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Impact of Genetic Discoveries on the Classification of Lone Atrial Fibrillation

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Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, represents a major burden to patients and health care systems through its sequelae of heart failure and stroke. Its age-dependent increase in prevalence has led to worrisome predictions of an expanding burden secondary to our aging population. This growing epidemic is further exacerbated by a current lack of highly effective therapies for the arrhythmia stemming from our incomplete understanding of its complex pathophysiology. Recent genetic studies, triggered in part by evidence of a hereditary component of AF, have begun to identify predisposing genes and offer further insights into the mechanisms of lone AF. A variety of ion channels and most recently a circulating hormone have been implicated. The apparent genetic diversity underlying the arrhythmia has served to emphasize the heterogeneity of factors that govern its initiation and maintenance. The different causative genes seem to predispose to AF through distinct putative mechanisms, including enhanced and delayed atrial action potential repolarization, cellular hyperexcitability, and conduction velocity heterogeneity. Classification of lone AF into mechanistic subgroups serves to emphasize its heterogeneity and has the potential to guide developmental and clinical treatment strategies. The frequent recalcitrant nature of the arrhythmia to contemporary pharmacological and invasive therapies may be overcome through an ability to identify, through genetics, the mechanistic subclass of AF for an individual patient. Proper identification of the culprit pathophysiology may permit administration of a targeted form of therapy that carries maximal efficacy and minimal risk in a manner consistent with the vision of pharmacogenomics.   (J Am Coll Cardiol 2010;55:705–12) © 2010 by the American College of Cardiology Foundation

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, represents a major health burden to individuals and health care systems within the Western world (1). The lifetime risk of the development of AF at age 40 years has been estimated to be approximately 1 in 4 (2). Through its sequelae of stroke and heart failure, along with serving as an independent risk factor for death, AF is currently estimated to cost the American health care system more than $1 billion annually (1,3). Given its increasing prevalence with age, coupled with our aging population, the number of affected Americans is expected to surge from approximately 2.3 million in the year 2000 to nearly 16 million by 2050 (4). These worrisome prospects are further exacerbated by our current lack of highly effective therapies.

Rational design of effective therapies requires improved insight into the factors that govern both the initiation and maintenance of the arrhythmia. Indeed, more than one-half a century after the initial proposal of the multiple wavelet hypothesis by Gordon Moe, there continues to be a variety of proposed theories regarding the precise electrical phenomena that define the arrhythmia (5,6). This lack of consensus likely reflects, as opposed to incorrect competing theories, heterogeneity in the pathophysiologic processes that trigger and perpetuate AF.

Insight into the diverse mechanisms governing lone AF has been furthered by the discovery of specific genes that predispose to the arrhythmia. Evidence of a genetic contribution in the development of AF was first provided in 1943 by Wolff (7), who documented transmission of lone AF in a family with an autosomal dominant pattern of inheritance. Since that time, large epidemiologic studies have documented evidence of heritability in AF, in particular in the context of lone AF (8–10). In 2003, the first gene responsible for an autosomal dominant form of familial AF was identified, namely, *KCNQ1* (11). Encoding a potassium channel, this work was followed by subsequent studies that implicated numerous other genes encoding ion channels in the pathogenesis of AF. As an exception, the most recent culprit gene identified encodes a circulating hormone, the atrial natriuretic peptide (ANP) (12). These diverse proteins are thought to predispose to AF through different electrical mechanisms, a notion that emphasizes the degree of heterogeneity that governs initiation and maintenance of the

**Abbreviations
and Acronyms**

AF = atrial fibrillation

ANP = atrial natriuretic
peptide

APD = action potential
duration

Cx40 = connexin 40

ERP = effective refractory
period

LQTS = congenital long
QT syndrome

arrhythmia. This heterogeneity may underlie the variable efficacy of non-specific, contemporary treatment strategies for AF, thereby reinforcing the need for improved insight into the subtypes of lone AF to facilitate targeted therapy that carries maximal efficacy and minimal risk.

Classification of lone AF into subtypes on the basis of causative mechanisms and their putative effects on atrial electrophysiology serves to highlight the heterogeneous physiology that contributes to the disorder. Such a classification approach may ultimately serve as a guide for clinical treatment strategies consistent with a pharmacogenomic paradigm (Table 1).

