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Genetics of AF: rare mutations, common polymorphisms and clinical relevance

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The limited success in therapy of AF is likely the result of heterogeneity of the underlying electrical substrate and incomplete understanding of fundamental mechanisms in disease pathogenesis. In addition, there is increasing evidence of a heritable component to some forms of AF, and in particular to idiopathic or lone AF. Recent data also suggests that AF in the setting of underlying disease may also be under genetic control. These findings suggest that there may be an inherited intrinsic threshold for vulnerability to the arrhythmia. Ultimately, the identification of genetic loci for AF may provide insight into the pathogenesis of AF and eventually may lead to improved, patient-specific rhythm control strategies to treat this common and morbid condition.

Heritability of lone AF

The heterogeneous clinical presentations of AF suggest multiple mechanisms for the arrhythmia. Heritability of AF is suggested by two recent population-based studies demonstrating that the presence of AF in first-degree relatives was associated with an increased risk of developing AF.^{1, 2} We and others have also found a family history of AF in one-third of patients with lone AF indicating that familial AF is more common than previously recognized.^{3, 4}

While most AF is seen in association with other cardiac or systemic conditions, 10–30% of patients have lone AF. These relatively homogeneous subsets of the arrhythmia can serve as a unique population for understanding the genetic contributions to AF. Since Wolff's original description of three brothers with AF in 1943,⁵ there have been multiple families identified in which AF segregates as a monogenic trait. Studies in such kindreds have been used to map genetic loci in AF. Recently, we identified a novel AF locus on chromosome 5p15 and demonstrated that affected individuals with AF and mutation carriers can be identified by a prolonged signal-averaged P-wave duration.⁶ Identification of the intermediate or endophenotype not only aided ascertainment of additional family members but has helped in the fine mapping of the AF locus. Collectively, these reports support the idea that familial AF is a genetically heterogeneous disorder.

Ion channel mutations and AF

Recently, the first genes for AF have been identified, providing a link between ion channelopathies and the disease. *KCNQ1* was the first disease gene linked to adult-onset

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familial AF with a single missense mutation, S140G, found in 1 family.⁷ This gene encodes the pore-forming α -subunit of the cardiac I_{Ks} channel. Expression of the mutant gene product in vitro with *KCNE1* (the β -subunit) resulted in a marked increase in current density as well as more rapid activation and deactivation of the channel. While these biophysical changes would be expected to result in a reduction of the action potential duration, some of the affected family members had a prolonged rather than shortened QT interval, an observation that remains unexplained. The same group established a link between *KCNE2* and AF by identification of a gain-of-function mutation in two families with AF.⁸ Recently, a truncating mutation in *KCNA5* encoding a voltage-gated potassium channel ($K_{V1.5}$) underlying the ultrarapid delayed rectifier current (I_{Kur}) was associated with familial AF.⁹ While these potassium channel subunit gene mutations have been important in establishing the role of single gene disorders in AF, such isolated or “private” sequence variations are often in residues of unknown function, effects on channel conductance are inconsistent and in most instances it can be difficult to discriminate rare polymorphisms of no functional significance and true mutations. Thereby, the role of potassium channel subunit gene mutations in AF remains unclear at present, but screening of large patient cohorts suggests that such mutations are not a major cause of AF. It can therefore be assumed that additional disease genes for familial AF remain to be discovered. Genes that encode other types of ion channels or structural proteins in the atria can also be considered as potential candidates for familial AF.

AF associated with other monogenic diseases

Studies of other cardiac monogenic disorders have also provided evidence for the genetic basis for AF. These include diseases such as hypertrophic cardiomyopathy, skeletal myopathies, familial amyloidosis, and atrial myopathies. However, it is likely that AF in these cases is related at least in part to morphological changes in the atria caused by the underlying cardiac pathology. AF can also present in other ion channelopathies like long QT syndrome (LQTS) type 4, Brugada syndrome, and short QT syndrome. The high incidence of atrial arrhythmias in patients with the short QT syndrome and the gain of function mutations in I_{Ks} , point to an important role for shortening of the action potential in the development of AF. Sodium channel gene (*SCN5A*) defects have also been associated with a syndrome of early-onset dilated cardiomyopathy (DCM) and AF. Moreover, mutations in the gene for the nuclear membrane protein lamin A/C (LMNA) have pleiotropic noncardiac and cardiac manifestations including DCM, AF, and conduction system disease. Collectively, these studies attest to the heterogeneous nature of AF and strongly suggest that defects in many more genes remain to be identified.

