Genome-Wide Linkage Scan Identifies a Novel Genetic Locus on Chromosome 5p13 for Neonatal Atrial Fibrillation Associated With Sudden Death and Variable Cardiomyopathy

Carlos Oberti, MD, MS*; Lejin Wang, MD*; Lin Li, PhD; Jiamei Dong, MD; Shaoqi Rao, PhD; Wei Du, BS; Qing Wang, PhD, MBA

Background—Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and patients with AF have a significantly increased risk for ischemic stroke. Approximately 15% of all strokes are caused by AF. The molecular basis and underlying mechanisms and pathophysiology of AF remain largely unknown.

Methods and Results—We have identified a large AF family with an autosomal recessive inheritance pattern. The AF in the family manifests with early onset at the fetal stage and is associated with neonatal sudden death and, in some cases, ventricular tachyarrhythmias and waxing and waning cardiomyopathy. Genome-wide linkage analysis was performed for 36 family members and generated a 2-point logarithm of the odds (LOD) score of 3.05 for marker D5S455. The maximum multipoint LOD score of 4.10 was obtained for 4 markers: D5S426, D5S493, D5S455, and D5S1998. Heterozygous carriers have significant prolongation of P-wave duration on ECGs compared with noncarriers (107 versus 85 ms on average; \( P=0.000012 \)), but no differences between these 2 groups were detected for the PR interval, QRS complex, ST-segment duration, T-wave duration, QTc, and R-R interval (\( P>0.05 \)).

Conclusions—Our findings demonstrate that AF can be inherited as an autosomal recessive trait and define a novel genetic locus for AF on chromosome 5p13 (arAF1). A genetic link between AF and prolonged P-wave duration was identified. This study provides a framework for the ultimate cloning of the arAF1 gene, which will increase the understanding of the fundamental molecular mechanisms of atrial fibrillation. (Circulation. 2004;110:3753-3759.)

Key Words: arrhythmia ■ genetics ■ atrium ■ fibrillation ■ death, sudden

Atrial fibrillation is “a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.”1 It is the most common sustained cardiac rhythm disturbance, and its prevalence increases as the population ages.2 Atrial fibrillation affects 2.2 million Americans, and each year 160,000 new cases are diagnosed.3 It is associated with significant morbidity and mortality.4,5 An estimated 70,000 strokes each year in the United States are caused by atrial fibrillation.4 Atrial fibrillation can be associated with heart diseases, including coronary artery disease, congestive heart failure, hypertension, congenital heart disease, diabetes, rheumatic or other significant valvular heart disease, significant left ventricular systolic dysfunction, and hyperthyroidism.2,6 However, it can also occur in many patients without any other detectable cardiac and systemic diseases, known as “lone atrial fibrillation” (20% to 50% of the patients with atrial fibrillation).1,6

Electrophysiological studies have demonstrated that ectopic foci of repetitive atrial activity, usually arising from the pulmonary veins, may initiate atrial fibrillation.7 Furthermore, atrial fibrillation can cause changes in cellular electrophysiology (electrical remodeling; altered gene expression of the L-type calcium channel, potassium channels \( I_{\text{To}}, I_{\text{Kr}}, I_{\text{KAdo}}, \text{etc} \)).8 Atrial fibrillation is also associated with adaptive and maladaptive changes in tissue and cellular architecture (structural remodeling).9

Atrial fibrillation can occur in families, suggesting a genetic propensity for atrial fibrillation in some patients. Two
genetic loci for autosomal dominant atrial fibrillation have been mapped to chromosomes 10q22-2410 and 6q14-1611; however, the specific genes have not yet been identified. A gain-of-function mutation (S140G) in the cardiac potassium channel gene KCNQ1 (KvLQT1) on chromosome 11p15.5, the type-1 long-QT syndrome (LQTS) gene,12 was found to be associated with autosomal dominant atrial fibrillation in a Chinese family.13 However, it is important to note that more than 50% of the affected members (9 of 16) in the family are also affected with LQTS, which is caused by loss-of-function or dominant-negative mutations in KCNQ1. The molecular basis of the majority of atrial fibrillation cases, however, remains unknown.

In this study, we describe the identification of a form of atrial fibrillation that is inherited in an autosomal recessive manner. We then used genome-wide linkage scan to map the genetic locus for this type of atrial fibrillation (arAF1) and performed genotype-phenotype correlation studies for heterozygous carriers and noncarriers in the family.

