Congenital long-QT syndrome (LQTS) is a rare heritable disorder that is associated with a high risk of syncope and sudden cardiac death. Since 1996, LQTS has been categorized based on mutations to genes that encode cardiac ion channel subunits or proteins that modulate ionic currents in the heart. The most common LQTS gene mutations involve $KCNQ1$ (LQT1), $KCNH2$ (LQT2), and $SCN5A$ (LQT3). Multiple other rare gene mutations have been identified and postulated to cause LQTS (LQT4–LQT13). However, in some cases, the identified mutations are part of a more complex clinical disorder (ie, LQT7 and LQT8) and may not be part of the LQTS in the classical sense. In other cases, such as LQT9, there are limited data supporting a causative link between a mutation and LQTS.

The $CAV3$ gene encodes an integral membrane protein called caveolin 3. Caveolins play an important role in signal transduction and vesicular transport within cells. Mutations to $CAV3$ have been found to cause diseases of both skeletal and cardiac muscle. Furthermore, mutations to $CAV3$ were recently identified as rare, potentially disease-causing mutations in a series of patients referred for LQTS genetic testing. In 2006, Vatta et al. reported finding 1 of 4 novel $CAV3$ mutations (T78M, A85T, F97C, and S141R) in 6 (0.7%) of 904 unrelated patients. Cellular electrophysiological characterization of 2 of these mutations (F97C and S141R) revealed that the mutations resulted in as much as a 4-fold increase in the late sodium current ($I_{NaL}$). Based on the recognition that multiple ion channels and transporters have been localized to caveolae, and that caveolin 3 interacts with various signaling molecules, the authors speculated that “modulation of other ion channels or signaling pathways regulating ionic currents also may contribute to the pathophysiology (of the QT prolongation).” In fact, prior and subsequent studies have shown that caveolin 3 is involved in the increase in $I_{NaL}$ that occurs during β-adrenergic stimulation. In 2007, Cronk et al. identified 6 family members with the T78M mutation. Specifically, the T78M mutation was found in a family with a history of syncope and cardiac arrest. The authors screened the family of the affected proband and identified 6 family members with the T78M mutation. Importantly, the proband was also a carrier of a $KCNH2$ (LQT2) mutation. Subsequently, the authors screened the family of the affected proband and identified 6 family members with the $KCNH2$ (LQT2) mutation. Similar to the proband, 3 of the 6 family members with the $KCNH2$ (LQT2) mutation also had a $KCNH2$ (LQT2) mutation; 3 of the 3 had a history of syncope. This phenotype was consistent with clinical LQTS and was not more severe than the phenotype of family members with the LQT2 mutation alone. In contrast, the 3 family members carrying only the $KCNH2$ (LQT2) mutation had normal QT intervals (QTc ≥ 470 ms). Although all 3 had a history of syncope, it was not exertional syncope. The authors describe that 1 of these was an elderly man with marked PR prolongation, 1 had syncope associated with a painful delivery, and 1 had syncope associated with a painful accident. Although these episodes may not represent classic LQTS-related exertional syncope, 2 of the episodes occurred during adrenergic stimulation. It is interesting to recall that Vatta et al. reported on a 13-year-old patient with asthma with the F97C $CAV3$ mutation whose QT prolongation was absent at rest but reproducibly present on β-agonist therapy for her asthma.

To Be or Not to Be
Long-QT Syndrome Type 9
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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Based on the borderline phenotypic evidence for LQTS in Vatta et al’s report and in their own study, Hedley et al concluded that T78M CAV3 mutations in isolation cannot be considered LQTS disease-causing mutations. Furthermore, Hedley’s group conducted functional studies and concluded that although caveolin interacts with Kv11.1 (encoded by KCNH2), the T78M CAV3 mutation in isolation alters neither the interaction between caveolin and Kv11.1 nor the Kv11.1 current. Although they acknowledge Cronk et al’s demonstration of a marked increase in INa with T78M, they assert that it is “meaningless to assess the effects CAV3 mutations have on a single ion channel without being able to assess the effect on the action potential as a whole.” The authors allow that CAV3 mutations may have highly variable phenotypic expression but recommend that LQT9 be considered a provisional entity.

Can CAV3 mutations cause LQTS? Can we conclude that they do not? It is always difficult to know with certainty which rare genetic variants are disease-causing. Let us consider the points on which Hedley et al base their argument. First, the small number of patients with T78M did not have significant resting QTc prolongation. This, in itself, is not sufficient to discount T78M as a LQTS susceptibility mutation. The literature is full of examples of individuals with known pathogenic LQTS mutations and normal phenotype. In some studies, penetrance has been estimated to be only 25%. The absence of resting QTc prolongation among affected individuals has given rise to the common use of provocative testing with exercise and epinephrine to unmask latent LQTS because patients with normal resting QTc may still be at risk of syncope and sudden cardiac death during adrenergic stimulation. Furthermore, there are mutations (and even polymorphisms) that tend to be silent until a second condition (bradycardia, hypokalemia, addition of a drug) arises. However, in some patients, these same mutations are disease-causing without the presence of a second condition. So, an absence of resting QTc prolongation in a small sample size (n=6) cannot exclude T78M as a pathogenic mutation. What about the cellular expression data? The authors of the current study agree that teasing out the effect of a mutation on the action potential as a whole is complex and cannot be solved by studies of individual ion channel function in isolation. This provocative study by Hedley et al does not eliminate LQT9 as a diagnostic entity. However, it clearly sets the stage for further investigation to elucidate the mechanisms underlying LQT9. Future studies using inducible pluripotent stem cell technology seem ideal for helping to resolve the question of whether LQT9 is to be or not to be.

Disclosures

None.

References


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