SUPPLEMENTAL DATA

I. SUPPLEMENTAL METHODS

Ia. Data collection and end-point definition

Postoperative ventricular arrhythmias were defined as new onset sustained ventricular tachycardia (lasting ≥30 s or requiring cardioversion) or ventricular fibrillation. The Duke Clinical Research Institute Follow-up Services Group conducted long-term follow-up, by collecting annual information on death and non-fatal events for the Duke Databank for Cardiovascular Disease.[1] Patients are surveyed by means of a mailed, self-administered questionnaire, with non-responders surveyed by telephone. Information on death is collected through next-of-kin interviews, reviews of hospital discharge summaries and death certificates, supplemented by annual queries of the National Death Index for patients lost to follow-up (2%) or withdrawn (3%).

QT interval duration was recorded in leads II and V_4 for 3 consecutive beats from the start of the QRS complex to the end of the T wave, which was the visual return of the T wave to the isoelectric line. Where a U wave followed the T wave, the end of the T wave was defined as the nadir between the T and U waves. When it was not possible to clearly identify the T wave, the lead was excluded from further analysis.[2]

Ib. Candidate gene and polymorphism selection

Using the SeattleSNPs Variation Discovery Resource (http://pga.gs.washington.edu/), we selected 45 single nucleotide polymorphisms (SNP) within these candidate genes, with an emphasis on common (minor allele frequency >5%) variants functionally relevant to the physiological disturbances underlying arrhythmia susceptibility, based on preliminary functional characterization of variant proteins in vitro, in genetically modified animals, or computer simulations, as well as previous genetic epidemiological analyses. A list of the candidate genes and polymorphisms studied is provided in **Table S1**. Additionally, an external reference panel of 54 ancestry-informative unlinked markers was used to assess and control for population structure, as previously described (see **Ie** and **Table S3**).[3]

Supplemental Table 1. Candidate genes and polymorphisms evaluated in the study*

Pathway	Chr	SNP	BP	Gene
Ion channels	3	rs1805124	38645420	*SCN5A* (Na channel, Long QT)
	11	rs1057128	2797237	*KCNQ1* (K channel, voltage-gated IKs)
Adrenergic tone	10	rs1801253	115805056	*ADRB1* (beta-1 adrenergic receptor)
	10	rs1801252	115804036	
	5	rs1042711	148206348	*ADRB2* (beta-2 adrenergic receptor)
	5	rs1042713	148206440	
	5	rs1042714	148206473	
	5	rs1800888	148206885	
	8	rs4994	37823798	*ADRB3* (beta-3 adrenergic receptor)
	12	rs5443	6954875	*GNB3* (G-protein beta-3 subunit)
	10	rs2072362	119014023	*VMAT2* (SLC18A2-vesicular amine transporter 2)
	22	rs165688	19951271	*COMT* (catecholamine-O-methyl transferase)
Tissue/matrix remodeling	1	rs4762	230845977	*AGT* (Angiotensinogen)
	1	rs699	230845794	
	1	rs5051	230849872	
	17	rs4646994	61565904	*ACE* (Angiotensin Converting Enzyme)
	17	rs4344	61566724	
	17	rs4291	61554194	
	3	rs5186	148459988	*AGTR1* (Ag receptor 1)
	11	rs3025058	102715948	*MMP3* (Matrix metalloproteinase 3)
	20	rs3918242	44635976	*MMP9* (Matrix metalloproteinase 9)
Inflammation	6	rs1800629	31543031	*TNFA* (Tumor Necrosis Factor alpha)
	6	rs361525	31543101	
	6	rs1800610	31543827	
	1	rs1061622	12252955	*TNFRSF1B* (Tumor necrosis factor receptor superfamily member 1B)
	2	rs17561	113537223	*IL1A* (Interleukin-1 alpha)
	2	rs1800587	113542960	
	2	rs1143633	113590467	*IL1B* (Interleukin-1 beta)
	2	rs16944	113594867	
	2	rs315952	113890304	*IL1RN* (Interleukin receptor-1 receptor antagonist)
	2	rs419598	113887207	
	7	rs1800795	22766645	*IL6* (Interleukin-6)
	7	rs1800796	22766246	
	1	rs1800871	206946634	*IL10* (Interleukin-10)
	1	rs1205	159682233	*CRP* (C-reactive protein)
	19	rs1800468	41860587	*TGFB1* (Transforming growth factor beta-1)
	19	rs1800469	41860296	
	19	rs1800471	41858876	
	19	rs1800470	41858921	
	19	rs1800472	41847860	
Oxidative stress	7	rs2070744	150690079	*NOS3* (endothelial nitric oxide synthase)
	7	rs1799983	150696111	
	7	rs1799985	150709570	
	11	rs769214	34459717	*CAT* (catalase)
	11	rs1001179	34460231	

