

# Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization

The QT interval, an electrocardiographic measure reflecting myocardial repolarization, is a heritable trait. QT prolongation is a risk factor for ventricular arrhythmias and sudden cardiac death (SCD) and could indicate the presence of the potentially lethal mendelian long-QT syndrome (LQTS). Using a genome-wide association and replication study in up to 100,000 individuals, we identified 35 common variant loci associated with QT interval that collectively explain ~8–10% of QT-interval variation and highlight the importance of calcium regulation in myocardial repolarization. Rare variant analysis of 6 new QT interval-associated loci in 298 unrelated probands with LQTS identified coding variants not found in controls but of uncertain causality and therefore requiring validation. Several newly identified loci encode proteins that physically interact with other recognized repolarization proteins. Our integration of common variant association, expression and orthogonal protein-protein interaction screens provides new insights into cardiac electrophysiology and identifies new candidate genes for ventricular arrhythmias, LQTS and SCD.

Prolongation and shortening of the QT interval on the electrocardiogram (ECG) are non-invasive markers of delayed and accelerated myocardial repolarization, respectively, and of increased risk of SCD and fatal arrhythmia as a side effect of medication therapy. Mendelian LQTS and short-QT syndrome (SQTS)<sup>1</sup> stem from mutations of strong effect (increase or decrease, respectively, in QT interval per mutation of >~20–100 ms) in genes encoding ion channels or channel-interacting proteins. In unselected community-based individuals, variation in continuous QT interval is normally distributed (ranging from 380 to 460 ms), with heritability estimates of 30–40% (ref. 2). Common genetic variants that are associated individually with modest increments (~1–4 ms/allele) in QT-interval duration have been detected through candidate gene and genome-wide association studies (GWAS) in large sample sizes including the QTGEN<sup>3</sup> and QTSCD<sup>4</sup> consortia, as well as others<sup>5–9</sup>.

Several loci have been discovered independently in both genome-wide linkage studies of families with mendelian LQTS and GWAS of QT-interval duration in unselected populations, including those harboring *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1* and *KCNJ2*, highlighting the value of both approaches and the overlap of common and rare variant loci. Thus far, hundreds of rare mutations in 13 LQTS susceptibility genes have been reported, with 75% of LQTS cases stemming from mutations in *KCNQ1* (LQT1), *KCNH2* (LQT2) and *SCN5A* (LQT3), <5% of cases due to LQT4–LQT13 and ~20% remaining genetically elusive. Identification of the causal genes underlying QT-interval variation in the general population has been more challenging.

Here the QT Interval–International GWAS Consortium (QT-IGC) performed an expanded meta-analysis of GWAS in 76,061 individuals of European ancestry with targeted genotyping in up to 33,316 additional individuals, completed mutational analysis in probands with genetically elusive LQTS, determined whether QT interval-associated SNPs have effects on gene expression in various tissues (acting as eQTLs) or on other human phenotypes, and further

annotated QT interval-associated genes using protein-protein interaction analyses.

## RESULTS

### GWAS identifies 22 new loci for QT interval

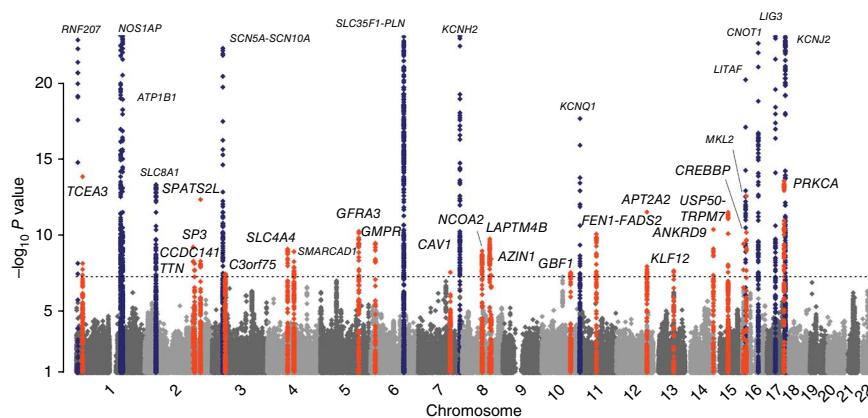
Clinical characteristics of 31 study cohorts of individuals of European ancestry who contributed to the stage 1 GWAS are shown in **Supplementary Table 1**. All studies excluded individuals with atrial fibrillation, QRS duration greater than 120 ms, bundle branch block or intraventricular conduction delay, and, when available, electronic pacemaker use or QT-altering medication use. In each cohort, QT-interval duration adjusted for age, sex, RR interval (inverse heart rate) and principal components of genetic ancestry was tested for association with 2.5 million directly genotyped or imputed SNPs under an additive genetic model (**Supplementary Tables 2 and 3**). We performed inverse variance-weighted meta-analysis on the GWAS results from 76,061 individuals and observed only modest overdispersion of the test statistics given the sample size ( $\lambda_{GC} = 1.076$ ; **Supplementary Fig. 1a**). Exclusion of SNPs within 500 kb of the sentinel SNP at genome-wide significant loci (some identified only after incorporation of replication genotyping) did not significantly attenuate the excess of low *P* values, consistent with a polygenic model of variation in QT interval<sup>10</sup> ( $\lambda_{GC} = 1.069$ ; **Supplementary Fig. 1b**).

In an interim meta-analysis of GWAS results, SNPs were selected for two forms of replication. First, a set of the top 35 independent SNPs (1 per locus) was selected for targeted replication genotyping in as many as 31,962 individuals of European ancestry (**Supplementary Table 1**) on a variety of platforms (**Supplementary Table 2**). Second, a set of ~5,000 linkage disequilibrium (LD)-pruned SNPs ( $r^2 > 0.2$ ) with nominal evidence of association with QT interval ( $P \leq 0.015$ ) was included in a custom genotyping array (Metachip) and genotyped in 1,354 individuals (**Supplementary Tables 1, 4 and 5, and Supplementary Note**)<sup>11</sup>. Meta-analysis of all

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**Figure 1** Genome-wide association results for GWAS meta-analysis, annotated with gene names. Shown are association results from meta-analysis of QT-interval GWAS in 76,198 individuals of European ancestry across 22 autosomes (results are truncated at  $P = 1 \times 10^{-25}$  for display purposes). Loci meeting association  $P < 5 \times 10^{-8}$  upon meta-analysis with replication data are annotated for new (large font, red peaks) and previously reported (small font, blue peaks) loci. Nearest genes are used for annotation, but the causal gene at any given locus is unknown. The dashed line represents the threshold for genome-wide significance ( $P < 5 \times 10^{-8}$ ). The *KCNE1* locus is not labeled, as the low-frequency variant was poorly imputed in GWAS results and largely dependent on direct replication genotyping.



GWAS and replication genotyping results in up to 103,331 individuals (**Supplementary Note**) identified a total of 35 genome-wide significant ( $P < 5 \times 10^{-8}$ ) loci, of which 22 were new and 13 have been reported previously<sup>3–5,9</sup> (**Fig. 1**, **Table 1** and **Supplementary Table 6**). Some SNPs initially selected for replication genotyping were not ultimately the most significant SNP at a locus (**Supplementary Table 7**). Many loci had evidence of multiple independent signals on the basis of having low LD ( $r^2 < 0.05$ ) with other genome-wide significant SNPs, with a total of 68 independent SNPs at 35 loci (**Supplementary Fig. 2**, **Supplementary Table 8a** and **Supplementary Note**).

