Long QT Syndrome: A Prototype Disease for Precision Medicine

Long QT syndrome (LQTS) is an inherited cardiac disorder that exemplifies the transition toward precision medicine in cardiology. Advances in genetic and mechanistic understanding have fundamentally reshaped diagnosis and risk stratification, while enabling more targeted therapeutic approaches. Today, LQTS serves as a model for individualized, mechanism-based patient care.

Marina Rieder[1], Miriam Barbieri[2], Katja E Odening[1,2]

ABSTRACT

Congenital long QT syndrome (LQTS) is an inherited arrhythmia disorder that has aided in defining the principles of precision medicine in cardiology. Initially characterized primarily by QTc (heart rate-corrected QT interval) prolongation on the electrocardiogram, LQTS is now recognized as a heterogeneous group of inherited channelopathies in which discrete genetic variants and molecular defects give rise to distinct arrhythmogenic mechanisms.

Genotype-specific insights have reshaped clinical management, enabling tailored recommendations and mechanism-based therapies. Accurate risk stratification remains challenging due to marked variability in disease expression, even among carriers of the same pathogenic variant. Although central to diagnosis, the QTc exhibits temporal variability and overlaps substantially between affected and unaffected individuals. A conceptual shift from viewing LQTS as a purely electrical disorder toward an integrated electromechanical disease has further improved our understanding, with emerging evidence emphasizing the significance of electromechanical coupling in arrhythmogenesis.

Therapeutic strategies are evolving from uniform approaches toward increasingly individualized interventions. While beta blockers remain the cornerstone of treatment, adjunctive therapies such as the sodium channel blocker mexiletine, as well as interventional approaches including sympathetic denervation and device therapy, are applied in a risk-adapted manner. In parallel, novel strategies targeting ion channel dysfunction, intracellular signaling, and the underlying genetic cause are redefining the therapeutic landscape.

LQTS serves as a prototype for precision medicine in cardiovascular disease. This review outlines how advances in molecular understanding are driving increasingly individualized approaches to risk stratification and therapy (see figure 1 for a visual summary of the main concepts).

1Translational Cardiology, Department of Cardiology, Inselspital (University Hospital Bern), University of Bern, Bern, Switzerland.
2 Department of Physiology, University of Bern, Bern, Switzerland

Congenital long QT syndrome (LQTS) is an inherited cardiac channelopathy (1). Initially estimated to affect approximately 1 in 2,000 individuals and therefore classified as a rare disease (2), its true prevalence is likely underestimated (1). Regardless of its exact prevalence, LQTS carries substantial clinical relevance due to the risk of life-threatening arrhythmic events. LQTS is believed to contribute to a meaningful proportion of sudden cardiac death (SCD) in the young, including around 10% of all cases of sudden infant death syndrome (3,4). On the mechanical level, LQTS is characterized by the dysfunction of cardiac ion channels, resulting in delayed ventricular repolarization (visible as QTc [heart rate-corrected QT interval] prolongation on the electrocardiogram [ECG]) and creating an arrhythmogenic substrate that predisposes to torsade de pointes tachycardia, which may manifest as syncope and can culminate in SCD (5).

Since its clinical recognition in the mid-20th century, LQTS has evolved from an "ECG diagnosis" into a genetically well-characterized disease entity, becoming a model disorder in the field of precision medicine (6).

Genetic Background

LQTS comprises two principal hereditary forms. The autosomal dominant Romano–Ward syndrome accounts for the vast majority of cases, whereas the rarer autosomal recessive Jervell and Lange-Nielsen syndrome is characterized by a severe cardiac phenotype and additional congenital sensorineural hearing loss (7–9). The molecular era of LQTS began with the identification of pathogenic variants in genes encoding cardiac potassium channels (10,11). To this date, variants in more than a dozen genes have been associated with the syndrome; however, the vast majority of genotype-positive cases are attributed to three canonical genes: *KCNQ1, KCNH2,* and *SCN5A* (12,13). These genes encode pore-forming subunits of the cardiac ion channels that govern the cardiac action potential. Loss-of-function (LOF) variants in *KCNQ1* and *KCNH2* impair the slow and rapid components of the delayed rectifier potassium current (I_{Ks} and I_{Kr}, respectively), thus delaying repolarization and prolonging

the action potential duration (APD) (6). In contrast, gain-of-function (GOF) variants in SCN5A result in an impaired inactivation and enhanced late sodium current (late I_{Na}), similarly prolonging the APD (6). These distinct molecular mechanisms underlie the three major LQTS subtypes—LQTS type 1 (LQT1) *(KCNQ1)*, LQTS type 2 (LQT2) *(KCNH2)*, and LQTS type 3 (LQT3) *(SCN5A)* (6).

