Chapter 15.

Inherited Conduction Disease and Atrial Fibrillation

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Introduction

Normal atrial contraction requires an electromechanical impulse to propagate in an orderly way across myocardial cells. Any disruption in the structural and ionic components may result in chaotic electrical activity known as atrial fibrillation (AF). Similarly, a break down in the structural or electrical integrity of the sinus node or conduction system can result in conduction system disease.

This chapter will discuss the main molecular mechanisms known to underlie the development of AF and conduction system disorders, focusing on the genes and association loci that have been linked to these conditions and the possible ways in which treatment options for these conditions could be influenced by knowledge of the underlying genetic pathways.

Research efforts have focused on two approaches – examining genetic variants in the human population, and then investigating expression of specific genes in animal models or human tissue. Genetics in the human may involve analysis of AF/conduction disease as a monogenic disease in individuals with primary electrical disease, analysis of AF/conduction disease presenting in the setting of another familial disease, or the genetic background that might predispose to the disease without it necessarily segregating in a family. The first two pathways provide definitive insight into the aetiology and require analysis of families with the disease segregating across generations and following Mendelian inheritance in the context of a large effect size.

The third method involves investigating common variants. This can be performed through candidate single nucleotide polymorphism (SNP) studies, where a relatively small number of SNPs are examined in genes that are suspected to be associated with a disease, and uses known biology or associations to select the most relevant SNPs. Alternatively, genome wide association studies (GWAS) examine millions of SNPs throughout a large population sample for unsuspected associations and can identify new biological mechanisms. Non-related cases of AF/conduction disease matched to controls by age and gender are compared to identify differences in segregation of genetic backgrounds between both groups that may explain susceptibility to the disease. These methods examine common variants which have a small effect size, conferring susceptibility to AF along with a number of acquired factors or co-morbidities (Figure 1).

Studies looking at alterations in gene expression of ion channels and regulatory subunits are usually performed in animal models of the disease, but can be undertaken on a more limited scale in humans (Figure 2). They provide information on molecular changes triggered by the disease, which may uncover the mechanisms leading to, for example, conduction disease or that allow paroxysmal AF to become permanent. In AF for example, this may provide insight into whether changes in the atria form the aetiology of the disease, are a maladaptation or a compensatory mechanism (1–3).

Cardiac conduction disease

Conduction diseases encompass an important group of potentially life-threatening cardiac conditions accounting for approximately 50% of the one million permanent pacemakers implanted worldwide each year (4). Morgagni was the first In 1761 to link recurrent fainting episodes with a slow pulse in a family, and similar observations were later made by Adams and Stokes. The development of the electrocardiogram at the end of the nineteenth century provided tighter definitions of related phenotypes, but it was not until 1964 that two independent researchers published reports on a form of progressive CCD combining clinical observations, ECG recordings and detailed post mortem studies of the heart (5,6). Their descriptions were subtly different, with Lev describing a diffuse fibrotic degeneration through the fibrous skeleton of the heart, whilst in Lenègre's description the fibrosis was limited to the conduction fibres. However, both involved progressive conduction slowing through the His-Purkinje system with left bundle branch block (LBBB) or right bundle branch block (RBBB) and widening of QRS complexes leading to complete AV block and sometimes causing syncope or sudden cardiac death (SCD). Lenègre-Lev Syndrome is now synonymous with 'Progressive Cardiac Conduction Disease' (PCCD).

Thus, conduction diseases comprise a heterogeneous group of conditions that may be either inherited or acquired, and either associated with structural abnormalities of the heart or manifest as 'primary electrical diseases' (7). Cardiac activation is initiated in the sino-atrial node with the rate of depolarization dependent on the magnitude of the Na^+ (sodium) current involving Na^+ channel function and availability. The depolarizing current then spreads between cells through intercellular gap junctions. These each comprise hemi-channels, each containing 6 connexin protein subunits (Figure 3) (8), which are low-resistance channels that provide electrical coupling and intercellular electrical communication (9). Thus conduction disease can result in abnormalities in any of the molecular components involved in electrophysiological activity, contractile function and cell–cell adhesion.

Sodium channel mutations causing PCCD

SCN5A

The first gene to be associated with PCCD was *SCN5A*, which encodes the alpha subunit of the voltage gated Na^+ channel. Na^+ channels are essential for the transmission of the cardiac impulse through both the fast conducting system and the working myocardium (10), and it is therefore unsurprising that 'loss-of-function' mutations might result in conduction disease. In 1999, Schott's group (11) described a family with PCCD with various types of conduction disorder displayed in its members: RBBB, LBBB, left anterior or posterior hemi-block and long PR intervals. These defects were progressive over time (Figure 4). Linkage analysis mapped the disease locus to chromosome 3 near *SCN5A*. Direct sequencing of affected members identified a splice donor site mutation in exon 22 of *SCN5A* (IVS.22+2T->C) in 25 affected members. These observations suggest that PCCD associates *SCN5A* loss of function together with an additional permissive factor related to aging. Heterozygote Scn5a+/- mice demonstrate prolonged PR intervals, AV block and prolonged QRS intervals that worsen with age, associated with a pronounced myocardial rearrangement, including fibrosis and redistribution of connexin43 expression (12,13).

There have subsequently been many reports identifying new *SCN5A* mutations causing PCCD or non-progressive CCD. Mutations have been found in various locations on *SCN5A* (Figure 5), and have been postulated to give rise to loss of Na^+ channel function. Some mutations result in a non-functioning protein (14–16), whilst in others there is a defect in the trafficking mechanisms or in the channel gating behaviour once the protein is inserted into the membrane (17–21). In the case of a Dutch family segregating a specific missense allele (G514C), the mutation causes unequal depolarizing shifts in the voltage-dependence of activation and inactivation such that a smaller

number of channels are activated at typical threshold voltages (17). Two *SCN5A* mutations causing isolated conduction disturbances (G298S and D1595N) are also predicted to reduce channel availability by enhancing the tendency of channels to undergo slow inactivation in combination with a complex mix of gain- and loss-of-function defects (22).

There are also cases in which individuals with severe impairment in conduction have inherited mutations from both parents. Lupoglazoff et al. described a child homozygous for a missense *SCN5A* allele (V1777M) who exhibited rate-dependent atrio-ventricular (AV) conduction block (23). In a separate report, probands from 3 families exhibited perinatal sinus bradycardia progressing to atrial standstill ('congenital sick sinus syndrome' (SSS)) and were found to have compound heterozygosity for mutations in *SCN5A* (24). Compound heterozygosity in *SCN5A* has also been observed in 2 cases of neonatal wide complex tachycardia and a generalized cardiac conduction defect (18). These unusually severe examples of *SCN5A*-linked cardiac conduction disorders illustrate the clinical consequence of near complete loss of Na^+ channel function.

Recently, mutations have been found which have a modulator effect on SCN5A. Niu et al (25) described a W1421X mutation where four generations of a family demonstrated cardiac conduction abnormalities and several cases of SCD. However, one member with the mutation was unaffected, and was found to have a second mutation *SCN5A-R1193Q,* postulated to have a protective role in moderating the impact of the first mutation. Polymorphisms in connexin genes have also been found to have effects. Groenewegen et al (26) identified *SCN5A-D1275N* co-segregating with two connexin40 genotypes in familial atrial standstill (AS). Whilst SCN5A-D1275N channels showed only a small depolarizing shift in activation compared with wild type the combined effect led to the severe conduction defects.

All the above variants result in purely functional conduction disorders; however, *SCN5A* mutations may also result in structural abnormalities along with CCD. In 2004, a large family with members suffering from sinus node dysfunction, arrhythmia and ventricular dysfunction, was found to harbour *SCN5A-D1275N* (27) demonstrating that genes encoding ion channels can also be associated with dilated structural phenotypes. Since then, other families with SCN5A mutations have been identified who display heart failure and atrial arrhythmias as well as conduction disorder (28–30). Whilst it is possible that such structural abnormalities arise through tachycardia-induced cardiomyopathy, most evidence suggests that DCM may well be a primary manifestation of the *SCN5A* mutation (41). This may result from interactions of the cardiac Na^+ channel with cytoskeletal components or through altered calcium homeostasis as a consequence of alterations in intracellular Na^+ concentrations ([Na]i).

SCN5A overlap syndrome

SCN5A mutations are associated not only with CCD but also Long QT (LQT3) and Brugada Syndromes (BrS). A gain-of-function mutation of the Na^+ channel is seen in LQT3 leading to a more prolonged depolarizing current, increasing the action potential duration (APD). BrS is associated with reduced Na^+ channel function and is characterized electrocardiographically by ST elevation in the right precordial leads and RBBB. Whilst isolated PCCD does not usually involve the ECG changes seen with BrS or LQT3, *SCN5A* mutations may also be associated with more complex phenotypes that appear to represent combinations of the characteristics of BrS, conduction system disease and LQT3 (Figure 6). In one example, deletion of lysine-1500 in *SCN5A* was associated with impaired inactivation, resulting in a persistent Na^+ current, but also reduction in Na_V channel availability by opposing shifts in voltage-dependence of inactivation and activation (31). These complex relationships between genotype and phenotype may underlie clinical findings that individuals with BrS and an identifiable *SCN5A* mutation have longer PR intervals (32) and may experience more bradyarrhythmias (33) than

BrS individuals with BrS who do not have an identifiable *SCN5A* mutation. However, Lenègre-Lev and Brugada Syndromes remain two distinct clinical entities, as only those individuals with a BrS phenotype display ST elevation and ventricular arrhythmias.

SCN1B

The cardiac Na^+ channel protein $Na_v1.5$ constitutes the pore-forming subunit of a multi-protein complex (34). There are at least four beta subunits that modulate the expression and function of the Na^+ channel (35). 3 pathogenic mutations have been found in the *SCN1B* gene, encoding the Na^+ channel β1 subunit, which decreased the $Na_v1.5$ mediated current in cellular expression system compared with controls (36).