#### Association of QT-interval SNPs in individuals of African ancestry

We examined the association of 67 of these SNPs in 13,105 individuals of African ancestry in the CARE-COGENT Consortium<sup>12</sup> (1 SNP was poorly imputed owing to low minor allele frequency, MAF). Despite the limited power due to smaller sample size, ten SNPs at nine loci were significantly associated with QT interval ( $P < 0.0007 = 0.05/67$ ) in the same direction as in QT-IGC (**Supplementary Table 9**). The direction of effect for the SNP was concordant between European- and African-ancestry samples for 51 of 67 SNPs (binomial  $P = 5 \times 10^{-5}$ ), and effects were highly correlated ( $r = 0.60$ ,  $P = 9 \times 10^{-10}$ ; **Supplementary Table 9**). These findings are consistent with the hypothesis that a majority of common variants are associated with QT interval in both ancestral populations.

#### Variants with additional non-QT effects

Because heart rate is a strong determinant of unadjusted QT interval ( $r^2 \sim 0.5–0.8$ ), we examined the 68 independent SNPs at the 35 QT interval-associated loci in a GWAS of heart rate in 92,355 individuals of European or Indian-Asian ancestry<sup>13</sup>. Among the 35 loci examined, we found significant association with heart rate for 5 SNPs at 4 loci, including *PLN*, *FEN1-FADS2*, *ATP2A2* and *SCN5A-SCN10A* ( $P < 0.0007 = 0.05/68$ ; **Supplementary Table 10**). Arguing against inadequate adjustment for heart rate as the source of association of QT-interval variants with heart rate was the modest correlation of QT-interval effects (in models adjusting for RR interval, inverse heart rate) and heart rate effects for QT interval-associated SNPs ( $r^2 = 0.16$ ). The effects on heart rate of only 38 of the 68 SNPs showed the inverse relationship that has been well established between QT interval and heart rate (binomial  $P = 0.20$ ). In ARIC ( $n = 8,524$ ), we found no evidence that QT interval–SNP associations were altered with additional adjustment for  $RR^2$ ,  $RR^3$ ,  $RR^{1/2}$  or  $RR^{1/3}$ . In total, these findings favor independent pleiotropic effects of the SNPs on heart rate and QT interval.

QRS prolongation due to bundle branch block can result in delayed myocardial repolarization and QT prolongation, hence, our exclusion of individuals with prolonged QRS duration or bundle branch block (**Supplementary Note**). We examined QT interval-associated SNPs in a published GWAS of QRS duration ( $n = 40,407$ ), which reflects electrical impulse propagation in the cardiac ventricles<sup>14</sup>. Of the 68 QT interval-associated SNPs, 15 at 8 loci were significantly associated with QRS duration ( $P < 0.0007$ ) (**Supplementary Table 10**)<sup>7,14</sup>. Because QRS duration is a subinterval of the QT interval on the ECG, it is perhaps not surprising that some QT-prolonging variants are also positively associated with QRS duration. However, significant genetic effects showed concordant ( $n = 6$ ) as well as discordant ( $n = 9$ ) effects. Across all SNPs, there was no significant excess of concordant versus discordant effects (37 versus 31; binomial  $P = 0.27$ ) or significant correlation of effect sizes ( $r^2 = 0.03$ ,  $P = 0.18$ ; **Supplementary Table 10**). Collectively, these findings suggest that, although the fundamental electrophysiological mechanisms underlying the SNP–QT and SNP–QRS relationships for some SNPs may be shared, many involve cell type-specific effects and that a consistent general relationship between SNP effects on QT interval and QRS duration does not hold.

Examination of the National Human Genome Research Institute (NHGRI) GWAS database (**Supplementary Note**) identified additional associations of our QT-interval SNPs (or their close proxies with  $r^2 > 0.8$ ) at *SCN5A-SCN10A* with PR interval<sup>15</sup>, at *MKL2* with age of menarche<sup>16</sup> and at *FEN1-FADS2* with high-density lipoprotein cholesterol, triglycerides<sup>17</sup>, n-3 fatty acids<sup>18</sup>, fasting plasma glucose levels and homeostasis model assessment of  $\beta$  cell function (HOMA-B)<sup>19</sup>, and alkaline phosphatase<sup>20</sup> (**Supplementary Table 11**), which may point to new repolarization mechanisms or simply reflect independent (pleiotropic) effects of the same genetic variation in different tissues.

#### Functional annotation of associated variants

Because common variants that code for changes in protein structure have an increased potential to be causal, we investigated the presence of coding variants among QT interval-associated loci using 1000 Genomes Project data (CEU, Utah residents of Northern and Western European ancestry). Among the 68 total genome-wide significant SNPs at 35 loci, there were 5 loci in which the index SNP or a highly correlated SNP was nonsynonymous. (**Supplementary Table 8b**). Whereas most loci had multiple genes in associated intervals (**Supplementary Fig. 2**), the genes that harbored genome-wide significant missense SNPs highly correlated with the top SNP are high-priority candidates to underlie the QT-interval association at those loci.

