

Pre-Test Probability and Genes and Variants of Uncertain Significance in Familial Long QT Syndrome



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The genetics underlying familial long QT syndrome (LQTS) are among the best characterised of all of the inherited heart conditions. Cohort and registry studies have demonstrated important genotype-phenotype correlations that are now essential in guiding clinical practice of patients with the most common three genotypes; *KCNQ1* (LQT type 1), *KCNH2* (LQT type 2) and *SCN5A* (LQT type 3). However, the growing number of genes—now more than 16—is confusing, and there is much doubt as to whether many actually cause LQTS at all. Furthermore, changes in sequencing techniques, evolving variant classification criteria and new scientific discoveries make all genes and variants subject to a continuous process of re-classification. This review discusses the nature of variant adjudication, the important concept of pre-test probability in interpreting a genetic result and how the nomenclature of LQTS is shifting in response to this new knowledge. It further discusses the role of deep phenotyping, the inclusion of evaluation of family members in interpreting a genetic test result, or even deciding if genetic testing should occur at all, and the role of specialist multidisciplinary teams to translate this continuously evolving knowledge into the best clinical advice, in partnership with referring cardiologists.

Keywords

Long QT syndrome • Genetics • Genotype-phenotype correlations • Genetic testing • Cohort registry

Introduction

Long QT syndrome is a usually autosomal dominant inherited cardiac condition characterised by QT-prolongation on a 12-lead surface electrocardiogram (ECG) predisposing to Torsade de Pointes (TdP) and sudden cardiac death (SCD). It has an estimated incidence of 1 in 2,000 people. It is characterised by arrhythmogenic syncope, seizures and SCD caused by delayed ventricular repolarisation reflected by a prolonged QT interval [1,2]. Clinical diagnosis can be difficult due to variable phenotypic expression and

the fact that other conditions can prolong the QT interval [3,4].

Genetic testing for a definite case of familial long QT syndrome (LQTS) is informative in up to 80% of cases; the highest hit-rate of all of the inherited cardiac conditions. The genetic test results consolidate the diagnosis, facilitate family screening, and guide risk-stratification and choice of therapies. Over the last 20 years, the number of genes implicated has multiplied from the three major genes to, now, a list of 16 or more. Hundreds of variants in each gene are implicated or under suspicion. But, as time passes, it becomes clear that

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some of these genes, such as *ANKB*-encoded long QT type 4 (LQT4), may not truly cause LQTS outside of a very small number of families. Other genes, such as *KCNE2* (long QT type 6) may solely be risk modifiers, rather than truly disease causing. Many of these genes are, in a sense, *genes of uncertain significance*. Furthermore, each gene has within it, *variants of uncertain significance*. Some of these variants of uncertain significance (VUS) were originally thought to be likely pathogenic and have since been downgraded as normative population data has come to light. Many of these genes were discovered in an era where it was scientifically accepted to call a variant pathogenic if absent in 50 to 100 healthy controls [5], whereas now we have many tens of thousands of fully sequenced human genomes for reference (Genome Aggregation Database, gnomAD, Exome Aggregation Consortium, ExAC [6] and ClinVar) to which to compare our findings. Consequently, variants once thought uncommon and pathogenic, are often actually very common and therefore unlikely to be pathogenic [7].

In contrast, some variants have been upgraded based on further co-segregation studies, *in-vitro* experiments or induced pluripotent stem cells—or animal models. To the genetically untrained physician, having to consider all these factors therefore often leads to misdiagnosis and over reactive treatments, which severely impacts our patients' lives.

After an era of exciting acceleration of knowledge, it is time to take a careful review of where we are now and how we keep our patients informed on the true meaning of their genetic finding. The constant re-evaluation of our patient's clinical progress therefore needs periodic re-evaluation of the genotype assigned to the patient and appropriate modification to their treatment plan along with this re-assessment. This requires an awareness of the science—or perhaps the art—of genetic variant curation critical to all cardiologists taking care of patients with LQTS.

Long QT Syndrome: Phenotype, Genotype and the Effect on Management

The Major LQTS Genes

Approximately 75% of LQTS is caused by variants in the *KCNQ1*, *KCNH2* and *SCN5A* genes causing LQTS types 1, 2 and 3 respectively [8–10]. The remaining genes implicated in LQTS pathogenesis are very uncommon or may be part of a syndrome with systemic features such as Andersen-Tawil (ATS) or Timothy syndrome. In Five (5) to 15% of cases, LQTS variants have been found when performing genetic testing in autopsy negative sudden death [11].

Defining the genotype of LQTS has important implications in the assessment of risk, and choice of advice and therapies. Patients with LQT1 are at particular risk of events in male patients between age 5 and 15, with typical triggers of exercise and swimming, and beta blockers and left cardiac sympathetic denervation are particularly efficacious in

reducing risk [12]. LQT1 is rarely a disease requiring an implantable cardioverter defibrillator (ICD). Those with LQT2 at highest risk are women, particularly in the first 9 post-partum months, and cardiac events commonly occur at night or following emotional or auditory startle [13,14]. Women with LQT2 and severe QT prolongation are the group most likely to benefit from an ICD. Individuals with LQT3 tend to often present with a sentinel sudden death event at night, rather than syncope, and severe cases (especially females), respond particularly well to the antiarrhythmic mexiletine [15].