Mechanisms of Lone AF

Enhanced atrial action potential repolarization. The first causative gene for AF, *KCNQ1*, was identified through a linkage analysis study of a Chinese family with an autosomal dominant form of lone AF (11). *KCNQ1* encodes the pore forming α-subunit of the K$_v$7.1 voltage-gated potassium channel that is responsible for the slow component of the delayed rectifier potassium current (13). As illustrated in Figure 1A, the slow component of the delayed rectifier potassium current contributes to repolarization of cardiac myocytes (13). The importance of *KCNQ1* in cardiac arrhythmogenesis was previously documented through its identification as the causative gene for congenital long QT syndrome (LQTS) type 1 (14). Family members with AF were found to carry a mutation affecting amino acid position 140 that resulted in the substitution of a glycine for a serine residue (Ser140Gly) (11). In vitro functional analysis revealed markedly increased current densities conducted by the mutant channel indicating that, unlike the *KCNQ1* loss-of-function mutations observed in LQTS type 1, the
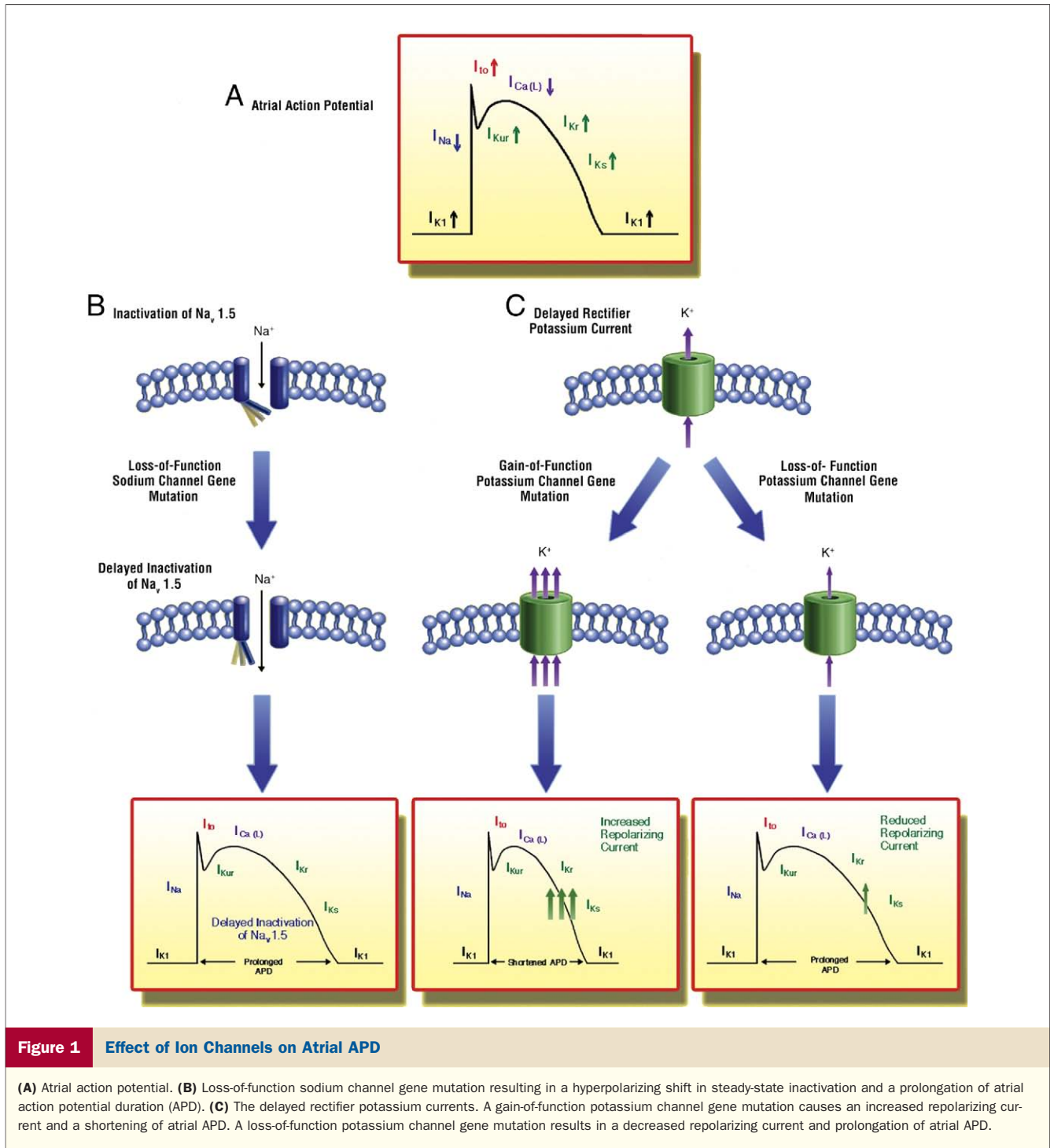
Ser140Gly substitution resulted in a gain of function (11). Interestingly, QT prolongation on electrocardiography was evident in 9 of 16 affected patients, suggesting that the mutation may have opposing electrophysiological effects in atrial and ventricular tissue. Subsequently, other *KCNQ1* gain-of-function mutations have been reported to be associated with familial and sporadic cases of AF (15,16). After the identification of *KCNQ1* as a causative gene for AF, multiple other gain-of-function mutations within potassium channel genes have been reported in association with AF and normal QT intervals, including *KCNE2*, *KCNJ2*, and *KCNE5* (17–19). Further evidence supporting the role of potassium channels in AF comes from the observation that as many as 30% of patients with short QT syndrome, a condition that develops secondary to *KCNQ1* or *KCNH2* gain-of-function mutations, have frequent paroxysms of AF (20,21).

