

# Fetal heart rate reflects mutation burden and clinical outcome in twin probands with *KCNQ1* mutations



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## Introduction

We present the case of a twin pregnancy of heterozygous and homozygous long QT syndrome (LQTS) type 1 (LQT1) genotype, referred because of in utero bradycardia in the homozygous twin at 19 weeks of gestation, with follow-up until >12 months of age. Fetal heart rate may predict both genotype and disease severity, as previously shown in 2 LQTS founder populations.<sup>1</sup> This unique case report is a comparison of fetal heart rate and clinical outcome in twin probands of heterozygous and homozygous genotype, in a family without prior diagnosis of LQTS. In this setting, we discuss the early management of LQTS and Jervell and Lange-Nielsen syndrome (JLNS) detected in utero.

## Case report

A primigravida 30-year-old woman was referred to the pediatric cardiology tertiary center in Umeå, Sweden, because of fetal bradycardia in 1 of 2 twins. The bradycardia had been detected during a routine ultrasound that was offered as part of primary maternal health care. The dichorionic twin pregnancy had been achieved by in vitro fertilization after 8 attempts and 8 years of unexplained infertility. The pregnancy had proceeded normally according to routine ultrasound at 12 weeks' gestation. At 19 weeks' gestation, the twin farthest from the cervix (twin B or twin II, with twin II used throughout this case report) presented with sustained bradycardia, around 100 beats per minute (bpm).

At the tertiary center, intermittent fetal heart rate monitoring every third hour plus daily echocardiograms revealed a mean heart rate between 125 and 145 bpm in twin I and between 95 and 128 bpm in twin II, during the first 2 days (Figure 1). The echocardiographic recordings revealed

M-mode recordings suggestive of sinus rhythm, and normal anatomical conditions and arterial flows, for both fetuses.

Except for the unexplained infertility, the twins' parents had an unremarkable medical history (Figure 2). Family history on the maternal side included autoimmune disease; however, maternal autoantibody blood test screening came back negative. On the paternal side, notably, the twin's aunt had a history of recurrent syncope, and the grandmother had suffered from recurrent syncope and epilepsy, and had died of drowning (Figure 2). Based on our experiences with 2 large LQT1 founder populations,<sup>1</sup> the paternal family history combined with the sinus bradycardia in twin II led us to suspect LQTS as the underlying disorder. The parental electrocardiograms were uninformative, with borderline QT prolongation in the mother (QTc 468 ms) and normal QTc in the father (QTc 428 ms), although some suspect but nonspecific findings were reported regarding the father's relatives (Figure 2). Both parental lineages could be traced to the Piteå River valley region, the origin of the R518X-KCNQ1 founder population.<sup>2</sup> After genetic counseling, the father was tested for carriership of the R518X-KCNQ1 pathogenic sequence variant by targeted mutation analysis. Within 1 week of referral, he was found to be genotype positive.

Although *KCNQ1* mutations in fetuses typically have a benign obstetrical course,<sup>1,3,4</sup> the pregnancy was closely monitored by primary and tertiary health care providers. Throughout gestation, twin I had a mean heart rate within the 120 to 160 bpm normal range, whereas twin II remained below 120 bpm, and from gestational week 28 remained below 100 bpm (Figure 3). No ventricular tachyarrhythmia or atrioventricular block was observed. Repeated echocardiograms revealed no significant signs of heart enlargement or failure, or hydrops, in either twin. Fetal growth proceeded as expected, including amniotic fluid levels and umbilical arterial flows.

The twins were carried to 38 weeks and delivered at Umeå University Hospital by elective cesarean section. Both twins were transferred to the neonatal care unit for treatment of mild respiratory distress and further LQTS-related assessment. Throughout the hospitalization, twin I had heart rates that remained around 130 bpm, whereas twin II was bradycardic with heart rates between 85 and 90 bpm. Electrocardiograms revealed QTc of 492 ms and nonspecific T-wave

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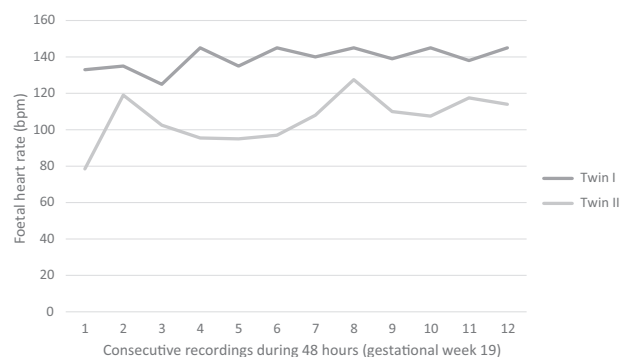
## KEY TEACHING POINTS

