Biophysical and Molecular Characterization of a Novel De Novo KCNJ2 Mutation Associated With Andersen-Tawil Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia Mimicry

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Background—Mutations in KCNJ2, the gene encoding the human inward rectifier potassium channel Kir2.1 (I_K1 or I_Kir2.1), have been identified in Andersen-Tawil syndrome. Andersen-Tawil syndrome is a multisystem inherited disease exhibiting periodic paralysis, cardiac arrhythmias, and dysmorphic features at times mimicking catecholaminergic polymorphic ventricular tachycardia.

Methods and Results—Our proband displayed dysmorphic features including micrognathia, clinodactyly, and syndactyly and exhibited multiform extrasystoles and bidirectional ventricular tachycardia both at rest and during exercise testing. The patient’s symptoms continued after administration of nadolol but subsided after treatment with flecainide. Molecular genetic screening revealed a novel heterozygous mutation (c.779G>C/p.R260P) in KCNJ2. Whole-cell patch-clamp studies conducted in TSA201 cells transfected with wild-type human KCNJ2 cDNA (WT-KCNJ2) yielded robust IK1 but no measurable current in cells expressing the R260P mutant. Coexpression of WT and R260P-KCNJ2 (heterozygous expression) yielded a markedly reduced inward IK1 compared with WT alone (-36.5±9.8 pA/pF versus -143.5±11.4 pA/pF, n=8 for both, P<0.001, respectively, at -90 mV), indicating a strong dominant negative effect of the mutant. The outward component of IK1 measured at -50 mV was also markedly reduced with the heterozygous expression versus WT (0.52±5.5 pA/pF versus 23.4±6.7 pA/pF, n=8 for both, P<0.001, respectively). Immunocytochemical analysis indicates that impaired trafficking of R260P-KCNJ2 channels.

Conclusions—We report a novel de novo KCNJ2 mutation associated with classic phenotypic features of Andersen-Tawil syndrome and catecholaminergic polymorphic ventricular tachycardia mimicry. The R260P mutation produces a strong dominant negative effect leading to marked suppression of IK1 secondary to a trafficking defect. (Circ Cardiovasc Genet. 2011;4:51-57.)

Key Words: inward rectifier current • I_K1 • cardiac arrhythmias • catecholaminergic polymorphic ventricular tachycardia • electrophysiology • genetics

Andersen-Tawil syndrome (ATS) is a rare inherited disorder with autosomal dominant inheritance (OMIM No. 170390) characterized by potassium-sensitive periodic paralysis, cardiac arrhythmias, and dysmorphic features.1,2 ATS has been associated with a variable degree of QT interval prolongation and abnormal T-wave morphology often presenting with very prominent U waves.3 Life-threatening ventricular arrhythmias, such as torsade de pointes (TdP), are rare in ATS, although sudden death has been reported.3

Clinical Perspective on p 57

ATS is caused by mutations in KCNJ2, the gene that encodes Kir2.1 (OMIM No. 600681), the inward rectifier potassium channel (I_K1), located at 17q23.1-q24.2. It is highly expressed in the heart, where it plays a determining role in phase 4 repolarization and of resting membrane potential. Kir2.1 also plays a major role in developmental signaling, accounting for the dysmorphic facial features that characterize ATS.4 The disorder shows marked intrafamilial variability and incomplete penetrance,5 at times mimicking catecholaminergic polymorphic ventricular tachycardia (CPVT) by presenting with bidirectional ventricular tachycardia (BiVT) and exertion/emotion-induced arrhythmia. Recent KCNJ2 mutations have been designated as CPVT3.6,7

The present study identifies a young girl with ATS and CPVT mimicry, presenting with dysmorphic features, syn-
cope, frequent ventricular extrasystoles, nonsustained polymorphic ventricular tachycardia (PVT), BiVT, and prolonged QTc, secondary to a novel de novo mutation in \textit{KCNJ2}.

**Methods**

**Clinical Subjects**

The study was approved by the regional institutional review board. All members of the immediate family underwent clinical and genetic evaluation after giving informed consent. The proband underwent Holter monitoring as well as an exercise stress test.