The predicted physiological consequences of gain-of-function mutations within potassium channels include an acceleration of cardiomyocyte repolarization. This enhanced repolarization results in a shortening of the overall action potential duration (APD) and presumably a related reduction in the effective refractory period (ERP) (Fig. 1C). This reduced ERP is likely responsible for the increased predisposition for AF in these affected families, a concept that is consistent with the multiple wavelet hypothesis.

The multiple wavelet hypothesis, which suggests that the irregular atrial activity associated with AF is secondary to multiple self-perpetuating micro–re-entrant circuits exhibiting spatiotemporal variability in conduction and refractoriness, was proposed by Moe et al. (5,22) in 1959 following experimental work with dogs and was supported by a subsequent mathematical model. The theory, which became the dominant conceptual model of AF, received further validation approximately 3 decades later when high-resolution electrode mapping systems recorded multiple randomly propagating wavelets as the cause of turbulent atrial activity in human hearts (23). Central to this self-sustaining model is the requirement for a critical number of

Table 1	Mechanistic Subclassification of Lone AF		
AF Subclassification	**Culprit Gene(s)**	**Functional Effect**	
1. Enhanced atrial action potential repolarization	*KCNQ1* (11,15,16)	Enhanced slow component of the delayed rectifier potassium current (I$_{Ks}$)	
	KCNE2 (17)	Enhanced *KCNQ1-KCNE2* potassium current	
	KCNJ2 (18)	Enhanced inward rectifier current (I$_{K1}$)	
	KCNE5 (19)	Enhanced I$_{Ks}$	
2. Delayed atrial action potential repolarization	*KCNA5* (28)	Decreased ultrarapid component of the delayed rectifier potassium current (I$_{Kur}$)	
	SCN5A (35)	Hyperpolarizing shift in Na$_v$1.5 inactivation	
3. Conduction velocity heterogeneity	*GJA5* (40)	Decreased gap junction conduction	
4. Cellular hyperexcitability	*SCN5A* (44,45)	Depolarizing shift in Na$_v$1.5 inactivation	
5. Hormonal modulation of atrial electrophysiology	*NPPA* (12)	Increased circulating levels of mutant atrial natriuretic peptide	
6. Cholinergic	Unknown	Enhanced cholinergic sensitivity	

Figure 1   Effect of Ion Channels on Atrial APD

(A) Atrial action potential. (B) Loss-of-function sodium channel gene mutation resulting in a hyperpolarizing shift in steady-state inactivation and a prolongation of atrial action potential duration (APD). (C) The delayed rectifier potassium currents. A gain-of-function potassium channel gene mutation causes an increased repolarizing current and a shortening of atrial APD. A loss-of-function potassium channel gene mutation results in a decreased repolarizing current and prolongation of atrial APD.

