Queen Mary University of London

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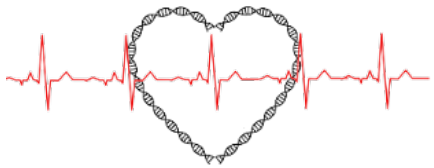
Electrogenomics Group



UCL

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

Stefan van Duijvenboden, Julia Ramírez, Michele Orini, Andrew Tinker, Pier D Lambiase, Patricia B Munroe

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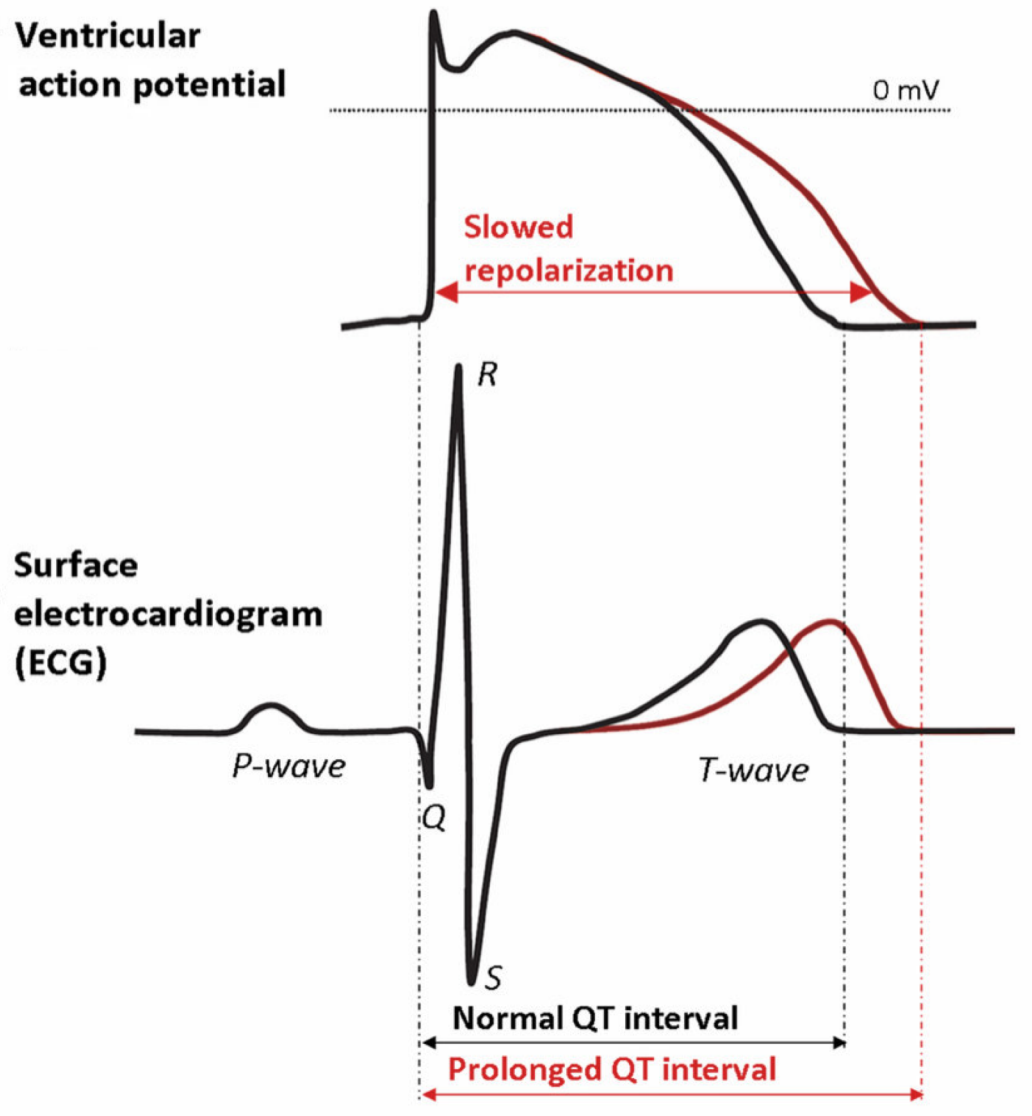
Ventricular repolarisation

- Represents a crucial stage in electrical cardiac activity
- The QT interval from the ECG reflects cardiac repolarisation
- Marked prolongation can be pro-arrhythmic and is associated with CV events

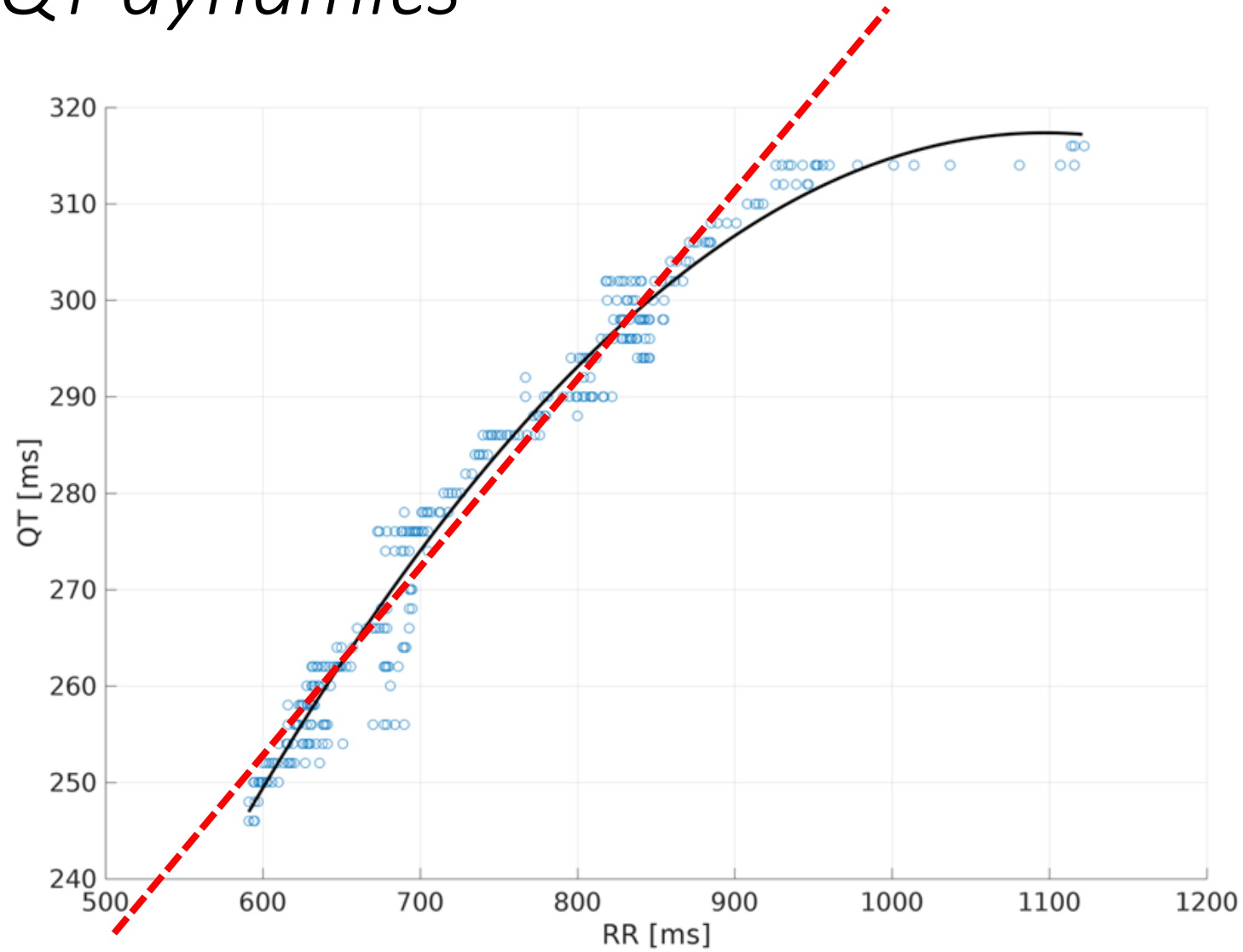


Resting QT interval is genetically influenced

- Pathological prolongation of the QT interval can occur as part of (rare) monogenic Mendelian hereditary syndromes
- Estimated heritability in general population: ~25%
- Research has been focussed on identifying common genetic variants underlying QT interval variation
- At present, 52 loci identified collectively explaining ~10% of heritability, ~15% remaining genetically elusive

