

MTMR4 variants have opposite gene-specific impact on life-threatening arrhythmic risk in type 1 and 2 long QT syndrome

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Abstract

Background and Aims

Modifier genes may cause different clinical phenotypes in patients with long QT syndrome (LQTS) carrying the same pathogenic variant. Variants in the *MTMR4* gene have been previously associated, via patient-specific cardiomyocytes derived from induced pluripotent stem cells, with variable arrhythmic risk in a family with the p.Y111C-LQT1 mutation. This study aimed to evaluate the broader clinical impact of *MTMR4* variants in patients with LQT1 and LQT2.

Methods

A total of 1192 LQTS patients were analysed: 638 with LQT1, 432 with LQT2, and 122 Swedish carriers of the p.Y111C-LQT1 variant. The association between *MTMR4* variants and clinical severity was assessed by comparing patients with severe symptoms (cardiac arrest or syncope on beta-blockers) vs asymptomatic or mildly symptomatic individuals. ECG parameters, including Tpeak-Tend and T-wave heterogeneity, were also evaluated.

Results

In the LQT1 cohort, there was a significant decreasing pattern for cardiac events across *MTMR4* genotypes (AA:15.9%, Aa:11.6%, aa:6.3%), while an opposite trend was apparent in the LQT2 cohort (AA:16.5%, Aa:18.2%, aa:27.6%). No pattern was apparent in the Swedish cohort. In the combined LQT1 cohort, the aa genotype was found in 15% of 702 mild/asymptomatic vs 1.7% of 58 with severe symptoms ($P = .002$). Vice versa, in LQT2, aa was more frequent in severe cases (24.1% vs 11.9%, $P = .014$). QTc was not associated with *MTMR4*, but the repolarization markers supported a gene-specific directionality of arrhythmic risk.

Conclusions

The *MTMR4* minor allele in homozygosis exerts a gene-specific and opposite impact on arrhythmic risk in LQTS. This finding should influence risk stratification in clinical practice.

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Structured Graphical abstract

Key Question

In a familial p.Y111C-LQT1 duo, *MTMR4* gene variants reduced the NEDD4L-dependent ubiquitination-mediated ion channel degradation resulting in a decreased arrhythmogenic substrate. Is this finding generalizable to a more heterogeneous LQT1 cohort? Do *MTMR4* variants similarly impact arrhythmic risk among LQT2 patients?

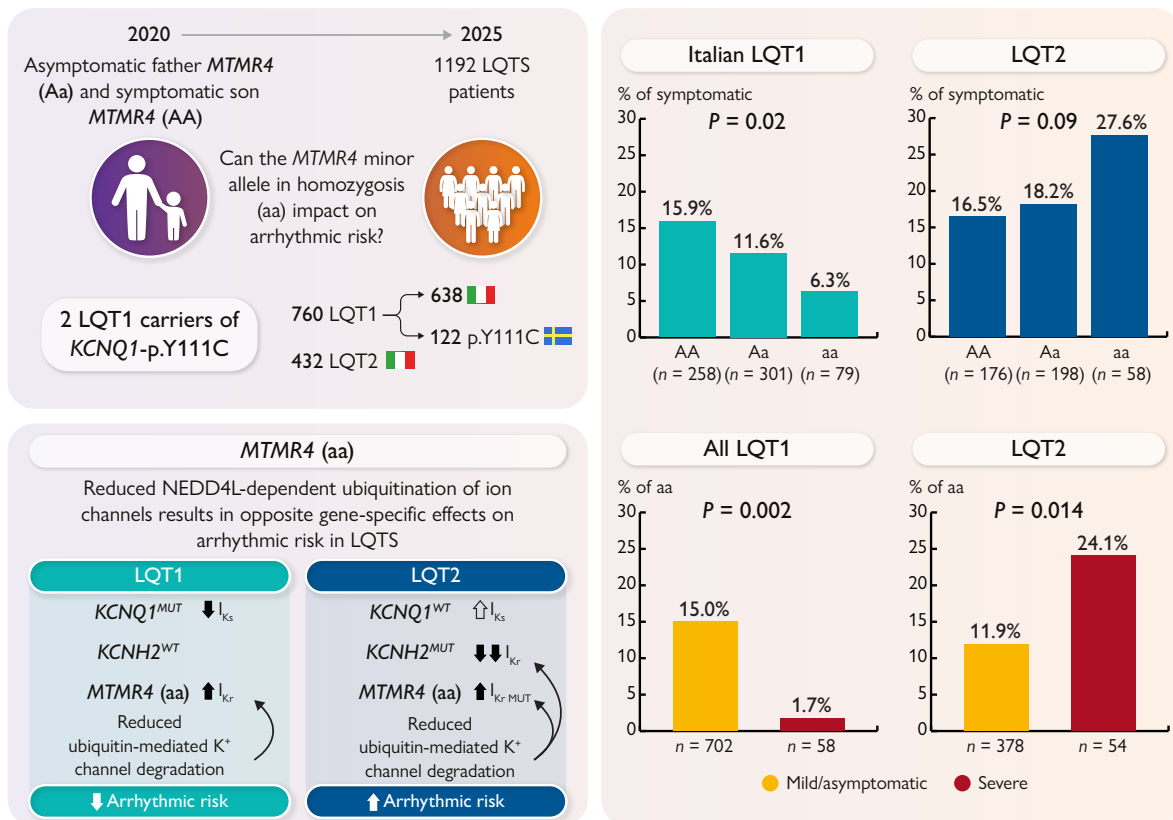
Key Finding

MTMR4 minor allele in homozygosity (aa) associated with lower arrhythmic risk for LQT1 and with a higher arrhythmic risk for LQT2 patients. Furthermore, among LQT1 patients aa genotype was found in 15% of mild/asymptomatic patients versus 1.7% of those with severe symptoms. Among LQT2, this association was in the opposite direction.

Take Home Message

MTMR4 variants act as modifiers of the LQTS phenotype in a gene-specific manner. Genetic screening for recognized modifier genes in LQTS may impact on risk stratification and guide in clinical practice.

Impact of *MTMR4* variants on arrhythmic risk



Upper panel on the left: Based on the original observation in a familial LQT1 duo carrying the *KCNQ1*-p.Y111C variant, the association between *MTMR4* minor allele homozygosity and clinical severity was investigated in a large cohort of LQT1 and LQT2 patients. Panel on the right: (Top) Prevalence of Italian LQT1 and LQT2 patients experiencing any cardiac event according to *MTMR4* genotype (A = major allele; a = minor allele). In LQT1, the proportion of symptomatic patients progressively decreases across carriers of zero (AA), one (Aa), or two (aa) *MTMR4* minor alleles, whereas the opposite trend is observed in LQT2. (Bottom) The aa genotype was identified in 15% of mild/asymptomatic LQT1 patients compared with 1.7% of those with a severe phenotype; in LQT2 patients, the association was observed in the opposite direction. Lower panel on the left: Schematic illustration of the proposed mechanistic hypothesis explaining the gene-specific opposite impact of *MTMR4* minor allele homozygosity on arrhythmic risk in LQTS. It is proposed that *MTMR4* variants modulate arrhythmic risk in LQT1 and LQT2 patients by differentially impacting the repolarization reserve through enhancement of I_{Kr}, being protective when I_{Kr} is not mutated (LQT1), detrimental when it is mutated (LQT2).

LQTS, long QT syndrome; LQT1, long QT syndrome type 1; LQT2, long QT syndrome type 2

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Keywords

Long QT syndrome • Arrhythmias • Sudden cardiac death • Induced pluripotent stem cell-derived cardiomyocytes • NEDD4L • *MTMR4*

Introduction

A daunting question for cardiologists caring for patients with arrhythmias of genetic origin is why siblings carrying the same disease-causing variant may have a strikingly different arrhythmic risk. The answer probably lies in those genetic factors capable of modifying, in either direction, the consequences of disease-causing variants commonly referred to as 'modifier genes'.¹ A number of them have been identified, especially for the long QT syndrome (LQTS),^{2,3} a genetic disorder characterized by a rather clear genotype-phenotype correlation.⁴ Although the underlying mechanism remains incompletely understood for several of these modifiers,^{5–10} it has been partially clarified for two variants in the myotubularin-related protein 4 (*MTMR4*) gene, which is an upstream regulator of NEDD4L, an E3 ubiquitin-protein ligase involved in channel protein degradation.¹¹

By using human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) from a severely symptomatic son and from his asymptomatic father carrying the same LQT1-causing *KCNQ1*-p.Y111C variant, we provided biological evidence that variants of the *MTMR4* gene partly correct the defect in potassium channel turnover, thus mitigating the clinical manifestations of the disease in the asymptomatic father.¹¹ This is the consequence of the reduction of the NEDD4L-dependent ubiquitination-mediated ion channel degradation, which results in a decreased arrhythmogenic substrate, most likely by a compensatory increase in I_{Kr} .¹¹ Despite its conceptual importance, the significance of our finding was greatly limited by being dependent on just one pair of patients.

To verify whether our observation had a real clinical impact, we had to see whether the apparently 'protective' minor allele would, or not, be associated with a different arrhythmic risk in an adequate number of LQT1 patients. Accordingly, we examined the association with a severe arrhythmic phenotype of the minor allele in homozygosity, as we thought that a 'double dose' would be necessary for any meaningful 'therapeutic effect.'