The Minor Genes and Change in Nomenclature

The familial LQTS genes were named in order of their discovery, LQT1 (*KCNQ1*), LQT2 (*KCNH2*) and LQT3 (*SCN5A*) etc. [16] and are in general strongly linked to familial LQTS. While in the early days, each new gene was assigned sequentially, increasing knowledge has taught us that after LQT1, 2 and 3, this nomenclature can be misleading and misses the subtle phenotypes that some of the patients with variants in these genes possess. For example, the fourth gene to be discovered (*AnkB*) turned out to be extraordinarily rare with many features not typical for LQTS at all—including atrial fibrillation, heart block and commonly a normal QT interval, which has, over the years, led to it being more commonly referred to as “Ankyrin-B syndrome” [17]. Variants in the fifth gene, *KCNE1*, can have a functional consequence on repolarisation but seem to cause hereditary LQTS when in combination with other variants rather than alone. The commonest variant (Asp85Asn) has been termed “LQT5-lite” to reflect this [18,19]. Variants in *KCNE2* (previously referred to as LQT6), are associated strongly with drug induced QT prolongation, and not hereditary LQTS *per se*. LQT7 is due to *KCNJ2* variants which typically cause ATS with a significant extra-cardiac phenotype including skeletal muscle weakness and typically a normal QT interval [9]. Variants in *CACNA1C* (LQT8) are usually associated with the very rare severe Timothy syndrome, with dysmorphism, autistic features, crowded dentition and syndactyly, or familial sudden death and cardiac arrest *with and without* a long QT interval [20].

Because of this, many experts have suggested we should move away from the traditional sequential numbering (Table 1), at least beyond LQT8, and instead describe them by their syndromic names and or genes involved (Table 2).

Furthermore, it is worthy of note that some of the latecomers, including genes encoding calmodulin (*CALM1,2* and *3*; *calmodulinopathies*) and Triadin (*TRDN*; *triadin knockout syndrome* [TKOS]) while certainly demonstrating QT prolongation, are generally very rare and seem to display an extremely severe phenotype caused usually by *de novo* cases (with neither parent a gene carrier). In addition to QT prolongation, patients with a calmodulinopathy or TKOS seem to show characteristics of catecholaminergic polymorphic ventricular tachycardia (CPVT) as well.

Table 1 Traditional classification of LQTS genotypes.

Old Classification [12]	
LQT1	<i>KCNQ1</i>
LQT2	<i>KCNH2</i>
LQT3	<i>SCN5A</i>
LQT4	<i>ANKB</i> (Ankyrin-B syndrome)
LQT5	<i>KCNE1</i>
LQT6	<i>KCNE2</i>
LQT7	<i>KCNJ2</i> (Andersen-Tawil syndrome)
LQT8	<i>CACNA1C</i> (Timothy syndrome)
LQT9	<i>CAV3</i>
LQT10	<i>SCN4B</i>
LQT11	<i>AKAP9</i>
LQT12	<i>SNTA1</i>
LQT13	<i>KCNJ5</i>
LQT14	<i>CALM1</i>
LQT15	<i>CALM2</i>
JLNS1	<i>KCNQ1</i>
JLNS2	<i>KCNE1</i>

Abbreviations: LQTS, long QT syndrome; JLNS, Jervell and Lange-Nielson Syndrome

Classification of Variants

Once a genetic abnormality is identified, the next step is to classify this finding to determine its potential role in disease and whether it can be used for clinical decision making. The nomenclature and classification criterion are subject to continuous change, starting with the definition of mutation itself. Often misinterpreted, the use of the term “mutation” is being used less and less because of its emotive nature and the false sense that “mutation” implies it always causes disease. Instead “variant” is the favoured term to use. Within each gene, the nature and location of each variant [21] is critical in determining the biophysical effect of the variant on cardiac ion channel function [22]. This complexity led the American College of Medical Genetics and Genomics (ACMG) to define guidelines for the interpretation of sequence variants in 2015 [6]. Variants are now classified along a continuum of pathogenicity from benign (B, class 1), likely benign (LB, class 2), uncertain significance (VUS, class 3), likely pathogenic (LP, class 4), to pathogenic (P, class 5) (Figure 1) [6].

Final variant classification depends on the interpretation of evidence from a variety of sources including disease prevalence, computational and predictive analyses, functional *in-vitro* evaluation, co-segregation of the variant in question with clinical phenotype, frequency of the variant in population databases, and preservation of that part of the gene across species [6]. Variant curation is complicated and requires a solid understanding of both genetics and clinical phenotype, and is thereby best performed by a specialised multi-disciplinary team. In fact, testing laboratories frequently classify variants differently from each other and according to

Table 2 Proposed classification of clinical LQTS genotypes.