**Methods**

**Study Subjects and Phenotyping**

The autosomal recessive atrial fibrillation family was identified in Uruguay, South America, and subsequently recruited to our laboratory for genetic analysis. Informed consent was obtained from the participants or their guardians in accordance with standards established by the Cleveland Clinic Foundation Institutional Review Boards on Human Subjects.

Phenotyping was performed on the basis of clinical history, physical examinations, and the data from resting 12-lead ECG. Echocardiography was also performed for a few selected family members. The diagnosis was based on the criteria by the ACC/AHA/ESC Joint Committee of Experts on the Management of Patients with Atrial Fibrillation, which include the following typical ECG features.

1. Discrete P waves are absent or difficult to count.
2. Rapid oscillations or fibrillatory waves (f waves) that vary in size, shape, and timing are present.
3. An atrial rate (frequency of f waves) of 150 to 300 bpm is seen or is difficult to detect at high atrial rates.
4. There is an irregular, frequently rapid, ventricular rate because of constant stimulation from the atria, 100 to 200 bpm; irregularly irregular rhythm; or inconsistent R-R interval. QTc was measured as the QT interval corrected for heart rate.14,15 P-wave duration was measured from lead II.

**Isolation of Genomic DNA and Genotyping**

Genomic DNA was prepared from whole blood with the DNA Isolation Kit for Mammalian Blood (Roche Diagnostic Co). A genome-wide scan was performed using 398 polymerase chain reaction–based short tandem repeat polymorphic markers from chromosomes 1 to 22 (ABI Prism Linkage Mapping Set MD10) as described previously.16 These markers span the human genome by every 10 cM. Amplification of each short tandem repeat was performed by polymerase chain reaction using the PE 9700 PCR System with the standard procedure as instructed by the manufacturer (ABI). Genotyping was performed using an ABI 3100 Genetic

**Figure 1.** Mapping of a novel genetic locus for autosomal recessive atrial fibrillation (arAF1). Pedigree structure of a family with autosomal recessive atrial fibrillation is shown. Genome-wide linkage analysis was performed with 398 polymorphic markers that span entire human genome by an average interval of 10 cM. Results of genotypic analysis are shown for markers DSS1506, DSS426, DSS493, DSS545, DSS1998, DSS1964, and DSS1490 below each individual. Affected individuals are shown as filled circles (females) and squares (males). Normal individuals are shown as empty symbols, and deceased individuals are indicated by slashes. Proband is indicated by an arrow. Obligate carriers by genotyping are denoted with black dots in symbols. Disease haplotype is denoted with a filled vertical bar, and normal haplotypes are indicated by open vertical bars. ECG analysis of normal family members and obligate heterozygous carriers did not reveal any clinical features of atrial fibrillation. Seven consanguineous marriages are indicated by =.
Analyzer. Genotyping data were scored using the GeneMapper 2 software (ABI).

Fine mapping was performed using additional markers identified at the Genethon and Center for Medical Genetics, Marshfield Medical Research Foundation, databases.

**Linkage Analysis**

Phenotyping data, genotyping data, and pedigree information were introduced into a computer, and pairwise linkage analysis was performed using the Fastlink software package.\(^1^7\) Two-point linkage analysis was performed assuming an autosomal recessive pattern of inheritance, a disease-allele frequency of 0.001, and penetrance of 0 for carriers and noncarriers and 0.99 for homozygous affected individuals. The logarithm of the odds (LOD) scores were calculated using the actual allele frequencies of each marker that were calculated from the genotyping data of 38 independent individuals from Uruguay (Data Supplement Table). Gene frequency was assumed to be equal between males and females. Multipoint linkage analysis was performed using the Simwalk2 program,\(^1^8\) with the fine mapping data formatted with the Mega2 (version 2.5) program.\(^1^9\) The parameters used for multipoint linkage analysis are identical to those for 2-point linkage analysis. The distance (cM) between markers was based on the data from the Center for Medical Genetics, Marshfield Medical Research Foundation, database.

