QT Interval Determinant
Mutations, Rare Variants, or Single-Nucleotide Polymorphisms?

Takeshi Aiba, MD, PhD; Atsushi Takahashi, PhD

Long-QT syndrome (LQTS) is typically characterized by QT interval prolongation on ECG associated with syncpe or sudden cardiac death in young individuals when prolongation of the QT interval induces torsade de pointes, a polymorphic ventricular tachycardia that can degenerate into ventricular fibrillation. LQTS is characterized by mutations in several ion channel genes. Although >10 susceptible genes have been identified, KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) are the most common LQTS genes, accounting for >90% of all genotype-positive cases. Only <5% of cases are diagnosed as LQT4~15, and 20% to 30% of cases remain genetically elusive. In the past 2 decades, lots of LQTS clinical databases have revealed genotype–phenotype correlations in the 3 major LQTS (LQT1~3) subtypes and have indicated that the genotype, together with QTc interval, age, and sex, is a determinant of arrhythmic risk and response to medication therapy. Furthermore, not only genotype but also mutation site–specific differences in arrhythmic risk could be reported in LQT1 and LQT2.6

See Article by Rosenberg et al

However, as in most Mendelian disorders, patient management is complicated by the variability in disease severity among LQTS mutation carriers.7 Even in the same mutation, for example, KCNQ1-A341V, mutation carriers had a wide range of QTc values (406–676 ms), and 12% of individuals had a normal QTc (≤440 ms).8 Furthermore, in addition to the LQTS-causing gene mutations, other genetic polymorphisms, such as NOS1AP, KCNE1-D85N may affect the QT interval as modifiers.9~10 One study reported, however, that the rare genetic variants previously associated with congenital LQTS have little or no effect on the QT interval.11

A recent genome-wide association study (GWAS) and replication study on ≈100,000 individuals identified 35 common variant loci associated with the QT interval that collectively explain ≈8% to ≈10% of the QT interval variation and highlighted the importance of calcium regulation in myocardial repolarization.12 Variation of the QT interval, however, which reflects myocardial repolarization, occurs in both patients with LQTS and in healthy individuals. Prevalence of QT interval in hospital-based subjects was previously reported,13 in which the histograms of the QTc interval were also right-skewed, so it failed to fit to a normal distribution.

GWASs have uncovered tremendous associations between single-nucleotide polymorphisms (SNPs) and complex phenotypic traits in numerous cardiovascular and noncardiovascular diseases over the last 10 years.14 Although GWASs identified many genetic variants associated with phenotypes, the results showed that each SNP had only small effects on the phenotype, in which the odds ratio is ≤1.3. To separate some pathogenic variants from common genetic noises, many statistical tests in GWASs require significantly smaller P values, such as 5e-8, as genome-wide significance thresholds. Thus, the problem of missing heritability arises15 as many considerations should be taken into account between genetic variants and phenotypic variations.

Recently, a polygenic model was proposed to explain the missing heritability16 because the polygenic model, including many common variants that are usually masked below a statistically significant level in GWASs, may potentially be associated with complex traits. Variants with true association may not exceed the genome-wide significance because of the small effect size and lack of power of study. The polygenic model treats variants with P value <α, where α is the significance threshold, for example, α≤0.05, or α≤0.01. Associated and unassociated variants with phenotypes are mixed in the polygenic model. The polygenic risk score (PGS) can be calculated using these variants with a regression coefficient. It is assumed that the distributions of the PGS depend on phenotypes, and that risk variants cannot be distinguished. If many risk variants are included in the model, case and control individuals will have high and low PGS scores, respectively. To date, numerous studies have applied the polygenic model to various complex traits as a modifier of genetic risk. The results suggest that the polygenic model holds.17 This implies that there are many variants with a moderate effect size in GWAS data.

Rosenberg et al18 applied a polygenic model to the QT interval of an ECG. They studied the polygenic model of the QT interval among 2 populations, one of European descent and one of African descent. They found that PGS results differed compared with other complex traits. Their results show that the PGS explained the variation of the QT interval for individuals of European ancestry but not for individuals of African descent. They suggest that this race difference is because of the sample size of model construction: 70 K individuals of European decent whereas 13 K individuals of African descent
were used. Many functional SNPs seem to have major adverse effects in some races but not others. This study may have a potential population sizes to mask these particular functional SNPs. However, much larger sample size in African population may be necessary to estimate the PGS. If the sample size is small, the PGS for the QT interval may not work well.

Another important result is the behavior of the PGS model when the number of variants increases as a result of changing the significance threshold. The explanation of heritability in complex binary traits is usually improved according to increasing the number of variants applied in the model. The PGS with a much larger number of variants for the QT interval does not, however, always improve the relationship between the PGS and the QT interval. This might be because of a few significant genetic variants, such as NOS1AP, which seem to explain most of the heritability of the QT interval. These findings suggest that only several variants that exceed the genome-wide significance level may be enough for consideration of the QT interval.

The QT interval is a quantitative trait, and the results of this study\(^6\) may thus reflect the nature of quantitative traits. Variants associated with the QT interval may have a smaller effect size than complex traits. Only a few variants may be associated with the QT interval. Other factors, such as the interaction between genetic and environmental factors, may be important to alter the QT interval. The difference in behavior in the PGS between the QT interval and other complex traits may affect the characteristics of the QT interval.