Chr, chromosome; SNP, single nucleotide polymorphism; BP, base pair position

*Based on Entrez SNP (http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed)

Ic. Genotyping and quality controls

Blood was collected immediately before surgery. Genomic DNA extraction was performed using the Puregene system (Gentra Systems, Minneapolis, MN), quantified via PicoGreen fluorescence enhancement (Molecular Probes, Eugene, OR), and stored at -80°C. Genotyping was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on a Sequenom™ MassARRAY system (Sequenom, San Diego, CA) at a core facility (Agencourt Bioscience Corporation Beverly, MA).[4] Primers used and polymorphisms details can be found in **Table S2**. SpectroTyper 3.1 software (Sequenom, San Diego, CA) was used for raw data analysis, with spectra and cluster plots checked by visual inspection of intensity plots and manual curation of genotype calls. A SNP call rate threshold of >85% was imposed on all variants genotyped. Genotyping accuracy of the Sequenom MassARRAY system was estimated at 99.6%.[5] Reproducibility of genotyping was validated in our cohort at >99% by scoring a panel of 6 SNPs in 100 randomly selected patients using ABI 3700 capillary sequencer (Applied Biosystems, Foster City, CA). Hardy-Weinberg equilibrium (HWE) was evaluated in controls using an exact test.[6] Eight SNPs were found to deviate from HWE ($P < 0.001$, based on Bonferroni corrected threshold of 45 markers) and were excluded from subsequent analyses.