**Molecular Genetic Analysis**

Genomic DNA was extracted from peripheral blood leukocytes using a commercial kit (Genta System, Puregene, Valencia, CA). All exons and intron borders of \textit{KCNJ2} (Kir\textsubscript{2.1}) gene were amplified and direct sequenced from both directions using an ABI PRISM 3100-Avant Automatic DNA sequencer (Applied Biosystems, Foster City, CA). Genomic DNA from 430 ethnically matched healthy reference alleles were used as controls. The \textit{KCNJ2} primers used for screening of family members are shown in Table 1.

**Site-Directed Mutagenesis and Transfection of the TSA201 Cell Line**

\textit{KCNJ2} mutation and wild-type (WT) were prepared using the QuickChange Site-Directed Mutagenesis kit (Stratagene, La Jolla, CA). Full-length human \textit{KCNJ2} cDNA (kind gift of C. Vandenberg) were subcloned into pcDNA3.1(+) plasmid (Invitrogen, Carlsbad, CA). The mutation was confirmed by direct DNA sequencing. Kir2.1 constructs were expressed in TSA201 cells. A total of 2 μg cDNA was transfected for whole-cell voltage-clamp experiments. To mimic the heterozygous state, WT and R260P Kir2.1 were coexpressed together at one-half of the amounts of total transfected DNA. Cells were transfected with FuGENE 6 reagent (Roche Molecular Biochemicals, Indianapolis, IN) according to manufacturer instructions. In addition, CD\textsubscript{4} cDNA was cotransfected as a reporter gene to visually identify transfected cells using Dynabeads (M-450 CD\textsubscript{4}, Dynal Biotech, Oslo, Norway). The cells were grown on 35-mm culture dishes (Cell+, Sarstedt, Newton, NC) and placed in a temperature-controlled chamber (37°C, 5% CO\textsubscript{2}) for 24 to 48 hours before patch-clamp study.

**Electrophysiology Patch-Clamp Recording Techniques**

Human embryonic modified kidney (TSA) 201 cells were grown and transfected as previously described. Current recordings were conducted in the whole-cell configuration at room temperature (22°C). Pipettes had a tip resistance of 1.5 to 2.5 mol/L at when filled with the pipette solution containing (in mM): 140 KCl, 2 MgCl\textsubscript{2}, 1 EGTA, and 10 HEPES, pH 7.3. Cells were bathed in a solution containing (in mM): 135 NaCl, 5 KCl, 1 MgCl\textsubscript{2}, 10 glucose, and 10 HEPES, pH 7.3. Currents were elicited by 500-ms pulses applied in 10 mV increments to potentials ranging from −140 mV to +30 mV from a holding potential of −80 mV.

**Immunocytochemistry and Confocal Analysis**

Forty-eight hours after transfection, TSA201 cells were washed with phosphate-buffered saline (PBS) and fixed with 4% paraformaldehyde for 10 minutes. Cells were then washed with PBS 3 times. Cells were then permeabilized with 0.1% Triton-X and blocked with 5% serum. Cells were then incubated overnight with primary antibodies then washed with PBS, followed by 2-hour incubation with thefluorophore-conjugated secondary antibody in 1:1000 dilution at room temperature. Staining of nDNA was accomplished by addition of propidium iodide (Sigma, St Louis, MO). After the final wash, the coverslips were mounted with Prolong Gold Antifade (Molecular Probes, Eugene, OR). XYZ images of labeled cells were collected as previously described using a Fluoview confocal microscope. An argon or krypton-argon laser (dependent on fluorophore) provided the excitation light. Fluorescence signals were collected with a ×40 oil-immersion objective lens. XY frame was set to 512×512 pixels and laser intensity was set to 6% to 10% power. The Z-axis was changed in approximately 0.5-μm increments by computer control through the entire volume of the cell. Analysis of labeled cells was performed using both Fluoview and Image J software. The primary antibodies used in this study were rabbit polyclonal antibody raised against amino acids 378 to 417 mapping within a C-terminal cytoplasmic domain of human Kir2.1 (H-40; 1:100; Alomone Labs, Jerusalem, Israel). For fluorescence detection, a secondary donkey anti-rabbit IgG antibody, conjugated with Alexa Fluor 488 (1:1000; Molecular Probes Invitrogen Corp, Carlsbad, CA), was added.