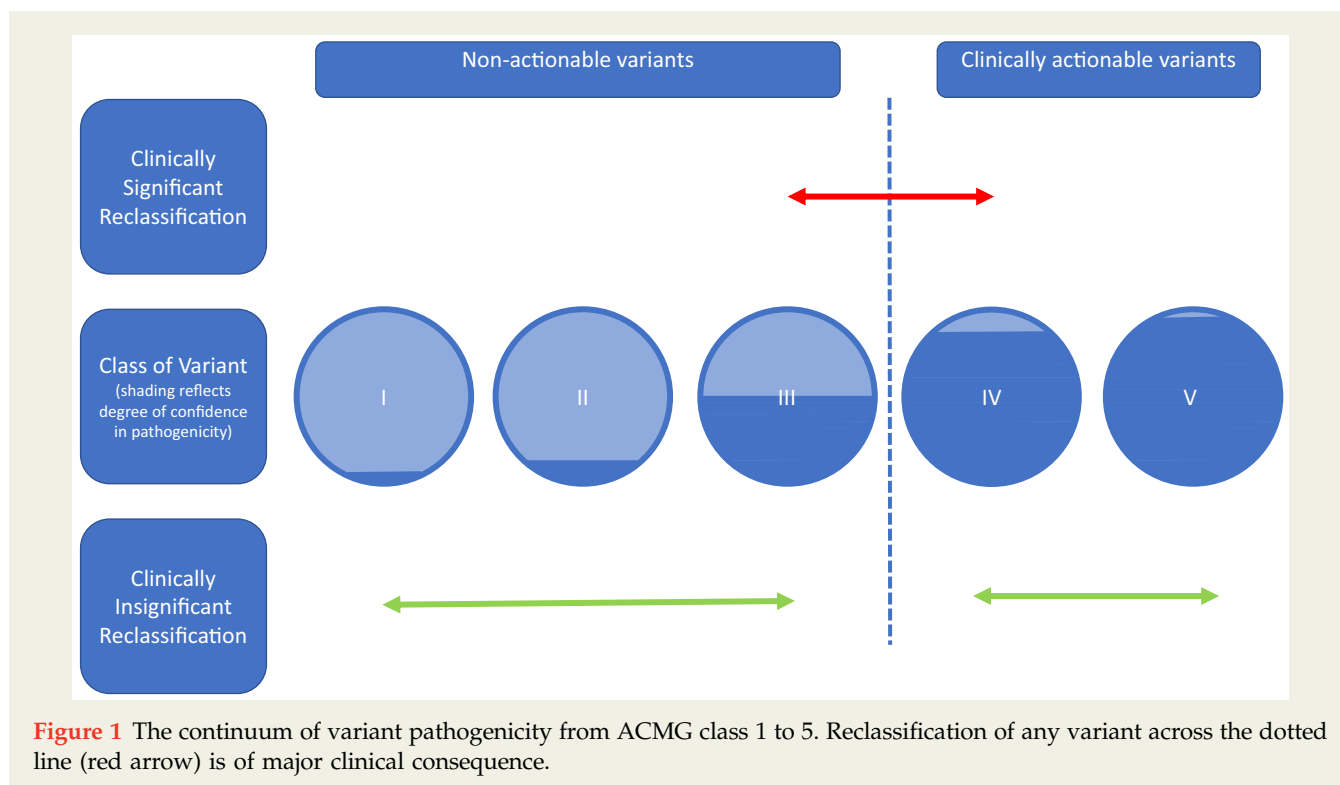
Proposed Classification [17]	
Non-syndromic LQTS (major genes)	<i>KCNQ1</i> (LQT1) <i>KCNH2</i> (LQT2) <i>SCN5A</i> (LQT3)
Non-syndromic LQTS (minor genes)	<i>CACNA1C</i> -LQTS (Cardiac-only Timothy syndrome) <i>KCNE1</i> -LQTS <i>KCNE2</i> -LQTS <i>CALM1</i> -LQTS <i>CALM2</i> -LQTS <i>CAV3</i> -LQTS <i>SCN4B</i> -LQTS <i>AKAP9</i> -LQTS <i>SNTA1</i> -LQTS <i>KCNJ5</i> -LQTS
Multi-system conditions	<i>ANK2</i> (Ankyrin-B syndrome) <i>KCNJ2</i> (Andersen-Tawil Syndrome) <i>CACNA1C</i> (Timothy Syndrome)
Jervell and Lange-Nielson syndrome	<i>KCNQ1</i> (JLNS1) <i>KCNE1</i> (JLNS2)
Other	<i>TRDN</i> (Triadin knockout syndrome)

Abbreviation: LQTS, long QT syndrome.

a recent study comparing results from different laboratories, the best concordance between nine United States (US) laboratories was a moderate 70% [23]. Therefore, we need to be continuously sceptical of all results we receive and need to develop or have access to skills of gene variant curation at a local level to minimise significant clinical mistakes.

When variants are determined as being pathogenic (P, class 5) or likely pathogenic (LP, class 4), they are “clinically actionable”; that is, they can be used for predictive testing amongst potentially affected relatives. Variants of uncertain significance (VUS, class 3) cannot be used for predictive familial testing.

However, in clinical practice, it turns out this is not so simple, especially with the growing use of large scale sequencing techniques, such as whole exome—and whole genome sequencing. On the one hand, patients with a phenotype clearly fitting a genetic origin might present with a VUS, while on the other hand a LP/P variant could be identified in an individual without any evidence of diseases. The ACMG mandates that class 4 and 5 variants must be reported in hypertrophic cardiomyopathy (HCM) and LQTS genes when genomes or exomes are analysed for other reasons. However evidence is accumulating that the chance findings of such variants are not usually clinically relevant [24]. To this end, it is of the utmost importance for us to consider a genetic test’s *pre-test probability*.



