Maternal mosaicism in long QT syndrome due to a pathogenic variant in *KCNH2*

Briana L. Sawyer, MS,* Martin Tristani-Firouzi, MD,* Layne E. Wells, BA,† Matteo Vatta, PhD,‡§ Susan P. Etheridge, MD, FHRS*

*From the *Division of Pediatric Cardiology, Department of Pediatrics, University of Utah, Salt Lake City, Utah, †Department of Precision Genomics, Intermountain Primary Children's Hospital, Salt Lake City, Utah, ‡Invitae Corporation, San Francisco, California, and §Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana.*

Introduction

We present the case of a singleton pregnancy presenting in utero with periods of 2:1 heart block with persistent fetal bradycardia and suspected fetal ventricular tachycardia. Postnatal clinical genetic testing identified a pathogenic variant in *KCNH2*. When familial site-specific genetic testing for the pathogenic variant was performed, the patient's mother was identified as having possible mosaicism for the familial *KCNH2* pathogenic variant. A subsequent pregnancy was also confirmed to have this pathogenic variant with similar prenatal and postnatal course as the proband. Other cases of mosaicism have been previously presented in genes related to inherited arrhythmias, including in *SCN5A*, but, to date, mosaicism has not been reported in *KCNH2*.

KEY TEACHING POINTS

- Next-generation sequencing (NGS) technology allows for the detection of low-level mosaicism; as mosaicism is increasingly recognized for its role in disease pathology, it is important to consider the possibility of gonosomal mosaicism in inherited arrhythmias.
- Parental testing should be conducted in probands even when the clinical picture is most consistent with a *de novo* variant.
- Identifying parental gonosomal mosaicism is useful to refine recurrence risk, as well as to provide the most appropriate care in future pregnancy management.

Case report

This study was approved by the University of Utah Institutional Review Board (IRB_00057688).

A G3P1 30-year-old woman was referred by her obstetrician to maternal fetal medicine (MFM) for supervision of a high-risk pregnancy at 33 weeks. There were concerns of fetal bradycardia, as well as possible umbilical cord varix. The obstetrician noted a fetal heart rate reportedly close to 60 beats per minute (bpm), and there was concern for fetal 2:1 atrioventricular (AV) block with an atrial rate around 111 bpm and ventricular rate close to 50 bpm. anti-Ro/SSA and anti-La/SSB antibodies were sent and were reported to be negative. One day later, at a visit to the Fetal Cardiology Clinic at our institution, a fetal echocardiogram identified normal intracardiac anatomy and cardiac function, and there was 1:1 AV contraction with a normal mechanical PR interval of 125 ms. The care plan included weekly follow-up with MFM with weekly biophysical profile, nonstress test and ultrasound with 1-minute auscultation and twice-weekly fetal heart rate checks, and a scheduled cesarean section at 39 weeks, for appropriate fetal monitoring during delivery.

The mother presented to her MFM at 35 weeks with fetal ultrasound concerning for periods of a rapid heart rate alternating with normal rhythm and without evidence of fetal distress or hydrops. At 37 weeks the patient was seen by the MFM with headache and fevers. The fetus was in persistent tachycardia concerning for ventricular tachycardia. With consideration of gestational age, a cesarean delivery was performed.

A live female infant without evidence of hydrops and with Apgar scores of 8 and 9 and birthweight of 2.75 kg was born following uncomplicated primary cesarean section. Postnatal telemetry monitoring identified 3 brief episodes of

KEYWORDS Genetic testing; Gonosomal mosaicism; Inherited arrhythmia; Ion channel; Long QT syndrome; Mosaicism
(Heart Rhythm Case Reports 2021;7:74–78)

Conflict of Interest: Matteo Vatta is an employee and stockholder of Invitae Corporation. The remaining authors have no conflicts of interest relevant to this article to disclose. Funding Source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. **Address reprint requests and correspondence:** Dr Susan P. Etheridge, University of Utah Division of Pediatric Cardiology, Department of Pediatrics, 81 N. Mario Capecchi Dr, Salt Lake City, UT 84113. E-mail address: susan.etheridge@hsc.utah.edu.