**Statistical Analysis**

Results are reported as mean±SEM (n=number of cells). Statistical differences between WT and mutant channels were evaluated by Student unpaired t test. Significance was assumed for $P<0.05$; “NS” indicates nonsignificant changes.

**Results**

**Clinical Features of Andersen-Tawil Syndrome**

A 10-year-old girl presented with ATS characterized by dysmorphic features and cardiac arrhythmias. Her plasma potassium and calcium concentrations were in the normal range. Echocardiographic evaluation and thyroid levels were normal. The patient exhibited micrognathia and retrognathia, hypertelorism, a broad-based nose (Figure 1A), clinodactyly of the third digit (Figure 1B and 1C), and syndactyly of the second, third, and fourth toes (Figure 1D). The ECG showed frequent ventricular extrasystoles; nonsustained, relatively slow PVT; and BiVT (Figure 1E). The PR interval and QRS duration were normal. QTc was 460 ms; QUc was prolonged to a maximum of 626 ms (Figure 1F). BiVT and a slow PVT (multiform extrasystoles) were observed at rest as well as during exercise testing. There was no indication of periodic paralysis, and the arrhythmic manifestations were associated with palpitation and dizziness.

The patient’s symptoms persisted after administration of nadolol during and after stress testing (Figure 2A and 2B). Flecainide (300 mg) suppressed BiVT developing at rest and during exercise (Figure 2C and 2D). The patient remained largely asymptomatic over a 4-year follow-up period while maintained on 2 mg/kg/d of flecainide. Sporadic extrasystolic events were observed, particularly when flecainide doses were missed.

**Molecular Genetics Analysis in \textit{KCNJ2} Gene**

Genetic screening revealed a novel heterozygous mutation consisting of a G-to-C transition at nucleotide 779 (c.779
G>C) in KCNJ2 predicting a substitution of a proline for arginine at residue 260 (p.Arg260Pro) of Kir2.1 channel (R260P) (Figure 3B). This mutation was not found in 430 reference alleles from healthy controls. This mutation was absent in family members, all of whom were clinically unaffected (Figure 3). Paternity testing supported the conclusion that the genetic variation uncovered in the proband was a de novo mutation (Figure 3A). Residue P260 is located at the carboxyl terminal region of Kir2.1 (Figure 3C). Alignment of the amino acid sequence of Kir2.1 proteins shows that arginine at position 260 is highly conserved among species (Figure 3D). This missense mutation predicts substitution of an arginine (R), an amino acid with strong positive polarity, for proline (P), a nonpolar neutral amino acid. Table 2 compares the sequence of homologous regions of related Kir channels, showing that the mutated residue appears critical for the normal function of all classes of inward rectifier channels.

**Table 2. Alignment of Amino Acid Sequences of Kir Channels**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Channel</th>
<th>Chromosome</th>
<th>Amino Acid Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNJ2</td>
<td>Kir2.1</td>
<td>17q24.3</td>
<td>INVGFDSGIDIFLVSPTTV</td>
</tr>
<tr>
<td>KCNJ4</td>
<td>Kir2.3</td>
<td>22q13.1</td>
<td>LNQYDGLDRIFLVSPIIV</td>
</tr>
<tr>
<td>KCNJ5</td>
<td>Kir3.4</td>
<td>11q24</td>
<td>INVGFSGIDRIFLVSPLIS</td>
</tr>
<tr>
<td>KCNJ6</td>
<td>Kir3.2</td>
<td>21q22.1</td>
<td>INVGFSGIDRIFLVSPLIS</td>
</tr>
<tr>
<td>KCNJ9</td>
<td>Kir3.3</td>
<td>1q23.2</td>
<td>LSVGFSGIDRIFLVSPIIV</td>
</tr>
<tr>
<td>KCNJ12</td>
<td>Kir2.2</td>
<td>17q11.1</td>
<td>IDVSDKGLDRIFLVSPTTV</td>
</tr>
<tr>
<td>KCNJ14</td>
<td>Kir2.4</td>
<td>19q13</td>
<td>VDVGFDGSTDRIFLVSPTTV</td>
</tr>
</tbody>
</table>

Novel mutations affect residue 260 as indicated. Sequence homology is shown in bold type.
mixture of WT and R260P-KCNJ2 plasmid to simulate allelic heterozygosity (Figure 4C). Figure 5A shows the current-voltage relationship. Both inward and outward currents measured with an equimolar concentration of WT and R260P-KCNJ2 yielded a significantly reduced current relative to WT. As summarized in Figure 5B and 5C, current densities for coexpression of WT and R260P of KCNJ2 were significantly smaller than those displayed by WT and consistent with a strong dominant negative effect of the mutant allele.

