Developmental and genetic aspects of atrial fibrillation

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Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice. The abnormal rhythm is associated not only with a variety of symptoms, such as palpitations, dizziness, or shortness of breath, but also with increased risk of stroke, heart failure, and mortality. A genetic predisposition is suggested by the fact that the relative risk for the development of AF is estimated at 85% in individuals with at least one parent with a history of AF. Current therapeutic strategies include control of rate or rhythm with medication and catheter ablation procedures. Especially in the pathophysiology of paroxysmal AF, ectopic electrical activity originating in the myocardial sleeves surrounding the pulmonary veins is considered causal. In these cases, ablation is applied to isolate the pulmonary venous myocardium from the remainder of the left atrial myocardium. Other recent evidence has shown that genetic and developmental defects can be involved in the development of AF. In this review, it is our aim to discuss the possible underlying causes of AF from a combined genetic and cardiac developmental view. (Trends Cardiovasc Med 2009;19:123–130) © 2009, Elsevier Inc.

- Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice. The occurrence of AF increases with age, with a prevalence rising from 0.5% of people in their 50s to nearly 10% of the octogenarian population. The abnormal rhythm is not only associated with a variety of symptoms, such as palpitations, dizziness or shortness of breath, but also increased risk of stroke, heart failure, and mortality (Kannel & Benjamin 2008). Several cardiac disorders, such as hypertension, coronary artery disease, pericarditis, mitral valve disease and congenital heart disease, predispose to AF. Such conditions are thought to promote AF by increasing the atrial pressure and/or by causing atrial dilation, although the precise mechanistic links are still incompletely understood. The abnormal rhythm is held to be due to either reentry, triggered activity, or abnormal automaticity (Nattel 2003). Atrial fibrillation also occurs in individuals without any other evidence of heart or systemic disease, a condition known as lone AF.

Current therapeutic strategies include control of rate or rhythm, in combination with antithrombotic treatment, in case of increased thromboembolic risk. Radiofrequency catheter ablation procedures, in which the pulmonary venous myocardium is isolated from the remainder of the left atrial myocardium, has become commonplace in recent years (Jais et al. 2008). Recent evidence has shown that genetic and developmental defects can be involved in the pathogenesis of AF. In this review, it is our aim to discuss potential contributing factors from a combined genetic and cardiac developmental view. To explain the complex development of the
embryonic heart, we embedded three-dimensional reconstructions of various developmental stages in this document. To view these reconstructions, the reader needs an up-to-date version of Adobe Reader (9.1 at time of creation, http://get.adobe.com/reader/). Please visit http://3d.hfrc.nl for frequently asked questions and/or additional resources.

- Development of the Morphological and Molecular Atrial Phenotype

The atria have a complicated genetic makeup that can only be understood by establishing the mechanisms of atrial development. The four-chambered heart of mammals develops from a tube, which, when first laid down, contains the precursors for the left ventricle only. With further development, the precursors for the remainder of the heart are added at both the arterial and venous pole (Buckingham et al. 2005, van den Berg et al. 2009). By the stage of looping, at mouse embryonic day 9.5 (E9.5), which is comparable to 23 days in human development, the heart tube has started to form a ventricular chamber at its original ventral side and an atrial chamber, the future atrial appendages, at its venous pole by dorsolateral expansion and differentiation of atrial chamber myocardium (Figure 1, 3D-pdf E9). The differentiating chamber myocardium, that is, the myocardium that will form the future ventricles and atria, develops a distinct morphology and function, along with the expression of a distinct subset of genes (Christoffels et al. 2004, Christoffels & Moorman 2009, Moorman & Christoffels 2003). In short, the myocardium of the original heart tube and the myocardium subsequently added to its poles display slow conduction and contraction, along with the property to spontaneously depolarize, that is, it displays high automaticity. A hallmark feature of this so-called primary myocardium is the expression of connexin (Cx) 30.2 and 45, which form low-conductance gap-junction channels. The transcriptional repressor genes Tbx2 and Tbx3 are fundamental for the maintenance of the primary phenotype of the myocardium (Habets et al. 2002, Hoogaars et al. 2007).

