# Artificial Intelligence and Induced Pluripotent Stem Cells in Long QT Syndrome: An Overview

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## Introduction

Long QT Syndrome, a cardiac channelopathy caused by inhomogeneities in the electrical activity of the heart, occurs in an estimated 1 in 2500 live births (1). LQTS occurs when myocardial repolarization is thereby resulting in prolonged QT intervals on an electrocardiogram reading (2). Patients with LQTS have an increased risk of experiencing life-threatening arrhythmias, and typically present with symptoms of syncope, cardiac arrest, and sudden cardiac death. LQTS can be categorized by a clear-cut separation into two types: acquired and congenital, each of different origin (3). Acquired LQTS can occur for several agents such as drugs and medication, but it can be reversed if proper therapeutic interventions are made. Congenital LQTS is a direct consequence of genetic inheritance, and it can further be divided by sub-classification, of which 17 subtypes of congenital LQTS are currently detectable, of which mutations to LQT1 (KCNQ1 gene), LQT2 (KCNH2 gene), and LQT3 (SCN5A gene) make up approximately 90 percent of cases (5). Personalized medicine is crucial since various subtypes can have different manifestations of symptoms owing to different triggers from different events (6). For instance, patients with LQT1 are more prone to experience uninvited sinus rhythms during exercise, but patients under the onslaught of LQT2 may develop this condition due to anxiety, fear or anger. In the case of LQT3, it is most often exhibited during sleep and arousal cycles (7). Thus, the main problem is that there is an urgent need for accurate and proper treatment with respect to the different types of LQTS. Unfortunately, current state-of-the-art diagnosis of LQTS remains largely unreliable, as symptoms among different subtypes of LQTS are enormously variable. In recent years, tremendous strides have been made in artificial intelligence and induced pluripotent stem cell technology, therefore opening the avenue for their potential applications. This review discusses studies that successfully demonstrated the enormous promise these approaches hold in identifying high-risk patients and in the creation of tailored therapeutic strategies. It specifically talks about the effectiveness of the different methods and what potential future impact these methods will have on medicine.

## Challenges in Subtype Differentiation

The distinction between LQTS subtypes presents a significant challenge for researchers and health workers in clinical practice, primarily due to the overlapping clinical features and the genetic heterogeneity observed among those affected (8). Furthermore, the ambiguous categorization of these subtypes, coupled with human error, diminishes the accuracy of the current diagnostic methods for LQTS. A clinical study was conducted to determine the accuracy of normal diagnosis of LQTS by having a panel of cardiologists receive a data set of four electrocardiograms (ECGs). The study concluded that fewer than 50 percent of cardiologists surveyed could accurately compute the QTc interval from the ECGs (9). This evidence illustrates the human component that undoubtedly includes existent diagnosis methods. Moreover, most of the currently used strategies and protocols for subclassification of the disease strongly rely on a combination of clinical criteria, genetic testing, and advanced electrocardiogram (ECG) assessments (10). One of the major disadvantages of these approaches is their tendency to produce inconclusive results; therefore, they become poorly applicable or even ineffective in various clinical settings. As noted earlier, a major obstacle to LQTS subtype distinction lies in the remarkable extent of phenotypic heterogeneity among LQTS patients, even among those carrying the same genetic subtype (11). Such variability is manifested by a wide spectrum of