**Immunocytochemistry Studies**

Using immunocytochemistry and confocal image analysis, we found that the R260P mutation causes defective trafficking of KCNJ2 channels to the surface membrane. Figure 6 (A through I) shows representative confocal images. TSA201 cells were transfected with WT-KCNJ2, R260P-KCNJ2, or without anything. R260P-KCNJ2 channels exhibited surface membrane fluorescence intensity that was 9.93 ± 1.77% that of WT-KCNJ2 (Figure 6M), suggesting impaired trafficking of the mutant channel. Nontransfected controls exhibited little to no fluorescence (0.93 ± 0.47% of WT-KCNJ2).

**Discussion**

**Clinical and Genetic Characteristics of ATS With KCNJ2 Mutations**

ATS, also known as LQT7, is a disorder that leads to a triad of clinical manifestations, including episodes of muscle weakness (periodic paralysis), arrhythmia, and developmental abnormalities.1,2 The most common cardiac manifestations are QT prolongation and ventricular arrhythmia. If untreated, it can cause palpitation, fainting (syncope), or cardiac arrest. In addition to periodic paralysis, the female proband was identified with dysmorphic features such as micrognathia, clinodactyly, and syndactyly. The patient’s ECG also presented with prolongation of QTc, BiVT, and exercise-induced arrhythmia, the latter demonstrating similarity to what is commonly observed in CPVT.

Two types of ATS are distinguished by genetic causes. Type 1, which accounts for approximate 60% of cases, is caused by the KCNJ2 gene mutations.4,11 The remaining cases with unknown cause are designated as type 2. A number of mutations in distinct regions of KCNJ2 have previously been identified in patients diagnosed with ATS. Defective trafficking or decreased affinity for PIP2 have been shown to contribute to loss of channel function associated with some of these mutations.12–15 In both trafficking and nontrafficking defective channels, a dominant-negative effect of the mutant allele has been observed.15 We report a novel de novo KCNJ2 C-terminal missense mutation, R260P, capable of causing total loss of function when homozygously expressed and greatly diminished current when heterozygously expressed.
A recent publication associated with ATS showed that some carboxy terminal KCNJ2 mutations affect the structure and the proper assembly of the cytoplasmic domains of Kir2.1.\textsuperscript{13,16} The V302 mol/L, E303K, R312C, and A314 to 315 mutations occur within the C-terminus, a domain that has been implicated with channel trafficking and assembly. In our case, the R260P-KCNJ2 mutation is also located in the C-terminus and it is therefore not surprising that that loss of function of I_{K1} is mediated by impaired trafficking of the mutant channels (Figure 6).

**ATS or CPVT?**

KCNJ2 mutations have been previously established as a cause of the pleiotropic ATS.\textsuperscript{17} Patients clinically diagnosed with CPVT and shown to be genotype-negative for RYR2 or CASQ2, have been identified to carry mutations in KCNJ2, and consequently classified as CPVT3. The discovery of KCNJ2 mutations in CPVT patients has been described as phenotypic mimicry.\textsuperscript{6,17} This variant of ATS may present a diagnostic challenge, especially when the proband lacks the muscular disorder and has mild dysmorphic features; several factors can assist in the differential diagnosis. TU wave patterns, including prolonged terminal T-wave downslope, a wide TU junction, and biphasic and enlarged U wave, increased QUc, U-wave duration and amplitude may be useful in distinguishing ATS patients with KCNJ2 mutations from other subjects, especially among those patients presenting with BiVT during exercise.\textsuperscript{18} Relatively slow PVT (multifocal extrasystolic activity) and BiVT, and frequent ectopy at rest, as displayed by our proband, are helpful in distinguishing ATS from typical CPVT. In typical CPVT a rapid PVT and BiVT generally appear only after exercise. Another set of important distinguishing characteristics of ATS are the dysmorphic facial features due to the defective development. Physical abnormalities associated with ATS typically affect the head, face, and limbs. Kir2.1 mutant channels have also been linked with muscle and skeletal weakness in some ATS patients.\textsuperscript{4} The frequency of periodic paralysis associated with ATS has been reported to be 64%, dysmorphic features 78%, LQT 71%, and ventricular arrhythmias 64% in KCNJ2 mutation carriers.\textsuperscript{11}

