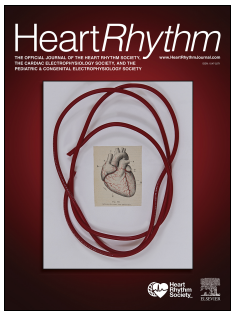

Risk Stratification in the Short-QT Syndrome: Findings From a Pooled Analysis.

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Risk Stratification in the Short-QT Syndrome: Findings From a Pooled Analysis.

Moshe Giladi, MD, PhD,[1,2] Aviv Solomon, MD,[2] Dana Viskin, MD,[2,3] Raphael Rosso, MD,[2,3] Chris van der Werf, MD,[4] Soesja Pinto, MD,[4] Arthur A. Wilde, MD,[4] Reem Elbassel, MD [2,3] Louise Henriques, MD,[2,3] J. Martijn Bos, MD, PhD,[5] Michael J Ackerman, MD, PhD,[5] Sami Viskin, MD,[2,3] and Ehud Chorin, MD, PhD[2,3]

[1] Department of Internal Medicine D, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

[2] Gray Faculty of Medical & Health Sciences, Tel Aviv University, Israel.

[3] Department of Cardiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

[4] Department of Cardiology, Cardiovascular Sciences, Heart Failure and Arrhythmias, University of Amsterdam, Amsterdam, The Netherlands.

[5] Departments of Cardiovascular Medicine, Pediatric and Adolescent Medicine, and Molecular Pharmacology & Experimental Therapeutics; Divisions of Heart Rhythm Services and Pediatric Cardiology; Windland Smith Rice Genetic Heart Rhythm Clinic and Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA

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Corresponding Author:
Sami Viskin, M.D.
Tel Aviv Sourasky Medical Center.
Tel Aviv University, Tel Aviv, Israel.
E-mail: samiviskin@gmail.com

Abstract.

Background. In the *long* QT syndrome, longer QT intervals indicate increased arrhythmic risk, and a QTc ≥500 msec denotes high risk. Establishing similar associations in the *short* QT syndrome (SQTS) remains elusive.

Objective. To demonstrate that shorter QT intervals denote a higher risk of malignant arrhythmias in the SQTS and to define the "high-risk" QTc value in the SQTS.

Methods. Pooled analysis of patients treated in our institutions or reported in the literature revealed 162 SQTS patients and known symptomatic status; 57 (35.2%) of them had arrhythmic symptoms (sudden death, cardiac arrest, or malignant syncope).

Results. There was a significant inverse association between the QTc and arrhythmic symptoms [with a median QTc of 315.0 (IQR 300.5 - 338.0) msec among symptomatic patients, vs 330.0 (IQR 312.5 - 355.0) msec among asymptomatic patients, p=0.0023]. Receiver operator characteristics (ROC) analysis showed that shorter QTc values were associated with higher risk (AUC = 0.64 ±0.04, p=0.0024). When patients were grouped by QTc range, the majority of those with QTc ≤320 msec had malignant arrhythmic symptoms, whereas the reverse was true for QTc ≥320 msec. Male patients were overrepresented in the SQTS cohort and more so in the subgroup with malignant symptoms.

Conclusion. This pooled analysis of patients with SQTS demonstrates that, among patients with congenital SQTS, a shorter QTc is associated with a higher risk of malignant ventricular arrhythmias. A QTc shorter than 320 msec correlates with higher arrhythmic risk. Males appear to be at higher risk.

Keywords

Short QT syndrome, Sudden death, Cardiac arrest, Arrhythmic risk, QTc interval

Abbreviations.

IQR = interquartile range.

LQTS = long QT syndrome.

ROC = Receiver operating characteristic.

SQTS = short QT syndrome.

Introduction.

Cardiac arrest is often the presenting symptom in the congenital short QT syndrome (SQTS).[1-3] Therefore, identifying reliable tests for risk-stratifying patients with *asymptomatic* SQTS is an urgent challenge. One logical parametric test is the QT interval duration, specifically the rate-corrected QTc. Indeed, in the congenital *long* QT syndrome (LQTS), the linear correlation between *longer* QT intervals and increased risk has been known for over 30 years,[4] with a QTc ≥500 msec denoting very high risk.[4,5] However, demonstrating a similar association in the opposite direction for the *short* QT syndrome remains elusive, with important series reporting no significant correlation between symptoms and the QTc.[1,2] Based on data collected from 15 published reports of SQTS, Gollob reported that the mean QTc of symptomatic patients tends to be shorter than that of asymptomatic family members but there was considerable overlap between both groups.[6] Furthermore, the definition of "symptomatic SQTS" in that study did not focus exclusively on life-threatening or fatal ventricular arrhythmias but also included a history of atrial fibrillation.[6] Finally, a "hot spot" QTc cut-off value implying excess risk (the equivalent of the QTc ≥500 msec figure in the *long* QT syndrome) could not be identified.[6] This is understandable given the limited number of patients with SQTS reported at the time.[6] While studies defining a QTc ≥500 msec as "high-risk trademark" included data on over 1,000 patients with LQTS,[4,5] only 61 patients with SQTS were available for Gollob's calculations.[6] In the present study, we present data from 166 patients with SQTS to analyze the role of the QT interval in defining risk in this condition.

