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.

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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.1 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 (INaL). More recently, Cheng et al showed that the F97C CAV3 mutation alters the activity of neuronal NO synthase 1 on the cardiac sodium channel (SCN5A). Specifically, this mutation was shown to remove the repressive effect of caveolin on NO synthase 1, resulting in increased S-nitrosylation of SCN5A and a concomitant increase in INaL.

Other studies have pointed to important interactions between caveolin 3 and potassium channel function. KCNH2 expression in the membrane (and thus IKr current) is regulated by caveolin 3.2 Mutations of CAV3 reduce cell surface expression of Kir2.1 (IK1 current). In addition, caveolins are involved in low K+ -induced degradation of mature IKr channels.3

Although these data suggest plausible mechanisms for LQTS in individuals with CAV3 mutations, the clinical data supporting CAV3 mutations as pathogenic, particularly T78M, are sparse. In Vatta et al’s initial report,1 T78M was seen in 3 patients, 1 of whom had a concomitant known LQT2 mutation. The 3 patients had normal or at most modestly prolonged QT intervals. One was asymptomatic, and 2 (both with sinus bradycardia) had nonexertional syncope.

In this issue of *Circulation: Cardiovascular Genetics*, Hedley et al screened a series of LQTS probands (n=167) for mutations in the CAV3 gene. The authors identified a single case (0.6%) of CAV3 mutation in this population, specifically 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 T78M CAV3 mutation. Similar to the proband, 3 of the 6 family members with the T78M CAV3 mutation also had a CAV3 (LQTS) mutation; these 3 individuals had QT prolongation (QTc ≥470 ms), and 2 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 T78M CAV3 mutation had normal QT intervals (QTc, 410–420 ms). Although all 3 had a history of syncope, it was not exertional syncope. The authors describe that 1 of these was an elderly woman 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.
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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To Be or Not to Be: Long-QT Syndrome Type 9
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