To assess the clinical significance of the *MTMR4* variants, we examined a large cohort of LQT1 patients, comprising Italian patients with unselected disease-causing variants and a Swedish LQT1 founder population segregating the *KCNQ1*-p.Y111C variant, the same present in the father-son duo.^{12,13} Since our mechanistic hypothesis was suggesting the possibility of a gene-specific effect, we also verified the relevance of *MTMR4* variants in a large cohort of LQT2 patients.

Methods

Patients

We studied two Italian cohorts of LQT1 and LQT2 patients with different disease-causing variants and a Swedish founder population carrying the *KCNQ1*-p.Y111C variant,^{12,13} henceforth SWE-p.Y111C-LQT1. Patients with digenic or double variants on the same gene, including Jervell Lange-Nielsen syndrome patients,¹⁴ or with a first cardiac event after age 50, were not included.

Phenotype characterization

We defined as 'severe arrhythmic phenotype' at least three syncope off therapy or just one on β -blocker therapy or any of the following: documented ventricular tachycardia/ventricular fibrillation, aborted

cardiac arrest (ACA), appropriate implantable cardioverter-defibrillator (ICD) shock, or sudden cardiac death (Severe). Conversely, we regarded the occurrence of 1–2 syncope off therapy, followed by the complete lack of symptoms once on β -blocker therapy, as a marker of low risk ('mild phenotype') and not significantly different from being asymptomatic (Mild/Asymptomatic). Accordingly, we compared the severe phenotype vs the joint asymptomatic and mild phenotype.

ECG analysis

We analysed three ECG parameters associated with risk for life-threatening arrhythmias: QT interval, Tpeak-Tend interval,¹⁵ and the T-wave heterogeneity index (TWH).¹⁶ Heart rate-corrected QT interval (QTc) and Tpeak-Tend interval were calculated by Bazett's formula. In a subset of 110 Italian LQT1 and 109 LQT2 subjects, paper ECGs were scanned at a high-resolution (600 DPI) and digitized with a widely used high-resolution commercial software, 'ECGScan' (AMPS-LLC, New York, NY, USA).¹⁷ The resulting waveforms were exported as digital ECG files for subsequent analysis. The Tpeak-Tend interval was assessed on the 12-lead vector magnitude (VM), e.g., the square root of the sum of squares from the individual median beats of each lead. On the VM lead, the Tpeak point is defined as the apex of the T wave, whereas the Tend is computed by applying the least squares (return to baseline) approach. The TWH index was computed on each beat by applying a method previously described, based on the second central moment analysis.¹⁸ Briefly, for each patient during rest, the index is defined on the averaged waveform as the maximum splay in microvolts from the J-point to the end of the T wave (JT interval).¹⁸ This is a semiautomated process performed by an investigator blinded to genotypes.

Genetic screening

For the Italian cohort, comprehensive genetic testing of *KCNQ1* and *KCNH2* genes was conducted with standard genetic protocols mainly through next-generation sequencing gene panels. All clinically relevant genetic variants identified were confirmed with Sanger sequencing. The only exception is represented by genotype-positive LQTS patients screened before 2013 by denaturing high performance liquid chromatography and/or Sanger sequencing.

Genetic variants were classified in accordance with the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology guidelines¹⁹ as pathogenic (P) or likely pathogenic (LP). A few variants of unknown significance (VUS) were also included if novel (i.e. absent from all publicly available exome/genome databases and published data) and considered to be linked to the disease on the basis of ECG features and/or clinical events highly suggestive of a specific LQTS genetic subtype. Genotype-phenotype correlation in the family and functional data conclusive for a trafficking defect were examined for further support.

For the Swedish p.Y111C-LQT1 variant, the genetic analysis has been previously reported.¹²

MTMR4 variant genotyping

Targeted genotyping of two proposed modifier variants (rs2302189 and rs3744108) in the *MTMR4* gene was performed using a TaqMan qPCR assay, using commercially available TaqMan probes (Thermo Fisher Scientific). For rs2302189, we used C__15757289_10 TaqMan SNP Genotyping assay, and for rs3744108, we used C__25960112_20 TaqMan SNP Genotyping assay (Thermo Fisher Scientific). TaqMan Genotyping Master Mix was used for both assays (cod.4371355, Thermo Fisher Scientific). The rs-numbers for denoting the *MTMR4* variants were obtained from the dbSNP database (www.ncbi.nlm.nih.gov/projects/SNP). Ancestral (major) and derived (minor)

alleles were denoted as 'A' and 'a,' respectively (AA- major homozygote, Aa- heterozygote, and aa- minor homozygote).

Polygenic risk score

The QT polygenic risk score (QT-PRS) was calculated using PLINK v2 with the $-score$ function, based on a weighted sum of risk alleles across 68 independent common variants (single nucleotide polymorphisms) that reached genome-wide significance in the study by Arking et al.²⁰ For variants with missing genotypes, allele dosages were imputed using the product of the population minor allele frequency and the sample ploidy. The resulting scores were then standardized to a mean of 0 and a standard deviation consistent with the normalization approach described by Lahrouchi et al.²¹

Statistical analysis

Continuous data, reported as mean $\pm$ standard deviation, were analysed by the Mann-Whitney U test or by Student's t-test and by Kruskal-Wallis test, as appropriate. The relationship between PRS and QTc was assessed by non-parametric Spearman's correlation. Categorical data were reported with frequencies and relative percentages and compared by the χ^2 or Fisher's exact tests. For association analyses involving the ordered *MTMR4* genotype variable (AA, Aa, aa), the Cochran-Armitage trend test for proportions and the Jonckheere-Terpstra trend test for continuous variables were used. Odds ratios (ORs) with 95% confidence interval (CI) were calculated to estimate the association of phenotype with the LQTS groups and with the *MTMR4* genotypes. Two-sided *P*-values $< .05$ were considered statistically significant. IBM SPSS Statistics version 29.0 and R software version 4.5.2 were used for computation.

Results

Study population

We studied a total of 1192 LQTS patients: 638 LQT1 and 432 LQT2 with unselected disease-causing variants (Supplementary data online, Table S1), and 122 SWE-p.Y111C-LQT1. Allele and genotype frequencies of *MTMR4* variants in the study population are shown in Table 1. Targeted genotyping of the two proposed modifier variants in the *MTMR4* gene revealed a relatively high minor allele frequency (MAF) in all three study cohorts,

consistently with the reported MAF for rs2302189 and rs3744108 in the dbSNP database (range 0.35–0.38). In the SWE-p.Y111C-LQT1 population, MAF was even higher for both *MTMR4* variants (0.47–0.48). Linkage disequilibrium between the two loci was complete in the two Italian cohorts and almost complete in the SWE-p.Y111C-LQT1 population.

Table 2 shows the clinical characteristics of the study cohorts. The mean QTc in the Italian LQT1 cohort was significantly shorter compared to the other two cohorts (466 ± 35 vs 483 ± 35 and 483 ± 44 ms, respectively, $P < .0001$); no significant differences were observed across *MTMR4* SNP genotypes in each group. Patients symptomatic for any cardiac event were 120/760 (15.8%) among LQT1 and 81/432 (18.8%) among LQT2. An important difference was noted between the two LQT1 groups as the Italian patients with symptoms were 81/638 (12.7%) compared to a much higher frequency among the Swedish patients, 39/122 (32.0%) (OR 0.31; 95% CI 0.20–0.48, $P < .0001$). A severe phenotype was observed in 58/760 LQT1 (7.6%) and 54/432 LQT2 (12.5%).

Symptoms and *MTMR4* allelic distribution

The Italian LQT1 cohort showed a significant progressive reduction of symptomatic patients across carriers of no (AA), one (Aa), or two (aa) *MTMR4* minor alleles (15.9%, 11.6%, 6.3%; $P = .019$) (Figure 1A), while the LQT2 cohort showed an opposite trend (16.5%, 18.2%, 27.6%; $P = .099$) (Figure 1B). Irrespective of their statistical significance, but given their opposite directionality, these trends were regarded as biologically intriguing. Of note, the 39 SWE-p.Y111C-LQT1 patients with cardiac events were equally distributed by *MTMR4* variant genotypes (35.5%, 29.7%, 33.3%).

Arrhythmic risk, *MTMR4* alleles, and LQTS genotype

We then determined the association between risk for life-threatening arrhythmias and the minor allele in homozygosis, representing a 'double dose' of the putative 'protective allele,' by comparing the frequency of aa genotype carriers between two groups of patients: those with a history of severe arrhythmic

Table 1 Allele and genotype frequencies of *MTMR4* single nucleotide polymorphisms in the three study cohorts

<i>MTMR4</i> variant ID	Alleles (derived allele in bold)	Genotype ^a	LQT1 (n = 638)		LQT2 (n = 432)		SWE-p.Y111C-LQT1 ^b (n = 122)	
			N (%)	MAF	N (%)	MAF	N (%)	MAF
rs2302189	A/C	AA (AA)	258 (40.4)	0.36	176 (40.7)	0.36	31 (25.4)	0.48
		AC (Aa)	301 (47.2)		198 (45.8)		64 (52.5)	
		CC (aa)	79 (12.4)		58 (13.4)		27 (22.1)	
rs3744108	G/C	GG (AA)	258 (40.4)	0.36	176 (40.7)	0.36	33 (27.1)	0.47
		GC (Aa)	301 (47.2)		198 (45.8)		63 (51.6)	
		CC (aa)	79 (12.4)		58 (13.4)		26 (21.3)	

Data are absolute and relative (%) frequencies.

MAF, minor allele frequency.

^aA/a denotes ancestral/major (A) and derived/minor (a) alleles.

^bLinkage disequilibrium between the two loci was near-complete in the Swedish founder population and complete in the two Italian cohorts.

