Cardiovascular Research (2011) **89**, 701–709
doi:10.1093/cvr/cvr001

SPOTLIGHT REVIEW

Genome-wide association studies of atrial fibrillation: past, present, and future

Moritz F. Sinner[1,2,3], Patrick T. Ellinor[2,4], Thomas Meitinger[5,6], Emelia J. Benjamin[3,7,8], and Stefan Kääb[1]*

[1]Department of Medicine I, University Hospital Munich, Campus Grosshadern, Marchioninistrasse 15, 81377 Munich, Germany; [2]Cardiovascular Research Center, Massachusetts General Hospital, Charlestown, MA, USA; [3]National Heart, Lung, and Blood Institute's and Boston University's Framingham Heart Study, Framingham, MA, USA; [4]Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA, USA; [5]Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; [6]Institute of Human Genetics, Klinikum rechts der Isar, Technische Universität Munich, Munich, Germany; [7]Department of Epidemiology, School of Public Health, Boston University, Boston, MA, USA; and [8]Cardiology and Preventive Medicine Sections, Evans Department of Medicine, Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA, USA

Received 20 September 2010; revised 27 December 2010; accepted 4 January 2011; online publish-ahead-of-print 18 January 2011

Abstract Genome-wide association studies (GWAS) for atrial fibrillation (AF) have identified three distinct genetic loci on chromosomes 1q21, 4q25, and 16q22 that are associated with the arrhythmia. Susceptibility loci also have been identified by GWAS for PR interval duration, a quantitative phenotype related to AF. In this review article, we have sought to summarize the latest findings for population-based genetic studies of AF, to highlight ongoing functional studies, and to explore the future directions of genetic research on AF.

Keywords Atrial fibrillation • Genetics • Genome-wide association study • Single nucleotide polymorphism • Arrhythmia

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

1. Introduction

Atrial fibrillation (AF) is a common condition and numerous, well-established risk factors have been described, including advancing age, male sex, hypertension, obesity, ischaemic heart disease, myocardial infarction, valvular diseases, and hyperthyroidism.[1–3] In addition, for many forms of AF a heritable, genetic component has been demonstrated. In the recent past, several genome-wide association studies (GWAS) have been published reporting chromosomal loci in association with AF, but these studies have not yet succeeded to explain the heritable fraction of the disease. With this review, we aim to provide a comprehensive overview of how the genetics of AF so far has been addressed by GWAS. Further, we will address the present challenges and future opportunities on the way to elucidate the missing heritability, the heritable component of AF that has not yet been clarified sufficiently by present GWAS designs.

2. Heritability of AF

The first description of familial clustering of AF dates back to the 1940s.[4] Since then, there have been a number of reports of AF inherited as a rare, familial Mendelian disorder (please see accompanying review article in this issue). More recently, several studies have examined AF in the community and found a familial predisposition. It is only within the last decade that we have come to appreciate family history as a risk factor for common AF. Investigators from the Framingham Heart Study demonstrated that when at least one parent had AF, his/her offspring were at significantly increased risk of AF with an odds ratio (OR) 1.85 [95% confidence interval (CI) 1.12–3.06, $P = 0.02$].[5] Interestingly, this risk was further increased, when the respective parent developed AF before the age of 75 years (OR 3.23, 95% CI 1.87–5.58, $P < 0.001$). The findings in the Framingham Heart Study were corroborated by a study from Iceland, which demonstrated a similar pattern.[6] In the Iceland Study, the relative risk for AF was 1.77 if a first-degree relative had AF. When a first-degree relative was diagnosed with AF before the age of 60 years, the relative risk for AF was 4.67. With an almost five-fold increased risk for disease, this order of magnitude is comparable with the risk in type 2 diabetes in those with a family history of diabetes mellitus.[7] In 2009, the authors of a Danish Twin Registry study found that the concordance rate of AF was higher among monozygotic ($n = 356$) compared with dizygotic ($n = 781$) twins (22.0 vs. 11.6%, $P < 0.0001$). They estimated the heritability of AF at 62%.[8]

3. Genome-wide association studies

GWAS have been conducted on a wide variety of diseases and intermediate traits. A recent review article that has since been

* Corresponding author. Tel: +49 89 7095 3060; fax: +49 89 7095 6076, Email: skaab@med.lmu.de

continuously updated in an online catalogue lists 904 investigations that studied 165 different conditions and reported hundreds of associated common variants, although most of them with very moderate effects on the phenotypes under investigation (*Figure 1*).[9,10] A reliable identification of such common risk variants was only possible after several principles were observed. The first principle applies to the sample size of a study. The effect sizes conferred by common genetic variants are typically small (median OR for one risk allele under an additive genetic model: 1.33, inter-quartile range 1.20–1.61).[11] Thus in most examples, only a large sample size yields sufficient statistical power to identify true associations.[12,13] If an adequate number of subjects cannot be acquired by a single study, a pooled analysis of the results from several studies may become necessary. The second principle in GWAS analysis is the application of rigorous statistical methods. Owing to the large number of variants tested—current genotyping platforms require several hundreds of thousands, often millions of statistical tests in a single experiment—the detection of false-positive associations becomes the rule. To avoid such spurious findings, adjustment for multiple comparisons is needed. Current standards accept significance of findings at a *P*-value of $\leq 5 \times 10^{-8}$, commonly referred to as the threshold for genome-wide significance. Apart from sound statistical methods, high-quality control standards are required to assure genotyping accuracy. Such quality control standards include high call rates, assessment of Hardy–Weinberg equilibrium, or population substructure. A third principle in the conduct of GWAS is the replication of initial significant findings in independent studies.[14,15] Using a two-stage study design, associated genetic variants, mostly single nucleotide polymorphisms (SNPs), are carried over to the replication stage, if they showed evidence of association at the GWAS level. Following a first replication stage—further rounds of replication may follow—the SNP-phenotype association becomes more reliable the more data available from independent replications. But even after careful application of the mentioned guidelines, false-positive findings may remain. Therefore, ultimately functional validation is required.

Despite high heritability estimates of a variety of phenotypes, GWAS published to date have left us with a sizeable gap in explaining the genetic contribution to variation in quantitative traits and disease. All the variants detected so far account only for a small fraction of the variance observed, often less than 1%.[16] Given the often very small effects sizes of common variants and the limit of less than 100 000 functional loci in the genome, common variants and current methodology alone will not be able to explain current high heritability estimates.[17] Another, more promising hypothesis is that the missing heritability, which is not explained by common SNPs, can be attributed to less common variants.[18] The issue of missing heritability will be

