Genetic architecture of QT dynamics and resting QT in the general population

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1. Introduction

The resting QT interval, an electrocardiographic measure of myocardial repolarisation, is a heritable risk factor for cardiovascular (CV) events and genetic studies have provided new insights into the underlying biology[1]. Patient studies have reported that QT adaptation to heart rate (QT dynamics) improves cardiac risk prediction[2], but its prognostic value in the general population remains to be investigated. Furthermore, it is well recognised that the QT interval is a heritable trait and characterisation of genetic variation has provided new insights and suggests candidate genes that could predispose to CV risk. However, common variants thus far reported leave an important part of its heritability unexplained. In addition, the genetic architecture underlying QT dynamics has not been explored and might further inform about new biological mechanisms that specifically target rate adaptation of the QT interval. The objectives of this work were: (1) Evaluate the CV prognostic value of QT dynamics in the general population, (2) discover genetic variants associated with QT dynamics and (3) further investigate the genetic basis and biology of resting QT interval.

2. Methods

Exercise ECGs from 52,107 individuals of Europeans ancestry from UK Biobank (general population) where analysed for resting QT interval and QT dynamics. The resting QT interval was measured as the interval between the QRS-onset and the T-wave end from the averaged ECG waveform at rest (pre-exercise). QT dynamics were computed for exercise and recovery by dividing the changes in RT interval (ΔRT) by the corresponding changes in RR interval (ΔRR) as a surrogate marker[3] (Fig 1).

Genome wide association studies (GWASs) and heritability analyses

were conducted for each trait using BOLT software[4]. As we did not have access to an independent study that could serve as a replication study, we randomly divided our dataset into discovery (N ~ 30,000) and replication (N ~ 22,000) datasets. Replication was confirmed if the genetic variant remained significant after Bonferroni correction with same direction observed in the discovery analyses. A full dataset GWAS for both markers was also conducted and additional loci reaching genome-wide significance ($P \leq 5 \times 10^{-8}$) were reported. We performed bioinformatics analyses to annotate novel variants and prioritise candidate genes. We also investigated whether the genetic variants associated with the QT interval modulate CV outcome and resting QT interval by computing a genetic risk score (GRS).