https://doi.org/10.1016/j.hrcr.2020.11.006

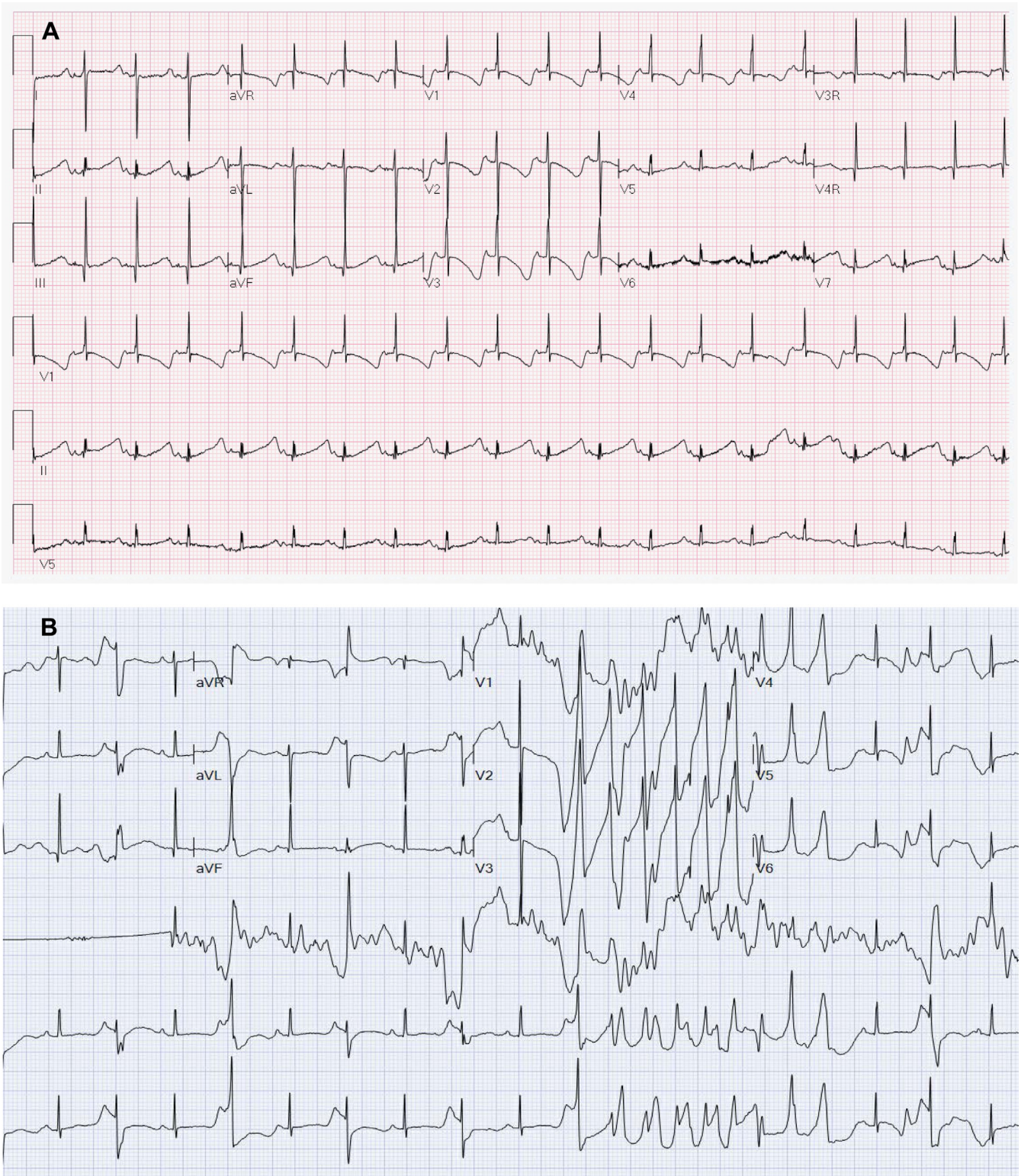

Figure 1 **A:** The initial sinus rhythm 15-lead electrocardiogram (ECG) and rhythm strip in the proband demonstrates significant QTc prolongation and abnormal, late-peaking T waves. **B:** A 12-lead ECG and rhythm strip of the proband at day of life 1 demonstrating QTc prolongation, ventricular ectopy, and ventricular tachycardia.

ventricular tachycardia. Her rhythm included frequent ventricular bigeminy with 2:1 AV block. Subsequent electrocardiograms (ECGs) demonstrated sinus rhythm with 1:1 AV conduction and marked QTc prolongation at 600 ms (Figure 1A) and ECGs with ectopy and ventricular tachycardia (Figure 1B). In light of a clinical diagnosis of long QT syndrome (LQTS), oral propranolol therapy was initiated, and genetic consultation and testing were pursued.

