein beta3 subunit gene and atrial fibrillation: association of the TT genotype with a reduced risk for atrial fibrillation. *Am Heart J* 2004;**148**:545–550.
37. 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**:107–112.
38. Firouzi M, Ramanna H, Kok B, Jongsma HJ, Koeleman BP, Doevendans PA *et al*. Association of human connexin40 gene polymorphisms with atrial vulnerability as a risk factor for idiopathic atrial fibrillation. *Circ Res* 2004;**95**:e29–e33.
39. Tsai CT, Lai LP, Lin JL, Chiang FT, Hwang JJ, Ritchie MD *et al*. Renin–angiotensin system gene polymorphisms and atrial fibrillation. *Circulation* 2004;**109**:1640–1646.
40. 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**:353–357.
41. Bowles KR, Gajarski R, Porter P, Goytia V, Bachinski L, Roberts R *et al*. Gene mapping of familial autosomal dominant dilated cardiomyopathy to chromosome 10q21–23. *J Clin Invest* 1996;**98**:1355–1360.
42. Bowles NE, Bowles KR, Towbin JA. The final common pathway hypothesis and inherited cardiovascular disease. The role of cytoskeletal proteins in dilated cardiomyopathy. *Herz* 2000;**25**:168–175.
43. Sylvius N, Tesson F, Gayet C, Charron P, Benaiche A, Peuchmaurd M *et al*. A new locus for autosomal dominant dilated cardiomyopathy identified on chromosome 6q12–q16. *Am J Hum Genet* 2001;**68**:241–246.
44. Bosch RF, Nattel S. Cellular electrophysiology of atrial fibrillation. *Cardiovasc Res* 2002;**54**:259–269.
45. Nattel S. New ideas about atrial fibrillation 50 years on. *Nature* 2002;**415**:219–226.
46. Jalife J, Berenfeld O, Skanes A, Mandapati R. Mechanisms of atrial fibrillation: mother rotors or multiple daughter wavelets, or both? *J Cardiovasc Electrophysiol* 1998;**9**: S2–S12.
47. Moe GK. On the multiple wavelet hypothesis of AF. *Arch Int Pharmacodyn Ther* 1962; **140**:183–188.
48. Nattel S. Atrial electrophysiology and mechanisms of atrial fibrillation. *J Cardiovasc Pharmacol Ther* 2003;**8**(Suppl. 1):S5–S11.
49. Restier L, Cheng L, Sanguinetti MC. Mechanisms by which atrial fibrillation-associated mutations in the S1 domain of KCNQ1 slow deactivation of IKs channels. *J Physiol* 2008;**586**:4179–4191.
50. Wang DW, Yazawa K, George AL Jr, Bennett PB. Characterization of human cardiac Na^+ channel mutations in the congenital long QT syndrome. *Proc Natl Acad Sci USA* 1996;**93**:13200–13205.
51. Sesti F, Goldstein SA. Single-channel characteristics of wild-type IKs channels and channels formed with two minK mutants that cause long QT syndrome. *J Gen Physiol* 1998;**112**:651–663.
52. Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL *et al*. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation* 2000;**102**:1178–1185.
53. Isbrandt D, Leicher T, Waldschutz R, Zhu X, Luhmann U, Michel U *et al*. Gene structures and expression profiles of three human KCND (Kv4) potassium channels mediating A-type currents I(TO) and I(SA). *Genomics* 2000;**64**:144–154.
54. Tinel N, Diochot S, Lauritzen I, Barhanin J, Lazdunski M, Borsotto M. M-type KCNQ2–KCNQ3 potassium channels are modulated by the KCNE2 subunit. *FEBS Lett* 2000;**480**:137–141.
55. 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**:433–440.
56. 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**:1146–1153.
57. Abbott GW, Goldstein SA. Potassium channel subunits encoded by the KCNE gene family: physiology and pathophysiology of the MinK-related peptides (MiRPs). *Mol Interv* 2001;**1**:95–107.
58. Ravn LS, Aizawa Y, Pollevick GD, Hofman-Bang J, Cordeiro JM, Dixen U *et al*. Gain of function in IKs secondary to a mutation in KCNE5 associated with atrial fibrillation. *Heart Rhythm* 2008;**5**:427–435.