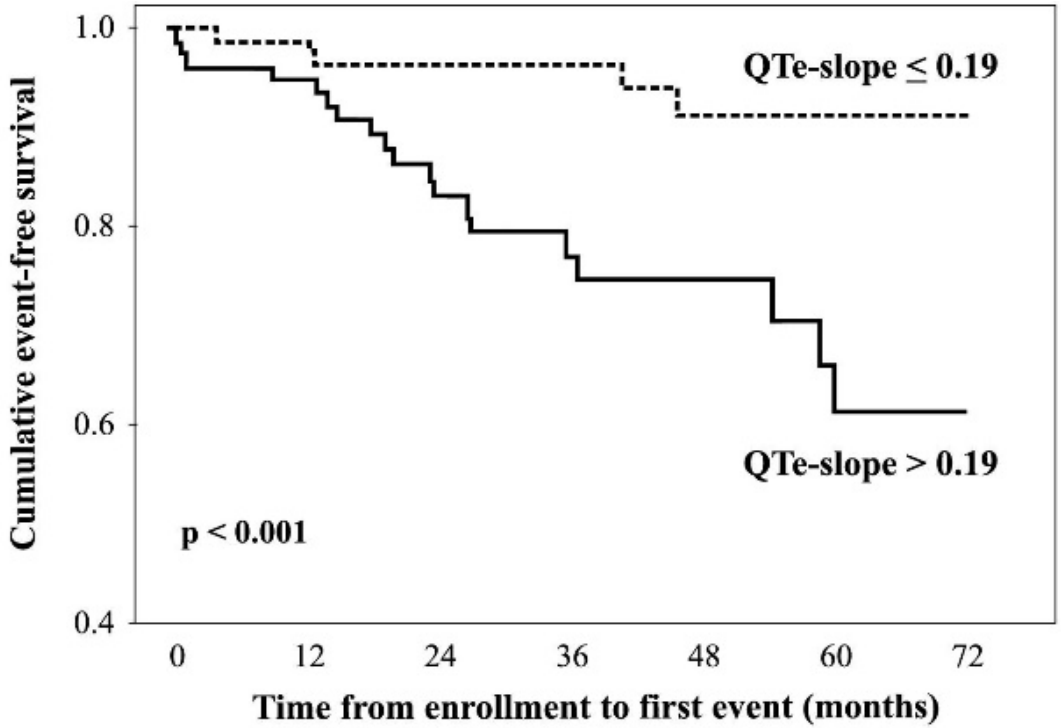
QT adaptation to changing heart rate: *QT dynamics*

- QT interval is **not** static but varies with heart rate and autonomic nervous activity
- The slope of the QT/RR profile indicates how QT adapts to heart rate
- Steeply sloped curves can create unstable wave propagation that results in wave break and fibrillation



Prognostic value of QT dynamics

- Multiple studies claim that increased QT dynamics is associated with poor prognosis in cardiac patients
- Prognostic value in general population?
- Genetic contribution?



No. at risk							
QTe slope ≤ 0.19	86	80	64	45	25	16	9
QTe slope > 0.19	93	81	58	38	25	15	10

Ventricular Repolarization Dynamicity Provides Independent Prognostic Information Toward Major Arrhythmic Events in Patients With Idiopathic Dilated Cardiomyopathy, Iacoviello et al., JACC, 2007

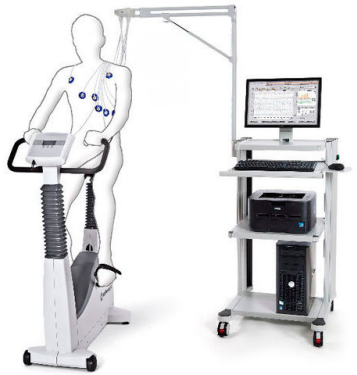
Research Objectives

1. Evaluate the prognostic value of QT dynamics for CV hospitalisation or death in general population

2. Identify the genetic basis of QT dynamics and its overlap with resting QT interval

3. Expand current knowledge on the genetic basis and biology of QT interval and assess the genetic risk on CV risk and QT interval

Workflow



Survival analysis
(N = 51,119)

Full UKB dataset
(N = 502,536)

Specific exclusion for survival analyses and missing values
N = (2,622)

Exercise ECG data
(N = 79,772)

ECG analysis

QT dynamics

exercise
N = **51,884**

recovery
N = **51,503**

Resting QT interval
N = **52,107**

QT dynamics GWAS

Resting QT GWAS

- failed genetic QC
- phenotypic exclusion
- non-European ancestry

QT interval–prolonging alleles

Genetic Risk Score analyses

CV outcome
(N = **374,332**)

QT interval
(N = **20,211**)

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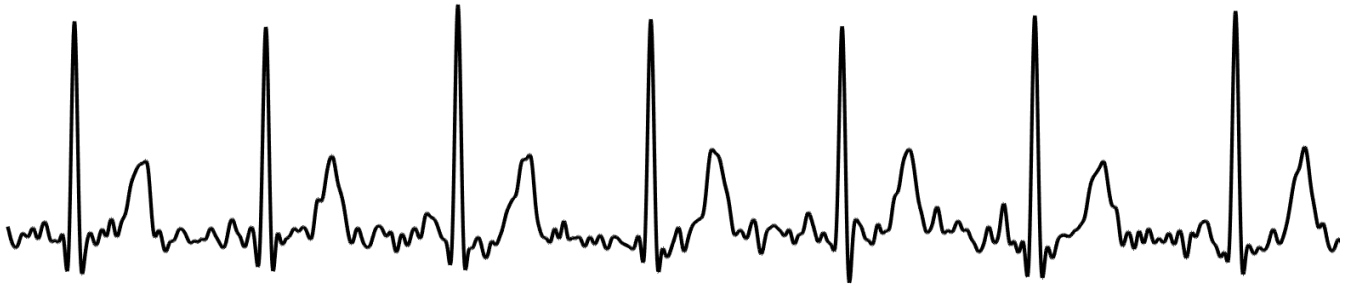
ECG analysis