SCN10A

Several large GWAS have demonstrated that loci within the SCN10A, encoding the Na^+ channel $Na_v1.8$, associate with AV conduction (37) and BrS (38). A recent study has demonstrated cardiac expression of *SCN10A*, and identified an association of a non-synonymous SNP in the *SCN10A* with prolonged cardiac conduction. The PR interval is shorter in *Scn10a–/–* mice than in wild-type mice, suggesting that SCN10A in humans acts to lengthen cardiac conduction, and that this SNP in *SCN10A* is a gain-of-function variant (39). Furthermore there is evidence that a cardiac enhancer in SCN10A interacts with and regulates the promoter of SCN5A, thus providing an explanation for how SCN10A genetic variants may affect conduction (40).

Other genes causing CCD in structurally normal hearts

Mutations in genes encoding other relevant proteins have been identified in families with conduction disorders, although these do not usually exhibit the progression with age seen in Lenègre-Lev syndrome. Often mutations at the same site may result in either purely functional conduction defects or may also be associated with dilated or restrictive cardiomyopathy or other structural defects.

Connexins

There are four connexin isoforms in the human heart, which have a regional distribution. Cx40 are found in large, Cx43 in medium, Cx45 in small and Cx31.9 in ultra-small conductance gap junction channels respectively (41). Mutations in connexins have been linked to abnormal cardiac activation and conduction disorders. A causal relationship between nucleotide substitutions in gene coding for Cx40 and progressive familial heart block has been demonstrated, with heterologous expression resulting in a reduction in junctional conductance and diffuse localization of Cx40 proteins at plasma membrane without formation of gap junctions (42).

TRPM4

There have been several descriptions of CCD in families in South Africa, with progressive RBBB and other conduction disturbances and a family history of SCD, which has been termed type I progressive familial heart block (PFHB) (43–45). A distinct clinical entity, PFHB type II was also characterized, with complete heart block but narrow complexes. A similar disease was prevalent in Lebanon, with conduction defects, especially RBBB, progressive over time (46,47). A number of microsatellite markers in the South African and Lebanese families have been mapped to chromosome 19q13.2-13 (48,49). Subsequently, the genetic interval for the PFHBI disease locus has been defined, with a

missense mutation in *TRPM4* isolated as the cause of blunted cardiac conduction in several branches of a large Afrikaner family (50). *TRPM4* encodes a Ca^{2+}-activated channel (CAN) in *in vitro* expression systems (51) and has been suggested to contribute to the transient inward current (I_{ti}) initiated by Ca^{2+} waves. The *PFHBI*-associated mutation, which results in an amino acid sequence change in the TRPM4 N terminus, was found to lead to constitutive SUMOylation of TRPM4 and impaired TRPM4 endocytosis, resulting in a dominant gain of TRPM4 channel function (Figure 7).

More recently, three more mutations in TRPM4 were reported in French and Lebanese families with PCCD (52). Functional experiments expressing these three mutant variants of TRPM4 suggested a similar gain-of-function phenomenon related to altered deSUMOylation. In another recent study (53), an additional six TRPM4 mutations in patients with RBBB and AV block were identified, but electrophysiological or biochemical studies have yet to be carried out in order to elucidate the potential mechanisms involved. Altogether, these recent studies strongly suggest that TRPM4 plays a key role in the pathogenesis of genetically determined conduction disorders. It may be that gain-of-function mutant TRPM4 channels lead to cell membrane depolarization in the conduction system, thus reducing the number of available Na^+ channels and resulting in the observed conduction abnormalities.

KCNK17

In a PCCD patient with idiopathic VF, whole exome sequencing has identified a missense mutation in the KCNK17 gene (54), which encodes the potassium (K^+) channel TASK-4. A gain of function of TASK-4-mediated current may reduce the availability of Na^+ current by depolarizing the membrane of conduction system cells.

CCD associated with structural cardiac defects

Cardiac transcription factors are known to be critical in formation of the cardiac conduction system as well as cardiac septation and morphogenesis. It is thought that 10% of sporadic congenital heart disease involve de novo mutations which may affect cardiac conduction (55–57). For example, the molecular pathway involving *TBX5*, *NKX2.5* and *Id2* genes controls specification of ventricular myoctyes into the ventricular conduction system lineage (58) as well as formation of the cardiac chambers and endocardial cushions, and modifies gene expression of ion channel proteins that contribute to properties of conduction system and contraction of myocardium (59). Mutations have been linked to CCD associated with congenital heart disease (60).

NKX2.5

NKX2.5 (cardiac-specific homeobox) regulates proliferation of atrial working and conduction myocardium in coordination with the Notch pathway (61). *NKX2.5* mutations have been identified in cases of CCD, and also Wenckebach conduction block, ventricular non-compaction and SCD. These cases are associated with septal defects (62) and a variety of other congenital heart defect phenotypes such as tetralogy of Fallot, truncus arteriosus, double outlet right ventricle, L-transposition of great arteries, interrupted aortic arch and hypoplastic left heart syndrome (63–65).

Tbx5

Mutations in the gene encoding the T-box transcription factor *Tbx5* have been found in 2 families with Holt-Oram syndrome (66). This syndrome has an autosomal dominant transmission pattern and may include radial ray upper limb abnormalities, cardiac septation defect and coarctation (67,68). A

range of conduction disorders may be seen, such as sinus bradycardia or AV block, even in the absence of overt structural heart disease. Mutations in the *TBX3* gene, which lies close to *TBX5* on chromosome 12q24, result in ulnar-mammary syndrome. A case of contiguous deletions of both *TBX5* and *TBX3* displaying clinical features of both, had rapidly progressive cardiac conduction disease (69).

Others

An intact cytoskeleton is required for proper myocyte structure and is involved in cell signalling processes. Mutations in genes encoding cytoskeletal proteins can lead to cardiomyopathy or muscular dystrophy, an example being the LMNA A/C gene, encoding laminin. However, often the first and most prominent disease manifestation is isolated CCD, without or before the development of detectable structural cardiac abnormalities. It appears that mutations in cytoskeletal proteins directly or indirectly alter ion channel function. This is supported by recent studies showing that alpha-syntrophin interacts with the alpha-subunit of the cardiac Na^+ channel, thereby regulating its membrane expression and gating behaviour (70). Interactions of cytoskeletal proteins with mutant Na^+ channels may explain the exaggerated fibrosis seen in some cases of Lenègre-Lev syndrome (16,18).

Mutations in *PRKAG2* encoding an AMP-activated protein kinase, have been found in cases of both isolated CCD (71) and conduction disease with cardiac hypertrophy (72). These mutations may influence cardiac conduction by affecting the phosphorylation state of several cardiac ion channels; for example T172D that is known to affect the inactivation properties of the human cardiac Na^+ channel in heterologous cell expression (73).

Inborn errors of metabolism that affect normal transport and metabolism of fatty acids due to enzymatic defects may present as conduction disease and atrial arrhythmias without structural heart disease, although they can also be associated with cardiomyopathies. Usually, patients have defects in enzymes that regulate mitochondrial transport of long-chain fatty acids (74). The accumulation of fatty acid metabolites downstream from the enzyme defect cannot only be myotoxic, but may also influence ion channels. They have been shown to reduce the inward rectifying K^+ and depolarizing Na^+ current, to activate Ca^{2+} channels, and to impair gap-junction hemi-channel interaction (75).

The role of common genetic variants

Several GWAS have identified variants in multiple loci that show evidence of association with heart rate (37,76–78) (Figure 8). Although none of the heart rate loci have shown association with the risk of AV block, SSS, pacemaker implantation or sudden cardiac death individually, a higher genome-wide polygenic score (GPS) was associated with reduced risk of SSS and pacemaker implantation. A range of approaches, including proteomics experiments and gene expression quantitative trait locus analysis, labelled 49 of the 234 genes located within the 21 loci as candidate genes for heart rate regulation (79). Experiments in animal models supported a role in heart rate regulation for 20 of the 31 candidate genes tested, including ones that have a role in embryonic development (*EPHB4*, *PLXNA2*, *PLD1*and *CALCRL*), as well as those with a role in the pathophysiology of dilated cardiomyopathy, congestive heart failure and/or SCD (*TTN*, *MFN1*, *CHRM2* and*PLD1*). These findings provide new insights into the mechanisms that regulate heart rate and may impact upon management strategies in future.

Management of patients with inherited PCCD

PCCD is diagnosed mainly in the presence of unexplained progressive conduction abnormalities in patients under 50. The index patient should have clinical data collected including history, family history, 12 lead ECG and an echo/MRI to investigate the presence of structural heart disease. Early onset PCCD in a structurally normal heart should trigger PCCD genetic testing (80).

There is currently no genotype based risk stratification strategy, but with genotype positive patients there should be a low threshold for investigating symptoms or ECG findings. Patients should avoid drugs with conduction slowing properties and there should be active treatment of fever in SCN5A mutation carriers to minimise the risk of ventricular arrhythmias. A recent HRS/EHRA/APHRS expert consensus statement concludes that pacemaker implantation should be recommended in PCCD patients with either intermittent or permanent third degree and high grade AV block, or symptomatic Mobitz I or II second degree AV block (class I recommendation). PPM can be useful in PCCD patients with bifascicular block with or without first degree AV block (class IIa recommendation) (81). Targeted genetic screening of first degree relatives of a mutation positive PCCD patients is also recommended, to allow prospective follow up of asymptomatic mutation carriers.

Conclusions

There have been recent advances in the understanding of the development and pathophysiology of CCD, and in particular in the genetic backgrounds behind rare forms of familial PCCD. A large number of genes have been linked to cardiac conduction disorders. Genotype-phenotype correlations have demonstrated that PCCD is associated not only with aging, but also processes that lead to AV block and intra-ventricular block. Once more is known regarding the genetic pathways determining cardiac conduction, genetic analysis may become a routine part of management, with gene-mutation based risk stratification helping to determine optimal timing for pacemaker implantation. Mechanistically driven preventative strategies might also be employed to slow the development of the disease e.g. to modulate transcription or improve ion channel trafficking.