circulating wavelets to maintain sufficiently chaotic activity to prevent coalescence of colliding wave fronts within the atria (22). The initial mathematical model by Moe and Abildskov (22) suggested that a minimum of 15 to 30 wavelets were necessary to sustain the arrhythmia, although subsequent work has indicated that as few as 4 to 6 wavelets may be sufficient in the canine heart (5,24). The number of wavelets that can be established and sustain AF is dependent on both atrial size and a concept termed the wave-

length of re-entry. The wavelength of re-entry concept may be viewed as a means to predict the size of a micro–re-entrant circuit using the product of conduction velocity and ERP (25). A reduction in ERP results in the formation of smaller micro–re-entrant circuits, allowing an increased number of circulating wavelets within atria of a given size. The aforementioned gain-of-function mutations, through enhanced repolarization and reduced ERP, therefore presumably increase the potential number of circulating atrial

wavelets and promote perpetuation of AF through a mechanism consistent with the multiple wavelet hypothesis.

Delayed atrial action potential repolarization. The discovery that gain-of-function mutations within potassium channels predispose to lone AF was consistent with the dominant conceptual model of AF. However, evidence of mechanistic heterogeneity was suggested by contemporary electrophysiology studies involving both animals and humans. Administration of cesium chloride, a potassium channel blocker, into the sinus node artery of dogs induced early afterdepolarizations that triggered polymorphic atrial tachycardias with subsequent degeneration into AF (26). This finding prompted the investigators to coin the term *atrial torsade de pointes* (26). Support for this concept in humans was provided by electrophysiology studies on patients with LQTS that revealed prolongation of both atrial APDs and ERPs along with short, spontaneous episodes of polymorphic atrial tachycardia, a finding not observed in controls (27).

Genetic support for a subtype of AF resembling atrial torsades was obtained after identification of a loss-of-function mutation in the *KCNA5* gene in a family with hereditary lone AF (28). The *KCNA5* gene encodes the $K_v1.5$ voltage-gated potassium channel responsible for the ultrarapid component of the delayed rectifier potassium current (28). The identified *E375X* mutation resulted in the erroneous insertion of a stop codon at position 375, which led to the expression of a truncated protein that was unable to conduct any significant current during in vitro functional analysis (28). Unlike the previous gain-of-function mutations, a loss-of-function mutation of the $K_v1.5$ voltage-gated potassium channel would result in delayed action potential repolarization and an increased ERP (Fig. 1C). Subsequent in vitro and in vivo studies inducing a reduction in $K_v1.5$ current through the use of 4-aminopyridine, a specific $K_v1.5$ blocker, revealed early afterdepolarizatons triggering episodes of AF, providing support for the concept of atrial torsades (28).

Another ion channel with a known role in mediating APD is the voltage-gated sodium channel $Na_v1.5$ (13). Encoded by the *SCN5A* gene, $Na_v1.5$ is already associated with numerous other disorders that carry an increased risk of AF, including Brugada syndrome, LQTS type 3, and sick sinus syndrome (29–31). In the 2 largest reported cohorts of Brugada syndrome patients assessed for coexisting AF, the prevalence of AF was in the range of 15% (32,33). Mutations of *SCN5A* were reported in 20% of patients with AF, although the biophysical properties of these variants were not assessed. A study involving 375 lone AF patients identified 8 novel mutations in 10 separate probands, 6 of whom had a family history of the arrhythmia (34). Although biophysical functional work was not performed, identified mutations seemed to segregate with the disease, providing evidence of causality. Subsequently, physiological consequences of a loss-of-function *SCN5A* mutation in lone AF have been described. In a small kindred harboring a novel *Asn1986Lys* mutation, the variant was characterized by a loss of function, demonstrating a hyperpolarizing shift in steady-state inactivation, which would be predicted to prolong APD (Fig. 1B) (35). Although not investigated further, this mutation would presumably predispose to AF through a manner consistent with the previously described atrial torsades.