Methods.

We performed a pooled analysis of individual patient data from patients treated in our institutions and from those reported in the literature. Our cohorts consist of 17 patients treated at the Tel Aviv Medical Center (including 11 patients from a recently reported family),[7] 10 patients treated at the Amsterdam Medical Center (including one previously reported),[8] and four unreported patients treated at the Mayo Clinic. For the online search, we used PubMed following the recommendations in the Cochrane Handbook for Systematic Reviews.[9] Our search included publications from 2000 (the year of the original report)[10] until November 2025, using the following terms: SQTS, sudden cardiac death, QT interval, and QTc. All patients with SQTS who had reported QTc values, along with their symptom status, were included. The diagnosis of SQTS was in accordance with the most recent guidelines:[11] 1) Patients received a class I diagnosis of SQTS in the presence of a QTc $\leq$360 msec and one or more of the following: a pathogenic genetic variant, a family history of SQTS, or survival from cardiac arrest in the absence of heart disease; 2) patients were considered to have a class IIa diagnosis if they had a QTc $\leq$320 msec or 320 to 360 msec in the presence of arrhythmic syncope.[11] Two independent reviewers verified that patients who were repeatedly reported were entered only once. Of the 541 articles retrieved in the initial search, 16 studies met all inclusion criteria.[6,12-26] The final number of patients with SQTS reported here is 162, including 131 from the literature and 31 from our centers. A total of 82 patients had variants in genes considered to have definite, strong, or moderate evidence of causation for SQTS by an expert panel[27] (Table 1).

At all participating centers institutional review board approval and informed consent were obtained if needed for this type of research.

Statistics. Data normality was assessed with the Shapiro-Wilk test. Normally distributed data were compared using an unpaired Student's *t*-test, and non-normal data with a Mann-Whitney *U* test. Two-tailed $p < 0.05$ was considered significant. QTc diagnostic performance for predicting symptoms was evaluated by receiver operating characteristic (ROC) analysis. All analyses were conducted in GraphPad Prism 10 (GraphPad Software, San Diego, CA, USA).

Results.

We report 162 patients with SQTS from 67 families, for whom information on QTc and symptoms was available. Of these patients, 132 (81.5%) have a class I diagnosis of SQTS [including patients with a QTc ≤360 msec who, in addition, had a history of cardiac arrest (32 patients), a pathogenic genetic variant (36 patients), or a familial history of SQTS (64 patients)], whereas 10 have a class IIa diagnosis (all with a QTc ≤320 msec**)**. The remaining 20 patients were included despite a QTc >360 msec because they are carriers of a familial pathogenic/likely pathogenic genetic variant identified in a proband with a class I SQTS diagnosis.

Of the 162 patients with SQTS, 57 (35.2%) had arrhythmic symptoms related to ventricular arrhythmias, including sudden death in 9 patients, cardiac arrest with resuscitation in 23, recorded malignant ventricular arrhythmias in 5, and malignant syncope in 39 patients, for a total of 76 events. Only 23 patients had malignant syncope as their only qualifying event. The median age at the time of arrhythmic symptoms was 25.0 years (IQR, 17.8 – 35.5 years), whereas the age of asymptomatic patients (at their last available follow-up) was 23.0 years (IQR 14.5 - 38.0, **Figure 1**). Data on age at the time of first symptom are missing for 15 patients.

Males were overrepresented in the entire cohort, accounting for 106 (65.4%) of SQTS patients. Moreover, males accounted for 45 (79.0%) of symptomatic patients. In contrast, only 56 (34.6%) of the entire cohort and only 12 (21.0%) of the symptomatic patients were female (p<0.001). The prevalence of arrhythmic symptoms was 42.5% for males and 21.4% for females (OR 2.71, 95% CI 1.29 – 5.72). Cardiac arrest or sudden death occurred in 24.5% of males and 14.3% of females (OR 1.95, 95% CI 0.82 – 4.66).