clinical presentations, ranging from silent QT prolongation to potentially life-threatening arrhythmias and sudden cardiac death. Further complexity in classification arises because of the genetic heterogeneity inherent in LQTS, characterized by mutations in multiple genes encoding cardiac ion channels and their accessory proteins (12). Thus, clinicians are often left in the dark while trying to classify patients into specific LQTS subtypes based solely on clinical and genetic criteria. At present, electrocardiography is an integral part of diagnosing LQTS, but the subtle differences between the prolongation of the QT interval and other associated electrocardiographic features render the subtyping quite challenging; for instance, some subtypes of the LQTS may have only minimal prolongation of the QT interval at rest, while others may have far more prominent prolongation during stress testing (11-12). Moreover, overlapping ECG features that are related to other cardiovascular disorders may further complicate the diagnostic challenge. Genetic testing is an alternative method for diagnosing LQTS, but it is often both time-consuming and costly. More importantly, even if a genetic mutation is detected, determining the exact subtype of LQTS may not always be clear-cut (12). Some genetic mutations may result in heterogeneous clinical presentations, while specific subtypes may be associated with mutations in multiple genes. The clinical presentations of LQTS may also be nonspecific, further making the diagnosis difficult. Dizziness, syncope, and palpitations are common in so many other heart conditions; hence, it would be very tough to pinpoint LQTS without further investigation. Genetically, LQTS is also categorized heterogeneously, as mutations in several genes encoding cardiac ion channels and their accessory proteins underlie its classification complexity. It is thus common for clinicians to be in a dilemma when trying to classify patients into specific subtypes of LQTS using solely clinical and genetic criteria.

**The Role of Artificial Intelligence**

AI, particularly machine learning algorithms, may be expected to come up with approaches that can help in developing predictive models for the differentiation of LQTS subtypes. For instance, AI deep-learning algorithms can mine vast databases of clinical and genetic information, including ECGs, patient history, and Schwartz Score, to recognize discrete or even subtle patterns or features associated with a specific LQTS subtype, hence providing the means for a more precise diagnosis and risk management (13). Moreover, it can easily integrate multi-omics data, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics, into patient profiles, thereby making possible a holistic understanding of the pathophysiology underlying each subtype of LQTS (14). One study aimed at establishing whether deep learning models could be used in making predictions on genotype-phenotype correlations in patients with a diagnosis of LQTS. The study epitomizes the potential of an AI-driven approach in the diagnosis of LQTS and personalized treatment strategies through the analysis of 12-lead ECG readings. In this study, a deep learning model analyzing 4521 ECG readings from 900 patients was used; it presented an AUC of 0.93 for LQTS detection and an AUC of 0.91 for genotype differentiation. This exceeded the accuracy of expert-measured QTc intervals in detecting LQTS. The authors especially highlighted the model's impressive capability in distinguishing LQT1 from LQT2 accurately (15). Another study developed machine learning models that could help in predicting the risk of sudden cardiac death in patients with LQTS. This kind of research typifies how AI algorithms could identify people at high risk, who might greatly benefit from early intervention strategies by bringing together clinical variables, genetic information, and longitudinal follow-up data. The deep learning model provided a very good AUC of 0.889 for SCD cases in the internal dataset and validated its results in an external

dataset with an AUC of 0.820. Compared to the traditional methods of ECG, this deep learning model showed a much better performance with an AUC of 0.712 in the internal cohort and 0.743 in the external cohort (16).

**Development of AI models for LQTS Subtyping**

The development of the AI models for the distinction between LQTS subtypes falls within a sequential design where each step is important toward the final outcome. First, large databases containing clinical and genetic data of patients with confirmed LQTS diagnoses are compiled into research databases. Next, feature selection techniques will identify relevant clinical variables, genetic mutations, and ECG parameters that are useful in distinguishing among the different LQTS subtypes. Such extracted data are then used in training machine learning algorithms—be it support vector machines, random forests, or deep learning neural networks—that will classify patients into specific subtypes of LQTS based on recognizable characteristics. The performance and accuracy of the AI model are usually evaluated by cross-validation techniques and external validation datasets or cohorts, together with the quantification of sensitivity and specificity. Many studies have been published to investigate the use of AI in diagnosing LQTS. Among these researches, one was about the efficacy of machine learning algorithms in interpreting ECG data concerning the early detection of LQTS and prediction of arrhythmic events. It has been stated that the use of AI methods can increase the sensitivity and specificity in detecting patients vulnerable to malignant cardiac events. Such a development can refine risk stratification and help guide clinical decision-making. It is also helpful in the diagnosis of LQTS in patients with normalized resting QTc intervals (17).