Atrial fibrillation

AF is the most common cardiac arrhythmia, estimated to affect 1-2% of the UK population. Its prevalence is increasing and is estimated to have doubled by 2040 (82,83). The most serious chronic sequelae of AF include stroke, heart failure, and dementia with devastating effects on an individual's health and high socio-economic costs (84).

The increased incidence of AF is driven partly by ageing populations, but other factors are also implicated. Although hypertension remains the most well described risk marker, metabolic factors also play a part. Investigators of the Framingham Heart Study estimated that obesity was associated with a 50% increase in risk of AF (85). A linear association has been reported between BMI and AF and short-term increases in body mass contributed substantially to risk of AF (86). Although some of the effects of obesity might be haemodynamic (eg, through impaired ventricular relaxation or atrial stretch), more direct metabolic effects seem likely (85,86). Diabetes is also independently associated with AF (87). Epidemiological data for prevalence of AF in racial groups and various geographical locations provide evidence of intrinsic (presumably genetic) interactions. Black people have a higher prevalence of hypertension and metabolic disease but a lower incidence of AF than a comparable white population (88).

AF is a clinically and genetically heterogeneous condition, which can be thought of as representing the final common phenotype of multiple diverse pathways. Conditions that promote AF involve atrial

structural, electrical and autonomic abnormalities and/or remodelling that lead to re-entry or triggered activity (89). Slow conduction velocities and short effective refractory periods (ERP) allow the establishment and stabilization of multiple re-entrant circuits (Figure 9). Delayed afterdepolarizations (DAD) emerge from abnormal Ca^{2+} release from the sarcoplasmic reticulum during diastole, acting as triggers for re-entry or, when sustained, as a focal source for AF (90,91).

AF as a monogenic disease

If AF occurs in the absence of any obvious predisposing factors it is known as 'lone AF' (92). Lone AF can be thought of as a primary electrical disease caused by changes in ionic currents. It was in fact first reported in a family in 1943 (93), and it is estimated that 5% of pts with AF and up to 15% of individuals with lone AF may have a familial form (94). There have been significant advances in the last 10 years in investigating the genetic elements of AF, with data from the Framingham study and Icelandic population showing that parental AF leads to a relative risk of AF in offspring of 4.7, if parents are affected before 60 years (95,96). The risk of developing lone AF at young age increases with the number affected of relatives with lone AF and decreasing age at onset in family members (97). While this may of course reflect common exposure to environmental factors, it is likely that genetic susceptibility plays a significant role (94–96,98,99).

Various AF loci and genes with large effect sizes in AF kindreds have been identified in positional cloning and linkage analyses. The first AF locus was discovered in 1997 (100); to date, mutations in over 25 genes have been associated with AF, including those encoding cardiac gap junctions, signalling molecules, ion channels and accessory subunits (Table 1). Gain or loss of function mutations in genes encoding proteins controlling cardiac depolarization or repolarization can increase susceptibility to AF (Figure 10). Cardiac APD shortening has been shown to lead to re-entrant wavelets (101,102), whilst prolonging the ERP enhances the likelihood of early afterdepolarsiations (EADs) (103,104). Interestingly, both gain and loss of function mutations in the same gene can cause AF.

Genes associated with AF

Potassium channel mutations

One model proposed for AF pathogenesis describes reduced atrial ERP as a substrate for re-entrant arrhythmias (101). This model is supported by reports of gain-of-function mutations in genes encoding subunits of cardiac ion channels responsible for generating repolarising K^+ currents; these mutations are predicted to decrease atrial APD and, therefore refractoriness. Familial AF has been associated with mutations in KCNQ1, which encodes the pore-forming alpha subunit of the cardiac K^+ channel Iks. In one mutation, functional studies have demonstrated an increase in current density, along with altered gating and kinetic properties, which results in shorter APD and ERP (105). Other gain of function mutations have also been described (106,107). Another gain of function mutation in KCNQ1 has been identified with high penetrance in 5 different families with early onset AF, which also leads to an abnormal QTc, syncope and SCD (108).

KCNE1-5 encodes the regulator beta subunits of IKs, and mutations in these genes resulting in gain of function of IKs have been identified in families with AF (KCNE1: (109), KCNE2: (110), KCNE3: (111), KCNE4 (112), KCNE5: (113)). KCNH2 encodes the alpha subunit IKr; mutations in this gene resulting in increased IKr have been related to Short QT Syndrome (SQTS) and AF (112,114,115).

KCNJ2 encodes the inward rectifier channel Kir2.1 responsible for the IK1 current, which determines the late phase (3) of repolarisation and maintains the resting membrane potential (phase 4). Missense mutations causing gain of function have been identified in a Chinese family with AF (116). KCNJ8 encodes the cardiac KATP channel Kir6.1, which controls a non-voltage-gated inwardly rectifying K^+ current, and leads to shortened APD under conditions of metabolic stress (117). A missense mutation causing gain of function (118) has been identified in a cohort of lone AF patients (117).

The KCNA5 gene encodes the atria specific $K_v1.5$ channel which plays a role in the ultra-rapid delayed rectifier K^+ channel I_{Kur} involved in cardiac repolarization. *A* deletion in a kindred with early-onset lone familial AF (119) disrupts a proline-rich motif involved in tyrosine-kinase regulation of I_{Kur}, and renders the channel kinase-resistant. The precise mechanism for AF in this kindred is not certain, and might involve gain-of-function or loss-of-function of I_{Kur} but importantly, this study established the tyrosine-kinase signalling pathway as a potential therapeutic target in AF. A nonsense mutation causing loss of function has been identified in a familial case of AF (120), leading to APD prolongation and EADs. These data also predicted increased vulnerability to stress-induced triggered activity, and carriers of this *KCNA5* variant were prone to develop AF when challenged with isoproterenol (120). This postulated mechanism for increased susceptibility to AF is supported by two studies in which investigators discovered loss-of-function mutations in *KCNA5* in patients with lone AF (103,121). Therefore, AF-associated mutations are likely to trigger AF by multiple mechanisms other than shortening of the atrial APD (122,123). The high prevalence of early-onset AF in patients with congenital long QT syndrome also supports a similar mechanism for AF in these patients (124).

Lastly, the ABCC9 gene encodes the SUR2A KATP channel subunit, which provides electrical stability under stress, including adrenergic challenge. A missense mutation causing loss of function has been identified in a case of early onset AF originating from triggers in the vein of Marshall (125).

Na^+ channel mutations

As mentioned above, the SCN5A gene encodes the alpha subunit of the cardiac Na^+ channel which controls the I_{Na} current involved in cardiac depolarization. Rare variants in SCN5A have been identified in a familial form of AF, several of which cause overlapping phenotypes with cardiomyopathy (126). 8 mutations in SCN5A have been seen in a cohort of lone AF patients, leading to decreased transient peak current and increased sustained current (127). Both gain or loss of function alterations in cardiac Na^+ current can be involved in early onset AF.

SCN1B-4B encodes modifying beta subunits of the cardiac Na^+ channel. Loss of function mutations have been found in cohort of AF patients (SCN1B and SCN2B: (128), SCN3B: (129), as well as in patients with BrS (130). SCN1Bb encodes the second beta1 transcript, Navbeta1B. A missense mutation has been found in patients with lone AF and with BrS (131), resulting in decreased peak Na^+ current and increased $K_v4.3$ transient outward current. (132).

Non-ion channel mutations

Table 1 also summarises known genes other than ion channels associated with AF. The NUP155 gene on chromosome 5q13 76 encodes nucleoporin, a component of the nuclear pore complex involved in nucleo-cytoplasmic transport. An AF locus has been mapped to chromosome 5q13 in a large AF family with autosomal recessive inheritance (133), which was then identified as NUP155 (134). A

homozygous mutation was seen in all affected family members, and heterozygous knock-out (KO) mice also demonstrated an AF phenotype.

NPPA encodes ANP, a circulating hormone produced in cardiac atria involved in BP regulation through natriuresis, diuresis and vasodilation (135). In a family with an autosomal dominant pattern of AF, a heterozygous frameshift mutation in NPPA co-segregated with AF, and the mutant peptide shortened the atrial APD and ERP in a rat heart model (136). A novel missense mutation in NPPA also co-segregates with early onset AF (137).

GATA4 and GATA6 genes encode cardiac transcription factors. They work synergistically with NKX2-5 in regulation of target gene expression, especially cardiogenesis (138). A GATA4 mutation has been identified in lone AF (139). Other studies have shown GATA4 mutations which co-segregate with AF, and lead to a decreased transcriptional effect (140–142). 2 heterozygous GATA6 mutations in 2 of 110 probands with familial AF co-segregated with AF in an autosomal dominant pattern, and were also associated with congenital cardiac defect in 3 AF patients (143). Other studies have shown mutations in GATA6 which co-segregate with AF and lead to decreased transcriptional activity (144,145).

The LMNA gene, mentioned above in conjunction with PCCD, encodes lamin A/C, an intermediate filament protein associated with inner nuclear membrane. A heterozygous missense mutation in LMNA have been seen in a family with AF as well as SVT, VE, muscle weakness and SCD (146). Two further variants have been identified in 2 probands with AF, one with episodes of AV block, the other with reduced LV function, LBBB and a family history of heart disease (147).

The critical role of *PITX2* in the development of the pulmonary myocardium (see more below) has led investigators to examine other developmental genes important for atrial differentiation and cardiac development. A novel interaction was identified between AF and a rare variant (Q76E) within the coding region of gremlin-2 (*GREM2*; an antagonist of bone morphogenetic protein), which increases its inhibitory activity and cardiac development (148). In a Zebra fish model GREM2 is required for cardiac laterality and atrial differentiation, and GREM2 over-activity results in slower cardiac contraction and lower contraction velocity. BMP is regulated by PITX2, and it is possible that GREM2 acts as an upstream regulator.

