Arrhythmia Phenotype During Fetal Life Suggests Long-QT Syndrome Genotype
Risk Stratification of Perinatal Long-QT Syndrome

Bettina F. Cuneo, MD; Susan P. Etheridge, MD; Hitoshi Horigome, MD; Denver Sallee, MD; Anita Moon-Grady, MD; Hsin-Yi Weng, MPH; Michael J. Ackerman, MD, PhD; D. Woodrow Benson, MD, PhD

Background—Fetal arrhythmias characteristic of long QT syndrome (LQTS) include torsades de pointes (TdP) and/or 2° atrioventricular block, but sinus bradycardia, defined as fetal heart rate <3% for gestational age, is most common. We hypothesized that prenatal rhythm phenotype might predict LQTS genotype and facilitate improved risk stratification and management.

Method and Results—Records of subjects exhibiting fetal LQTS arrhythmias were reviewed. Fetal echocardiograms, neonatal ECG, and genetic testing were evaluated. We studied 43 subjects exhibiting fetal LQTS arrhythmias: TdP±2° atrioventricular block (group 1, n=7), isolated 2° atrioventricular block (group 2, n=4), and sinus bradycardia (group 3, n=32). Mutations in known LQTS genes were found in 95% of subjects tested. SCN5A mutations occurred in 71% of group 1, whereas 91% of subjects with KCNQ1 mutations were in group 3. Small numbers of subjects with KCNH2 mutations (n=4) were scattered in all 3 groups. Age at presentation did not differ among groups, and most subjects (n=42) were live-born with gestational ages of 37.5±2.8 weeks (mean±SD). However, those with TdP were typically delivered earlier. Prenatal treatment in group 1 terminated (n=2) or improved (n=4) TdP. The neonatal heart rate–corrected QT interval (mean±SE) of group 1 (664.7±24.9) was longer than neonatal heart rate–corrected QT interval in both group 2 (491.2±27.6; \( P<0.001 \)) and group 3 (483.1±13.7; \( P<0.001 \)). Despite medical and pacemaker therapy, postnatal cardiac arrest (n=4) or sudden death (n=1) was common among subjects with fetal/neonatal TdP.

Conclusions—Rhythm phenotypes of fetal LQTS have genotype-suggestive features that, along with heart rate–corrected QT interval duration, may risk stratify perinatal management. (Circ Arrhythm Electrophysiol. 2013;6:946-951.)

Key Words: arrhythmias, cardiac ▪ atrioventricular block ▪ fetal ▪ long-QT syndrome ▪ sinus bradycardia torsade de pointes

Although congenital long-QT syndrome (LQTS) may be as common as 1 in 2500 individuals, findings during fetal life have been reported in <100 cases. Sinus bradycardia is the most common rhythm manifestation of fetal LQTS but may go unrecognized.1 Torsades de pointes (TdP) and unexplained 2° atrioventricular block (AVB) are the complex signature fetal LQTS rhythms but have been reported in only ≈25% of fetal LQTS cases. In some cases, the fetal LQTS cardiac arrhythmias may be of short duration and clinically insignificant in utero, whereas in other cases, they may be prolonged and result in severe heart failure, leading to premature delivery or fetal demise.2–8

Clinical Perspective on p 951

In most cases, genetic studies in fetal LQTS subjects have identified mutations in known LQTS-susceptibility genes. Yet, little is known about the genotype–phenotype characteristics of fetal LQTS, that is, do specific genotypes predict clinical severity of arrhythmia phenotype? Nor is the extent to which genotype–phenotype characteristics are age dependent known, that is, does the same genotype have a different clinical phenotype in prenatal life compared with postnatal life? We hypothesized that the pre- and postnatal clinical profile of subjects with fetal LQTS arrhythmias might be genotype...
specific, which, in turn, could be used to risk stratify patients and improve their perinatal care.

### Methods

#### Study Cohort

The study cohort was derived from a fetal cardiac database as previously described. Fetuses with LQTS were identified because of a family history of LQTS and because of a fetal arrhythmia characteristic of LQTS, that is, sinus bradycardia (fetal heart rate ≤ third percentile for gestational age), 2° A VB (in the absence of maternal Sjögren antibodies), or ventricular tachycardia with an irregular R-R interval confirmed to be TdP either by fetal magnetocardiography or by postnatal ECG. Pre- and postnatal therapy, indications for delivery, and gestational age at delivery were reviewed from the medical record. LQTS was confirmed by postnatal ECG and genetic testing. The protocol was approved by institutional review boards.