The properties of the developing chamber myocardium, on the other hand, are different, and a hallmark feature of this working myocardium is the expression of Cx40 (see below) and Cx43, which form high-conductance gap-junction channels, and the expression of the α-subunit of the sodium channels Nav 1.5, encoded by Scn5a, providing the atrial compartment with high conduction velocity, at least in those parts of the wall that do express these genes.

 Whereas at day E8.5 of mouse development, the entire heart tube lies in the midline, 1 day later, the atrioventricular canal, which consists of primary myocardium, has become positioned in its entirety to the left of the midline, however, the inflow and outflow are maintained in the midline (Figure 2, 3D-pdf E9.5 and E10.5). At day E10.5 the entire atrioventricular canal, the floor of the forming atrium, and the venous pole have moved to the right, by which the atrioventricular canal once again becomes positioned in the midline, but the venous pole becomes positioned to the right of the midline. Consequently, the left and right systemic tributary veins exclusively drain to the future right atrium. In humans, the left systemic tributary or common cardinal vein loses its connection with the body circulation and becomes the coronary sinus or venous return of the cardiac circulation. Marshall ligament is a remnant of this embryonic history.

The atrial roof remains positioned in the midline because it is attached to the...
body wall via the dorsal mesocardium. Within this dorsal mesocardium, the initially single pulmonary vein (PV) develops and enters the atrium flanked by the pulmonary ridges (3d-pdf e9.5; inflow view). The scene is now set for atrial septation, by which the pulmonary orifice becomes positioned in the left atrium, and for the formation of the smooth-walled dorsal atrial wall from cardiac precursor cells recruited from the mediastinal, or pulmonary mesenchyme, which are positive for transcription factors Nkx2-5 and Isl1 (Mommersteeg et al. 2007, Snarr et al. 2007). From the outset, this so-called pulmonary myocardium has the working phenotype because it expresses Cx40, although it is distinct.

**Figure 2.** Alignment of the venous pole and atrioventricular canal (AVC). The figure contains two three-dimensional reconstructions of mouse hearts, embryonic day 9.5 (E9.5) and 10.5, respectively. Myocardium positive for Cx40 has been rendered sky blue as opposed to Cx40 negative myocardium in gray. For didactic reasons, the ventricles and outflow tract have been removed. Each stage is rendered three times: ventral (top), dorsal (middle), and schematic (bottom) view. In the schematic view, the alignment of the AVC, PV, and systemic venoatrial junction (SVJ) in relation with the midline (green line) is shown. Initially, the heart tube is laid down along the midline, whereby all three structures are aligned along the midline (not shown). Shortly thereafter—at the E9.5 stage—the AVC shifts to the left of the midline, whereas the PV and SVJ remain centered. Just 1 day later (E10.5), the AVC is recentered, whereas the SVJ shifts to the right of the midline and appears to have undergone a rotation. Not surprisingly, the PV remains centered during this seemingly complex rearrangement within such a small region, which also occurs in a very short time span (see attached interactive figure in online version of this article. You will need Acrobat Reader 8.0 or later to view the interactive features of the pdf file.).

**Figure 3.** Reconstruction of the Tbx3 expression (red) in the myocardium (gray) of a mouse heart of 12.5 days of development. Tbx3 is known to be an inhibitor of chamber formation and encompasses the early conduction system. The top half (cranial) of the myocardium and Tbx3 has been sliced off to give a four-chamber view. Dorsocranial from right venous valve (demarcating the crista terminalis) the sinus node (blue dot; not shown in its entirety) is located, in which Tbx3 is abundantly present. Internodal myocardium (green dots) can be seen running between the sinus node and atrioventricular junction (see attached interactive figure in online version of this article. You will need Acrobat Reader 8.0 or later to view the interactive features of the pdf file.).
from the appendage myocardium that expresses also atrial natriuretic peptide (ANP, see below) encoded by Nppa. It is only with subsequent development that the pulmonary venous component becomes incorporated into the roof of the left atrium, such that each of the four PVs, with short myocardial sleeves of various length, opens at a corner of the atrial roof.