Another mechanism by which rare ion-channel and signalling-molecule variants might increase susceptibility to AF is through abnormal and heterogeneous disturbance of cell-to-cell impulse propagation. GJA1 and GJA5 genes encode connexin 43 and connexin 40. Four heterozygous missense mutations in GJA1 have been identified in families with AF (149). A frameshift mutation in GJA5 leading to a protein–trafficking defect not present in lymphocyte DNA i.e. genetic mosaicism, causes failure of electric coupling between cells and has been associated with familial AF (150). Germline mutations have also been identified in *GJA5* in patients with lone AF, and impairment of cell-to-cell communication has been confirmed in functional studies (151–153). Furthermore, common polymorphisms in the promoter region of *GJA5* have been associated with AF, and functional studies showed that this promoter haplotype was associated with reduced luciferase activity, which is indicative of cardiac conduction heterogeneity (154) and decreased activity of two transcription factors: Sp1 and GATA-4 (155). These data suggest that rare genetic variants in connexin-40 modulate expression of this gap-junction protein, with reduced expression causing impaired electrical cell-to-cell communication and creating conduction heterogeneity and a substrate for AF maintenance.

The role of common genetic variants

The aim in the use of GWAS is to validate genetic markers for the population and assess how accurately these can differentiate patients from controls. Rare variants usually exhibit a large effect, result in early-onset AF and show Mendelian inheritance. Candidate SNP studies examine a small number of SNPs suspected to associate with the disease and use known biology. Genome wide association studies (GWAS) have shown that common SNPs have a role in the development of AF (Table 2). As of 2014, nine SNPs had been associated with AF and may allow elucidation of biological pathways and the genetic component of the more common forms of AF (Figure 11). Huge sample sets are needed to establish deleterious or protective rare variants. By increasing sample size, the AFGen Consortium (www.afgen.org) have recently identified 12 more loci for AF. Further studies from large sample sizes are underway currently and the NHLB1 TOPMed program for Whole Genome Sequencing in early-inset AF is also in progress.

From these studies, functional groups can be seen, with variants in transcriptions factors, ion channels and related proteins and known myocyte proteins associating with AF. None of the GWAS hits are in amino-acid coding regions of genes. It would appear that they act instead as regulators of adjacent genes, possibly to alter the function of a promotor or enhancer, leading to up or down regulation of downstream processes. Work is needed to correlate GWAS hits with mRNA expression of genes located in the proximity of regions of SNPs. It should be remembered that the top hits from GWAS are not necessarily disease causing variants and GWAS hits may be in high linkage disequilibrium with low frequency variants (156).

4q25 locus

The first SNP identified identified by GWAS was rs2200733 (Figure 12), located in proximity of gene PITX2 on chromosome 4q25 and highly associated with AF (157). The PITX2 gene encodes the paired-like transcription factor PITX2. In the human heart, PITX2c is the major isoform expressed (158) and is involved in the control of asymmetric cardiac morphogenesis (157). A genetic variant on chromosome 4q25 has been associated with altered levels of PITX2 transcripts in left atrial (LA) tissue samples (159) and the role of PITX2 in the development of LA has been demonstrated in a KO mouse model (160). It is thought to be required for the development of a sleeve of cardiomyocytes extending from the LA to the initial potion of the pulmonary veins (161). This would fit with the known anatomical substrate for AF of ectopic foci from within PVs and posterior LA initiating and maintaining AF (162), and the basis of current strategy of pulmonary vein isolation as the cornerstone for ablation treatment (163).

Heterozygous KO PITXx +/- mice have normal cardiac morphology and function, but the expression of Ca^{2+} ion binding proteins, gap and tight junction and ion channels are altered, as well as showing differential expression of genes in Wnt signalling, a key fibrosis signalling pathway, with increased expression of collagen and extracellular matrix genes. Isolated mouse hearts go into AF during programmed pacing, showing shortened APDs and ERPs (164) (Figure 13). Human studies have shown that PITX2c expression is decreased in patients with persistent AF (165). There is much still to learn about PITx, including the mRNA levels in atrial tissue and target proteins.

Variants modulating cardiac ion channels

Several AF-susceptibility loci encoding cardiac ion channels have been identified. These include the K^+/Na^+ hyperpolarization-activated cyclic nucleotide-gated channel gene *HCN4* on chromosome 15q24, which encodes the cardiac pacemaker channel responsible for the funny current, and which as described above has been linked with sinus node dysfunction. The gene is expressed in most of the conduction system and is the predominant isoform of primary pacemaker in mouse hearts (166). Rs13376333 is found on chromosome 1q21 in the KCNN3 gene, which encodes the small

conductance Ca^{2+}-activated K^+ channel and is involved in atrial repolarization. Rabbit burst-pacing models which aim to mimic ectopic PV foci have shown that PV and atrial APDs are shortened, an effect inhibited by apamin which is known to block Ca^{2+}-activated K^+ channels (167).

Rs3807989 is found close to the caveolin-1 gene CAV-1 on chromosome 7q31, which encodes a cellular membrane protein selectively expressed in the atria and involved in signal transduction. This is expressed in atrial myoctyes, and is needed for the development of caveolae involved in electric signal transduction (168). CAV1 KO mice have dilated cardiomyopathy and pulmonary hypertension (169). Importantly, the caveolin-1 protein co-localises with, and negatively regulates the activity of, KCNH2 protein, a K^+ channel involved in cardiac repolarization, and *KCNH2* has been associated with AF in a candidate-gene association study (170).

GWAS loci with potential links to atrial fibrosis

In 2009, two separate groups identified common risk alleles on chromosome 16q22 that associated with AF (OR 1.1–1.2). Both SNPs are close to the gene that encodes the zinc finger homeobox protein 3 (*ZFHX3*). Similarly to PITX2, ZFHX3 (also known as AT motif binding-factor 1) is a transcription factor that regulates skeletal muscle and neuronal development, with variable expression in many tissues, including the heart (171). Interestingly, ZFHX3 regulates the transcription of the *POU1F1* gene (encoding POU class 1 homeobox 1), which not only facilitates DNA binding, but also modulates transcriptional activity of *PITX2* (172). *ZFHX3* might also mediate its effect on the risk of AF by modulating oxidative stress (173). The gene associates with runt-related transcription factor 3 (RUNX3), which translocates in response to TGF-beta signalling and is an important fibrosis mediator (174,175). It might therefore increase susceptibility to AF by modulating pathways to increase inflammation and oxidative stress, which are important in pathogenesis of AF (176).

Rs3903239 is found on chromosome 1q24, 46kb upstream from PRRX1, which encodes a homeodomain transcription factor which is highly expressed in developing heart (177). Studies in KO mice show that PRRX1 is needed for normal development of great vessels and lung vascularization, and is linked to pulmonary and liver fibrosis (37,178).

SYNE2 encodes nesprin-2 that, with nesprin-1, forms a network in muscle linking the nucleoskeleton to nuclear membrane structures and the actin cytoskeleton (179). α-Catenin interacts with nesprin-2 and emerin to regulate Wnt signalling-dependent transcription, a pathway implicated in fibrosis in the heart, kidney, and lung (180,181). Rs1152591 is found on chromosome 14q23 in the intron of gene SYNE2. Mutations are found in families with Emery-Dreifuss muscular dystrophy, who present with cardiomyopathy and cardiac conduction defects (177,182). Rs10821415 is in an open reading frame on chromosome 9, near to genes FBP1 and FBP2, which are involved in gluconeogenesis (177), although a further link has not yet been made. Rs10824026 is found on chromosome 10q22, 5kb upstream of SYNPO2L (177), which encodes the cytoskeletal protein CHAP (cytoskeletal heart-enriched actin-associated protein). This is highly expressed in the Z-disc of cardiac and skeletal muscle and play an important role in skeletal and cardiac muscle development. Knock-down of this gene in zebrafish causes aberrant cardiac and skeletal muscle development and function (183). It has been shown to be a susceptibility locus for AF in a family with autosomal dominant AF (100).

Taken together, there considerable evidence suggests that many common AF-susceptibility variants have the potential to modulate atrial fibrosis. Additionally, all these risk variants are likely to mediate their effect not only by regulating atrial conduction slowing, but also by modulating electrical remodelling processes that promote AF, such as shortening of the ERP.

Two hit hypothesis

Most patients with AF have one or more identifiable risk factors, such as hypertension or structural heart disease; however, many patients with these risk factors do not develop AF. Thus one might hypothesise that genetic determinants increase AF susceptibility in some individuals with other identifiable risk factors (genetic or acquired). In early GWAS, patients with non-familial AF were compared with controls and a small number of variants in candidate genes previously implicated in AF pathogenesis were tested. Subsequently, the GWAS paradigm of surveying the whole genome has been used successfully to identify new genomic loci contributing to AF susceptibility. For example, the risk of developing AF markedly increases (odds ratio [OR] 12–26) when a rare AF variant interacts with common AF risk alleles at the 4q25 locus (184). Therefore, these data support the idea of a 'two-hit' hypothesis—the combination of a genetic variant with additional risk factors, such as left atrial dilatation or other genomic variants, is important in AF pathogenesis (Figure 14) (185).

Bioinformatics

Exome data from NHLBI GO Exome Sequencing Project (ESP) (Seattle, WA, USA, URL. http://evs.gs.washington.edu/EVS/) reveals genetic variation in the general population. It uses next generation sequencing (NGS) of DNA from 6500 unrelated people recruited from different population studies, and is therefore representative of genetic variation in healthy subjects (127). Rare variants associated with AF are mostly not present in the ESP population ie the variants are not random findings, but are disease-causing (186). This is in contrast to studies showing that mutations previously thought to be disease causing in LQTS, sudden infant death syndrome (SIDS) and BrS show high prevalence in the ESP population and therefore may not in fact be disease causing (187–189).

