Review

Genetic aspects of atrial fibrillation

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Abstract

Atrial fibrillation (AF) occurs predominantly in the elderly and is commonly associated with underlying cardiac diseases. A significant number of patients, however, have early onset AF that is not associated with any underlying disease. At present, it is unknown how often this form of AF is familial and how frequently familial AF is due to genetic causes. Recent data suggest that familial AF occurs more frequently than previously recognized. Also, in AF in the setting of underlying diseases, it is suggested that some form of genetic control may be present. Understanding the molecular mechanisms underlying AF may provide insight into the pathogenesis of AF and eventually may lead to improved, patient-tailored rhythm control strategies.

Keywords: Arrhythmia (mechanisms), Gene expression; Gene polymorphisms; Supraventricular arrythmia

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is associated with an unfavorable prognosis [1,2]. The majority of patients have AF in association with underlying (cardiac) diseases [3]. In 15–30% of the patients, however, an etiology is absent [4,5]. This condition is called lone AF. Some of these patients have a positive family history for AF and may have a genetic cause or predisposition [6,7]. Darbar et al. [8] recently observed that familial AF is more common than previously recognized. Of the 914 patients with AF, 36% had lone AF and of that population a family history of AF was present in 15% of the patients (5% of all AF patients) [8,9].

The prognosis of AF patients is determined by the associated cardiovascular disease as well as by arrhythmia-related events. Identifying patients with genetic defects predisposing to AF may have important implications. Identification of the genes that play a role in the initiation of the arrhythmia may give us new insights into the development of the disease and improve our understanding and therapeutic options. Also, recognition of patients at risk may, eventually, decrease the prevalence of AF in turn reducing morbidity and mortality [1,3].

In this overview we will focus on (a) genetic defects that cause familial forms of lone AF, (b) speculate on the mechanisms of AF in the respective genetic disorders, and (c) discuss polymorphisms that have been identified to be associated with the occurrence of AF in the setting of precipitating factors, like hypertension and coronary artery disease.

Familial AF may also occur in the setting of other inherited (structural) heart diseases, e.g. in association with dilated or hypertrophic cardiomyopathy [10–13]. The latter group, however, is not subject of the present review.

2. Mechanism of AF

Ever since the first recognition of AF, the underlying mechanism has been a subject of interest. It may either be (a) one or more rapidly discharging, spontaneously active,
atrial ectopic foci, (b) a single reentry circuit, or (c) multiple functional reentrant circuits. At present, the multiple wavelet hypothesis, as has been formulated by Moe and Abildskov [14] and experimentally confirmed by Allessie et al. [15,16], is the generally accepted hypothesis to explain AF. Recent observations, however, have challenged the multiple wavelet hypothesis. Optical mapping studies of AF in sheep hearts point to a primary local generator being either an ectopic focus or a small reentry circuit [17].

The wavelength, being the product of the refractory period and conduction velocity, is the distance traveled by an impulse in one refractory period. Stability of AF is determined by the number of wavelets being present simultaneously. Thus, the shorter the wavelength and the larger the atria, the more waves fit into the atria and the more stable AF will be. Consequently, changes in refractory period and conduction velocity will affect the wavelength and thus stability of AF. Another important parameter for the vulnerability and stability of AF are inhomogeneous in electrophysiological properties, i.e. dispersion in atrial refractoriness which is associated with conduction block, being a prerequisite for the start of reentrant arrhythmias. AF induction may occur (a) in diseased atria, e.g. due to haemodynamic overload as is the case with hypertension or heart failure, (b) in the presence of genetic disorders affecting refractory period and/or conduction velocity heterogeneously, but also (c) by AF it self. AF may, by shortening of the atrial refractory period, reduction of conduction velocity and structural remodeling, set the stage for sustenance of AF (‘AF begets AF’) [18].

For the start of AF, triggers are necessary to induce the arrhythmia. Triggers include atrial ectopic foci predominantly occurring from the sleeves of atrial tissue within the pulmonary veins and the vena caval junction, but also bradycardia and other (supra)ventricular tachycardias. Triggers may initiate reentry if the wavelet is sufficiently short. Factors like wavefront curvature and spatial and temporal organization are relevant for the start of AF by the interaction of the propagating wavefronts with anatomical and functional obstacles and may be considered initiators of AF. The substrate ensures the perpetuation of AF for longer periods. It includes electrophysiologic changes, as mentioned above, and, eventually, structural remodeling including the occurrence of fibrosis and dilatation of the atria [19].