Table S2. MALDI-TOF Genotyping Assay Primers

SNPid*	P2	P1	UEP
rs4344	ACGTTGGATGACAATGTTGTGATGGGTGCC	ACGTTGGATGATCTATGTCGGGCAAGTCAC	CAAGATTATTAACTTCTTCCCC
rs4291	ACGTTGGATGGCAGAGGAAGCTGGAGAAAG	ACGTTGGATGTCGGGTGTTCCGGCAAACTG	CTGGAGAAAGGGCCTCCTCTCTTT
rs1801253	ACGTTGGATGATCATCTACTGCCGCAGCCC	ACGTTGGATGTCTCCGTGGGTCGCGTGGC	CGACTTCCGCAAGGCCTTCCAG
rs1801252	ACGTTGGATGCTCGTTGCTGCCTCCCGCC	ACGTTGGATGATGAGCGCCATCAGCAGACC	CTGCCTCCCGCCAGCGAA
rs1042711	ACGTTGGATGAATGAGGCTTCCAGGCGTCC	ACGTTGGATGTCTGGCAGGTAAGCGCACTG	CCCGCCGTGGGTCCGCC
rs1042713	ACGTTGGATGAACGGCAGCGCCTTCTTGCT	ACGTTGGATGCACACCTCGTCCCTTTGCTG	CGCCTTCTTGCTGGCACCCAAT
rs1042714	ACGTTGGATGAGACATGACGATGCCCATGC	ACGTTGGATGTTGCTGGCACCCAATGGAAG	ACCCACACCTCGTCCCTTT
rs1800888	ACGTTGGATGAGTGCATCTGAATGGGCAAG	ACGTTGGATGTGCTGACCAAGAATAAGGCC	CATCTGAATGGGCAAGAAGGAG
rs4994	ACGTTGGATGGAGGCAACCTGCTGGTCATC	ACGTTGGATGGCGAAGTCACGAACACGTTG	CTGGTCATCGTGGCCATCGCC
rs699	ACGTTGGATGTGTGACAGGATGGAAGACTG	ACGTTGGATGGTGGACGTAGGTGTTGAAAG	AAGACTGGCTGCTCCCTGA
rs5051	ACGTTGGATGTACCTTCTGCTGTAGTACCC	ACGTTGGATGCCCCTCAGCTATAAATAGGG	AACAACGGCAGCTTCTTCCCC
rs4762	ACGTTGGATGACAAACGGCTGCTTCAGGTG	ACGTTGGATGTGTACAGGGCCTGCTAGTGG	CTGTGAACACGCCCACCACC
rs5186	ACGTTGGATGATTCCTCTGCAGCACTTCAC	ACGTTGGATGCGGTTCAGTCCACATAATGC	GCACTTCACTACCAAATGAGC
rs17880664	ACGTTGGATGACCCTCAGCAGGCAAATCTG	ACGTTGGATGCTGATTGGCTGAGCCTGAAG	ATCTGCCTGTTGCCCCGAG
rs1001179	ACGTTGGATGAGGATGCTGATAACCGGGAG	ACGTTGGATGTCTGGCCCAGCAATTGGAGAG	CGCCCTGGGTTCGGCTAT
rs165688	ACGTTGGATGACCCAGCGGATGGTGGATTTC	ACGTTGGATGGCCCTTTTTCCAGGTCTGAC	GATGGTGGATTTCGCTGGC
rs1205	ACGTTGGATGGCCATCTTGTTTGCCACATG	ACGTTGGATGGTTTGTCAATCCCTTGGCTC	TTGTTTGCCACATGGAGAGAGACT
rs5443	ACGTTGGATGTCTCCCACGAGAGCATCATC	ACGTTGGATGTCGTAGCCAGCGAATAGTAG	ATCATCTGCGGCATCACGTC
rs1800587	ACGTTGGATGTTGGGAGAAAGGAAGGCATG	ACGTTGGATGTTCTACCACCTGAACTAGGC	TTTTTACATATGAGCCTTCAATG
rs17561	ACGTTGGATGTTTCACATTGCTCAGGAAGC	ACGTTGGATGATCTGCACTTGTGATCATGG	GCTCAGGAAGCTAAAAGGTG
rs16944	ACGTTGGATGATTTTCTCCTCAGAGGCTCC	ACGTTGGATGTGTCTGTATTGAGGGTGTGG	TGCAATTGACAGAGAGCTCC
rs1143633	ACGTTGGATGTGACCGTATATGCTCAGGTG	ACGTTGGATGTAAAATCAGAAGGGCAGGCC	CCTCCAAGAAATCAAATTTTGCC
rs315952	ACGTTGGATGGAACAGAAAGCAGGACAAGC	ACGTTGGATGAGGCGGCAGACTCAAAACTG	CGCCTTCATCCGCTCAGACAG
rs419598	ACGTTGGATGTGGGATGTTAACCAGAAGAC	ACGTTGGATGAATTGACATTTGGTCCTTGC	CTGAGGAACAACCAACTAGTTGC
rs1800795	ACGTTGGATGAGCCTCAATGACGACCTAAG	ACGTTGGATGGATTGTGCAATGTGACGTCC	TTTCCCCCTAGTTGTGTCTTGC
rs1800796	ACGTTGGATGACGCCTTGAAGTAACTGCAC	ACGTTGGATGTCTTCTGTGTTCTGGCTCTC	CAGGCAGTCTACAACAGCC
rs1800871	ACGTTGGATGTAGTGAGCAAACTGAGGCAC	ACGTTGGATGATTCTCAGTTGGCACTGGTG	GCAAACTGAGGCACAGAGAT
rs1057128	ACGTTGGATGAAGAAATTCCAGCAAGCGCG	ACGTTGGATGATGCGCACCATGAGGTTGAG	GACGTCATTGAGCAGTACTC
rs3025058	ACGTTGGATGGTCCTCATATCAATGTGGCC	ACGTTGGATGCTATGGTTCTCCATTCCTTTG	GGACAAGACATGGTTTTT
rs3918242	ACGTTGGATGAAAAATTTAGCCAGGCGTGG	ACGTTGGATGGGTTCAAGCAATTCTCCTGC	CCAGGCGTGGTGGCGCA
rs1799983	ACGTTGGATGAAACGGTCGCTTCGACGTGC	ACGTTGGATGATCCCTTTGGTGCTCACGTG	GCTGCAGGCCCCAGATGA
rs1799985	ACGTTGGATGAGCGGCTGCATGACATTGAG	ACGTTGGATGGTCCCTAGATTGTGTGACTC	TGAGAGCAAAGGTGAGGCTG
rs2070744	ACGTTGGATGAGTTTCCCTAGTCCCCCATG	ACGTTGGATGAGTCAGCAGAGAGACTAGGG	CATCAAGCTCTTCCCTGGC
rs1805124	ACGTTGGATGGGGCCAGGGCACCAGCAGT	ACGTTGGATGACAGCGCGGGAGAGCGAGA	GGGCACCAGCAGTGATGTG
rs1800468	ACGTTGGATGTTGACCACTGTGCCATCCTC	ACGTTGGATGTGGAGTGCTGAGGGACTCTG	GTCCGGGGTGTGGATGGTGGTGA
rs1800469	ACGTTGGATGTCTTACAGGTGTCTGCCTCC	ACGTTGGATGAGGGTGTCAGTGGGAGGAG	GCCTCCTGACCCTTCCATCC
rs1800471	ACGTTGGATGTGCTGTGGCTACTGGTGCTG	ACGTTGGATGCACCAGCTCCATGTCGATAG	GGTGCTGACGCCTGGCC
rs1800472	ACGTTGGATGACCATTCATGGCATGAACCG	ACGTTGGATGAGCAATAGTTGGTGTCCAGG	CCTTTCCTGCTTCTCATGGCCA
rs1800629	ACGTTGGATGGATTTGTGTGTAGGACCCTG	ACGTTGGATGGGTCCCCAAAAGAAATGGAG	ACCCTGGAGGCTGAACCCCGTCC
rs1800610	ACGTTGGATGGAAAGATGTGCGCTGATAGG	ACGTTGGATGCTTGCCACATCTCTTTCTGC	GGGAGGGATGGAGAGAAAAAAAC
rs361525	ACGTTGGATGACACAAATCAGTCAGTGGCC	ACGTTGGATGATCAAGGATACCCCTCACAC	GAAGACCCCCCTCGGAATC
rs2072362	ACGTTGGATGACGTCATGGGAATCGCCTTG	ACGTTGGATGAGGCCCCTCTTGCCAGTTTG	CTTAGGTGGGTAAGGCCCC