Pre-Test Probability

The concept of pre-test probability is best discussed in the setting of a number of examples or clinical vignettes. As an example, a QTc interval of 0.46 seconds on a routine ECG in an adult female, perhaps prior to an anaesthetic, would generally be considered normal; approximately 10% of women will have such a value or higher. Prior to the ECG, the pre-test probability of her having LQTS was 1 in 2,000 (disease prevalence), but with the QTc value, it has now increased to the order of 1 in 200 (0.5%). However, if her father turns out to have proven LQTS prior to the ECG, she would have already had a 50% pre-test probability of having familial LQTS (i.e. the chance of her inheriting the disease in autosomal dominant fashion) and with a QTc of 0.46 seconds, her likelihood of having true LQTS is now in the order of 90%; same clinical ECG result, entirely different clinical implications.

The same is true of the pre-test probabilities of genetic test results, outlined recently in CPVT [25]. Sixty-five per cent (65%) of cases with definite CPVT have rare variants in the gene RyR2, while rare variants in RyR2 occur in 3% of the general population. Thus, if we find a rare variant in RyR2 in our patient with definite CPVT, and the laboratory classify it as a VUS (class 3), the odds are 65:3, or more than 20:1, (greater than 95%), that this rare variant is the cause of the condition.

Similarly, the phenotype of a likely pathogenic (“LP”) variant identified in KCNQ1 can guide us into different directions (Figure 2). If the patient having the test has definite LQTS, with a phenotype fitting LQT1, the pre-test probability that we will find KCNQ1 is over 70%, so this genetic result is a good fit. It is very likely indeed this variant is disease causing,

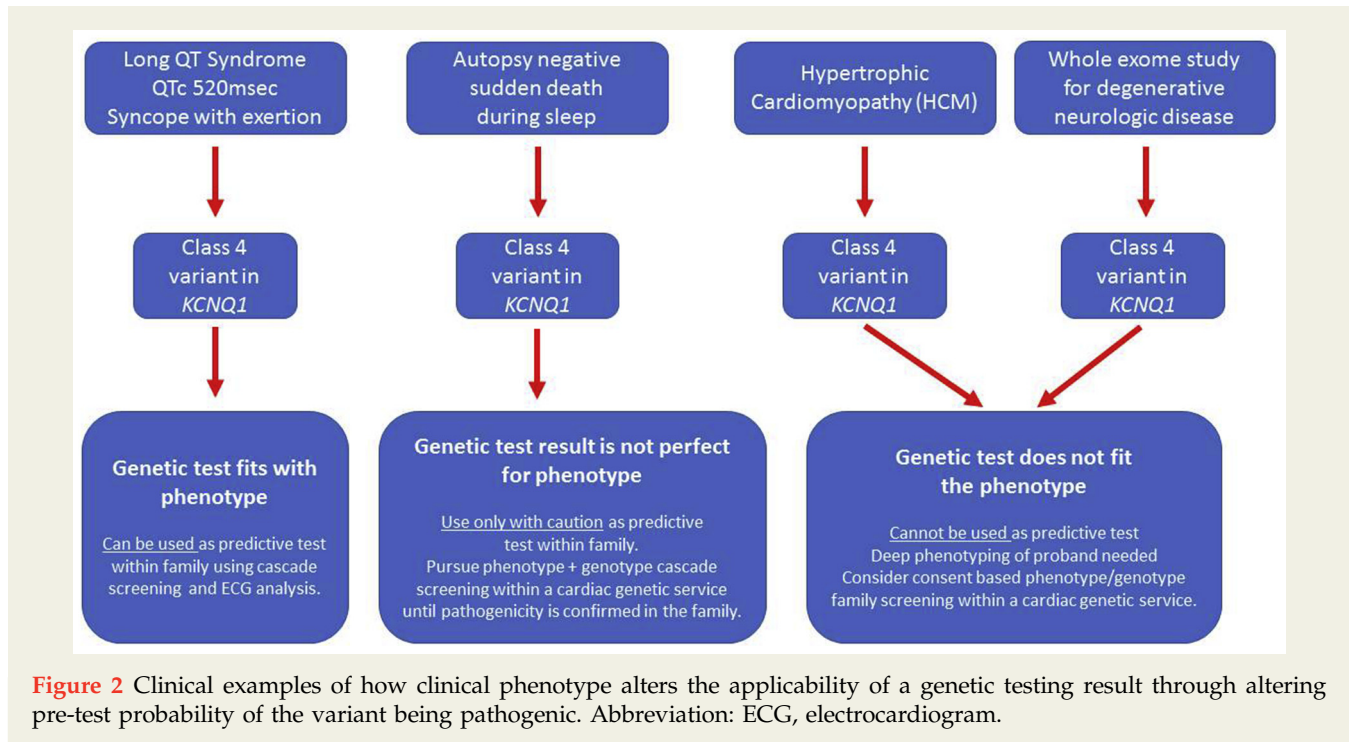
much higher than 95%, and the results can be applied to safely inform clinical management and determine (along with a 12-lead ECG) who is at risk in the family. If, however, this variant was found as part of a whole exome/genome screen (more than 10,000 genes) in a subject with a degenerative neurological condition, then the pre-test probability of LQTS is 1 in 2,000, and it is much less likely that this rare variant is disease causing in this person. At this stage of knowledge, we can’t ignore this result, but when the ECGs come back normal, it seems likely we can discard it. In between these two extremes is a spectrum, as shown in Figure 2.