Finally, there is a significant number of individuals with borderline or slightly prolonged QT interval but not identified major LQTS genes. Some of them have a risk of acquired LQTS. The authors’ group recently demonstrated that genome-wide significant SNPs were associated with drug-induced QT prolongation and torsade de pointes.\(^9\) It would be more clinically relevant if we know how much degree of the PGS was associated with this borderline QT subjects. Their findings demonstrated that a relatively small number of common variants probably may explain most of the clinical variation of the QT interval. Further research is needed to solve these questions.

**Sources of Funding**

Drs Aiba and Takahashi acknowledge the support from a Grant-in-Aid for Scientific Research (C) (15K09150) from MEXT of Japan, Health Science Research Grants from the Ministry of Health, Labor and Welfare of Japan for Clinical Research on Measures for Intractable Diseases (H24-033, H26-040, and H27-032), and a research grant from Japan Agency for Medical Research and Development, AMED (15km0305015h0101, 16ek0210073h0001).

**Disclosures**

None.

**References**

1. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ Arrhythm Electrophysiol. 2012;5:868–877. doi: 10.1161/CIRCEP.111.962019.

2. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med. 2003;348:1866–1874. doi: 10.1056/NEJMoa022147.

3. Moss AJ, Shimizu W, Wilde AA, Towbin JA, Zareba W, Robinson JL, et al. Clinical aspects of type-I long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. Circulation. 2007;115:2481–2489. doi: 10.1161/CIRCULATIONAHA.106.665406.

4. Shimizu W, Moss AJ, Wilde AA, Towbin JA, Ackerman MJ, January CT, et al. Genotype-phenotype aspects of type II long-QT syndrome. J Am Coll Cardiol. 2009;54:2052–2062. doi: 10.1016/j.jacc.2009.08.028.

5. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome clinical impact. Circulation. 1999;99:529–533.

6. Brink PA, Crotti L, Corfield V, Goosen A, Durhheim G, Hedley P, et al. Phenotypic variability and unusual clinical severity of congenital long-QT syndrome in a founder population. Circulation. 2005;112:2602–2610. doi: 10.1161/CIRCULATIONAHA.105.572453.

7. Newton-Cheh C, Eigelsheim M, Rice KM, de Bakker PJ, Yin X, Estrada K, et al. Common variants at ten loci influence QT interval duration in the QTGEN study. Nat Genet. 2009;41:399–406. doi: 10.1038/ng.364.

8. Kolder ICRM, Tanck MWT, Postema PG, Barc J, Sinner MF, ZUMHAGEN S, et al. Analysis for genetic modifiers of disease severity in patients with long-QT syndrome type 2. Circ Cardiovasc Genet. 2015;8:447–456. doi: 10.1161/CIRCGENETICS.114.000783.

9. Crotti L, Monti MC, Insolia R, Poljio A, Goosen A, Brink PA, et al. NOS1AP is a genetic modifier of the long-QT syndrome. Circulation. 2009;120:1657–1663. doi: 10.1161/CIRCULATIONAHA.109.879643.

10. Lahtinen AM, Marjamaa A, Swan H, Kontula K. KCN1E D8SN polymorphism–a sex-specific modifier in type 1 long QT syndrome? BMC Med Genet. 2011;12:11. doi: 10.1186/1471-2350-12-11.

11. Ghose J, Have CT, Weeke P, Bille Nielsen J, Ahlberg G, Balslev-Harder M, et al. Rare genetic variants previously associated with congenital forms of long QT syndrome have little or no effect on the QT interval. Eur Heart J. 2015;36:2523–2529. doi: 10.1093/eurheartj/ehv297.

12. Arking DE, Pulit SL, Crotti L, van der Harst P, Munroe PB, Koopmann TT, et al; CARE Consortium; COGENT Consortium; DCCT/EDIC; eMERGE Consortium; HRGEN Consortium. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. Nat Genet. 2014;46:826–836. doi: 10.1038/ng.3014.

13. Miyamoto A, Hayashi H, Yoshino T, Kawaguchi T, Taniguchi A, Itoh H, et al. Clinical and electrocardiographic characteristics of patients with short QT interval in a large hospital-based population. Heart Rhythm. 2012;9:66–74. doi: 10.1016/j.hrthm.2011.08.016.

14. MacArthur J, Bowler E, Cerezo M, Gil L, Hill P, Hastings E, et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). Nucleic Acids Res. 2017;45(D1):D896–D901. doi: 10.1093/nar/gkw1133.

15. Maher B. Personal genomes: the case of the missing heritability. Nature. 2008;456:18–21. doi: 10.1038/456018a.

16. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF et al. Common polymorphic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009;460:748–752.

17. Stahl EA, Wegmann D, Trynka G, Gutierrez-Achury J, Do R, Voight BF, et al; Diabetes Genetics Replication and Meta-analysis Consortium; Myocardial Infarction Genetics Consortium. Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis. Nat Genet. 2012;44:483–489. doi: 10.1038/ng.2252.

18. Rosenberg MA, Lubeiz SA, Lin H, Kosova G, Castro VM, Huang P, Ellinor PT, Perlis RH, Newton-Cheh C; Validation of polygenic scores for QT interval in clinical populations. Circ Cardiovasc Genet. 2017;10:e001724. doi: 10.1161/CIRCGENETICS.117.001724.

19. Strauss DG, Vicente J, Johannesen L, Blinova K, Mason JW, Weeke P, et al. Common genetic variant risk score is associated with drug-induced QT prolongation and torsade de pointes risk: a Pilot Study. Circulation. 2017;135:1300–1310. doi: 10.1161/CIRCULATIONAHA.116.023980.

**Key Words**: Editorsials • genome-wide association study • long QT syndrome • mutation • polymorphism, single nucleotide