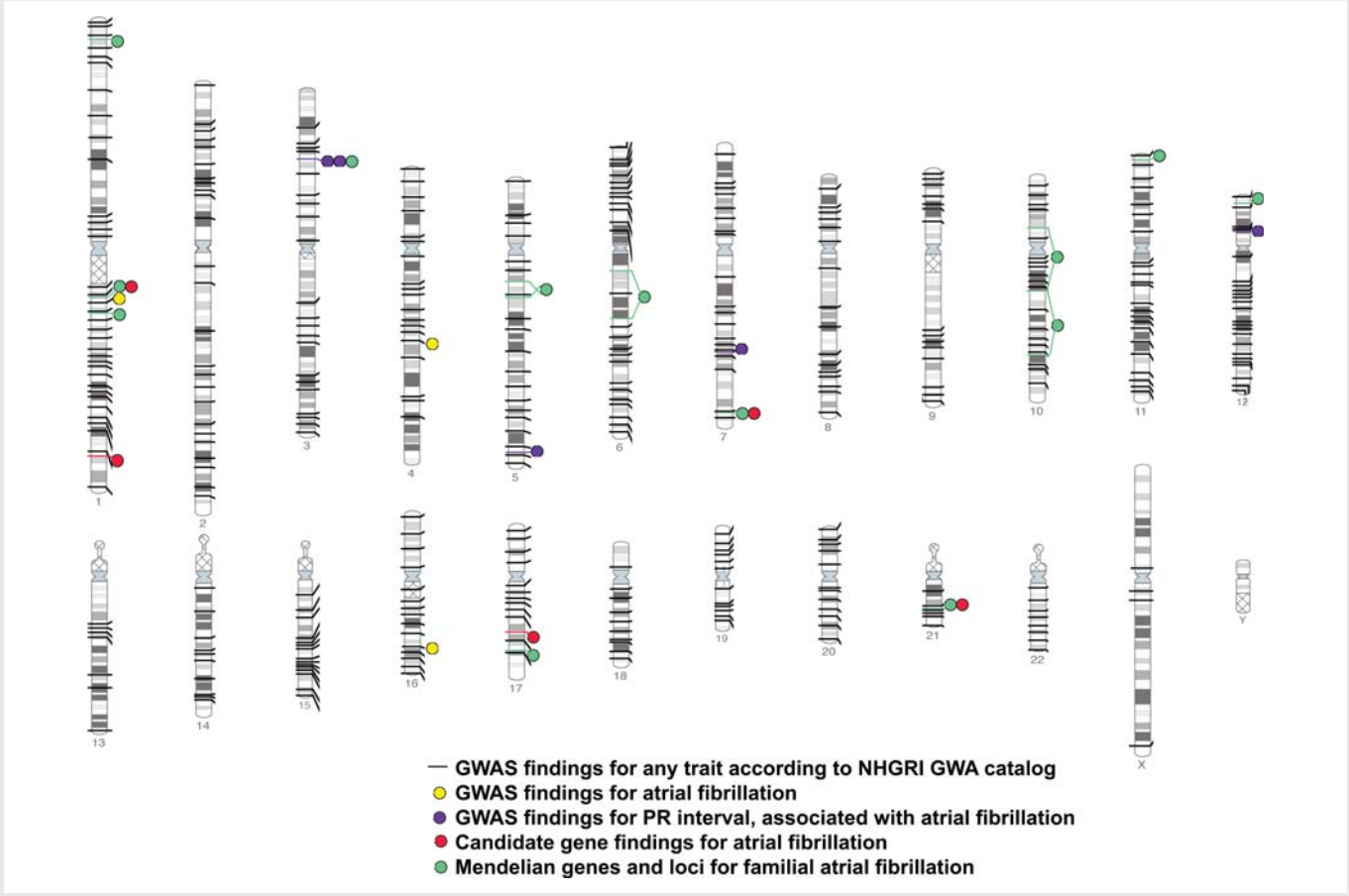

Figure 1 Genes and genetic loci associated with AF. The 22 human autosomes and the 2 sex chromosomes are displayed. Black marker-lines in chromosomes highlight, where GWAS for any trait have reported significant findings. GWAS findings for AF are highlighted (yellow), as well are GWAS findings for the PR interval, where association with AF could be established (blue). Replicated findings for candidate-gene based association studies are depicted in red, and genes and loci for Mendelian forms of AF are in green. Adapted with permission from the National Human Genome Research Institute GWA catalog at www.genome.gov/GWAStudies.[9,10]

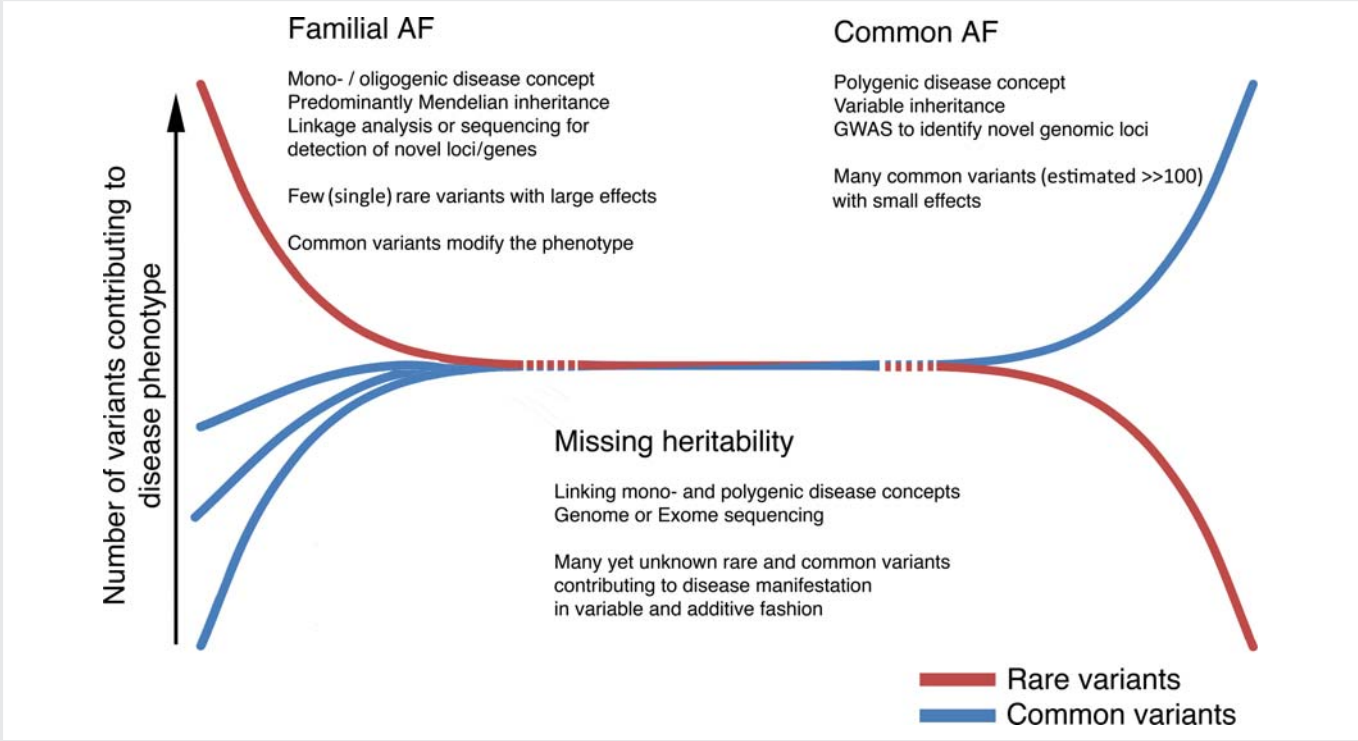

Figure 2 GWAS, Mendelian families, and the missing heritability of AF. The figure illustrates three situations typically encountered in current genetic studies. The blue and red lines symbolize the number of rare and common variants contributing to a trait's heritability. High-frequency variants that usually confer only small effect sizes can be identified by GWAS; low-frequency variants often exert strong effects and are detected by sequencing. The missing heritability can primarily be found in the middle, where many variants with intermediate frequency explain the phenotypic variability. Such variants cannot be reliably detected with current techniques. In GWAS situations, undetected rare variants account for missing heritability; in Mendelian AF situations, rare variants patterns are modified by common variants.

of major importance in the future of complex genetics and will be discussed later in this article (*Figure 2*).