**Results**

**Identification of Autosomal Recessive Atrial Fibrillation**

We identified a large consanguineous atrial fibrillation family from Uruguay, South America with 57 family members (32 males and 25 females; ages from 3 months to 93 years) in 5 living generations (Figure 1). Seven consanguineous marriages occurred in the family. The ECG from proband V:11 and patient VI:2 showed the typical features of atrial fibrillation: absent or difficult-to-count P waves, a fast atrial rate, and inconsistent R-R intervals (Data Supplement Figure). QTc (the QT interval corrected for heart rate) is 0.42 and 0.40 second for the proband V:11 and affected member VI:2, respectively. LQTS was not detected in any members from this family (Table 1). No abnormalities were found in other organ systems. The atrial fibrillation in the family appeared to be chronic atrial fibrillation. Interestingly, multiple sudden deaths occurred in the family: the proband (V:11) died at the age of 15 months, and affected members V:9, V:10, and VI:1 also died suddenly at the ages of 3 months, 2 months, and 18
months, respectively. The family history study also revealed 2 other claimed cases of sudden death (IV:17, IV:18; Figure 1), but the exact cause of the death was not known. Patient VI:2 died suddenly at the age of 1 year and 7 months after this article was submitted. Thus, autosomal recessive atrial fibrillation in this family appears to be associated with a particularly severe form of clinical outcome, early onset, and association with sudden death.

The proband (V:11) was delivered by caesarean section at week 36 of pregnancy because of fetal tachycardia, with a heart rate of 250 bpm and atrial fibrillation/flutter. Supraventricular tachyarrhythmias continued after the delivery. The first echocardiogram at the age of 2 days showed marked dilatation of both atria and an ejection fraction of 52%, and amiodarone (10 mg/d) was prescribed. At the age of 1 month, an electrophysiological study was performed and detected atrial fibrillation/flutter. Because of the mild response to amiodarone and the family history of sudden death, linear ablation on the left atrium was attempted but was unsuccessful. After application of a Farman catheter, ablation of the atrioventricular node was performed, setting a ventricular rate of 100 bpm. Two days later, a permanent pacemaker was implanted because of the high frequency of sudden death in the family. At the age of 2 months, only mild atrial dilatation was observed, and the ejection fraction was borderline normal, even though no antiarrhythmic therapy was exercised. The ejection fraction was 52% at the age of 4 months. The patient, however, died suddenly at the age of 15 months.

For patient VI:2, a recent echocardiogram at the age of 15 months was normal. Echocardiography did not detect structural heart abnormalities in her mother and grandmother (data not shown), the obligate carriers. This patient was on medical treatment with digoxin (0.07 mg twice a day) and propafenone (30 mg/d), which apparently maintained the patient in sinus rhythm with a heart rate of 125 bpm. The patient, however, died recently at the age of 1 year and 7 months.

Affected member V:9 was born with supraventricular tachycardia. He was delivered by caesarean section at week 37 of pregnancy because of fetal tachycardia. An ECG at the age of 24 days showed atrial flutter, with a heart rate of 200 bpm. No structural heart abnormalities were detected by echocardiography at the age of 24 days, but a later echocardiogram showed dilatation of the left ventricle and left atrium and a decrease of contractility (ejection fraction of 43%).

Affected member V:10 was born with atrial tachycardia, and echocardiography did not detect structural heart disease.

Affected member VI:1 was born with atrial tachycardia, and electrical cardioversion was performed at the age of 20 days. At the age of 1 month, an echocardiogram showed normal ventricular and atrial sizes.

The atrial fibrillation in the family is inherited with an autosomal recessive pattern, because all parents have normal phenotype, and occurrence of atrial fibrillation is associated with consanguineous marriages (Figure 1). These results suggest that atrial fibrillation can be inherited as an autosomal recessive trait.

<table>
<thead>
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</tr>
<tr>
<td>DSS493</td>
<td>0.22 0.08 -0.03 -0.17 -0.19 -0.13</td>
</tr>
<tr>
<td>DSS426</td>
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</tr>
<tr>
<td>DSS455</td>
<td>3.05 2.61 2.17 1.39 0.84 0.43</td>
</tr>
<tr>
<td>DSS1998</td>
<td>2.23 1.98 1.74 1.26 0.81 0.39</td>
</tr>
<tr>
<td>DSS1964</td>
<td>1.91 1.77 1.60 1.20 0.78 0.37</td>
</tr>
<tr>
<td>DSS1490</td>
<td>-3.24 -0.58 -0.11 0.20 0.24 0.16</td>
</tr>
</tbody>
</table>