#### Prenatal Evaluation

Prenatal assessment included indication for evaluation (family history of LQTS or fetal arrhythmia), gestational age at which the LQTS rhythm abnormality was noted, and characteristics of fetal heart rhythm. No fetus underwent prenatal genetic testing. The fetal echocardiogram, used for rhythm surveillance, generally lasted between 15 and 30 minutes. Fetal heart rate was determined by averaging 5 consecutive cardiac cycles measured by Doppler or M-mode during fetal quiescence. Sinus bradycardia was defined as 1:1 AV conduction, normal mechanical PR interval, and rate less than third percentile for gestational age. Detection of nonsustained, irregular tachycardia with AV dissociation, that is, atrial rate slower than ventricular rate, led to a diagnosis of ventricular tachycardia (VT), presumably TdP. Second-degree AVB was recognized when some atrial contractions did not result in a ventricular contraction, and a regular atrial rate exceeded the ventricular rate.

#### Postnatal Evaluation

Postnatal ECGs were performed on all infants; the heart rate–corrected QT interval (QTc) was calculated based on the Bazett formula. Mutation analysis of the 3 canonical LQTS-susceptibility genes and the 9 or 10 minor genes (depending on year of testing) was performed using commercially available testing (Familion; Transgenomic Inc, New Haven, CT, and GeneDx, Gaithersburg, MD). One subject with negative commercial tests participated in a genetic research study.

#### Statistical Analysis

Means are reported with SDs when describing the variability of individual subjects, but means are reported with SEs when describing the precision of the mean estimates if the variable is being reported as the outcome variable in a regression model. Given that the 43 subjects were clustered within 32 families, all effect estimation and statistical significance testing was performed using mixed-effects, random intercept linear regression models, with specification of the precision of the mean estimates if the variable is being reported as the outcome variable in a regression model. Given that the 43 subjects were clustered within 32 families, all effect estimation and statistical significance testing was performed using mixed-effects, random intercept linear regression models, with specification of all analyses were performed using SAS version 9.2 statistical software (SAS, Inc).

### Results

#### Study Cohort

During a 13-year period, 43 subjects from 32 families were enrolled, including 8 families with ≥2 affected subjects in the cohort. Prenatally, 7 subjects had TdP±2° AVB (group 1), 4 had isolated 2° AVB (group 2), and 32 had sinus bradycardia alone (group 3; Table 1). Thus, 11 (26%) of the cohort had complex signature fetal LQTS arrhythmias. Twenty-seven subjects were monitored consistently between 19 and 40 weeks of gestation because of a family history of LQTS: only 3 of these 27 developed 2° AVB (at 22 and 32 weeks of gestation) or TdP (at 34 weeks of gestation). Sixteen subjects were evaluated only after detection of fetal arrhythmias, suggestive of LQTS (19–30 weeks of gestation); arrhythmias included either sinus bradycardia (n=9) or complex signature LQTS arrhythmias (n=11). Follow-up time ranged from 1 to 13 years.

The mean (±SD) gestational age of presentation for all subjects was 28.5±4.9 weeks, and age at presentation did not differ by group. Pregnancy was terminated electively in 1 case because of incessant TdP associated with hydrops fetalis; other subjects were live-born. Subjects in group 1 were delivered significantly earlier (mean±SE, 34.0±1.0; range, 31–39 weeks) than those in group 2 (38.3±1.5; range, 38–39 weeks; \( P=0.04 \)) or group 3 (38.1±0.5; range, 30–41 weeks; \( P=0.008 \)). Indications for delivery included term pregnancy (37 subjects), fetal distress (3 subjects), fetal well-being concerns (1 subject), and rupture of membranes with spontaneous onset of premature labor (1 subject).

#### Characteristics of Fetal Arrhythmias

Among the 7 group 1 fetuses, tachycardia rate was 200 to 300 bpm (Figure A and B). In all subjects, TdP was intermittent with periods of sinus bradycardia or 2° AVB between TdP bursts (Figure C). The TdP duration was variable and lasted seconds to several minutes (Table 2).