In contrast, the myocardium that is added at the systemic part of the venous pole, or sinus venosus myocardium, is derived from Nkx2-5-negative, Isl1-negative, and Tbx18-positive mesenchymal cardiac precursors (Christoffels et al. 2006). The sinus venous myocardium starts to form at day 9.5 of mouse development and initially is Cx40-negative but expresses the pacemaker channel Hcn4 and the transcriptional repressor Tbx3 (Christoffels et al. 2006, Hoogaars et al. 2004). With further development, the sinus myocardium matures into atrial working myocardium, apart from the region where the sinus node is formed, which remains Tbx3-positive, Nkx2-5-negative, Cx40-negative, and Hcn4-positive. The developmental expression of Tbx3 is shown in Figure 3 and 3-d-pdf e12.5. Its pattern of expression highlights those regions that are significantly more prone to arrhythmias than the chamber-forming regions, being the orifice of the coronary sinus, the terminal crest, and the lower rim of the atrium, part of which gives rise to the tricuspid annulus in the adult. The (cavitricuspid) isthmus, close to the coronary sinus, also plays a crucial role in atrial flutter. Interestingly, in human fetal hearts, the coronary sinus is equally intense in HCN4 protein staining as the sinus node (unpublished observations).

- **Developmental Implications for AF**

In most cases of paroxysmal AF, the myocardial sleeves surrounding the PVs at the orifice to the left atrium are considered to carry the triggers and possibly the substrate for this arrhythmia. Indeed, cells with presumed pacemaker activity have been found in the PVs of rat hearts (Masani 1986) and in the PVs of patients with AF (Perez-Lugones et al. 2003), albeit these observations are debated. Data from our laboratory have shown that the pulmonary myocardium is formed from a distinct lineage of precursor cells, different from the lineage that forms the sinus muscle encompassing the sinus node (Christoffels et al. 2006, Mommersteeg et al. 2007, Mommersteeg et al. 2006, Wiese et al. 2009). In contrast to the sinus muscle, this pulmonary myocardium expresses from the outset transcription factor Nkx2-5 and its target gap-junction gene Cx40. Intriguingly, when Nkx2-5 protein levels were lowered experimentally, the pulmonary myocardium switched to a Cx40-negative, Hcn4-positive phenotype, resembling sinusatrial nodal-like cells. Taken together, there is no developmental base for a nodal-like phenotype in the pulmonary myocardium. However, in abnormal development, under a reduced dose of Nkx2-5, the pulmonary myocardium converts more easily into a nodal phenotype than the working myocardium of the atrial appendages. Thus, with reduction in expression level of only a single transcription factor, a gene program potentially sufficient to provide automaticity is activated in the pulmonary myocardium. This observation suggests that genetic variation between individuals in Nkx2-5 dosage could be an important contributing trigger to the development of AF. Indeed, some mutations in Nkx2-5 are suggested to be linked to AF (Gutierrez-Roelens et al. 2006). Taken together, variations in the regulatory sequences of the Nkx2-5 gene (and its interacting partners) are prime candidates for further research into the underlying cause of AF.

- **Anatomical and Clinical Aspects of AF in the Adult Heart**

In clinical literature, nomenclature for the left atrial structures relevant for catheter treatment of AF is not used consistently and can differ from anatomical descriptions. The gradual transitional zone between de PVs and the left atrium, or the PV atrial junction, is without clear anatomical landmarks; as a consequence, this ambiguous region is variably defined in the literature (Konin et al. 2008). Similarly, on a histological level, a continuum between the left atrium and the PVs exists. Atrial myocardial muscle sleeves extend into the PVs, and conversely, venous smooth muscle cells overlap with atrial myocardium (Hassink et al. 2003). To address this complexity, electrophysiologists use the terms “ostium” and “antrum,” in which the PV ostium is the more distal portion of the PV atrial junction and preferably avoided because of the risk of postablation stenosis; the region of the left atrium advancing toward the PV ostium is called the antrum; electrophysiologists generally aim for this area for making lesions.