A form of AF initiated by delayed atrial repolarization, with an ensuing pathophysiology reflective of atrial torsades, contrasts markedly with AF that behaves in accordance with the multiple wavelet hypothesis promoted by reduced ERP. This mechanistic heterogeneity may provide insight into the variable response observed in different individuals treated with identical forms of therapy, such as potassium or sodium channel–blocking agents.

Conduction velocity heterogeneity. Although the initial genes implicated in familial AF encoded potassium channels, subsequent screening of lone AF cohorts suggested that these channels were a rare cause of the arrhythmia (36,37). These findings implied that there were likely other classes of genes that played an important role in the development of the more common sporadic form of AF. Attractive candidate genes included connexins, transmembrane-spanning proteins that form gap junctions, which serve as intercellular pores, providing low-resistance pathways for the passage of current between adjacent cells (38). Of the 5 connexin isoforms expressed in the heart, connexin 40 (Cx40) seemed the most intriguing in the context of AF given its high level of expression within the atria and absence from ventricular myocardium (39).

Work by our group involving cases of sporadic lone AF identified Cx40 mutations in 4 of the 15 patients screened (40). In vitro characterization revealed a loss of function of the Cx40 mutant proteins secondary to intracellular trafficking defects and/or impaired cell-to-cell coupling. Equally important, the Cx40 mutations seemed to be of somatic rather than germ cell origin in 3 of the 4 cases. In these 3 cases, the mutant form of Cx40 was identified only from atrial tissue and was absent from the peripheral lymphocytes of affected patients. Through allele subcloning analysis from atrial tissue, the proportion of atrial cells estimated to harbor the mutant connexins ranged from 20% to 34% (40). This inhomogeneous distribution of loss-of-function gap junctions would be expected to promote or exaggerate regional differences in conduction velocity, creating a heterogeneous substrate promoting electrical re-entry. Immunostaining of atrial tissue specimens from affected patients carrying the trafficking-defective Cx40-Pro88Ser mutant revealed a mosaic multicellular pattern of intracellular retention, supporting the heterogeneous nature of somatic or tissue-specific mutations within a subpopulation of atrial myocytes.

The loss of function associated with these connexin mutations, coupled with their heterogeneous distribution throughout the atria, likely results in a predisposition to AF and maintenance of the arrhythmia through mechanisms

consistent with an enhanced vulnerability to electrical re-entry in the context of an exaggerated dispersion of conduction velocity (Fig. 2). This gap junction-induced spatio-temporal variability of conduction and tissue refractoriness allows for the establishment of the multiple re-entrant circuits necessary to satisfy the multiple wavelet hypothesis and therefore create a sustained form of AF.

Cellular hyperexcitability. The concept of cellular hyperexcitability received much attention after a landmark article that documented rapidly firing ectopic foci from the pulmonary veins that were sufficient to both trigger and maintain AF (41). Studies involving isolated sheep heart demonstrated that a rapid self-sustaining circuit of re-entry, termed a mother rotor, is capable of transmitting fractionated spiral waves to adjacent atrial tissue at a frequency sufficient to both induce and maintain AF (42). Figure 3 illustrates a rapidly firing ectopic focus in the vicinity of a pulmonary vein os mediating AF through disorganized propagation of wave fronts to surrounding tissue. Support for a rapid self-sustaining re-entry circuit as the mechanism driving the ectopic foci in AF has subsequently come from high-resolution optical mapping of canine pulmonary vein sleeves (43). The factors contributing to these foci are not entirely clear; however, they may include aberrant vagal influences from nearby autonomic ganglia coupled with the complex architecture of the pulmonary veins or posterior left atrium that result in an ideal substrate for re-entry.