Given the heterogeneity of the genotype/phenotype relationship in LQTS, it is abundantly clear that *the implantation of an ICD for LQTS should never be on the basis of genotype alone*; a lesson which has a real human cost, such as ICD-related complications, when this goes wrong [26].

Genetic Variants as Disease Modifiers

An important problem with the current ACMG genetic variant classification is that it is essentially binary. The variant causes disease, or it does not. However, there are some clear examples of genetic variants which modify risk, without necessarily causing LQTS *per se*.

One such aforementioned variant, p.Asp85Asn (D85N) in KCNE1 (the LQT5 gene) is present in approximately 1% of the world’s population and contributes to a longer QTc. Its high prevalence means it is, by definition, a (single nucleotide) polymorphism (SNP) and not a rare variant. It is



associated with an increased risk of drug-induced Torsades de Pointes, a mild form of familial LQTS amongst Japanese, and worsening severity of familial LQTS, if co-inherited with a primary familial LQTS pathogenic *KCNQ1* or *KCNH2* variant [18]. Another variant, p.Ser1103Tyr in *SCN5A* is found in 10% of individuals of African descent and has been associated with a prolonged QTc and slightly increased risk of sudden cardiac death throughout life when a pharmacological or pathological “second hit” co-exists [18]. Another SNP in a gene called *NOS1AP* is so important in determining QT length and adverse events in those with LQTS [27,28] that some leaders in the field consider that it should be routinely part of risk stratification [29].

These variants are not classifiable using ACMG criteria and laboratories usually do not include this information in their reports since they do not cause familial LQTS. There is a pressing need for a means to report this second tier of variants, the disease modifiers. But for now, 10 years after the *NOS1AP* reports, this still only happens in research laboratories. Again, similar to the pre-test probability, getting the best picture of a patient’s phenotype will aid in final genotyping

Deep Phenotyping

Deep-phenotyping means taking all efforts to manifest an apparently concealed condition. In LQTS, a borderline or normal QT interval may become clearly abnormal in a gene carrier in recovery after exercise, or in response to the transient tachycardia of standing [30]. Given that the value of the genetic test result depends heavily on the pre-test probability, it follows that we should be sure of our clinical diagnosis

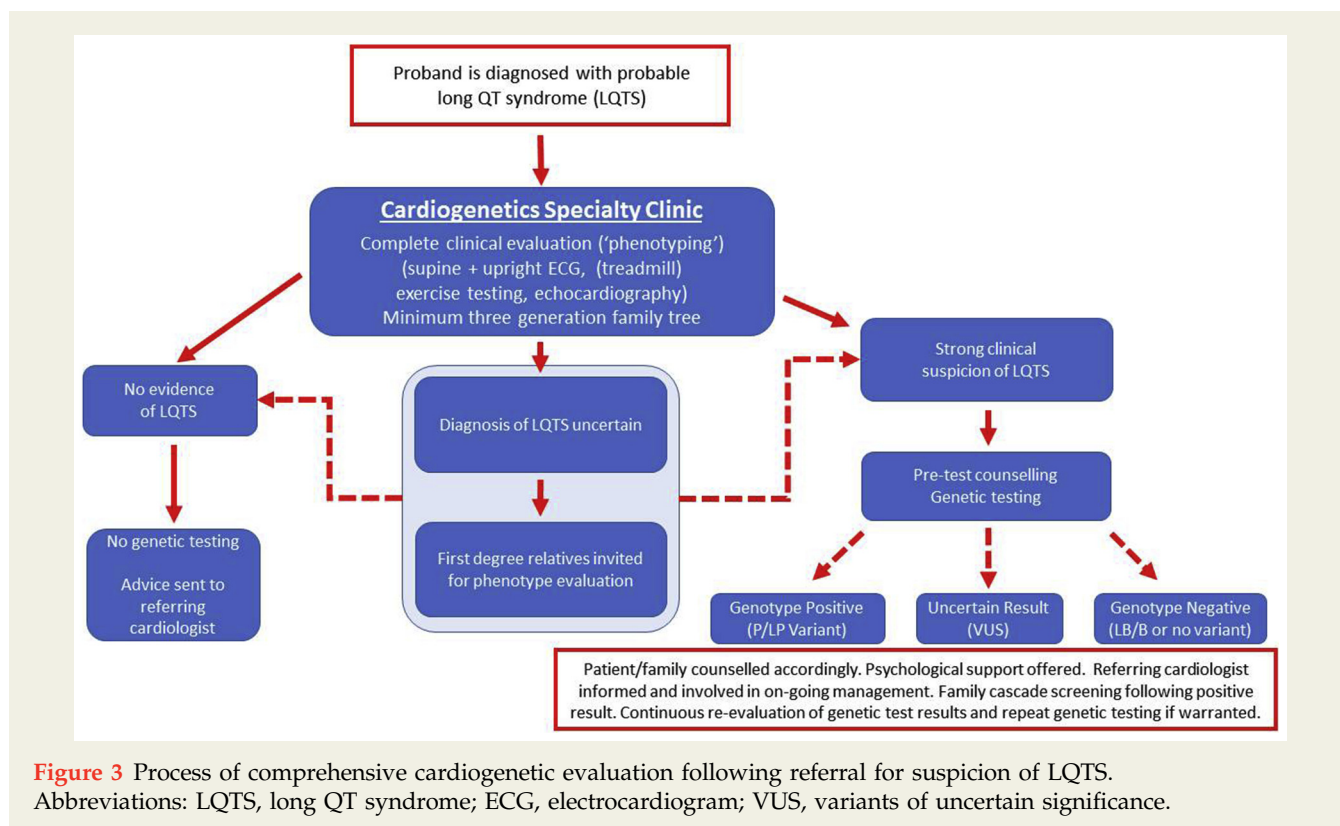
of LQTS before doing the genetic test in the proband. And when we cascade through the family to check the variant co-segregates with LQTS, we must be as sure as possible which family member has the phenotype by making sure cascade genotyping is performed in combination with at least an ECG, but preferably a full clinical evaluation.