Based on animal experiments and clinical observations, the PVs are considered crucial for the initiation and perpetuation of AF. The pioneering work of Haissaguerre et al. (1998) already suggested that foci exist in the PVs. Until now, it is not understood which mechanism underlies this focal activity, both local automaticity and micro reentry have been suggested. Experimental work indicates that the PVs not only hold the rapidly firing foci initiating AF; heterogeneous conduction and extremely short refractory periods in the muscle sleeves of the PVs may also underlie the substrate maintaining AF. Later work has shown that in addition to these PVs, which constitute the most important focal source by far, other structures, such as the ligament of Marshall, the superior vena cava, and the left posterior free wall, may carry paroxysmal foci as well (Lin et al. 2003). The first two structures are derived from sinus muscle, whereas the third structure is derived from pulmonary mesenchyme. Interestingly, as discussed above, it has already been demonstrated that—under experimental conditions—myocardium originating from the pulmonary mesenchyme can show pacemaker properties. Nevertheless, the developmental origin of these three structures is fundamentally different, making a final common pathway involved in the developmental origin for these arrhythmias unlikely.

A large body of evidence on catheter-based treatment of paroxysmal AF made PV isolation an accepted treatment option (Fuster et al. 2006). Nevertheless, concern exists on long-term success (Shah et al. 2008). Because paroxysmal AF is mostly trigger-dependent, isolation of the left atrium from the profibrillatory PVs is the most effective treatment (O’Neill et al. 2007). Moreover, in the treatment of the persistent and chronic patterns of AF, isolation of the PVs is also key for successful catheter treatment (Oral et al. 2006). Recent evidence suggests that additional ablation of complex atrial fractionated electrograms in the body of the left atrium is of no incremental
clinal value compared to pulmonary vein isolation alone in patients with persistent AF (Oral et al. 2009).

- **Genetic Basis of AF**

  Most patients with AF have underlying heart disease, as mentioned earlier, although some patients develop AF in the absence of any known risk factor. The relative risk of AF is estimated at 85% in individuals with at least one parent with a history of AF (Fox et al. 2004), suggesting a genetic predisposition. Familial AF, as a monogenic disorder with a Mendelian inheritance pattern, is uncommon, but in recent years, linkage studies have succeeded in elucidating loci and genes that play a major role in familial AF (Tsai et al. 2008). In 2003, a four-generational family with hereditary persistent AF was identified, and a causative mutation in the KCNQ1 gene was found, which encodes the pore-forming α-subunit of the cardiac channel for the slowly activating delayed rectifying current (IKs). Functional analysis of the mutant revealed a gain-of-function effect on IKs currents (Chen et al. 2003), which contrasts with the dominant-negative or loss-of-function effects of the KCNQ1 mutations previously identified in patients with long QT syndrome. The mutation is likely to initiate and maintain AF by reducing action potential duration and the effective refractory period in atrial myocytes. Subsequently, mutations in KCNQ1 (Yang et al. 2004), encoding the pore-forming α-subunit of the cardiac IKr channel were identified. Subsequently, mutations in KCNE2 (Yang et al. 2004), a β-subunit that interacts with KCNQ1; KCNJ2 (Xia et al. 2005), encoding the inward rectifier potassium current (IK1) of the heart; and KCNH2, encoding the α-subunit of the cardiac IKr channel were identified (Hong et al. 2005). Interestingly, all these AF-associated mutations in potassium channels resulted in a gain of function effect, likely leading to a shortened action potential, analogous to the effect of the KCNQ1 gain of function mutation. Moreover, a SCN5A gain of function mutation is associated with lone AF at a young age (Makiyama et al. 2008). SCN5A encodes the pore-forming subunit of the cardiac sodium channel responsible for the fast initial depolarization of cardiac myocytes. No persistent inward current was present (relating to LQT type 3) in mutant channels, but a pronounced shift of the INa steady-state inactivation curve to positive potentials was found. These biophysical properties are compatible with increased atrial excitability and normal QT interval, as seen in the affected individuals. Interestingly, two recent studies established that loss-of-function mutations are also associated with lone AF. KCNA5, encoding a voltage-gated potassium channel expressed in human atria, was found to be mutated in familial AF (Olson et al. 2006). The mutant channel protein failed to generate the ultrarrapid delayed rectifier current IKur crucial for atrial repolarization and exerted a dominant-negative effect on wild-type current. This loss of function channel translated into action potential prolongation and early afterdepolarization in human atrial myocytes, resulting in increasing vulnerability to stress-provoked triggered activity. In addition, a novel SCN5A mutation was observed in familial AF, the expression of which revealed a shift of the Ina steady-state inactivation curve toward negative potentials. This would result in an effective loss of sodium channel function in affected individuals and consequently a predicted prolongation of the action potential duration (Ellinor et al. 2008).