The elucidation of genotype-specific mechanisms marked an important early step towards the now central precision medicine approaches to LQTS management. A key advance was the identification of genotype-specific triggers for arrhythmic events (14). Patients with LQT1 are particularly susceptible during physical exertion or emotional stress, reflecting an impaired ability to augment I_{Ks} in response to adrenergic stimulation; notably, swimming has emerged as a characteristic trigger in this subgroup. In LQT2, arrhythmias are frequently precipitated by sudden auditory stimuli or emotional arousal, based on the faster $I_{Ca,L}$ activation than I_{Ks} activation, which leads to a particularly long APD in the initial arousal situation (15). In contrast, LQT3 is characterized by events occurring predominantly at rest or during sleep, in line with the pathophysiological consequences of an enhanced late sodium current at lower heart rates (6,16). Accordingly, patients with LQTS are advised to avoid genotype-specific triggers. In addition, regardless of genotype, general preventive strategies are essential to reduce the arrhythmic risk. These include the avoidance of QT prolonging medications (regularly updated resources are available from https://www.crediblemeds.org/) and the correction of electrolyte imbalances (17).

Diagnosis

The diagnosis of LQTS relies on a combination of clinical, electrocardiographic, and genetic criteria. QTc prolongation remains the cornerstone of the clinical diagnosis. A QTc duration ≥ 480 ms on repeated ECG or, if lower, a diagnostic score > 3 incorporating factors such as syncope and family history of SCD, supports the diagnosis of LQTS (17,18).

Given its central role in risk stratification and therapeutic decision-making, genetic testing is recommended in all patients. Furthermore, the identification of a pathogenic variant (for example, through family screening) is sufficient to establish an LQTS diagnosis (17,18). This reflects the recognized limitations of QTc as a standalone marker. QTc values overlap between mutation carriers and unaffected individuals, and severe arrhythmic events may still arise even without a pronounced prolonged QTc (19,20). Consistent with this, asymptomatic carriers of LQTS-associated variants with a normal QTc still have an approximately tenfold increased risk of SCD if untreated. This observation has led to the current clinical approach of managing genotype-positive individuals as affected and at risk (17,20).

Risk Stratification

While the diagnostic path for LQTS is relatively well established, risk stratification remains considerably more challenging and is critical for guiding management. Untreated LQTS individuals carry a substantial risk of life-threatening cardiac events, particularly in patients with prior symptoms (21,22). Because targeted, risk-adapted therapeutic strategies can substantially reduce the incidence of adverse events, accurate risk stratification is essential (22).

Current risk stratification in patients with established LQTS integrates QTc duration, genotype, age, sex, and syncope history (23,24). However, it remains heavily dependent on QTc duration as a central variable. This reliance represents an important limitation, as QTc is highly dynamic and influenced by autonomic tone, hormonal status, and circadian variation (25–32). Sex-related differences further complicate interpretation, with women generally showing longer QTc intervals than men even in healthy populations (33). Consequently, the use of uniform, sex-independent QTc thresholds in current clinical practice may not provide optimal risk distinction (17).

In this context, emerging parameters such as the electromechanical window (EMW) have gained increasing attention (34,35). These developments reflect a shift in the conceptual framework of LQTS, which was traditionally regarded as a purely electrical disorder. Increasing evidence indicates that this view is incomplete, as it does not account for the interaction between electrical repolarization and mechanical contraction and relaxation. Mechanical aspects are now recognized as relevant contributors to arrhythmic vulnerability alongside electrical abnormalities (36). The EMW, defined as the difference between mechanical and electrical systole, integrates both dimensions, providing a more comprehensive assessment of arrhythmogenic vulnerability. A negative EMW indicates a mismatch between contraction and repolarization and has been associated with increased arrhythmic risk in LQTS and other cardiac conditions (34–37). Recent data showed that EMW is an independent predictor of imminent ventricular tachyarrhythmias in patients with LQTS, outperforming QTc alone (38).

Treatment

Beta blockers remain the first-line pharmacological treatment for LQTS, significantly reducing the incidence of arrhythmic events (39,40). Notably, non-selective beta blockers such as propranolol and nadolol are more effective in LQTS than cardioselective beta blockers (41).

Current guidelines therefore recommend non-selective beta blockers as first-line therapy in all symptomatic patients and, in many cases, also as prophylaxis in asymptomatic genotype-positive individuals, depending on their estimated arrhythmic risk (17). Despite their central role in therapy, optimal treatment remains challenging in clinical practice. Adverse effects, including fatigue, hypotension, and bronchospasm in patients with asthma, can limit tolerability, and long-term adherence is often suboptimal, leaving a relevant portion of patients inadequately protected (40).