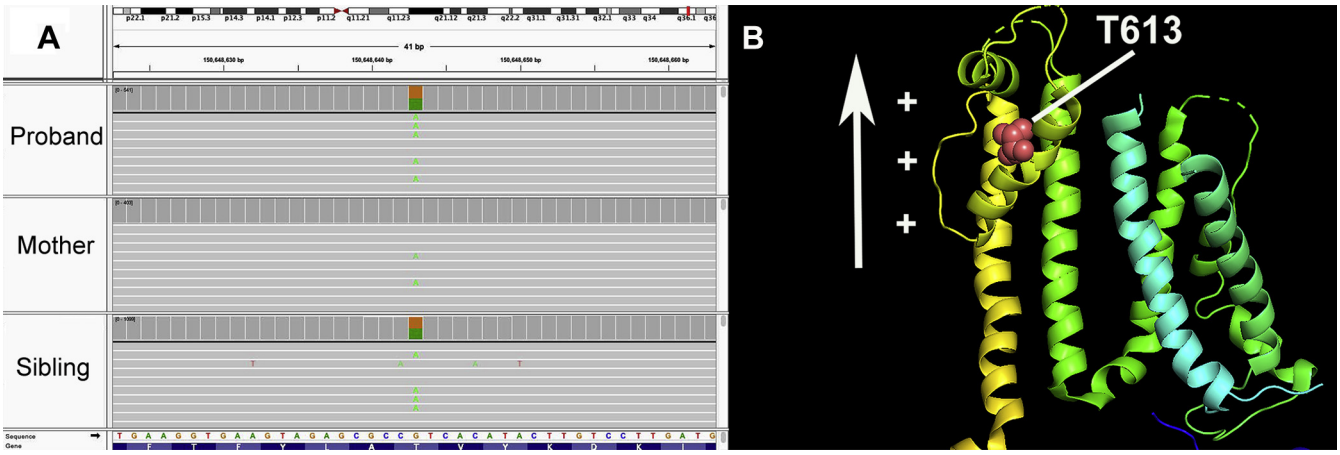

Figure 2 **A:** Next-generation sequencing reads at the variant site for proband, mother, and sibling, visualized by the Integrative Genomics Viewer. By convention, green represents the mutant nucleotide, with the reference nucleotide in orange. The sizes of the green and orange boxes are nearly equivalent for the proband and sibling, indicating both are heterozygous for the mutant allele. The mosaic nature of the mother is apparent by the low number of mutant nucleotides at this site. **B:** *KCNH2* channel structure illustrating the position of the p.Thr613Met variant within the pore helix. The proximity of the affected amino acid to the ion permeation pathway (*white arrow*) and potassium binding sites (denoted by +) suggest that substitutions at this position substantially impact channel function.

During consultation with a cardiovascular genetic counselor, a standard 3-generation family history was obtained. The female proband is the first shared biological child to her parents, third pregnancy to her mother. She has an older maternal half-sister and 3 older paternal half-siblings. Her mother had a previous spontaneous abortion at 7 weeks. All living children are reportedly healthy. There was no reported family history of LQTS, sudden cardiac arrest, death, or concerning syncope.

Both parents underwent ECG testing. The father's ECG was normal with a QTc of 419 ms, and the mother's ECG was also normal with QTc of 435 ms (Supplemental Figure 1). Based on the patient's significant fetal and neonatal history of arrhythmia and concern for LQTS, genetic testing was pursued. A 13-gene panel was ordered