Pre-processing

Quantification of the QT interval

Computation of QT dynamics



ECG analysis

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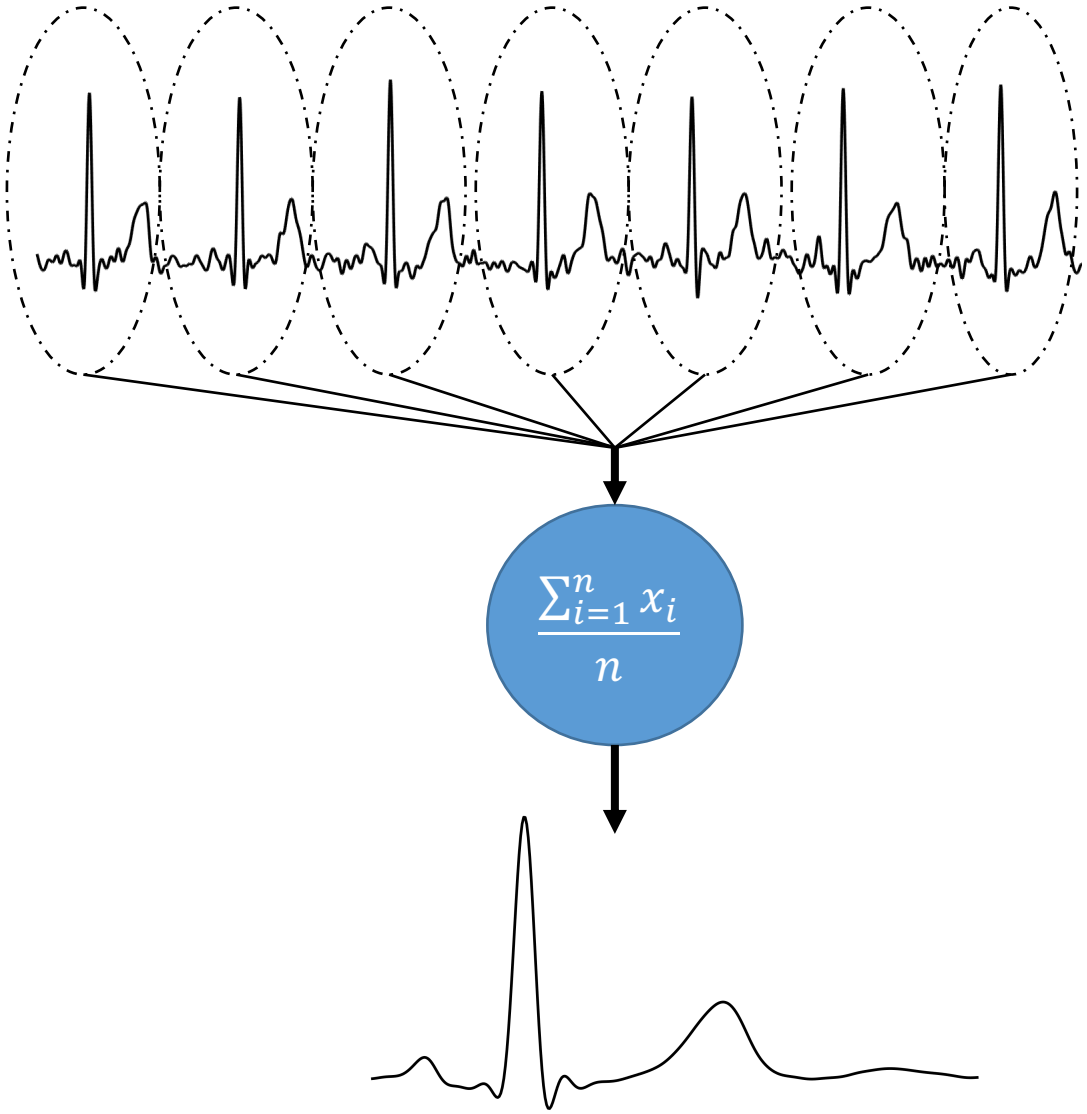


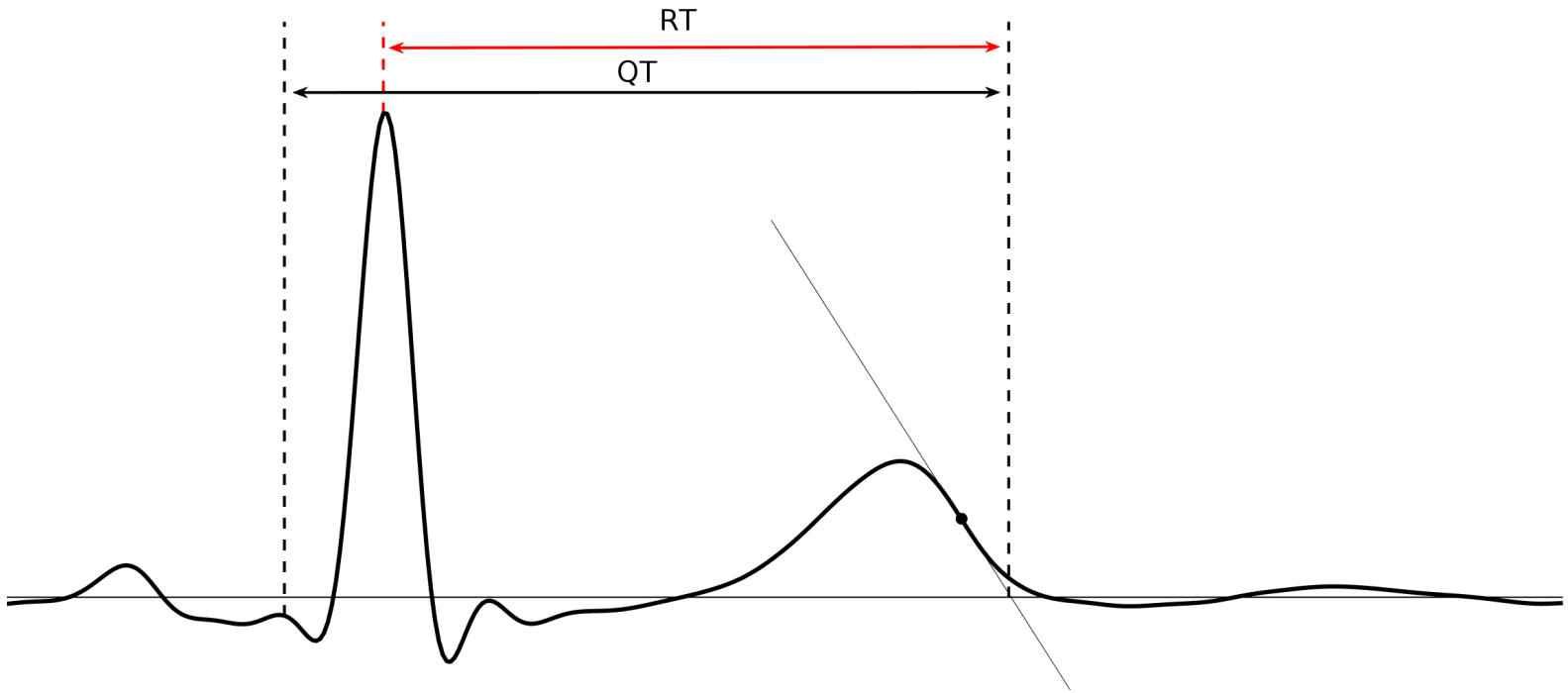
ECG analysis

Pre-processing

Quantification of the QT interval

Computation of QT dynamics

- QT dynamics was approximated by the interval between R-wave and T-wave end (RT interval)[1]



Porta, JACC 2014: 65, 367-74

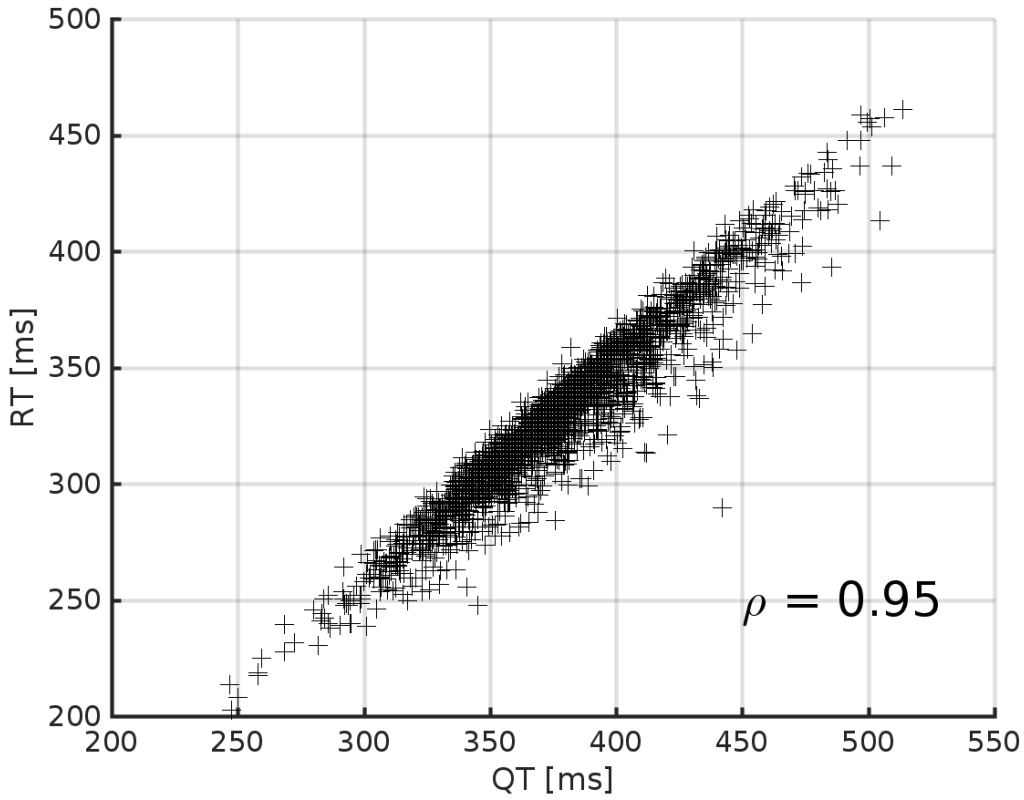
ECG analysis

Pre-processing

Quantification of the QT interval

Computation of QT dynamics

- Validation: QT interval vs. RT interval in resting ECG in high quality signals (SNR> 11.6 dB, N=2712)
- High correlation: RT interval was validated as surrogate