In conclusion, mutations in ion channels play a fundamental role in the pathogenesis of familial AF by producing gain of function effects that lead to shorter action potential duration and refractory periods, providing an ideal substrate for reentry, or by a loss of function leading to a prolonged action potential duration and subsequent repolarization failure or early afterdepolarizations that could induce triggered activities (see Table 1). Nonetheless, even in the most familial AF, no causative mutation could be identified, suggesting additional genes and pathogenic mechanisms.

Recent studies demonstrated that familial AF is not only associated with mutations in genes encoding cardiac ion channels. In one family with 11 clinically affected members, linkage was found to a locus containing the NPPA gene, encoding ANP. Sequencing of this gene revealed a frameshift mutation leading to a chimeric ANP protein containing 12 additional amino acids (Hodgson-Zingman et al. 2008). This chimeric protein was present at significantly higher concentrations in affected family members than normal ANP, probably as a result of increased stability. Increased ANP dosage is known to result in electrophysiological derangements in atrial myocytes (Lonardo et al. 2004), and exposure of isolated hearts to the chimeric ANP protein resulted in shortened action potentials and refractory periods. Recently, in a family with a recessive form of AF, screening of a nuclear pore complex protein NUP155, which is part of the nuclear envelope, revealed a homozygous mutation in all affected family members (Zhang et al. 2008). Heterozygous knockout mice for NUP155 also show the AF phenotype. Problems with the nuclear envelope might delay or block mitosis, which, in turn, reduces myocyte survival and could lead to apoptosis and cardiac fibrosis.

Electrical coupling is vital to atrial myocytes, and this is provided by intercellular channels termed Cxs, one of which, Cx40 (GJA5), is selectively found in the atria and the conduction system. Interestingly, knockout mice for GJA5 have conotruncal malformations and endocardial cushion defects, but the molecular mechanisms by which a Cx40-deficiency could lead to cardiac malformations are unknown (Gu et al. 2003). Apparently, Cx40 is not essential for cardiogenesis, but its absence or limited expression increases the probability of cardiac malformations. Juang et al. (2007) found that a GJA5 haplotype (−44A +71G), common to the population, was associated with a significantly higher risk for AF. Previously, with the use of electrophoretic mobility shift assays and luciferase reporter assays, Firouzi et al. (2006) had demonstrated that, among others, at least two transcription factors (Sp1 and GATA4) are important regulators of Cx40 gene transcription and that the −44A polymorphism negatively affects the promoter activity. These results indicate that common genetic variants in the GJA5 promoter may decrease Cx40 expression, and this in turn, may impair electrical coupling between atrial myocytes, creating conduction heterogeneity and thereby providing a substrate for AF. Interestingly, mutations have also been found in GJA5, in the genomic DNA of atrial tissue specimens from patients with lone AF, although, importantly, three of four mutations were absent from the genomic DNA of the lymphocytes of these patients (Gollób et al. 2006). This indicates that these mutations are of somatic origin, that is, a change in the genetic structure that is neither inherited nor passed to offspring and consequently that potentially causative mutations are only
Table 1. Genes containing mutations associated with atrial fibrillation

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>Mutation effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPPA</td>
<td>Natriuretic peptide precursor A</td>
<td>Chimeric protein, highly stable</td>
<td>Hodgson-Zingman et al. 2008</td>
</tr>
<tr>
<td>NUP155</td>
<td>Nucleoporin 155kDa</td>
<td>Weakening of nuclear envelope</td>
<td>Zhang et al. 2008</td>
</tr>
<tr>
<td>GJA5</td>
<td>Gap junction protein, alpha 5, 40kDa</td>
<td>Impaired transport/electrical coupling</td>
<td>Gollob et al. 2006</td>
</tr>
</tbody>
</table>