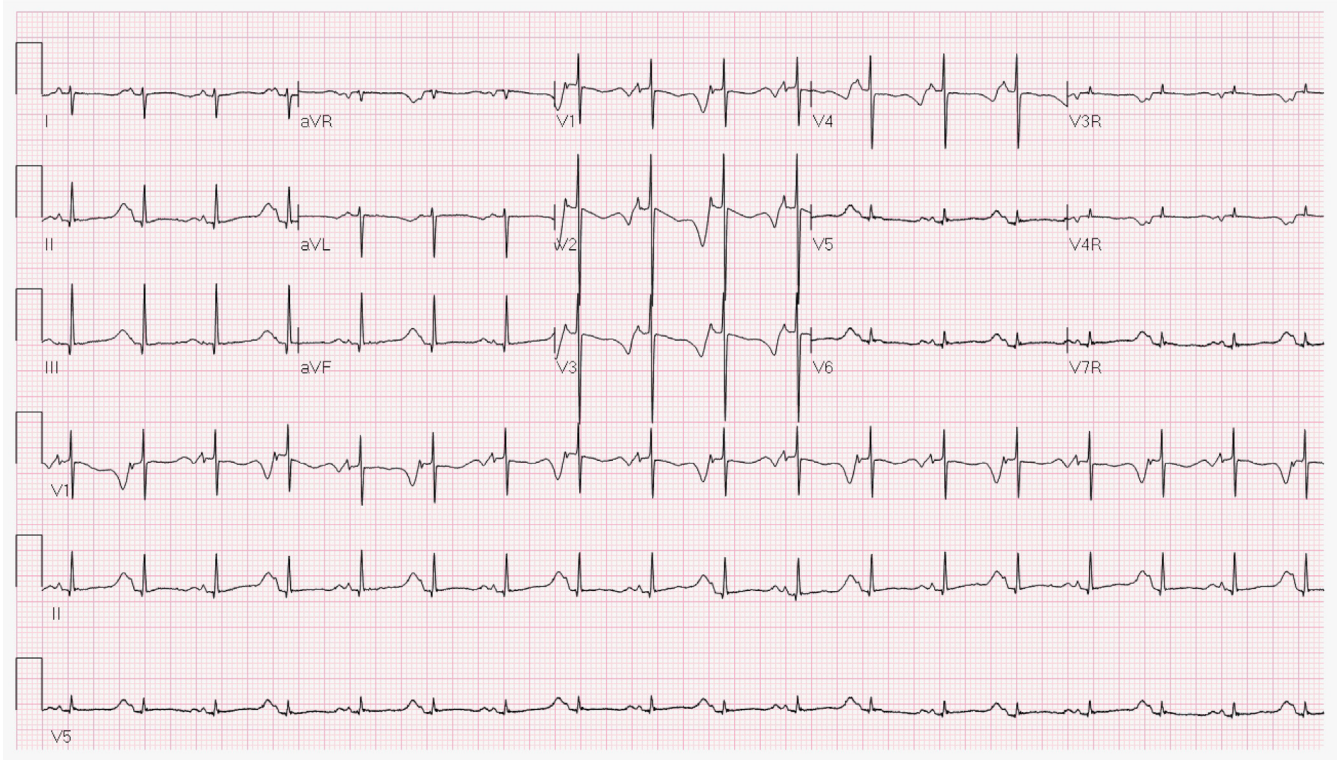

Figure 3 The initial 12-lead electrocardiogram and rhythm strip in the proband's sibling demonstrating QTc prolongation and abnormal late-peaking T waves.

through Invitae laboratories (San Francisco, CA). Genetic testing identified a well-described missense pathogenic variant in *KCNH2*, c.1838C>T (p.Thr613Met). This variant is absent from the gnomAD database, but has been reported in individuals with LQTS,[1–4] including *de novo* presentation in 2 cases.[5,6] This variant alters an amino acid that localizes to the pore helix of the HERG channel, a region critical for ion permeation. This location is associated with more severe arrhythmogenic symptoms than other regions of the channel.[7]

After assessment of the patient's noncontributory family history, including normal parental ECGs, the significant clinical course of the proband, and a review of the literature, the family was counseled that this was possibly a *de novo* variant, with a recommendation for the patient's parents to undergo site-specific genetic testing. Pretest counseling included a discussion of the possibility of gonadal mosaicism and reduced penetrance.

The proband's mother proceeded with site-specific genetic testing for the *KCNH2* variant, and she was identified to harbor the familial pathogenic variant. However, the observed read ratios from the sequencing panel were not consistent with heterozygotic carrier status in that 60 reads corresponded to the alternate (mutant) A and 332 to the reference (wild-type) G nucleotide (Figure 2). Although the next-generation sequencing (NGS-based test was not a validated quantitative analysis, nonetheless the approximately 15% of the reads corresponding to the mutant allele, instead of the expected ~50%, suggest the possible presence of both somatic and germline mosaicism given that her offspring inherited the variant. The mother's initial clinical history and ECG were benign, with the longest QTc measured at 456 ms. Upon further work-up and evaluation with an electrophysiologist, she did report occasional heart racing with sharp chest pain on exertion. The treating physician recommended initiation of a beta blocker, and the mother has since done well clinically. The proband's father did not undergo site-specific genetic testing. Additional testing in the family included our proband's maternal half-sister, who was negative for the familial pathogenic variant.