Id. Controlling for population stratification

We employed a modified EIGENSTRAT method to control for population stratification,[3, 7] using an external reference panel of 54 ancestry-informative unlinked markers **(Table S3).** This method derives the principal components (PCs) of correlations among gene variants and corrects for those correlations in the association tests. Using principal component analysis implemented in Eigensoft v5.0.1 (www.hsph.harvard.edu/alkes-price/software/),[3, 7] we modeled ancestry differences on both the categorical and continuous postoperative QTc traits. All 15 principal components (PCs) were independently computed for the binary and continuous postoperative QTc phenotypes. We then performed multivariate regression analyses with a strategy of keeping all PCs up to the last PC with $p<0.05$ in each step to determine the number of PCs to be used for correction in the final analysis. For instance, starting with 15 PCs in the model, if PC(i) is the last PC with $p<0.05$, we included PC(1) to PC(i) in the next multivariate model, and then repeat the process until the last PC remained nominally significant. Using this iterative multivariate analysis we selected the top 6 PCs for inclusion as covariates to adjust for ancestry, along with clinical variables, in multivariate logistic regression analysis of prolonged postoperative QTc (binary trait); similarly, the top 4 PCs were selected for models of the continuous postoperative QTc trait **(Table S4).**

Table S3. Unlinked SNP panel

dbSNP ID#	Position in Human Genome (HG6)	Cytogenetic Position	Mean MAF in Pooled Caucasians, Japanese, and African American Samples	MAF in PEGASUS samples
rs551585	86456981	1p31.2	0.093	0.062
rs1024059	61223356	1p32	0.094	0.138
rs1366733	5406765	2p25	0.320	0.268
rs1400239	86279645	3p12.3	0.110	0.014
rs916288	55949982	3p21.31	0.224	0.291
rs975302	27842485	3p24.3	0.336	0.476
rs1372727	150715756	3q23	0.077	0.065
rs1371569	180717779	3q26.1	0.025	0.026
rs707341		4p16.3	0.017	0.031
rs894533	87763683	4q23	0.075	0.090
rs1430935	121723954	4q26	0.264	0.277
rs1506806	186333138	4q34.3	0.314	0.224
rs974722	1806579	5p15.33	0.354	0.212
rs464513	83190873	5q13.3	0.392	0.389
rs1546911	43781989	6p12.3	0.043	0.017
rs1362189	8494	6p25.3	0.025	0.014
rs534355	103316931	6q16.1	0.374	0.371
rs1478811	128864928	6q22.31	0.391	0.433
rs1033917		6q25.1	0.250	0.409
rs940870	5582573	7p22.1	0.323	0.224
rs1548622	100060865	7q22.1	0.103	0.050
rs1547958	157291812	7q36.1	0.129	0.196
rs1466060	43242322	8p11.21	0.175	0.129
rs1391629	92111225	8p21.3	0.171	0.119
rs1365034	77900792	8q21.13	0.013	0.030
rs1600339		8q23.1	0.317	0.294
rs1506508	142291940	8q24.3	0.345	0.363
rs1417269	82500835	9q21.32	0.280	0.321
rs1359711	112635178	9q32	0.150	0.097
rs827931	48760330	10p11.21	0.090	0.137
rs1259606	80683283	10q22.2	0.300	0.366
rs898256	113481767	10q25	0.328	0.371
rs1374372	36896809	11p13	0.240	0.290
rs1381911	5375134	11p15.4	0.080	0.462
rs1451613	94519857	11q14.3	0.089	0.115
rs982511	9962029	12p13.31	0.034	0.117
rs1358351	129626795	12q24.23	0.287	0.406
rs743760	31087241	13q13.1	0.209	0.297
rs1350848	20950896	14q11.2	0.146	0.153
rs1255351	49810455	14q22.1	0.405	0.492
rs1467372	75312520	14q24.3	0.244	0.114
rs1375168	23934318	15q11.2	0.083	0.171
rs876549	48157119	15q21.2	0.150	0.038
rs756803	28168864	16p12	0.131	0.106
rs1382938	79196193	16p13.3	0.117	0.097
rs889402		16q22.2	0.181	0.175
rs739360	11239931	17p12	0.060	0.010
rs1476813	71704561	17q24.2	0.188	0.143
rs1405726		18q12.3	0.073	0.026
rs1484729	72974243	18q22.2	0.310	0.401
rs929215	21792407	19p13.12	0.174	0.277
rs760998	38520696	20q11.23	0.264	0.289
rs1474537	27043297	21q21.3	0.225	0.355
rs1018799	30061708	22q12.3	0.113	0.063