Genetic overlap with other cardiac diseases

There is a large overlap between different genes involved in arrhythmic disease such as LQT, BrS, SQTS, SIDS, cardiomyopathy and AF. Indeed, most of the genes associated with AF are also associated with other arrhythmic diseases (Table 3). 9 genes associated with AF have not been associated with other arrhythmic diseases (KCNE4, KCNA5, SCN2B, NUP155, GJA5, GATA4, GATA6, NKX2-5 and GREM2). These may be specific for AF, but another possibility is that these cohorts have simply not been examined yet. Patients with genetically proven SQTS or LQTS have a higher risk of early-onset AF (190,191). Early-onset AF occurs in 2% of patients with genetically proven LQTS as compared with a background prevalence of 0.1% (190). In general, both shortened and prolonged QTc appear to be risk factors for AF, and especially lone AF (192).

Genetic testing in AF

A recent HRS/EHRA expert consensus document has set out recommendations for genetic testing in channelopathies and cardiomyopathies (80). Genetic testing is currently not indicated for AF as none of the known disease associated genes account for more than 5% of cases. Furthermore, there are no clear links between SNPs and clinical outcome.

A novel risk prediction model using data from 20,822 women without cardiovascular disease at baseline has been constructed (193). This generates a genetic risk score using the 9 loci known to be common variants. Adding this genetic score to an AF risk algorithm improves the predictive accuracy, and may pave the way for the use of common variants for risk stratification. This may be a practical

possibility with the advent of NGS, where the whole genome can be sequenced in a few days. This could lead to a personalized medicine approach, where specific variants could potentially predict whether the patient will elicit a response to a specific drug.

Role of genomics in therapy for AF

First line therapy for AF usually comprises anti-arrhythmic drugs, with a proportion of symptomatic patients selected for catheter ablation. Several factors contribute to the considerable variation in treatment options available – a lack of mechanism based and reliable effective treatments, together with adverse effects of both pharmacological and ablation therapy. Studies comparing rhythm and rate control have so far failed to show a survival benefit, and therefore there is an argument that there is no rationale in maintaining sinus rhythm if the patient has minimal symptoms (194). However, maintaining sinus rhythm still has a role to play in the cases of symptomatic individuals, and large prospective studies now recruiting, may show a survival benefit including the prevention of progressive heart failure and stroke. Identifying genes responsible for AF will help understand its pathophysiology, especially in terms of heterogeneity of substrate and differences in disease mechanisms. Results from prospective, adequately powered, genotype directed clinical trials may allow us to then target therapy to the underlying molecular AF mechanisms in an individual patient, rather than relying on empiric approaches. Tailored therapy will lead to improved efficacy and reduced risk of adverse effects.

The response to drug therapy is highly variable between patients and there is currently little data to base selection of antiarrhythmic drugs in a particular individual. There is a lack of well-defined end points to measure efficacy of treatment. Often time to first symptom is used, but this correlates poorly with frequency of symptomatic episodes, and is unable to assess asymptomatic episodes. Limitations in continuous ambulatory monitoring technology has led to practical difficulties in assessing AF burden, but this is now easier with new miniaturised technology (195,196).

Genetic factors have an important role in modulating drug responses. For rare ion-channel and other variants there are clear possible therapeutic implications. For example, in gain of function K^+ mutants, K^+ channel blockers such as sotolol might be employed. Equally, Na^+ channel blockers should be avoided if there is a loss-of-function variant in the Na^+ channel or its modifiers. However, although these mutations have a large effect size, they are rare and therefore the effects not widely applicable.

Common variants identified by GWAS have a greater aggregate effect, with combinations modulating AF risk. There have been few studies of genomic predictors of response to therapy, and they have been limited by being retrospective and of small sample size, meaning few results have been independently validated (Table 4). Reference 4q25 genotype has been independently associated with an improved response to class I or II antiarrhythmic drugs (OR 4.7). Beta1-adrenergic receptor polymorphisms (Arg389Gly) are significantly associated with inadequate ventricular rate control (OR 1.44) (197). Loci with multiple SNPs associated with failure to response to 3 of more AV blocking drugs have been identified in 3 genes: MYO7A, SOX5, LANCL2. SOX5 codes for a transcription factor involved in the regulation of embryonic development and cell fate and is expressed in the heart. GWAS data have implicated SOX5 polymorphisms as PR modulators (198).

The NIH Pharmacogenomics Research Network (199) has recruited a large number of patients with well-characterized drug-response phenotypes. One project within the network is to establish a DNA repository for the large Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, in which two major approaches for the management of AF—ablation and drugs to

maintain sinus rhythm—will be compared. Thus will hopefully allow investigators to address questions such as which patients are most likely to respond to, or develop complications with, ablation or drug therapy.

The Fire and Ice study (200) compared cryoballoon ablation and RF ablation. One clear point was that despite advances in technology and over 15 years' experience, recurrence rates have not dramatically fallen. The well-established parameters for determining ablation strategy include clinical presentation of AF, length of time in AF, LA diameter and presence of low voltage regions. However, genetic factors may help us better understand mechanisms for AF recurrence and therefore selection criteria for listing for ablation and allow a personalized approach in ablation strategy.

Using a candidate SNP approach, AF susceptibility alleles have been examined to identify which may potentially be associated with recurrence of AF after ablation. The main 3 loci which have been studied are 1q21/KCHN3, 4q25/PITX2 and 16q22/ZFHX3. No overall effect on recurrence has been found with 1q21/KCHN3 or 16q22/ZFHX3, with different effects seen depending on the cohort (201,202). 3 SNPs have been found at the 4q25/PITX2 locus - rs10033464, rs2200733, rs6843082. Of these, the rs2200733 has shown a significant association with AF recurrence in several European studies (202–204) but not in a Korean study (201).

There are several potential mechanisms for AF recurrence, including non-PV triggers, LA remodelling and PV sleeve reconnection. The current cornerstone for AF ablation is PVI, so those patients with non-PV triggers are likely to have worse outcomes as the procedure has not addressed the underlying mechanism for their arrhythmia. Mohanty et al (205) tested 400 AF patients for an association between candidate panel of 16 SNPs and non-PV triggers. 2 SNPs were associated with a lower risk of non-PV triggers, those at the SCN5A and 4q25/PITX2 loci, and 2 with a higher risk - 4q25/PITx2 and ZFHx3. SNP 16q22 was associated with ectopic foci in the SVC in paroxysmal AF but not persistent AF, with a specificity of 97% in a single centre Japanese centre. PVI sleeve reconnection is a leading cause of recurrence of AF following ablation; however so far no studies have specifically examined genetic variants potentially associated with this. SNPs might also be independent predictors of AF recurrence after DCCV, with 4q25 SNPs showing higher recurrence of AF after DCCV.

The presence of LA fibrosis is also associated with poorer outcome following AF ablation (206), again because PVI does not address the issue of substrate in the rest of the LA. There have been several studies mostly in individual cohorts, with candidate genes involved in LA remodelling/fibrosis including ACEI/D (207,208), CYP11B2 (208), AGT (209), IL6R (210), eNOS3 (211) and EPHX2 (212). ACE I/D polymorphism may be the most promising, as it was found to be significant in both European and Asian cohorts.

Conclusion

Various rare, mostly 'private' genetic variants affecting only a single kindred that encode diverse ion-channel and signalling proteins have been found to increase the risk of developing AF through distinct genetic mechanisms. This diversity is likely to contribute to the genetic heterogeneity of AF and the differential response to therapies. The extent to which genetic variants, or combinations of genetic variants with variable penetrance determine susceptibility to AF is an area of active investigation.

Positional cloning and candidate-gene approaches have provided novel insights into the genetic mechanisms of AF, and since 2007 several GWAS have identified further genetic loci and genes

implicated in AF. However, there is a disconnect between identifying genes and elucidating their mechanism. Indeed, some might argue that finding a GWAS is relatively straightforward, but determining function is not. The challenge now is to move from association to mechanism.

Current literature on genetic variation and AF ablation outcome is predominantly focused on common variants. Most studies have reported small or modest effect sizes and some contradictory findings. Previously reported associations need replication in larger cohorts of both European and non-European ancestries. Using additional genetic information could allow risk stratification based on pre-procedural characteristics to determine which patients are most likely to benefit, and tailoring ablation/drug/ablation-drug hybrid strategy for an individual patient. The development of genetic risk scores will likely be needed to clinically utilise common variant data. A large scale GWAS focused on AF recurrence after ablation may be useful to discover new genetic loci and determine the relative effect of SNPs on AF recurrence. From this, once we have a better understanding of the genetic basis of AF, we can translate this genetic knowledge to the care of patients. Critically, this should include assessment of how combinations of clinical and genetic factors predict development of AF and to what extent genomic variation adds to ordinary predictors such as hypertension or ischaemic heart disease.

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Tables

Table 1: Atrial Fibrillation Genetic Variants Identified in Families and Individuals. From Tucker and Ellinor (213).