Fifteen months after the birth of the proband, a healthy boy was born, sharing both mother and father. Prenatal and postnatal course were reportedly uncomplicated. He underwent genetic testing following delivery and was negative for the family's pathogenic variant. Three years after the birth of the proband, the mother presented with her fifth pregnancy, with the same father as the proband. At 32 weeks' gestation an evaluation revealed fetal bradycardia, 2:1 AV conduction, and a structurally normal heart. Following a 2-minute episode of ventricular tachycardia detected by fetal monitoring, the child was delivered by repeat cesarean section at 35 weeks. A female child was born with Apgar scores of 8 and 8. Following delivery, telemetry revealed intermittent 2:1 AV block alternating with 1:1 AV conduction. The QTc was significantly prolonged at 634 ms (Figure 3). Macroscopic T-wave alternans were present. The child was admitted to the neonatal intensive care unit and treated with propranolol, magnesium sulfate, and potassium chloride. She also tested positive as a heterozygous carrier of the familial pathogenic variant in *KCNH2*.

Discussion

This case report documents the first case of mosaicism identified in *KCNH2* as a cause of LQTS. Although other LQTS genes are known to be associated with mosaicism, including *SCN5A*[8,9] and *CACNA1C*,[10] this case illustrates novel gonosomal mosaicism in *KCNH2*, defined by Biesecker and Spinner[11] as a combination of germline and somatic mosaicism. Notably, this report highlights the value of parental testing even when a proband's presentation is consistent with a *de novo* variant, as additional explanations could include reduced penetrance or gonosomal mosaicism that may affect future pregnancies. In a post-Sanger era of genetic technology and precision medicine, where most sequencing is done by NGS, we are now discovering that a portion of *de novo* presentation is, in actuality, due to a postzygotic pathogenic variant in parents. With NGS, it is possible to identify low-level mosaicism, previously unattainable with Sanger sequencing technology.[11] However, to confirm the exact level of mosaicism follow-up testing using validated quantitative assessment should be considered.

The mosaicism seen in our proband's mother likely arose as a postzygotic *de novo* variant, as opposed to a variant occurring in a single egg or sperm, which would not lead to mosaicism. This postzygotic event resulted in mosaicism with lower levels of identifiable variant in the maternal blood, and possibly in her cardiac tissue, and may account for her benign clinical course. It should be noted that a level of mosaicism of only 8% in heart cells can cause an arrhythmia phenotype.[8] The mother's variant is clearly germline, though at an unknown level; but, hypothetically, it could be at most 50%, as would be seen in someone without mosaicism, because she has 2 unaffected and 2 affected children. Because growing evidence suggests that somatic mosaicism plays a role in the pathology of a variety of diseases, including inherited arrhythmias like LQTS, continued investigation of the genetic causes of disease and potential mosaicism in family members is of paramount importance.

Identifying maternal mosaicism in this family had important clinical relevance for management of future pregnancies. Closer monitoring of additional pregnancies, as well as delivery at a tertiary care center and a birth plan that included neonatal intensive care unit admission for a potentially affected fetus, was crucial for optimal neonatal course and survival. This variant is known to be problematic with fetal presentation.[6] This pathogenic variant resulted in significant arrhythmias during pregnancy, after which, despite rapid control of the arrhythmia, the fetus developed severe periventricular leukomalacia, was delivered preterm at 32 weeks' gestation, and died on the sixth day after birth. In our proband as well as the family's subsequent affected pregnancy, the fetal diagnosis allowed for important fetal and neonatal LQTS management and impacted survival. Additional

information could have been attained from a fetal magnetocardiogram, particularly in the proband. The use of fetal magnetocardiogram is well established for prenatal LQTS diagnosis and management of fetal LQTS.[12,13] A prenatal diagnosis of LQTS can improve outcomes by limiting maternal medications that prolong the QT interval and allows the recognition of fetal LQTS as the etiology of an arrhythmia such as sinus bradycardia rather than fetal distress.[14] This will facilitate closer-to-term delivery.