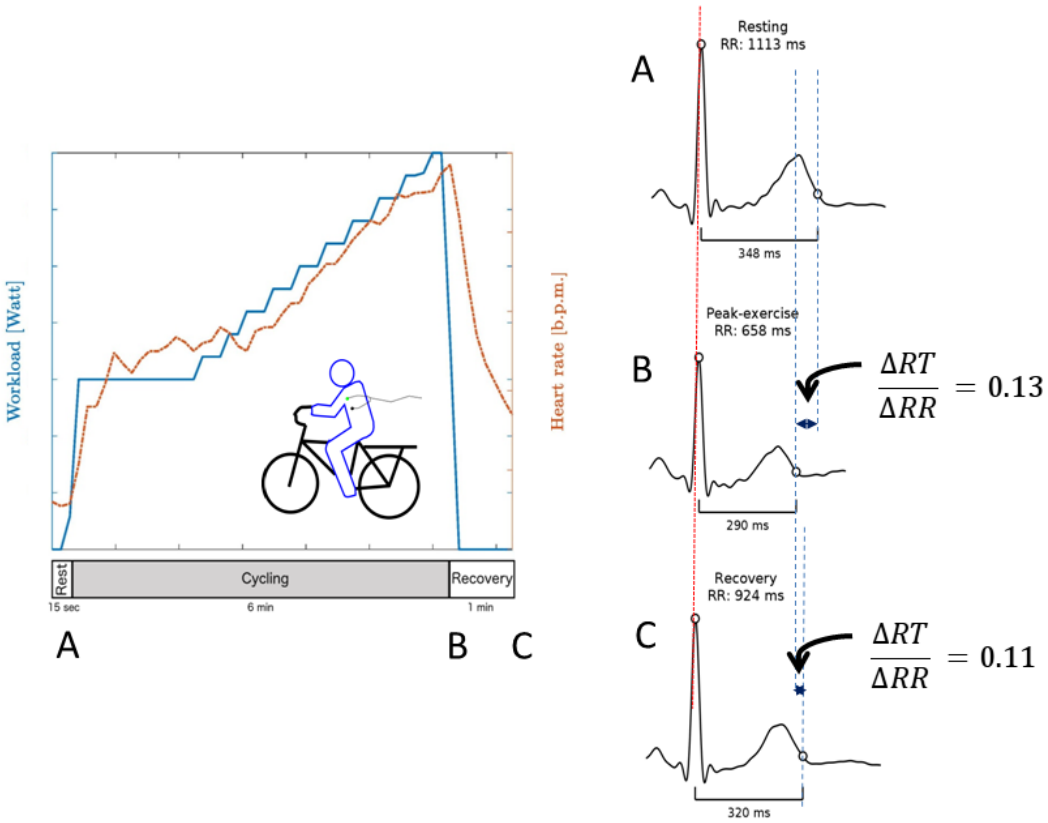


Figure 1 *Overview of the exercise protocol (left) and the computation of the QT dynamics during exercise and recovery (right). QT dynamics during exercise were approximated by computing the difference in RT interval between rest and peak-exercise by the corresponding changes in RR interval. Similarly, QT dynamics recovery was approximated by the RT/RR slope during recovery. The marker quantifies the change in RT interval per*

ms change in RR interval.

3. Results

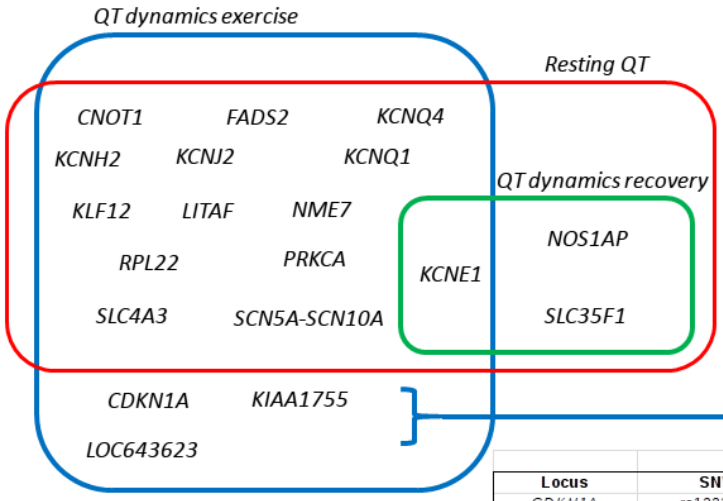
A total of 1,601 (3.0%) individuals reached the endpoint (CV events). Wilcoxon rank-sum tests showed no association between QT dynamic during exercise and recovery and CV risk. GWASs identified 20 loci for QT dynamics and indicated heritability up to 10% and we discovered 15 novel loci for resting QT. There was a substantial overlap of shared loci between QT dynamics and resting QT (Fig. 2). A GRS for resting QT was associated with QT interval ($P<0.001$) but not CV events in independent samples from UK Biobank. Bioinformatic analyses of new QT loci suggest genes involved in Ca2+ cycling and genes causing life-threatening arrhythmogenic cardiomyopathy.

4. Discussion

During exercise, the QT interval shortens with increasing heart rate and due to sympathetic innervation. During recovery, withdrawal of sympathetic activity and increase of vagal activity reduces heart rate and causes the QT interval to prolong. This is the first study to systematically investigate the prognostic value and genetic basis of QT dynamics during exercise and recovery in a large cohort of the general population and compare findings with resting QT interval. This study did not find an association between QT dynamics and CV outcome, which might be explained by the fact that we tested in a low-risk population resulting in low power to detect events. QT dynamics was found to be a heritable trait, but compared to resting QT interval, environmental factors play a more significant role in this phenotype. The associated loci show important overlap with resting QT, which may indicate that at least a part of the biological mechanisms underlying resting QT are also important in modulating QT interval during exercise and recovery. Finally, we found 15 variants for resting QT interval, which have not been previously reported. Two potential novel candidate genes were *SERCA1* and *PKP2*. *SERCA1* is involved in the re-sequestration of Ca2+ into the sarcoplasmic reticulum[5] and may therefore affect the calcium handling and the repolarisation duration. *PKP2* encodes Plakophilin 2 and mutations in this gene have been associated arrhythmogenic cardiomyopathy[6]. This process may also affect cardiac conduction

and ventricular repolarisation.

In summary, our findings indicate that QT dynamics is not associated with CV events in a general population. The genetic architecture underlying QT dynamics shows important overlap with resting QT. Finally, new biological findings for resting QT interval improve the current understanding of the biological functions underlying myocardial repolarisation.



		QT dynamics GWAS	Resting QT GWAS
Locus	SNV	*P*	*P*
CDKN1A	rs1321311	1.60E-13	5.50E-04
KIAA1755	rs6069151	3.30E-08	2.00E-03
LOC643623	rs35846768	2.50E-11	1.00E-03

Figure 2 *Genetic overlap between QT dynamics and resting QT loci. Three lead variants for QT dynamics during exercise were not genome-wide significant for resting QT, but their p-value was still lower than 0.05.*

References

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