Table 1 Common genetic variants at loci associated with QT interval

| Nearest gene                      | SNP        | Chr.     | Position (hg18) | Coded/noncoded allele | Coded allele frequency | <i>n</i> | Effect in ms (SE) | <i>P</i>             | LQTS gene locus | Function         | eQTL transcript  | PPI interactor known QT loci | IP interactor                                       | LV enhancer |
|-----------------------------------|------------|----------|-----------------|-----------------------|------------------------|----------|-------------------|----------------------|-----------------|------------------|--|------------------------------|---|-------------|
| <b>Previously discovered loci</b> |            |          |                 |                       |                        |          |                   |                      |                 |                  |  |                              |   |             |
| <i>RNF207</i>                     | rs846111   | 1p36     | 6,201,957       | C/G                   | 0.28                   | 47,041   | 1.73 (0.13)       | $7 \times 10^{-40}$  |                 | G603A            |  |                              |   |             |
| <i>NOS1AP</i>                     | rs12143842 | 1q23     | 160,300,514     | T/C                   | 0.24                   | 75,053   | 3.50 (0.11)       | $1 \times 10^{-213}$ |                 |                  |  |                              |   | S           |
| <i>ATP1B1</i>                     | rs10919070 | 1q24     | 167,365,661     | C/A                   | 0.13                   | 75,707   | -1.68 (0.14)      | $1 \times 10^{-31}$  |                 | Intron           | <i>ATP1B1</i> ,<br><i>NME7</i>                                       |                              | ATP1B1-K1,<br>ATP1B1-K2,<br>ATP1B1-CA,<br>ATP1B1-CV | I,S         |
| <i>SLC8A1</i>                     | rs12997023 | 2p22     | 40,606,486      | C/T                   | 0.05                   | 70,311   | -1.69 (0.22)      | $5 \times 10^{-14}$  |                 |                  |  | ANK2, CAV3                   |   | I,S         |
| <i>SCN5A-SCN10A</i>               | rs6793245  | 3p22     | 38,574,041      | A/G                   | 0.32                   | 73,697   | -1.12 (0.10)      | $4 \times 10^{-27}$  | LQT3            | Intron           |  | SCN5A-SNTA1                  |   | S           |
| <i>SLC35F1-PLN</i>                | rs11153730 | 6q22     | 118,774,215     | T/C                   | 0.50                   | 74,932   | -1.65 (0.10)      | $2 \times 10^{-67}$  |                 |                  |  |                              | PLN-CV,<br>PLN-CA                                   | S           |
| <i>KCNH2</i>                      | rs2072413  | 7q36     | 150,278,902     | T/C                   | 0.27                   | 65,331   | -1.68 (0.11)      | $1 \times 10^{-49}$  | LQT2,<br>SQT1   | Intron           |  | KCNE1                        |   | S           |
| <i>KCNQ1</i>                      | rs7122937  | 11p15    | 2,443,126       | T/C                   | 0.19                   | 72,978   | 1.93 (0.12)       | $1 \times 10^{-54}$  | LQT1,<br>SQT2   | Intron           | <i>C11ORF21</i> ,<br><i>PHEMX</i> ,<br><i>TSPAN32</i>                | KCNE1,<br>KCNH2              |   | I           |
| <i>LITAF</i>                      | rs735951   | 16p13    | 11,601,037      | A/G                   | 0.46                   | 62,994   | -1.15 (0.10)      | $2 \times 10^{-28}$  |                 |                  | <i>LITAF</i>   |                              |   | S           |
| <i>CNOT1</i>                      | rs246196   | 16q21    | 57,131,754      | C/T                   | 0.26                   | 76,513   | -1.73 (0.11)      | $2 \times 10^{-57}$  |                 | Intron           | <i>NDRG4</i> ,<br><i>CNOT1</i>                                       |                              | GOT2-CV,<br>GOT2-K1                                 | I,S         |
| <i>LIG3</i>                       | rs1052536  | 17q12    | 30,355,688      | C/T                   | 0.53                   | 75,961   | 0.98 (0.10)       | $6 \times 10^{-25}$  |                 | 3' UTR           | <i>LIG3</i> ,<br><i>CCT6B</i>  |                              | UNC45B-K1,<br>UNC45B-CV                             | I           |
| <i>KCNJ2</i>                      | rs1396515  | 17q24    | 65,942,588      | C/G                   | 0.52                   | 77,058   | -0.98 (0.09)      | $2 \times 10^{-25}$  | LQT7,<br>SQT3   |                  |  |                              |   | S           |
| <i>KCNE1</i>                      | rs1805128  | 21q22    | 34,743,550      | T/C                   | 0.01                   | 20,061   | 7.42 (0.85)       | $2 \times 10^{-18}$  | LQT5            | D85N             |  | KCNQ1,<br>KCNH2              |   |             |
| <b>New loci</b>                   |            |          |                 |                       |                        |          |                   |                      |                 |                  |  |                              |   |             |
| <i>TCEA3</i>                      | rs2298632  | 1p36     | 23,583,062      | T/C                   | 0.50                   | 83,031   | 0.70 (0.09)       | $1 \times 10^{-14}$  |                 | Intron           | <i>TCEA3</i>   |                              |   |             |
| <i>SP3</i>                        | rs938291   | 2q31.1   | 174,450,854     | G/C                   | 0.39                   | 101,902  | 0.53 (0.09)       | $6 \times 10^{-10}$  |                 |                  |  |                              |   |             |
| <i>TTN-CCDC141</i>                | rs7561149  | 2q31.2   | 179,398,101     | C/T                   | 0.42                   | 85,299   | -0.52 (0.09)      | $7 \times 10^{-9}$   |                 |                  |  |                              | CCDC141-CV,<br>TTN-K2,<br>TTN-CV                    | I           |
| <i>SPATS2L</i>                    | rs295140   | 2q33     | 200,868,944     | T/C                   | 0.42                   | 103,331  | 0.57 (0.09)       | $2 \times 10^{-11}$  |                 |                  | <i>SPATS2L</i>   | SGOL2-SCN5A                  |   | I           |
| <i>C3ORF75</i>                    | rs17784882 | 3p21     | 47,519,007      | A/C                   | 0.40                   | 76,184   | -0.54 (0.10)      | $3 \times 10^{-8}$   |                 | Intron           | <i>KLHL18</i> ,<br><i>PTPN23</i> ,<br><i>SCAP</i> ,<br><i>SETD2</i>  |                              | MYL3-CA   | I           |
| <i>SLC4A4</i>                     | rs2363719  | 4q13     | 72,357,080      | A/G                   | 0.11                   | 70,821   | 0.97 (0.16)       | $8 \times 10^{-10}$  |                 | Intron           |  |                              |   |             |
| <i>SMARCAD1</i>                   | rs3857067  | 4q22     | 95,245,457      | A/T                   | 0.46                   | 101,382  | -0.51 (0.08)      | $1 \times 10^{-9}$   |                 |                  |  |                              |   |             |
| <i>GFRA3</i>                      | rs10040989 | 5q31     | 137,601,624     | A/G                   | 0.13                   | 87,942   | -0.85 (0.13)      | $5 \times 10^{-11}$  |                 |                  | <i>FAM13B</i>  | ETF1-RPL22                   |   |             |
| <i>GMPR</i>                       | rs7765828  | 6p22     | 16,402,701      | G/C                   | 0.40                   | 93,262   | 0.55 (0.09)       | $3 \times 10^{-10}$  |                 | Intron (F2561-p) | <i>ATXN1</i>   | ATXN1-ACOT7,<br>ATXN1-KCNAB2 |   | I           |
| <i>CAV1</i>                       | rs9920     | 7q31     | 115,987,328     | C/T                   | 0.09                   | 102,060  | 0.79 (0.14)       | $3 \times 10^{-8}$   |                 | 3' UTR           |  | CAV-ATP1B1,<br>CAV2-ATP1B1   | CAV1-CA,<br>CAV1-S1,<br>CAV1-CV,<br>CAV2-CV         |             |
| <i>NCOA2</i>                      | rs16936870 | 8q13     | 71,351,896      | A/T                   | 0.10                   | 74,196   | 0.99 (0.16)       | $1 \times 10^{-9}$   |                 | Intron           |  |                              |   | I           |
| <i>LAPTM4B</i>                    | rs11779860 | 8q22.1   | 98,919,506      | C/T                   | 0.47                   | 73,404   | -0.61 (0.10)      | $2 \times 10^{-10}$  |                 | Intron           |  |                              |   | I           |
| <i>AZIN1</i>                      | rs1961102  | 8q22.3   | 104,002,021     | T/C                   | 0.33                   | 82,677   | 0.57 (0.10)       | $3 \times 10^{-9}$   |                 |                  |  |                              |   |             |
| <i>GBF1</i>                       | rs2485376  | 10q24    | 104,039,996     | A/G                   | 0.39                   | 70,552   | -0.56 (0.10)      | $3 \times 10^{-8}$   |                 | Intron           |  |                              | ACTR1A-CV   | I           |
| <i>FEN1-FADS2</i>                 | rs174583   | 11q12    | 61,366,326      | T/C                   | 0.34                   | 100,900  | -0.57 (0.09)      | $8 \times 10^{-11}$  |                 | Intron           | <i>FADS1</i> ,<br><i>FADS2</i> ,<br><i>FADS3</i>                     |                              |   | I           |
| <i>ATP2A2</i>                     | rs3026445  | 12q24    | 109,207,586     | C/T                   | 0.36                   | 95,768   | 0.62 (0.09)       | $3 \times 10^{-12}$  |                 | Intron           | <i>VPS29</i> ,<br><i>GNP3</i> ,<br><i>ARPC3</i> ,<br><i>C12ORF24</i> | PLN                          | ATP2A2-CV,<br>ATP2A2-CA                             | I           |
| <i>KLF12</i>                      | rs728926   | 13q22    | 73,411,123      | T/C                   | 0.36                   | 69,219   | 0.57 (0.10)       | $2 \times 10^{-8}$   |                 | Intron           | <i>KLF12</i>   |                              |   | I           |
| <i>ANKRD9</i>                     | rs2273905  | 14q32    | 102,044,752     | T/C                   | 0.35                   | 83,532   | 0.61 (0.09)       | $4 \times 10^{-11}$  |                 | 5' UTR           | <i>ANKRD9</i>  |                              |   | I           |
| <i>USP50-TRPM7</i>                | rs3105593  | 15q21    | 48,632,310      | T/C                   | 0.45                   | 77,240   | 0.66 (0.10)       | $3 \times 10^{-12}$  |                 |                  |  |                              |   |             |
| <i>CREBBP</i>                     | rs1296720  | 16p13.3  | 3,813,643       | C/A                   | 0.20                   | 59,812   | 0.83 (0.13)       | $4 \times 10^{-10}$  |                 | Intron           |  |                              | CV-TRAP1  |             |
| <i>MKL2</i>                       | rs246185   | 16p13.12 | 14,302,933      | C/T                   | 0.34                   | 77,411   | 0.72 (0.10)       | $3 \times 10^{-13}$  |                 |                  |  |                              |   |             |
| <i>PRKCA</i>                      | rs9892651  | 17q24    | 61,734,255      | C/T                   | 0.43                   | 74,683   | -0.74 (0.10)      | $3 \times 10^{-14}$  |                 | Intron           | <i>PRKCA</i>   | CACNA1C,<br>KCNE1            |   | I           |