By making sure the genes tested are relevant to the suspected phenotypic condition, one minimises the risk of finding a VUS in genes of uncertain significance. This is a strong argument against the routine use of very large gene panels. For example, the incidental finding of a VUS in *RyR2* (from a wide “arrhythmia panel”) in a 30-year-old with classical LQTS does not mean the patient has CPVT but does add an unnecessary level of confusion.

Bottom line, genetic testing should be used cautiously, and be aimed at supporting a near-certain diagnosis for our proband. If comprehensive phenotyping leads to suspicion of disease, the patient should, if possible, be referred to a cardiac genetic clinic for further evaluation and possible genetic testing (Figure 3). In evaluating an LQTS proband, aside from ECG, an echocardiogram is recommended to exclude, for example, potential myocardial disease. Electrocardiograms should be taken whilst off any QT prolonging drugs.

Variant Reclassification?

Continuous research discoveries and studies, such as the recent CPVT paper discussed [25], provide a vast amount of data that requires ongoing reclassification of genetic findings and a good laboratory will update the referring service about a variant reclassification. A variant going from uncertain to



likely pathogenic or vice-versa, can have enormous implications and have significant clinical, psychological, social, life-style, employment, treatment and, potentially, reproductive consequences. Treatments such as left cardiac sympathetic denervation (LCSD) and ICD can come with significant morbidity [31,32], and might now become necessary, or in reverse, might not have been necessary to begin with.

On the other hand, reclassification in an asymptomatic relative can be particularly hard for parents of affected children to cope with [33], and being recontacted may cause distress, anxiety, affect family relationships [34], and introduce further miscommunication between the patient and their relatives [35].

It is therefore of the utmost importance to try to get it right the first time, and to have adequately counselled the patient and family prior to the test that such an outcome is possible down the line [36]. On top of that, rather than being a static process (genetic test done, genotype is final), the continuous ongoing care applied to the management of the patient's phenotype is also applied to re-assessment of their genotype, altered along the way when new knowledge comes to light (Figures 4A and 4B).

Despite the known confusion genetics causes [37], the process of variant reclassification will ultimately benefit the health care provider-patient relationship when it is done well. Patients maintain or increase trust with their health care providers, and most are not remorseful about genetic-testing or variant-reclassification [38].

Summary, Consequences and Challenges

Genetic testing in LQTS can be of great benefit, contributing to family cascade screening, risk stratification and choice of treatments. Several of the genes originally believed to cause familial LQTS now are thought not to, and the genes notated as LQT5 (*KCNE1*) and 6 (*KCNE2*) should rather be mostly, or entirely, considered disease modifiers, respectively. The challenge for the laboratories is to aim for accuracy and consistency of their reports, to develop the ability to include phenotype data in their interpretation and to report on disease modifying variants.

The consequence for clinicians is that we must be mindful of the importance of accurate pre-test phenotyping and thorough pre-test genetic counselling. We should remain sceptical of all genetic test results, and evaluate each result in terms of these pre-test observations. Having access to the expertise of a cardiac genetic service is becoming of increasing importance (if not necessity), to help with phenotyping, (re)classification, and dealing with issues when the phenotype and genotype don't seem to fit. Finally, an ICD should never be based on genotype data alone in LQTS.

Attention should remain on growing cardiac genetic multidisciplinary services well-equipped to deal with this avalanche of patients, families and genomic data. These services would maintain expertise in variant calling and reclassification, and efficiency in contacting families when genetic variants are reclassified, or new therapies become available [39,40].

