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SUPPLEMENT PAPER

Role of genetics in atrial fibrillation management

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Abstract Atrial fibrillation (AF) management has significantly improved during the career of professor Crijns. Research was implemented into guidelines and clinical practice. However, despite advances in AF management, large differences between individual treatment responses still exist and the mechanisms underlying initiation and perpetuation of AF are not completely understood. International collaborations have revealed the genetic contribution to AF and steps towards improving AF management are being made. In this short review, the most important paradigms shifts in the field of AF genetics are recognized and the future role of genetics in personalized management of AF is discussed.

Keywords Atrial fibrillation • Risk factors • Genetics • Treatment

Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia that increases the risk of serious adverse events, such as stroke, heart failure, cognitive impairment, and death.[1] Million of people worldwide are affected, and efforts have been made to optimize risk assessment and treatment strategies.[2] Over the past 33 years of professor Crijns' career as a cardiologist, the management of patients with AF has significantly improved with the implementation of research into guidelines and clinical practice. The list of risk factors for AF has increased significantly from advancing age, sex, hypertension, diabetes mellitus, heart failure, to others such as obesity, lifestyle, heart failure with preserved ejection fraction, and vascular disease. The prognosis of AF has seen improvements in the treatment with continuous anticoagulation, irrespective of the rhythm, and the development of the $CHADS_2$ and subsequent CHA_2DS_2-VASc scores to guide management decisions for anticoagulation.[3] Rate and rhythm control strategies were optimized to improve symptomatology, quality of life, and lower hospital visits.[2] However, despite these advances, the mechanisms underlying initiation and perpetuation of AF are still not completely understood. Further, the management of AF is far from optimal, and large differences between individual treatment responses exist. With these knowledge gaps in mind, in this short review, we summarize the most important paradigms in the field of AF genetics and focus on the future role of genetics in personalized management of AF (*Figure 1*).[4]

Paradigms in the recent past of atrial fibrillation genetics

The first paradigm—familial clustering of atrial fibrillation

The discovery of hereditary patterns of AF in families sparked the initial interest in AF genetics. One of the earliest genetic approaches applied to AF was linkage analyses in families. Linkage analyses take advantage of the tendency of a genetic marker to be inherited together with the disease-causing gene. Mutations can then be