Common genetic variants at loci associated with QT interval ( $P < 5 \times 10^{-8}$ ) on meta-analysis of GWAS and replication results (Supplementary Table 7). *n* is the effective number of samples contributing to the signal. For a given SNP, the effective sample size is the sum of the product of the cohort-specific sample size and imputation quality (ranging from 0 to 1). Function shown for coding variants with  $r^2 = 1$  to sentinel SNP or proxy with  $1.0 > r^2 > 0.8$  (-p) to the sentinel SNP. eQTL transcripts are shown if associated at  $P < 5 \times 10^{-8}$  with sentinel SNPs or their close proxies ( $r^2 > 0.8$ ; Supplementary Table 12; in bold if the eQTL was found in left ventricle for the sentinel SNP). Protein-protein interactor (PPI) relationships for nearby genes to genes in loci previously established to influence myocardial repolarization are provided (Supplementary Table 17). Interactors from immunoprecipitation (IP) experiments are shown from mouse cardiac tissue using five baits (K1, KCNQ1; K2, KCNH2; CV, CAV3; CA, CACNA1C; S1, SNTA1) with protein identified in parentheses if different from the nearest gene listed. Loci at which a SNP (index or secondary) or a close proxy ( $r^2 > 0.8$ ) falls in a left ventricular enhancer are marked with I or S. Parentheses indicate annotations for secondary signals of association (Supplementary Table 8a). SE, standard error.

**Table 2 Association of QT-interval SNPs with gene expression in human left ventricle**

| QT-interval SNP   | Chr. | Position    | Transcript           | Best eQTL SNP for transcript | $r^2$ between QT SNP and eQTL SNP | Direction of eQTL SNP effect for QT-increasing allele | Transcript association of QT SNP ( $P$ ) | Transcript association of QT SNP with adjustment for best eQTL SNP ( $P$ ) | Attenuated significance | QT association of QT SNP ( $P$ ) | QT association of best eQTL SNP ( $P$ ) |
|-------------------|------|-------------|----------------------|------------------------------|-----------------------------------|---|--|--|-------------------------|----------------------------------|---|
| <b>rs17457880</b> | 1    | 160,434,778 | <b><i>FCGR2B</i></b> | rs17457880                   | Same                              | Increase  | $1 \times 10^{-5}$                       | 0.99   | Yes                     | $3 \times 10^{-10}$              | Same                                    |
| rs17457880        | 1    | 160,434,778 | <i>FCGR3A</i>        | rs9727076                    | 0                                 | Increase  | $1 \times 10^{-7}$                       | $9 \times 10^{-9}$   | No                      | $3 \times 10^{-10}$              | NA                                      |
| rs295140          | 2    | 200,868,944 | <i>SPATS2L</i>       | rs295113                     | 0.53                              | Decrease  | $8 \times 10^{-7}$                       | 0.74   | Yes                     | $4 \times 10^{-13}$              | 0.76                                    |
| <b>rs174583</b>   | 11   | 61,366,326  | <b><i>FADS2</i></b>  | rs174548                     | 0.80                              | Decrease  | $6 \times 10^{-8}$                       | 0.94   | Yes                     | $1 \times 10^{-10}$              | $8 \times 10^{-8}$                      |
| <b>rs3026445</b>  | 12   | 109,207,586 | <b><i>VPS29</i></b>  | rs6606686                    | 0.86                              | Increase  | $1 \times 10^{-6}$                       | 0.84   | Yes                     | $1 \times 10^{-8}$               | $2 \times 10^{-7}$                      |
| <b>rs728926</b>   | 13   | 73,411,123  | <b><i>KLF12</i></b>  | rs1886512                    | 0.93                              | Increase  | $4 \times 10^{-5}$                       | 0.25   | Yes                     | $2 \times 10^{-8}$               | $4 \times 10^{-8}$                      |
| <b>rs735951</b>   | 16   | 11,601,037  | <b><i>LITAF</i></b>  | rs7187498                    | 0.93                              | Increase  | $4 \times 10^{-13}$                      | 0.62   | Yes                     | $2 \times 10^{-28}$              | NA                                      |
| rs246196          | 16   | 57,131,754  | <i>SETD6</i>         | rs42945                      | 0.30                              | Increase  | $4 \times 10^{-7}$                       | 0.20   | Yes                     | $2 \times 10^{-57}$              | $9 \times 10^{-22}$                     |
| <b>rs9892651</b>  | 17   | 61,734,255  | <b><i>PRKCA</i></b>  | rs11658550                   | 0.97                              | Increase  | $2 \times 10^{-41}$                      | 0.22   | Yes                     | $3 \times 10^{-14}$              | NA                                      |

Shown are QT-interval SNPs associated with expression of a transcript within 1 Mb at experiment-wide significance (**Supplementary Note**). For each transcript, the best eQTL SNP for that transcript is shown. The QT SNP association with transcript is shown with and without adjustment for the best eQTL SNP for that transcript. QT SNPs and transcripts are shown in bold if the QT SNP and best eQTL SNP are highly correlated ( $r^2 > 0.8$ ), show attenuation of association in conditional models and show comparable strength of association with QT interval for both the QT SNP and best eQTL SNP when available.

Because noncoding variants may influence gene expression, we examined the index SNPs or proxies ( $r^2 > 0.8$ ) at the 68 SNPs in 35 loci in publicly available eQTL data sets from diverse tissues. Twelve QT interval-associated loci were associated with the variable expression of at least one gene in one or more tissues, with high correlation ( $r^2 > 0.8$ ) between the top QT interval-associated SNP and the top eQTL SNP (**Table 1, Supplementary Table 12 and Supplementary Note**). QT interval-associated SNPs were associated with expression of the nearest gene at loci including *ANKRD9*, *ATP1B1*, *CNOT1*, *FADS1*, *LIG3* and *TCEA3*. The eQTL data help point to specific genes at these loci as a potential source of the repolarization association signal, presumably through regulatory variation. However, some loci were associated with the expression of multiple genes. We did not observe a significant signature of eQTLs among the QT interval-associated loci that implicated a specific tissue or cell type in an atlas of human and mouse expression ( $P > 0.01$ ; **Supplementary Note**)<sup>21</sup>.

Because genetic variants that influence gene expression may do so in a cell type-specific manner, we examined the association of QT-interval SNPs with gene expression in a collection of 313 left ventricular biopsy samples in the MAGNet Consortium. This collection included samples from the hearts of individuals transplanted for heart failure ( $n = 177$ ) or healthy hearts from potential donors ( $n = 136$ ) that were ultimately not used (**Supplementary Note**). We examined 63 of the 68 QT interval-associated SNPs that were well imputed from genome-wide genotyping in relation to *cis* expression of all genes within 1 Mb of each SNP.