59. Lundquist AL, Manderfield LJ, Vanoye CG, Rogers CS, Donahue BS, Chang PA *et al*. Expression of multiple KCNE genes in human heart may enable variable modulation of I(Ks). *J Mol Cell Cardiol* 2005;**38**:277–287.
60. Bendahhou S, Marionneau C, Haurogne K, Larroque MM, Derand R, Szuts V *et al*. In vitro molecular interactions and distribution of KCNE family with KCNQ1 in the human heart. *Cardiovasc Res* 2005;**67**:529–538.
61. Lundquist AL, Turner CL, Ballester LY, George AL Jr. Expression and transcriptional control of human KCNE genes. *Genomics* 2006;**87**:119–128.
62. Brundel BJ, Van Gelder IC, Henning RH, Tieleman RG, Tuinenburg AE, Wietses M *et al*. Ion channel remodeling is related to intraoperative atrial effective refractory periods in patients with paroxysmal and persistent atrial fibrillation. *Circulation* 2001;**103**:684–690.
63. Lai LP, Su MJ, Lin JL, Lin FY, Tsai CH, Chen YS *et al*. Changes in the mRNA levels of delayed rectifier potassium channels in human atrial fibrillation. *Cardiology* 1999;**92**: 248–255.
64. Moe G. Evidence for reentry as a mechanism of cardiac arrhythmias. *Rev Physiol Biochem Pharmacol* 1975;**72**:55–81.
65. Nerbonne JM. Molecular basis of functional voltage-gated K^+ channel diversity in the mammalian myocardium. *J Physiol* 2000;**525**(Pt 2):285–298.
66. Temple J, Frias P, Rottman J, Yang T, Wu Y, Verheijck EE *et al*. Atrial fibrillation in KCNE1-null mice. *Circ Res* 2005;**97**:62–69.
67. Zobel C, Cho HC, Nguyen TT, Pekhletski R, Diaz RJ, Wilson GJ *et al*. Molecular dissection of the inward rectifier potassium current (IK1) in rabbit cardiomyocytes: evidence for heteromeric co-assembly of Kir2.1 and Kir2.2. *J Physiol* 2003;**550**:365–372.
68. Lopatin AN, Nichols CG. Inward rectifiers in the heart: an update on I(K1). *J Mol Cell Cardiol* 2001;**33**:625–638.
69. Andersen ED, Krasilnikoff PA, Overvad H. Intermittent muscular weakness, extrasystoles and multiple developmental abnormalities: a new syndrome? *Acta peditr Scand* 1971;**60**:559–564.
70. Wang Z, Yue L, White M, Pelletier G, Nattel S. Differential distribution of inward rectifier potassium channel transcripts in human atrium vs. ventricle. *Circulation* 1998;**98**:2422–2428.
71. Giles WR, Imaizumi Y. Comparison of potassium currents in rabbit atrial and ventricular cells. *J Physiol* 1988;**405**:123–145.
72. Zhang H, Garratt CJ, Zhu J, Holden AV. Role of up-regulation of IK1 in action potential shortening associated with atrial fibrillation in humans. *Cardiovasc Res* 2005;**66**: 493–502.
73. Bosch RF, Zeng X, Grammer JB, Popovic K, Mewis C, Kuhlkamp V. Ionic mechanisms of electrical remodeling in human atrial fibrillation. *Cardiovasc Res* 1999;**44**:121–131.
74. Workman AJ, Kane KA, Rankin AC. The contribution of ionic currents to changes in refractoriness of human atrial myocytes associated with chronic atrial fibrillation. *Cardiovasc Res* 2001;**52**:226–235.
75. Pandit SV, Berenfeld O, Anumonwo JM, Zaritski RM, Kneller J, Nattel S *et al*. Ionic determinants of functional reentry in a 2-D model of human atrial cells during simulated chronic atrial fibrillation. *Biophys J* 2005;**88**:3806–3821.