Gene	Gene Name	Function	Citation(s)
ABCC9	ATP-binding cassette, subfamily C, member 9	I_{KATP} current	(214)
GATA4	Transcription factor GATA-4	Cardiac development	(116,170,182,215)
GATA5	Transcription factor GATA-5	Cardiac development	(117,182,216)
GATA6	Transcription factor GATA-6	Cardiac development	(217–219)
GJA5	Connexin 40	Formation of atrial gap junctions	(119,193,220–223)
GREM2	Gremlin-2	BMP antagonist	(224)
HCN4	Hyperpolarization activated cyclic nucleotide-gated K^+ channel 4	I_f current	(225)
JPH2	Junctophilin-2	Ca^{2+} homeostasis	(226)
KCNA5	K^+ voltage-gated channel, shaker-related subfamily, member 5	I_{Kur} current	(125,143,145,149)
KCND3	K^+ voltage-gated channel, Shal-related subfamily, member 3	I_{to1} current	(140)
KCNE1	K^+ voltage-gated channel, Isk-related family, member 1	K_v channel activity modulation	(139)
KCNE2	K^+ voltage-gated channel, Isk- related family, member 2	K_v channel activity modulation	(153)
KCNE3	K^+ voltage-gated channel, Isk- related family, member 3	K_v channel activity modulation	(227)
KCNE5	KCNE1-like	K_v channel activity modulation	(228)
KCNH2	K^+ voltage-gated channel, subfamily H (eag-related), member 2	I_{Kr} current	(80,229)
KCNJ2	K^+ inwardly-rectifying channel, subfamily J, member 2	I_{K1} current	(141,142)
KCNJ5	Potass K^+ ium inwardly-rectifying channel, subfamily J, member 5	I_{KACh} current	(230)
KCNJ8	K^+ inwardly-rectifying channel, subfamily J, member 8	I_{KATP} current	(231)
KCNQ1	K^+ voltage-gated channel, KQT- like subfamily, member 1	I_{Ks} current	(105,107,232–236)
LMNA	Lamin A/B	Nuclear envelope structure	(237,238)
NKX2.5	Homeobox protein Nkx2.5	Cardiac development	(113)
NPPA	Natriuretic Peptide Precursor A	Systemic sodium homeostasis	(197,239)
NUP155	Nucleoporin 155	Nuclear pore formation	(240)
PITX2c	Paired-like homeodomain 2c	Great vein development, left right asymmetry	(114)
RYR2	Ryanodine Receptor 2	Ca^{2+} release from sarcoplasmic reticulum	(241)
SCN1B	Na^+ channel, voltage-gated, type I, beta subunit	I_{Na} current modulation	(103,242)
SCN2B	Na^+ channel, voltage-gated, type II, beta subunit	I_{Na} current modulation	(103)
SCN3B	Na^+ channel, voltage-gated, type III, beta subunit	I_{Na} current modulation	(120,121)
SCN4B	Na^+ channel, voltage-gated, type IV, beta subunit	I_{Na} current modulation	(225)
SCN5A	Na^+ channel, voltage-gated, type V, alpha subunit	I_{Na} current	(148,151,152,243–245)

Table 2. Genes associated with AF through GWAS studies

Transcription factors	Ion channels and related proteins	Known myocyte proteins	Others
PITX2	KCNN3	MYOZ1	C90RF3
PRRX1	HCN4	TTN	SYNE2
ZFHX3	CAV1/2	PLN	CAND2
TBX5	GJA1		NEURL
CUX2	KCNN2		METTL11B
WNT8A	SCN5A		ANXA4
	KCNJ5		CEP68
			THRB
			ASAH1
			HSF2/SERINC
			SH3PXD2A

Table 3. Genes implicated in overlap syndromes.

	LQTS	BrS	SQTS	SIDS	Cardiomyopathy
KCNQ1	✔ (189)		✔ (189)	✔ (186)	
KCNE1	✔ (189,246)			✔ (186)	
KCNE2	✔ (189,246)			✔ (186)	
KCNE3	✔ (189,246)	✔ (247)			
KCNE5		✔ (248)			
KCNJ8				✔ (186)	
KCNH2	✔ (189)	✔ (249)	✔ (189)	✔ (186)	
KCNJ2	✔ (189)		✔ (189)		
KCND3		✔ (250)			
SCN5A	✔ (189)	✔ (251)		✔ (186)	✔ (126)
SCN1Bb		✔ (131)		✔ (186)	
SCN3B		✔ (252)		✔ (186)	
ABCC9					✔ (253)
NPPA					✔ (254)
LMNA					✔ (187)
GJA1				✔ (186)	

Table 4. Common genetic polymorphisms that modulate the response to therapies for AF. From (255)Darbar and Roden. Nat Rev Cardiol. 2013 Jun; 10(6): 317–329.. doi: 10.1038/nrcardio.2013.53

	Gene or SNP	Results	Replicated?	Reference
Rhythm control therapy	Angiotensin-converting enzyme I/D	D/D and I/D – increased AF recurrence after drugs	No	(256)
	Beta1-adrenergic receptor polymorphisms (G389R, S49G)	Arg389Arg – increased flecainide potency and increased HR during AF	Yes	(257)
	4q25: rs2200733, rs100334464; 16q22: rs7193343; 1q21: rs13376333	Re10033464 – increased AF recurrence after drugs	Yes	(197)
	4q25: rs2200733, rs100334464	Any variant allele – increases early or late AF recurrence after ablation	Yes	(237,258)
	4q25: rs2200733, rs100334464; 16q22: rs7193343; 1q21: rs13376333	Any common SNP increases AF recurrence after DCCV	No	(238)
Rate control therapy	Beta1-adrenergic receptor polymorphisms (G389R, S49G)	G389R - better rate control	Yes	(231)

Figures

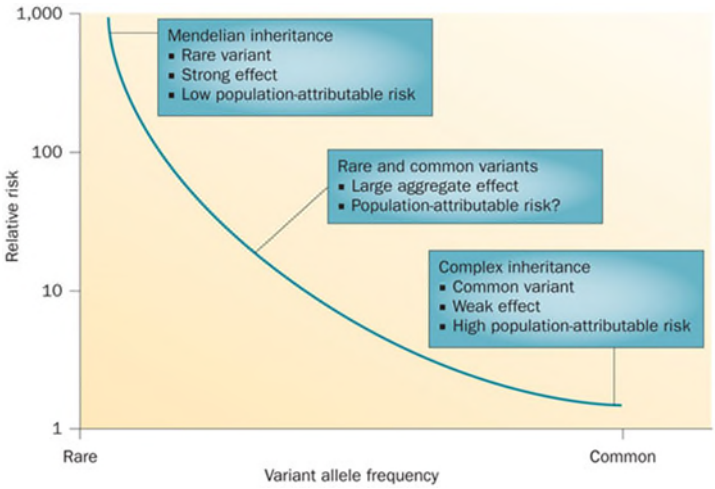

Figure 1 Allele frequencies and risk in families and populations. From Darbar and Roden (255).

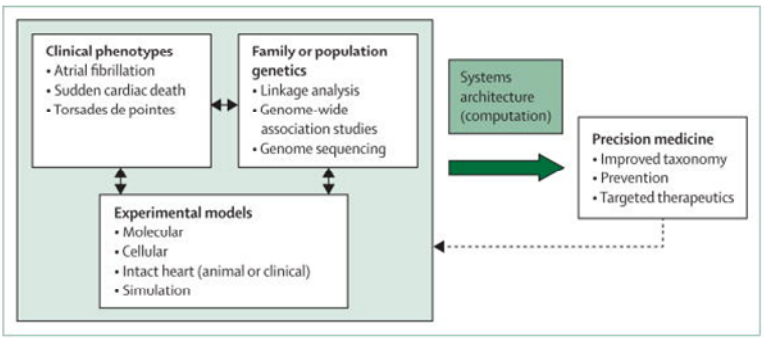

Figure 2. Integrating disease model paradigms to translational outputs in inherited disorders. From Grace and Roden (84).

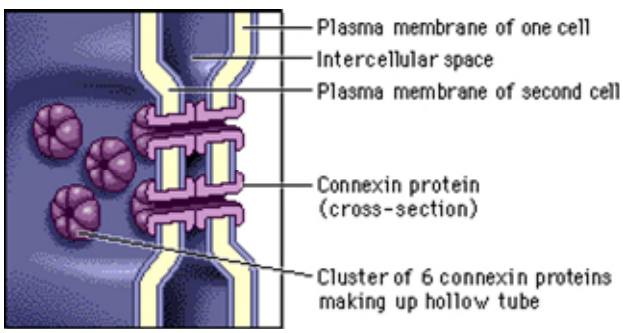

Figure 3. Gap junction structure.

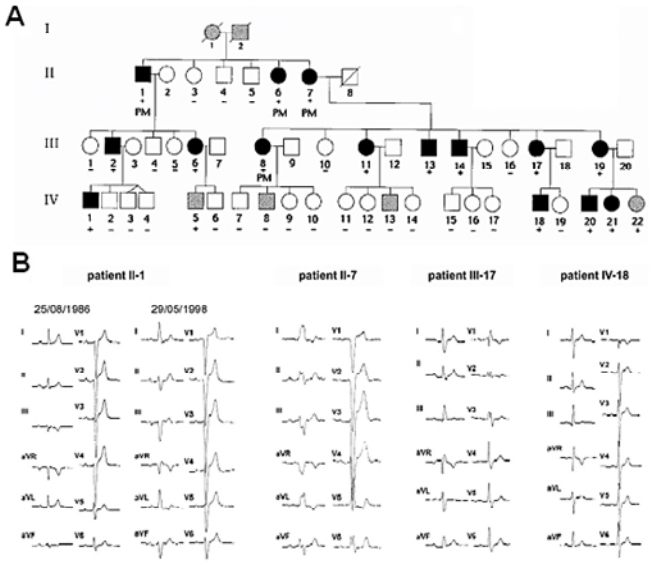

Figure 4. A Pedigree of the French family identified by Schott et al. Patients with an unknown status (stippled) were not included in the linkage study. Individuals carrying the mutation are indicated (+), as are patients with a pacemaker (PM). **B**. Representative ECGs from the French family. Patient II-1 had an unspecified conduction defect (QRS duration 120 ms) at age 60, but at age 72 had left anterior hemi-block with wide QRS complexes and a long PR interval (240 ms). ECGs from patients II-7, III-17 and IV-18 show complete LBBB, complete RBBB and left posterior hemi-block, respectively. Adapted from Schott et al (11).