Our findings provide additional support for a distinctive link between defects in KCNJ2 and developmental processes. In addition to the classic clinical phenotypes of ATS, some patients are reported to exhibit neuropsychiatric phenotypes, including major depression and pyramidal tract signs.\textsuperscript{19} Other studies show that KCNJ2 mutations in ATS are associated with infantile afebrile seizures\textsuperscript{20} and deficits in executive function and abstract reasoning.\textsuperscript{21}

Functional expression studies are obviously helpful in discriminating between ATS and CPVT but also helpful in expressed, thus demonstrating a very strong dominant-negative effect.

### Figure 6

**Immunocytochemical analysis of plasma membrane expression of R260P-KCNJ2 mutant channels in permeabilized TSA201 cells.** All images from the center of the cell were recorded 48 hours after transfection. A through C, Photomicrographs showing phase-contrast light transmission images. D through F, Images of transmitted light using nucleus (red) stained with propidium iodide. G through I, Fluorescence images of cells stained with Kir2.1 (H-40) antibody (green). J through L, Images of Kir2.1 channels (green) and nucleus (red). Left panel (A, D, G, and J), WT-KCNJ2; Kir2.1 channel staining was abundant both in the periphery and the center of the cell, indicating normal trafficking of WT-KCNJ2 channels to the surface membrane. Middle panel (B, E, H, and K), R260P-KCNJ2; Kir2.1 channel staining was localized in the perinuclear region of the cell, indicating failure of trafficking to the surface membrane. Right panel (C, F, I, and L), Nontransfected controls; little to no green fluorescent signal was visible, indicating the absence of endogenous Kir2.1 channel in TSA201 cells. Bottom (M), Quantitative measurement of relative surface expression of Kir2.1 channels. KCNJ2 staining of surface membrane was quantified by measurement of green fluorescence within the 2-μm border in the peripheral regions. Total channel protein expression in the membrane was compared with WT. Compared with WT, R260P-KCNJ2 significantly reduced membrane expression of Kir2.1 channel (**P<0.01**). Numbers of cells are as follows: WT-KCNJ2, n=15; R260P-KCNJ2, n=20; and nontransfected control, n=15. Values are mean ± SEM.
discriminating between traditional form of ATS and those that exhibit CPVT mimicry. A recent mutation categorized as CPVT, Kir2.1-V227F, was shown to display an unusual latent loss of function of biophysical phenotype modulated by PKA-dependent Kir2.1 phosphorylation. This biophysical feature, distinct from typical ATS mutations, suggests a specific mechanism for PKA-dependent Ik1 dysfunction for this KCNJ2 mutation, which correlates with adrenergic conditions underlying the clinical arrhythmia in CPVT.7

De Novo Mutation in KCNJ2 in a Patient With ATS

More than 20 de novo mutations in KCNJ2 have been reported to be associated with ATS, including R67W, D71N, T75R, G146A, G146S, R218Q, and R218W.11,12,18,20,22 Those de novo mutations were found in 27%, 29%, 30%, and 37.5% of total discovered mutations located in different part of the channel in the ATS cohorts.

Mechanism of ATS or LQT7 and Clinical Implication

Experimental models of LQT7 have been developed by our group and others using canine coronary-perfused left ventricular wedge preparations exposed to barium to block Ik1.23 Interestingly, QT interval was prolonged without an increase in transmural dispersion of repolarization. Unlike other long-QT models, early afterdepolarizations and TdP were not observed, not even in the presence of low K+, isoproterenol, and abrupt increase in temperature. These observations explain why QT prolongation associated with ATS is relatively benign. TdP is rarely observed in patients with ATS; in those cases in which it is observed, secondary mutations in KCNH2 or KCNJ1 have been uncovered.