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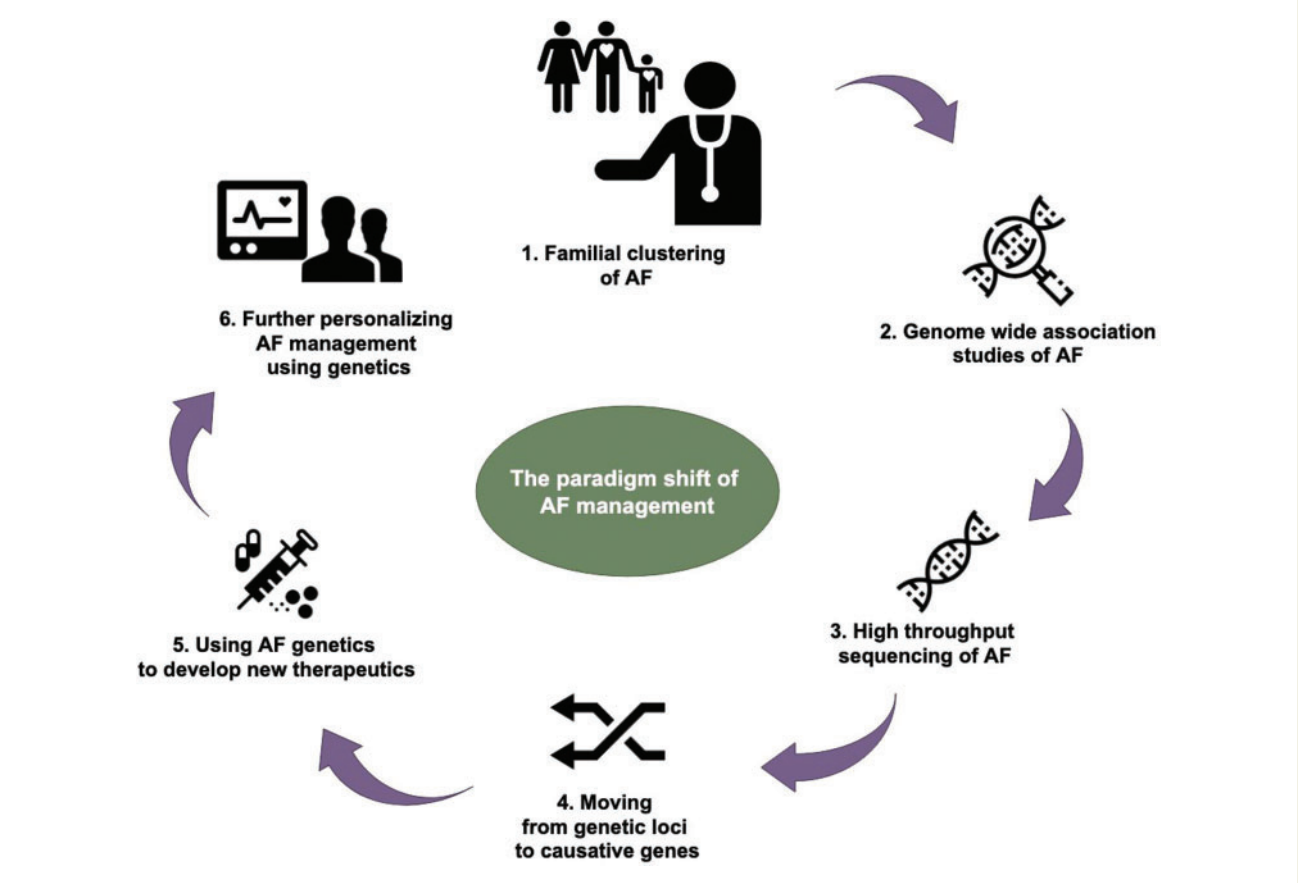

Figure 1 Central figure. Paradigms of AF genetics. AF, atrial fibrillation.

identified by sequencing the genes in the region of the genetic markers that track with disease. This approach identified AF-related mutations in ion channels.[5] More discoveries of familial mutations of AF followed, contributing to insights in the biology of AF. However, the sample sizes of families with AF are inherently small, and the identified mutations are limited in utility. These mutations are rare, and not linked to the development of AF in much more common, non-familial forms of AF.

The second paradigm—genome-wide association studies of atrial fibrillation

Data of the Framingham Heart Study, the Icelandic community-based cohort, and Danish twin studies strongly suggested that familial aggregation in common forms of AF reveals a genetic basis for the arrhythmia.[6–8] Recent advances in technology contributed to the rise of genome wide association studies (GWAS) that allow comparison of common genetic variants between large populations with and without AF. The novel approach of GWAS has led to an accelerated discovery of AF associated loci. In 2007, Gudbjartsson *et al.*[9] reported the first GWAS for AF that included a few hundred cases and discovered a genetic locus for AF on chromosome 4q25. *PITX2* was nearest gene in the region, and is known to be involved in embryonic development of the atria, sinus node, and left–right heart asymmetry. Genetic variants near *PITX2* have continued to be highly associated with AF in subsequent GWAS.[9,10] A second locus at the *ZFHX3* gene was identified in 2009 when GWAS data were expanded to a few thousand individuals with AF.[11,12] The *ZFHX3* locus encodes a transcription factor with unknown cardiac function but has been reported to interact with PITX2 and TBX5 increasing the risk of AF.[10,12] The third locus associated with AF, at the *KCNN3* gene, was discovered in 2010.[13] *KCNN3* is a calcium-gated potassium channel engaged in the process repolarization of the atria.

