**WILL THE REAL LONG QT GENES PLEASE STAND UP**

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NO CONFLICTS OF INTEREST

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Our understanding of the genetic landscape for inherited long QT syndrome (LQTS) has evolved since the first discovery of the molecular basis of LQT1-3 in 1995 [1-3]. With rapid advances in technology, particularly large-scale next generation sequencing, there has been haste to discover the “next” LQTS gene. This has led to a rapid expansion of the list of so-called LQTS genes to at least 16 genes, many without any strong functional or linkage data to support pathogenicity [4]. As population datasets have grown to the current size [more than 138,000 exomes and genomes in the gnomAD database (gnomAD.broadinstitute.org) alone], the fact that many of these less-established genes are harbouring considerable background genetic variation, has become the harsh reality. Therefore, it is timely that the underlying genetic basis for LQTS requires reassessment and reappraisal.

In this issue of *Trends in Cardiovascular Medicine* Giudicessi et al highlight the changing landscape of genetic testing in LQTS, particularly the paucity of evidence for pathogenicity for the minor-LQTS susceptibility genes [5]. The authors propose a rational tiered approach to genetic testing in LQTS with pre- and post- test cardiac genetic counselling considerations clearly highlighted in Figure 3. As highlighted by the authors, the minor LQTS-susceptibility genes were largely discovered through candidate gene studies, in small pedigrees or even singletons during a time of rapid genetic advancement, but unfortunately without strong genetic and functional evidence to support disease pathogenesis [5].

Increased use of large panels, whole exome and whole genome approaches have expanded the genetic testing menu beyond the levels of understanding of many of those attempting to understand the meaning of the individual genetic changes and associations with disease pathogenesis [6]. The so-called “bigger is better” approach of the last 5-10 years is now increasingly questioned as our appreciation of the nuances of variant interpretation and determining pathogenicity have evolved [6]. The lack of strong linkage or functional evidence to give substantive weight to any ACMG- criteria for the minor LQTS genes, means that at best, the variants can be classified as variants of uncertain significance (VUS) leaving them in “genetic purgatory” [7, 8]. Importantly, there is little clinical utility in identifying an ambiguous VUS in a minor LQTS gene in a patient or small pedigree with LQTS, and in untrained hands, this information can be dangerous with potential for misdiagnosis and misinterpretation [5]. This “*VUS crisis”* is best managed in specialized inherited cardiac disease multidisciplinary clinics.

In the current review, the authors highlight the “mistaken identity” of the Andersen-Tawil Syndrome (ATS) and Ankyrin-B Syndrome (ABS) so called LQT7 and LQT4 respectively. In 2005, Zhang et al first proposed the renaming of KCNJ2-ATS as ATS1 rather than LQT7 [9]. The authors should be praised for once-again highlighting these misnomers and bringing the discussion forward [5]. The authors propose a new, unified, gene-derived naming convention for the minor LQTS-susceptibility genes which would allow for particular genotype associated syndromes to be tested individually. The genes (*KCNJ2* and *ANK2*) are historically included on LQTS panels, despite the LQTS phenotype largely being absent in their associated syndromes, particularly when the U-wave has been excluded from the QTc measurement [9, 10]. Whether these genes, particularly *KCNJ2* should be removed from LQTS testing panels, as proposed by Giudicessi et al, remains to be established. Indeed, the ATS phenotype has its own clear pathognomonic features, that in experienced hands, can be tested for with single gene (*KCNJ2*) testing alone.

The authors highlight the importance of reassessing genetic variants for pathogenicity with regards to re-examining the clinical phenotype and the body of evidence supporting the genetic association. The ClinGen Resource funded by the National Institutes of Health, aims to clarify the ambiguity surrounding interpretation of genetic testing, by providing an important, publically-available, evidence-based database which highlights the strength (or lack thereof) of data linking genotype and phenotype for each gene that has been curated in the resource [11]. The ClinGen initiative is an essential and foundational initiative which will facilitate the accurate assessment and interpretation of the genetic basis of many human diseases, including inherited cardiovascular diseases [12]. As nicely highlighted by Giudicessi et al in Table 3, 67% of the minor LQT genes will likely receive ClinGen designations downgrading them to either “disputed evidence” (*KCNE2, KCNJ5*) or “limited evidence” (*AKAP9, ANK2, SCN4B, SNTA1*) [5, 13]. A recent study by Roberts et al, highlighted the limited evidence for *KCNE2* causing LQTS (so called LQT6) in isolation and proposed that this gene does not cause monogenic LQTS, but rather an underlying arrhythmia susceptibility [14]. We should expect a flux of similar studies downgrading the significance of other minor LQT genes in the near future, led by the role out of ClinGen.

It is likely we will see evolving evidence of oligogenicity and polygenic inheritance patterns in LQTS. We have previously proposed LQTS to be mid-way on the spectrum of monogenic-polygenic inheritance, between progressive cardiac conduction disease and idiopathic ventricular fibrillation [15]. Giudicessi et al highlight two particular variants, p.Ser1103Tyr-SCN5A and p.Asp85Asn-KCNE1 (shown in Table 4) to be present in up to 10% of some ethnicity-specific population databases. The likelihood that a variant this frequent in the population is the monogenic cause of disease is unlikely, given LQTS disease prevalence of 1:2000. However, it is clear they play some role in arrhythmic-predisposition. The ACMG criteria are restrictive in their evaluation of those common variants having a clear functional role but not reaching the level of monogenic causality. As highlighted by the authors, at best these variants can be classified as “functional risk alleles” and should be reported in a distinct “other reportable” category to highlight their functional importance. Despite not being monogenic causes of disease, these variants are risk markers that may act with some biological and clinical significance in the presence of another insult such as the commencement of a QT prolonging medication [16].

The authors also propose a new category, “LQTS-lite”, for important variants falling between functional risk alleles, and full causative variants. These variants, with population frequencies beyond that which is expected for the particular subtype of LQTS, typically will not cause overt phenotypes in heterozygous state, however with homozygosity or when heterozygotes are given QT prolonging medications the functional affects can be seen. These clinically relevant genomic factors are important and are not ignored by using simple ACMG classifications. As we move into an exciting era of genomic precision medicine, patients will have the access and availability to their own genetic profile at unprecedented levels. It is therefore important that the clinical cardiologist is vigilant in the genomic assessment process, with the ultimate goal to improve the diagnosis and management of their patients and families with inherited heart diseases such as LQTS.

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