In group 2 fetuses, ventricular rate varied from 45 to 75 bpm (Figure D and E). Subjects 8 and 11 had persistent 2° AVB, whereas in subjects 9 and 10, 2° AVB was seen transiently only at 19 and 28 weeks, respectively. Ventricular rates during 2° AVB were similar between group 1 and group 2 subjects (data not shown). Sinus bradycardia rates (group 3) varied but were <3% for gestational age.

### Table 1. Forty-three Fetal LQTS Subjects

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<th>Group</th>
<th>QTc, ms (Mean±SE)*</th>
<th>KCNQ1</th>
<th>KCNH2</th>
<th>SCN5A</th>
<th>Uncharacterized</th>
<th>Untested</th>
<th>Other</th>
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<td>Group 1 TdP (n=7)</td>
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<td>Group 2 2° AVB (n=4)</td>
<td>491.2±27.6 (P=0.004)†</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Group 3 sinus brady (n=32)</td>
<td>483.1±13.7 (P&lt;0.001)†</td>
<td>21</td>
<td>4</td>
<td>1</td>
<td>2</td>
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AVB indicates atrioventricular block; LQTS, long-QT syndrome; QTc, heart rate–corrected QT interval; and TdP, torsades de pointes.

*Adjusted group means, after adjusting for genotype in a mixed-effects linear regression model.

†P value comparing group 2 with group 1 and comparing group 3 with group 1.
Mutations in LQTS-susceptibility genes were found in 38 of 40 subjects undergoing genetic testing, including 23 with KCNQ1, 6 with KCNH2, 6 with SCN5A, and 3 with other mutations. Two subjects had uncharacterized mutations (Table 1). De novo mutations were found in 7 subjects: 6 in group 1 (4 with SCN5A-R1623Q, 1 each with SCN5A-L409P and KCNH2-G628S) and 1 in group 2 with CALM2. The portion of subjects with a familial/inherited mutation varied: group 1 (14%), group 2 (75%), and group 3 (92%).

Among subjects with complex signature fetal LQTS arrhythmias (group 1 and group 2), 5 of 11 had familial/inherited mutations. Two mutations were novel (KCNH2-T613K and CALM2), 2 mutations had been reported previously (KCNQ1-G168R and KCNQ1-G314D), and 1 subject did not undergo genetic testing. Group 3 subjects had previously reported mutations (Table in the online-only Data Supplement).

Prenatal Treatment

Because subjects were cared for at multiple institutions and over time, management strategy was not uniform. Only group 1 fetuses received prenatal treatment; however, 14 mothers with personal history of LQTS were treated with β-adrenergic blocking agents, and 2 fetuses of treated mothers developed TdP (subject 2) or 2° AVB (subject 8). After fetal TdP developed in subject 2, propranolol was given instead of metoprolol because of its relatively favorable transplacental transfer characteristics. Combinations of propranolol, mexiletine, magnesium, and lidocaine were used in subjects 1, 2, 4, and 5. Maternal sotalol (120 mg orally every 12 hours) was administered to twin subjects 5 and 6 for 2 days (Table 2).

Pharmacological treatment restored sinus rhythm in 2 fetuses (subjects 1 and 2) with KCNH2 and SCN5A mutations, respectively and decreased frequency and duration but did not fully abolish TdP in 2 fetuses (subjects 5 and 2 with SCN5A and KCNH2 mutations, respectively). Magnesium was the treatment common to all 4 fetuses who seemed to benefit. Subject 3 did not receive antiarrhythmic treatment because the pregnancy was interrupted.

Postnatal Treatment

All subjects received postnatal treatment. The 6 live-born neonates in group 1 received oral propranolol (2–3.5 mg/kg per day) or continuous esmolol infusion, with transition to propranolol as standard postnatal drug therapy for LQTS. Use of mexiletine was influenced by prenatal treatment experience and response to therapy. In addition to medical therapy, 2 subjects (1 and 5), received pacemakers in the first 3 days of life because of persistent ventricular bradycardia (rate, 48–60 bpm) during 2° AVB. Subject 2, who had transient TdP in the first 48 hours after birth, was discharged with an external cardiac defibrillator (Table 2).