During the past decade, both the scale and the scope of the worldwide collaboration on AF genetics increased. This expansion has been facilitated by the international Atrial Fibrillation Genetics (AFGen) Consortium. From 2007 to 2018 available genetic data for AF increased from a few hundred to more than 65 000 individuals with AF.[14,15] As a result, there are currently more than 140 AF loci discovered by GWAS analyses, and an extensive description of AF GWAS analyses is provided in the review of Kalstø *et al.*[16]

Through international collaboration, current AF GWAS analyses provide more statistical power, and are able to reveal true genetic associations. The magnitude of recent GWAS analyses is close to identify most common genetic variants for AF in individuals from European descent.[17] However, still a large proportion of undiscovered genetic contribution to AF is estimated to contribute to heritability. Despite the current large-scale of AF GWAS analyses, the known genetic variants only account for about 40% of the estimated

heritability of AF.[18] Larger GWAS analyses in both European and non-European ancestry groups may reveal other loci associated with AF. Further missing heritability may be accounted by rare genetic variation, copy number variation, and other genetic mechanisms such as gene–gene interactions.

The third paradigm—high-throughput sequencing of atrial fibrillation

In contrast to GWAS, high-throughput exome and genome sequencing allow the identification of low-frequency genetic variants that can be associated with large effects on AF risk. One of the first high-throughput sequencing was performed in families. The elegant use of large-scale sequencing in the Icelandic population resulted in the discovery of a recessive frame shift mutation in MYL4 that increased the risk of AF.[19] MYL4 or myosin light chain 4 is highly expressed in the atria and loss of function variants likely result in atrial cardiomyopathy and subsequent AF.[20] In a recent study of 2781 individuals with AF development at an young age who had undergone whole-genome sequencing, an association was found in *TTN* with loss of function variants.[21] An exome sequencing data in nearly 50 000 individuals from the UK Biobank confirmed the association between *TTN* mutations and AF. The association between mutations in two sarcomeric proteins, *MYL4*, and *TTN*, suggests that AF sometimes may be considered an atrial cardiomyopathy in addition to the well-known associated ion channel deviations.[22] Future sequencing efforts will focus on considerably larger sample sizes and on populations of non-European ancestry to enhance to diversity and generalizability of these findings.

Paradigm shifts and the future of atrial fibrillation genetics

The scope and pace of AF genetics have been incredibly rapid and we currently have a solid understanding of the role of genetics in AF—at least in individuals of European descent. In the next decade, it will be critical to pivot from genetic discovery to translation of these findings into new molecular targets, treatment outcomes, and personalized therapies (*Figure 2*).

The fourth paradigm—moving from genetic loci to causative genes

A current challenge of GWAS is that the pace of genetic discovery has exceeded our capability to identify the causative genes. At many GWAS loci, there can be multiple potential candidate genes and deciphering which is causally related to AF is difficult. Genetic data have been combined with approaches such as expression quantitative trait loci (eQTL) mapping to discover the causative gene. In an eQTL analysis, a genetic variant is linked to expression of a gene in a relevant tissue such as the left atrium[23] or pulmonary veins.[24] Such an approach will identify a likely causative gene in ~25–30% of AF loci. A complimentary approach is to perform epigenetic analyses that focus on defining the three-dimensional architecture of the genome. Many AF genetic variants are in non-coding regions of the genome and likely regulate the expression of nearby genes. Epigenetic methods such as HiC, STARR-seq, and others can help to identify these three-dimensional interactions and lead to the identification of another