76. Samie FH, Berenfeld O, Anumonwo J, Mironov SF, Udassi S, Beaumont J *et al*. Rectification of the background potassium current: a determinant of rotor dynamics in ventricular fibrillation. *Circ Res* 2001;**89**:1216–1223.
77. Sekar RB, Kizana E, Cho HC, Molitoris JM, Hesketh GG, Eaton BP *et al*. IK1 heterogeneity affects genesis and stability of spiral waves in cardiac myocyte monolayers. *Circ Res* 2009;**104**:355–364.
78. Voigt N, Trausch A, Knaut M, Matschke K, Varro A, Van Wagoner DR *et al*. Left-to-right atrial inward-rectifier potassium current gradients in patients with paroxysmal versus chronic atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:472–480.

79. Tamkun MM, Knoth KM, Walbridge JA, Kroemer H, Roden DM, Glover DM. Molecular cloning and characterization of two voltage-gated K^+ channel cDNAs from human ventricle. *FASEB J* 1991;**5**:331–337.
80. Wang Z, Fermini B, Nattel S. Delayed rectifier outward current and repolarization in human atrial myocytes. *Circ Res* 1993;**73**:276–285.
81. Simard C, Drolet B, Yang P, Kim RB, Roden DM. Polymorphism screening in the cardiac K^+ channel gene KCNA5. *Clin Pharmacol Ther* 2005;**77**:138–144.
82. Yang Y, Li J, Lin X, Yang Y, Hong K, Wang L *et al*. Novel KCNA5 loss-of-function mutations responsible for atrial fibrillation. *J Hum Genet* 2009;**54**:277–283.
83. Van Wagoner DR, Pond AL, McCarthy PM, Trimmer JS, Nerbonne JM. Outward K^+ current densities and Kv1.5 expression are reduced in chronic human atrial fibrillation. *Circ Res* 1997;**80**:772–781.
84. Dobrev D, Ravens U. Remodeling of cardiomyocyte ion channels in human atrial fibrillation. *Basic Res Cardiol* 2003;**98**:137–148.
85. Ellinor PT, Moore RK, Patton KK, Ruskin JN, Pollak MR, Macrae CA. Mutations in the long QT gene, KCNQ1, are an uncommon cause of atrial fibrillation. *Heart* 2004;**90**: 1487–1488.
86. Ellinor PT, Petrov-Kondratov VI, Zakharova E, Nam EG, MacRae CA. Potassium channel gene mutations rarely cause atrial fibrillation. *BMC Med Genet* 2006;**7**:70.
87. 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**:447–454.
88. Ellinor PT, Nam EG, Shea MA, Milan DJ, Ruskin JN, MacRae CA. Cardiac sodium channel mutation in atrial fibrillation. *Heart Rhythm* 2008;**5**:99–105.
89. Watanabe H, Darbar D, Kaiser DW, Jiramongkolchai K, Chopra S, Donahue BS *et al*. Mutations in sodium channel beta1- and beta2-subunits associated with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2009;**2**:268–275.
90. 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**:1326–1334.
91. 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**:1927–1935.
92. 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**:29–34.
93. 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**:1019–1028.
94. Schott JJ, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M *et al*. Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet* 1999;**23**:20–21.
95. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P *et al*. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998;**392**: 293–296.
96. Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL *et al*. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995;**80**: 805–811.
97. Hu D, Barajas-Martinez H, Burashnikov E, Springer M, Wu Y, Varro A *et al*. A mutation in the beta 3 subunit of the cardiac sodium channel associated with Brugada ECG phenotype. *Circ Cardiovasc Genet* 2009;**2**:270–278.
98. Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott JJ *et al*. Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest* 2008;**118**:2260–2268.
99. Groenewegen WA, Firouzi M, Bezzina CR, Vliex S, van Langen IM, Sandkuijl L *et al*. A cardiac sodium channel mutation cosegregates with a rare connexin40 genotype in familial atrial standstill. *Circ Res* 2003;**92**:14–22.
100. Makiyama T, Akao M, Tsuji K, Doi T, Ohno S, Takenaka K *et al*. High risk for bradyarrhythmic complications in patients with Brugada syndrome caused by SCN5A gene mutations. *J Am Coll Cardiol* 2005;**46**:2100–2106.