Despite continued treatment, cardiac arrest or sudden death occurred in subjects 4 to 7 at 2 weeks to 8 months of age. The 3 cardiac arrest survivors (subjects 5–7) received implantable cardioverter-defibrillator plus cardiac sympathetic denervation (n=3) 1 week to 4 months later. However, all 3 implantable cardioverter-defibrillator recipients have continued to

Figure. Illustrative cardiac rhythms of group 1 and group 2 subjects. A, Simultaneous atrial and ventricular M-mode of established torsades de pointes (TdP) in a fetus with SCN5A R1623Q mutation at 32 weeks of gestation. Although M-mode cannot definitively diagnose TdP, atrioventricular (AV) dissociation and the irregular tachycardia (arrows, top tracing) at a cycle length varying from 200 to 300 ms are highly suggestive of TdP. The atrial (bottom tracing, a) rhythm is regular (arrows), and the cycle length is 540 ms. B, Ventricular (V) M-mode at initiation (red arrow) of TdP in the same fetus. Based on the V-V interval of ≈1000 ms, rhythm preceding the initiation of TdP is probably 2° AV block (AVB). C, Simultaneous ventricular and atrial M-mode of established TdP in a fetus with KCNH2 mutation and at 34 weeks of gestation. The atrial (a) cycle length is regular at a rate of 120 bpm (cycle length 500 ms), and the ventricular rhythm is irregular at a rate of 212 bpm (cycle length 284 ms, arrows, bottom tracing). D, Simultaneous atrial and ventricular M-mode of sinus bradycardia and intermittent 2° AVB in a 34-week fetus with KCNH2 mutation. Atrial contractions (a, bottom arrows) are regular at a cycle length of 517 ms. The AV relationship is initially 1:1, but there is ventricular silence between the fourth and fifth and fifth and sixth ventricular contractions while atrial contractions continue at the original rate. This identifies 2° AV block. E, Pulsed Aortic (Ao) and mitral valve Doppler tracing of the same fetus during a period of sustained 2° AV block. The mitral a waves (white arrows) occur at a regular rate while only every other aortic outflow waveform is conducted. Together, these findings identify 2° AV block.
receive appropriate ventricular fibrillation (VF)-terminating shocks, despite denervation surgery and ongoing pharmacological therapy.

All 4 subjects in group 2 were treated with β-adrenergic blocking agents; subject 10 was also given mexiletine, and subject 11 received a pacemaker in the neonatal period. Subject 10 had cardiac arrest at 4 weeks of age and received implantable cardioverter-defibrillator implantation. As with the implantable cardioverter-defibrillator recipients in group 1, subject 10 continues to receive appropriate VF-terminating shocks.

All subjects in group 3 were treated with β-adrenergic blocking agents, 2 received additional therapies with mexiletine, and 2 received pacemakers for marked sinus bradycardia thought to be secondary to treatment with β-blocking medication. During the follow-up of 2 to 14 years, subjects have remained asymptomatic.

### Prenatal/Postnatal Rhythm Concordance

For subjects in groups 1 and 3, pre- and postnatal rhythm was 100% concordant. All group 1 subjects with prenatal TdP had postnatal TdP at least once during the first 8 postnatal months. However, neither TdP nor 2° AVB was identified postnatally in any group 3 subject. However, for the 4 subjects in group 2, postnatal rhythm concordance was 50%; 3 subjects had postnatal episodes of 2° AVB, and the subject with the CALM2 mutation (10) had multiple episodes of postnatal TdP and ventricular fibrillation.

### Genotype–Phenotype Relationship

In this cohort, the varied rhythm phenotypes suggested certain genotypes. For example, most subjects in group 1 had de novo mutations and SCN5A mutations. In contrast, the majority of subjects in group 3 had a KCNQ1 mutation (Table 1).

### Predictors of Outcome

As genotype suggested arrhythmia phenotype, arrhythmia phenotype and QTc duration predicted clinical outcome. Table 1 shows the average QTc for each group after adjusting for phenotype in a linear mixed-effects model, with significant differences found between groups. There was no dependency of QTc on observations from the same family with similar genotype.