4. Genome-wide association studies in AF

In 2007, the first GWAS for AF in subjects of European descent was reported by investigators from Iceland.[19] Two SNPs on chromosome 4q25 were found that were strongly associated with AF. The authors subsequently replicated these findings in two additional European cohorts with an overall total of 3580 AF cases and 19 256 control subjects. SNP rs2200733 showed the strongest association and conferred an OR of 1.72 (95% CI 1.59–1.86, $P = 3.3 \times 10^{-41}$). In the same report, the investigators also replicated this association in a cohort of Chinese descent from Hong Kong (333 AF cases, 2836 controls, OR 1.42, 95% CI 1.16–1.73, $P = 6.4 \times 10^{-4}$). The second SNP, rs10033464, reached genome-wide significance in European subjects (OR 1.39, 95% CI 1.29–1.53, $P = 6.93 \times 10^{-11}$), but failed to replicate in the Chinese subset. Thus, these findings need to be interpreted with caution. Reasons might include differences in allele frequencies, the ethnic background or population stratification.

Following this initial report, several research groups provided independent replication analyses. One large study combined two community-based studies and two case-control cohorts from Europe and the USA, for a total of 3508 AF cases and 12 173 referent subjects.[20] The community-based studies followed their cohort and included those subjects as cases that developed AF during the cohort study's follow-up (incident AF). In the case–control studies, patients with prevalent AF were collected in the community or in hospital-based studies and then compared with disease-free controls. The association with rs2200733 was consistently replicated in all four cohorts; however, rs10033464 was not replicated in two of the studies. It was interesting to note that in both the Icelandic study and the European/US replication consortium, the effect size of the association with the strongest hit, rs2200733, appeared higher in younger individuals.[19,20]

Further replication between the 4q25 locus and AF also was demonstrated in a small study from Italy,[21] and one in Han Chinese patients.[22] Another report investigated the relationship between rs2200733 and AF in post-operative patients, who underwent coronary artery bypass graft surgery, and found a significant association.[23] In subsequent, large GWAS in which several other loci for AF were identified, the association with 4q25 remained consistently the strongest finding.[24,25] Finally, in a recent meta-analysis that included 10 115 AF cases and 65 229 control subjects the minor T allele of rs2200733 had an overall OR of 1.68 (95% CI 1.50–1.87, $P = 7.0 \times 10^{-20}$) (*Table 1*, *Figure 1*).[26]

A recent fine-mapping analysis of 4q25 identified two additional, independent association signals for AF at this locus. When the original SNP associated with AF and these two novel SNPs were considered in combination a stepwise increased risk was detected. For the

Table 1 AF susceptibility loci suggested by GWAS

Locus	Study design[a]	SNP	Adjacent gene	OR	95% CI	*P*-value	Reference
Genome-wide significant loci							
1q21	AF	rs13376333	*KCNN3*	1.52	1.40–1.74	1.83×10^{-21}	25
4q25	AF	rs2200733	*PITX2*	1.72	1.59–1.86	3.3×10^{-41}	19
	AF	rs10033464	*PITX2*	1.39	1.26–1.53	6.9×10^{-11}	19
	AF	rs6843082	*PITX2*	2.03	1.79–2.30	2.5×10^{-28}	25
	AF	rs17042171	*PITX2*	1.65	1.55–1.75	3.9×10^{-63}	24
	Fine-mapping	rs17570669	*PITX2*	0.71	0.61–0.84	4.3×10^{-5}	27
	Fine-mapping	rs3853445	*PITX2*	0.78	0.71–0.87	1.8×10^{-6}	27
16q22	AF	rs2106261	*ZFHX3*	1.25	1.19–1.33	1.8×10^{-15}	24
	AF	rs7193343	*ZFHX3*	1.21	1.14–1.29	1.4×10^{-10}	29
Endophenotype PR GWAS, subsequently associated with AF							
3p22	PR	rs11708996	*SCN5A*	0.90	0.84–0.96	7.0×10^{-4}	38
3p22	PR	rs6800541	*SCN10A*	0.92	0.88–0.96	1.5×10^{-4}	38
5q35	PR	rs251253	*NKX2.5*	1.07	1.03–1.12	2.3×10^{-3}	38
7q31	PR	rs3807989	*CAV1/CAV2*	0.91	0.87–0.95	2.2×10^{-5}	38
7q31	PR	rs3807989	*CAV1*	0.92	0.87–0.96	3.2×10^{-4}	39
12p12	PR	rs11047543	*SOX5*	1.13	1.06–1.20	2.1×10^{-4}	38
12q24	PR	rs3825214	*TBX5*	0.88	0.83–0.94	4.0×10^{-5}	39

Overview of the genetic associations with AF to date.
[a]Design of the study included: AF: GWAS using AF as primary phenotype; PR: GWAS using the PR interval as primary phenotype; Fine-mapping: In-depth analysis of findings at the 4q25 locus after adjustment for rs2200733 findings by the means of conditional analysis. The SNP rs-number is the most significantly associated variant in each study. The gene is the closest and/or presumably most relevant one.

combination of six risk alleles, present in ~1% of cases, the OR was 6.02 (95% CI 4.56–7.96, $P = 1.2 \times 10^{-36}$) (*Figure 3*).[27] The mechanism by which SNPs at this locus lead to AF is currently unknown, but an adjacent transcription factor gene could be considered an intriguing candidate.

After the initial AF-GWAS, large consortia have formed to increase the statistical power and to further dissect the genetic architecture of AF. One such effort is in the CHARGE-AF consortium or the 'Cohorts for Heart and Aging Research in Genomic Epidemiology'.[28] A recent meta-analysis of GWAS for AF in the CHARGE-AF consortium encompassed 5558 AF cases and 41 178 control subjects. The strongest association signal was found with the previously reported 4q25 locus. However, a new susceptibility locus for AF was identified with rs2106261 on chromosome 16q22 (overall relative risk 1.25, $P = 1.8 \times 10^{-15}$). A parallel endeavour by investigators from Iceland identified rs7193343, a SNP located adjacent to rs2106261, with an OR of 1.21 (95% CI 1.14–1.29, $P = 1.4 \times 10^{-10}$).[29] Both variants are in strong linkage disequilibrium with each other ($r^2 = 0.78$, HapMap 3, CEU panel) (*Table 1*, *Figure 1*). The Icelandic investigators attempted to replicate the finding in a cohort of Chinese descent, but the association did not reach significance.[29] In the study by the CHARGE consortium, a second locus on chromosome 1p36 appeared promising, but failed to reach significance at the replication stage.[24]

A third GWAS focused on patients who developed AF at younger ages and in the absence of overt structural heart disease, such as valve disease, ischaemic heart disease, and dilative or hypertrophic cardiomyopathy.[25] With the exception of this GWAS on early-onset AF, the previous GWAS had included all patients with AF irrespective of possible accompanying diseases, although some studies excluded patients who developed AF in the context of coronary artery bypass graft surgery. The early-onset AF investigation was driven by the notion that patients, who develop AF in the absence of major non-genetic risk factors, might have a different underlying genetic structure for the arrhythmia. Such a phenotype of early-onset AF in the absence of other risk factors has been referred to as lone AF. Owing to the high population prevalence of arterial hypertension, patients with this condition were not excluded, but analyses were adjusted accordingly. In a study comprising 1335 early-onset AF patients and 12 844 control subjects, SNP rs13376333 at chromosome 1q21 marked a third susceptibility locus for AF that was independently replicated and reached genome-wide significance. The overall OR was 1.52 (95% CI 1.40–1.64, $P = 1.83 \times 10^{-21}$) (*Table 1*, *Figure 1*).