Establishment of a high-frequency micro–re-entrant circuit within the pulmonary veins requires a trigger for initiation, and therefore ion channels involved in depolarization are likely critical to this pathophysiologic process. An obvious candidate includes the previously discussed $Na_v1.5$ responsible for the predominant inward sodium current during early cellular excitability. At this point, there have been 2 studies that identified *SCN5A* gain-of-function mutations in patients with lone AF who did not have LQTS type 3, the only previous condition associated with *SCN5A* gain-of-function mutations (30). In 1 study, affected members of a Japanese family with an autosomal dominant form of lone AF harbored a novel *M1875T* mutation (44). Functional analysis of the mutant channel using in vitro studies revealed a pronounced depolarizing shift in the voltage-dependent steady-state inactivation of the channel, which is predicted to lower the threshold potential for cellular excitability. This concept of cellular hyperexcitability was supported by observations from radiofrequency catheter ablation of the proband in which numerous ectopic firings and increased excitability of the right atrium were documented (44). Another study from our group identified a *K1493R* mutation in a mother and son who had lone AF that exhibited a similar depolarizing shift in steady-state inactivation when expressed in tsA201 cells (45). In addition, transfection of the mutant *K1493R* into HL-1 atrial cardiomyocytes resulted in spontaneous action potential
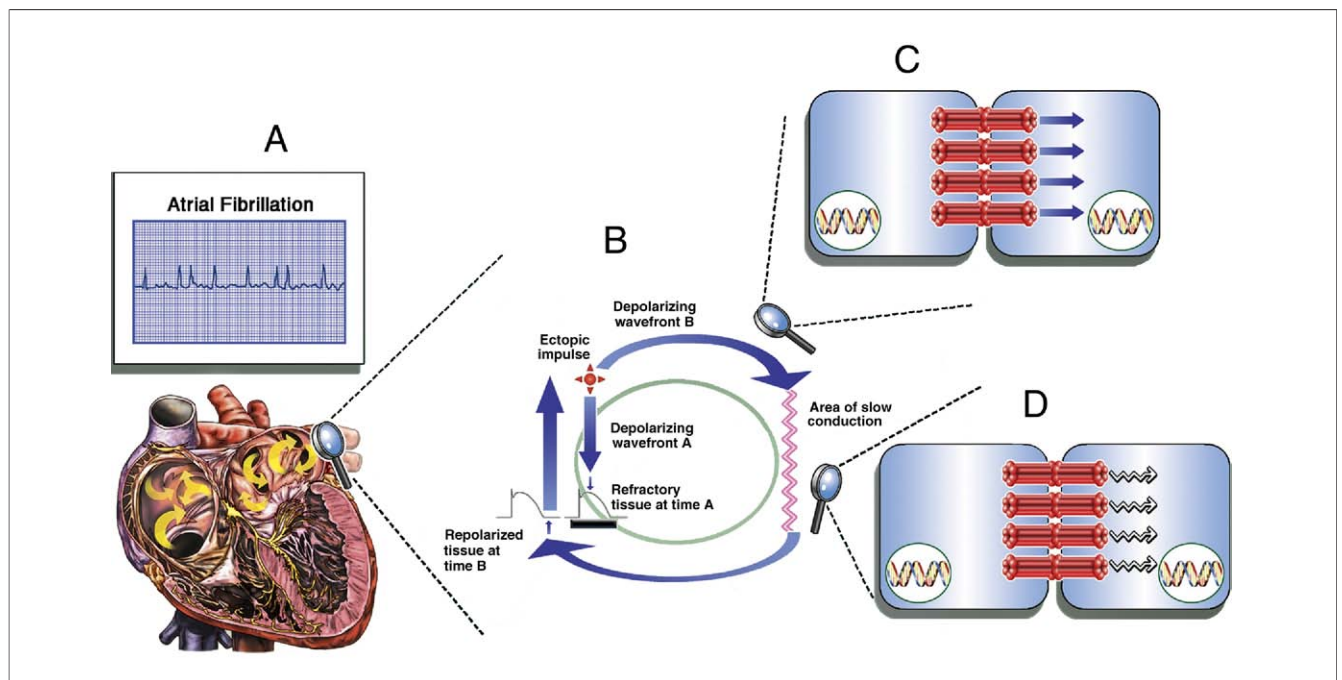

Figure 2   **Micro Circuit Re-Entry Secondary to Conduction Velocity Heterogeneity**