MAF, minor allele frequency

Table S4. Principal Component Analysis of Population Stratification

	Prolonged postop QTc (categorical)		Rank transformed postop QTc (continuous)	
	OR	**P_value**	**Beta**	**P_value**
PC1	2.782144	0.188495	3.310165	0.055593
PC2	2.619778	0.239167	0.43679	0.810379
PC3	0.571449	0.493139	-0.49459	0.785682
PC4	3.708797	0.112516	5.078131	**0.005579**
PC5	0.803228	0.786529	0.719328	0.68942
PC6	7.522505	**0.013284**	3.311688	0.06764
PC7	1.732723	0.493214	0.555689	0.755627
PC8	0.991199	0.991299	0.997271	0.579531
PC9	0.305062	0.149448	0.513325	0.779599
PC10	0.931034	0.930361	-0.52439	0.773114
PC11	0.816319	0.806348	-2.39437	0.193202
PC12	5.161198	0.045033	2.322211	0.202128
PC13	3.379618	0.129392	1.059284	0.554466
PC14	0.491801	0.401016	-1.01822	0.588307
PC15	1.799248	0.478951	-0.46184	0.802142

Ie. Statistical analysis

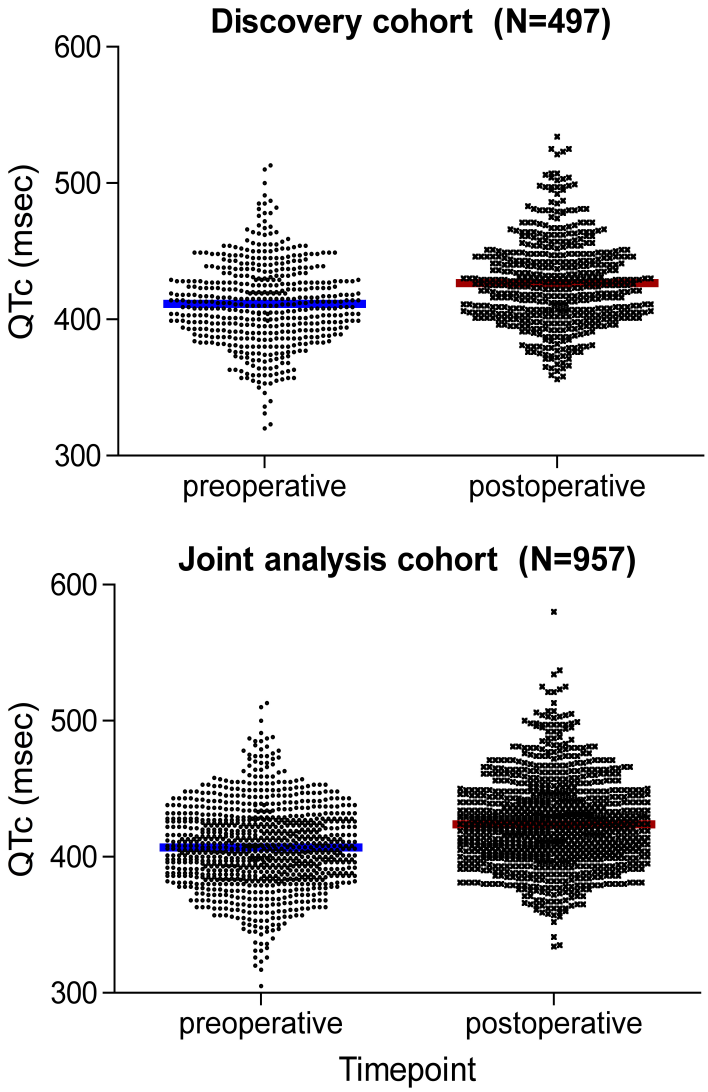
To assess whether genetic information independently adds prognostic value for postoperative QTc interval prolongation, univariately significant SNPs were entered into a clinico-genetic model in the expanded dataset and compared to the clinical model using area under the receiver operating characteristic curve (C-statistic) as well as 3 global measures of model fit (likelihood ratio test, Akaike information criterion and Bayesian information criterion).