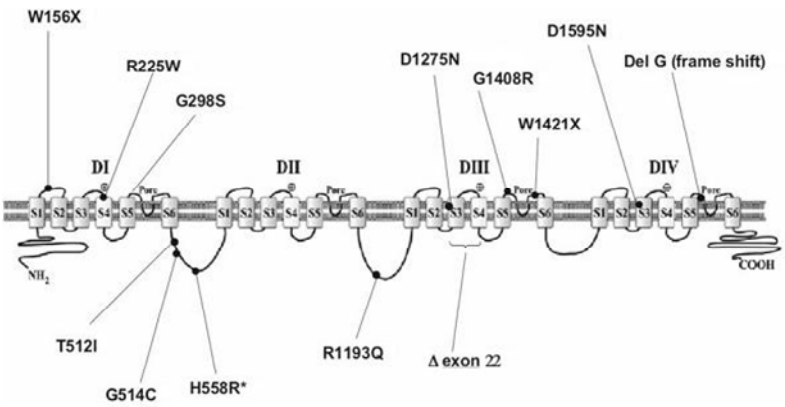

Figure 5. Location of identified SCN5A mutations that result in conduction system disease. *common polymorphism. Adapted from Moric et al (259). For complete updated list of SCN5A variants associated with PCCD see http://www.fsm.it/cardmoc/

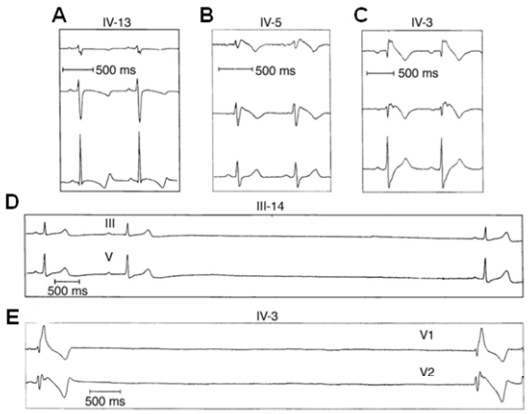

Figure 6. ECG traces of mutation carriers showing leads V1, V2, and V5. A) QT interval prolongation B) ST segment elevation (patient IV-5 of the pedigree). C) ST segment elevation and right bundle branch block (patient IV-3 of the pedigree). D First-degree AV block and E sinus arrest (patient III-14 of the pedigree). From Grant et al (31).

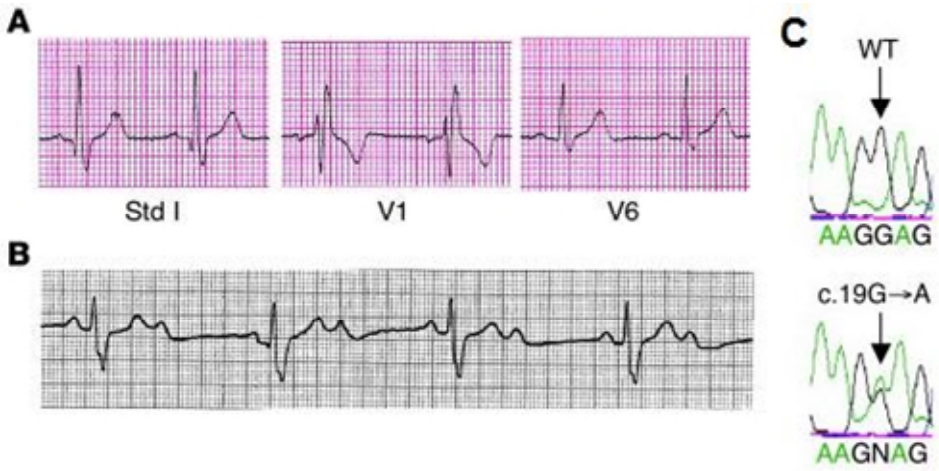

Figure 7 (A,B) Cardiac phenotype of PFHBI patients. (A) Sinus rhythm with a RBBB in an 8-year-old asymptomatic boy on a standard 12-lead ECG, with leads Std I, V1, and V6 shown. (B) 2:1 atrioventricular node block (atrial rate, 76 bpm; ventricular rate, 38 bpm) with a broad QRS complex on Holter monitoring in a 54-year-old man who had recently become symptomatic. ECGs were recorded at a 25 mm/s paper speed and 10 mm/mV signal amplitude. (C) TRPM4 missense mutation in exon 1 associated with PFHBI. Electropherograms show TRPM4 WT sequence and the heterozygous sequence change c.19G→A in the DNA of PFHBI-affected individuals. From Kruse et al (50).

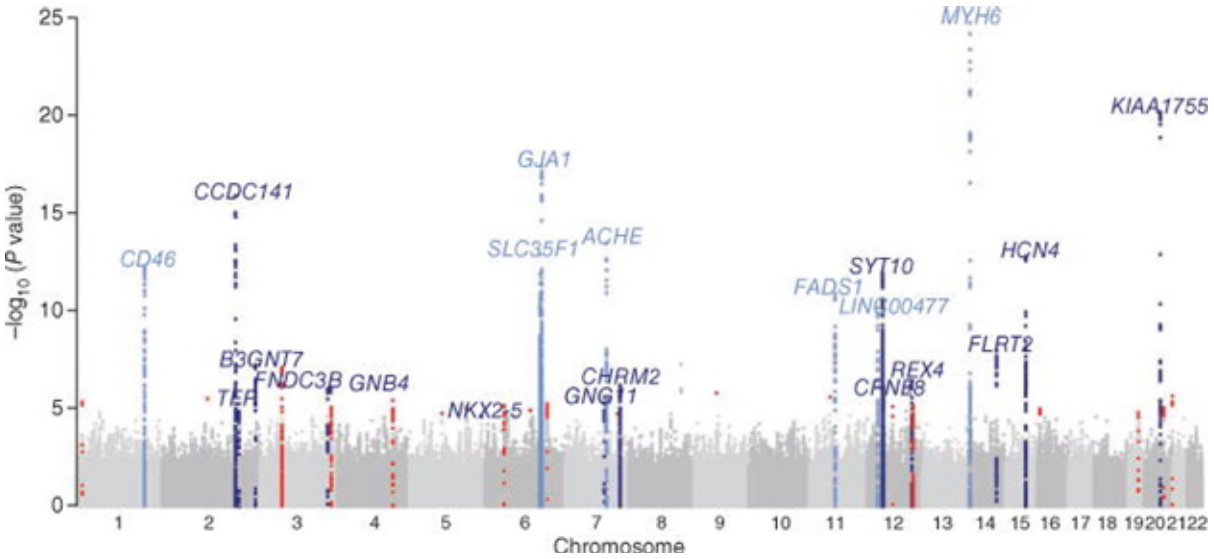

Figure 8. Manhattan plot of SNPs associated with heart rate. The 7 loci that were previously identified are highlighted in light blue; the 14 newly associated loci are highlighted in dark blue. Loci that reached $P < 3 \times 10^{-5}$ after stage 1 but did not reach $P < 5 \times 10^{-8}$ after multi-stage meta-analysis are highlighted in red. From den Hoed et al (79).

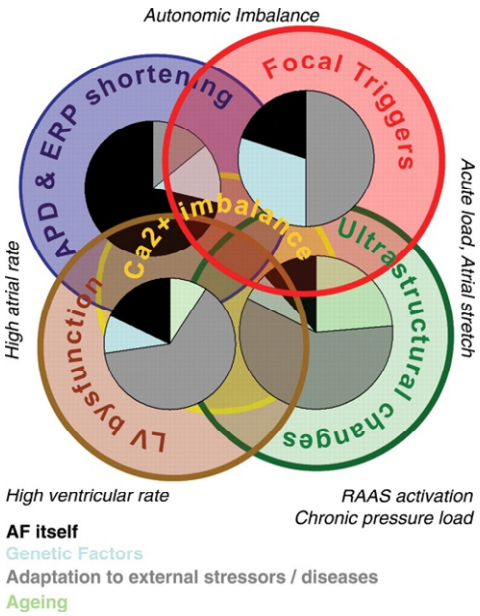

Figure 9. The interaction between structural and functional anomalies promoting AF and Left ventricular dysfunction. From Kirchhof et (260).

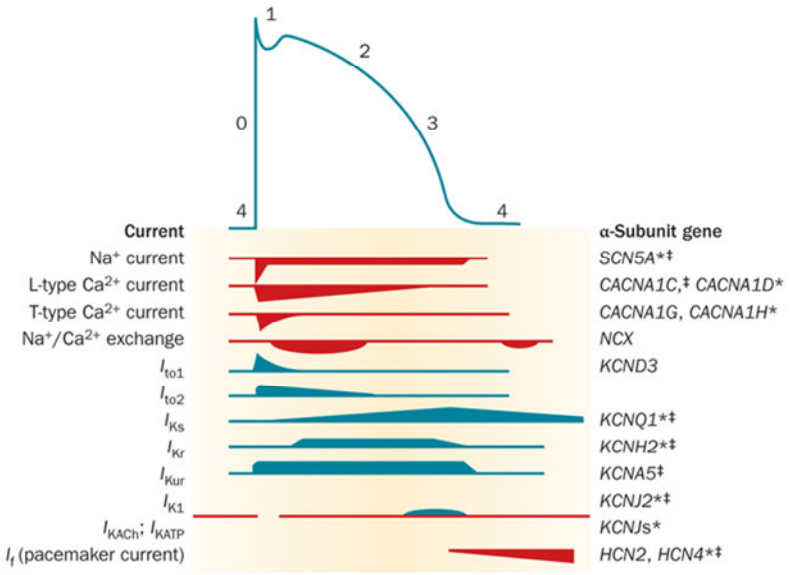

Figure 10. The AP is initiated by a rapid influx of Na ions (phase 0), followed by early (phases 1 and 2) and late (phase 3) stages of repolarization, before returning to the resting membrane potential (phase 4). Repolarization is controlled by a balance between inward (red) and outward (blue) currents. The genes encoding the major currents of the atrial AP are shown. *Function-modifying subunit. #Mutation in this gene associated with atrial fibrillation. From Darbar and Roden (255).