- Long QT syndrome (LQTS) may present with relative intrauterine bradycardia. Lower fetal heart rates are associated with more severe phenotypes and occurrence of double mutations (including Jervell and Lange-Nielsen syndrome [JLNS]).
- Clinical management should include monitoring, intention to not deliver preterm based on fetal heart rate alone, and delivery by elective cesarean section to ensure satisfactory perinatal monitoring for mother and fetus.
- Neonatal management differs depending on genotype. LQTS is typically associated with a low neonatal cardiac event risk. JLNS is associated with high morbidity and mortality in infancy, requiring early identification and risk management.
- Prophylactic beta-blocker therapy is well tolerated by LQTS and JLNS infants. Beta-blocker levels >1 mg/kg/d can be reached during the first week of life, under controlled conditions.
- We emphasize using a collaborative team approach when managing families with JLNS.

changes in twin I, and QTc of 679 ms in twin II. Sustained sinus bradycardia and extreme QT prolongation raised the suspicion that twin II might be suffering from JLNS, caused by double LQT1 mutations, and strongly associated with the specific R518X-KCNQ1 genotype.<sup>5</sup>

Homozygous carriership of R518X-KCNQ1 in twin II, and heterozygous carriership in twin I and their mother, was confirmed within 1 week of targeted mutation analysis. Clinically, auditory screening using otoacoustic emission testing confirmed bilateral profound hearing loss in twin II, completing the JLNS diagnostic criteria. Twin I had normal auditory test results.

Because of the clinical suspicion of JLNS, which is associated with a high risk of life-threatening cardiac events from fetal life onward,<sup>1,6,7</sup> prophylactic beta-blocker treatment was initiated in twin II at 2 days of age, while genetic test results were awaited. A 24-hour electrocardiographic recording revealing a heart rate of 78 to 110 bpm and an extensive echocardiographic assessment confirming stable circulation without any significant defects had been obtained previously. Low-dose beta-blocker therapy was initiated (propranolol 0.5 mg/kg/d split into 3 doses) and slowly up-titrated to a prophylactic level, under continuous blood pressure and blood glucose monitoring. During up-titration, some episodes of borderline blood pressure (lowest recorded 56/21 mm Hg), transient hypoglycemia, and frequent episodes of bradycardia <70 bpm were noted; however, the neonate tolerated these episodes well. By 1 week of age, mean heart rate had



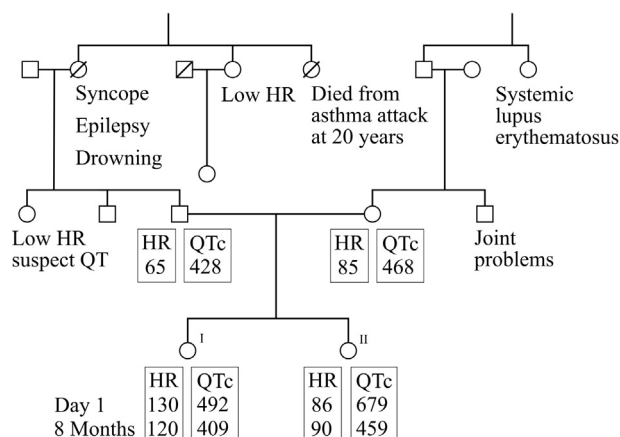
**Figure 1** Consecutive recordings for 48 hours at 19 weeks' gestation revealed a lower mean fetal heart rate in twin II (95–128 beats per minute) compared to twin I (125–145 beats per minute).

stabilized (day 1, before therapy: 86 bpm, 78–110 bpm; day 8, on propranolol 1.2 mg/kg/d: 87 bpm, 78–108 bpm).

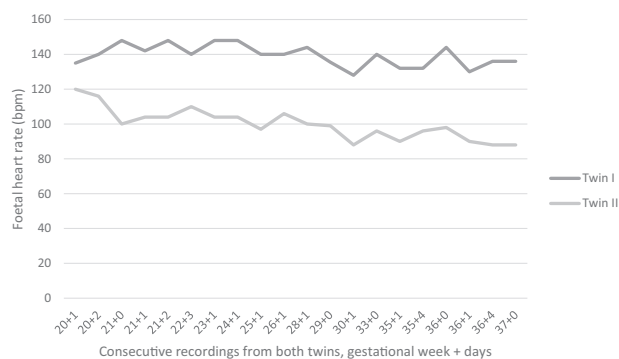
At 1 week of age, the twins were transferred to a secondary care hospital for successive up-titration of propranolol treatment in twin II and then discharged 2 weeks later, with no incidents of hypotension, hypoglycemia, or exacerbated bradycardia during the in-hospital stay. Before discharge, the parents received training in pediatric cardiopulmonary resuscitation.

During the following months, beta-blocker treatment (reaching 3 mg/kg/d by 6 months of age) was well tolerated by twin II, with stable heart rate and blood pressure, and general well-being. Although pacemaker treatment was initially considered, it never became necessary.