A complementary GWAS approach used the PR interval duration as an endophenotype for AF. The PR interval is a quantitatively measurable signature on the surface electrocardiogram. It is considered a marker for atrial and atrioventricular conduction.[30] Prolongation of the PR interval has been demonstrated to be a predictor for increased AF risk.[31,32] In a risk score for AF developed at the Framingham Heart Study, PR prolongation remained a significant risk factor for AF even after adjustment in an extensive multivariable model.[33] For the PR interval, comparable with other electrocardiographic traits, heritability has been reported in the range of 30–50%.[34–37] In a GWAS investigating the PR interval, a total of nine distinct genetic signals reached genome-wide significance.[38] Five of these nine loci showed significant association with AF using 5741 cases and 41 342 controls (adjacent, but speculative candidate genes are *SCN5A*, *SCN10A*, *NKX2.5*, *CAV1/CAV2* and *SOX5*). Also a parallel investigation performed in Iceland identified two genetic loci associated with the PR interval and AF

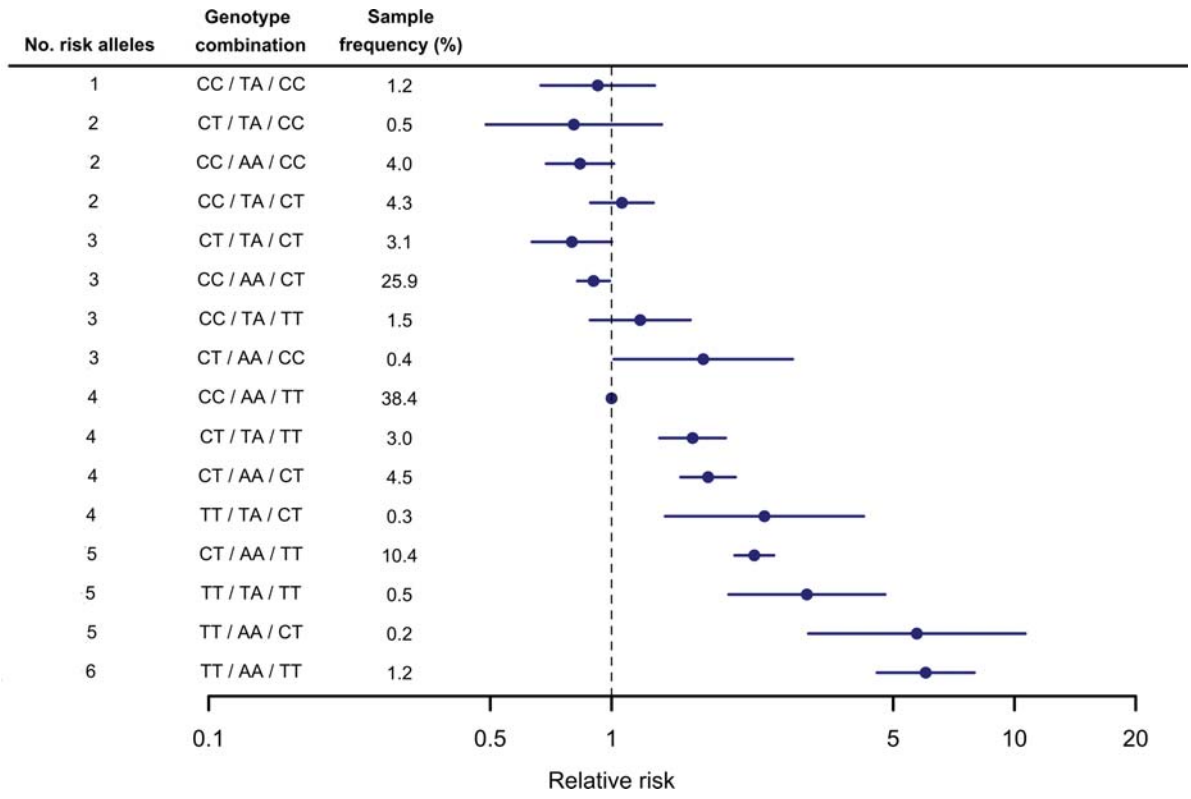

Figure 3 Multiple susceptibility loci on chromosome 4q25 associated with AF. A combination of three SNPs, rs2200733, rs7570669, and rs3853445, at the 4q25 locus for AF are associated with an increased risk of the arrhythmia. The most common combination (four risk alleles) was considered the reference. A combination of six risk alleles, although rare in the general population, confers the highest risk for AF [relative risk 6.02 (95% CI 4.56–7.96), *P*-value $P = 1.2 \times 10^{-36}$]. Reprinted with permission.[27]

(*Table 1*, *Figure 1*).[39] One of these two loci was identical between the GWAS (*CAV1/CAV2*), the other one was novel (*TBX5*). However, all of these associations with AF failed to reach genome-wide significance and thus have to be considered tentative until further evidence arises.

5. Insights into AF pathophysiology, inspired by genome-wide association studies

SNPs at three distinct genetic loci have been associated with AF by GWAS: 4q25, 16q22, and 1q21. In addition, there is evidence from GWAS on the PR interval, that six further loci might potentially be involved in AF. Since the underlying pathophysiology at these loci is unknown, the findings have catalysed the exploration of novel molecular pathways underlying AF.

At the chromosome 4q25 locus, rs2200733 and the related SNPs associated with AF are located in what is commonly called a 'genomic desert', or a large, intergenic region without any known genes. Whereas it might be that the effect is mediated through unresolved involvement of distant genes, the closest gene in the region is a promising candidate. The paired-like homeodomain 2 gene (*PITX2*) encodes a transcription factor, which is crucial during cardiac development. *PITX2c* is involved in the determination of cardiac right-left asymmetry.[40–42] Furthermore, *PITX2c* suppresses the formation of a left-atrial sinus node in development and is crucial for the formation of the pulmonary vein myocardium.[43,44] A recent report investigated Pitx2c knock-out mice by programmed stimulation and found that adult mice had higher rates of atrial arrhythmias. Microarray and *in situ* studies pointed to a direct involvement of Pitx2c with other genes that determine sino-atrial node formation.[45]

The role of *PITX2* in the development of the left atrium and pulmonary veins fits well with our understanding of the initiation in many cases of paroxysmal AF in which the arrhythmia is triggered by ectopic foci originating from pulmonary vein myocardial sleeves.[46] Such an observation has led to the increasingly frequent use of pulmonary vein isolation procedures in the treatment of AF.[47,48]