(A) Atrial fibrillation depicted on electrocardiography and conceptually within the heart. **(B)** An ectopic impulse triggering depolarizing wave fronts A and B. Wave front A encounters refractory tissue and terminates, whereas wave front B travels along an alternate pathway of slowed conduction velocity providing a time delay allowing the previously refractory tissue to repolarize. Wave front B now encounters excitable tissue, and a re-entry circuit is established. **(C)** Cell-to-cell transmission of depolarizing current through gap junctions resulting in normal conduction velocity. **(D)** Decreased conduction velocity secondary to loss-of-function gap junction channels.
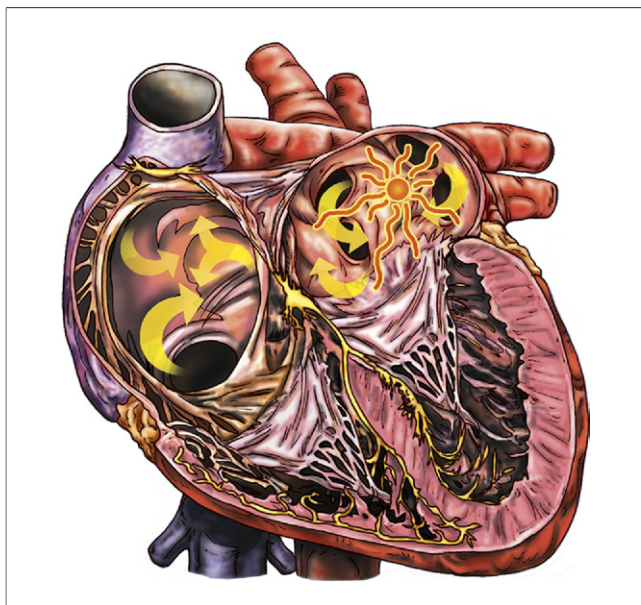
Figure 3   **Atrial Fibrillation Secondary to Cellular Hyperexcitability**

A rapidly firing ectopic focus in the vicinity of a pulmonary vein os transmitting electrical wave fronts to adjacent atrial tissue with sufficient spatiotemporal dispersion to generate atrial fibrillation.

depolarizations and a lower threshold for action potential firing. Of note, the late persistent current characteristic of gain-of-function *SCN5A* mutations responsible for LQTS type 3 was absent in the mutants from both studies, thus accounting for the normal QT interval in these patients.

The mechanism translating cellular hyperexcitability secondary to *SCN5A* gain-of-function mutations into the phenotype of AF potentially relates to enhanced automaticity of atrial cardiomyocytes. The resultant triggers, in the setting of an ideal substrate such as the pulmonary veins, may be sufficient to both induce and maintain AF. A complementary mechanism may involve the intracardiac ganglia that densely innervate this region of the heart (46). Recent work revealed that Na$_v$1.5 channels are highly expressed within intracardiac ganglia, alluding to the possibility that hyperexcitability of surrounding neurons may be the driving force behind the rapidly firing ectopic foci (47).

The distinct electrophysiological features of an AF driven by cellular hyperexcitability again serve to reinforce the clinical relevance of a subclassification system for lone AF. Treatment strategies effective against a form of AF reflective of the multiple wavelet hypothesis, such as potassium channel blockers, would likely be ineffective in the case of focal forms of AF driven by cellular hyperexcitability. Sodium channel modification affecting the kinetics of Na$_v$1.5 channel inactivation might provide a more efficacious response in the setting of cellular hyperexcitability.

Hormonal modulation of atrial electrophysiology. *NPPA* represents the most recent gene identified as being causative

for AF and, unlike the previously implicated genes that involve ion channels, encodes the circulating hormone ANP (12). This somewhat surprising discovery was obtained from a linkage analysis study of a family with an autosomal dominant form of lone AF (12). Before this work, ANP had generally been viewed as a cardioprotective hormone with an important role in sodium balance and blood pressure regulation (48). There was evidence, however, that ANP was capable of modulating the activity of various ion channels within the heart (49,50).

The mutation identified in the affected family resulted in the loss of the stop codon, resulting in the expression of a 40-amino-acid peptide that was significantly longer than the 28-amino-acid wild-type peptide (12). The mutant peptide was detected in the plasma of heterozygote carriers and was present at 5- to 10-fold the concentration of wild-type ANP, suggesting resistance to degradation and a prolonged half-life. The mechanism through which this mutant peptide triggered AF was not entirely clear; however, in vitro studies using an isolated whole heart model suggested that the mutant peptide shortened the atrial APD with a corresponding effect on the ERP (12). These findings allude to a mechanism involving enhanced repolarization analogous to that observed with gain-of-function potassium channel mutations.