101. Bordachar P, Reuter S, Garrigue S, Cai X, Hocini M, Jais P *et al*. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. *Eur Heart J* 2004;**25**:879–884.
102. Kneller J, Kalifa J, Zou R, Zaitsev AV, Warren M, Berenfeld O *et al*. Mechanisms of atrial fibrillation termination by pure sodium channel blockade in an ionically-realistic mathematical model. *Circ Res* 2005;**96**:e35–e47.
103. Song Y, Shryock JC, Belardinelli L. An increase of late sodium current induces delayed afterdepolarizations and sustained triggered activity in atrial myocytes. *Am J Physiol Heart Circ Physiol* 2008;**294**:H2031–H2039.
104. Oberti C, Wang L, Li L, Dong J, Rao S, Du W *et al*. Genome-wide linkage scan identifies a novel genetic locus on chromosome 5p13 for neonatal atrial fibrillation associated with sudden death and variable cardiomyopathy. *Circulation* 2004;**110**:3753–3759.
105. Zhang X, Yang H, Corydon MJ, Pedersen S, Korenberg JR, Chen XN *et al*. Localization of a human nucleoporin 155 gene (NUP155) to the 5p13 region and cloning of its cDNA. *Genomics* 1999;**57**:144–151.
106. Weis K. Regulating access to the genome: nucleocytoplasmic transport throughout the cell cycle. *Cell* 2003;**112**:441–451.
107. Ehrlich JR, Biliczki P, Hohnloser SH, Nattel S. Atrial-selective approaches for the treatment of atrial fibrillation. *J Am Coll Cardiol* 2008;**51**:787–792.
108. Kanno S, Saffitz JE. The role of myocardial gap junctions in electrical conduction and arrhythmogenesis. *Cardiovasc Pathol* 2001;**10**:169–177.
109. Polontchouk L, Haefliger JA, Ebelt B, Schaefer T, Stuhlmann D, Mehlhorn U *et al*. Effects of chronic atrial fibrillation on gap junction distribution in human and rat atria. *J Am Coll Cardiol* 2001;**38**:883–891.
110. Dupont E, Ko Y, Rothery S, Coppen SR, Baghai M, Haw M *et al*. The gap-junctional protein connexin40 is elevated in patients susceptible to postoperative atrial fibrillation. *Circulation* 2001;**103**:842–849.
111. Gaborit N, Steenman M, Lamirault G, Le Meur N, Le Bouter S, Lande G *et al*. Human atrial ion channel and transporter subunit gene-expression remodeling associated with valvular heart disease and atrial fibrillation. *Circulation* 2005;**112**:471–481.
112. Kostin S, Klein G, Szalay Z, Hein S, Bauer EP, Schaper J. Structural correlate of atrial fibrillation in human patients. *Cardiovasc Res* 2002;**54**:361–379.
113. Nao T, Ohkusa T, Hisamatsu Y, Inoue N, Matsumoto T, Yamada J *et al*. Comparison of expression of connexin in right atrial myocardium in patients with chronic atrial fibrillation versus those in sinus rhythm. *Am J Cardiol* 2003;**91**:678–683.
114. Wilhelm M, Kirste W, Kuly S, Amann K, Neuhuber W, Weyand M *et al*. Atrial distribution of connexin 40 and 43 in patients with intermittent, persistent, and postoperative atrial fibrillation. *Heart Lung Circ* 2006;**15**:30–37.
115. Kanagaratnam P, Cherian A, Stanbridge RD, Glenville B, Severs NJ, Peters NS. Relationship between connexins and atrial activation during human atrial fibrillation. *J Cardiovasc Electrophysiol* 2004;**15**:206–216.
116. Dhein S, Duerrschmidt N, Scholl A, Boldt A, Schulte JS, Pfannmuller B *et al*. A new role for extracellular Ca^{2+} in gap-junction remodeling: studies in humans and rats. *Naunyn Schmiedebergs Arch Pharmacol* 2008;**377**:125–138.