Association studies

Most patients with AF have one or more identifiable risk factors, but many or even most patients with these same risk factors do not develop AF. Thus, it is likely that genetic determinants favor AF in some individuals with identifiable risk factors. Studies comparing cases of non-familial AF to age-related and gender-matched controls (association studies) have provided some insight into the genetic basis of ‘acquired’ AF. One study identified an association with the S38G variant in *KCNE1* and AF.¹⁰ The 38G allele appears to reduce I_{Ks} ,¹¹ consistent with the finding that mice lacking *KCNE1* are prone to AF.¹² In addition, AF has also been associated with common DNA polymorphisms in genes that alter regulation of ion channel function (e.g., *GNB3* encoding G-protein β_3 -subunit and *NOS3* encoding nitric oxide synthase), intracellular calcium handling, and gap junction formation (e.g. *GJA5* that encodes connexin 40).

Over the last several years there has also been increasing evidence that activation of the renin-angiotensin-aldosterone (RAAS) activation may be an important risk factor for the

development of AF. There are retrospective and prospective data suggesting that angiotensin-converting-enzyme (ACE) inhibitor therapy and angiotensin receptor blockers may be associated with a lower incidence of AF. In addition, a case control study of 250 Taiwanese subjects with AF and 250 controls identified polymorphisms in this pathway as risk factors for AF.¹³ Added support for the increasingly important role of RAAS activation in the pathophysiology of AF comes from a recent study which for the first time demonstrated a pharmacogenetic interaction between the ACE *I/D* polymorphism and efficacy of antiarrhythmic drug therapy in patients with lone AF.¹⁴

Uncovering common genes for AF

The above studies in ageing patients with non-familial AF in the presence of underlying heart disease suggest some form of genetic control in the pathogenesis of the more common form of AF. These data may help clarify why some people develop AF under specific circumstances while others may not. The genetic basis for the majority of patients with AF however remains unknown. Although Mendelian forms of lone AF are not rare, large kindreds such as those used to identify disease genes in other inherited arrhythmia syndromes, e.g., congenital LQTS, are unusual. One possible explanation for such complexity may be a smaller genetic contribution to the ultimate clinical phenotype, and thus reduced penetrance with less apparent heritability. Another possible mechanism is that the phenotype may be the result of interaction of several genes, i.e., polygenic, each with a small overall contribution. Finally, AF may require additional environmental events e.g., hypertension, to reduce the 'AF threshold' sufficiently to trigger an episode of arrhythmia.¹⁵

The paroxysmal nature and variable symptoms in AF, a high prevalence in the general population, and a late age of onset in many individuals all make assignment of the clinical phenotype challenging. A number of strategies can be used to minimize misphenotyping, including "affecteds only" analysis and "diagnosis by offspring", all of which unfortunately reduce the power. This complexity has compelled a search for new more effective methods for investigating the genetics of complex diseases, such as AF. One approach is to use the families of affected individuals as an enriched target population for the definition and evaluation of intermediate or endophenotypes, i.e. subtle or novel phenotypes which are causally related to the poorly penetrant classical clinical syndromes. In the case of AF, examples of potential endophenotypes include signal-averaged P-wave duration, surface ECG fibrillatory wave characteristics, pulmonary venous anatomy, and profiles of biomarkers such as atrial natriuretic peptide. If such markers of a reduced threshold for AF can be defined, then not only will they be useful clinically (i.e., to subset patients with AF), but they will also accelerate the identification of causal AF genes.

Because of these limitations, researchers have begun to apply other approaches to identify genes that are involved in complex diseases such as AF. Genetic association studies using a candidate-gene approach are likely to be more effective tools than linkage studies for studying complex traits because they have greater statistical power to detect several genes of small effect. Candidate-gene studies focus on genes that are selected because of *a priori* hypotheses about their etiological role in disease (ion channels, gap junctions, renin-angiotensin pathway, etc). Furthermore, a candidate-gene study is usually conducted in a population-based sample of affected and unaffected individuals (a case-control study). A candidate-gene study therefore takes advantage of both the increased statistical efficiency of association analysis of complex diseases and the biological understanding of the phenotype, tissues, genes and proteins that are likely to be involved in the disease. However, in spite of their promise, candidate-gene studies do have two important limitations. First, the significant findings of association in many candidate-gene studies have not been replicated when followed up in subsequent association

studies. Second, because candidate-gene studies are based on the ability to predict functional candidate genes and variants, current knowledge may be insufficient to make these predictions.