Five group 1 subjects and 1 group 2 subject had postnatal TdP with cardiac arrest; despite medical therapy, all 6 device recipients continued to receive VT/VF-terminating shocks. However, subjects with sinus bradycardia and most subjects who had isolated prenatal 2° AVB did not have postnatal TdP and did not receive device therapy (Table 2). Subjects in group 3 have all remained asymptomatic.

### Discussion

We evaluated arrhythmias in the largest reported fetal LQTS cohort and sought to determine the extent to which the perinatal arrhythmia clinical profile might be genotype specific. We identified several important findings. First, TdP is most likely...
to occur in fetuses with sporadic mutations, and although the incidence of SCN5A mutations in our cohort is nearly the same (=10%) as the percentage reported historically for LQTS,15 SCN5A mutations were found much more frequently in fetuses with TdP. In contrast, fetuses presenting with persistent sinus bradycardia were most likely to have KCNQ1 mutations.6 Second, we found that prenatal therapy for TdP can be effective, but such fetuses are likely to be delivered prematurely and, despite aggressive treatment strategies, provide ongoing postnatal management challenges. In our experience, fetuses tolerate sinus bradycardia or 2° AVB without in utero therapy. Thus, prenatal arrhythmia phenotype informs prenatal and neonatal management while awaiting the results of genetic testing.

The severe arrhythmia phenotypes observed in fetal LQTS have been explained partly by mutations with severe biophysical phenotypes. For example, studies of SCN5A-R1623Q, noted in sporadic LQTS cases with severe perinatal arrhythmia,2,4,12 identified a novel LQTS mechanism characterized by early channel reopenings and increased probability of long openings.13 However, sporadic occurrence of SCN5A-L409P in combination with H558R caused significant depolarized shifts in voltage dependence of inactivation and activation, faster recovery from inactivation, and a greater level of persistent current potentiated by a developmentally regulated alternative splicing event in SCN5A.1 In contrast, KCNH2-G628S, a mutation in the pore of the KCNH2-encoded Kv11.1 potassium channel, was reported to have a dominant-negative effect on wild-type Ik.13,14 However, biophysical phenotype alone does not explain phenotype severity. For example, although subjects in our study with KCNQ1-G168R and KCNQ1-G314D mutations had only 2° AVB, both mutations have been associated with cardiac arrest in adolescence and adulthood.15 Furthermore, among subjects we studied, 2 of the 3 familial LQTS mutations resulted in fetal arrhythmias in the proband but a much milder phenotype in the other family member, implicating that factors other than the ion channel mutation contribute to variable expressivity, a phenomenon previously noted in studies of large families.16,17

Although most TdP episodes we observed spontaneously terminated, the risk of postnatal cardiac arrest in fetuses with TdP was much higher than in LQTS fetuses without TdP. For example, ≥25% of LQTS fetuses previously reported had complex signature LQTS arrhythmias, and ≥30% of these fetuses had a subsequent cardiac arrest.2,5,17 In a previous study that limited treatment to β-adrenergic blocking agents plus pacing, mortality within the first year of life exceeded 60% when complex signature LQTS arrhythmias were documented18 but was <10% among subjects when only sinus bradycardia was observed.16 Thus, it is not unexpected that none of the 32 fetuses with isolated sinus bradycardia in the current study had postnatal TdP or cardiac arrest during infancy. However, extrapolating from these findings, one may speculate that fetuses with mutations causing protracted TdP may not survive to delivery.

Previous studies comparing genotype–phenotype relationships with time of presentation (fetal or postnatal) have reported conflicting results. For example, infants presenting during the first year of life with complex LQTS-associated arrhythmias usually had either KCNH2 or KCNQ1 mutations, and only 16% had SCN5A mutations.5,6,17 In contrast, among individuals with LQTS-associated genotypes in sudden infant death syndrome cohorts, SCN5A mutations were more frequent.19,20 Similarly, a high prevalence of SCN5A mutations in LQTS subjects presenting with TdP during fetal life has been reported,4,5,7,12,22 and this was true for >70% of subjects we studied.

