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A KCNE1 Missense Variant (V47I) Causing Exercise-Induced Long QT syndrome (Romano Ward)

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Dear editor

We present a case of a 28-year-old female who was referred for a second opinion regarding management of mitral valve prolapse (MVP). At age 14 years she was diagnosed with a murmur. At age 23 years she developed daily episodes of palpitations with exertion, occasionally with dizziness but never with syncope. She was not on any medications or diet supplements known to prolong the QT interval. Her family history was significant for the witnessed sudden death of her mother at age 40 years. The cause of death per the autopsy report was “mitral valve prolapse”. Her younger sister, age 24 years also has MVP. On examination, a late systolic murmur was appreciated at the apex, consistent with MVP and moderate mitral regurgitation (MR).

Electrocardiogram (ECG) showed sinus rhythm with right axis deviation, S1Q3T3 and normal corrected QT (QTc) interval of 477 msec (Figure 1). Echocardiography showed myxomatous degeneration of both mitral leaflets and 2+/4+, posteriorly-directed, MR. She underwent stress testing to evaluate her exertional palpitations. Interestingly, during the exercise component of a Bruce protocol stress test, her QTc interval prolonged to greater than 500msec (Figure 1). Subsequently an event monitor showed occasional PVCs and a 4-beat run of nonsustained ventricular tachycardia (NSVT) at 150 bpm (Figure 2). Because of her prolonged QTc interval and family history of sudden death, she was referred for genetic testing. She underwent genetic testing for long QT (LQT), dilated cardiomyopathy, mitochondrial abnormalities and mitochondrial genes. The only pathogenic variant identified was in the KCNE1 gene, V47I (Figure 3). This variant was not identified in 400 control alleles and has previously been reported only once in the literature.

Genetic data are unavailable from her deceased mother who died in 1995 and her father is unavailable for participation. Her sister did not have prolonged QT and gene testing did not

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show a KCNE1 Val47Ile mutation. There is no evidence of cardiomyopathy based on a three-generation family history obtained by a certified genetic counselor. Beta-blocker therapy was initiated and this was associated with reduction in palpitations, NSVT and normalization of the QT interval with exercise.

This case is noteworthy in that we report the discovery of a variant in the KCNE1 gene in a patient with structural heart disease and dysrhythmia. This KCNE1 gene encodes a β -subunit, which controls the function of potassium channels that are crucial to cardiac repolarization. The presentation of this case of Long QT Syndrome (LQTS) is also unusual in that the QTc prolongation was an incidental finding on an exercise stress test.

LQTS is a collection of inherited channelopathies characterized by prolongation of the QT interval on the ECG and predisposition to syncope and sudden death, due to torsades de pointes. Genetically-mediated LQTS have an incidence estimated to be 1:2000 to 1:5000¹. Romano-Ward syndrome, which is inherited in an autosomal dominant pattern, has an exclusively cardiac phenotype and is the most prevalent heritable LQTS (incidence of ~1:2500). In general, mutations of the KCNE gene, such as our case, causes LQT-5 and results in a milder phenotype with incomplete penetrance, in contrast to mutations in the gene encoding the pore forming unit of the channel (KCNQ1, LQT-1)². The V47I variant has not been previously reported in conjunction with cardiac or arrhythmic disease.

LQT-1 and LQT-5 predispose to arrhythmias when heart rate is increased, whether triggered by exercise or β -adrenergic stimulation. Probands with KCNE1 mutations are generally older and have shorter QTc than other LQTS genotypes³. Both of these attributes were observed in our patient, who presented in her 3rd decade with palpitations, presyncope and failure to shorten the QTc with exercise.

In 2500 patients referred for the FAMILION LQT syndrome genetic testing, Kapplinger et al found that 903 (36%) hosted a possible LQTS-causing mutation. In 91% of cases there was a single mutation⁴. In this study only 24/821 single mutation LQTS were due to KCNE1 mutations (0.3%). Kapplinger et al reminds us, that “*as with most genetic tests, LQTS genetic test results are probabilistic rather than binary*”. Definitive proof that a mutation is pathologic in heterologous expression systems is available in only a minority of cases. Thus, careful checking of the variant against control subjects of the same ethnicity as the proband (as was done in our case) is mandatory.

The V47I variant that we report, only previously described in a patient with tinnitus⁵, is a missense variant in the highly conserved region encoding the KCNE1 transmembrane domain. KCNE1 normally increases the repolarizing K⁺ current, slows its activation and reduces its inactivation. In the absence of KCNE1, KCNQ1 gives rise to a small potassium current that inactivates during depolarization. These contributions of the β -subunit make this current especially important for repolarization during tachycardia, explaining why we were only able to make the diagnosis during exercise. This variant is likely pathologic because it was not identified in our survey of 400 control alleles from individuals of African-American or Caucasian background. When Sand et al. described the same KCNE1 variant in one patient with tinnitus, they did not find the variant in 201 normal subjects, and concluded that it was pathogenic. The authors did not comment on whether their patient had cardiac pathology⁵. However, of note, our patient does describe intermittent episodes of tinnitus in her left ear.

The exact nature of the relationship between long QT, MVP and LV dilatation is undetermined. It will be instructive to define the electrical function of this subunit. There are some clues linking KCNE1 to ventricular function. For example, a KCNE1 S38G single-

nucleotide polymorphism (SNP) has been associated with QTc prolongation and a predisposition to heart failure⁶.

Beta-blockers are central to the treatment of LQT-5. In a large population study, β -blockers provided a 60% reduction in the combined end-point of the risk of syncope, aborted cardiac arrest and LQTS-related sudden death⁷. In patients who experience cardiac events despite compliance with β -blockers, ICD placement or left cardiac sympathetic denervation can be considered.

We report a new cause of Romano-Ward syndrome, namely the KCNE1 V47I variant. This case is especially interesting because of the normal resting ECG and the discovery of a KCNE1 mutation that has not previously been described in a manner relevant to heart disease or dysrhythmia.

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Figure 1.
 (A) Resting EKG-HR 62 bpm and QTc 477 msec and (B) Exercise EKG-at 11:50 min of Bruce protocol exercise test. HR 166 bpm and QTc 512 msec

Figure 2.
Non-sustained ventricular tachycardia on Holter monitor, which corresponded with symptoms