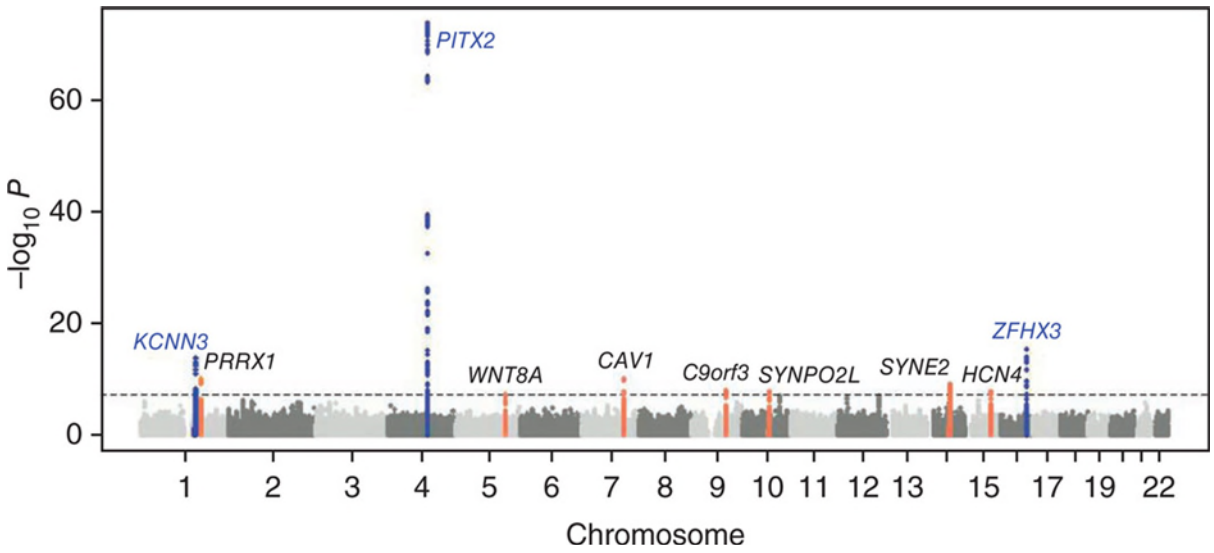

Figure 11 (1st version)

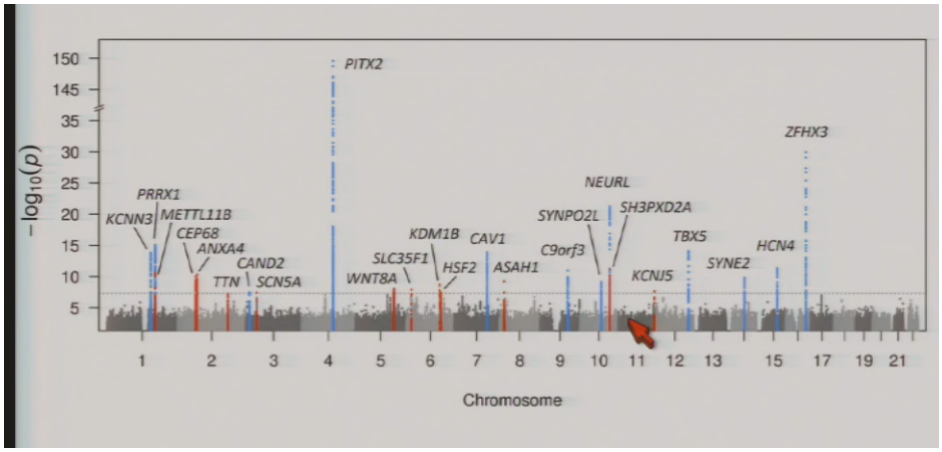

Figure 11 (2nd version). Manhattan plot of meta-analysis results for genome-wide association with atrial fibrillation. The $-\log_{10}$ (*P* value) is plotted against the physical position of each SNP on each chromosome. The threshold for genome-wide significance, $P < 5 \times 10^{-8}$, is indicated by the dashed line. The previously reported loci for AF are indicated in blue, and the new loci that exceeded the genome-wide significance threshold are indicated in orange. First version is from Ellinor et al (177), but up to date figure is from talk by Ellinor at HRS.

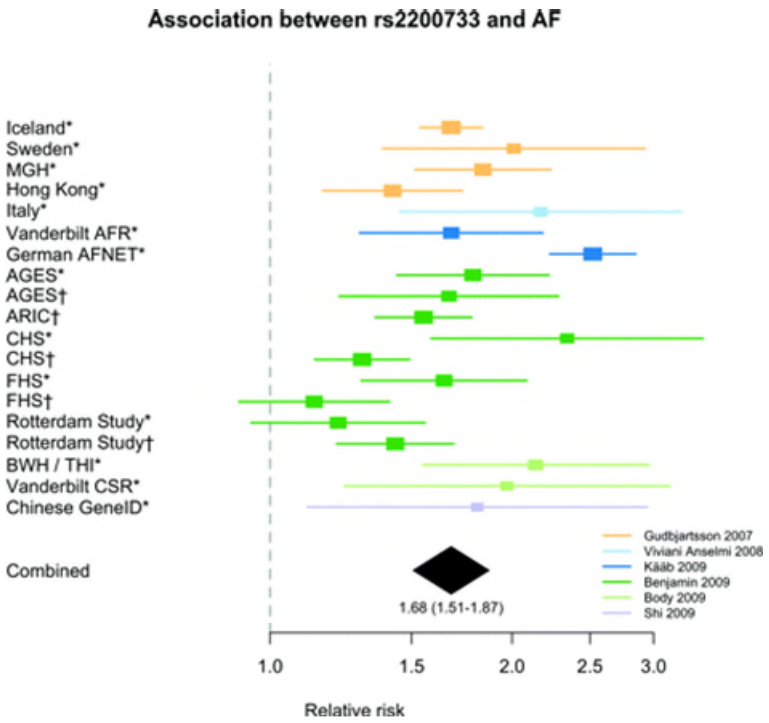

Figure 12. The association between AF and the T-allele of rs2200733, which tags an AF susceptibility locus on chromosome 4q25, is displayed across independent samples from published studies (total n=10 115 affected, 65 229 unaffected). Colours indicate the different studies from which the samples were reported. *Case-control study sample. †Prospective cohort study. AFR indicates Atrial Fibrillation Registry; BWH, Brigham and Women's Hospital; CSR, Cardiac Surgery Registry; ARIC, Atherosclerosis Risk in Communities Study; AGES, Age, Gene/Environment Susceptibility Reykjavik Study; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; MGH, Massachusetts General Hospital; and THI, Texas Heart Institute. From Lubitz et al (261).

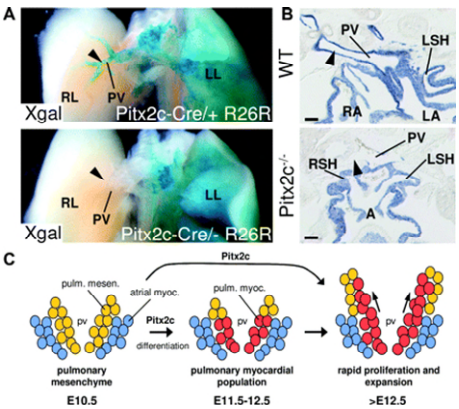

Figure 13. The activity of β-galactosidase was detected in PITX2c-Cre/+R26R mice by using X-gal staining of embryos (A, upper panel). The absence of β -galactosidase activity in the Pitx2c-Cre/-R26R pulmonary vein indicates the deficiency of PITX2c myocardial cell (A, lower panel). Cardiac troponin I (cTnI) staining demonstrated differentiated myocardial cells in a wild-type heart (B, upper panel), but an absence of myocardial cells in the heart of a Pitx2c KO KO littermate (B, lower panel). The process of the development of pulmonary myocardium (pulm. myoc.) with either differentiation of pulmonary mesenchyme (pulm. mesen.) to myocardium or invasion of pulmonary vein by atrial myocardium requires presence of Pitx2c (C). PV indicates pulmonary vein; LL, left lung, RL, right lung; RA, right atrium; LSH, left sinus horn; RSH, right sinus horn; (R/L) A, right/left atrium. From Lubitz et al (261).

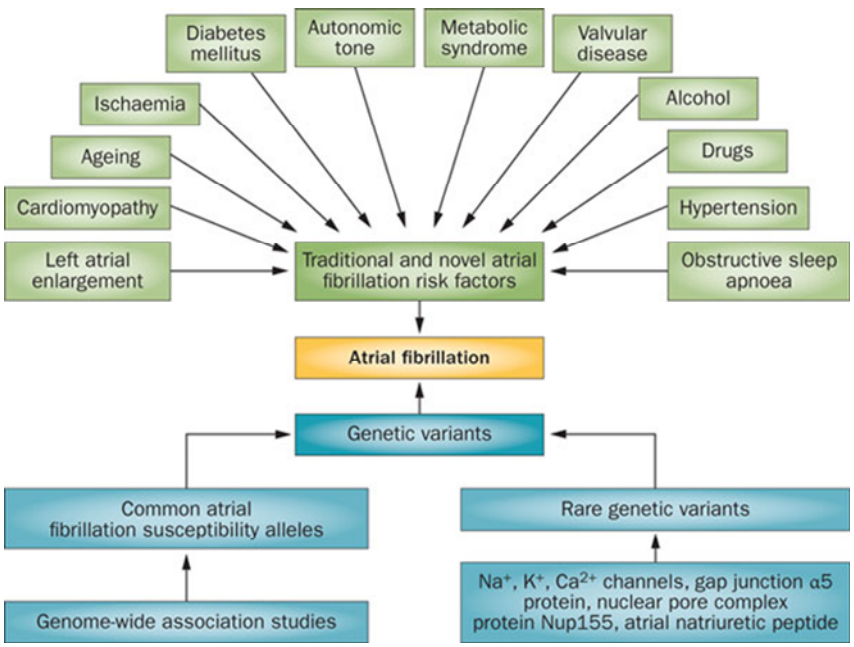

Figure 14. Integration of environmental and genetic factors in AF pathogenesis. From Darbar and Roden (255).