**Identification of a Novel Genetic Locus for Autosomal Recessive Atrial Fibrillation by Genome-Wide Linkage Analysis**

A genome-wide scan was performed for 36 family members from kindred arAF1 (Figure 1) using markers that span the human genome by every 10 cM. Analysis of the pairwise LOD scores identified significant linkage to one marker, DSS455, on chromosome 5p13 (Table 2; Figure 1). A peak LOD score of 3.05 was obtained for DSS455 at a recombination fraction of 0 with the actual marker allele frequencies (Data Supplement Table) specific to the Uruguay population. The LOD scores were also calculated with the commonly used allele frequencies of 1/n, where n is the number of alleles observed, which increased the LOD score for DSS455 to 3.44, 3.448, and 3.450 at a disease frequency of 0.001, 0.0001, respectively.

<table>
<thead>
<tr>
<th>Marker</th>
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<tr>
<td>DSS455</td>
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</tr>
<tr>
<td>DSS1490</td>
<td>-3.24 -0.58 -0.11 0.20 0.24 0.16</td>
</tr>
</tbody>
</table>

**TABLE 2. Pairwise LOD Scores for Chromosome 5p13 Markers at the arAF1 Locus**

LOD scores were calculated by use of the FASTLINK linkage program assuming autosomal recessive inheritance, 99% penetrance, and the disease frequency of 0.001. Allele frequencies for LOD score calculation are actual frequencies in the Uruguay population derived from genotyping data of 38 independent individuals (76 chromosomes) (supplementary Table 1). LOD scores varied little with the estimated disease frequencies: the LOD score for DSS455 increased to 3.06 at a disease frequency of 0.0001 and 0.00001. The LOD scores were also calculated using the allele frequencies of 1/n (where n is the number of alleles observed), which increased the LOD scores for marker DSS455 to 3.440, 3.448, and 3.450 at a disease frequency of 0.001, 0.0001, and 0.00001, respectively.

**P-Wave Duration Is Significantly Prolonged in Heterozygous Carriers in the arAF1 Family**

Genotypic analysis identified 24 family members in kindred arAF1 as heterozygous carriers who share one disease haplotype (Figure 1). ECGs were recorded from 19 carriers and 5 noncarriers (Table 1). None of the heterozygous carriers are
affected with atrial fibrillation. Detailed ECG parameters for the 19 carriers and 5 noncarriers were measured and analyzed (Table 1 and Figure 4). No significant differences between the carriers and noncarriers were detected for the PR interval, QRS complex, ST-segment duration, T-wave duration, QT interval and QTc (412 ms for carriers versus 416 ms for noncarriers), and R-R interval ($P>0.05$) (Figure 4). By contrast, a highly significant difference was observed for the P-wave duration between the carriers and noncarriers (107 ms for carriers versus 85 ms for noncarriers, $P=0.0000122$) (Figure 4).

**Discussion**

Our study demonstrates that atrial fibrillation can be inherited as an autosomal recessive trait. Furthermore, we have mapped the autosomal recessive atrial fibrillation gene to chromosome 5p13 ($arAF1$). The identification of the autosomal recessive form of atrial fibrillation may have an implication for our understanding of the more common sporadic atrial fibrillation cases. The majority of atrial fibrillation cases are considered to be sporadic. Although major mutations in the genes for inherited atrial fibrillation would be anticipated to be responsible for monogenic forms of atrial fibrillation (such as in the family studied here), more common variants or single-nucleotide polymorphisms could be responsible for “sporadic” forms of atrial fibrillation in adults. After the autosomal recessive atrial fibrillation gene is identified, it will be interesting to perform mutation analysis or single-nucleotide polymorphism identification in sporadic cases to validate the above hypothesis.
The atrial fibrillation in the family studied here appeared to be very severe, because it is manifested by early, fetal or infantile, age at onset and is associated with sudden death. Remarkably, the heterozygous carriers did not show signs of atrial fibrillation. These features are consistent with the recessive mode of inheritance, as in other diseases, including LQTS. Patients with autosomal recessive LQTS have a much more severe clinical outcome than those with the autosomal dominant form of LQTS.20–23

Ventricular tachyarrhythmia was detected at the fetal stage in 2 of the 5 affected individuals, proband V:11 and affected member V:9. Although ventricular tachyarrhythmia has been demonstrated in atrial fibrillation patients,24,25 it is still interesting to detect ventricular tachyarrhythmia at the fetal stage in the arAF1 family. This is consistent with the earlier argument that the autosomal recessive form of atrial fibrillation in the arAF1 family is associated with a severe outcome.