Another model developed by Morita et al used cesium to block Ik1. The electrophysiological features of ATS, including prolonged APD, delayed afterdepolarizations, multifocal VT, BiVT, and U wave were observed. Delayed afterdepolarizations and associated arrhythmic activity was abolished by verapamil in this ATS model, suggesting that Ca2+ overload contributes to arrhythmogenesis in the setting of reduced Ik1.24 Studies involving rabbit heart failure models have shown that reduced Ik1 contributes to enhanced membrane response to changes in [Ca2+]; and thus to propensity for triggered arrhythmias.25 Thus, preventing Ca2+ overload may be a logical remedy for ATS patients. Recently, a case of an elderly patient with ATS whose symptomatic ventricular arrhythmia including BiVT were effectively suppressed by oral verapamil therapy.26

Several studies, including the present one, have shown that flecainide is an effective treatment for ATS as well as CPVT.27–29 Although the mechanisms by which flecainide suppresses ventricular arrhythmia are not fully understood, the IC agent probably acts via a direct inhibition of calcium release by the sarcoplasmic reticulum ryanodine receptor29 and/or by reducing intracellular sodium concentration and subsequently [Ca2+], via sodium-calcium exchange, thereby reducing SR calcium loading and associated triggered activity.

The ameliorative effect of flecainide may also be due to its ability to increase Ik1, as recently reported by Caballero et al.30 These authors elegantly showed that acute incubation of flecainide can rescue R67W-KCNJ2 mutant channels associated with ATS.

Conclusion

ATS with CPVT mimicry was diagnosed in a 10-year-old girl on the basis of dysmorphic features, prolonged QUC and cardiac arrhythmias including frequent ventricular extrasystoles, multifocal PVT, and BiVT. Genetic analysis revealed a novel de novo R260P missense mutation in KCNJ2 that was not observed in 430 reference control alleles. The mutation caused trafficking impairment, dominant-negative loss of function of Ik1 when expressed heterozygously in TSA201 cells. Our data provide further evidence in support of the use of flecainide for therapy of ATS with CPVT mimicry when β-blockers are ineffective.

Acknowledgments

The authors thank Judy Hefferon and Robert J. Goodrow, Jr, for technical assistance and Susan Bartkowiak for maintaining our genetic database.

Sources of Funding

This work was supported by grant HL47678 (to Dr Antzelevitch) from the National Heart, Lung, and Blood Institute and New York State and Florida Grand Lodges, Free and Accepted Masons.

Disclosures

None.

References

Andersen-Tawil syndrome is a rare inherited disorder with autosomal dominant inheritance, characterized by potassium-sensitive periodic paralysis, cardiac arrhythmias, dysmorphic features, and a variable degree of QT interval prolongation, often presenting with prominent U waves. Although associated with frequent ectopy, life-threatening ventricular arrhythmias, such as torsade de points, are rare in Andersen-Tawil syndrome. In 60% of cases, Andersen-Tawil syndrome is caused by mutations in KCNJ2, the gene that encodes Kir2.1, the inward rectifier potassium channel (I\textsubscript{K1}). The ECG features of this syndrome at times mimic catecholaminergic polymorphic ventricular tachycardia (CPVT) by presenting with bidirectional ventricular tachycardia and exertion/emotion-induced arrhythmia. Recent KCNJ2 mutations have been designated as CPVT3. The present study identifies a young girl with Andersen-Tawil syndrome and CPVT mimicry, presenting with dysmorphic features, syncope, frequent ventricular extrasystoles, nonsustained polymorphic ventricular tachycardia, bidirectional ventricular tachycardia, and prolonged QTc, secondary to a novel de novo mutation in KCNJ2 (R260P), which disrupts normal trafficking of the channel to the membrane. Heterozygous expression of wild-type and mutant channels in human embryonic kidney cells yielded a markedly reduced I\textsubscript{K1}, indicating a strong dominant negative effect of the mutant. The patient’s symptoms continued after administration of nadolol but subsided after treatment with flecainide. The effectiveness of flecainide may be due to its ability to increase I\textsubscript{K1} in this setting, among other mechanisms.
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Circ Cardiovasc Genet. 2011;4:51-57; originally published online December 10, 2010; doi: 10.1161/CIRCGENETICS.110.957696
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1942-325X. Online ISSN: 1942-3268

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