Gauging the Risk of Arrhythmic Death by Common Genetic Variants
Resurgence of the Sinister QT

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The holy grail of personalized medicine in clinical cardiac electrophysiology is to establish a reproducible genetic imprint or the associated intermediate phenotype (“endophenotype”) that would with high accuracy predict arrhythmic death in an individual. Although we are far from it, the study in this issue of Circulation: Cardiovascular Genetics by Noseworthy et al is another step in the right direction. It is well established that an abnormal QT interval (ie, too long or too short) is a predictor of arrhythmogenic risk in patients with the rare syndromes caused by ion channel mutations. However, the role of QT in gauging the risk of death in the general population is recent, complex, and laced with fundamental questions that remain unanswered. Noseworthy et al tackle this problem straight on and investigate the value of common genetic variants for predicting QT duration and sudden cardiac death (SCD) risk.

Are Genetic Determinants of QT Interval Better Suited to Predict SCD?
The lack of consistency of repeated QT measurements over time raises an intriguing question: Are genetic determinants of QT a better predictor of SCD? In the present study, Noseworthy et al study a large, population-based cohort in Finland to replicate the association between 15 common genetic variants identified in 2 separate genome-wide association studies to the QT interval and SCD. By creating a novel QT score (QTscore) that takes into account the joint effect of these genetic variants and QT interval individually and in aggregate, these data not only serve as internal control in validating the results of the current study but also make their novel concept of QTscore worthy of further investigation.

Simplistically, the QTscore takes into account the prevalence of the study allele and based on prior studies the contribution of the respective allele toward the study endophenotype: QT score (QTscore) calculated from genetic variants found commonly in the population to answer this question.

Epidemiological studies are highly dependent on a number of study variables: the definition of the study phenotype, study population, exclusion criteria, and authenticity of the data source, to name a few. Thus, Noseworthy et al use well-characterized, population-based cohorts from Finland that have been interrogated for previous epidemiological research to study their hypothesis. The methodology used is scientifically sound with respect to exclusion criteria, definition of arrhythmic death, and genotyping and statistical analyses adding to the validity of the study results. The authors use a normogram-corrected QT interval measurement (QTnc) for their study, which has been previously validated.

The authors study a large, population-based cohort in Finland to replicate the association between 15 common genetic variants identified in 2 separate genome-wide association studies to the QT interval and SCD. By creating a novel QT score that takes into account the joint effect of these variants on the QT, they go a step further and study the relationship between QTscore and the risk of SCD.

The findings confirm the previously held notion that QT prolongation predicts SCD in a population. They also replicate the association between recently identified common genetic variants and QT interval individually and in aggregate. These data not only serve as internal control in validating the results of the current study but also make their novel concept of QTscore worthy of further investigation.

QT Genotype Score: An Intriguing Concept Worth Studying
Despite the lack of the QTscore in predicting SCD, it does show promise. First, even though it did not reach statistical significance, the increase in SCD risk correlated well with increasing QTscore in primary analysis. Furthermore, when patients were “binned” on the basis of their respective

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The QT interval is an inexpensive, easily measurable, generally reproducible endophenotype, which makes it attractive for predicting risk of SCD as shown by present and prior studies. However, the QT is a “read-out” of complex interactions between multiple genes encoding both ion channel1 and non–ion channel proteins5 and multiple environmental factors (drugs, electrolytes, hormones, body temperature, etc). As a result, the QT duration can fluctuate widely in an individual over time,6 making it difficult to use a single QT measurement as predictor of individual SCD risk.

The findings confirm the previously held notion that QT prolongation predicts SCD in a population. They also replicate the association between recently identified common genetic variants and QT interval individually and in aggregate. These data not only serve as internal control in validating the results of the current study but also make their novel concept of QTscore worthy of further investigation.

Simplistically, the QTscore takes into account the prevalence of the study allele and based on prior studies the contribution of the respective allele toward the study endophenotype: QT interval. The formula used for QTscore=[(SNP1 allele copy number) × (SNP1 effect estimate in predicted ms)] + [(SNP2 allele copy number) × (SNP2 effect estimate in predicted ms)] + … through SNP14. The QTscore is then expressed as “predicted milliseconds” of expected change in the QT interval (Figure 1 of journal article). As expected, it displays a close relationship with QT but falls short of robustly predicting the risk of SCD.

The lack of consistency of repeated QT measurements over time raises an intriguing question: Are genetic determinants of QT a better predictor of SCD? In the present study, Noseworthy et al investigate the utility of a QT genotype
QTscore, the hazard ratio for SCD in the 4th and the 5th quintile was higher and statistically significant when compared with the 3rd quintile (reference category). Interestingly, the patients in the lower 2 quintiles also displayed an increase in hazard ratio for SCD when compared with the reference category but fell short of reaching statistical significance. This U-shaped relationship between SCD and QTscore is intriguing and begs further study. The U-shape relationship between common QT variants and SCD risk resembles that of monogenetic forms of SCD caused by long or short QT mutations. Several other factors may explain the lack of linear correlation of QTscore and SCD risk: First, not all QT-prolonging alleles are created equal with respect to their arrhythmogenic propensity. QT prolongation by itself may not be sufficient for SCD. The interaction between environmental factors (as mentioned) and the “intrinsic” genetically determined QT seems crucial in predisposing to SCD. None of these explanations are novel, again attesting to the validity of the study results. In a myocardial syncitium, QT prolongation predisposes to early afterdepolarizations, causing torsade de pointes.12 Dispersion of repolarization across the myocardium,13 supporting functional reentry of these aberrant ventricular beats caused by early afterdepolarizations, is generally considered the mechanism for maintenance of torsade de pointes. However, the data in the present study suggest that additional, as-yet unidentified mechanism(s) that do not depend on APD prolongation may be at play.

Conclusion
One could argue: If the QTscore does not robustly predict risk of SCD, unlike QT, then why study it? The authors astutely suggest that QTscore in essence is a subject’s lifelong exposure to genetically determined QT interval rather than a shotgun in time, like QT on an ECG. Also, the QTscore may be a measure of susceptibility to an arrhythmogenic stimuli, also described as the concept of “repolarization reserve.” At any rate, there probably is truth to the concept of QTscore associated with SCD; with the discovery of additional genetic determinants of QT, the role of QTscore in predicting SCD will become more robust. We congratulate Noseworthy et al on their study, which strengthens a number of key concepts in the domain of common genetic variants, QT interval, and SCD and identifies the need and basis for future research in assessing the use of endophenotypes in predicting SCD.

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