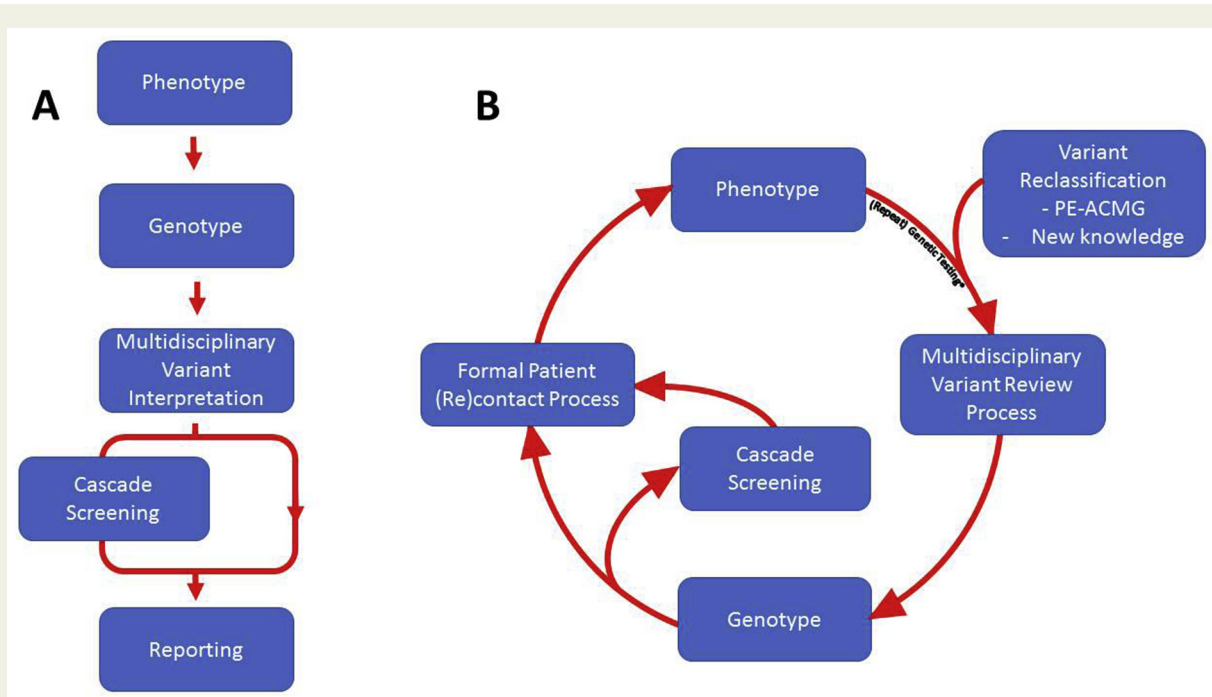


Figure 4 (A) Current 'longitudinal' process of genetic cardiology patient care and variant interpretation. (B) Proposed 'cyclical' process of genetic cardiology patient care and variant (re)-interpretation. Abbreviations: PE, phenotype-enhanced; ACMG, American College of Medical Genetics and Genomics.

Such teams, in partnership with managing clinicians, need to ensure our LQTS patients receive the most precise care available to them at all stages of their health care journey, not just at their initial diagnosis.

Conflicts of Interests

There authors have no conflicts of interest to declare.

References

- [1] Waddell-Smith KE, Skinner JR. Update on the diagnosis and management of familial long QT syndrome. *Heart Lung Circ* 2016;25:769–76.
- [2] Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggreffe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;36:2793–867.
- [3] Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. *N Engl J Med* 1992;327:846–52.
- [4] Waddell-Smith K, Gow RM, Skinner JR. How to measure a QT interval. *Med J Aust* 2017;207:107–10.
- [5] Ackerman MJ. Genetic purgatory and the cardiac channelopathies: exposing the variants of uncertain/unknown significance issue. *Heart Rhythm* 2015;12:2325–31.
- [6] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–24.
- [7] Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* 2016;536:285–91.
- [8] Skinner JR, Winbo A, Abrams D, Vohra J, Wilde AA. Channelopathies that lead to sudden cardiac death: clinical and genetic aspects. *Heart Lung Circ* 2019;28:22–30.
- [9] Tester DJ, Ackerman MJ. Genetics of long QT syndrome. *Methodist Debakey Cardiovasc J* 2014;10:29–33.
- [10] Eddy CA, MacCormick JM, Chung SK, Crawford JR, Love DR, Rees MI, et al. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. *Heart Rhythm* 2008;5:1275–81.
- [11] Bagnall RD, Weintraub RG, Ingles J, Dufloy J, Yeates L, Lam L, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med* 2016;374:2441–52.
- [12] Nakano Y, Shimizu W. Genetics of long-QT syndrome. *J Hum Genet* 2016;61:51–5.
- [13] Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT Syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95.
- [14] Seth R, Moss AJ, McNitt S, Zareba W, Andrews ML, Qi M, et al. Long QT syndrome and pregnancy. *J Am Coll Cardiol* 2007;49:1092–8.
- [15] Mazzanti A, Maragna R, Faragli A, Monteforte N, Bloise R, Memmi M, et al. Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3. *J Am Coll Cardiol* 2016;67:1053–8.
- [16] Havakuk O, Viskin S. A tale of 2 diseases: the history of long-QT syndrome and Brugada syndrome. *J Am Coll Cardiol* 2016;67:100–8.
- [17] Giudicessi JR, Wilde AAM, Ackerman MJ. The genetic architecture of long QT syndrome: a critical reappraisal. *Trends Cardiovasc Med* 2018;28:453–64.
- [18] Giudicessi JR, Roden DM, Wilde AAM, Ackerman MJ. Classification and reporting of potentially proarrhythmic common genetic variation in long QT syndrome genetic testing. *Circulation* 2018;137:619–30.
- [19] Lane CM, Giudicessi JR, Ye D, Tester DJ, Rohatgi RK, Bos JM, et al. Long QT syndrome type 5-Lite: defining the clinical phenotype associated with the potentially proarrhythmic p.Asp85Asn-KCNE1 common genetic variant. *Heart Rhythm* 2018;15:1223–30.
- [20] Gardner RJM, Crozier IG, Binfield AL, Love DR, Lehnert K, Gibson K, et al. Penetrance and expressivity of the R858H CACNA1C variant in a five-generation pedigree segregating an arrhythmogenic channelopathy. *Mol Genet Genomic Med* 2018;7:e00476.