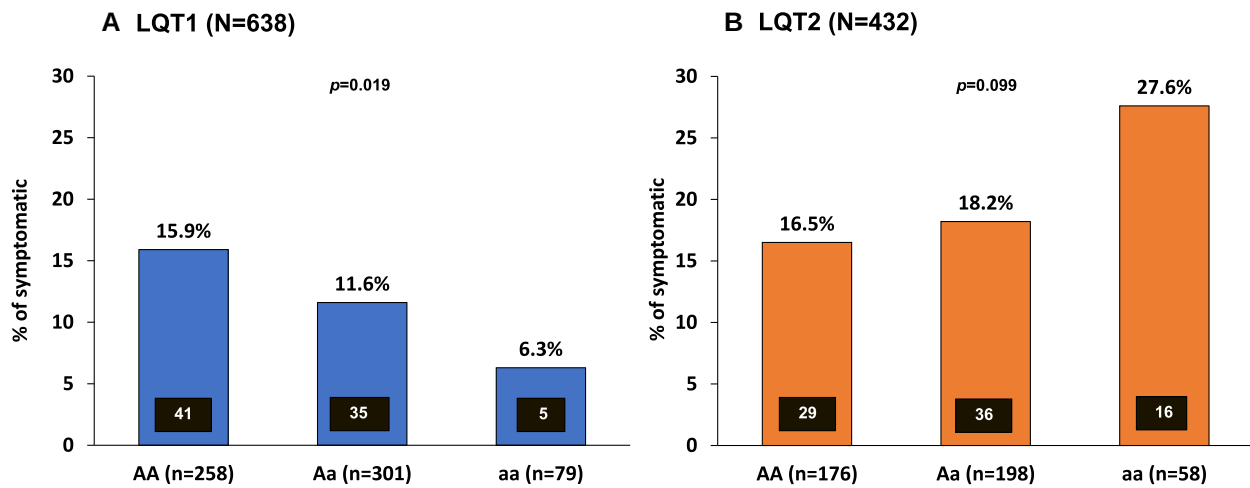
Table 2 Clinical characteristics of the three study cohorts

	All LQT1	LQT1 Italian cohort	SWE-p.Y111C-LQT1	LQT2
Genotype-positive cases, N	760	638	122	432
Females, n (%)	431 (57)	364 (57)	67 (55)	205 (47.5)
QTc (ms), mean $\pm$ SD ^a	469 $\pm$ 36	466 $\pm$ 35	483 $\pm$ 35	483 $\pm$ 44
QTc <440 ms, n (%)	144 (19)	137 (21)	7 (6)	60 (14)
QTc (ms) by <i>MTMR4</i> genotype, mean $\pm$ SD ^b				
AA	467 $\pm$ 34	465 $\pm$ 34	476 $\pm$ 26	479 $\pm$ 42
Aa	470 $\pm$ 37	467 $\pm$ 35	484 $\pm$ 41	487 $\pm$ 46
aa	471 $\pm$ 36	466 $\pm$ 36	487 $\pm$ 30	481 $\pm$ 42
Symptomatic (any CE), n (%)	120 (16)	81 (13)	39 (32)	81 (19)
Mild	62 (8)	36 (6)	26 (21)	27 (6)
Severe	58 (8)	45 (7)	13 (11)	54 (13)
Asymptomatic	640 (84)	557 (87)	83 (68)	351 (81)

Due to near-complete linkage disequilibrium between the two loci, producing minimal differences between the two variants, in all analyses involving the Swedish p.Y111C-LQT1 population data presentation refers for simplicity to *MTMR4* rs2302189.

^aP < .001 for QTc in the LQT1 Italian cohort vs LQT2 and SWE-LQT1 cohort.

^bQTc by *MTMR4* genotype was not significantly different in each of the three study cohorts (Italian LQT1, P = .87; SWE-LQT1 P = .24; LQT2 P = .18).

**Figure 1** Frequency of symptomatic patients across *MTMR4* SNPs genotypes in the LQT1 and LQT2 cohorts

events and those who were either asymptomatic or with a mild phenotype ('mild/asymptomatic').

Among all 702 'mild/asymptomatic' LQT1 patients, the aa genotype was carried by 105 (15.0%), while it was present only in one patient (1.7%) among the 58 subjects with a severe phenotype, thus suggesting a potential 'protective' role of the minor allele in homozygosis (OR 0.10; 95% CI: 0.01–0.55, P = .002) (Figure 2A). Among the LQT2 cohort, there was an opposite pattern. The aa genotype was carried by 11.9% of patients of the 'mild/asymptomatic' group (45/378), while by contrast, it was almost twice as frequently present (13/54,

24.1%) in patients with a severe phenotype (Figure 2B), thus indicating its association with a higher arrhythmic risk (OR 2.35; 95% CI: 1.14–4.69, P = .014).

A subgroup analysis of the LQT1 population confirmed the protective role of the aa genotype in the Italian cohort (13.3% in the 'mild and asymptomatic' patients vs 0% in the severely symptomatic; P = .004) (Figure 3A). The same trend was found in the SWE p.Y111C-LQT1 patients (23.9% and 22.9% for rs2302189 and rs3744108, respectively, vs 7.7%), but without reaching statistical significance (Figure 3B).

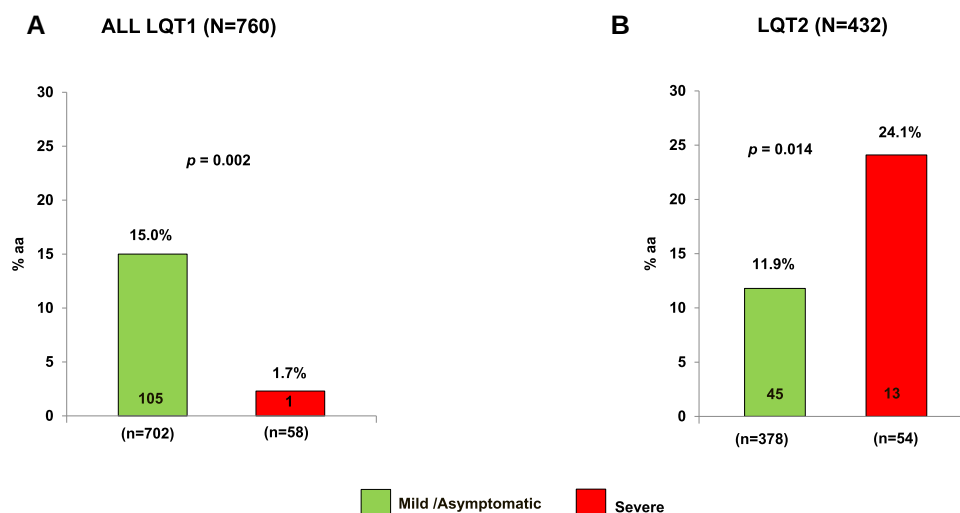


Figure 2 Frequency of *MTMR4* SNPs aa genotype among patients according to the predefined phenotype characterization of LQTS patients in the study cohorts. (A) All LQT1 patients; (B) LQT2 patients

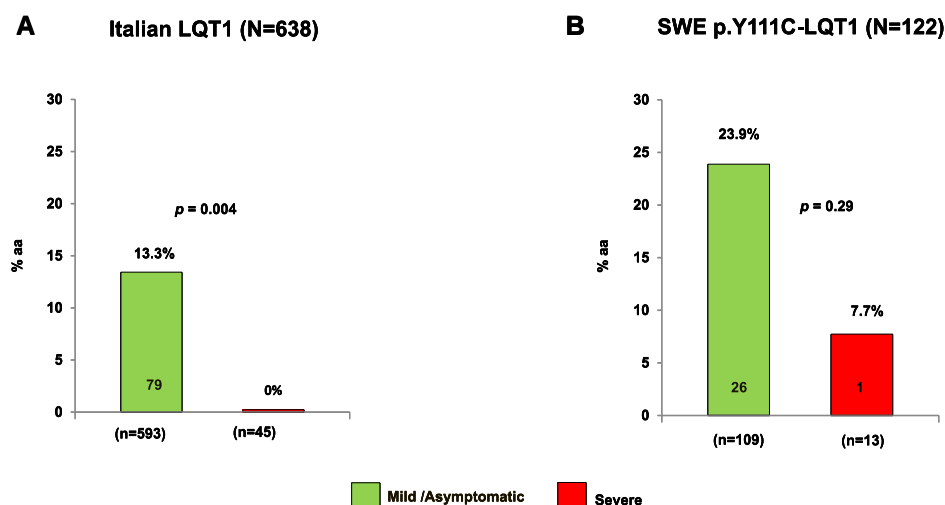


Figure 3 Frequency of *MTMR4* SNPs aa genotype among patients according to the predefined phenotype characterization of LQTS patients in the study cohorts. (A) Italian LQT1 cohort; (B) Swedish LQT1 cohort

Arrhythmogenic substrate

The above findings suggested that the aa genotype of *MTMR4* variants might be associated with either a decrease or an increase in cardiac electrical instability, depending on the primary genetic defect. In the LQT1 subset, there was no significant difference between aa carriers ($n = 26$) and those with no (AA) or just one minor allele (Aa) of either *MTMR4* variant ($n = 83$) in QTc (453 ± 38 ms vs 457 ± 33 ms) and Tpeak-Tend (89 ± 21 ms vs 86 ± 15 ms) (Figure 4A). However, a significantly lower TWH was measured among the aa patients ($n=27$) compared to those with the AA and Aa genotypes (47 ± 35 μ V vs 83 ± 59 μ V, $P = .001$) (Figure 4B), with the mean value in normal

controls being 35 ± 23 μ V.²² This lower TWH fits with the lower risk among the aa LQT1 patients. Interestingly, the only symptomatic LQT1 patient with the protective allele in homozygosis exhibited the highest TWH level. Similarly, in the LQT2 subset, there was no significant difference in QTc within the *MTMR4* genotypes (462 ± 41 ms vs 451 ± 38 ms). However, the ECG analysis revealed a different picture compared to the LQT1 group: the Tpeak-Tend was significantly prolonged in aa ($n = 31$) vs AA + Aa ($n = 76$) (113 ± 33 ms vs 91 ± 23 ms, $P = .0002$), representing increased arrhythmogenicity (Figure 4C), while the TWH was not significantly different by *MTMR4* genotype groups (Figure 4D).