For twin I, beta-blocker treatment was initiated at 8 months of age. By then, electrocardiographic characteristics in both twins had largely normalized (Figure 2). At >12 months of age, both twins have tolerated their beta-blocker treatment well and have not had any arrhythmia symptoms reported by their parents.



**Figure 2** Clinical presentations in the twin family pedigree. Available clinical data are given below the individuals. Females are indicated by circles; males are indicated by squares. Hatched symbols indicate deceased. HR = heart rhythm (in beats per minute); I = twin I; II = twin II; QTc = corrected QT interval (in milliseconds).



**Figure 3** Mean fetal heart rate of dichorionic twins for gestational weeks 20 to 37.

During the first year of life, both twins followed their expected growth curves. However, twin II presented with balance problems and signs of gross motor developmental delay, in line with our previous findings in JLNS children.<sup>8</sup> These symptoms were verified by a physiotherapist and were present at 5 months of age, before cochlear implantation at 6 months of age, and they persist at >1 year of age.

## Discussion

We previously showed that fetal heart rate can predict mutation burden and later phenotype in families with an LQT1 diagnosis.<sup>1</sup> However, whether this identification strategy would be valid in an unselected population was not clear. This case report supports our view that evaluation of heart rates already being monitored in the general fetal population has the potential to significantly improve presymptomatic identification of the most severe LQTS cases.<sup>1</sup> Also, it highlights the benefit of knowledge about the regional mutation spectrum, facilitating rapid molecular genetics diagnosis ascertainment.<sup>2,5</sup>

Isolated relative fetal bradycardia is increasingly recognized as a marker for LQTS.<sup>1,3,4,9,10</sup> As previously noted, the definition of bradycardia  $\leq 110$  bpm typically fails to identify LQT1 fetuses, even though they often present with a low-for-gestational-age heart rate.<sup>1,3,4</sup> Twin I had a fetal heart rate within the normal range throughout gestation and would not have been identified had it not been for her JLNS twin. One could argue that only severe LQTS cases need early perinatal identification. Nevertheless, early detection enables individual risk management, as well as identification of immediate family members via cascade screening (in this case, 3 first-degree family members) who may benefit from information on the disorder and prophylactic treatment.

Based on our experience, clinical management of these pregnancies should include close monitoring, awareness of risk for intrauterine ventricular arrhythmias in fetuses with tendencies toward manifest bradycardia,<sup>1</sup> intention to not deliver preterm based on fetal heart rate alone (ie, monitor

fetuses with echocardiography to assess circulation and fetal distress), and planning for delivery by elective cesarean section in a tertiary center where both mother and foetus can be monitored satisfactorily perinatally.

With regard to neonatal management of LQT1, cardiac event risk is typically low in infancy, especially without concomitant marked QTc prolongation. Although prophylactic beta-blocker therapy is well tolerated by LQTS infants, which LQT1 infants require this prophylaxis during the first year of life remains unclear. Importantly, in our previous study, fetal heart rate showed a significant association with later development of arrhythmia symptoms, with lower fetal heart rates in symptomatic mutation-carriers compared to asymptomatic mutation-carriers ( $122 \pm 10$  bpm vs  $137 \pm 9$  bpm;  $P < .0001$ ).<sup>1</sup> Hence, fetal heart rate could potentially be used as an additional risk stratification tool when deciding on prophylactic beta-blocker therapy in infants without QT prolongation. Clearly, further evaluation of fetal heart rate to ascertain for LQTS genotype and later phenotype in this relative low-risk population is necessary.

With regard to neonatal management of JLNS, the syndrome is associated with early symptom onset (50% symptomatic by 3 years of age)<sup>7</sup> and a staggeringly high mortality, such that early identification and risk management are essential.<sup>5-7</sup> Here we demonstrate that it is possible to reach beta-blocker levels  $>1$  mg/kg/d during the first week of life, under controlled conditions. We further demonstrate that the higher beta-blocker dosage required when treating JLNS, compared to LQTS, can be tolerated and maintained in a growing infant. The need for pacemaker support must be actively evaluated on an individual basis.<sup>11</sup> As noted for twin II, QTc may change over time and is not a static risk factor. Close clinical follow-up with electrocardiograms to assess further QTc or T-wave changes remains important as the child grows. We also emphasize using a team approach when managing JLNS families, as this is a complex syndrome with emerging issues to manage, stressing the need to collaborate with audiologists, cochlear implant clinics, physiotherapists, and pediatricians throughout the development of the child.

## Conclusion

Fetal sinus bradycardia noted during routine maternal health care may enable early diagnosis of LQTS in families in which the disorder is yet unidentified, especially in high-risk fetuses, including those with a diagnosis of JLNS. Correct diagnosis may prevent elective preterm delivery and enable presymptomatic prophylaxis.

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