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Is it time to develop a 'pathogenicity' score to distinguish long QT syndrome causing mutations from 'background' genetic noise?

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The congenital long QT syndromes (LQTS) are a group of genetic disorders that affect cardiac ion channels, are characterized by prolongation of the QT interval, and carry a risk for the life-threatening ventricular tachycardia, Torsades de Pointes. Shortly after the autosomal recessive syndrome of congenital deafness, prolongation of the QT interval, and sudden cardiac death was described by Jervell and Lange-Nielsen in 1957,[1] Romano and Ward each independently described an "autosomal dominant" form without congenital deafness.[2, 3] In the late 1990's, the first 5 LQTS genes were identified, all of which encode ion channel subunits that underlie the cardiac action potential.[4–7] The most commonly affected genes, *KCNQ1* and *KCNH2* (underlying LQT1 and LQT2 respectively), encode proteins that form the α-subunits of 2 major repolarizing potassium currents, I_{Ks} and I_{Kr}. Two other LQTS genes encode for the corresponding β-subunits (*KCNE1* and *KCNE2* underlying LQT5 and LQT6, respectively). The other major LQTS gene, *SCN5A* (underlying LQT3) encodes the α-subunit of the cardiac sodium channel. Additional ion channel mutations have been associated with rare arrhythmia syndromes (Andersen-Tawil syndrome, *KCNJ2* and Timothy syndrome, *CACNA1C*) that may include QT prolongation, as well as significant extracardiac phenotypes.[8] Andersen-Tawil syndrome (ATS) patients do not uniformly display prolonged QT intervals, and due to clinical features that differ from LQTS, is better termed ATS1 rather than LQT7.[9] The previously-termed LQT4 has been linked to mutations in *ANK2*, encoding the structural protein ankyrin-B, which when mutated, results in altered localization and expression of ion channels.[10] Patients with *ANK2* mutations do not uniformly have prolonged QT intervals, and it has been suggested that LQT4 be renamed 'sick sinus syndrome associated with bradycardia' or 'ankyrin-B syndrome'.[11]

The incidence of congenital LQTS has been estimated at 1 in 5000, and the incidence of Jervell-Lange-Nielsen (JLN) syndrome estimated as 1 in 500 congenitally deaf individuals. Without treatment, 13% of LQTS patients will suffer cardiac arrest or sudden death prior to 40 years of age; when syncopal events are included, 36% will have symptoms by age 40.[12] The JLN syndrome is more severe, with 90% experiencing syncope, cardiac arrest, or sudden death by age 18, and mortality exceeding 25% even with therapy.[13] Important clinical differences among affected patients depending on the underlying affected gene have been observed – so called genotype-phenotype correlation. As the majority (>90%) of genotyped LQTS patients have LQT1, LQT2, or LQT3 most of the differences are observed among these genotypes, and include different ECG T-wave patterns,[14] clinical course,[15] triggers of cardiac events,[16]

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response to sympathetic stimulation,[17, 18] and effectiveness and limitations of β-blocker therapy.[19]

Over the past decade, genetic testing for LQTS, particularly the three most common genotypes of LQT1 to LQT3, was performed in a few research laboratories worldwide with very high diagnostic yield. However, since 2004, clinical LQTS genetic testing has become available through a commercially available diagnostic test (FAMILION), which provides mutational analysis of the 3 major LQTS-susceptibility genes along with the 2 minor genes (*KCNE1* [LQT5] and *KCNE2* [LQT6]). Clinically, genetic testing has been used to not only risk-stratify patients, but also guide treatment decisions, and precisely elucidate the carrier status of potential at-risk relatives. To date, hundreds of non-synonymous mutations and splice-site altering mutations have been identified in the 12 LQTS- or LQTS overlap-susceptibility genes.

In this issue of *Heart Rhythm*, Kapplinger et al[20] describe the spectrum and prevalence of mutations in the first 2500 cases scanned for mutations in 5 of the LQTS-susceptibility genes at FAMILION. The major results are: 1) 36% of all patients tested hosted a possible LQTS-causing mutation; 2) 91% of the mutation-positive cases had single genotypes while the remaining 9% had >1 mutation and 3) 60% of the mutations were novel to this cohort. All prior publications on the yield of genetic testing in consecutive patients originated in a few research laboratories. In general, those laboratories will only perform genetic testing (usually at no charge) after receiving clinical information and ECGs from the patient tested and will perform the test when there is a reasonable chance of finding a mutation in the tested gene. In contrast, the present data originate from the first clinical genetic laboratory that performs the test on a commercial basis without the need for any prerequisite phenotypic data. This probably explains the relatively low yield of positive tests (lower than recent numbers of positive results in research laboratories). The 36% yield of positive results in this cohort also suggests that physicians are at least semi-prudently evaluating the need for the test particularly in light of the high cost.

It has been well over a decade since the first LQTS-causative mutations were discovered but still one-third of mutations discovered in this cohort were novel. This highlights one of the major challenges when interpreting the results of genetic testing: distinguishing pathogenic mutations from rare variants that actually have no relationship to the disease. In this particular study, this is made even more difficult as no clinical data are available permitting genotype-phenotype correlations. As this group has previously shown, the availability of clinical phenotype strongly correlates with the likelihood of elucidating a pathogenic mutation.[21]

Multiple approaches have been used to distinguish between pathogenic and benign rare variants: 1) screening large ethnically-matched control populations to establish variant frequency; 2) examining cosegregation of disease and genetic variant in extended kindreds; 3) analyzing the degree of conservation of the mutated amino acid across species; 4) examining the mutation type and location and 5) performing functional studies. Variants cosegregating in kindreds, absent in matched control populations with a high degree of conservation and demonstrating functional effects, are most likely to be disease-causing. Thus, when these criteria are systematically applied to the novel mutations identified in this study, it is likely that many of the variants constitute ‘background’ genetic noise and are not pathogenic for the LQTS. With increasing availability of genetic testing, distinguishing pathogenic mutations from rare variants is increasingly becoming more important. Consequently, a ‘pathogenicity score’ based on some or all of the elements mentioned above would prove invaluable when interpreting the results of genetic tests. Such an approach has been proposed by a number of groups including the authors of this paper. The authors of the present study, however, should be congratulated as this compendium of novel and rare variants associated with the LQTS and

it does provide a useful starting point for further studies of the pathogenesis of these rare diseases.

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