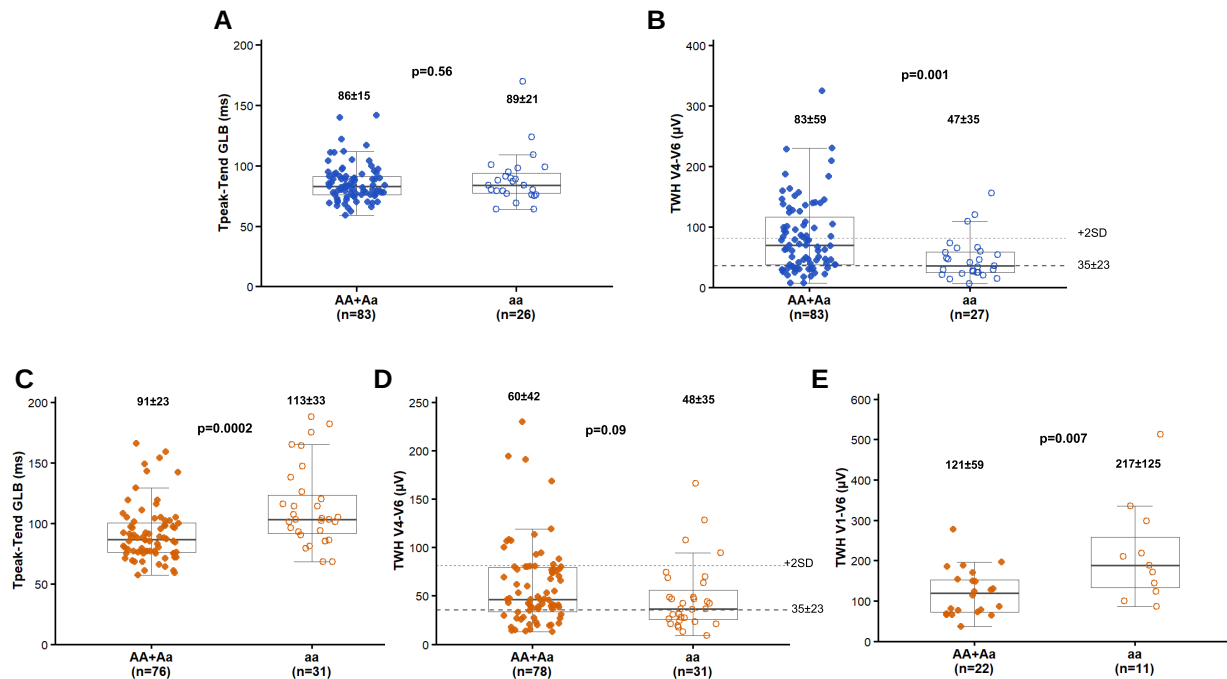


Figure 4 Dot plots showing the distribution of Tpeak-Tend and TWV values according to *MTMR4* SNPs genotype (AA + Aa vs aa). (A) Individual Tpeak-Tend values in the Italian LQT1 sample (data missing for one patient in the aa genotype group). (B) Individual TWV values in LQT1 patients. Dashed line represents the average TWV recorded in normal controls²² and the dotted line corresponds to 2 SD above this mean value. The number of subjects with TWV exceeding the limit of +2 SD over the mean for normality was significantly smaller in the aa group compared to the pooled AA + Aa group (3/27, 11% vs 35/83, 42%, $P = .003$). (C) Individual Tpeak-Tend values in the LQT2 sample. (D) Individual TWV values in LQT2 patients. (E) Individual TWV values in the small subset of LQT2 patient carriers of trafficking defective variants. GLB stands for global lead, i.e. the 12-lead vector magnitude. In all panels, the box-and-whisker plots depict median and interquartile range (IQR 25th – 75th percentile); whiskers correspond to $1.5 \times \text{IQR}$

When we analysed the subgroup of 33 LQT2 patients known to carry a trafficking defect variant, the mean value of TWV was significantly higher among the aa vs AA + Aa ($217 \pm 125 \mu\text{V}$ vs $121 \pm 59 \mu\text{V}$, $P = .007$) (Figure 4E). In the Discussion, we will present our mechanistic hypothesis that is consistent with this finding.

Polygenic risk score in the *MTMR4* study sample

The possibility that the gene-specific opposite impact of *MTMR4* variants on clinical outcome could be somehow confounded by a more complex genetic architecture was considered. In a subset of 468 LQTS patients of the Italian cohort (280 LQT1, 188 LQT2), a QT-PRS was created based on the genotyping of 68 common variants known to be associated with the QT interval in the general population,²⁰ and possibly to modulate the arrhythmic risk in both drug-induced QT prolongation²³ and in LQTS.²⁴ QT-PRS showed a weak positive correlation with QTc (Spearman's rho 0.116, $P = .053$, in LQT1; rho 0.21, $P = .004$ in LQT2). As a whole, QT-PRS was neither significantly different according to the LQTS genotype ($P = .25$) nor between symptomatic and asymptomatic individuals ($P = .52$), although, as expected, QTc was significantly longer among LQT2 patients ($P < .0001$) and among patients with a history of arrhythmic events ($P < .0001$). When we focused on the small number of

homozygous carriers of *MTMR4* minor allele with a different risk of severe events according to LQTS genotype (0/38 LQT1 vs 4/20 LQT2, $P = .01$), the difference in QT-PRS between LQT1 and LQT2 patients was not statistically significant (Figure 5). This suggests an independent role of the *MTMR4* variants in the propensity to arrhythmias.

Discussion

The present study shows that relatively common genetic variants, of which we have identified the molecular mechanism of action,¹¹ are associated in a gene-specific manner with either an increased or decreased risk of life-threatening arrhythmias among LQTS patients. Specifically, the *MTMR4* minor allele in homozygosis is associated with lower arrhythmic risk for LQT1 and higher arrhythmic risk for LQT2 patients (Structured Graphical Abstract).

This finding has major clinical and conceptual implications. The presence, in homozygosis, of the minor allele should alert the cardiologists managing LQT1 and LQT2 patients to implement either a less or a more aggressive management strategy, according to precision medicine.²⁵ The present data also indicate that targeting ion channel degradation might become a novel strategy for arrhythmia prevention in LQTS.

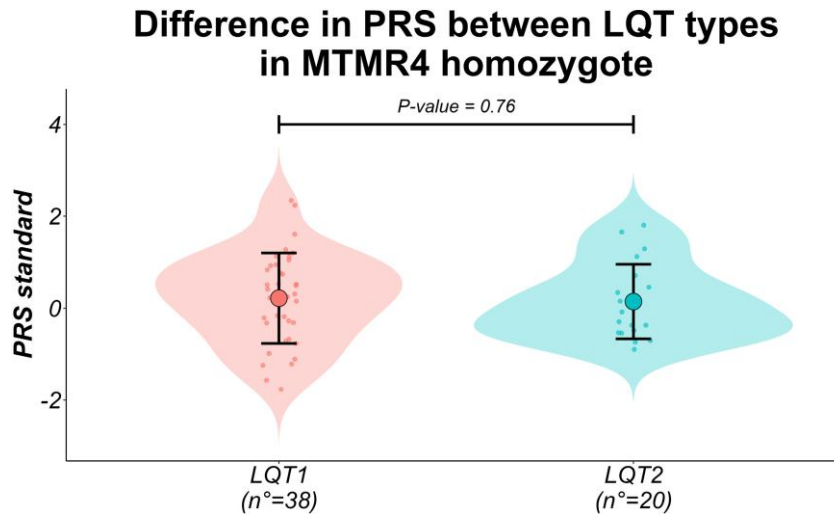


Figure 5 Distribution of QT polygenic risk score (PRS) values in the small subset of 38 LQT1 and 20 LQT2 homozygous carriers of the *MTMR4* minor allele for whom the PRS was available. Circles and error bars represent mean and SD

A mechanistic hypothesis

The differences observed between LQT1 and LQT2 patients could be explained by the relative weight of I_{Ks} and I_{Kr} in cardiac repolarization under basal conditions.^{26,27} In our cell modelling study, we had shown that the presence of the minor allele of *MTMR4* resulted in an increase in I_{Kr} current in the asymptomatic LQT1 subject compared to the symptomatic one,¹¹ due to both reduced degradation and increased turnover at the plasma membrane level of hERG, thus conferring antiarrhythmic protection by increasing repolarization reserve.²⁸ In the case of LQT2 patients, we hypothesize that a similar compensatory mechanism intervenes at the level of the $Kv7.1$ channel, but since the I_{Ks} current provides a limited contribution to arrhythmic susceptibility compared to that of I_{Kr} , this results in insufficient protection for the patient.