- [21] Ruwald MH, Xu Parks X, Moss AJ, Zareba W, Baman J, McNitt S, et al. Stop-codon and C-terminal nonsense mutations are associated with a lower risk of cardiac events in patients with long QT syndrome type 1. *Heart Rhythm* 2016;13:122–31.
- [22] Moss AJ, Shimizu W, Wilde AA, Towbin JA, Zareba W, Robinson JL, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation* 2007;115:2481–9.
- [23] Amendola LM, Jarvik GP, Leo MC, McLaughlin HM, Akkari Y, Amaral MD, et al. Performance of ACMG-AMP variant-interpretation guidelines among nine laboratories in the Clinical Sequencing Exploratory Research Consortium. *Am J Hum Genet* 2016;98:1067–76.
- [24] Hyland RJ, Chandler S, Skinner J, Abrams D. Genetic testing for inherited cardiac arrhythmias-current state-of-the-art and future avenues. *J Innov Card Rhythm Manag* 2018;9:3406–16.
- [25] Giudicessi JR, Lieve KVV, Rohatgi RK, Koca F, Tester DJ, van der Werf C, et al. Assessment and validation of a phenotype-enhanced variant classification framework to promote or demote RYR2 missense variants of uncertain significance. *Circ Genom Precis Med* 2019;12:e002510.
- [26] Ackerman JP, Bartos DC, Kapplinger JD, Tester DJ, Delisle BP, Ackerman MJ. The promise and peril of precision medicine. *Mayo Clin Proc* 2016;91:1606–16.
- [27] Earle N, Yeo Han D, Pilbrow A, Crawford J, Smith W, Shelling AN, et al. Single nucleotide polymorphisms in arrhythmia genes modify the risk of cardiac events and sudden death in long QT syndrome. *Heart Rhythm* 2014;11:76–82.
- [28] Crotti L, Monti MC, Insolia R, Peljto A, Goosen A, Brink PA, et al. NOS1AP is a genetic modifier of the long-QT syndrome. *Circulation* 2009;120:1657–63.
- [29] Tomas M, Napolitano C, De Giuli L, Bloise R, Subirana I, Malovini A, et al. Polymorphisms in the NOS1AP gene modulate QT interval duration and risk of arrhythmias in the long QT syndrome. *J Am Coll Cardiol* 2010;55:2745–52.
- [30] Waddell-Smith KE, Skinner JR, members of the CGCWC. Update on the diagnosis and management of familial long QT syndrome. *Heart Lung Circ* 2016;25:769–76.
- [31] Waddell-Smith KE, Ertresvaag KN, Li J, Chaudhuri K, Crawford JR, Hamill JK, et al. Physical and psychological consequences of left cardiac sympathetic denervation in long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia. *Circ Arrhythm Electrophysiol* 2015;8:1151–8.
- [32] Gaba P, Bos JM, Cannon BC, Cha YM, Friedman PA, Asirvatham SJ, et al. Implantable cardioverter-defibrillator explantation for overdiagnosed or overtreated congenital long QT syndrome. *Heart Rhythm* 2016;13:879–85.
- [33] Hendriks KS, Grosfeld FJ, van Tintelen JP, van Langen IM, Wilde AA, van den Bout J, et al. Can parents adjust to the idea that their child is at risk for a sudden death?: psychological impact of risk for long QT syndrome. *Am J Med Genet A* 2005;138A:107–12.
- [34] Otten E, Plantinga M, Birnie E, Verkerk MA, Lucassen AM, Ranchor AV, et al. Is there a duty to recontact in light of new genetic technologies? a systematic review of the literature. *Genet Med* 2015;17:668–78.
- [35] Burns C, James C, Ingles J. Communication of genetic information to families with inherited rhythm disorders. *Heart Rhythm* 2018;15:780–6.
- [36] Ingles J, Semsarian C. Conveying a probabilistic genetic test result to families with an inherited heart disease. *Heart Rhythm* 2014;11:1073–8.
- [37] Burns C, Yeates L, Spinks C, Semsarian C, Ingles J. Attitudes, knowledge and consequences of uncertain genetic findings in hypertrophic cardiomyopathy. *Eur J Hum Genet* 2017;25:809–15.
- [38] Wong EK, Bartels K, Hathaway J, Burns C, Yeates L, Semsarian C, et al. Perceptions of genetic variant reclassification in patients with inherited cardiac disease. *Eur J Hum Genet* 2019;27:1134–42.
- [39] Carrieri D, Lucassen AM, Clarke AJ, Dheensa S, Doheny S, Turnpenny PD, et al. Recontact in clinical practice: a survey of clinical genetics services in the United Kingdom. *Genet Med* 2016;18:876–81.
- [40] Earle NJ, Crawford J, Hayes I, Rees MI, French J, Stiles MK, et al. Development of a cardiac inherited disease service and clinical registry: a 15-year perspective. *Am Heart J* 2019;209:126–30.