**Inherited Mutations**

- **KCNQ1**: K+ voltage-gated channel, KQT-like, 1 (Gain of function on Ik1 current) - Chen et al. 2003
- **KCN2**: K+ voltage-gated channel, Isk-related, 2 (Gain of function Ik1 current) - Yang et al. 2004
- **KCNJ2**: K+ inwardly-rectifying channel, J, 2 (Gain of function IK1 current) - Xia et al. 2005
- **KCNJ1**: K+ inwardly-rectifying channel, H (eag-related), 2 (Gain of function IK1 current) - Hong et al. 2005
- **SCN5A**: Na+ channel, voltage-gated, type V, alpha subunit (Steady-state inactivation->+) - Makiyama et al. 2008
- **KCNA5**: K+ voltage-gated channel, shaker-related, 5 (Dominant negative effect on IKur current) - Ellinor et al. 2008
- **KCNE2**: K+ voltage-gated channel, Isk-related, 2 (Gain of function IKr current) - Olson et al. 2006
- **KCNH2**: K+ voltage-gated channel, H (eag-related), 2 (Gain of function IKr current) - Hong et al. 2005

**Somatic Mutations**

- **GJA5**: Gap junction protein, alpha 5, 40kDa (Impaired transport/electrical coupling) - Gollob et al. 2006

confined to the diseased tissue. The identified GJA5 mutations were transfected into a gap-junction-deficient cell line and this revealed impaired intracellular transport or reduced intercellular electrical coupling. These results suggest that in addition to traditional germline variants or mutations, somatic mutations might also play an important role in predisposition to AF.

**Atrial Fibrillation and the Holt-Oram Syndrome: A Gain of Function?**

Atrial fibrillation can also occur in the setting of congenital heart defects, which can appear spontaneously or as part of a syndrome. One syndrome in which congenital heart defect and AF come together is the Holt-Oram syndrome, a heart-hand syndrome clinically characterized by upper limb and cardiac malformations. The congenital heart malformations in patients with Holt-Oram are generally atrial septal or ventricular septal defects, but other defects have been reported (Basson et al. 1994). Mutations in T-box transcription factor 5 (TBX5) underlie this syndrome. TBX5 is a member of the T-box transcription factor family that regulates a wide variety of developmental processes in vertebrates and invertebrates including specification of the mesoderm and development of the heart, vasculature, and limbs (Naiche et al. 2005).

All TBX5 mutations described so far are caused by protein loss of function. This leads to the question what the effect of Tbx up-regulation on cardiac development and function would be. Data on this derive mostly from overexpression models in chicken or in transgenic mice in which Tbx5 ventricular overexpression results in loss of ventricular-specific gene expression and aberrant morphogenesis (Liberatore et al. 2000). Furthermore, a patient with a chromosome 12q23 duplication, probably resulting in increased Tbx5 dosage, has a Holt-Oram phenotype similar to that of TBX5 haploinsufficiency. At first glance, these data suggest that under- and overexpression result in comparable phenotypes, the caveat being that cardiac-specific overexpression and chromosomal duplications are far more disruptive and probably influence many more factors than TBX5 alone. Nonetheless, it is clear that a balanced level of Tbx5 protein is critical for its function.

We recently described a Holt-Oram family in which affected patients have mild skeletal deformations and very few have congenital heart disease; however, most presented with paroxysmal AF (Postma et al. 2008). Atrial fibrillation has occasionally been described in sporadic patients with Holt-Oram (Basson et al. 1994), although principally in the setting of congenital heart disease and the resultant hemodynamic effects (atrial enlargement). However, one of the most striking features in this family was the occurrence of paroxysmal AF at an unusually young age and in the absence of congenital heart disease. Sequencing of TBX5 revealed a novel mutation, p.G125R, cosegregating with the disease. The mutant protein displayed significantly enhanced DNA-binding properties, resulting in augmented expression of Nppa, Cx40, KCNj2, and Tbx3 genes in comparison to wild-type TBX5. This is in contrast to all known Holt-Oram mutations to date (as mentioned above), which result in a loss-of-function phenotype. Although the various phenotypes of the individual family members fall within the spectrum of Holt-Oram syndrome, the combined effect of all the family members is distinctively atypical and likely the result of the gain-of-function pathophysiological mechanism. Overall, we speculate that the TBX5 gain-of-function mechanism underlies the mild phenotype and paroxysmal AF and suggests a possible role of TBX5 in the development of (paroxysmal) AF based on a gain-of-function. This gain of function may act either through a direct stimulation of target genes known to be involved in familial AF (NPPA, KCNJ2, Cx40 see above) via TBX5 or indirectly via TBX5 stimulated TBX3 (see above) because recent publications established that TBX3 is highly sensitive to TBX5 dosage (Mori et al. 2006). Moreover, TBX5 controls the sinusatrial node gene program (Hoogaars et al. 2007), is selectively expressed in the entire central conduction system (Hoogaars et al. 2004), and ectopic expression induces pacemaker genes and leads to ectopic pacemaker activity, which is a trigger for AF.