So far, data in humans involving *PITX2* or other genomic elements in the region are sparse. While mutations in *PITX2* have been described to cause syndromic Mendelian disorders,[49,50] no mutations in *PITX2* have been found in AF patients.[51] To assess the impact of SNPs at the 4q25 locus for AF on patient prognosis, Husser *et al.*[52] associated SNP risk alleles with increased recurrence of AF after pulmonary vein isolation. The relation between genetic findings and AF prognosis is a promising approach for future research. However, several methodological concerns arose with the study including the heterogeneous disease phenotype, small sample size, and the lack of independent replication.[53]

At the chromosome 16q22 locus, the SNPs most significantly associated with AF map to the first intron of a gene encoding the zinc finger homeobox 3 (*ZFHX3;* previously referred to as

AT-binding transcription factor 1, *ATBF1*).[24,29] The gene has not been implicated in cardiac pathophysiology or AF. The initial descriptions reported the gene to be an enhancer of human α-fetoprotein in the liver.[54,55] Furthermore, it was considered a tumour suppressor gene in several different types of cancer,[56,57] and a differentiation factor in neuronal tissue and skeletal muscle.[58,59] A recent GWAS on Kawasaki disease suggested an association with *ZFHX3*, but the association failed to reach genome-wide significance—possibly due to modest sample size.[29,60] ZFHX3 is expressed in mouse hearts,[61] and in several human tissues, including the heart, liver, lung, kidney, pituitary gland, and brain; in the recent Icelandic AF GWAS, however, an association between expression levels and the top SNP rs7193343 was not established.[29] Thus, relatively little is presently known about the functional link between *ZFHX3* and its role, if any, in AF.

The GWAS findings at the chromosome 1q21 locus appear to involve a more discernable mechanism related to AF. The most significantly associated SNP, rs13376333, maps to intron 1 of the *KCNN3* gene.[25] *KCNN3* is also known as SK3 or KCa2.3, and encodes a calcium-activated, small conductance potassium channel. The family of these channels has been demonstrated to be of importance in excitable tissue and expression has been shown in the brain[62] and heart.[63,64] After repetitive action potential stimulation in the brain, the intracellular calcium concentration increases and the channels become activated. The consequence is an influx of potassium, which leads to classical afterhyperpolarizations.[62] In the heart, the role of the *KCNN*-family is less clear. In a rabbit burst-pacing model, pharmacological blockage of the channels resulted in inhibited pacing-induced shortening of pulmonary venous and atrial action potential duration.[65] Such shortening of the atrial action potential duration leads to a reduced atrial myocyte refractory period, which predisposes to the development and maintenance of AF.[66] Despite this plausible explanation, the burst-pacing did not cause a detectable change in *KCNN3* expression. However, *KCNN2*, another member of the calcium-activated potassium channel family, showed increased expression levels.[65] The functional link might be co-assembly and heteromultimeric channel complexes of *KCNN2* and *KCNN3*.[67] This co-assembling might be of importance, because, when *KCNN2* was differentially expressed in mice, altered pacemaker cell action potential duration and spontaneous firing rates,[68] and increased blood pressure were observed.[69]

KCNN3 is an intriguing potential candidate to be causally involved in AF pathophysiology. As an ion channel in the heart, it could be a potential drug target and thus open up a new line of pharmacological AF therapy. Recently, it was shown in several animal models that the inhibition of channels in the SK-family helped to terminate AF and to protect against AF occurrence.[70]

In conclusion, there are at least three distinct genomic loci that have a strong association with AF. As expected for common genetic susceptibility markers, the risk conferred by any single one is small with ORs between 1.2 and 1.7. However, since all of these SNPs are relatively common in the population there are a large number of subjects who carry two risk alleles and some individuals have a marked increased risk of AF ranging from ~1.5 to 3 fold (equal to ORs 1.2^2–1.7^2). Although none of the molecular pathways through which these SNPs lead to AF have been definitively determined, the recent genetic findings provide a starting point for the dissection of these novel pathways related to AF.

6. Future implications of genome-wide association studies in AF

Although the recent GWAS findings have left us with promising novel molecular pathways for AF, the translation into clinical application has not yet happened. Over the next years, a wide variety of basic, genomic, and clinical studies are needed to translate genetic findings into clinical applications. Specific challenges include addressing the missing heritability of AF, determining the molecular mechanism through which the identified SNPs lead to AF, and relating these SNPs to AF risk prediction and clinical outcomes. So far, a measurable value of the genetic findings for AF risk prediction or medical care of AF patients has yet to be demonstrated.

6.1 What is next for genome-wide association studies of AF?

The most direct way to identify additional loci for AF is to simply increase the number of subjects studied. Another cardiovascular trait, the QT interval, is a good demonstration of this approach. An initial GWAS counting on 200 subjects at the extremes of the QT interval duration of a general population of 4000 individuals, only identified one locus around the gene *NOS1AP*.[71] In two independent follow-up studies of 13 685 and 15 842 subjects, 10 distinct susceptibility signals were identified.[72,73] Variants that are detected only in larger samples will typically be associated with smaller effect sizes. With a limited effect size, these SNPs may still provide useful information about molecular pathways leading to AF, but will be less likely to be useful for risk prediction or assessing clinical outcomes.[16,18]

Another extension of GWAS for AF is to dissect the genetic architecture at identified loci in more detail. The utility of this approach has been demonstrated at the 4q25 locus. As an example of the complexity of the genetics of common diseases, three independent signals were identified at the 4q25 locus after adjusting for the initial, genome-wide significant finding.[27] When combinations of these three independent signals were considered simultaneously, an increasing number of risk alleles accounted for an increased disease risk. Whereas one risk allele of the most significantly associated SNP rs2200733 conferred an OR of 1.8, a combination of six risk alleles increased the AF risk six-fold. Similarly, it is likely that there are additional, as yet unidentified signals, at the other reported loci for AF. As a consequence, it is very likely that a multitude rather than a low, circumscribed number of variants will finally explain a fraction of the heritability of AF. Future sequencing efforts at the 4q25 and other GWAS-loci for AF might help to identify even further independent signals, and bear the potential to detect the true functional variants rather than SNPs tagging it. The advancement of next-generation sequencing technologies will substantially improve the detection of rare and structural variation and thus further help to expedite the discovery of genetic factors.

Future studies also will likely be directed at GWAS for AF in diverse populations. To date, all GWAS for AF have been conducted in subjects of European descent. It remains unclear if AF in Africans and Asians has a similar or distinct aetiology for AF. Using the combined information from multiple ethnicities can be a powerful tool for narrowing genetic loci and identifying causative SNPs. Of major importance also will be the investigation of potentially distinct genetic

background in patients with underlying concomitant diseases, such as heart failure or hypertension. Such investigations could either be performed by studying AF in the context of the concomitant conditions, or by analysing the gene-environment interaction for AF. The latter option might be particularly suitable to investigate continuous environmental factors, such as age and sex.