It has been reported that atrial fibrillation with a rapid ventricular response may lead to a nonischemic cardiomyopathy.25 In the arAF1 family studied here, dilatation of both atria and an ejection fraction of 52% were found at the age of 2 days in proband V:11, but these disappeared or minimized later in his life. The patient was under medication with amiodarone (10 mg/d) and had a pacemaker implanted, but it is unknown whether these therapies led to the later improvements on the echocardiographic parameters. Dilatation of left atrium and left ventricle and a low ejection fraction of 43% were found for affected member V:9. No structural abnormalities were detected in other affected members, including VI:2, V:10, and VI:1. It is unknown whether atrial and ventricular dilatation in 2 of the 5 affected members in the arAF1 family are caused by atrial fibrillation or whether they are accompanying features of the autosomal recessive atrial fibrillation in this family.

Although the heterozygous carriers in the arAF1 family studied here did not manifest the typical ECG features of atrial fibrillation, their P-wave duration, on average (107 ms), was abnormal (normal P-wave duration, 80 to 100 ms) and significantly longer than the value of 85 ms from the noncarriers (P=0.00012, Figure 4). Thus, this study identifies a genetic link between prolongation of P-wave duration and atrial fibrillation. On the basis of this interesting observation, we can speculate that prolonged P-wave duration may be a precursor to atrial fibrillation in this family, although it remains to be determined whether prolonged P-wave duration is a predictor for common sporadic or lone atrial fibrillation. Because the P wave on the standard ECG corresponds to the intra-atrial conduction times,26 prolonged P-wave duration may be an indication of abnormal atrial conduction. Thus, atrial fibrillation can be an atrial conduction disorder. It is interesting to note that a parallel comparison can be made for atrial fibrillation and LQTS, because LQTS is characterized by prolongation of QTc and abnormalities in ventricular conduction.21 The P-wave durations for patients VI:1 and VI:2 were 80 ms and 60 ms, respectively, on ECGs at sinus rhythm; however, caution should be exercised in interpreting these readings, because the ECGs were recorded while atrial fibrillation in the patients was cardioverted electrically and controlled pharmacologically.

It is anticipated that, like ventricular fibrillation, atrial fibrillation may be caused by mutations in ion channel genes. The arAF1 gene is defined within a 7.76-cM region, and the only channel gene identified at this locus is SLC1A3, which encodes glial high-affinity, Na+-dependent glutamate transporter. Sequence analysis of all exons, including exon-intron boundaries, of SLC1A3 failed to identify any mutation in our arAF family. Furthermore, no cardiac ion channel genes were mapped to the 2 autosomal dominant atrial fibrillation loci on chromosomes 10 and 6. Continued mutational analysis with other candidate genes at the arAF1 locus should lead to the identification of the specific atrial fibrillation gene at this locus. Identification of an atrial fibrillation gene is likely to greatly further our understanding of the molecular mechanism underlying the pathogenesis of atrial fibrillation, the most common cardiac arrhythmia.

Figure 4. ECG characterization of heterozygous carriers and noncarriers. A 2-tailed probability value was obtained by use of a Student’s t test with assumption of unequal variances and null hypothesis of no difference between mean values. Error bar represents SD. Only significant difference between carriers and noncarriers was identified for duration of P wave (P=0.000122). P wave indicates P-wave duration recorded from lead II (normal range for P-wave duration is from 80 ms to 100 ms); PR, length of PR interval; QRS, duration of QRS complex; ST, length of ST segment; T, T-wave duration; QT, length of QT interval; RR, length of RR interval; QTc, QT corrected for heart rate.
Acknowledgments
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### Supplementary Figure 1. Diagnosis of atrial fibrillation in family arAF1.

**A**, Electrocardiogram from the proband V:11 (fig. 1). **B**, Electrocardiogram from the patient VI:2 (fig. 1). Typical electrocardiographic features with a diagnosis of atrial fibrillation were observed in both proband V:11 and patient VI:2. **C**, Normal echocardiogram for patient VI:2, and corresponding values derived from the echocardiogram in comparison to the normal ranges.

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<th>N(^a)</th>
<th>Doppler value</th>
<th>Case(^b)</th>
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Case\(^a\), observed values (mm); N\(^a\), normal range (mm); Case\(^b\), observed values (m/s); N\(^b\), Normal range (m/s)