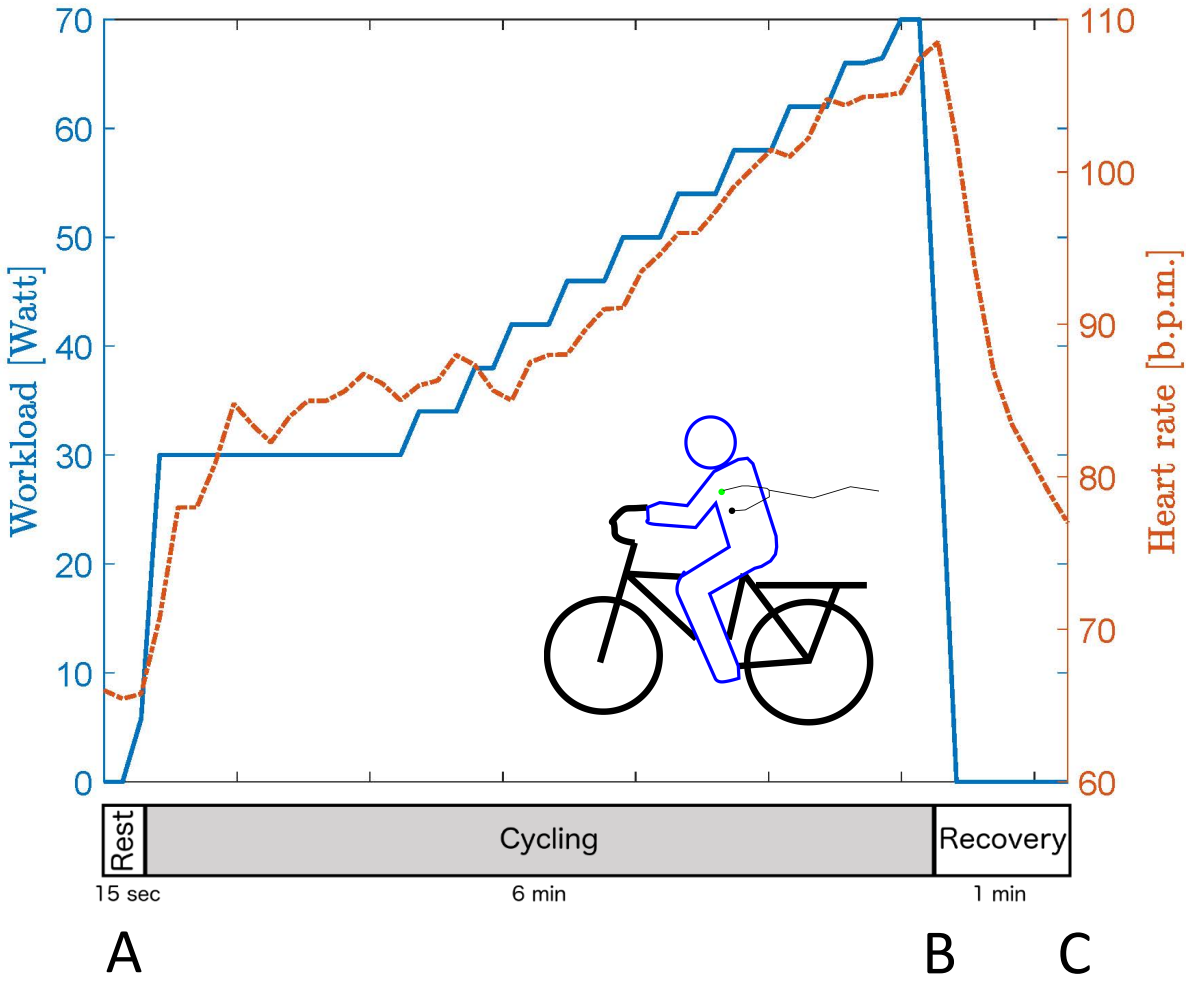


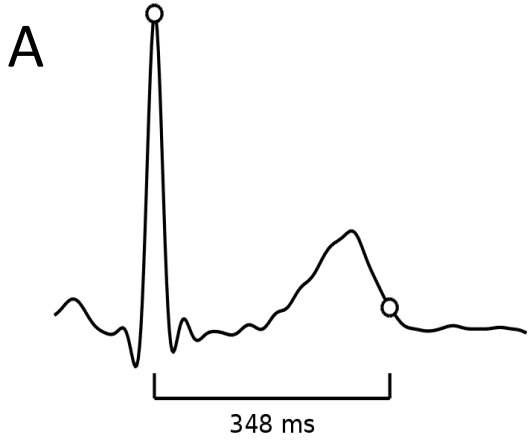
QT dynamics

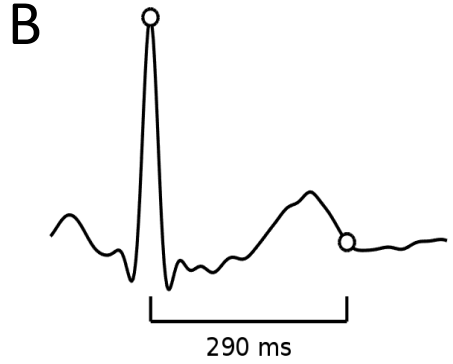
Pre-processing

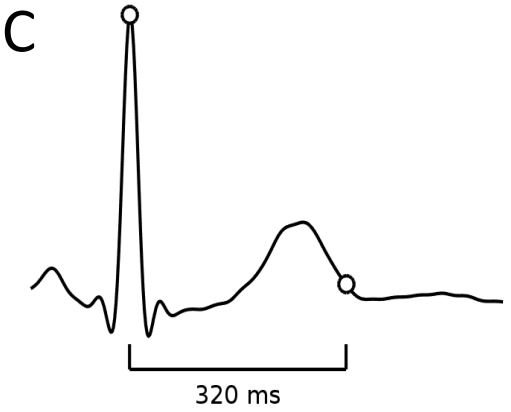
Quantification of the RT interval

Computation of QT dynamics







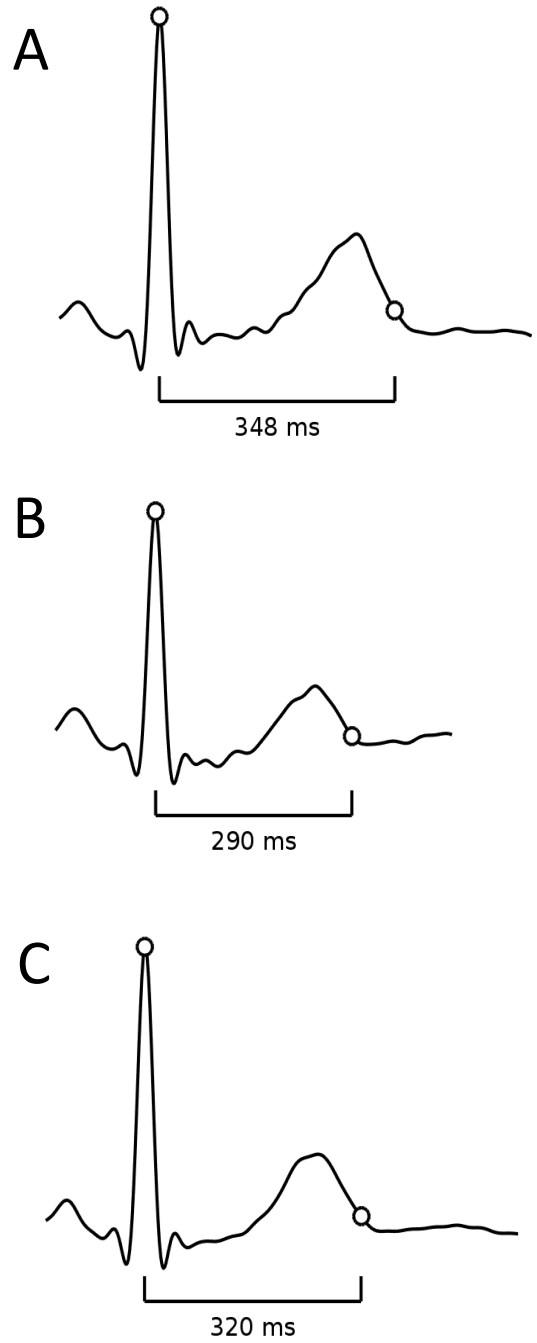


QT dynamics

Pre-processing

Quantification of the RT interval

Computation of QT dynamics

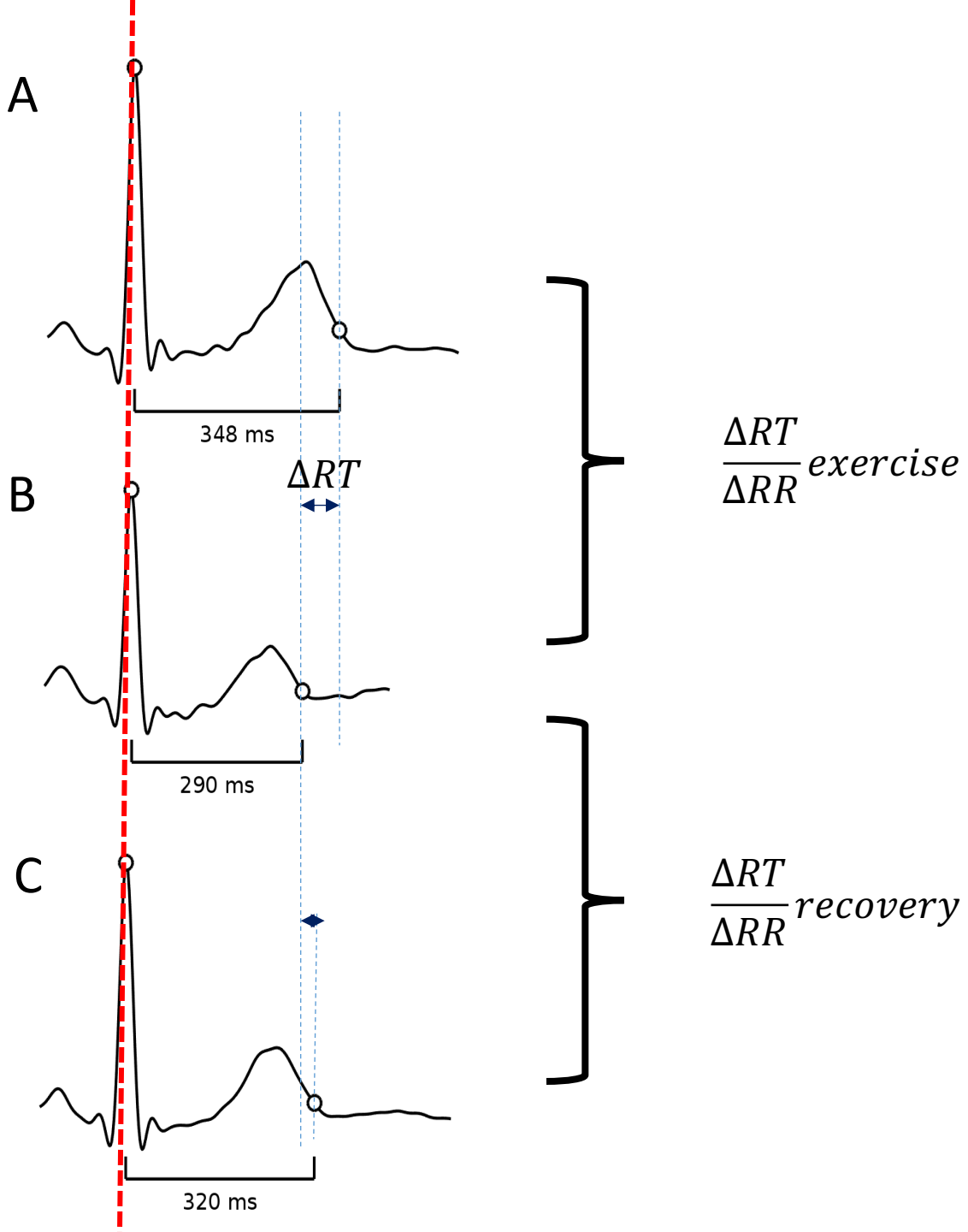


QT dynamics

Pre-processing

Quantification of the RT interval

Computation of QT dynamics



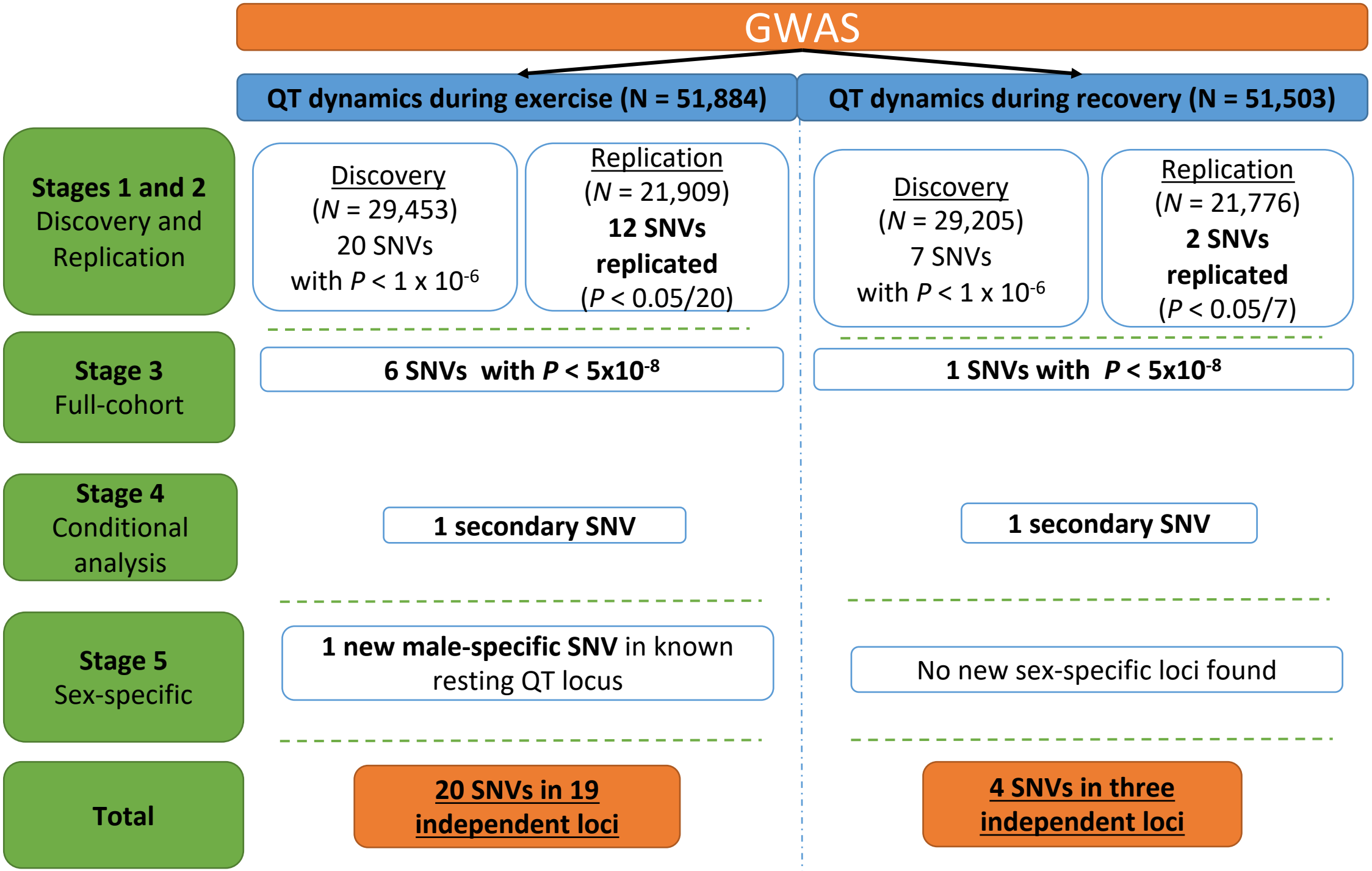
Predictive value of QT dynamics

Clinical Variables	Cardiovascular event		
	event (N=1,601)	**event free (N=48,492)**	p
age (yr)	63 (58 - 66)	58 (51 - 64)	**6.64E-96**
sex (% man)	1130 (71)	22417 (46)	**1.89E-86**
BMI	27.78 (25.2 - 30.9)	26.4 (23.95 - 29.28)	**2.49E-38**