The efficacy of beta blockers varies across genotypes. In LQT1, beta blockers are highly effective, and with good ad-

herence, the risk of arrhythmic events is very low (40). In LQT2 and LQT3, however, breakthrough events occur more frequently, indicating a reduced protective effect (42). Especially in LQT3, beta blocker-induced bradycardia can paradoxically increase arrhythmic risk, potentially attenuating the therapeutic benefits (16). Monitoring treatment response remains challenging as the conventional surrogate marker, QTc, often only shows minimal or non-significant changes during therapy (43). Emerging ECG parameters such as the T-peak to T-end interval, which reflects spatial dispersion of ventricular repolarization, may offer additional insight into the antiarrhythmic effects of beta blocker therapy (43).

The concept of precision therapy in LQTS was first exemplified in 1995 with the use of mexiletine in patients with LQT3. As a blocker of the late I_{Na}, mexiletine directly targets the pathologically enhanced late sodium current associated with the GOF variants in SCN5A in LQT3 (6,44). Clinical studies have demonstrated significant QTc shortening and reduction in arrhythmic events, particularly in high-risk patients with baseline QTc ≥ 500 ms (45). Consequently, mexiletine is now incorporated as a guideline-recommended therapy in symptomatic LQT3 in addition to beta blocker treatment (17).

Furthermore, current evidence indicates that mexiletine could provide benefit in patients with LQT2 (46). Experimental and clinical studies have demonstrated that mexiletine significantly shortens repolarization across different LQT2 models, including reductions in field potential duration in patient-specific induced pluripotent stem cells and APD in rabbit cardiomyocytes. Clinically, a substantial number of LQT2 patients (70%) respond to mexiletine therapy, with acute oral drug testing predicting long-term QTc shortening and treatment associated with an approximately 60% reduction in arrhythmic events (47). These observations provide a substantial rationale for considering mexiletine in LQT2 patients with marked QTc prolongation.

For patients who remain symptomatic despite optimal pharmacologic therapy, when beta blockers are contraindicated, additional interventions are warranted. Left cardiac sympathetic denervation has emerged as an effective adjunctive therapy, reducing arrhythmic burden in high-risk LQTS patients (48) and potentially decreasing the need for implantable cardioverter-defibrillator (ICD) implantation. ICD therapy remains indicated in patients with recurrent arrhythmic events despite maximal medical therapy or in SCD survivors (17). However, the early onset of LQTS presents unique challenges, as long-term ICD therapy is associated with complications including lead failure, repeated generator replacements, and inappropriate shocks (50). These limitations further highlight the importance of strategies that reduce ICD dependence while also promoting the development of genotype-directed approaches.

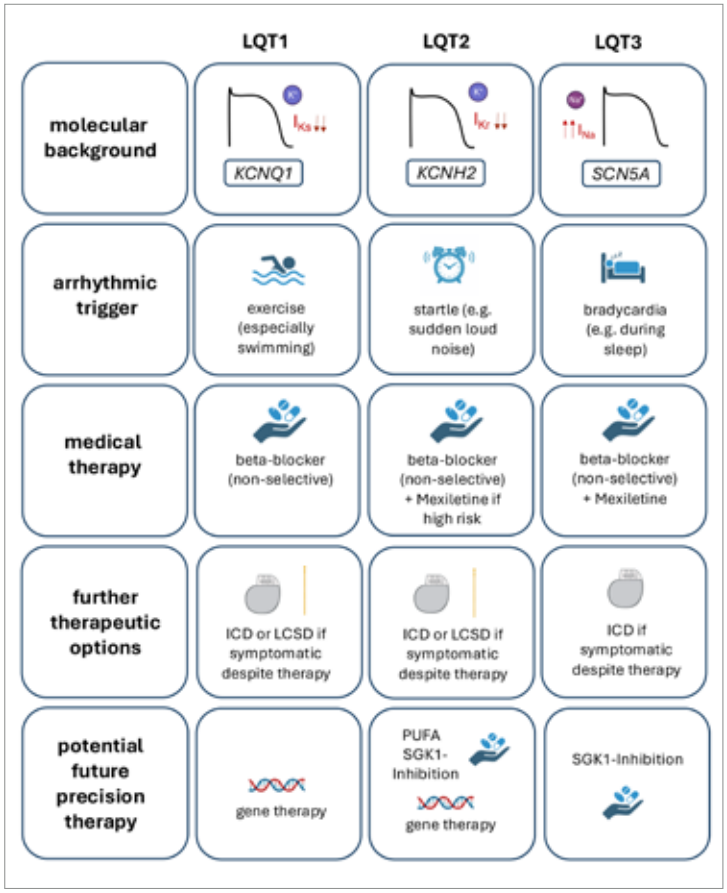

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Figure 1: Overview of genotype-specific molecular defects, common arrhythmic triggers, current therapeutic strategies including lifestyle modification and pharmacological treatment, indications for device therapy, and emerging precision medicine approaches such as gene therapy and targeted inhibition in long QT syndrome (©BioRender.com). ICD: Implantable cardioverter-defibrillator; LCSD: Left cardiac sympathetic denervation; LQT1: Long QT syndrome type 1; LQT2: Long QT syndrome type 2; LQT3: Long QT syndrome type 3; PUFA: Polyunsaturated fatty acids; SGK1: Serum- and glucocorticoid-regulated kinase 1.

