

Genetic variants in long QT syndrome genes: classification and frequency analysis from public databases

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Background: Long QT syndrome (LQTS) is an inherited arrhythmic disorder linked to an increased risk of sudden cardiac death. It is mainly caused by pathogenic variants in KCNQ1, KCNH2, and SCN5A. The availability of large public genomic repositories enables systematic evaluation of variant distribution and clinical classification, but data consistency and interpretation remain challenging.

Purpose: This study aimed to characterise the frequency and clinical classification of KCNQ1, KCNH2, and SCN5A variants related to LQTS in public databases, highlighting the current gaps in variant interpretation.

Methods: A descriptive exploratory analysis was performed using ClinVar and gnomAD (v4.1) databases. Variants associated with LQTS in the genes KCNQ1, KCNH2, and SCN5A were retrieved from ClinVar in September 2025. Variants classified as pathogenic, likely pathogenic, or variant of uncertain significance (VUS) based on multiple reports or expert panel review were included. Additional information on selected variants was extracted from gnomAD (gene, type, molecular consequence, clinical classification, and exome allele frequency). Data were analysed using R (v4.5.0). Variants were grouped by gene and classification, following the American College of Medical Genetics and Genomics (ACMG) guidelines, plus an additional category, reported in ClinVar as pathogenic/likely pathogenic, for variants with conflicting interpretations among different submitters.

Results: A total of 1,506 variants were identified: 45.4% in KCNH2, 30.9% in KCNQ1, and 23.7% in SCN5A. Most variants (64.4%) were classified as VUS, 3.8% as likely pathogenic, 16.1% as pathogenic/likely pathogenic, and 15.7% as pathogenic. Allelic frequency data from gnomAD, visualised in Manhattan-like scatter plots, reinforces that VUS were the most prevalent across all genes (Figure 1a). When excluding this category (Figure 1b), KCNQ1 harboured the variants with the highest population frequencies, including the most frequent pathogenic variant: KCNQ1:c.1552C>T (p.Arg518Ter), with an allele frequency of 0.015%. Overall, allele frequencies were low, consistent with the rarity of long QT syndrome. Thirty-five percent lacked population frequency data in gnomAD. Single-nucleotide variants predominated at over 80%, followed by deletions and duplications.

Conclusions: The findings confirm the marked genetic heterogeneity of LQTS and the predominance of VUS, underscoring current limitations in clinical interpretation and database coverage. KCNQ1 harboured the highest proportion of pathogenic variants, while KCNH2 exhibited the greatest absolute number. Integration of clinical, functional, and population data remains crucial to refining variant classification and enhancing the translational value of genomic information in inherited arrhythmia management.

Arrhythmias and Device Therapy – Arrhythmias, General, Pathophysiology and Mechanisms, Genetic Aspects of Arrhythmias

Frquency distribution.

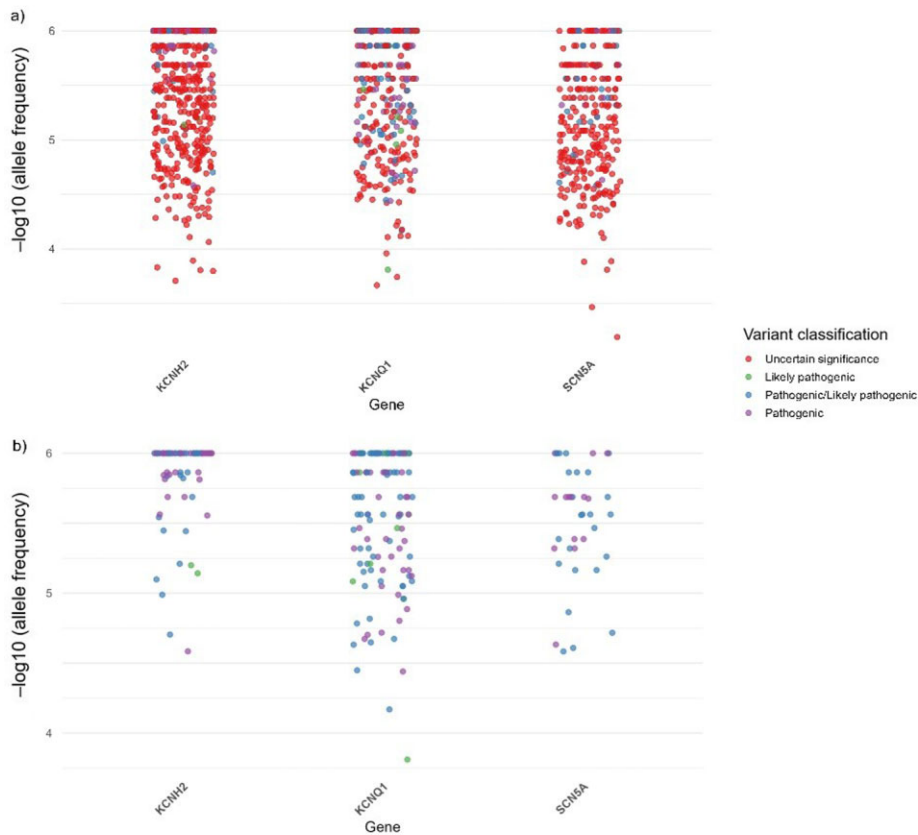


Figure 1: Frequency distribution. a) Global overview. b) Excluding VUS.