Furthermore, since the majority of LQT2 variants exert their pathogenic role through trafficking defects of $Kv11.1$ channels,²⁹ a reduction in the ubiquitination-dependent degradation rate of mutant $Kv11.1$ via NEDD4L would increase the chances of incorporating mutant $Kv11.1$ sub-units into the heterotetramers, thus enhancing the potential dominant negative effects of some $Kv11.1$ trafficking-deficient variants, ultimately leading to a further reduction of I_{Kr} and increasing the risk of arrhythmias. This concept has recently provided a mechanistic explanation for the worse outcome of LQT2 carriers of *KCNH2* missense variants.^{30,31} The fact that LQT2 patients with trafficking defects presented high TWH values represents evidence in support of our hypothesis.

Rationale for analysis

We made two choices important for our data analysis. The first was to focus on the potential effect of the minor allele in homozygosis. We hypothesized that to counteract significant arrhythmogenic cardiac electrical instability, it would have been necessary to have a 'double dose' of the 'protective' allele (aa). The second was to accept the experience-based clinical

knowledge that not all arrhythmic episodes have the same importance in LQTS and that one or two syncopal episodes off therapy, followed by the complete lack of symptoms once on β -blocker therapy have very different implications compared to either syncope despite therapy or cardiac arrest and could thus be analysed together with the absence of symptoms (mild/asymptomatic).

Cardiac electrical instability

TWH is a measure of interlead non-uniformity of repolarization. This index of susceptibility to life-threatening arrhythmias has been studied in numerous experimental conditions of myocardial ischaemia and sympathetic stimulation, demonstrating a link between elevated heterogeneity and susceptibility to malignant ventricular arrhythmias.¹⁶ TWH stratified sudden cardiac death risk in almost 6000 patients with a broad spectrum of clinical conditions.³² The main distinction between TWH and QTc is that the former method examines the spatiotemporal relationship among adjoining leads. By comparison, QTc is determined as the longest value in a single lead such as V_5 . In a head-to-head comparison of repolarization indices in >5600 Finnish subjects, TWH was found to be superior to QTc in estimating sudden cardiac death risk.^{32,33} Tpeak-Tend has also been recognized as a marker of susceptibility to life-threatening events.^{15,34} Its prolongation, reflecting increased transmural dispersion of repolarization, has proven to be useful in identifying patients at risk for sudden cardiac death in different settings even when QTc was not discriminating.^{35,36}

In the selected sample of our Italian LQT1 cohort, the homozygous carriers of the *MTMR4* variants' minor allele had significantly lower values of TWH, whereas Tpeak-Tend was similar across different *MTMR4* genotypes. Vice versa, Tpeak-Tend was markedly prolonged among LQT2 patients who were homozygous carriers of the minor allele, but the TWH values in the overall LQT2 cohort did not show variations among the different *MTMR4* genotypes. However, as already mentioned, in those

LQT2 carriers of variants causing trafficking defects, the TWH was significantly higher in the aa group. Overall, these data support our mechanistic hypothesis and may explain why the risk of events in the presence of the aa genotype decreases in LQT1 patients while it increases in LQT2 patients, especially those with variants causing trafficking defects.

The minor allele and severe arrhythmias in LQT1

In the combined cohort of LQT1 patients, the percentage of carriers of the *MTMR4* aa genotype was significantly lower among those with a severe phenotype compared to those belonging to the 'mild/asymptomatic' group. The subgroup analysis of the Swedish cohort showed the same trend which, however, did not achieve statistical significance. This could be explained by both insufficient numerosity compared to variant effect size and especially by the fact that the SWE-p.Y111C-LQT1 cohort is a founder population^{12,13} whose genetic background likely diverges from that of a more mixed population.^{37,38} Indeed, the QTc of the 20 *KCNQ1*-p.Y111C present in the Italian LQT1 cohort is 464 ± 28 ms, quite different from that of the Swedish cohort (483 ± 35 ms, $P < .05$) but perfectly in line with that of the entire Italian LQT1 cohort (466 ± 35 ms). Among the Swedish patients, a founder-specific genetic background, enriched in additional modifier variants, may drive clinical severity and mask the protective role of the *MTMR4* minor allele. Conversely, in the Italian LQT1 cohort, where milder phenotypes predominate, the influence of *MTMR4* minor allele emerges clearly and is consistently associated with a less severe clinical phenotype. We suggest that the unique genetic background of the SWE-p.Y111C-LQT1 founder population might act as a confounder to the modifying effects of the *MTMR4* variant.^{37,38} The findings in the large Italian LQT1 cohort show that the impact of the *MTMR4* variant is not affected by the different disease-causing *KCNQ1* variants and that, therefore, it can be generalized.

Limitations

The patient population did not undergo whole exome or whole genome sequencing. Thus, we cannot exclude the possibility that unknown and masked synergistic effects between the *MTMR4* variants and other genes/variants might exist and play a role. However, the analysis of QT-PRS strengthens the direct association between *MTMR4* variants and arrhythmogenicity. The analyses of TWH, Tpeak-Tend, and LQT2 variants causing trafficking defects were performed on a limited subset of patients. While the present study focused on the main clinical aspects, we are aware that the validation of the mechanistic hypothesis proposed to interpret them requires additional evidence to determine the reasons underlying the observed divergent response in LQT1 and LQT2 patients. While our assumption that I_{Kr} was higher in LQT1 carriers of the aa *MTMR4* variants had already been proven,¹¹ the evidence that the same aa genotype causes a severe impairment of the I_{Kr} current in LQT2 patients, especially those with a trafficking defect, still needs to be experimentally validated and addressed in future *in vitro* studies. The study results were not adjusted for potential confounders, whose role, albeit unlikely, cannot be excluded.

Clinical implications and conclusions

The present study shows an unexpected and opposite impact on arrhythmic risk, lower for LQT1 and higher for LQT2 patients, associated with the *MTMR4* minor allele in homozygosis. The validity of this finding is supported by the large number of patients involved. The *MTMR4* and *NEDD4L* interaction offers new insights into the mechanisms of action of modifier genes and their role in arrhythmogenic disorders of genetic origin.¹

The present results prove, perhaps as never before, the importance of genetic screening for a state-of-the-art management of LQTS.^{3,39} Besides searching for variants of LQTS disease-causing genes, it is becoming necessary to screen also for the identified and validated modifier genes.¹ These data have already impacted our own clinical management. Indeed, when we genotype our LQTS patients, our laboratory is now routinely providing us also with the information about the *MTMR4* genotypes. If we learn that an LQT2 patient carries the minor allele in homozygosis, we consider the patient at a somewhat higher risk—obviously in the context of all other clinical information—and make sure, for example, that the β -blocker dose is the highest tolerated.

Cardiologists will have to be careful in assessing the relevance of these modifiers because their impact might be opposite in patients with the disease-causing variant located on different genes, such as those we have shown for LQT1 and LQT2. This novel concept should force all those dealing with LQTS patients to get acquainted with the strengths and weaknesses of 'precision medicine,'²⁵ as the presence of specific variants might impact risk stratification and dictate a more or less aggressive therapeutic strategy. Finally, the development of a drug mimicking the actions of these *MTMR4* SNPs might raise useful options for LQT1 patients.

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Supplementary data

Supplementary data are available at [European Heart Journal](#) online.

Declarations

Disclosure of Interest

Nothing to declare.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding authors.

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Ethical Approval

The analysis of clinical and genetic data was approved by the Ethics Committee of the Istituto Auxologico Italiano number 051806, and by the Regional Ethical Committee in Umeå, Umeå University, Sweden (Dnr 05 – 127 M).

Pre-registered Clinical Trial Number

Not applicable.

