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Arrhythmia genetics: Not dark and lite, but fifty shades of grey

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The congenital long QT syndromes (cLQTS) were first described over half a century ago: we now recognize multiple genetic and clinical subtypes and the exploration of the disease has informed not only family screening but also our fundamental understanding of the electrophysiology of repolarization. Along with this new knowledge has come a new set of challenges centered around interpretation of the relationship between the presence of a variant in a known cLQTS disease gene and its relationship to phenotype.

There are over a dozen disease genes (some with not terribly robust evidence of association with disease) and hundreds of mutations that have a reasonable relationship to the disease. Faced with a mutation, the geneticist has a set of tools that drive assessment of pathogenicity: the variant generates abnormal function in *in vitro* testing, segregates with phenotype across a kindred, has been seen in multiple affected individuals across the globe, and is rare across ancestries.[1]

How rare must a variant be to be a plausible long QT variant? A key contemporary tool to answer this question is the Genomic Aggregation Database (gnomAD) that currently presents whole exome data in ~125,000 individuals and whole genome data in an additional ~15,000 individuals across multiple ancestries (gnomad.broadinstitute.org). A back of the envelope calculation suggests that if cLQTS occurs in 1:1000 subjects and there are 1000 causative mutations, we'd expect something like 1/1,000,000 subjects might carry any specific mutation. Interestingly, some *bona fide* cLQTS mutations, like *SCN5A* E1784K or *KCNQ1* A341V, have been seen in many kindreds, but have not been reported in gnomAD: they are in fact very rare. The corollary is that the more common a variant, the less likely it is that it is a disease-causing mutation. This approach can be used to reclassify semi-rare variants formerly considered pathogenic to likely benign, and to estimate allele frequency cutoffs for highly penetrant pathogenic variants (<3/100,000 has been proposed for cLQTS[2]).

We are also learning that common variants, often defined as a minor allele frequency (MAF) >1%, can modulate cLQTS penetrance and contribute to exaggerated responses to QT prolonging drugs. In a genome-wide association study (GWAS) in 100,000 subjects, there were 35 loci associated with QT interval and while the P value for the top association (with variants near *NOS1AP*) was extraordinarily low (10^{-220}), the effect size was very modest

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(3.5 msec – less that the width of the "ink" line on a standard ECG – per allele).[3] *NOS1AP* variants appear to modulate penetrance in cLQTS[4, 5] and risk for sudden death in the general population.[6] Another approach to understand the role of common polymorphisms in a trait like QT interval is to develop genetic risk scores that incorporate the contribution of many variants to a phenotype. A QT risk score did predict the extent of QT prolongation after drug challenge and the development of drug-induced torsades.[7] A preliminary study suggests that the 10-20% of patients with cLQTS and no disease-associated mutation have high genetic risk scores, i.e. their disease may be mediated by multiple common variants.[8]

One variant that is both common and repeatedly implicated in QT-associated disease is *KCNE1* D85N; the MAF in gnomAD varies from 0.1% in South Asians, 0.2% in Africans, 0.6% in East Asians, 1.7% in Europeans, and 2.5% in Ashkenazim. In the QT GWAS, it increased QT by 7.4 msec/allele ($p=2\times10^{-18}$), the largest effect size of any single variant in that study. In a series of 176 European patients with drug induced torsades, we found the MAF was much higher in cases (8.6%) compared to two control groups (1.8-2.9%), conferring an odds ratio of ~10.[9] Nishio et al. found the variant in 3.9% of Japanese subjects with cLQTS and 0.8% of controls, showed that it reduces both I_{Kr} and I_{Ks} in heterologous expression systems, identified patients with symptoms and no other known mutation, and suggested it could be disease causing.[10] The mantra in contemporary genome science is replication, so a timely contribution is the manuscript from Lane et al. and colleagues at the Mayo Clinic in the present issue of *Heart Rhythm*.[11] They found that D85N was commoner (2.6%) in subjects referred for testing because of QT issues than in gnomAD. They present clinical data that while carriers did have discernible phenotypes (like QT intervals at the upper end of the normal range), they tended to have fewer symptoms. They propose designating the carriers as having "LQT5-lite". We don't agree: this terminology labels patients as having a syndrome when in fact what they have is a common allele that seems to confer somewhat increased risk for arrhythmia symptoms, especially with other stressors (like other genetic variants or drugs). As we learn more about modifiers, many alleles may fall into this category and designating them all "Lite" will do patients and the field a disservice. A parallel issue is whether this variant should be reported in the course of genetic testing for cLQTS. Given the data that this is a believable risk modifier, this approach seems reasonable [12]and prospectively-evaluated outcomes would be nice to have.

The present study adds to an increasingly complex picture that cLQTS, like many other Mendelian diseases, is not a simple mutation positive/negative issue, and genetic background, in the form of common variants like D85N, can modulate the phenotype. Individual common variants tend to have modest (and often difficult to reproduce) effect sizes, and while the data for D85N do seem to consistently point to such a modest risk, it also seems likely that the clinical consequences will also be driven by other common (and rare) variants. It is time to start thinking about genetic variants and patients as falling along a continuous spectrum of risk: not black and white or dark and lite but 50 shades of grey.

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