**Clinical Implications and Future Directions**

Accurate subtype classification can help decide the best therapeutic strategy, which may include drug therapy, ICD implantation, and lifestyle modifications. Artificial intelligence-driven models may enable rapid identification of high-risk patients, providing a tremendous opportunity for targeted management and timely intervention to prevent devastating and often fatal cardiac events (18). These may have real-time integration of data from wearables, such as smartwatches or implanted monitoring systems, that allow for continual monitoring and risk stratification of patients diagnosed with LQTS. Given the myriad important issues that need to be addressed successfully before AI can be adopted into clinical practice effectively, there have been a number of promising developments in recent research and academic literature regarding the use of AI in diagnosis and treatment of LQTS (19). One particular example of such research is the investigation of a novel methodology to predict adverse events after an ICD replacement procedure utilizing machine learning algorithms. In one such group of patients with ICD replacement, large volumes of clinical data were gathered which included; profiled demographics, medical and treatment history, and procedure-specific information. The outcome was satisfying with increased accuracy in personalized treatment with this approach while being able to handle risks after the procedure efficiently. The study highlighted the role of artificial intelligence in identifying and managing different types of LQTS (20).

**Induced Pluripotent Stem Cells: An Overview**

Induced pluripotent stem cells are the cells reprogrammed to a pluripotent state similar to that of embryonic stem cells by the use of specific transcription factors and other environmental cues. They possess the capability to differentiate into many different types of cells, such as cardiomyocytes, and apart from drug screening, they are procured for the derivation of diseased

cells in order to study the processes at a molecular level. The technology behind iPSCs has become a promising avenue toward personalized cardiomyocyte development, hence opening the way for testing and thorough investigation. Deriving iPSCs from patients with LQTS diagnosis is an excellent approach in the study of the disease in vitro under highly controlled laboratory conditions (21).

**Modeling LQTS with iPSCs**

Different methods have been used by scientists to create iPSC models of various subtypes of LQTS; only a few examples are LQT1, where the disease is caused by mutations in the KCNQ1 gene. In a pioneering study, researchers reprogrammed fibroblasts from LQT1 patient's iPSCs, which were then differentiated in a next step into cardiomyocytes. The prolonged action potential duration (APD) and the occurrence of early afterdepolarizations (EADs) were critical markers in the in vitro diagnosis of the patient's disease as well as in testing the response to beta blockade. This approach eventually unraveled the suitability of the iPSC technology platform for testing a variety of potential drugs for LQTS (22). patient-specific iPSCs harboring a mutation in the KCNH2 gene causing LQT2 were demonstrated to faithfully recapitulate major aspects of the clinical presentation common for LQT2. One of the studies that explored this subtype was the one that produced the iPSC-derived cardiomyocytes from patients with LQT2 and saw an increased incidence of EADs and triggered activity. The cellular models of these studies have taught us how the mutation in the LQTS impairs the normal functioning of the cardiac potassium channels that may lead to lengthened QT intervals, thereby leading to arrhythmias (23). With LQT3, mutations become apparent in the SCN5A gene, which codes for the sodium channel. Scientists have used cardiomyocytes derived from iPSCs to study how these mutations affect the sodium channel. One study in particular demonstrated the capability of iPSCs in modeling LQT3, showing that the cells reprogrammed from patients possessed an abnormal inactivation of the sodium current; this resulted in an elongated depolarization and consequently an increased risk for arrhythmias (24).