A logical consequence of the availability of comprehensive genomic maps is the advent of high-density genome-wide searches for modest gene effects using large scale testing of single nucleotide polymorphisms (SNPs). This approach is increasingly being applied to tackle complex human diseases such as AF. Although early proponents suggested focusing on coding or promoter variants with potential functional significance, subsequent work has shown that non-coding or evenly spaced SNPs with high density can be used to identify disease loci taking advantage of extensive linkage disequilibrium across the genome. The availability of high-density mapping of marker SNPs and assessment of genomic structure, together with emerging information on functional pathways, have begun to provide powerful means of identifying genetic susceptibilities to common disease.¹⁶ In the first such study of AF, a novel locus on Chromosome 4q25 has recently been identified which confers a 1.6–2.0 (95% confidence intervals) fold increased risk of the arrhythmia across multiple different populations.¹⁷

One of the most challenging problems with non-Mendelian genetic approaches is the differentiation of signal from noise. Association studies may be confounded by etiologic heterogeneity, population stratification, or false positives, while the bias toward small effects may miss major genetic contributions relevant only in a subset of study subjects. It may also prove difficult to define the fundamental mechanisms of any true associations, as the responsible gene may be remotely linked to the locus identified. The development of more efficient models for the rapid validation of genome wide association study results, and improved understanding of the underlying biology will facilitate the interpretation of such studies.

Novel genetic mechanisms

Advances in genomic technologies and in our understanding of novel genetic mechanisms have also begun to impact our study of these emerging mechanisms in disease. Somatic mutation is a major cause of neoplastic disease, especially in rapidly dividing cell types, with ‘second hits’ thought to inactivate the wild-type allele in the context of germline inactivation of a gene copy. It is not clear how such mechanisms would operate in the heart where post-mitotic cell division is thought to occur at an extremely low rate if at all. Nevertheless, apparently myocardially-restricted somatic mutations in the connexin 40 gene (*GJA5*), encoding the major component of the cardiac gap junctions, were recently described in a small series of AF subjects.¹⁸ Mitochondrial mutations, another form of tissue specific variation, have been reported in multiple small series of AF subjects, as for many other conditions associated with ageing.¹⁹ The issues surrounding the validation of somatic mutation in non-clonal tissues are complex, but it should prove possible to prove this disease mechanism through in vivo modeling.

Other forms of inheritance have already been indirectly implicated in AF. The disparate atrial and ventricular phenotypes seen in the context of mutations in the *KCNQ1* gene may reflect the regional expression of individual alleles of this gene or longer range effects on neighboring genes as this locus is heavily imprinted. Although genetic variants provide a molecular blueprint for disease, factors in addition to the presence of mutant protein are determinant of the clinical phenotype, and chamber-specific expression of ion channel binding partners, modifying genetic and environmental factors, or additional unrelated defects might be involved. Combined atrial and ventricular phenotypes due to a single gene defect may be difficult to differentiate clinically from AF with secondary left ventricular dysfunction or ventricular myopathies with secondary AF. However, the presence of ventricular involvement in inherited syndromes that include AF is important to recognize as there are significant prognostic implications. Finally, as genomic advances uncover novel gene classes, including

microRNAs which affect the mRNA stability or translation efficiency of many different genes, these will each be explored in a broad range of human diseases.

Future directions

As AF is often associated with cardiac and systemic disorders, it has traditionally been regarded as a sporadic, non-genetic disorder. However, it is increasingly recognized that AF risk includes a prominent familial component. Functional characterization of genetic variants in kindreds and sporadic cases of AF provide compelling evidence that inherited defects could play a major role in AF development. Although the precise role of genetic factors in AF heritability is incompletely understood, considerable progress has been made understanding the role of isolated mutations in the pathogenesis of AF. However, as with many common diseases, familial forms of AF due to gene mutations with high penetrance are rare and only account for a small proportion of all cases. Nonetheless, the identification of single gene mutations in families will not only identify critical pathways or proteins important in the pathogenesis of AF but also enable interrogation of common DNA sequence variants that predispose to the more common forms of AF. Contemporary genetic studies have primarily focused on cardiac ion channel defects; AF however is a highly heterogeneous disorder and because the arrhythmia itself is not a single pathophysiologic entity but rather represents a final common pathway response to a variety of disease pathways that culminate in AF, perturbation of many diverse cellular pathways could provide the substrate for AF. Perhaps the greatest impact of genetics and genomics to date has been at the phenotypic level, highlighting the need for much finer resolution in our clinical diagnostic armamentarium. Hence, a key challenge in contemporary translational medicine and in particularly the application of genomic technologies to the bedside is accurate definition of intermediate phenotypes, the first step in subsetting patients for subsequent genomic analysis. AF can be considered an archetype for many other complex traits, where dilution of genetic effects by etiologic heterogeneity and substantial environmental influence makes systematic dissection challenging. Phenotyping issues are further complicated by the paroxysmal and often asymptomatic nature of AF, and consistent stable endophenotypes directly related to the underlying myocardial disorder will be required for a comprehensive understanding of the genetic architecture of AF. Ultimately, such endophenotypes are likely to incorporate functional genomic and physiologic data.

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