3. Atrial fibrillation without structural heart disease

The incidence of lone AF depends on the type of AF (paroxysmal versus persistent) and how rigorously the patient has been evaluated. Depending on its mechanism of initiation, lone AF may be distinguished into vagally induced AF, adrenergically induced AF, or a combination of both types. Although never systematically investigated, most patients seem to suffer from a combination of both types of AF.

3.1. Monogenic forms of lone atrial fibrillation

Possible genes responsible for triggering and maintaining AF may include genes that affect automaticity, atrial refractory period duration and conduction. In 1997 Brugada et al. were the first to identify linkage to a locus on chromosome 10q22-24 for familial AF in 3 different Spanish families [20]. In these families, AF segregated as an autosomal dominant disease with high penetrance. In a three-generation family 10 of the 26 living family members were affected. Mean age was 18 years and 9 had permanent AF, 7 of them being asymptomatic. In 2 of them an increase of the left ventricular diameters, with left ventricular ejection fractions of 51% and 54%, respectively, was observed. All others had no echocardiographic abnormalities. One patient died suddenly at the age of 36 years. In the other 2 families, all 9 affected persons had permanent AF and were asymptomatic without any echocardiographic abnormality (Table 1). The causative gene has not been identified yet. Several candidate genes including genes encoding α- and β-adrenergic receptors and G-protein receptor kinase are located nearby, on chromosome 10q23-q26. Sequencing these genes, however, did not reveal any mutations and could therefore be excluded as causative genes. Darbar et al. [8], however, could not confirm linkage to chromosome 10q23-q26 in 3 other families with familial paroxysmal AF and rapid ventricular response and in 1 AF family with a slow ventricular response (Table 1). In contrast to the other 3 families, AF in the latter family was often asymptomatic. Eventually, 4 of the 10 patients of this family developed a junctional rhythm and 5 of the 10 patients left ventricular enlargement with a low–normal left ventricular ejection fraction. The latter finding suggests that the phenotype of the fourth AF family is characterized by an additional cardiomyopathy and atrial conduction disease. Linkage was excluded to the LAMA and SCN5A genes which both have been associated with familial AF, conduction system disease and dilated cardiomyopathy [8,13,21]. Nevertheless, clinicians should be alert on the development of conduction disturbances or a cardiomyopathy in (young) patients with familial AF and a slow ventricular response. It also highlights the importance of adequately describing the phenotype in studies searching for genes underlying arrhythmias, e.g. AF. The second phenotype in the study by Darbar et al. is completely different from the first one and has a different clinical outcome. This suggests at least two distinct mechanisms (and possible associated genes) involved in AF in these families.

In a large family with autosomal dominantly inherited lone AF, 8 individuals with AF were identified [22]. In this family, AF started as paroxysmal AF in younger individuals and became permanent in older family members. The age of onset was variable, ranging from young to elderly family members. The left ventricular function was normal except for one individual who had a left ventricular ejection...
fraction of 40% while in AF with a rapid ventricular response (Table 1). Remarkably, two other individuals of this family had a history of peripartum cardiomyopathy but no AF. A locus was mapped to chromosome 6q14-16, but the causative gene has not been identified yet. Both the locus found by Brugada et al. [20] and this locus [22] overlap with known loci for familial autosomal dominant dilated cardiomyopathy on chromosome 10q21-23 and 6q12-q16 [10,11,23]. Whether indeed in this family there is a relation between AF and cardiomyopathy remains to be investigated.

In 2003 Chen et al. [24] published data of a large Chinese family with autosomally inherited lone AF (Table 1). AF was permanent in all patients. The causative mutation (S140G) was located in the KCNQ1 gene on chromosome 11p15.5. The KCNQ1 gene encodes the pore-forming α subunit of the cardiac IKs potassium channel (KCNQ1/KCNE1) and the KCNQ1/KCNE2, KCNQ1/KCNE3, KCNQ1/KCNE4 [25] and the KCNQ1/KCNE5 potassium channels [26]. Functional analysis of this mutation revealed a gain-of-function effect on the KCNQ1/KCNE1 and the KCNQ1/KCNE2 currents, thereby reducing the action potential duration and the effective refractory period in atrial myocytes, which in turn may set the stage for initiation and maintenance of AF. Although IKs and KCNQ1/KCNE2 are also expressed in the ventricle, the QT interval in the affected AF individuals was prolonged rather than shortened (in 9 of 16 patients the QT interval was between 460 and 530 ms). The clinical importance of this mutation may be limited since it could not be confirmed in 6 additional Chinese families nor in an unselected group of AF patients in the United States of America (largely of Northern European descent) [27].