6.2 What is the missing heritability of AF?

Despite the promising results from the GWAS of AF, a large percentage of the heritability of AF remains unexplained. Identification of the molecular basis for this 'missing heritability' will be an important challenge for understanding complex genetic traits, such as AF (*Figure 2*). It is a matter of debate, where and how the remaining variants can be found. One potential source for the missing heritability of AF lies in an unknown number of yet unidentified common variants. For the quantitative trait height, this number has estimated to be roughly 700.[74] Second potential sources are less common variants, which currently are not sufficiently covered by GWAS. It has been noted that there often is an inverse relation between the frequency of the variant and effect size; i.e. rare variants tend to have larger effect sizes and common variants often have small to modest effect sizes. The most probable scenario is that combinations of common and rare variants, in addition to other disease mechanisms, such as gene–gene and gene–environment interactions, copy-number polymorphisms, or DNA-methylation, add up to finally explain the heritability of AF.[16,18] Other potential mechanisms of disease include copy-number variation, inversions, deletions, insertions, or short tandem repeats. Currently, tools necessary to systematically identify these other forms of genetic variation are being developed. The application of new techniques like next generation sequencing will provide an important next step in our understanding of disease genetics, and it is anticipated that the costs for this technique will drop to a reasonable level in the near future. Apart from improving the tools to identify new variants, it also will be essential to advance analytical methods. Such improvements will have to include the optimization of genetic calling algorithms as well as a refinement of statistical methods. For instance, it will be of importance how to address problems arising from performing multiple comparisons when testing ever more variants.

6.3 How do the SNPs identified in genome-wide association studies lead to AF?

A considerable amount of future research will be directed at elucidating the functional pathways behind the association signals for AF. Quickly the focus of research will turn from statistical genetics back to laboratory-based approaches. Such research could include incorporation and subsequent expression of identified SNPs in cell-lines, knock-down of identified genes in model organisms and investigating electrophysiological alterations of mutated channel proteins.[75,76] Clarification of underlying pathways will help to identify the molecular pathways underlying AF. Since the phenotype of model organisms may not always be transferable to human AF directly, findings in models will have to be re-evaluated in humans. Success will ultimately open up the possibility to identify novel therapeutic targets for the arrhythmia.

6.4 How will these genetic findings influence patient care?

Ultimately, it will be essential to determine whether the GWAS findings for AF will remain a research tool or will translate into clinically useful information for AF risk prediction, assessment of outcomes, or response to therapies.

Initial attempts to relate genotypes to AF recurrence after pulmonary vein ablation procedures have shown a promising result,[52] but are likely premature.[53] Other avenues of exploration include response to genotype predicted drug therapy, and clinical outcomes of AF-related morbidities, such as stroke, heart failure, dementia, and death.

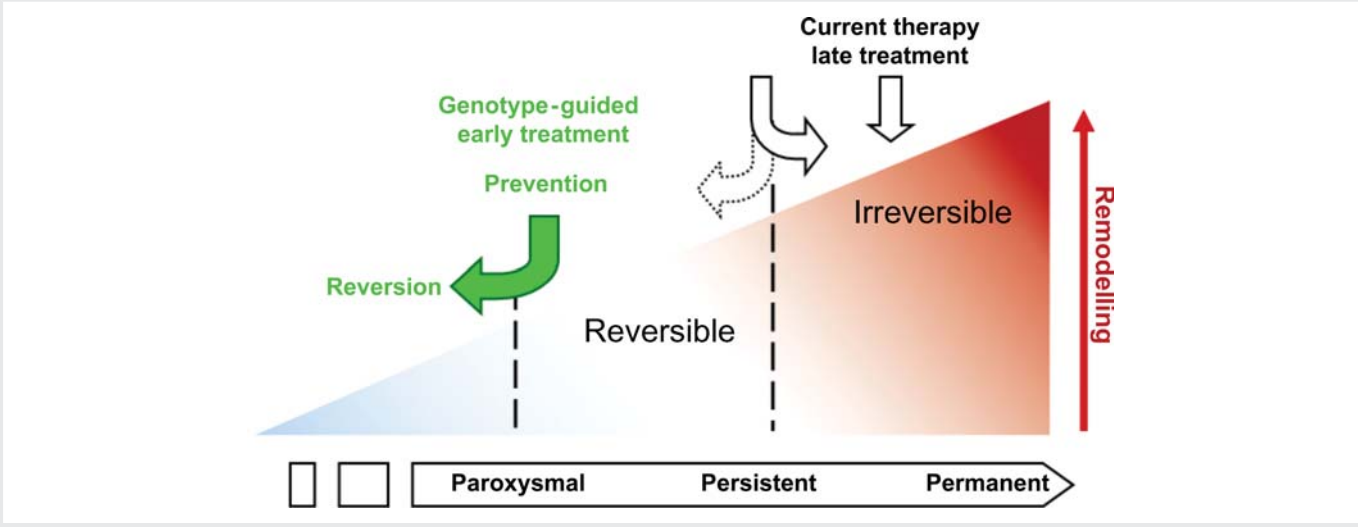

Figure 4 Schematic representation of the time-course of AF and potential opportunities for genotype guided therapies. Current pharmacological and procedural treatments for AF are initiated after the onset of the arrhythmia and in many cases after sustained periods of AF. Ultimately, genetic information may be useful in identifying high-risk patients, or those patients more likely to respond to currently therapies. An early, genotype-guided treatment might thus help to prevent or ameliorate progression of AF. In the transition from paroxysmal to persistent to permanent AF, many factors contribute. Hypertension, ischaemic heart disease, and heart failure contribute particularly to cardiac remodelling and thus to the transition of AF.

Similarly, it has to be determined whether AF risk prediction is improved by the incorporation of genetic findings.[33]

Genetic profiling may also help to more carefully ascertain AF subtypes including lone AF vs. more typical forms of the disease.[24,25] Other subtypes of AF, including paroxysmal, persistent, or permanent forms, may also have a distinct genetic background. As conceptualized in *Figure 4*, a genotype-based profile may ultimately allow for the identification and treatment of high-risk patients early in the disease when electrical and mechanical reverse remodelling is still possible. The importance of early treatment to prevent remodelling has been shown previously.[77] For example, identification of patients at high risk for the development of permanent AF may be treated with a genotype-guided early treatment in contrast to the current late diagnosis and treatment of AF, when cardiac remodelling is apparently irreversible.

7. Conclusion

In conclusion, AF is a heritable condition and at least three promising susceptibility loci have been identified by GWAS. While the ones near *PITX2* and *ZFHX3* suggest an involvement of developmental pathways in AF pathogenesis, *KCNN3* provides a mechanistic link between calcium handling, cellular electrophysiology, and AF. Despite the successful establishment of reliable associations, the identified signals explain only a small proportion of the heritability of AF. Future work will focus on larger-scale GWAS to identify more associated variants. GWAS, as well as new genotyping and imaging technologies and functional studies will help defining the mechanisms by which AF-associated SNPs lead to disease and how they ultimately relate genotypes to clinical outcomes and treatments.

Conflict of interest: none declared.

Funding

This work was supported by the National Institutes of Health (1R01HL092577 to E.J.B. and P.T.E.; 1RC1HL101056, 1R01HL102214 to E.J.B; 1R01HL104156, 5R21DA027021, 1K24HL105780 to P.T.E.); Bundesministerium für Bildung und Forschung BMBF (German Competence Network on AF AFNET 01 GI 0204/N, German National Genome Research Network NGFN 01GS0499, 01GS0838 to S.K.; Leducq Foundation (07-CVD 03 to E.J.B., P.T.E. and S.K.); LMU Excellence Initiative to S.K.; LMU Research grant (FöFoLe 557/569 to M.F.S.). M.F.S. is supported by the German Heart Foundation.