After adjusting for age, sex, study site and presence of heart failure, nine SNPs at eight loci were significantly associated with one of nine transcripts (one SNP was associated with two transcripts), after correction for multiple testing ( $P < 4.4 \times 10^{-5} = 0.05/1,146$  SNP-transcript associations; **Table 2 and Supplementary Note**). After adjustment for the best eQTL SNP for a given transcript, the QT-interval SNP associations became non-significant (all  $P \geq 0.01$ ) for eight of the nine SNP-transcript associations, consistent with a potentially causal effect for these eight eQTLs. Inclusion of interaction terms for heart failure status did not alter the results (data not shown). In sum, these findings highlight several genes the expression of which is plausibly modulated by the QT-interval SNP (or a correlated variant) and are thus high-priority targets for further experimental work.

Lastly, because genetic variation that influences gene expression may act through modulation of enhancers, we examined data available from the US National Institutes of Health (NIH) Roadmap Epigenomics Program<sup>22</sup>. We specifically focused on transcriptional enhancer elements marked by combinations of histone modifications (specifically, presence of monomethylation of histone H3 at lysine 4

(H3K4me1) and absence of trimethylation of histone H3 at lysine 4 (H3K4me3)), as emerging evidence indicates that variants associated with complex traits preferentially reside in these noncoding regulatory regions and can affect gene expression<sup>23,24</sup>. We tested whether lead QT interval-associated SNPs or highly correlated variants ( $r^2 > 0.8$ ) overlapped enhancers in adult left ventricular tissue. Of 68 lead (or correlated) SNPs, 34 overlapped a left ventricular enhancer, a substantially greater proportion than with randomly sampled sets of matched SNPs ( $z$  score = 9.45,  $P < 1 \times 10^{-200}$ ; **Supplementary Fig. 3 and Supplementary Note**). These findings highlight specific noncoding SNPs at QT interval-associated loci that can be prioritized for experimental follow-up (**Supplementary Table 13**).

We also examined the association results for over-representation of specific pathways in QT-interval loci compared to the genome as a whole using Gene Ontology (GO), the Kyoto Encyclopedia of Genes and Genomes (KEGG), Panther and Ingenuity gene set annotations (**Supplementary Note**). Three of the top ten pathways in this analysis are specifically involved in calcium processes, including 'regulation of the force of heart contraction' ( $P = 1 \times 10^{-4}$ ), 'cation transport' ( $5 \times 10^{-4}$ ) and 'cellular calcium ion homeostasis' ( $1 \times 10^{-3}$ ; **Supplementary Table 14 and Supplementary Note**)<sup>25</sup>. These signals were confirmed by a secondary analysis in which we matched the 68 QT interval-associated SNPs to randomly selected genome-wide SNPs to calculate statistical significance (**Supplementary Note**). Three GO terms involving 'ion transport' were significantly enriched for QT-interval associations ( $P < 0.00044$ ) as well as a gene set based on having a cardiac phenotype in knockout mice ( $P < 0.00025$ ; **Supplementary Note**).

### Population variation in QT interval explained

The common variants at the 12 previously published common variant loci from the QTGEN and QTSCD consortia explained 3–6% of variation in QT interval, after accounting for effects of age, sex and heart rate<sup>3,4</sup>. The top SNPs at the additional new loci increased the variance explained to 5.5–7.0%, whereas all 68 independent SNPs at the 35 loci explained 7.6–9.9% of variance (**Supplementary Tables 15 and 16**). A recent heritability analysis found that 21% of overall variance (>50% of heritable variation) in QT interval was explained by common autosomal SNPs captured on contemporary genome-wide genotyping arrays<sup>10</sup>. Because the current study was focused on identifying bona fide associations of specific loci rather than explaining overall variance, we set a stringent  $P$ -value threshold for identifying individual SNPs. Larger studies are likely to continue to identify additional QT-interval loci, as well as additional independent signals of association at the 35 loci described here.



**Table 3** Candidate gene mutational screening

| Gene          | Position (hg19)                    | Exon | Nucleotide change | Amino acid change | Number of cases | In controls (yes/ no) | Alt alleles in Exome Chip (yes/no) | In ESP   | PolyPhen, SIFT               |
|---------------|------------------------------------|------|-------------------|-------------------|-----------------|-----------------------|------------------------------------|----------|------------------------------|
| <i>ATP2A2</i> | Chr. 12: 110,734,419               | 5    | c.340A>G          | p.Asn114Asp       | 1               | No                    | No                                 | No       | Benign, tolerated            |
| <i>ATP2A2</i> | Chr. 12: 110,765,553 – 110,765,554 | 8    | c.826_827insA     | p.Ile276fs*281    | 1               | No                    | No                                 | No       | Stop                         |
| <i>SLC8A1</i> | Chr. 2: 40,656,318                 | 1    | c.1104C>T         | p.Ala368Val       | 1               | No                    | No                                 | 24/5,379 | Probably damaging, tolerated |
| <i>SLC8A1</i> | Chr. 2: 40,397,450                 | 6    | c.2009C>T         | p.Pro670Leu       | 1               | No                    | No                                 | No       | Benign, damaging             |
| <i>SLC8A1</i> | Chr. 2: 40,342,664                 | 10   | c.2651T>G         | p.Val884Gly       | 1               | No                    | No                                 | No       | Probably damaging, damaging  |
| <i>SRL</i>    | Chr. 16: 4,256,990                 | 2    | c.1177G>T         | p.Gly393Cys       | 1               | No                    | No                                 | No       | Probably damaging, damaging  |
| <i>SRL</i>    | Chr. 16: 4,256,754                 | 2    | c.1409G>A         | p.Arg470Lys       | 1               | No                    | No                                 | No       | Benign, tolerated            |
| <i>SRL</i>    | Chr. 16: 4,256,384                 | 7    | c.2566C>T         | p.Arg856Cys       | 1               | No                    | No                                 | 1/4,915  | Probably damaging, tolerated |
| <i>TRPM7</i>  | Chr. 15: 50,955,189                | 2    | c.58_59insA       | p.Ile19fs*59      | 1               | No                    | No                                 | No       | Stop                         |
| <i>TRPM7</i>  | Chr. 15: 50,935,731                | 5    | c.341A>T          | p.Asp114Val       | 1               | No                    | No                                 | No       | Probably damaging, damaging  |
| <i>TRPM7</i>  | Chr. 15: 50,884,537                | 26   | c.3895A>C         | p.Ser1299Arg      | 1               | No                    | No                                 | No       | Benign, tolerated            |
| <i>TRPM7</i>  | Chr. 15: 50,884,406                | 26   | c.4026A>T         | p.Glu1342Asp      | 2               | No                    | No                                 | No       | Benign, tolerated            |
| <i>TRPM7</i>  | Chr. 15: 50,884,280                | 26   | c.4152A>T         | p.Leu1384Phe      | 1               | No                    | No                                 | No       | Possibly damaging, tolerated |

Six genes (*ATP2A2*, *CAV1*, *CAV2*, *SLC8A1*, *SRL* and *TRPM7*) at 5 loci were screened for amino acid–altering variants in 298 LQTS cases and compared to >300 controls of the same ancestry, presence on an exome chip array designed from exome sequencing of >12,000 multi-ancestry samples (number of alternate alleles shown) and in the Exome Sequencing Project (alternate allele counts per total number of individuals shown). Predicted function by PolyPhen2 (benign, possibly damaging or probably damaging) or SIFT (tolerated or damaging) is also indicated. See **Supplementary Note** for details.