We further computed the category-free net reclassification index (NRI) and integrated discrimination index (IDI), which estimate the models' respective abilities to correctly classify patients with normal versus prolonged postoperative QTc.[8]

II. SUPPLEMENTAL RESULTS

IIa. Distribution of perioperative changes in QTc interval

To provide a clearer representation of the variance in QTc interval encountered in the perioperative period, we present below scatter plots of preoperative and postoperative QTc interval values in the discovery (N=497) and joint analysis (N=957) cohorts. Thick lines indicate median values (**Figure S1**);



Although some patients demonstrated a reduction in QTc interval perioperatively, overall the median postoperative QTc interval duration increased compared to preoperative values by 14 ms and 16 ms in the discovery and joint analysis cohorts, respectively ($p<0.0001$ for both).

IIb. Univariate and covariate-adjusted genetic association tests for all candidate gene polypmorphisms studied (based on additive inheritance model)

Table S5. Univariable and multivariable logistic regression analysis for the ***discovery dataset***

Chr	Gene	SNP	BP	Univariable analysis		Multivariable analysis	
				OR (95%CI)	P-value	OR (95%CI)	P-value*
1	CRP	rs1205	159682233	0.89 (0.64-1.24)	0.51	0.93 (0.65-1.37)	0.71
1	IL10	rs1800871	206946634	1.02 (0.73-1.43)	0.90	0.96 (0.70-1.52)	0.82
1	AGT	rs4762	230845977	0.79 (0.51-1.24)	0.31	0.92 (0.56-1.50)	0.75
1	AGT	rs5051	230849872	0.90 (0.70-1.16)	0.43	0.94 (0.78-1.44)	0.69
2	IL1A	rs17561	113537223	1.27 (0.92-1.74)	0.14	1.16 (0.76-1.56)	0.44
2	IL1A	rs1800587	113542960	1.09 (0.79-1.50)	0.59	1 (0.69-1.43)	0.99
2	IL1B	**rs1143633**	113590467	0.71 (0.51-0.99)	0.04	0.73 (0.49-1.08)	**0.1**
2	IL1B	**rs16944**	113594867	1.52 (0.98-1.70)	0.04	1.35(0.98-1.85)	**0.06**
2	IL1RN	rs419598	113887207	1.06(0.78-1.43)	0.73	1.26 (0.85-1.73)	0.21
2	IL1RN	**rs315952**	113890304	0.81 (0.60-1.08)	0.16	0.67 (0.50-1.00)	**0.03**
3	SCN5A	rs1805124	38645420	0.75 (0.52-1.09)	0.13	0.75 (0.49-1.14)	0.18
3	AGTR1	rs5186	148459988	1.16 (0.85-1.59)	0.36	1.13 (0.75-1.58)	0.54
5	ADRB2	rs1042711	148206348	0.82 (0.59-1.13)	0.21	0.89 (0.63-1.32)	0.54
5	ADRB2	rs1800888	148206885	1.53(0.54-4.39)	0.43	1.07 (0.31-3.69)	0.91
6	TNFA	rs1800629	31543031	1.17 (0.80-1.71)	0.42	1.06 (0.67-1.60)	0.79
6	TNFA	rs361525	31543101	1.11 (0.62-2.01)	0.72	1.33 (0.68-2.67)	0.41
6	TNFA	rs1800610	31543827	1.27 (0.72-2.23)	0.41	1.23 (0.58-2.12)	0.53
7	IL6	rs1800796	22766246	0.63 (0.32-1.26)	0.19	0.76 (0.35-1.65)	0.49
7	IL6	rs1800795	22766645	0.91 (0.68-1.24)	0.56	0.92 (0.58-1.21)	0.68
7	NOS3	rs2070744	150690079	0.93 (0.70-1.23)	0.59	1.05 (0.70-1.35)	0.77
7	NOS3	rs1799983	150696111	0.98 (0.73-1.31)	0.87	1.18 (0.77-1.55)	0.35
7	NOS3	rs1799985	150709570	0.96 (0.71-1.31)	0.81	0.8 (0.55-1.14)	0.24
8	ADRB3	rs4994	37823798	1.01 (0.61-1.69)	0.96	0.75 (0.44-1.48)	0.36
10	ADRB1	rs1801252	115804036	1.19 (0.80-1.76)	0.40	1.17 (0.77-1.89)	0.51
10	VMAT2	rs2072362	119014023	0.94 (0.58-1.51)	0.79	0.91 (0.53-1.65)	0.75
11	CAT	**rs769214**	34459717	0.78 (0.58-1.05)	0.10	0.71 (0.54-1.05)	**0.04**
11	CAT	rs1001179	34460231	1.10 (0.78-1.54)	0.59	1.24 (0.77-1.69)	0.29
12	GNB3	rs5443	6954875	1.11 (0.84-1.46)	0.46	1.17 (0.95-1.91)	0.35
17	ACE	rs4646994	61565904	0.97 (0.74-1.27)	0.81	0.95 (0.69-1.27)	0.72
17	ACE	rs4344	61566724	1.02 (0.78-1.35)	0.87	0.99 (0.72-1.33)	0.96
19	TGFB1	rs1800472	41847860	0.80 (0.28-2.27)	0.68	0.69 (0.21-2.24)	0.52
19	TGFB1	rs1800471	41858876	1.21 (0.75-1.95)	0.43	1.17 (0.62-1.85)	0.58
19	TGFB1	rs1800470	41858921	1.24 (0.93-1.66)	0.15	1.14 (0.82-1.60)	0.45
19	TGFB1	rs1800469	41860296	1.03 (0.75-1.42)	0.86	0.98 (0.68-1.41)	0.92
19	TGFB1	rs1800468	41860587	0.76 (0.42-1.39)	0.38	0.69 (0.36-1.45)	0.31
20	MMP9	rs3918242	44635976	1.20 (0.79-1.81)	0.39	1.16 (0.74-1.86)	0.54
22	COMT	rs165688	19951271	1.11 (0.84-1.45)	0.47	1.26 (0.89-1.64)	0.15