References

1. 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.
2. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV *et al.* Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;**285**:2370–2375.
3. 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.
4. Wolff L. Familial auricular fibrillation. *N Engl J Med* 1943;**229**:396–398.
5. Fox CS, Parise H, D'Agostino RB, 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.
6. 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.
7. Stolerman E, Florez JC. Genomics of type 2 diabetes mellitus: implications for the clinician. *Nat Rev Endocrinol* 2009;**5**:429–436.
8. Christophersen I, Ravn L, Budtz-Joergensen E, Skytthe A, Haunsoe S, Hastrup Svendsen J *et al.* Familial aggregation of atrial fibrillation—a study in Danish twins. *Circ: Arrhythm Electrophysiol* 2009;**2**:378–383.
9. Manolio TA. Genomewide association studies and assessment of the risk of disease. *N Engl J Med* 2010;**363**:166–176.
10. Hindorff LA, Junkins HA, Hall PN, Mehta JP, Manolio TA. A Catalog of Published Genome-Wide Association Studies. www.genome.gov/gwastudies. Published online ahead of print 4 January 2011.
11. Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS *et al.* Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc Natl Acad Sci USA* 2009;**106**:9362–9367.
12. Hunter DJ, Kraft P. Drinking from the fire hose—statistical issues in genomewide association studies. *N Engl J Med* 2007;**357**:436–439.
13. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. *J Natl Cancer Inst* 2004;**96**:434–442.
14. Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet* 2005;**6**:95–108.
15. Hunter DJ, Kraft P, Jacobs K, Cox DG, Yeager M, Hankinson SE *et al.* A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet* 2007;**39**:870–874.
16. Goldstein DB. Common genetic variation and human traits. *N Engl J Med* 2009;**360**:1696–1698.
17. Yang J, Benyamin B, Mcevoy B, Gordon S, Henders A, Nyholt D *et al.* Common SNPs explain a large proportion of the heritability for human height. *Nat Genet* 2010;**42**:565–569.
18. Gibson G. Hints of hidden heritability in GWAS. *Nat Genet* 2010;**42**:558–560.
19. 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.
20. Kääb S, Darbar D, van Noord C, Dupuis J, Pfeufer A, Newton-Cheh C *et al.* Large scale replication and meta-analysis of variants on chromosome 4q25 associated with atrial fibrillation. *Eur Heart J* 2009;**30**:813–819.
21. Viviani Anselmi C, Novelli V, Roncarati R, Malovini A, Bellazzi R, Bronzini R *et al.* Association of rs2200733 at 4q25 with atrial flutter/fibrillation diseases in an Italian population. *Heart* 2008;**94**:1394–1396.
22. Shi L, Li C, Wang C, Xia Y, Wu G, Wang F *et al.* Assessment of association of rs2200733 on chromosome 4q25 with atrial fibrillation and ischemic stroke in a Chinese Han population. *Hum Genet* 2009;**126**:843–849.
23. Body S, Collard C, Shernan S, Fox A, Liu K, Ritchie M *et al.* Variation in the 4q25 chromosomal locus predicts atrial fibrillation after coronary artery bypass graft surgery. *Circ Cardiovasc Genet* 2009;**2**:499–506.
24. Benjamin EJ, Rice K, Arking DE, Pfeufer A, van Noord C, Smith A *et al.* Variants in ZFHX3 are associated with atrial fibrillation in individuals of European ancestry. *Nat Genet* 2009;**41**:879–881.
25. Ellinor PT, Lunetta KL, Glazer N, Pfeufer A, Alonso A, Chung MK *et al.* Common variants in KCNN3 are associated with lone atrial fibrillation. *Nat Genet* 2010;**42**:240–244.
26. Lubitz S, Ozcan C, Magnani JW, Kääb S, Benjamin EJ, Ellinor PT. Genetics of atrial fibrillation: implications for future research directions and personalized medicine. *Circ Arrhythm Electrophysiol* 2010;**3**:291–299.
27. Lubitz S, Sinner M, Lunetta K, Makino S, Pfeufer A, Rahman R *et al.* Independent susceptibility markers for atrial fibrillation on chromosome 4q25. *Circulation* 2010;**122**:976–984.
28. Psaty B, O'donnell C, Gudnason V, Lunetta K, Folsom A, Rotter J *et al.* Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of Prospective Meta-Analyses of Genome-Wide Association Studies From 5 Cohorts. *Circ Cardiovasc Genet* 2009;**2**:73–80.
29. Gudbjartsson DF, Holm H, Gretarsdottir S, Thorleifsson G, Walters GB, Thorgeirsson G *et al.* A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. *Nat Genet* 2009;**41**:876–878.
30. Olsson SB, Cotoi S, Varnauskas E. Monophasic action potential and sinus rhythm stability after conversion of atrial fibrillation. *Acta Med Scand* 1971;**190**:381–387.
31. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D *et al.* Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA* 2009;**301**:2571–2577.
32. Soliman E, Prineas R, Case L, Zhang Z, Goff D. Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke* 2009;**40**:1204–1211.
33. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'agostino R *et al.* Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;**373**:739–745.
34. Havlik RJ, Garrison RJ, Fabsitz R, Feinleib M. Variability of heart rate, P-R, QRS and Q-T durations in twins. *J Electrocardiol* 1980;**13**:45–48.
35. Pilia G, Chen WM, Scuteri A, Orrú M, Albai G, Dei M *et al.* Heritability of cardiovascular and personality traits in 6,148 Sardinians. *PLoS Genet* 2006;**2**:e132.