### LQTS proband mutation screening

Common variant loci found in the current and previous studies include five genes previously established to cause monogenic LQTS (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1* and *KCNJ2*). Given the coexistence of common QT-interval variants at loci with established rare coding mutations in genes relevant to LQTS, we hypothesized that some of the new QT interval–associated loci might likewise contain previously unrecognized mendelian LQTS-associated genes. We selected, on the basis of statistical significance, proximity to the signal of association, absence of multiple nearby genes in the associated interval and known cardiac expression or involvement in ion flux, six genes (*ATP2A2*, *CAV1*, *CAV2*, *SLC8A1*, *SRL* and *TRPM7*) from five new loci for coding mutation screening. We studied 298 unrelated individuals with clinically diagnosed LQTS on the basis of the Schwartz score, but free from mutations in the LQTS1–LQTS3 genes, for rare exonic or splice-site sequence variants in these six genes (**Supplementary Table 17** and **Supplementary Note**). We identified 13 variants that altered amino acids present in cases but not in  $\geq 300$  controls of the same continental ancestry (**Table 3**). Of these variants, 11 were not observed in ~6,800 individuals on whom whole-exome sequencing was performed by the Exome Sequencing Project (ESP) or included on the Exome Chip array; several are predicted to be disruptive to protein function (**Table 3** and **Supplementary Note**).

Of the 13 variants that altered amino acids, 2 mutations in *ATP2A2* (encoding p.Ile276fs\*281) and *TRPM7* (encoding p.Ile19fs\*59) resulted in frameshifts and premature truncation of the corresponding protein product. The *ATP2A2* mutation was detected in a 6-year-old girl with LQTS diagnosed on the basis of a heart rate–corrected QT (QTc) of 492 ms without symptoms. The proband's mother carried the mutant allele and had borderline QTc prolongation and T wave abnormalities; the proband's father lacked the mutation and had a normal QTc. The *TRPM7* mutation was detected in a 14-year-old girl with LQTS diagnosed on the basis of a QTc of 500 ms without symptoms. The mutation was found in the proband's mother and brother, both of whom had a normal QTc, and was absent in the proband's father, who had a normal QTc. Whether or not these two loss-of-function alleles contribute to LQTS pathogenesis in these individuals cannot be determined from these observations alone.

### Protein-protein interaction networks

We next sought evidence that proteins encoded by genes at common variant loci interact physically with known myocardial repolarization proteins. We have constructed a protein-protein interaction network

from the InWeb database (**Supplementary Note**)<sup>26</sup>. Using the DAPPLE algorithm<sup>27</sup>, we seeded the network with the first 12 known mendelian LQTS-associated genes and 7 loci harboring previously identified common QT-interval variants (but not known mendelian genes)<sup>3,4</sup>. Consistent with the known relationships among several of the mendelian genes, significant interconnectivity was observed ( $P = 0.0006$  for direct connections,  $P = 0.008$  for indirect connections; **Supplementary Note**). We thus identified 606 proteins interacting directly with the seed proteins and investigated whether these protein-protein interactions could help identify candidate genes within any of the 22 new loci identified in the current study. We found eight interactors (*ATP2A2*, *CAV1*, *CAV2*, *PRKCA*, *SLC8A1*, *ATXN1*, *ETF1* and *SGOL2*) from seven new loci, representing significant enrichment compared to the null expectation (hypergeometric  $P = 0.03$ ; **Supplementary Table 18** and **Supplementary Note**). We hypothesized that the other proteins interacting directly with the seed network might nonetheless be enriched for association, even if not at genome-wide significance. We assigned association scores to all interacting proteins (except those in the 35 loci already identified) and tested for enrichment of association in those genes compared to all genes in the genome from non-associated regions. We found that interacting proteins were more associated than expected by chance (rank-sum  $P = 0.00012$ ), suggesting that they include true associations yet to be discovered (**Supplementary Fig. 4** and **Supplementary Note**). Protein interaction network analysis suggests that interactors of mendelian genes associated with LQTS are functionally involved in QT-interval duration.

This conclusion is further supported by *in vivo* data presented in an accompanying paper by Lundby *et al.*<sup>28</sup>. We immunoprecipitated proteins encoded by the mendelian LQTS-associated genes *KCNQ1*, *KCNH2*, *CACNA1C*, *CAV3* and *SNTA1* from mouse cardiac tissue and identified proteins they interact with by high-performance orbitrap tandem mass spectrometry. We found proteins encoded by 12 genes from 10 loci identified by our GWAS that physically interact with proteins encoded by the 5 mendelian genes associated with LQTS, a significant enrichment compared to random expectation ( $P = 1 \times 10^{-6}$  using permutation), including *ATP2A2* (SERCA2a), *SRL* (sarcalumenin), which regulates SERCA2a in cardiomyocytes<sup>29–31</sup>, *CAV1* (caveolin 1), *PLN* (phospholamban), which also regulates SERCA2a, and *ATP1B1* (**Table 1**). Molecular interactions of proteins encoded by genes at QT interval–associated loci with known mediators of the currents underlying myocardial repolarization strongly implicates these genes and not others in the relevant associated intervals as the causal genes underlying the QT-interval association.

## DISCUSSION

Altogether, our integrated analysis of genomic, transcriptomic and proteomic data highlight calcium signaling as having an important role in myocardial repolarization, the cellular process that underlies the QT interval, the derangement of which is arrhythmogenic (see detailed description of genes at several loci in the **Supplementary Note**).

Electrical activation and relaxation of the ventricular myocyte on average once per second requires the interplay of multiple coordinated ion channel fluxes. Cellular depolarization begins with Na<sup>+</sup> influx and is sustained by Ca<sup>2+</sup> influx, which triggers Ca<sup>2+</sup> release from the sarcoplasmic reticulum, leading to myocardial contraction (**Supplementary Fig. 5**). Prolonged inward (depolarizing) Ca<sup>2+</sup> current during the plateau phase of the cardiac action potential leads to delays in ventricular myocyte repolarization, a subsequent prolonged QT interval on electrocardiogram and a highly arrhythmogenic and potentially lethal substrate. In fact, gain-of-function mutations in the L-type Ca<sup>2+</sup> channel lead to the highly arrhythmogenic Timothy syndrome (LQT8) that is associated with extremely prolonged QT intervals<sup>32</sup>.

Normal myocyte repolarization results from efflux of potassium and, less so, Ca<sup>2+</sup>; Ca<sup>2+</sup> is actively taken up by the sarcoplasmic reticulum to halt myocardial contraction. The Na<sup>+</sup> that enters the myocyte is counterbalanced by an active Na<sup>+</sup>/K<sup>+</sup> ATPase (a  $\beta$  subunit of which is encoded by *ATP1B1*, at a common variant QT-interval locus). The Ca<sup>2+</sup> that enters the myocyte is counterbalanced by a Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCX1, encoded by *SLC8A1*) to ensure net even cation balance, at the expense of a net depolarizing effect (potentially prolonging repolarization). Disruption of this delicate cation balance and, in particular, Ca<sup>2+</sup> homeostasis can have a profound impact on action-potential duration, formation of early after depolarizations (EADs) and triggered activity, leading to potentially lethal arrhythmias including torsade de pointes and ventricular fibrillation. In fact, administration of an inhibitor of the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger is associated with reduced arrhythmia and shortened action-potential duration in models of LQTS<sup>33</sup> and heart failure<sup>34</sup>, and its overexpression delays myocardial repolarization and leads to ventricular arrhythmias<sup>35</sup>.