Current smoker or history of smoking	841 (53)	21418 (44)	**4.48E-12**
Systolic blood pressure (mmHg)	143 (132 - 154)	136(124 - 148)	**2.52E-53**
Diastolic blood pressure (mmHg)	84 (77 - 90)	81 (74 - 88)	**5.68E-18**
ECG variables			
Resting RR interval (ms)	843 (752 - 947)	855 (768 - 950)	**1.03E-03**
RR decrease during exercise (ms)	286 (214 - 367)	312 (241 - 392)	**1.57E-17**
RR increase during recovery (ms)	156 (105 - 217)	176 (126 - 242)	**3.34E-23**
QT dynamics during exercise (ms)	0.17 (0.13 - 0.21)	0.17 (0.14 - 0.21)	8.45E-01
QT dynamics during recovery (ms)	0.11 (0.07 - 0.17)	0.11 (0.07 - 0.16)	7.36E-01
Resting QT interval (ms)	368 (348 - 388)	366 (348 - 385)	1.29E-01
Corrected QT interval (ms)	400 (383 - 417)	396 (381 - 411)	**9.56E-08**

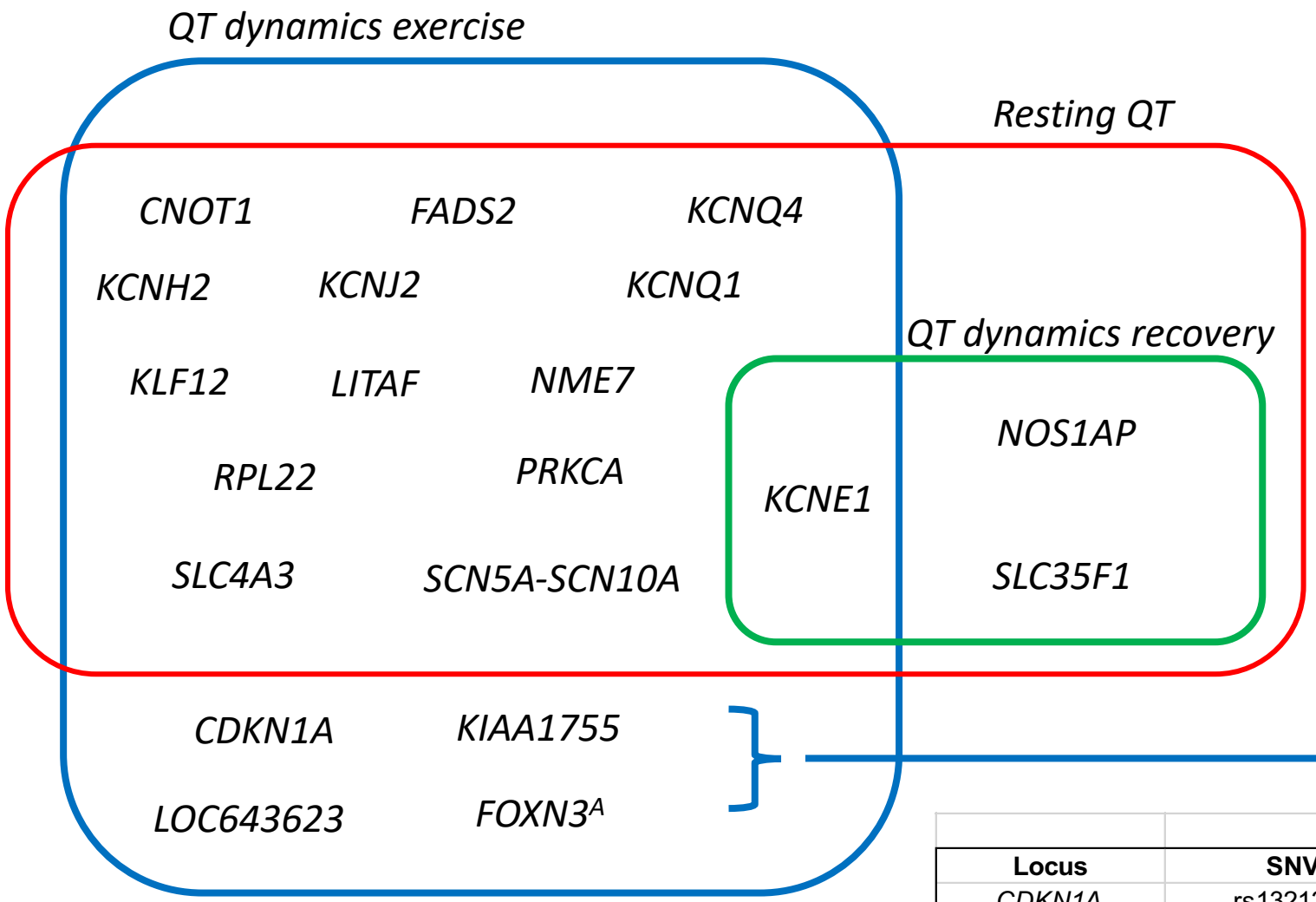
Part II: Genetic basis of QT dynamics

Heritability estimations

Trait	Heritability estimation
QT dynamics	
Exercise	10.7%
Recovery	5.4%
Resting QT	28.4%


GWAS
QT dynamics during exercise (N = 51,884)
QT dynamics during recovery (N = 51,503)
Stages 1 and 2
Discovery and Replication
Discovery
(N = 29,453)
20 SNVs
with P < 1 x 10-6
Replication
(N = 21,909)
12 SNVs replicated
(P < 0.05/20)
Discovery
(N = 29,205)
7 SNVs
with P < 1 x 10-6
Replication
(N = 21,776)
2 SNVs replicated
(P < 0.05/7)
Stage 3
Full-cohort
6 SNVs with P < 5x10-8
1 SNVs with P < 5x10-8
Stage 4
Conditional analysis
1 secondary SNV
1 secondary SNV
Stage 5
Sex-specific
1 new male-specific SNV in known resting QT locus
No new sex-specific loci found
Total
20 SNVs in 19 independent loci
4 SNVs in three independent loci

Genetic overlap between QT dynamics and resting QT



P < 0.05 for all variants in resting QT GWAS

		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**
FOXN3[A]	rs796647867	**2.90E-08**	**1.00E-02**