*Adjusted for age, female gender, self-reported ethnicity, left ventricular ejection fraction, preoperative QTc interval prolongation, diuretic use at hospital admission, aortic cross clamp time, procedure type, and the top 6 principal components identified in population stratification analysis. Reported P-values from Wald Chi-square tests, unadjusted for multiple testing. Markers with P≤0.1 (highlighted in bold) were selected for the stage II replication analysis. Excluded SNPs that deviated from HWE are: rs4291 (*ACE*), rs1801253 (*ADRB1*), rs1042713 (*ADRB2*), rs1042714 (*ADRB2*), rs699 (*AGT*), rs1057128 (*KCNQ1*), rs3025058 (*MMP3*), rs1061622 (*TNFRS1B*). Chr, chromosome; SNP, single nucleotide polymorphism ID (http://www.ncbi.nlm.nih.gov/SNP/); BP, variant base-pair position in human genome sequence.

IIc. Power calculation

The effect size detectable by our study sample size with 80% power was estimated using the Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/).[9] As an example, we used *IL1B* rs1143633, which has a minor allele frequency (MAF) of 0.3 and odds ratio (OR) of 0.7 from stage I analysis, and *IL1B* rs16944 – MAF=0.4 and OR=1.3 in stage I analysis. We assumed 30% disease prevalence and the stage I analysis sample sizes (151 cases and 346 controls). We varied the minor allele frequency of the disease locus (0.2, 0.3, 0.4) to assess the genotypic relative risk (GRR) that our study sample size can detect with 80% power. We used the same nominal significance threshold ($p \leq 0.1$) described the stage I analysis. We assumed an additive model to define GRR of Aa and AA genotypes. If the marker tested was in complete linkage disequilibrium (D' = 1) with the disease locus, we found that our stage I sample size has approximately 80% power to detect a GRR = 0.65 for a common disease locus (MAF = 0.2) and GRR = 1.55 for a very common disease locus (MAF = 0.4). The effect sizes become slightly higher when D' is assumed at 0.8 between disease locus and marker (**Table S6**). The OR for rs1143633 in stage I analyses was 0.71, which is consistent with the estimate here. As outlined in the paper, current evidence supports joint 2-stage analysis designs over replication analyses in GWAS, based on increased statistical power of joint analyses,[10-12] which formed the rationale for our study design.

Table S6: GRR estimates that our stage I analysis dataset can detect a given disease locus MAF at approximately 80% power when marker MAF = 0.1, sample size = 151 cases and 346 controls, and disease prevalence = 30%.

D'	Disease locus MAF	Odds Ratio	Power
1	0.2	0.65	0.84
	0.3	0.7	0.8
	0.4	1.55	0.82
0.8	0.2	0.55	0.81
	0.3	0.6	0.82
	0.4	1.75	0.8

IId. Reclassification analysis

To evaluate the added predictive ability of *IL1B* variants over that of clinical variables to identify patients at risk of postoperative QTc prolongation, we compared the performance of the clinical vs clinico-genetic risk prediction models using reclassification analysis.[8, 13]

The number of patients with complete genotype information at both *IL1B* polymorphisms was 707. Of those, n=187 had prolonged postoperative QTc (prolonged QTc) and n=520 had normal postoperative QTc (non-prolonged QTc). A reclassification table, indicating the proportions of positive and negative changes in predicted probabilities of postoperative QTc status between the clinico-genetic risk prediction model relative to the clinical risk prediction model is presented below.