**Advancements in iPSC Technology for LQTS Research**

Advancements in gene editing technologies, especially CRISPR, have considerably expanded the possibilities of induced pluripotent stem cells (iPSCs) in exploring LQTS. Researchers now have the ability to correct or introduce specific mutations into iPSCs, which has also enabled them to create models that accurately mimic LQTS. For instance, a recent study showed that variants of uncertain significance (VUS) resulted in prolonged action potentials once corrected or mutant iPSCs were transformed into cardiomyocytes. The researchers then used CRISPR-Cas9 to correct the KCNH2 mutation in LQT2 patient-derived iPSCs, thus bringing the APD to a healthy level in differentiated cardiomyocytes. This research, like others with iPSC technology, emphasizes, through concrete examples, its bright future, and potential areas of further research. It also means the power of gene editing to correct disease-causing mutations and to recover normal cardiac function present another avenue of research (25). On the other hand, CRISPR-Cas9 can be used to introduce point mutations in iPSCs, leaving the rest of the genome in its wild type state. The technology allows us, in this case, to distinguish diseased from healthy cardiomyocytes, and to study the particular effects of the mutations on them. Specifically, studies such as this one created isogenic iPSC lines with and without the SCN5A mutation, which is responsible for LQT3. The researchers showed that the induction of the mutation impairs sodium channel function and increases vulnerability to arrhythmias; therefore, such technology has the potential to uncover LQTS at a molecular level (26).

## Challenges and Future Directions

Besides disease modeling, the use of iPSCs is viewed as a promising avenue for new LQTS treatments. Drug testing of patient-specific iPSC-derived cardiomyocytes can be the alternative way to find reagents that control the electrophysiological permutations in LQTS. One example is a certain investigation with iPSC-derived cardiomyocytes from patients with LQT2 for drug screening. They identified several drugs that would restore APD to normal levels and also prevent arrhythmias and thus pointed to a road toward personalized medicine to cure LQTS. Another way iPSC technology can be utilized is for cell-based therapies, where stable cardiomyocytes developed from genetically modified iPSCs are generated and then transplanted into patients to replace the damaged heart tissue (27). Although this application is still under investigation, it holds much promise as an avenue for future study. It has been demonstrated to be possible, in some cases, to differentiate iPSCs into functional cardiomyocytes and integrate them successfully into diseased myocardium in animal models, thus highlighting the potential for clinical applications (28).

## Summary

LQTS is a life-threatening cardiac disorder if undiagnosed, yet current diagnostics are limited by so many challenges. The use of artificial intelligence has great promise to develop predictive models for diagnosing LQTS and for the differentiation between subtypes of the disease. Utilizing machine learning algorithms along with multi-omics data, AI-based models could help improve diagnostic accuracy, risk stratification, and personalized treatment approaches in patients with LQTS. Continued research in this area and innovation is important to realize the full potential of AI in improving outcomes for those affected by this life-threatening cardiac disorder. Technology with iPSCs may bring a paradigm change in the research and treatment of LQTS. It has transformed the ability to study LQTS in vitro and holds the potential for personalization of treatment strategies. By allowing the production of patient-specific cardiomyocytes, iPSCs give tremendous potential to the understanding of disease mechanisms, identification of therapeutic targets, and development of personalized treatments. Challenges notwithstanding, continued improvements in iPSC technology and gene editing hold great promise for improving life for people with LQTS. Future studies should continue to develop these technologies, ensuring their safety and exploring their full therapeutic potential.

Sources:

1. Crotti, L., Celano, G., Dagradi, F., & Schwartz, P. J. (2008). Congenital long QT syndrome. *Orphanet Journal of Rare Diseases, 3*(1), 18. https://doi.org/10.1186/1750-1172-3-18

2. UpToDate. (n.d.). Acquired long QT syndrome: Definitions, pathophysiology, and causes. Retrieved from https://www.uptodate.com/contents/acquired-long-qt-syndrome-definitions-pathophysiology-and-causes/print

3. Schwartz, P. J., Crotti, L., & Insolia, R. (2012). Long-QT syndrome: From genetics to management. *Circulation: Arrhythmia and Electrophysiology, 5*(4), 868–877. https://doi.org/10.1161/CIRCEP.111.962019