REFERENCES

- Schwartz PJ, Crotti L, George AL Jr. Modifier genes for sudden cardiac death. *Eur Heart J* 2018;**39**:3925–31. <https://doi.org/10.1093/eurheartj/ehy502>
- Schwartz PJ, Periti M, Malliani A. The long QT syndrome. *Am Heart J* 1975;**89**: 378–90. [https://doi.org/10.1016/0002-8703\(75\)90089-7](https://doi.org/10.1016/0002-8703(75)90089-7)
- Schwartz PJ, Crotti L. Long QT syndrome. *N Engl J Med* 2025;**393**:2023–34. <https://doi.org/10.1056/NEJMra2400853>
- Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long QT syndrome. Gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;**103**:89–95. <https://doi.org/10.1161/01.CIR.103.1.89>
- Crotti L, Lundquist AL, Insolia R, Pedrazzini M, Ferrandi C, De Ferrari GM, et al. KCNH2-K897T is a genetic modifier of latent congenital long QT syndrome. *Circulation* 2005;**112**:1251–8. <https://doi.org/10.1161/CIRCULATIONAHA.105.549071>
- Crotti L, Monti MC, Insolia R, Peljto A, Goosen A, Brink PA, et al. NOS1AP is a genetic modifier of the long-QT syndrome. *Circulation* 2009;**120**:1657–63. <https://doi.org/10.1161/CIRCULATIONAHA.109.879643>
- Duchatelet S, Crotti L, Peat R, Denjoy I, Itoh H, Berthet M, et al. Identification of a KCNQ1 polymorphism acting as a protective modifier against arrhythmic risk in the long QT syndrome. *Circ Cardiovasc Genet* 2013;**6**:354–61. <https://doi.org/10.1161/CIRCGENETICS.113.000023>
- de Villiers CP, van der Merwe L, Crotti L, Goosen A Jr, George AL, Schwartz PJ, et al. AKAP9 is a genetic modifier of congenital long-QT syndrome type 1. *Circ Cardiovasc Genet* 2014;**7**:599–606. <https://doi.org/10.1161/CIRCGENETICS.113.000580>
- Lahtinen AM, Marjamaa A, Swan H, Kontula K. KCNE1 D85N polymorphism—a sex-specific modifier in type 1 long QT syndrome? *BMC Med Genet* 2011;**12**: 11. <https://doi.org/10.1186/1471-2350-12-11>
- Chai S, Wan X, Ramirez-Navarro A, Tesar PJ, Kaufman ES, Ficker E, et al. Physiological genomics identifies genetic modifiers of long QT syndrome type 2 severity. *J Clin Invest* 2018;**128**:1043–56. <https://doi.org/10.1172/JCI94996>
- Lee Y-K, Sala L, Mura M, Rocchetti M, Pedrazzini M, Ran X, et al. MTMR4 SNVs modulate ion channel degradation and clinical severity in congenital long QT syndrome: insights in the mechanism of action of protective modifier genes. *Cardiovasc Res* 2021;**117**:767–79. <https://doi.org/10.1093/cvr/cvaa019>
- Winbo A, Diamant U-B, Stattin E-L, Jensen SM, Rydberg A. Low incidence of sudden cardiac death in a Swedish Y111C type 1 long-QT syndrome population. *Circ Cardiovasc Genet* 2009;**2**:558–64. <https://doi.org/10.1161/CIRCGENETICS.108.825547>
- Winbo A, Diamant U-B, Rydberg A, Persson J, Jensen SM, Stattin E-L. Origin of the Swedish long QT syndrome Y111C/KCNQ1 founder mutation. *Heart Rhythm* 2011;**8**:541–7. <https://doi.org/10.1016/j.hrthm.2010.11.043>
- Schwartz PJ, Spazzolini C, Crotti L, Bathen J, Amlie JP, Timothy K, et al. The Jervell and Lange-Nielsen syndrome. Natural history, molecular basis, and clinical outcome. *Circulation* 2006;**113**:783–90. <https://doi.org/10.1161/CIRCULATIONAHA.105.592899>
- Antzelevitch C, Di Diego JM. Tpeak-Tend interval as a marker of arrhythmic risk. *Heart Rhythm* 2019;**16**:954–5. <https://doi.org/10.1016/j.hrthm.2019.01.017>
- Verrier RL, Huikuri H. Tracking interlead heterogeneity of R- and T-wave morphology to disclose latent risk for sudden cardiac death. *Heart Rhythm* 2017;**14**:1466–75. <https://doi.org/10.1016/j.hrthm.2017.06.017>
- Badilini F, Erdem T, Zareba W, Moss AJ. ECGScan: a method for conversion of paper electrocardiographic printouts to digital electrocardiographic files. *J Electrocardiol* 2005;**38**:310–8. <https://doi.org/10.1016/j.jelectrocard.2005.04.003>
- Nearing BD, Verrier RL. Tracking cardiac electrical instability by computing interlead heterogeneity of T-wave morphology. *J Appl Physiol* 2003;**95**: 2265–72. <https://doi.org/10.1152/japplphysiol.00623.2003>
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**:405–24. <https://doi.org/10.1038/gim.2015.30>
- Arking DE, Pulit SL, Crotti L, van der Harst P, Munroe PB, Koopmann TT, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. *Nat Genet* 2014;**46**:826–36. <https://doi.org/10.1038/ng.3014>
- Lahrouchi N, Tadros R, Crotti L, Mizusawa Y, Postema PG, Beekman L, et al. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. *Circulation* 2020;**142**: 324–38. <https://doi.org/10.1161/CIRCULATIONAHA.120.045956>
- Araujo Silva B, Hauser TH, Nearing BD, Bortolotto AL, Marum AA, Tessarolo Silva F, et al. Regadenoson-induced T-wave heterogeneity complements coronary stenosis detection by myocardial perfusion imaging in men and women. *Eur Heart J Cardiovasc Imaging* 2021;**22**:1341–9. <https://doi.org/10.1093/ehjci/jeaa128>
- Strauss DG, Vicente J, Johannesen L, Blinova K, Mason JW, Weeke P, et al. Common genetic variant risk score is associated with drug-induced QT prolongation and torsade de pointes risk: a pilot study. *Circulation* 2017;**135**: 1300–10. <https://doi.org/10.1161/CIRCULATIONAHA.116.023980>
- Turkowski KL, Dotzler SM, Tester DJ, Giudicessi JR, Bos JM, Speziale AD, et al. Corrected QT interval-polygenic risk score and its contribution to type 1, type 2, and type 3 long-QT syndrome in probands and genotype-positive family members. *Circ Genom Precis Med* 2020;**13**:e002922. <https://doi.org/10.1161/CIRCGEN.120.002922>
- Gnecchi M, Sala L, Schwartz PJ. Precision medicine and cardiac channelopathies: when dreams meet reality. *Eur Heart J* 2021;**42**:1661–75. <https://doi.org/10.1093/eurheartj/ehab007>
- Johnson DM, Heijman J, Pollard CE, Valentin J-P, Crijns HJGM, Abi-Gerges N, et al. I_{Ks} restricts excessive beat-to-beat variability of repolarization during beta-adrenergic receptor stimulation. *J Mol Cell Cardiol* 2010;**48**:122–30. <https://doi.org/10.1016/j.yjmcc.2009.08.033>
- Volders PGA, Stengl M, van Opstal JM, Gerlach U, Spätsjens RLHMG, Beekman JDM, et al. Probing the contribution of I_{Ks} to canine ventricular repolarization: key role for beta-adrenergic receptor stimulation. *Circulation* 2003;**107**: 2753–60. <https://doi.org/10.1161/01.CIR.0000068344.54010.B3>
- Roden DM. Taking the "idio" out of "idiosyncratic": predicting torsades de pointes. *Pacing Clin Electrophysiol* 1998;**21**:1029–34. <https://doi.org/10.1111/j.1540-8159.1998.tb00148.x>
- Anderson CL, Delisle BP, Anson BD, Kilby JA, Will ML, Tester DJ, et al. Most LQT2 mutations reduce Kv11.1 (hERG) current by a class 2 (trafficking-deficient) mechanism. *Circulation* 2006;**113**:365–73. <https://doi.org/10.1161/CIRCULATIONAHA.105.570200>
- Aizawa T, Wada Y, Hasegawa K, Huang H, Imamura T, Gao J, et al. Non-missense variants of KCNH2 show better outcomes in type 2 long QT syndrome. *Europace* 2023;**25**:1491–9. <https://doi.org/10.1093/europace/ueac269>
- Crotti L. From gene-specific to function-specific risk stratification in long QT syndrome type 2: implications for clinical management. *Europace* 2023;**25**: 1320–2. <https://doi.org/10.1093/europace/uead035>
- Porthan K, Viitasalo M, Toivonen L, Havulinna AS, Jula A, Tikkanen JT, et al. Predictive value of electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval for sudden cardiac death in the general population. *Circ Arrhythm Electrophysiol* 2013;**6**:690–6. <https://doi.org/10.1161/CIRCEP.113.000356>
- Kenttä TV, Nearing BD, Porthan K, Tikkanen JT, Viitasalo M, Nieminen MS, et al. Prediction of sudden cardiac death with automated high-throughput analysis of heterogeneity in standard resting 12-lead electrocardiograms. *Heart Rhythm* 2016;**13**:713–20. <https://doi.org/10.1016/j.hrthm.2015.11.035>

34. Tse G, Gong M, Wong WT, Georgopoulos S, Letsas KP, Vassiliou VS, *et al.* The Tpeak-Tend interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: a systematic review and meta-analysis. *Heart Rhythm* 2017;**14**:1131–7. <https://doi.org/10.1016/j.hrthm.2017.05.031>
35. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, *et al.* Prolonged Tpeak-to-Tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol* 2011;**4**:441–7. <https://doi.org/10.1161/CIRCEP.110.960658>
36. Pham HN, Holmstrom L, Chugh H, Uy-Evanado A, Nakamura K, Zhang Z, *et al.* Dynamic electrocardiogram changes are a novel risk marker for sudden cardiac death. *Eur Heart J* 2024;**45**:809–19. <https://doi.org/10.1093/eurheartj/ehad770>
37. Winbo A, Diamant U-B, Persson J, Jensen SM, Rydberg A. To modify or not to modify: Allele-specific effects of 3'UTR-KCNQ1 single nucleotide polymorphisms on clinical phenotype in a long QT 1 founder population segregating a dominant-negative mutation. *J Am Heart Assoc* 2022;**11**:e025981. <https://doi.org/10.1161/JAHA.122.025981>
38. Winbo A, Stattin E-L, Westin IM, Norberg A, Persson J, Jensen SM, *et al.* Sex is a moderator of the association between NOS1AP sequence variants and QTc in two long QT syndrome founder populations: a pedigree-based measured genotype association analysis. *BMC Med Genet* 2017;**18**:74. <https://doi.org/10.1186/s12881-017-0435-2>
39. Schwartz PJ. 1970-2020: 50 years of research on the long QT syndrome. From almost zero knowledge to precision medicine. *Eur Heart J* 2021;**42**:1063–72. <https://doi.org/10.1093/eurheartj/ehaa769>

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***MTMR4* variants have opposite gene-specific impact on life-threatening arrhythmic risk in type 1 and 2 long QT syndrome**

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Main details of *KCNQ1* and *KCNH2* variants identified in the Italian cohort