*ATP2A2* encodes the SERCA2a cardiac sarcoplasmic reticulum calcium pump and, by alternative splicing, a ubiquitously expressed SERCA2b calcium pump (**Supplementary Fig. 5**). The protein is negatively regulated by phospholamban (*PLN*), also a QT interval-associated locus<sup>3,4,6</sup>. In turn, *PLN* is negatively regulated by *PRKCA*, a gene in a newly discovered QT interval-associated locus<sup>36</sup>. SERCA2a is responsible for Ca<sup>2+</sup> sequestration by the cardiac sarcoplasmic reticulum, and its dysregulation is implicated in heart failure owing to the centrality of calcium cycling to excitation-contraction coupling. Dominant SERCA2 mutations are a cause of keratosis follicularis Darier-White disease (MIM 124200)<sup>37</sup>. No study that we are aware of has described electrocardiographic or other cardiac changes in affected humans, but detailed investigation of heterozygous *Serca2*<sup>+/-</sup> mice showed a reduction in *Serca2* protein by about a third with deficits in myocardial relaxation and contractility and a reduced Ca<sup>2+</sup> transient by haploinsufficiency<sup>38</sup> as well as upregulation of the transient receptor potential canonical 1 (TRPC1) channel<sup>39</sup>. Moreover, overexpression of SERCA2a in a rat model of heart failure demonstrated a substantial reduction in arrhythmias<sup>40</sup>.

*TRPM7* encodes the widely expressed transient receptor channel melastatin 7 protein, a six-transmembrane molecule that is Mg<sup>2+</sup> and Ca<sup>2+</sup> permeable and has protein kinase function<sup>41,42</sup>. The *touchtone* (*nutria*)

zebrafish *TRPM7* mutant demonstrates defective skeletogenesis, kidney stones<sup>43</sup> and abnormal melanophores<sup>44</sup>. Homozygous *Trpm7* deletion in mice is embryonic lethal; targeted deletion disrupts normal thymogenesis<sup>41</sup>. Targeted cardiac deletion in cultured embryonic ventricular myocytes leads to downregulation of several genes involved in calcium cycling, including *SERCA2a*<sup>45</sup>. In migrating human embryonic lung fibroblasts, *TRPM7* mediates transduction of mechanical stretch into calcium influx underlying calcium flickers (focally high intracellular calcium microdomains), involved in steering cell migration<sup>46</sup>. In human atrial fibroblasts, atrial fibrillation is associated with increased *TRPM7*-mediated Ca<sup>2+</sup> influx, whereas *TRPM7* knockdown results in loss of spontaneous Ca<sup>2+</sup> influx<sup>47</sup>. More recently, targeted *Trpm7* deletion in mice has been shown to result in lethal cardiomyopathy in early cardiogenesis; cardiomyopathy, delayed repolarization and heart block in midcardiogenesis; and no recognizably aberrant phenotype in late cardiogenesis<sup>48</sup>. In total, this previous work raises the possibility that *TRPM7* in humans leads to altered myocardial repolarization through developmental differences or through ongoing functional effects in adulthood, potentially involving calcium signaling.

Potassium flux has long been recognized through rare mutations underlying LQTS as a critical effector of myocardial repolarization. Ca<sup>2+</sup> has been recognized as a central mediator in excitation-contraction coupling. However, our studies of common and rare genetic variation now place Ca<sup>2+</sup> as a central modulator of repolarization given the role of the proteins encoded by the mendelian Timothy syndrome-associated gene (LQT8) *CACNA1C*, as well as the following genes at common variant QT interval-associated loci: *ATP2A2*, *PLN*, *PRKCA*, *SRL* and *SLC8A1*. How the Mg<sup>2+</sup>/Ca<sup>2+</sup> channel *TRPM7* might contribute to repolarization is unclear, but its involvement in Ca<sup>2+</sup> flickers<sup>46</sup> suggests a potential role in localized Ca<sup>2+</sup> fluxes or indirect effects on Ca<sup>2+</sup>-sensitive potassium channels or the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger.

Much work will be needed to understand the normal physiological contribution to repolarization of these Ca<sup>2+</sup>-regulating proteins, as well as the pathophysiological consequences arising from their derangement. Although anti-arrhythmic agents targeting the I<sub>Kr</sub> (LQT2, corresponding to *KCNH2*) channel have a relatively limited contribution to clinical management of some arrhythmias because of their propensity to cause other arrhythmias, targeting the newly identified proteins that contribute to myocardial repolarization could potentially treat some arrhythmias without causing arrhythmia. Conversely, existing therapies that inadvertently target some of the newly discovered proteins could in fact contribute to arrhythmogenesis.

We have identified 22 new QT interval-associated loci, bringing the total number of common variant loci to 35. We have used diverse approaches to highlight specific genes at these loci likely to mediate the repolarization effects. Although we cannot say with certainty which gene underlies the QT-interval trait at every locus, these complementary experiments represent a quantum leap in our understanding of this critical electrophysiological process. The elucidation of fundamental mechanisms of arrhythmogenesis promises to expose new approaches to predict and prevent death from lethal ventricular arrhythmias in the general population.

## METHODS

Methods and any associated references are available in the [online version of the paper](#).

*Note: Any Supplementary Information and Source Data files are available in the [online version of the paper](#).*

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Author contributions are indicated by cohort and group. All coauthors revised and approved the manuscript.

**Writing group.** C.N.-C. takes overall responsibility for the QT-IGC study. The study design was developed by M.J.A., D.E.A., A. Chakravarti, L.C., P.I.W.d.B., T.T.K., P.B.M., C.N.-C., A. Pfeufer, S.L.P., P.J.S. and N.S. in consultation with the respective study groups. The manuscript was written by C.N.-C. The manuscript was critically revised in detail by members of the writing team before circulation to all coauthors.

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**Meta-analysis of GWAS and replication.** D.E.A. and S.L.P. independently performed quality control and meta-analysis of GWAS and replication association results. Polygenic analysis: R.D.K. P.I.W.d.B., A. Pfeufer. and C.N.-C. supervised the analyses.

**Non-QT trait lookups.** **CARE-COGENT:** Meta-analysis and lookup: J.G.S. **HRGEN:** Meta-analysis and lookup: M.d.H. Overall study supervision: R.J.F.L. **QRS GWAS:** Study supervision: N.S. Meta-analysis: D.E.A., P.I.W.d.B. Results lookup: S.L.P.

**Non-cardiac eQTL analyses.** Data set acquisition: A.S.P., V.E. Analysis and interpretation: A.D.J. Cell type-specific enrichment tests: S.R., K. Slowikowski.

**Left ventricle eQTL analyses.** Overall supervision: T.P.C. Recruitment, sample collection: K.M., C.E.M. Sample processing and expression analysis: J. Brandimarto. Statistical analysis: M.M.

**Left ventricle enhancer analyses.** Analysis: X.W. Overall supervision: L.A.B., M. Kellis.

**Mouse knockout.** Enrichment tests: S.R., K. Slowikowski. Candidate gene list: P.v.d.H.

**LQTS mutation screening.** **Amsterdam:** *SLC8A1* sequencing: T.T.K. Clinical data collection: A.B., N.H., A.A.M.W. Study supervision: C.R.B., A.A.M.W. **London:** Recruitment, phenotyping and strategy: E.R.B. Screening for mutations in LQT1, LQT2 and LQT3 and sample management: C.D. **Mayo Clinic:** LQTS cohort characteristic organization: D.J.T. *TRPM7* mutation analysis and interpretation: D.J.T., A.M.-D., J.R.G. Patient collection, study design, data review and overall supervision: M.J.A. **Munich:** Study oversight: S. Kääh, A. Pfeufer. Patient collection: B.M.B., E.M. Genotyping: H.P. **Nantes:** Scientific management: J.-J.S. Clinical, genetic information collection: S.C. *ATP2A2* sequencing: S.C. Screening for mutations in LQT1, LQT2 and LQT3 and clinical data collection: J. Barc. LQTS gene diagnosis management: F. Kyndt. Patient enrollment: V.P. **Pavia:** Patient collection, patient selection and molecular screening supervision: L.C., P.J.S. *SRL* mutation screening: A.G., R.I. **Toronto:** Identification of patients with LQTS free of LQT1, LQT2 and LQT3 mutations: R.M.H. Program codevelopment: S.W.S.

