Systematic Evaluation of KCNQ1 variant using ACMG/AMP Guidelines and Risk Stratification in Long QT Syndrome Type 1

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Background: Mutation/variant-site specific risk stratification in long-QT syndrome type 1 (LQT1) has been well investigated, but it is still challenging to adopt current enormous genomic information to clinical aspects caused by each mutation/variant. We assessed a novel variant-specific risk stratification in LQT1 patients.

Methods: We classified a pathogenicity of 142 KCNQ1 variants among 927 LQT1 patients (536 probands and 391 family members) based on the American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) guidelines and evaluated whether the ACMG/AMP-based classification was associated with arrhythmic risk in LQT1 patients.

Results: Among 142 KCNQ1 variants, 60 (42.3%), 58 (40.8%), and 24 (16.9%) variants were classified into pathogenic (P), likely pathogenic (LP), and variant of unknown significance (VUS), respectively. The ACMG/AMP guideline-based classification was significantly associated with syncopal events (particularly those during exercise) and LQT risk score (Schwartz score) in overall population. On the other hand, arrhythmic risk was completely different between probands and families even in the same variants. The baseline QTc interval and variant location could stratify the risk in family members but not in probands, however, the ACMG/AMP-based KCNQ1 variant classification stratified the risk in LQT1 probands as well as family members. Multivariate analysis showed that proband (HR=2.52; 95% CI: 1.93–3.30; p<0.0001), longer QTc interval (≥500ms) (HR=1.41; 95% CI: 1.11–1.79; p<0.0001), variants at membrane spanning (MS) (vs. those at N/C terminus) (HR=1.40; 95% CI: 1.07–1.85; p=0.02), C-loop (vs. N/C terminus) (HR=1.58; 95% CI: 1.11–2.24; p=0.01), and P variants [(vs. LP) (HR=1.71; 95% CI: 1.33–2.23; p<0.0001), (vs. VUS) (HR=1.96; 95% CI: 1.19–3.46; p=0.007)] were significantly associated with syncopal events. A clinical score (0–4) based on the proband, QTc (≥500ms), variant location (MS or C-loop) and P variant by the ACMG/AMP guidelines allowed identification of patients more likely to have arrhythmic events (Figure A and B).

Conclusion: Comprehensive evaluation of clinical findings and pathogenicity of KCNQ1 variants based on the ACMG/AMP-based evaluation may stratify arrhythmic risk of congenital long-QT syndrome type 1.

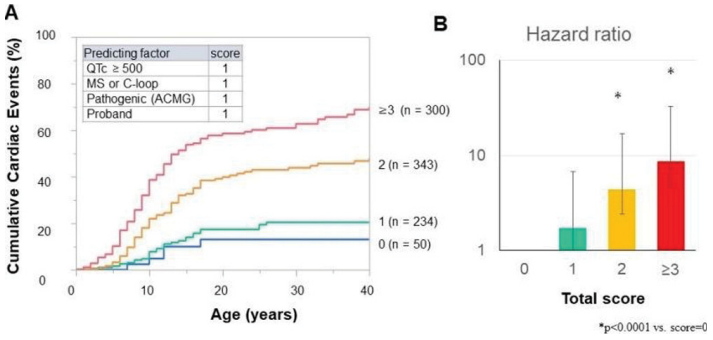

Figure 1