Gene	Location	Exon	Nucleotide change	Amino acid change	Number of subjects	Number of symptomatic	Number of MTMR4 aa genotype
KCNQ1	N-term	1	64G>C	G22R	2	0	0
KCNQ1	N-term	1	102C>A	C34X	3	0	0
KCNQ1	N-term	1	136G>A	A46T	3	0	0
KCNQ1		1	150_151insT	Y51Lfs*234	2	0	0
KCNQ1	N-term	1	172G>C	A58P	6	0	2
KCNQ1	N-term	1	181C>A	P61T	5	0	0
KCNQ1	N-term	1	319C>T	Q107X	2	0	0
KCNQ1	N-term	1	329T>C	V110A	2	0	0
KCNQ1	N-term	1	332A>G	Y111C	20	2	3
KCNQ1		1	364dupT	C122Lfs*163	2	0	0
KCNQ1		Intron 1	386+1G>A	IVS1+1G>A	1	0	0
KCNQ1	S1	2	409C>T	L137F	6	0	0
KCNQ1	Extracell. S1-S2	2	436G>A	E146K	1	0	0
KCNQ1	S2	2	444T>G	Y148X	5	0	0
KCNQ1		Intron 2	477+1G>A	IVS2+1G>A	1	0	1
KCNQ1		Intron 2	477+5G>A	IVS2+5G>A	3	1	0
KCNQ1	Cytopl. S2-S3	3	513 C>A	Y171X	8	0	0
KCNQ1		3	513_514insG TGGTCCGC CT	G179Sfs*62	2	0	1
KCNQ1	Cytopl. S2-S3	3	514G>A	V172M	3	0	0
KCNQ1	Cytopl. S2-S3	3	520C>T	R174C	4	0	0
KCNQ1	Cytopl. S2-S3	3	521G>A	R174H	7	0	0
KCNQ1	Cytopl. S2-S3	3	532G>A	A178T	1	0	0

KCNQ1	Cytopl. S2-S3	3	535G>A	G179S	10	0	3
KCNQ1	Cytopl. S2-S3	3	551dupA	Y184*	5	0	1
KCNQ1	Cytopl. S2-S3	3	565G>A	G189R	3	1	0
KCNQ1	Cytopl. S2-S3	3	568C>T	R190W	74	2	7
KCNQ1	Cytopl. S2-S3	3	569G>A	R190Q	13	1	2
KCNQ1	S3	3	604G>C	D202H	1	0	0
KCNQ1	S3	3	604G>A	D202N	2	0	0
KCNQ1		Intron 3	604+1G>T	IVS3+1G>T	2	0	0
KCNQ1	S3	4	612C>G	I204M	8	1	2
KCNQ1	S3	4	626C>T	S209F	2	0	0
KCNQ1	S3	4	642C>A	C214X	7	0	1
KCNQ1	Extracell. S3-S4	4	658C>T	Q220X	1	0	1
KCNQ1		4	663_664insG T	F222Vfs*16	9	0	5
KCNQ1	Extracell. S3-S4	4	671C>T	T224M	2	0	0
KCNQ1		Intron 4	683+5G>A	IVS4+5G> A	1	0	0
KCNQ1	S4	5	691C>T	R231C	24	6	0
KCNQ1	S4	5	724G>A	D242N	2	0	0
KCNQ1	S4	5	728G>A	R243H	2	0	0
KCNQ1	Cytopl. S4-S5	5	752T>C	L251P	3	0	2
KCNQ1	Cytopl. S4-S5	5	760G>A	V254M	9	3	0
KCNQ1	Cytopl. S4-S5	5	760G>C	V254L	4	0	0
KCNQ1	Cytopl. S4-S5	5	775C>T	R259C	9	1	1
KCNQ1		Intron 5	781-2A>G	IVS5-2A>G	9	2	3

KCNQ1		Intron 5	781-1G>A	IVS5-1G>A	6	0	0
KCNQ1	S5	6	785T>C	L262P	1	0	0
KCNQ1	S5	6	805G>C	G269R	1	0	0
KCNQ1	S5	6	805G>A	G269S	1	0	0
KCNQ1		6	807_810delC TTC	F270Wfs*1 8	2	0	0
KCNQ1	S5	6	821T>A	I274N	1	0	0
KCNQ1	S5	6	824_826delT CT	275delF	3	0	0
KCNQ1	S5	6	825_827delC TC	277delS	2	0	0
KCNQ1	S5	6	830C>T	S277L	3	0	1
KCNQ1	S5	6	839T>A	V280E	5	1	0
KCNQ1	S5	6	842A>G	Y281C	3	0	3
KCNQ1	Extracell. S5-pore	6	877C>T	R293C	1	0	0
KCNQ1	pore	6	899C>A	A300E	3	0	0
KCNQ1	pore	6	904G>A	A302T	2	0	2
KCNQ1	pore	6	905C>T	A302V	2	0	0
KCNQ1	pore	6	914G>C	W305S	16	1	1
KCNQ1	pore	6	915G>A	W305X	10	0	2
KCNQ1		Intron 6	921+1G>C	IVS6+1G> C	3	0	0
KCNQ1	pore	7	932C>T	T311I	2	1	0
KCNQ1	pore	7	940G>A	G314S	6	4	0
KCNQ1	pore	7	943T>A	Y315N	2	2	0
KCNQ1	Extracell. pore-S6	7	965C>T	T322M	4	2	1
KCNQ1		7	967delT	W323Gfs*3 0	1	0	0
KCNQ1	Extracell. pore-S6	7	973G>A	G325R	7	2	0
KCNQ1	S6	7	1015_1017del TTC	F339del	1	0	0
KCNQ1	S6	7	1022C>T	A341V	27	16	1

KCNQ1	S6	7	1028C>G	P343R	2	1	0
KCNQ1	S6	7	1031C>T	A344V	9	3	1
KCNQ1	S6	7	1032G>A	A344A	17	10	1
KCNQ1				deletion exon 7	1	0	1
KCNQ1	S6	8	1033G>C	G345R	15	6	0
KCNQ1	S6	8	1039C>T	L347F	3	0	1
KCNQ1	C-term	8	1048G>C	G350R	2	0	0
KCNQ1		8	1050_1051ins G	F351Sfs*11 2	1	0	0
KCNQ1	C-term	8	1066C>T	Q356X	1	0	0
KCNQ1	C-term	8	1075C>T	Q359X	4	0	3
KCNQ1	C-term	8	1075_1086del	Q359_K362 del	12	0	1
KCNQ1	C-term	8	1092C>G	F364L	2	0	0
KCNQ1	C-term	8	1096C>T	R366W	10	1	1
KCNQ1	C-term	8	1097G>A	R366Q	5	0	0
KCNQ1	C-term	8	1101G>T	Q367H	4	0	0
KCNQ1	C-term	8	1115C>A	A372D	3	1	0
KCNQ1	C-term	9	1138A>G	R380G	4	0	1
KCNQ1		Intron 9	1252-1G>A	IVS9-1G>A	4	1	0
KCNQ1		10	1265_1266ins C	K422Nfs*4 1	2	0	0
KCNQ1		10	1265delA	K422Sfs*10	5	0	2
KCNQ1		10	1291dupG	V431Gfs*3 2	4	0	1
KCNQ1		10	1343dupC	E449Rfs*14	2	0	0
KCNQ1	C-term	10	1351C>T	R451W	2	0	0
KCNQ1		Intron 10	1394-2A>G	IVS10- 2A>G	5	1	0
KCNQ1		11	1484_1485del CT	L496Afs*19	3	0	0
KCNQ1		11	1513_1514del CA	Q505Afs*1 0	1	0	0
KCNQ1	C-term	12	1541T>C	I514T	15	1	6

KCNQ1		Intron 12	1590+1G>A	1590+1G>A	3	0	2
KCNQ1	C-term	13	1615G>T	R539W	1	0	0
KCNQ1	C-term	13	1637C>T	S546L	6	0	2
KCNQ1	C-term	13	1661T>C	V554A	10	0	1
KCNQ1	C-term	13	1663C>T	R555C	3	0	0
KCNQ1	C-term	13	1664G>A	R555H	3	0	2
KCNQ1		Intron 13	1685+1G>A	IVS13+1G>A	1	0	0
KCNQ1	C-term	14	1700T>C	I567T	2	0	1
KCNQ1	C-term	14	1709C>T	P570L	1	1	0
KCNQ1	C-term	14	1717T>C	F573L	13	0	0
KCNQ1		14	1725_1728del CGTC	V576Qfs*16	5	1	2
KCNQ1		Intron 14	1733-1G>A	IVS14-1G>A	4	0	0
KCNQ1	C-term	15	1748G>A	R583H	1	1	0
KCNQ1	C-term	15	1756A>G	N586D	1	0	0
KCNQ1	C-term	15	1760C>T	T587M	2	0	0
KCNQ1	C-term	15	1768G>A	A590T	1	0	0
KCNQ1	C-term	15	1771C>T	R591C	1	0	0
KCNQ1	C-term	15	1772G>T	R591L	4	0	0
KCNQ1	C-term	15	1772G>A	R591H	8	2	0
KCNQ1	C-term	15	1780C>T	R594X	11	0	2
KCNQ1	C-term	15	1781G>A	R594Q	6	2	0
KCNQ1				deletion exon 12-13- 14-15	1	0	0
KCNQ1		16	1893_1894ins C	R632Qfs*20	5	0	2
KCNQ1				deletion exon 16	1	0	0
KCNH2	N-term	1	65T>A	F22Y	4	0	1
KCNH2	N-term	2	85T>G	F29V	1	0	0
KCNH2	N-term	2	86T>C	F29S	2	1	0