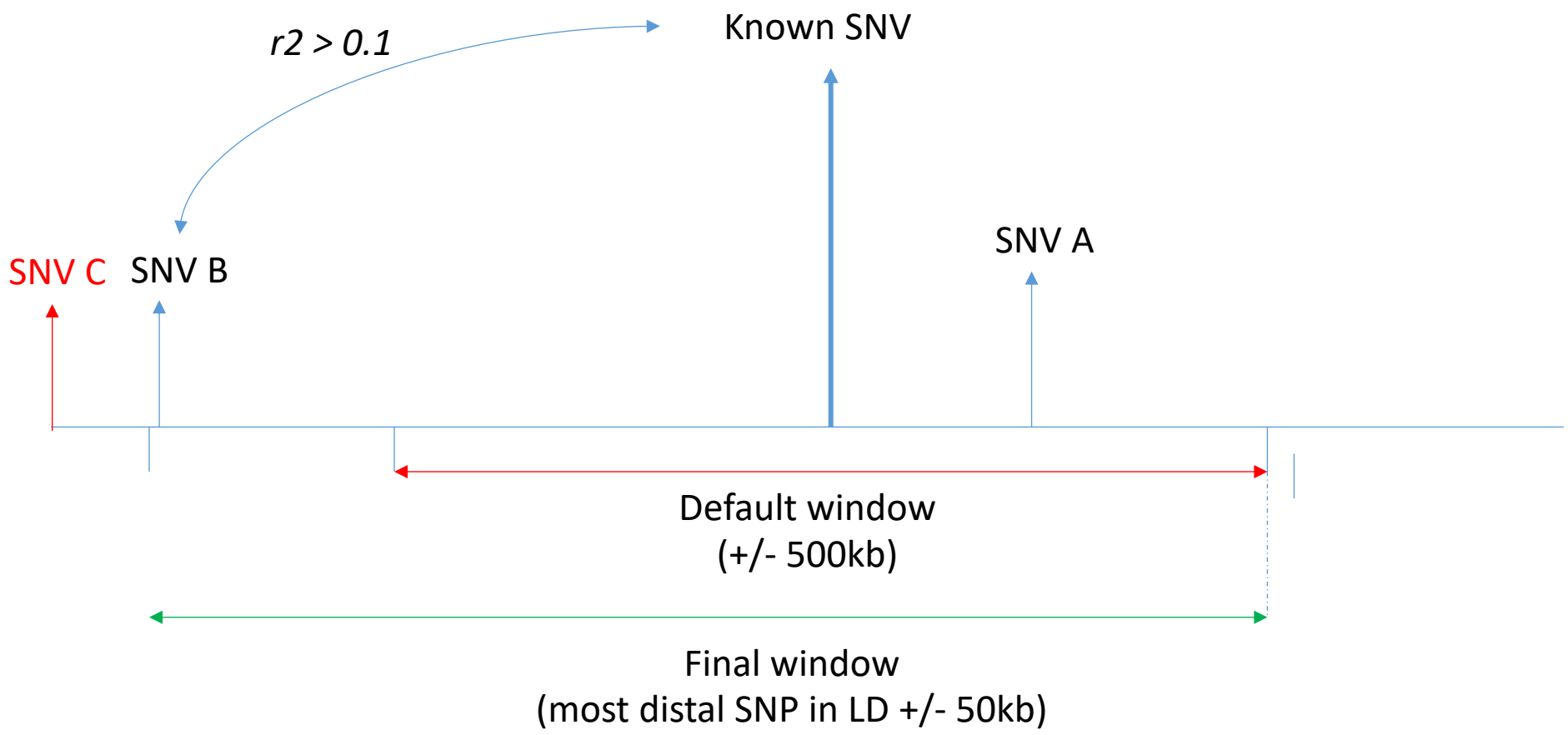
Discussion: QT dynamics

- First study to systematically investigate the prognostic value and genetic basis of QT dynamics
- No support for CV risk prediction in general population
- Significant genetic overlap with resting QT, indicating significant overlap in biology

- Prognostic value in patients possible driven by secondary effects e.g. reduced cardiac muscle perfusion or scar tissue rather than reflecting an inherited problem

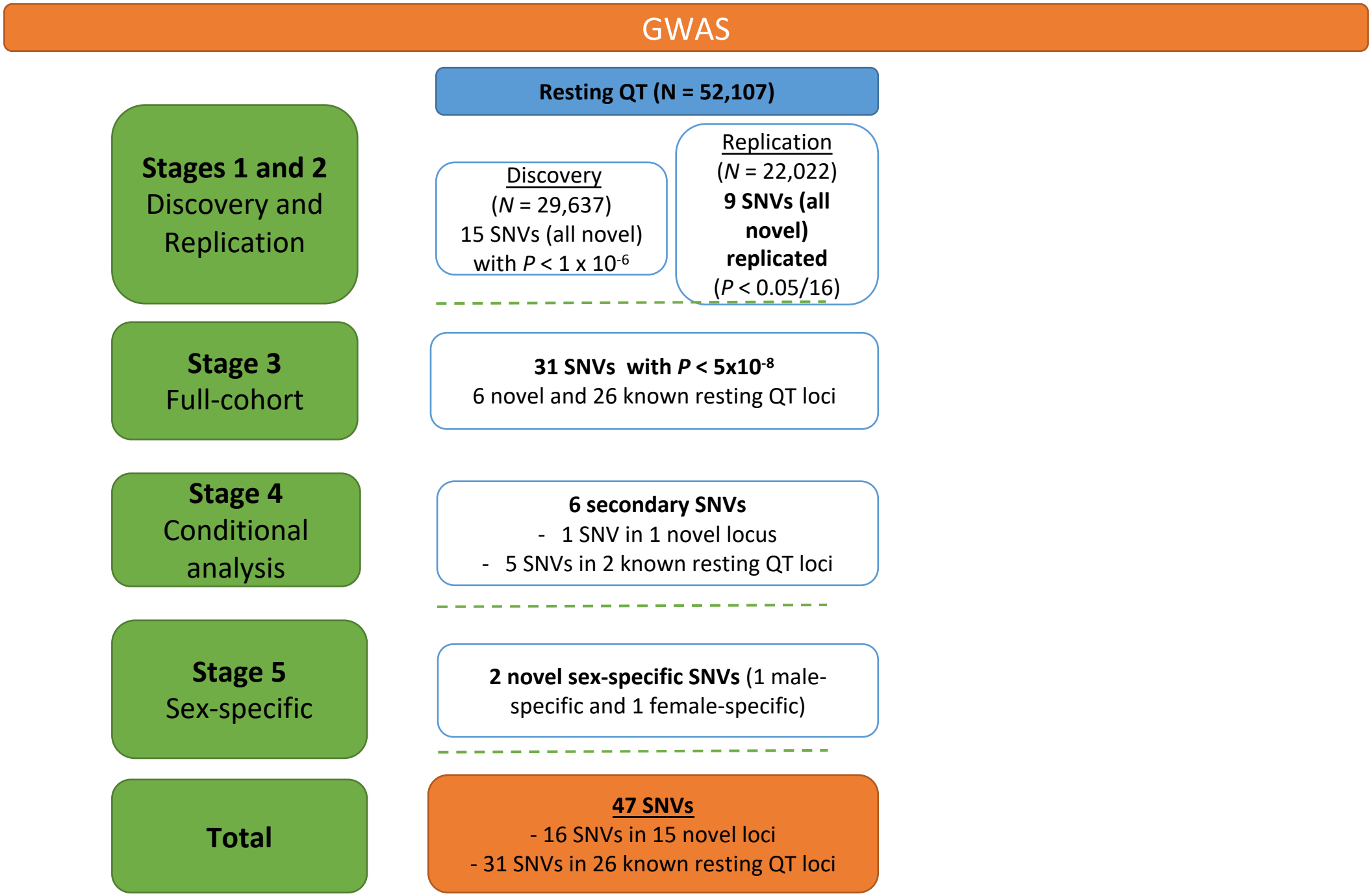
Part III: Novel variants for resting QT

Definition of new loci



Gene prioritisation methods

- Examined support for mediation of eQTLs in 53 tissues in the GTEx database
- Data-driven Expression-Prioritised Integration for Complex Traits (DEPICT)
- long-range chromatin interaction (Hi–C) data from adrenal, heart, and neural tissues


GWAS
Resting QT (N = 52,107)
Stages 1 and 2
Discovery and Replication
Discovery
(N = 29,637)
15 SNVs (all novel)
with P < 1 x 10-6
Replication
(N = 22,022)
9 SNVs (all novel) replicated
(P < 0.05/16)
Stage 3
Full-cohort
31 SNVs with P < 5x10-8
6 novel and 26 known resting QT loci
Stage 4
Conditional analysis
6 secondary SNVs
- 1 SNV in 1 novel locus
- 5 SNVs in 2 known resting QT loci
Stage 5
Sex-specific
2 novel sex-specific SNVs (1 male-specific and 1 female-specific)
Total
47 SNVs
- 16 SNVs in 15 novel loci
- 31 SNVs in 26 known resting QT loci