Although the potential role of ANP in directly modulating atrial electrophysiology and promoting an AF substrate is intriguing, other proarrhythmic actions of ANP are also conceivable, an example being inflammation that could stem from the important role of ANP in the regulation of the innate immune system (51,52). Given that ANP is a known mediator of inflammation, long-term exposure to altered levels of ANP might induce structural changes related to inflammation that ultimately result in atrial fibrosis and subsequent development of an AF substrate. Further work will be required to further our understanding into the mechanisms through which mutant ANP predisposes to AF.

Cholinergic AF. Genes encoding multiple different ion channels and now a circulating hormone have been implicated as predisposing factors to AF. However, somewhat surprisingly, there is as yet no described genetic link within a critical pathway in the arrhythmogenesis of AF, the autonomic nervous system. Sympathetic and parasympathetic influences have long been appreciated as mediators of the triggers and substrate modification necessary for the development of AF. The notion of a vagally mediated form of AF was first suggested by Coumel et al. (53) more than 3 decades ago in a report that described a cohort of young patients with structurally normal hearts in whom recurrent paroxysms of AF developed during periods of high vagal tone such as sleep and the postprandial period. Although sympathetic influences seem to be the predominant mediator of AF in diseased hearts, vagal input serves as the major culprit in the setting of lone AF.

The greatest density of vagal innervation within the atria occurs at the pulmonary veins, which correspond to the

location of rapidly firing ectopic foci capable of driving the arrhythmia (41,46). Identification of the pulmonary veins as a frequent source of rapidly firing ectopic foci provided the rationale for contemporary AF treatment strategies that use catheter ablation techniques to electrically isolate the pulmonary veins from surrounding atrial tissue (54). Although the complex architecture of the pulmonary veins likely serves as an ideal substrate for re-entry, the role of autonomic ganglia in the genesis of AF is becoming increasingly apparent. Ablation procedures whereby vagal responses are elicited by radiofrequency ablation in the regions of the pulmonary veins have shown increased efficacy, suggesting that the lesions are affecting vagal input or ganglia (55). This is complemented by recent studies in a dog model of cholinergic AF that demonstrated that electrical isolation of pulmonary veins alone could not suppress vagally stimulated AF, whereas ablation of the autonomic ganglia overlying all pulmonary vein ostia succeeded in suppressing AF with vagal stimulation (56). These findings identify the parasympathetic nervous system as a critical predisposing factor for AF, providing a clue that genetic mutations in the molecular constituents mediating the cardiac vagal response may represent an important, and potentially common, cause of the arrhythmia.

Summary

Genetic studies have revealed diverse mechanisms of AF vulnerability secondary to genetic defects in multiple ion channels and a circulating hormone. This heterogeneous pathophysiology highlights the difficulties of a common therapeutic approach to ameliorate this prevalent arrhythmia. A classification system that recognizes the mechanistic subtypes of lone AF, as predicted by culprit genes or clinical data, has the potential to guide clinical treatment strategies. As genetics are gradually incorporated into routine clinical practice, a classification system may facilitate individualized AF therapy based on pharmacogenomic principles.

Although single-gene disorders for AF provide the opportunity to understand primary electrophysiological mechanisms predisposing the atria to fibrillation, it is likely that, in many cases, disease vulnerability arises from the influence of multiple genes that may influence the putative mechanisms described here. Identifying common variations within the genome, which, either alone or in combination, may affect the biophysical properties of atrial tissue, remains a priority in future research. Genome-wide association studies have provided insight into common genetic loci that carry an increased risk of AF; however, the specific genes have yet to be identified (57–59). The discovery of these genes and insight into their effect on atrial electrophysiology will undoubtedly facilitate the implementation of a pharmacogenomic treatment approach for this common arrhythmia.

The classification of AF as either secondary to structural disease or as lone AF is now obsolete. It is now clear that lone AF, based on the mechanistic insights provided by genetic studies, requires a classification system reflecting the specific electrophysiological substrates that promote vulnerability to this heterogeneous disorder.

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