4. National Center for Biotechnology Information. (n.d.). Retrieved from https://pubmed.ncbi.nlm.nih.gov/35734489/

5. Heart Rhythm Open. (2024). Retrieved from https://www.heartrhythmopen.com/article/S2666-5018(24)00225-3/fulltext

6. National Center for Biotechnology Information. (n.d.). Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC5099327

7. National Center for Biotechnology Information. (n.d.). Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC5099327

8. Raissi Dehkordi, N., Raissi Dehkordi, N., Karimi Toudeshki, K., & Farjoo, M. H. (2024). Artificial intelligence in diagnosis of long QT syndrome: A review of current state, challenges, and future perspectives. *Mayo Clinic Proceedings: Digital Health, 2*(1), 21–31. https://doi.org/10.1016/j.mcpdig.2023.11.003

9. National Center for Biotechnology Information. (n.d.). Retrieved from https://pubmed.ncbi.nlm.nih.gov/15922261/

10. National Center for Biotechnology Information. (n.d.). Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC8862104/

11. Brink, P. A., Crotti, L., Corfield, V., et al. (2005). Phenotypic variability and unusual clinical severity of congenital long-QT syndrome in a founder population. *Circulation, 112*(17), 2602–2610. https://doi.org/10.1161/CIRCULATIONAHA.105.572453

12. Heart Rhythm Open. (2024). Retrieved from https://www.heartrhythmopen.com/article/S2666-5018(24)00225-3/fulltext

13. Bos, J. M., Attia, Z. I., Albert, D. E., Noseworthy, P. A., Friedman, P. A., & Ackerman, M. J. (2021). Use of artificial intelligence and deep neural networks in evaluation of patients with electrocardiographically concealed long QT syndrome from the surface 12-lead electrocardiogram. *JAMA Cardiology, 6*(5), 532–538. https://doi.org/10.1001/jamacardio.2020.7422

14. ScienceDirect. (n.d.). Retrieved from https://www.sciencedirect.com/science/article/pii/S2001037021002683

15. JAMA Network. (n.d.). Retrieved from https://jamanetwork.com/journals/jamacardiology/article-abstract/2815659

16. Nature Communications. (2024). Retrieved from https://www.nature.com/articles/s43856-024-00451-9

17. Mayo Clinic Proceedings: Digital Health. (2024). Retrieved from https://www.mcpdigitalhealth.org/article/S2949-7612(24)00015-4/fulltext

18. *Heart.* (2024). Retrieved from https://heart.bmj.com/content/108/5/332

19. Mayo Clinic Proceedings: Digital Health. (2023). Retrieved from https://www.mcpdigitalhealth.org/article/S2949-7612(23)00093-7/fulltext

20. *New England Journal of Medicine.* (2024). Retrieved from https://www.nejm.org/doi/full/10.1056/NEJMoa0908679

21. National Center for Biotechnology Information. (n.d.). Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC10302164/

22. National Center for Biotechnology Information. (n.d.). Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC3343213/

23. *Disease Models & Mechanisms.* (2024). Retrieved from https://journals.biologists.com/dmm/article/5/2/220/53559/Model-for-long-QT-syndrome-type-2-using-human-iPS

24. Yazawa, M., Hsueh, B., Jia, X., et al. (2011). Using induced pluripotent stem cells to investigate cardiac phenotypes in Timothy syndrome. *Nature, 471*(7337), 230–234. https://doi.org/10.1038/nature09855

25. Garg, P., Oikonomopoulos, A., Chen, H., et al. (2018). Genome editing of induced pluripotent stem cells to decipher cardiac channelopathy variant. *Journal of the American College of Cardiology, 72*(1), 62–75. https://doi.org/10.1016/j.jacc.2018.04.041

26. National Center for Biotechnology Information. (n.d.). Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10661835/

27. Aboul-Soud, M. A. M., Alzahrani, A. J., & Mahmoud, A. (2021). Induced pluripotent stem cells (iPSCs)—Roles in regenerative therapies, disease modelling, and drug screening. *Cells, 10*(9), 2319. https://doi.org/10.3390/cells10092319

28. Martínez-Falguera, D., Iborra-Egea, O., & Gálvez-Montón, C. (2021). iPSC therapy for myocardial infarction in large animal models: Land of hope and dreams. *Biomedicines, 9*(12), 1836. https://doi.org/10.3390/biomedicines9121836