Gene prioritisation results

locus	SNP	CHR	BP	Trait	Candidate Genes within 5kb	DEPICT	eQTL	Hi-C interactor Genes	Candidate Gene(s) at locus
Novel									
KCNQ4	rs116015634	1	41250961	Resting QT/ QT dynamics exercise	KCNQ4	KCNQ4			KCNQ4
TMEM44	rs1706003	3	194299967	Resting QT			ATP13A3		ATP13A3
RASGRF2	rs10063881	5	80278715	Resting QT	RASGRF2				RASGRF2
SLC27A6	5:128147544_CCTTCCTTCCTTTC	5	128147544	Resting QT		SLC27A6			SLC27A6
WNT8A	rs34750263	5	137434172	Resting QT		NPY6R; MYOT; KLHL3; FAM13B			
NKX2-5	rs35564079	5	172670611	Resting QT		NKX2-5			NKX2-5
BVES†	rs144483936	6	105585017	Resting QT	BVES;BVES-AS1	POPDC3; BVES	BVES		BVES
PREP	rs2793409	6	105710719	Resting QT	PREP				PREP
ZFPM2	rs72671655	8	106347897	Resting QT	ZFPM2				ZFPM2
PKP2	rs11052242	12	32950367	Resting QT	PKP2	PKP2			PKP2
ARID2	rs78341918	12	46199798	Resting QT	ARID2				ARID2
ZNF592	rs8023658	15	85323220	Resting QT	LOC642423;ZNF592	ALPK3			LOC642423;ZNF592
ATP2A1	rs9933198	16	28888409	Resting QT	ATP2A1-AS1;SH2B1;ATP2A1	ATP2A1			ATP2A1-AS1;ATP2A1
NDRG4	rs56336338	17	27645258	Resting QT					NDRG4
YPEL2	rs142166837	17	57471022	Resting QT	YPEL2			VEZF1; YPEL2	VEZF1; YPEL2
LINC00189	rs2832274	21	30600189	Resting QT	LINC00189				LINC00189

Potential candidate genes for resting QT

NDRG4 (chr 17)

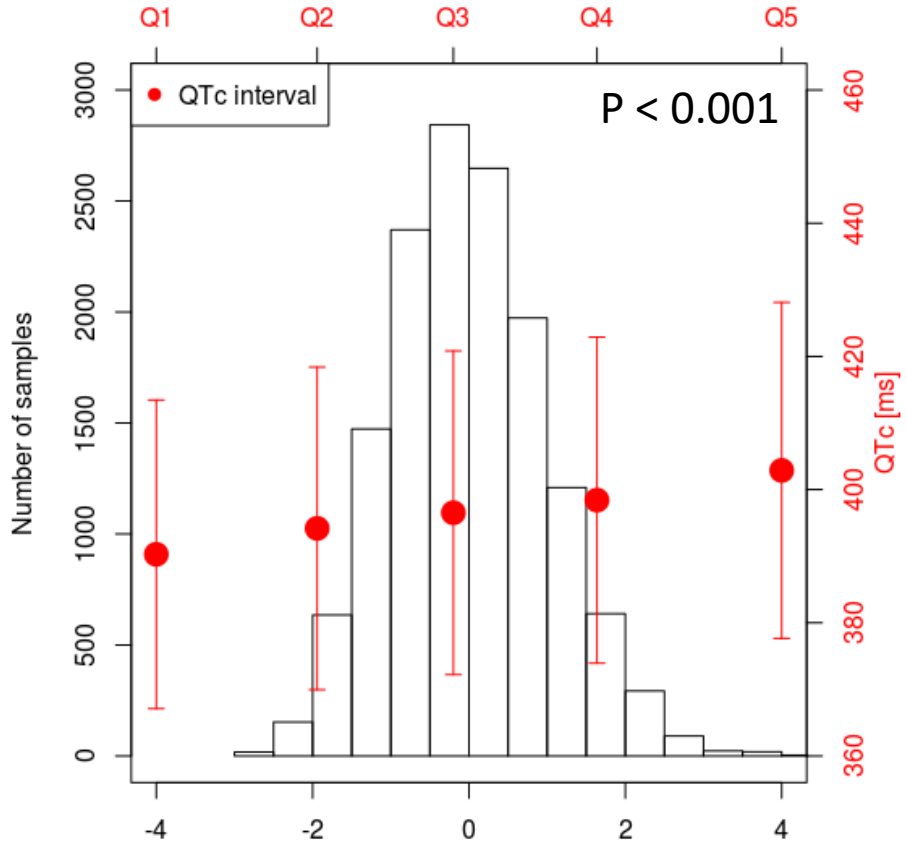
- Expression is detected specifically in the brain and heart
- Affects regulation of brain-derived neurotrophic factors that play a critical role in synaptic connectivity in the central nervous system

PKP2 (chr 12)

- Encodes Plakophilin 2
- Mutations have been associated arrhythmogenic cardiomyopathy
- Lack of *PKP2* in adult mouse hearts can cause arrhythmia in the absence of structural abnormalities: either due to conduction or repolarisation disorders

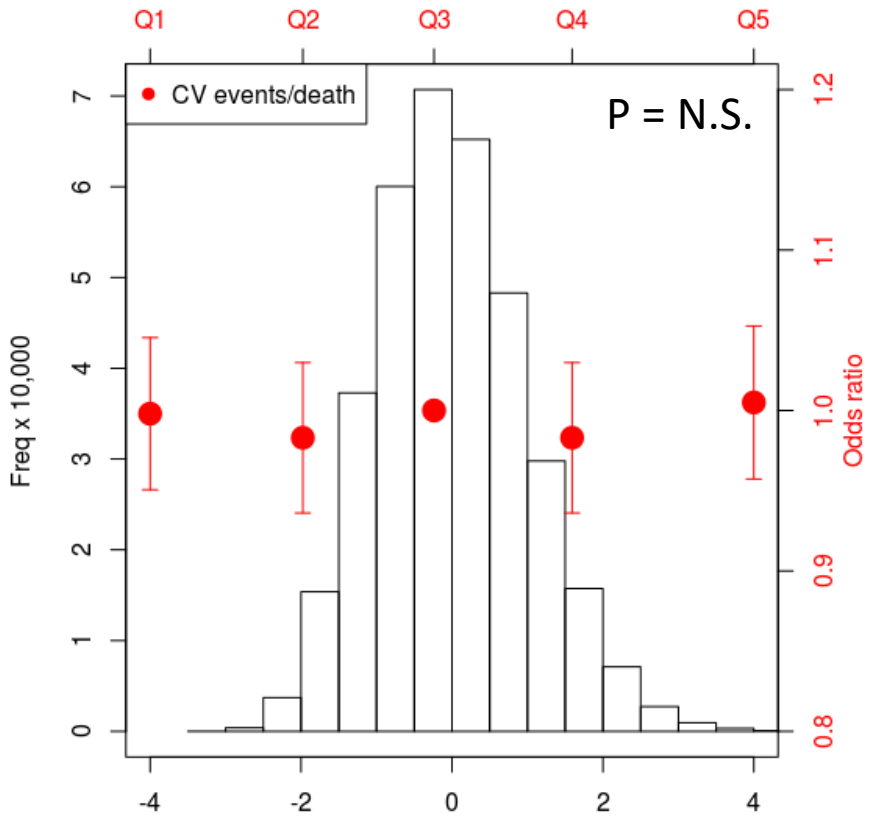
Genetic risk score analyses

QT interval



2.94 ± 0.14 ms (P < 0.001) increase in the mean QTc interval for each increase in quintile

CV events: 18,732 (5.2%)



Not significant

Discussion: Resting QT

- Largest single cohort study (N ~ 52k) for resting QT: 15 novel loci associated with resting QT interval, including 2 sex specific loci

- QT prolonging alleles did modulate QT but not CV risk: combination of low-risk population with relatively low variation in QT interval, hence not enough power to detect CV events

- Pathway analyses suggest a role for genes involved in Ca2+ cycling and genes that harbour mutations in life-threatening arrhythmogenic cardiomyopathy.

Electrogenomics Group

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Dr Julia Ramírez
Prof Andrew Tinker
Prof Patricia Munroe

UCL

Prof Pier D. Lambiase
Dr Michele Orini

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