36. Hanson B, Tuna N, Bouchard T, Heston L, Eckert E, Lykken D *et al*. Genetic factors in the electrocardiogram and heart rate of twins reared apart and together. *Am J Cardiol* 1989;**63**:606–609.
37. Newton-Cheh C, Guo CY, Wang TJ, O'donnell CJ, Levy D, Larson MG. Genome-wide association study of electrocardiographic and heart rate variability traits: the Framingham Heart Study. *BMC Med Genet* 2007;**8(**Suppl. 1):S7.
38. Pfeufer A, van Noord C, Marciante K, Arking DE, Larson MG, Smith AV *et al*. Genome-wide association study of PR interval. *Nat Genet* 2010;**42**:153–159.
39. Holm H, Gudbjartsson DF, Arnar DO, Thorleifsson G, Thorgeirsson G, Stefansdottir H *et al*. Several common variants modulate heart rate, PR interval and QRS duration. *Nat Genet* 2010;**42**:117–122.
40. Piedra ME, Icardo JM, Albajar M, Rodriguez-Rey JC, Ros MA. Pitx2 participates in the late phase of the pathway controlling left-right asymmetry. *Cell* 1998;**94**:319–324.
41. Logan M, Pagán-Westphal SM, Smith DM, Paganessi L, Tabin CJ. The transcription factor Pitx2 mediates situs-specific morphogenesis in response to left-right asymmetric signals. *Cell* 1998;**94**:307–317.
42. Yoshioka H, Meno C, Koshiba K, Sugihara M, Itoh H, Ishimaru Y *et al*. Pitx2, a bicoid-type homeobox gene, is involved in a lefty-signaling pathway in determination of left-right asymmetry. *Cell* 1998;**94**:299–305.
43. Mommersteeg MT, Hoogaars WM, Prall OW, de Gier-de Vries C, Wiese C, Clout DE *et al*. Molecular pathway for the localized formation of the sinoatrial node. *Circ Res* 2007;**100**:354–362.
44. Mommersteeg MT, Brown NA, Prall OW, de Gier-de Vries C, Harvey RP, Moorman AF *et al*. Pitx2c and Nkx2-5 are required for the formation and identity of the pulmonary myocardium. *Circ Res* 2007;**101**:902–909.
45. Wang J, Klysik E, Sood S, Johnson RL, Wehrens XH, Martin JF. Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification. *Proc Natl Acad Sci USA* 2010;**107**:9753–9758.
46. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G *et al*. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–666.
47. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ *et al*. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace* 2007;**9**:335–379.
48. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B *et al*. The structure of haplotype blocks in the human genome. *Science* 2002;**296**:2225–2229.
49. Semina EV, Reiter R, Leysens NJ, Alward WL, Small KW, Datson NA *et al*. Cloning and characterization of a novel bicoid-related homeobox transcription factor gene, RIEG, involved in Rieger syndrome. *Nat Genet* 1996;**14**:392–399.
50. Doward W, Perveen R, Lloyd IC, Ridgway AE, Wilson L, Black GC. A mutation in the RIEG1 gene associated with Peters' anomaly. *J Med Genet* 1999;**36**:152–155.
51. Boldt L, Posch M, Perrot A, Polotzki M, Rolf S, Parwani A *et al*. Mutational analysis of the PITX2 and NKX2-5 genes in patients with idiopathic atrial fibrillation. *Intl J Cardiol* 2010;**145**:316–317.
52. Husser D, Adams V, Piorkowski C, Hindricks G, Bollmann A. Chromosome 4q25 variants and atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2010;**55**:747–753.
53. Hall J, Barac A, Benjamin EJ. Genetic mutations as risk predictors of atrial fibrillation recurrence after catheter ablation? *J Am Coll Cardiol* 2010;**55**:754–757.
54. Yasuda H, Mizuno A, Tamaoki T, Morinaga T. ATBF1, a multiple-homeodomain zinc finger protein, selectively down-regulates AT-rich elements of the human alpha-fetoprotein gene. *Mol Cell Biol* 1994;**14**:1395–1401.
55. Morinaga T, Yasuda H, Hashimoto T, Higashio K, Tamaoki T. A human alpha-fetoprotein enhancer-binding protein, ATBF1, contains four homeodomains and seventeen zinc fingers. *Mol Cell Biol* 1991;**11**:6041–6049.
56. Sun X, Frierson HF, Chen C, Li C, Ran Q, Otto KB *et al*. Frequent somatic mutations of the transcription factor ATBF1 in human prostate cancer. *Nat Genet* 2005;**37**:407–412.
57. Kim CJ, Song JH, Cho YG, Cao Z, Lee YS, Nam SW *et al*. Down-regulation of ATBF1 is a major inactivating mechanism in hepatocellular carcinoma. *Histopathology* 2008;**52**:552–559.
58. Berry FB, Miura Y, Mihara K, Kaspar P, Sakata N, Hashimoto-Tamaoki T *et al*. Positive and negative regulation of myogenic differentiation of C2C12 cells by isoforms of the multiple homeodomain zinc finger transcription factor ATBF1. *J Biol Chem* 2001;**276**:25057–25065.
59. Jung CG, Kim HJ, Kawaguchi M, Khanna KK, Hida H, Asai K *et al*. Homeotic factor ATBF1 induces the cell cycle arrest associated with neuronal differentiation. *Development* 2005;**132**:5137–5145.
60. Burgner D, Davila S, Breunis WB, Ng SB, Li Y, Bonnard C *et al*. A genome-wide association study identifies novel and functionally related susceptibility Loci for Kawasaki disease. *PLoS Genet* 2009;**5**:e1000319.
61. Ido A, Miura Y, Watanabe M, Sakai M, Inoue Y, Miki T *et al*. Cloning of the cDNA encoding the mouse ATBF1 transcription factor. *Gene* 1996;**168**:227–231.
62. Köhler M, Hirschberg B, Bond CT, Kinzie JM, Marrion NV, Maylie J *et al*. Small-conductance, calcium-activated potassium channels from mammalian brain. *Science* 1996;**273**:1709–1714.
63. Tuteja D, Xu D, Timofeyev V, Lu L, Sharma D, Zhang Z *et al*. Differential expression of small-conductance Ca^{2+}-activated K^+ channels SK1, SK2, and SK3 in mouse atrial and ventricular myocytes. *Am J Physiol Heart Circ Physiol* 2005;**289**:H2714–H2723.
64. Xu Y, Tuteja D, Zhang Z, Xu D, Zhang Y, Rodriguez J *et al*. Molecular identification and functional roles of a Ca(2+)-activated K+ channel in human and mouse hearts. *J Biol Chem* 2003;**278**:49085–49094.
65. Ozgen N, Dun W, Sosunov EA, Anyukhovsky EP, Hirose M, Duffy HS *et al*. Early electrical remodeling in rabbit pulmonary vein results from trafficking of intracellular SK2 channels to membrane sites. *Cardiovasc Res* 2007;**75**:758–769.
66. Nattel S. New ideas about atrial fibrillation 50 years on. *Nature* 2002;**415**:219–226.
67. Monaghan AS, Benton DC, Bahia PK, Hosseini R, Shah YA, Haylett DG *et al*. The SK3 subunit of small conductance Ca^{2+}-activated K^+ channels interacts with both SK1 and SK2 subunits in a heterologous expression system. *J Biol Chem* 2004;**279**:1003–1009.
68. Zhang Q, Timofeyev V, Lu L, Li N, Singapuri A, Long MK *et al*. Functional roles of a Ca^{2+}-activated K^+ channel in atrioventricular nodes. *Circ Res* 2008;**102**:465–471.
69. Taylor MS, Bonev AD, Gross TP, Eckman DM, Brayden JE, Bond CT *et al*. Altered expression of small-conductance Ca^{2+}-activated K^+ (SK3) channels modulates arterial tone and blood pressure. *Circ Res* 2003;**93**:124–131.
70. Diness J, Sorensen U, Nissen J, Al-Shahib B, Jespersen T, Grunnet M *et al*. Inhibition of small-conductance Ca^{2+}-Activated K^+ channels terminates and protects against atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:380–390.
71. Arking DE, Pfeufer A, Post W, Kao WH, Newton-Cheh C, Ikeda M *et al*. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. *Nat Genet* 2006;**38**:644–651.
72. Newton-Cheh C, Eijgelsheim M, Rice K, de Bakker PI, Yin X, Estrada K *et al*. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat Genet* 2009;**41**:399–406.
73. Pfeufer A, Sanna S, Arking DE, Müller M, Gateva V, Fuchsberger C *et al*. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet* 2009;**41**:407–414.
74. Lango Allen H, Estrada K, Lettre G, Berndt S, Weedon M, Rivadeneira F *et al*. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 2010;**467**:832–838.
75. Milan D, Kim A, Winterfield J, Jones I, Pfeufer A, Sanna S *et al*. Drug-sensitized zebrafish screen identifies multiple genes, including GINS3, as regulators of myocardial repolarization. *Circulation* 2009;**120**:553–559.
76. Milan D, Lubitz S, Kääb S, Ellinor PT. Genome-wide association studies in cardiac electrophysiology: recent discoveries and implications for clinical practice. *Heart Rhythm* 2010;**7**:1141–1148.
77. Cosio FG, Aliot E, Botto GL, Heidbüchel H, Geller CJ, Kirchhof P *et al*. Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode. *Europace* 2008;**10**:21–27.