**Conclusion**

Atrial fibrillation is the most common cardiac arrhythmia and, therefore, represents a major public health problem. Its occurrence increases dramatically with age, and it is often associated with cardiac disorders, although it can occur without any heart or system disease. It is now established that a large fraction of the paroxysmal variant most often encountered in daily practice originates in the myocardial sleeves clothing the PVs (Haislaguerre et al. 1998). The relative risk of AF is estimated at 85% in individuals with
at least one parent with a history of AF (Fox et al. 2004), suggesting a genetic predisposition. Recent evidence has shown that genetic and developmental defects can be involved in the development of AF. Mutations in both potassium and sodium channels can cause either gain- or loss-of-function effects leading to AF. However, current evidence also suggests that mutations in transcription factors such as Nkx2-5 and Tbx5, involved in the development of the heart itself, can underlie AF. Importantly, small variations in expression levels of such transcription factors (eg, Nkx2-5) could already predispose individuals to AF. Such variations in expression are generally caused by single nucleotide polymorphisms, the most common genetic variation in the population. Further research into these areas is warranted because this will help provide insight into the mechanisms of AF, which could ultimately lead to improved therapy.

**Acknowledgments**

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**Supplementary Data**

Supplementary materials available online at [www.tcmnonline.org](http://www.tcmnonline.org).

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Tetralogy of Fallot as a Model to Study Cardiac Progenitor Cell Migration and Differentiation During Heart Development

Valentina Di Felice* and Giovanni Zummo

Tetralogy of Fallot (ToF) has long been considered a congenital disorder that occurs due to environmental alterations during gestation. Recently, several mutated genes have been discovered that are thought to be responsible for the malformations observed in ToF. These genetic mutations, which are microdeletions, are sporadic and are frequently also present in trisomy 21 patients. The ToF malformations can be lethal, but for the last 50 years, surgical repairs that place an artificial patch to repair the four features of ToF have improved the survival of patients with ToF. However, 0.5% to 6% of patients who survive after surgical repair of ToF die of sudden cardiac death caused by ventricular tachycardia. In fact, even if the septum has been repaired, the patch used to close the interventricular defect may cause deformation of the heart, altering the force lines essential for normal function of the right ventricle. In the present review, we hypothesize that mutations in the GATA binding protein 4 (GATA-4)/friend of GATA-2 transcriptional complex and NKX2.5 gene may play a role in the abnormal migration and behavior of precardiac cells during heart development in patients with ToF. An understanding of cardiac precursor cell behavior is needed in order for future research regarding therapeutic approaches to correct the defects seen in ToF without affecting cardiac hemodynamics to be successful. (Trends Cardiovasc Med 2009;19:130–135) © 2009, Elsevier Inc.

• Introduction

The four classic features that characterize Tetralogy of Fallot (ToF) are ventricular septal defect, biventricular connection (overriding) of the aorta, subpulmonary stenosis, and right ventricle (RV) hypertrophy (Ho et al. 2001). Surgical biventricular correction of this congenital heart defect was devised more than 50 years ago. In most cases, intracardiac repair consists of patch closure of the ventricular septal defect and patch enlargement of the pulmonary trunk. These procedures have excellent short-term outcomes, but the incidence of late complications is increasing in parallel with the growing number of postrepair survivors (Karamlou et al. 2006). Among the possible complications observed in long-term survivors, the most important are late mortality as well as right-sided and left-sided cardiac complications. The right-sided complications include pulmonary valve regurgitation, atrial and ventricular arrhythmias, tricuspid valve regurgitation, and residual RV outflow tract (OFT) obstruction.

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