The same group [28] also identified a mutation (R27C) of the KCNE2 gene in 2 Chinese families with lone AF (Table 1). The KCNE gene family encodes small proteins that function as β-subunits of several voltage-gated cation channels [29]. KCNE2 is the β subunit of the KCNQ1–KCNE2 channel, which produces a background potassium current. The age at diagnosis was older than observed in the families with the KCNQ1 mutation, between 40 and 60 years. Most patients had symptomatic paroxysmal AF and also frequent premature atrial complexes. Left atrial size and left ventricular ejection fraction were within normal limits. Functional analyses also revealed a gain-of-function effect resulting in both inward and outward KCNQ1–KCNE2 potassium currents leading to a shortening of the action potential duration, which again may trigger and perpetuate AF.

Recently, a locus on chromosome 5p13 has been identified in autosomally recessively inherited AF [30]. The affected children showed a rapidly progressive disease: AF with early onset at the fetal stage, neonatal sudden death, ventricular arrhythmias and cardiomyopathy (Table 1). The heterozygous parents, all without AF, could be identified by a broad P wave on the electrocardiogram. Whether this disease is caused primarily by AF or, more likely, by an underlying cardiomyopathy remains to be determined.

Table 1

<table>
<thead>
<tr>
<th>Genotype and phenotype of AF</th>
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**Monogenic forms of lone AF**

**Autosomal dominant**

1. No locus and gene identified
   - FAF 1–3 [8]
     - PAF 38–51 ? High Symp n=2 No Normal ? ?
   - FAF 4 [8]
     - PAF 37 ? Slow Asymp No No Too long in 2 ? ?

2. Locus identified
   - 10 q22-24 [20]
     - FAF 1
       - CAF, (PAF) 18 Cauc NA Asymp No No NA ? ?
     - FAF 2–3
       - CAF 2–46 Cauc NA Asymp No No NA ? ?
     - 6q14-16 [22]
       - PAF, laterCAF 21–72 Cauc NA NA No* No NA ? ?

3. Gene identified
   - KCNQ1 [24]
     - CAF >5 Chinese NA NA NA No 50% long No Yes (IKs up)
   - KCNE2 [28]
     - PAF >40 Chinese 118–138 Symp No No Normal No Yes

**Autosomal recessive**

1. Locus identified
   - Sp13 [30]**
     - CAF Young Chinese High Symp Some No Normal ? ?

**Polymorphisms associated with AF and concomitant underlying heart disease**

<table>
<thead>
<tr>
<th>Gene/ chromosome</th>
<th>Family</th>
<th>Type AF</th>
<th>Age</th>
<th>Race</th>
<th>HR</th>
<th>(A)symp</th>
<th>TCM</th>
<th>UHD</th>
<th>QTc (ms)</th>
<th>Trigger</th>
<th>Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>38G KCNE1 [31]</td>
<td>108#</td>
<td>CAF</td>
<td>63</td>
<td>Chinese</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>?</td>
<td>Possible (IKs)</td>
</tr>
<tr>
<td>-44AA connexin40</td>
<td>30#</td>
<td>PAF</td>
<td>33</td>
<td>Cauc</td>
<td>NA</td>
<td>Symp</td>
<td>No</td>
<td>WPW</td>
<td>Normal</td>
<td>?</td>
<td>Possible</td>
</tr>
<tr>
<td>M235T, G-217A and G-6A angiotensinogen [34]</td>
<td>250#</td>
<td>CAF</td>
<td>68</td>
<td>Chinese</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>?</td>
<td>Possible</td>
</tr>
</tbody>
</table>

AF=atrial fibrillation; (A)symp=(a)symptomatic; CAF=chronic/permanent AF; Cauc=caucasian; FAF=familial AF; NA=not available; PAF=paroxysmal AF; TCM=tachycardia induced cardiomyopathy; UHD=underlying heart disease; WPW=Wolff–Parkinson–White syndrome; ?: unknown; *1 patient had a reversible tachycardiomyopathy, 1 carrier had peripartum cardiomyopathy but no AF; **: multiple sudden deaths occurred at very young age; and #: no families but subjects.
4. Atrial fibrillation with structural heart disease