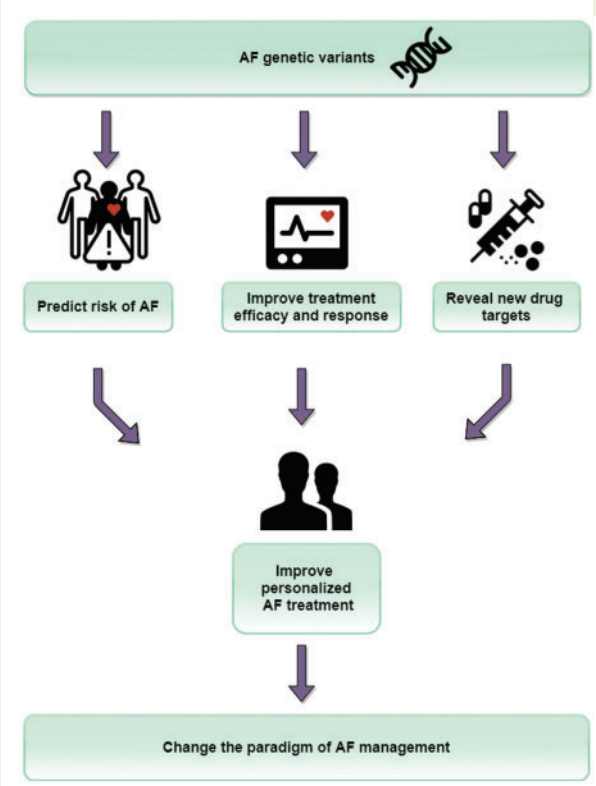

Figure 2 Atrial fibrillation genetic variants and AF management. AF, atrial fibrillation.

subset of causative AF genes.[25,26] Ultimately, given the sheer number of AF-related loci, it will be essential to develop high-throughput methods for identifying and characterizing these genes. Large-scale overexpression or gene knockout in stem cell-derived cardiomyocytes followed by an assessment of the resulting electrical and structural effects may be one approach to consider for gene prioritization.

The fifth paradigm—using atrial fibrillation genetics to develop new therapeutics

Despite considerable progress in our understanding of clinical risk factors, anticoagulation treatment algorithms, catheter ablation, and genetics, progress has been quite limited on the development of new antiarrhythmic medications to treat AF. While the causes are multifactorial, it is sobering that the traditional modalities of antiarrhythmic drug development seldomly lead to market approval in Europe. Interestingly, during this same time frame, it has become increasingly clear that therapeutic targets with genetic support in humans have a greater chance of ultimately making it to market.

One interesting application of this approach arose from the recent manuscript by Nielsen and colleagues. Out of 151 candidate genes for AF, they suggested 475 potential AF treatment targets, including 78 potential targets that are drugs that may control or trigger AF or other arrhythmias.[27] Some current antiarrhythmic medications are already targeting AF loci. For example, the *SCN5A* gene associated

with the sodium channel and the target for flecainide and propafenone.[28,29] *KCNH2* is associated with the alpha subunit of a potassium channel complex and is a target for sotalol and dofetilide.[14] While more refinement of this approach will be necessary, the conceptual model is interesting we anticipate that using the genetically driven therapeutic targets will be a promising avenue for future drug development.[30]

The sixth paradigm—further personalizing atrial fibrillation management using genetics

Current AF management guidelines emphasize the importance of implementing personalized treatment in clinical practice.[2] The heterogeneous nature of AF requires that physicians treat each patient according to their own risk profile.[31–33] However, patients may also present without clinical risk factors, and still develop AF. Prior studies show that a lower clinical risk profile is associated with higher AF genetic susceptibility.[34,35] Thus, genetics contributes more to the risk of developing AF in young individuals than in the older patients with more comorbidities. A powerful method for assessing this genetic susceptibility is to calculate a polygenic risk score that combines the AF risk variants present in an individual patient. In the future, it is highly likely that we will all be genotyped for common genetic variants, an approach that would enable the calculation of genetic risk for a range of complex diseases. For AF one could envision using polygenic risk to identify individuals at high risk for a stroke to guide screening for AF or after a cryptogenic stroke to help guide therapy. While these approaches are still too premature to implement in daily clinical practice, there have been some interesting recent studies exploring the clinical applications of AF genetics. Other explorations to include genetics into AF management are among others assessing outcomes of AF ablation based on genetic risk profile,[34] or genetic variant modulating pharmacodynamics relevant to AF such as has been observed with clopidogrel in the treatment of myocardial infarction.[36]

Conclusions

In the past two decades, the genetic contribution to AF has been recognized and steps towards improving AF management have been made through international collaborations. Techniques such as GWAS, high-throughput sequencing, eQTL, and epigenetic analyses have provided a new foundation for drug development but also highlights the limitations of our understanding of the molecular mechanisms of AF. Implementation of AF genetics in the daily clinical routine is therefore still some steps away, but the paradigm of AF management is shifting.

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Data availability

There are no new data associated with this article.

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