

Miller T, Estrella E, Myerburg R, Garcia J, Moreno N, Rusconi P, Ahearn ME, Baumbach L, Kurlansky P, Wolff G, and Bishopric NH. Recurrent third-trimester fetal loss and maternal mosaicism for Long-QT Syndrome. Circulation 2004; 109(24):3029-3034

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BACKGROUND: The importance of germ-line mosaicism in genetic disease is probably underestimated, even though recent studies indicate that it may be involved in 10% to 20% of apparently de novo cases of several dominantly inherited genetic diseases. **METHODS AND RESULTS:** We describe here a case of repeated germ-line transmission of a severe form of long-QT syndrome (LQTS) from an asymptomatic mother with mosaicism for a mutation in the cardiac sodium channel, SCN5A. A male infant was diagnosed with ventricular arrhythmias and cardiac decompensation in utero at 28 weeks and with LQTS after birth, ultimately requiring cardiac transplantation for control of ventricular tachycardia. The mother had no ECG abnormalities, but her only previous pregnancy had ended in stillbirth with evidence of cardiac decompensation at 7 months' gestation. A third pregnancy also ended in stillbirth at 7 months, again with nonimmune fetal hydrops. The surviving infant was found to have a heterozygous mutation in SCN5A (R1623Q), previously reported as a de novo mutation causing neonatal ventricular arrhythmia and LQTS. Initial studies of the mother detected no genetic abnormality, but a sensitive restriction enzyme-based assay identified a small (8% to 10%) percentage of cells harboring the mutation in her blood, skin, and buccal mucosa. Cord blood from the third fetus also harbored the mutant allele, suggesting that all 3 cases of late-term fetal distress resulted from germ-line transfer of the LQTS-associated mutation. **CONCLUSIONS:** Recurrent late-term fetal loss or sudden infant death can result from unsuspected parental mosaicism for LQTS-associated mutations, with important implications for genetic counseling.