KCNH2		2	106delG	V36Wfs*23	3	0	0
KCNH2	PAS	2	128A>G	Y43C	3	0	0
KCNH2	PAS	2	148G>T	E50*	1	0	0
KCNH2		2	160_170delT ACTCGCGG GC	Y54Rfs*87	1	0	1
KCNH2	PAS	2	160T>A	Y54N	1	0	0
KCNH2	PAS	2	174G>C	E58D	1	0	0
KCNH2	PAS	2	190T>C	C64R	1	1	1
KCNH2	N-term	2	211G>T	G71W	1	1	1
KCNH2	N-term	2	215C>G	P72R	1	0	0
KCNH2	N-term	2	217C>G	R73G	1	0	0
KCNH2	PAS	2	232G>C	A78P	3	1	0
KCNH2	N-term	2	235G>T	A79S	3	0	1
KCNH2	N-term	2	280G>C	V94L	2	0	0
KCNH2	N-term	2	299G>C	R100P	3	0	0
KCNH2	PAC	2	305A>T	D102V	4	0	0
KCNH2	N-term	2	305_307dupA TG	D102dup	1	1	0
KCNH2		3	324delT	L109Wfs*6	12	0	0
KCNH2	PAC	3	337_345delG TGCCCGTG	V113_V115 del	2	0	1
KCNH2	N-term	3	442C>T	R148W	5	1	0
KCNH2		3	453delC	T152Pfs*13	4	2	0
KCNH2		3	453dupC	T152Hfs*17 9	2	0	0
KCNH2	N-term	4	526C>T	R176W	19	1	3
KCNH2		4	606_618del	A204Sfs*8	2	0	1
KCNH2		4	678delG	A228Rfs*1 32	1	0	0
KCNH2	N-term	4	778G>C	A260P	1	0	0
KCNH2		4	784delG	G262Afs*9 8	5	2	0

KCNH2		4	800_801insC GGGCTCCA GCTGCAGC CT	A268Gfs*7 0	1	0	0
KCNH2	N-term	4	818G>A	R273Q	5	0	0
KCNH2		4	820_821delG A	E274Kfs*57	2	0	0
KCNH2		5	1025_1026ins A	D342Efs*14	1	1	0
KCNH2	N-term	5	1096C>T	R366*	8	1	0
KCNH2	N-term	5	1127A>G	Q376R	1	0	0
KCNH2		Intron 5	1129-1G>T	-	1	0	0
KCNH2		6	1139delT	L380Rfs*54	16	5	4
KCNH2	N-term	6	1194G>A	W398X	1	0	0
KCNH2	S1	6	1229G>A	W410*	2	0	0
KCNH2	S1	6	1235G>A	W412*	2	0	0
KCNH2		6	1283delC	S428Wfs*6	8	1	3
KCNH2	Extracell. S1-S2	6	1283C>A	S428*	1	1	0
KCNH2		6	1340dupA	Y447*	1	0	0
KCNH2	Cytopl. S2-S3	6	1445T>C	V482A	2	0	0
KCNH2	Cytopl. S2-S3	6	1468G>C	A490P	5	2	0
KCNH2	Cytopl. S2-S3	6	1468G>A	A490T	3	0	0
KCNH2		6	1478_1480du pACT	Y493dup	1	0	0
KCNH2	Cytopl. S2-S3	6	1478A>G	Y493C	1	1	0
KCNH2	S3	6	1490G>T	W497L	4	0	0
KCNH2	S4	7	1564_1581du p	G522_A527 dup	1	0	0
KCNH2	S4	7	1582C>T	R528W	3	0	0
KCNH2	S4	7	1600C>T	R534C	1	0	0
KCNH2	S4	7	1603G>A	V535M	1	0	0

KCNH2	Pore	7	1681G>A	A561T	1	0	0
KCNH2	Pore	7	1682C>T	A561V	5	3	1
KCNH2	Pore	7	1700T>C	I567T	1	0	0
KCNH2	Pore	7	1704G>T	W568C	2	1	1
KCNH2	Extracell. S5-pore	7	1742C>G	S581X	1	0	0
KCNH2	Extracell. S5-pore	7	1747A>G	I583V	8	0	0
KCNH2	Extracell. S5-pore	7	1756C>A	L586M	1	0	0
KCNH2	Extracell. S5-pore	7	1766T>C	L589P	1	1	1
KCNH2	Extracell. S5-pore	7	1810G>A	G604S	4	3	0
KCNH2	Extracell. S5-pore	7	1824G>C	K608N	1	0	0
KCNH2	Pore	7	1835T>C	V612A	4	1	2
KCNH2	Pore	7	1840G>A	A614T	2	2	0
KCNH2	Pore	7	1841C>T	A614V	2	1	0
KCNH2	Pore	7	1849T>C	F617L	3	0	0
KCNH2	Pore	7	1876G>C	G626R	1	0	0
KCNH2	Pore	7	1877G>C	G626A	1	1	0
KCNH2	Pore	7	1882G>C	G628R	1	1	0
KCNH2	Pore	7	1882G>A	G628S	1	1	1
KCNH2	Pore	7	1886A>G	N629S	1	1	0
KCNH2	Pore	7	1894C>G	P632A	2	0	0
KCNH2	Extracell. Pore-S6	7	1898A>G	N633S	2	2	1
KCNH2	Extracell. Pore-S6	7	1901C>T	T634I	3	0	0
KCNH2	Extracell. Pore-S6	7	1912_1914del AAG	K638del	10	3	5
KCNH2	Extracell. Pore-S6	7	1913A>G	K638R	2	0	1
KCNH2	S6	7	1930G>T	V644F	3	2	1

KCNH2		Intron 7	1945+6T>C	-	1	0	1
KCNH2		Intron 7	1946-1G>A	-	3	0	1
KCNH2	C-term	8	1979C>T	S660L	4	1	0
KCNH2	C-term	8	2042G>C	R681P	1	0	0
KCNH2		8	2077delC	L693Cfs*21	3	0	0
KCNH2	C-term	9	2201G>A	R734H	3	0	3
KCNH2	cNBD	9	2230C>T	R744*	23	5	3
KCNH2		9	2236delG	A746Pfs*11	5	3	1
KCNH2	cNBD	9	2254C>T	R752W	4	3	2
KCNH2		9	2299delG	D767Tfs*43	2	0	0
KCNH2	cNBD	9	2327T>C	L776P	4	2	0
KCNH2	cNBD	9	2336T>C	L779P	1	0	0
KCNH2	cNBD	9	2371C>T	R791W	1	0	0
KCNH2		9	2393dupT	L799Pfs*5	1	0	0
KCNH2		Intron 9	2399-28A>G	-	11	2	0
KCNH2		Exon 10-15	2400-3480del	-	3	2	0
KCNH2	cNBD	10	2406dupT	D803*	1	0	0
KCNH2	cNBD	10	2414T>C	F805S	5	1	1
KCNH2	cNBD	10	2416G>C	G806R	2	0	0
KCNH2	cNBD	10	2453C>T	S818L	2	0	0
KCNH2	cNBD	10	2467C>T	R823W	5	2	0
KCNH2	cNBD	10	2513T>G	L838R	1	0	0
KCNH2	cNBD	10	2521G>C	V841L	2	0	0
KCNH2	C-term	10	2581A>C	N861H	4	0	0
KCNH2	C-term	10	2585T>C	L862P	2	0	0
KCNH2	C-term	10	2587C>T	R863*	6	0	0
KCNH2	C-term	10	2588G>C	R863P	2	0	0
KCNH2		11	2616delC	G873Afs*5	2	1	0
KCNH2		11	2616dupC	G873Rfs*4 7	1	0	0

KCNH2		11	2616_2625del insGGGATC CC	T875Rfs*44	12	0	0
KCNH2		12	2758dupC	R920Pfs*19	1	0	0
KCNH2		12	2775_2776ins G	P926Afs*14	4	1	0
KCNH2		12	2775delG	P926Rfs*48	2	1	0
KCNH2	C-term	12	2780G>A	W927*	6	2	0
KCNH2	C-term	12	2932G>T	E978*	3	0	1
KCNH2		12	2959_2960del CT	L987Vfs*13 1	1	1	1
KCNH2		13	3039delT	R1014Dfs* 43	1	0	0
KCNH2	C-term	13	3040C>T	R1014*	7	0	0
KCNH2		13	3088_3097del	P1030Gfs*2 4	6	1	0
KCNH2		13	3093_3117del TCGGCGGC CCCGGGGC GACGTGGA G	R1032Afs* 17	2	0	0
KCNH2		13	3096_3097ins GTCGG	R1033Vfs* 26	4	0	1
KCNH2		13	3093_3106del TCGGCGGC CCCGGG	P1034Gfs*8 0	2	1	0
KCNH2		13	3099delG	R1035Gfs* 21	2	0	1
KCNH2		13	3103delC	R1035Gfs* 22	3	1	0
KCNH2		13	3103dupC	R1035fs*84	2	0	0
KCNH2		13	3107dupG	D1037Rfs* 82	2	0	2
KCNH2	C-term	13	3133C>T	L1045F	1	1	0
KCNH2	C-term	13	3139C>T	R1047C	3	1	1
KCNH2	C-term	14	3251C>T	P1084L	10	0	0
KCNH2		14	3254_3255del GG	G1085Afs* 33	12	1	4
KCNH2	C-term	15	3347C>T	A1116V	13	1	2

KCNH2		Exon 7-11	1558-2692del	-	2	1	2
KCNH2		All gene	-	-	1	0	0