With the identification of maternal gonosomal mosaicism, the recurrence risk was appropriately counseled at up to 50%. The accurate assessment of recurrence risk is important for families to make informed decisions about future pregnancies and allows medical care teams to consider appropriate pregnancy and delivery plans. Family planning decisions are influenced by their counseled recurrence risk, making correct assessments and understanding valuable pieces of their decision-making process.[15]

One limitation to this case report is that mosaicism was inferred but not directly confirmed in the proband's mother. Although an allele balance well below 50% in NGS is known to signify mosaicism, Invitae has not validated this approach for quantitative identification of mosaicism. However, the observed read ratios from the mother's sequencing clearly demonstrate lower levels than would be expected in a heterozygous carrier yet higher than expected for someone homozygous for a reference allele. Furthermore, the clinical course is consistent with mosaicism in cardiac tissue, as the *KCNH2* c.1838C>T Thr613Met variant is associated with a substantial clinical phenotype.[8] Many heterozygous carriers of this variant have significant clinical presentation, including sudden cardiac death and syncope in early life with abnormal QT prolongation, which was not the clinical course for our patient with suspected mosaicism.[1–6]

Overall, this case report expands our understanding of gonosomal mosaicism in LQTS. We highlight the importance of parental testing and its impact on future pregnancy management and clinical outcomes. Finally, identification of gonosomal mosaicism can allow for appropriate recurrence risk discussions that may impact family planning and decision-making.

Conclusions

We report the first case of mosaicism in *KCNH2*. Parental gonosomal mosaicism should be considered in probands with severe clinical phenotypes and otherwise noncontributory family histories and normal parental ECGs. Low-level mosaicism may not always be identified in genetic testing but should be considered for recurrence risk counseling, as well as considerations for family screening and follow-up medical management.

Acknowledgments

We acknowledge Lisa Mills, RN, for her kind care of this family and the SADS Foundation (www.stop-sads.org) for their support.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2020.11.006.

References

1. Jongbloed RJ, Wilde AA, Geelen JL, et al. Novel KCNQ1 and HERG missense mutations in Dutch long-QT families. Hum Mutat 1999;13:301–310.
2. Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes: KVLQT1, HERG, SCN5A, KCNE1, KCNE2. Circulation 2000;102:1178–1185.
3. Lupoglazoff JM, Denjoy I, Villain E. Long QT syndrome in neonates: conduction disorders associated with HERG mutations and sinus bradycardia with KCNQ1 mutations. J Am Coll Cardiol 2004;43:826–830.
4. Nagaoka I, Shimizu W, Itoh H, et al. Mutation site dependent variability of cardiac events in Japanese LQT2 form of congenital long-QT syndrome. Circ J 2008;72:694–699.
5. Laitinen P, Fodstad H, Piippo K, et al. Survey of the coding region of the HERG gene in long QT syndrome reveals six novel mutations and an amino acid polymorphism with possible phenotypic effects. Hum Mutat 2002;15:580–581.
6. Simpson JM, Maxwell D, Rosenthal E, Gill H. Fetal ventricular tachycardia secondary to long QT syndrome treated with maternal intravenous magnesium: Case report and review of the literature. Ultrasound Obstet Gynecol 2009;34:475–480.
7. Moss AJ, Zareba W, Kaufman ES, et al. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. Circulation 2002;105:794–799.
8. Priest JR, Gawad C, Kahlig KM, et al. Early somatic mosaicism is a rare cause of long-QT syndrome. Proc Natl Acad Sci U S A 2016;113:11555–11560.
9. Miller TE, Estrella E, Myerburg RJ, et al. Recurrent third-trimester fetal loss and maternal mosaicism for long-QT syndrome. Circulation 2004;109:3029–3034.
10. Dufendach KA, Giudicessi JR, Boczek NJ, Ackerman MJ. Maternal mosaicism confounds the neonatal diagnosis of type 1 Timothy syndrome. Pediatrics 2013;131:e1991–e1995.
11. Biesecker LG, Spinner NB. A genomic view of mosaicism and human disease. Nat Rev Genet 2013;14:307–320.
12. Cuneo BF, Strasburger JF, Yu S, et al. In utero diagnosis of long QT syndrome by magnetocardiography. Circulation 2013;128:2183–2191.
13. Horigome H, Iwashita H, Yoshinaga M, Shimizu W. Magnetocardiographic demonstration of torsade de pointes in a fetus with congenital long QT syndrome. J Cardiovasc Electrophysiol 2008;19:334–335.
14. Cuneo BF, Strasburger JF, Wakai RT. The natural history of fetal long QT syndrome. J Electrocardiol 2016;49:807–813.
15. Selkirk CG, McCarthy Veach P, Lian F, Schimmenti L, LeRoy BS. Parents' perceptions of autism spectrum disorder etiology and recurrence risk and effects of their perceptions on family planning: Recommendations for genetic counselors. J Genet Counsel 2009;18:507–519.