	Proportion
Increase for prolonged QTc (1)	0.583
Increase for non-prolonged QTc (2)	0.429
Decrease for prolonged QTc (3)	0.417
Decrease for non-prolonged QTc (4)	0.571

Net Reclassification Improvement (NRI)

	Index	*SE*	*Z*	*P*	*Lower 0.95*	*Upper 0.95*
NRI (1-3+4-2)	0.308	0.0853	3.61	0.000303	0.1410	0.475
NRI for prolonged QTc (1-3)	0.166	0.0731	2.27	0.023394	0.0224	0.309
NRI for non-prolonged QTc (4-2)	0.142	0.0439	3.25	0.001174	0.0564	0.228

Notations as in the table above – 1, increased risk for prolonged QTc; 2, increased risk for non-prolonged QTc; 3, decreased risk for prolonged QTc; 4, decreased risk for non-prolonged QTc. Reclassification table shows individual NRI values for cases, controls and an overall value, together with summary statistics - z-statistic for the test, the associated p-value, and 95% confidence intervals.

Analysis of Changes in Predicted Probabilities

	Mean Change in Probability
Increase for prolonged QTc (sensitivity)	0.01257
Decrease for non-prolonged QTc (specificity)	0.00778

Integrated Discrimination Improvement (IDI)
(average of sensitivity and 1-specificity over [0,1]; also is difference in Yates' discrimination slope)

IDI	*SE*	*Z*	*P*	*Lower 0.95*	*Upper 0.95*
0.0204	0.00482	4.23e+00	2.37e-05	0.0109	0.0298

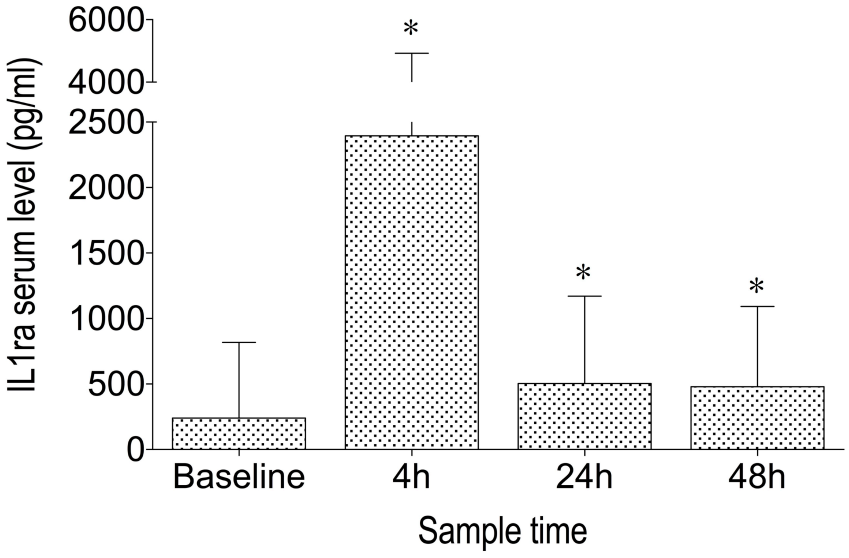
An IDI of 0.02 means that the difference in average predicted risks between patients with and without prolonged postoperative QTc increased by 2% in the clinico-genetic model compared to the clinical risk model.

By drawing attention to which proportion of patients are reclassified from low to high and from high to low risk, this presentation enables ready assessment of the incremental value of the genetic markers for improving clinical risk classification. The increase in sensitivity highlighted by the reclassification analysis is a key attribute in many clinical decision problems. Given the relatively small dataset used in out study, the effect estimates for markers may be exaggerated, and such overfit can lead to overoptimistic estimates of model performance.[14]

IIe. Perioperative temporal changes in serum levels of IL-1 receptor antagonist (IL-1Ra)

A time-course analysis of changes in serum IL1-Aa levels was conducted in a subset (n=288) of patients with available serial serum samples and *IL1RN* genotypes, based on selection of the *IL1RN* rs315952 polymorphism in stage I analyses (note: the gene code for interleukin 1-receptor antagonist is abbreviated *IL1RN*, whereas the protein is abbreviated IL1-Ra). To our knowledge, previous reports of temporal changes in circulating IL1-ra following cardiac surgery are currently lacking. In our cohort, serum levels of IL-1ra rose sharply at 4h post aortic cross-clamp release, and remained significantly elevated at 24 and 48h compared to preoperative values (**Figure S2**, $p<0.001$). We found no differences in IL1-Ra levels by rs315952 status (data not shown).

Figure S2. Perioperative changes in serum Interleukin-1 receptor antagonist (IL-1ra) in patients undergoing cardiac surgery (N=288)



Sampling timepoints are preoperative (base) and 4h, 24h and 48h after aortic cross-clamp removal. Results are expressed as means ± SD in all patients. *$p<0.01$ difference compared to preoperative (baseline) values (Kruskal-Wallis test with Dunn's post-hoc multiple comparison test)

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