AF predominantly occurs in the setting of structural (heart) diseases, in particular, hypertension, coronary artery disease and heart failure. Familial occurrence in these patients is uncertain. However, it is conceivable that genetic differences may also contribute to this more common form of AF since, e.g. in the setting of heart failure, some will suffer repeatedly from AF, while others will never do. This is also suggested by recent data. Fox et al. demonstrated that parental AF not only increases the risk for offspring AF in lone AF but also in the more common forms of AF in the setting of structural diseases [7]. In a cohort study within the Framingham Heart Study, they found that 681 out of 2243 persons (30%) had at least one parent with documented AF. During follow-up, 70 of these 681 persons (10%) developed AF. If AF was present in at least one parent, the risk of offspring AF increased by 1.85 (95% confidence interval 1.12–3.06, \( p = 0.02 \)) when compared with no parental AF. As expected, the results were stronger if only younger parents and offspring (<75 year) without a previous myocardial infarction, heart failure, or valve disease were assessed (odds ratio 3.17, 95% confidence interval 1.71–5.86, \( p < 0.001 \)).

The polymorphisms described below have been associated with the more common forms of AF, i.e. AF occurring in the presence of risk factors for AF.

4.1. Polymorphisms associated with AF in the presence of precipitating factors

Lai et al. performed a case control study in 108 consecutive non-familial AF patients from Taiwan with any underlying disease but excluding patients with hyperthyroidism [31]. Mean age was 63 years and a history of hypertension was present in 52% of the patients. More than 80% of the patients had permanent AF (Table 1). Matching was performed regarding sex, age, left ventricular dysfunction and valvular disease. An association between the KCNE1 (encoding the \( \beta \)-subunit of \( I_{Ks} \), potassium channel) 38G allele and AF was observed. The odds ratios for AF in patients with 1 and 2 KCNE1 38G alleles were 2.16 (95% confidence interval 0.81–5.74) and 3.58 (95% confidence interval 1.38–9.27), respectively, compared to patients without the KCNE1 38G allele. Unfortunately, the functional significance of this polymorphism was not investigated.

Firouzi et al. reported evidence that a connexin40 gene promoter polymorphism (-44AA genotype) is linked to enhanced atrial vulnerability as measured by an increased coefficient of dispersion, defined as the standard deviation of all local mean fibrillatory intervals expressed as a percentage of the overall mean fibrillatory interval, in 30 unrelated adults. On the basis of previous work, they defined a coefficient of dispersion of a value >3 to be associated with enhanced spatial dispersion of atrial refractoriness. These patients had no structural heart disease and underwent an electrophysiological study because of the presence of an accessory pathway (\( n = 27 \)) or atrioventricular nodal reentrant tachycardias (\( n = 3 \)). Of these subjects, 14 had prior documented sporadic episodes of AF and 16 had no history of AF. The AF patients suffered a mean of 1 (range 1–5) previous episodes of AF with a median duration of 1 h (range 15 min to 3 h). The AF free interval before the study was 148 days (range 9–365 days). The prevalence of the minor Cx40 allele (-44A) and -44AA genotype was significantly higher in subjects with increased dispersion (\( n = 13 \)) compared to patients with a normal coefficient of dispersion (\( n = 17 \), \( p = 0.00046 \) and \( p = 0.025 \), odds ratio 6.7 and 7.4, respectively). Subjects with the -44AA genotype had a significantly higher coefficient of dispersion compared with those with the -44GG genotype. Finally, all subjects with an increased dispersion had a history of AF compared with only 1 subject with a normal coefficient of dispersion. The mechanism is at present unknown. It may be surmised that an abnormal gap junction distribution may cause abnormal conduction with increased anisotropy. By creating a substrate, this may result in an increased propensity for AF.

Tsai et al. [34] investigated several gene polymorphisms of the renin angiotensin system in 250 patients with non-familial AF in the setting of underlying heart diseases and 250 matched controls. They observed, comparable to the data of Yamashita, no association between the angiotensin-converting enzyme gene insertion/deletion polymorphisms and AF.

In a case control study Yamashita et al. [33] could not demonstrate a significant association between angiotensin-converting enzyme gene insertion/deletion polymorphisms and AF.

The above observations in ageing patients with non-familial AF in the presence of underlying heart diseases suggest some form of genetic control in the pathogenesis of the more common form of AF. Obviously, these data are promising and may help to clarify why some people develop AF while others will never do. Furthermore, the data of Tsai et al. might explain why drugs that affect the renin angiotensin system may have beneficial effects on the prevention of AF [35].

5. Conclusion

Familial AF is clinically and genetically heterogeneous and seems more common than previously suspected. Proper
identification of the phenotype of patients with AF is of utmost importance. Different phenotypes may point to distinct mechanisms and genes underlying familial AF. Genetic heterogeneity and a relatively low genetic yield until now hampers extensive genetic evaluation in clinical practice.

References