**DAPPLE analysis.** Concept, design and analysis: E.J.R. Supervision: K.L., M.J.D.

**Immunoprecipitation experiments.** Proteomic experiments and analysis: A.L. Overall study supervision: J.V.O.

## COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the [online version of the paper](#).

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## ONLINE METHODS

**Study cohorts.** Cohorts for QT-interval association analyses included individuals largely with population- or community-based ascertainment and a few with case-control sampling for traits not strongly associated with QT interval. Mandatory exclusions included presence of atrial fibrillation or atrial flutter and presence of QRS duration of >120 ms or presence of right or left bundle branch block. Optional exclusions included use of QT interval-altering medications, presence of a pacemaker or implantable cardioverter defibrillator or pregnancy. All studies were reviewed by local ethics committees, and all participants provided informed consent.

**Genotyping, imputation and quality control.** GWAS used a variety of genome-wide genotyping arrays. All studies used hidden Markov model approaches to impute genotypes at unmeasured HapMap SNPs so that a common set of 2.5 million SNPs was available across all discovery samples. Monomorphic SNPs and SNPs with  $\beta$  estimates larger than 100,000 were removed from all results. Cohort-specific SNP filters on minimum MAF, imputation quality metric, call rate and Hardy-Weinberg equilibrium  $P$  value were selected to minimize any test statistic distortion of the quantile-quantile plot or genomic inflation factor ( $\lambda$ ). Replication genotyping was performed using a variety of arrays.

**Association analyses and meta-analysis.** Genomic control was applied to genome-wide results from each cohort before meta-analysis. Meta-analyses were performed in parallel at two analytic sites using MANTEL<sup>3</sup> or METAL<sup>49</sup> with inverse variance-weighted, fixed-effects meta-analysis. Genome-wide significance was set at  $P < 5 \times 10^{-8}$ , a threshold accounting for the effective number of independent common variant tests in the genome of European-ancestry populations<sup>50</sup>.

**Expression in cardiac samples.** Samples of cardiac tissue were acquired from individuals in the Myocardial Applied Genomics Network. Left ventricular free-wall tissue was collected at the time of cardiac surgery from subjects with heart failure undergoing transplantation or from unused donor hearts. DNA samples were genotyped using the Affymetrix 6.0 genome-wide array, and RNA expression was measured using the Affymetrix Genechip ST1.2 array. Imputation to SNP genotypes in the 1000 Genomes Project was performed. Analyses were restricted to samples with genetically inferred European ancestry. SNP genotype was tested for association with  $\log_2$ -transformed expression levels, after adjustment for age, sex, study site, disease status and batch. Association of each QT interval-associated SNP with all transcripts within 1 Mb of the SNP was examined for 63 QT interval-associated SNPs (5 SNPs were not available owing to poor imputation). SNP-transcript associations meeting experiment-wide significance ( $P < 4.4 \times 10^{-5} = 0.05/1,146$  tests) were examined after additional adjustment for the best *cis*-eQTL SNP for the transcript in question. We inferred that the SNP-transcript association could explain the SNP-QT interval association when the SNP-QT interval association was substantially attenuated after additional adjustment for the best *cis*-eQTL SNP.

**Cardiac enhancer analyses.** Enhancer annotations were generated by integrating combinations of histone modifications obtained from the Roadmap Epigenomics project using ChromHMM<sup>23,51</sup>. We identified SNPs in LD ( $r^2 > 0.8$ ) with each of the 68 QT interval-associated loci using genotype data from the 1000 Genomes Project (CEU population) and computed overlap with ChromHMM-annotated enhancer elements in the left ventricle tissue sample (BC Left Ventricle N41) in the US NIH Roadmap Epigenomics Program<sup>22</sup> using the intersectBED command in BEDTools (v2.12.0). To assess the significance of the overlap, we compared the set of SNPs at 68 QT interval-associated loci against 100,000 sets of randomly sampled control SNPs. Control SNPs

were chosen from the Affymetrix 660W genotyping array and were matched for size of the LD block ( $\pm 5$  SNPs), MAF of the lead SNP ( $\pm 0.1$ ) and distance to the nearest gene ( $\pm 25$  kb if outside of a gene).

**LQTS mutation analysis.** A cohort of 298 unrelated individuals with LQTS negative for mutations in LQT1-LQT3 (191 females (64%); average age = 27  $\pm$  20 years; average QTc = 529  $\pm$  58 ms), who satisfied the case inclusion criteria of QTc  $\geq$  480 ms ( $n = 261$ ; 86%) or Schwartz score<sup>52</sup>  $\geq$  3.0 ( $n = 298$ ; 100%), was derived from 7 international congenital LQTS recruitment centers (Institut du Thorax, Nantes, France ( $n = 91$ ); Mayo Clinic, Rochester, Minnesota, USA ( $n = 72$ ); University of Pavia, Pavia, Italy ( $n = 38$ ); Academic Medical Center, Amsterdam, The Netherlands ( $n = 30$ ); The Hospital for Sick Children, Toronto, Ontario, Canada ( $n = 24$ ); Munich Medical International, Munich, Germany ( $n = 23$ ); and St George's Hospital, London, UK ( $n = 20$ )). Of the 265 cases with a documented clinical history, 175 (66%) were symptomatic with  $\geq 1$  LQTS-related cardiac event (syncope or cardiac arrest). Six genes (*ATP2A2*, *CAV1*, *CAV2*, *SLC8A1*, *SRL* and *TRPM7*), derived from five new genome-wide significant loci, were selected for comprehensive ORF and splice-site mutation analysis. These six candidate genes were chosen on the basis of nominal statistical significance, proximity to the signal of association, absence of multiple nearby genes in the associated interval and known cardiac expression or involvement in ion channel macromolecular complexes. For each gene, mutational analysis was performed using either direct Sanger sequencing-based DNA sequencing of all case samples or an intermediate mutation detection platform (denaturing high-performance liquid chromatography, DHPLC) followed by direct DNA sequencing of only samples showing an aberrant DHPLC elution profile.

**Protein-protein interaction *in silico* analyses.** We used a public database of protein-protein interactions<sup>26</sup>. This database contains 428,430 interactions, 169,810 of which are high-confidence interactions across 12,793 proteins. All human interactions were pooled; reported interactions between proteins encoded by orthologous genes in other organisms, using stringent thresholds for orthology transfer, were also included. Each interaction was assigned a probabilistic score on the basis of the neighborhood of the interaction, the scale of the experiment in which the interaction was reported and the number of different publications in which the interaction had been cited. We used a published algorithm called DAPPLE (Disease Association Protein-Protein Link Evaluator) to build and analyze a network of seed genes<sup>27</sup>. We seeded the network with 12 known mendelian LQTS-related proteins (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *CAV3*, *SNTA1*, *KCNJ2*, *CACNA1C*, *ANK2*, *AKAP9* and *SCN4B*) as well as proteins encoded by genes from 7 previously associated common variant QT-interval loci<sup>3,4</sup>. We considered direct connections among the seed proteins as well as indirect connections through other proteins, filtering on connections between proteins from different loci. DAPPLE evaluates the significance of the network and individual proteins within it by comparing it to 10,000 random, matched networks that are generated using a within-degree node-label permutation<sup>27</sup>. We considered the ability of protein-protein interactions to identify proteins newly associated in the QT-IGC meta-analysis. We translated the new loci into genes, identifying 124 genes in total, 85 of which were in the InWeb database.

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## Erratum: Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization

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In the version of this article initially published online, the name of Fabiola del Greco M was misspelled in the author list. The error has been corrected for the print, PDF and HTML versions of this article.