The current study suggests that, to a limited extent, the beneficial effects of perinatal therapy can be predicted by the genotype and fetal arrhythmia characteristics. This may be explained partially by previous findings that sodium channel–blocking agents, including lidocaine and mexiletine, are useful in the treatment of LQTS caused by gain-of-function SCN5A mutations.23 However, β-adrenergic blocking agents, such as propranolol, have been shown to decrease transmural dispersion of repolarization and the induction of TdP partially explaining their superior efficacy for LQT1 and LQT2.23 Although an antifibrillatory effect from cardiac sympathetic denervation has been shown in children and adults with LQTS,24 denervation therapy did not seem to help in this small cohort of fetal LQTS subjects. We are not aware of an effective prenatal therapy for 2° AVB or sinus bradycardia, but in our experience, mothers of fetuses with these rhythms had uncomplicated pregnancies and delivered at term.

There remain unanswered questions on genotype–phenotype relationship of LQTS, in general, and fetal LQTS, specifically. The LQTS genotypes in the fetus with complex arrhythmias differ from the more common familial mutations because of their sporadic occurrence and severe life-threatening phenotype. Despite these unanswered questions, we are encouraged by observations that suggest that fetal LQTS arrhythmia phenotype and QTc measured after birth can risk stratify the care of these subjects in early life.

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Disclosures
Dr Ackerman is a consultant for Transgenomic Inc, New Haven, CT. Under a license agreement established between Mayo Clinic Health Solutions and then Genaissance Pharmaceuticals and now Transgenomic in 2004, Mayo Clinic and Dr Ackerman receive royalties from Transgenomic Inc. Dr Cuneo is a consultant for Philips Ultrasound. The other authors report no conflicts.

References
Prenatal treatment with combined medical therapy terminated or improved TdP in most cases; fetuses with isolated 2° A VB was longer than neonatal heart rate–corrected QT interval in fetuses with isolated 2° A VB or sinus bradycardia alone. However, fetuses with TdP were typically delivered earlier. The neonatal heart rate–corrected QT interval of fetuses with TdP±2° A VB did not differ based on arrhythmia type. Most subjects were live-born with gestational ages of 37.5±2.8 weeks (mean±SD); how-ever, fetuses with TdP had a sporadic SCN5A mutation (71%), whereas fetuses with sinus bradycardia alone usually had familial KCNQ1 mutation (91%). Small numbers of KCNH2 mutations occurred with all arrhythmia types. Age at presentation did not differ based on arrhythmia type. Most LQTS gene variants in sudden infant death syndrome. JAMA. 2001;286:2264–2269.


CLINICAL PERSPECTIVE

Characteristics of fetal long-QT syndrome (LQTS) arrhythmias include torsades de pointes (TdP) and 2° atrioventricular block (AVB), but sinus bradycardia, defined as fetal heart rate <3% for gestational age, is most common. We hypothesized that prenatal arrhythmia phenotype might predict LQTS genotype and facilitate improved risk stratification and management. We studied 43 subjects exhibiting fetal LQTS arrhythmias, including TdP±2° AVB, isolated 2° AVB, and sinus bradycardia alone. Mutations in known LQTS genes were found in 95% of subjects tested. We found that most fetuses with TdP±2° AVB had a sporadic SCN5A mutation (71%), whereas fetuses with sinus bradycardia alone usually had familial KCNQ1 mutation (91%). Small numbers of KCNH2 mutations occurred with all arrhythmia types. Age at presentation did not differ based on arrhythmia type. Most subjects were live-born with gestational ages of 37.5±2.8 weeks (mean±SD); however, fetuses with TdP were typically delivered earlier. The neonatal heart rate–corrected QT interval of fetuses with TdP±2° AVB was longer than neonatal heart rate–corrected QT interval in fetuses with isolated 2° AVB or sinus bradycardia alone. Prenatal treatment with combined medical therapy terminated or improved TdP in most cases; fetuses with isolated 2° AVB or sinus bradycardia alone did not require prenatal treatment. However, despite medical and pacemaker therapy, postnatal cardiac arrest or sudden death was common among subjects with fetal/neonatal TdP. These findings suggest that fetal LQTS arrhythmia phenotypes have genotype–suggestive features that, along with heart rate–corrected QT interval duration, may risk stratify perinatal management.
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Supplemental Table 1: QTc and LQTS Mutation of Subjects with Bradycardia (Group 3)

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