117. Takeuchi S, Akita T, Takagishi Y, Watanabe E, Sasano C, Honjo H *et al*. Disorganization of gap junction distribution in dilated atria of patients with chronic atrial fibrillation. *Circ J* 2006;**70**:575–582.
118. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998;**339**: 321–328.
119. Stambler BS, Guo GB. Atrial natriuretic peptide has dose-dependent, autonomically mediated effects on atrial refractoriness and repolarization in anesthetized dogs. *J Cardiovasc Electrophysiol* 2005;**16**:1341–1347.
120. Crozier I, Richards AM, Foy SG, Ikram H. Electrophysiological effects of atrial natriuretic peptide on the cardiac conduction system in man. *Pacing Clin Electrophysiol* 1993;**16**:738–742.
121. Le Grand B, Deroubaix E, Couetil JP, Coraboeuf E. Effects of atrionatriuretic factor on Ca^{2+} current and Cai-independent transient outward K^+ current in human atrial cells. *Pflugers Arch* 1992;**421**:486–491.
122. Lonardo G, Cerbai E, Casini S, Giunti G, Bonacchi M, Battaglia F *et al*. Atrial natriuretic peptide modulates the hyperpolarization-activated current (If) in human atrial myocytes. *Cardiovasc Res* 2004;**63**:528–536.
123. Kato T, Muraski J, Chen Y, Tsujita Y, Wall J, Glembotski CC *et al*. Atrial natriuretic peptide promotes cardiomyocyte survival by cGMP-dependent nuclear accumulation of zyxin and Akt. *J Clin Invest* 2005;**115**:2716–2730.
124. Nyberg MT, Stoevring B, Behr ER, Ravn LS, McKenna WJ, Christiansen M. The variation of the sarcolipin gene (SLN) in atrial fibrillation, long QT syndrome and sudden arrhythmic death syndrome. *Clin Chim Acta* 2007;**375**:87–91.
125. Tsai CT, Hwang JJ, Chiang FT, Wang YC, Tseng CD, Tseng YZ *et al*. Renin–angiotensin system gene polymorphisms and atrial fibrillation: a regression approach for the detection of gene-gene interactions in a large hospitalized population. *Cardiology* 2008;**111**:1–7.
126. Ravn LS, Benn M, Nordestgaard BG, Sethi AA, Agerholm-Larsen B, Jensen GB *et al*. Angiotensinogen and ACE gene polymorphisms and risk of atrial fibrillation in the general population. *Pharmacogenet Genomics* 2008;**18**:525–533.
127. Bedi M, McNamara D, London B, Schwartzman D. Genetic susceptibility to atrial fibrillation in patients with congestive heart failure. *Heart Rhythm* 2006;**3**:808–812.
128. Fatini C, Sticchi E, Gensini F, Gori AM, Marcucci R, Lenti M *et al*. Lone and secondary nonvalvular atrial fibrillation: role of a genetic susceptibility. *Int J Cardiol* 2007;**120**: 59–65.
129. Kato K, Oguri M, Hibino T, Yajima K, Matsuo H, Segawa T *et al*. Genetic factors for lone atrial fibrillation. *Int J Mol Med* 2007;**19**:933–939.
130. Gaudino M, Andreotti F, Zamparelli R, Di Castelnuovo A, Nasso G, Burzotta F *et al*. The −174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? *Circulation* 2003;**108**(Suppl. 1):II195–II199.
131. Lai LP, Deng CL, Moss AJ, Kass RS, Liang CS. Polymorphism of the gene encoding a human minimal potassium ion channel (minK). *Gene* 1994;**151**:339–340.
132. Dobrev D, Wettwer E, Himmel HM, Kortner A, Kuhlisch E, Schuler S *et al*. G-Protein beta(3)-subunit 825T allele is associated with enhanced human atrial inward rectifier potassium currents. *Circulation* 2000;**102**:692–697.
133. Dickson SP, Wang K, Krantz I, Hakonarson H, Goldstein DB. Rare variants create synthetic genome-wide associations. *PLoS Biol* 2010;**8**:e1000294.
134. Goldstein DB. Common genetic variation and human traits. *N Engl J Med* 2009;**360**: 1696–1698.