Novel Approaches for Future Therapy

Polyunsaturated fatty acids have emerged as modulators of cardiac ion channels with potential therapeutic relevance. Compounds such as docosahexaenoic acid (DHA) and its derivative docosahexaenoyl glycine (DHA-Gly) enhance I_{Ks} currents, thereby shortening repolarization (51,52). In transgenic LQTS rabbit models, DHA selectively normalized QTc in LQT2, where I_{Kr} is impaired but I_{Ks} remains functional, but showed no effect in LQT1 or other subtypes with I_{Ks} dysfunction (53). However, subsequent findings in LQT2 rabbits demonstrated that, despite these electrophysiological benefits, concomitant impairment of cardiac contractility limits its therapeutic applicability (54).

Beyond direct channel modulation, targeting upstream signaling pathways has gained attention as well. Serum- and glucocorticoid-regulated kinase 1 (SGK1) enhances late INa, thereby prolonging repolarization and promoting arrhythmias (55). Inhibition of SGK1 shortens repolarization and reduces arrhythmic susceptibility in patient-specific cardiomyocytes and animal models of LQT1, LQT2, and LQT3, although responses in LQT1 appear to be variant-de-

pendent (56). To note, recent studies in LQT2 rabbits and LQT3 mice further demonstrated that SGK1 inhibition suppresses elevated late I_{Na}, normalizes APD/QT, and reduces proarrhythmic markers, while remaining ineffective in LQT1 (57). These findings position SGK1 inhibition as a promising broad-spectrum, mechanism-based therapeutic approach across LQTS subtypes.

Despite significant progress, current therapies largely address downstream manifestations rather than the underlying genetic substrate. This has generated growing interest in gene-based therapies aimed at correcting the underlying genetic defects. Although cardiac gene therapy has historically lagged behind other fields, advances in vector design and delivery systems have enabled emerging applications in monogenic cardiovascular diseases (58).

Gene replacement therapy, typically employing adeno-associated viral vectors, aims to restore function through delivery of a wild-type gene copy and has shown promise in inherited cardiomyopathies. However, its applicability in LQTS is limited in the context of dominant-negative mutations, such as many of the LQT1 and LQT2 variants, where mutant proteins interfere with normal channel assembly (58).

Gene silencing therapy, including antisense oligonucleotides and RNA interference, aims to reduce expression of pathogenic alleles. While effective in principle, its implementation in LQTS is challenged by the large number of disease-causing variants and the need for variant-specific approaches. Moreover, silencing alone may be insufficient in dominant-negative conditions (58).

To overcome these limitations, hybrid suppression-and-replacement (SupRep) strategies have been developed. These combine variant-independent shRNA (short hairpin RNA)-mediated silencing of endogenous *KCNQ1* or *KCNH2* transcripts with delivery of a modified, shRNA-suppression-resistant wild-type gene. In patient-derived cardiomyocytes and transgenic rabbit models, these strategies have normalized repolarization and its spatial heterogeneity and prevented arrhythmia formation, effectively salvaging the disease phenotypes across both LOF and GOF variants, supporting their translational potential (59,60).

In parallel, pharmacological correction of protein trafficking defects has emerged as a complementary strategy. In LQT2, many variants impair intracellular processing of the IKr channel. Small molecules such as lumacaftor, originally developed for cystic fibrosis, have been shown to restore channel trafficking and improve functional expression in patient-derived cardiomyocytes (61,62), which shortened QTc in LQT2 in a first proof-of-principle study (63).

Conclusion

Together, these approaches illustrate a paradigm shift toward mechanism-based and genotype-directed therapies in LQTS, with the potential to move beyond symptom management toward true disease modification. □

Address for correspondence:
PD Dr. med. Marina Rieder
Oberärztin
Universitätsklinik für Kardiologie
Inselspital, Universitätsspital Bern
Herz Gefäss Zentrum
Freiburgstrasse 20
3010 Bern
Email: marina.rieder@insel.ch

Conflicts of interest:
The authors declare that they have no financial or personal relationships that could be perceived as potential conflicts of interest in relation to this manuscript

Received: April 28, 2026
Accepted: April 28, 2026
Published: May 21, 2026

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