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NEWS AND COMMENTARY

Genetics of the ECG

QT or not QT- A genetic analysis of a complex electrophysiological trait confirms several previously detected associations

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The heritability of electric excitability patterns of the heart – as reflected by electrocardiographic recordings at the body surface – has long been recognized.[1] Twin and family studies have revealed consistent and high heritability estimates of several quantitative measures of the ECG. This is especially valid for the QT interval, an electrocardiographic measure of the ventricular repolarization process with an estimated heritability between 25 and 50%.[2,3]

Ventricular repolarization terminates systole and is a fine-tuned process dependent on the delicate coordination of low strength ionic currents at the end of the action potential.[4] Strong epidemiological evidence has been gathered in recent years, that a disturbed repolarization process measured as prolonged QT interval – usually defined as QTc > 440 ms – is associated with adverse cardiac events and an increased mortality. Odds ratios in the range of 5 have been determined in patients with pre-existing heart failure[5] and even in middle-aged probands from the general population odds ratios are in the range of 1.5.[6]

Both the clinical importance and the heritability have inspired to identify genes and mechanisms of cardiac electrophysiology by utilizing genetic approaches to the QT interval. After initial linkage studies have been performed on QT interval candidate genes[3] as well as on genome-wide scales,[7] the interest has now shifted more towards association studies. This is due to the fact that association studies are better powered to pick up the relatively small effects, as locus and allelic heritabilities – despite the high overall heritability of the QT interval – are more and more recognized to be rather small for this trait.[8]

In the light of these findings, Gouas *et al* have undertaken a replication study of five common single nucleotide polymorphisms (SNPs) that have been found associated to QT interval length in recently published studies. SNPs are in and around five known Long-QT Syndrome genes all encoding cardiac ion channels. They confirm association in three of the five adding further evidence to the multiple small effect hypothesis of genetic QT variability.

Using 400 individuals selected for extreme QT intervals from a $n = 2008$ healthy population sample from the DESIR study, it is not especially large. But it gains efficiency and statistical power by selection from the extremes of the phenotypic distribution. The gain comes from two factors, first that phenotypic effects of gene variants may be enriched at the extremes and second that for associated SNPs the genotype frequencies are maximally different in the extreme phenotypic groups.[9] Moreover the positive replication of three variants in the light of miniscule *a priori* probabilities of association for any random SNPs speaks for itself.

In addition, the study is especially valuable as it uses the same sample from the DESIR study that has earlier been examined for 17 further SNPs and their association to QT interval with 5 being found associated.[10] Incremental genotyping of well-phenotyped large studies will finally not only provide confirmation or dismissal of individual SNP associations but, in addition, enable a comprehensive assessment of interactions between gene variants as well as exposure variables, that is deviations from the logarithmic additive model of association.

Interestingly, the earlier study of the same sample attempted but did not find association with the KCNQ1 gene using 10 SNPs. Now the later study detects association by testing just one previously published variant in intron 1 of the gene. This underscores the necessity to perform LD-based studies addressing all known tag SNPs if a candidate gene is to be comprehensively assessed.

The small allelic heritabilities observed for QT interval are in common with the view that important physiologic mechanisms are unlikely to tolerate large genetic variance at a single locus. Already the authors of an early heritability study on electrocardiographic traits noted that these reflected critical biologic functions, which evolved to an evolutionary optimum, and the attainment of this optimum would necessarily tend to eliminate large interindividual differences.[11]

With many small effects making up for the overall heritability, the QT interval seems ideally suited for the genome-wide association study approach to comprehensively unravel common genetic components. This approach has already led to the *de novo* identification of the NOS1AP gene.[12] The challenge of identifying a spectrum of multiple small QTLs rather than a few strong ones will require the assembly of exceedingly large study samples ($n > 10\,000$). But it comes with the advantage that a large number of QTLs will draw a much more complete map of underlying electrophysiological pathways pinpointing all relevant genes and their associated variants on this map. The strongest association signal is not necessarily pointing towards the physiologically most interesting gene. Genes that encode proteins with central relevance to physiology may contribute only modest or no association signals at all as they may

be subject to the strongest purifying selection. Consequently, there may be a lot of scientific value in thoroughly pursuing even very modest size association effects (ie $<0.5\%$ explained variance).

Clinicians – used to QT interval prolongations of $+100$ ms and more as seen in long-QT syndrome patients – may consider the identification of QT interval-modifying variants with modest effect sizes (ie $<+3$ ms per allele) a mere academic exercise. But as these variants point towards novel genes, which promise to increase our level of electrophysiological understanding, this exercise is not without justification. In addition – if the promise of the scientific approach outlined in the beginning holds true – variants may be associated not only to QT interval but also to outcome variables of cardiac morbidity and mortality such as sudden cardiac death and death after myocardial infarction. This would identify them as potentially useful predictive tests. As efficient arrhythmia therapies, such as medications and implantable defibrillators exist, the identification of at-risk individuals would provide a valuable key asset to improving prevention strategies in the field. As many population-based cohort samples are longitudinally followed up, they will also have information about prospective morbidity and mortality available and will immediately lend themselves to the investigation of these scientific questions.[13]

The question of biological causation of these associations will remain unanswered before the underlying physiological processes of newly identified genes will be fully elucidated, which measures in decades rather than in years. Even here, genetic associations may offer some clue. The disentanglement of true associations for covariates and confounding variables according to the Mendelian randomization concept,[14] may soon reveal whether the long-known association between QT interval and sudden cardiac death is due to a causal mechanistic chain or is rather an epiphenomenon. In any case, if a growing number of genetic associations to electrocardiographic parameters and outcome variables such as sudden cardiac death can reliably and reproducibly be identified, they will add considerably to our future scientific, therapeutic and preventive options■

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