There was a significant inverse association between the QTc and the presence of arrhythmic symptoms, with a median QTc of 315.0 (IQR 300.5 - 338.0) msec among symptomatic patients, vs 330.0 (IQR 312.5 - 355.0) msec among asymptomatic patients (*p*=0.0023, **Figure 2**). ROC analysis showed that shorter QTc values were associated with a higher risk of symptoms (AUC = 0.64 ± 0.04, *p*=0.0024) (**Figure 3**). On the ROC curve, the Youden Index was calculated for each potential threshold, identifying an optimal cutoff of <320 ms, yielding a sensitivity of 62.7% and a specificity of 64.5% for distinguishing symptomatic from asymptomatic patients. At this point, the Youden Index reached its maximum of 0.272 (arrow in **Figure 3**). Indeed, when patients were grouped by QTc range, the majority of those with QTc ≤ 320 msec had malignant arrhythmic symptoms, whereas the reverse was true for those with QTc ≥ 320 msec (**Figure 4**). The median QTc was similar for men and women with arrhythmic symptoms [313.0 (IQR 300.5 - 334.5) msec for males vs. 311.0 (IQR 260.5-337.8) msec for females, *p*=0.6519, **Supplemental Figure 1**].

Discussion.

We show, for the first time, that shorter QT intervals (reflected in a shorter QTc) are associated with a significantly higher risk of malignant arrhythmic symptoms in patients with SQTS. This correlation, although highly intuitive, eluded statistical demonstration in previous studies[1,2,6]

because of the following: First, previous reports were underpowered to demonstrate this association owing to their limited population sizes, ranging from 53 patients in the series by Giustetto,[2] to 61 patients by Gollob[6] and 73 patients by Mazzanti.[1] By including nearly as many patients as all previous series combined, our study demonstrates that patients with arrhythmic symptoms have, on average, shorter QTc than asymptomatic patients with SQTS (315 vs 330 msec, *p*=0.0023), albeit with considerable overlap between the groups (Figure 2). Second, *identification bias* existed across all SQTS series, including our own. This is because, while asymptomatic patients are more likely to be recognized when they have a markedly short QT interval, those with only moderate QT shortening may come to our attention only after arrhythmic symptoms develop. Finally, the shortcomings of the Bazett formula[28] may have contributed to the delayed recognition of the association between shorter QT intervals and increased risk. On the one hand, patients with a severe phenotype present with symptoms during infancy, when sinus tachycardia is prevalent. This relatively fast heart rate would lead to a "spuriously long" calculated QTc despite their very short absolute QT interval. On the other hand, as demonstrated in a reported family,[7] cascade screening may detect asymptomatic, healthy athletes who are carriers of the familial variant and exhibit only mild QT shortening, resulting in very short QTc values solely due to QT-overcorrection during marked sinus bradycardia.

Our study also demonstrates that once the QTc shortens below 320 msec, the risk of malignant arrhythmic events increases significantly. Accordingly, just as a QTc ≥500 msec is recognized as a marker of increased risk in the long QT syndrome, we suggest that a QTc <320 msec should be viewed as an indicator of higher arrhythmic risk in the SQTS. However, one cannot overemphasize that the ROC curve for QTc vs risk showed only moderate predictive accuracy (Figure 3).

Therefore, patients diagnosed with SQTS should *not* be assumed to be at low risk solely because their QTc is longer than 320 msec.

In the healthy population, adult males have shorter QT intervals than females,[29] and the same holds true for adult patients with long QT syndrome.[29] It is plausible that among patients with SQTS, males have shorter QT intervals and are therefore easier to recognize. This could explain why, despite the SQTS being of autosomal dominant inheritance, males predominate across all series, ranging from 65.4% in our series up to 75% and 83% in those diagnosed by Giustetto[2] and Mazzanti, respectively.[1] Furthermore, in the long QT syndrome, female sex is an independent predictor of risk, so women tend to develop arrhythmias at a lesser degree of QT prolongation than men.[30] It is tempting to speculate that males are at a higher risk of developing arrhythmias when they have a SQTS. Indeed, the overwhelming majority of patients with a history of malignant syncope or cardiac arrest in large series are male [91% (29/32) of symptomatic patients reported by Mazzanti, 84% (22/26) of symptomatic patients by Giustetto, and 86% (49/57) of patients with symptoms in our series are male]. We could not demonstrate a difference in QTc between symptomatic males and symptomatic females, which may be due to the limited number of diagnosed patients. Sex was significantly associated with symptomatic presentation in the pooled dataset (including the present study and the series by Mazzanti and Giustetto): Overall, 89 of 209 males (43.1%) were symptomatic, compared with 15 of 81 females (18.5%) (p=0.0002). Males demonstrated markedly higher odds of being symptomatic, with an odds ratio of 3.26 (95% CI 1.75–6.09) compared with females.

Our study has important limitations: 1) While representing the most extensive series of patients with SQTS reported so far, the number of SQTS reported is still significantly smaller than the number of reported cases with *long* QT syndrome. Thus, our results ought to be confirmed by

future studies, hopefully in the setting of a multicenter cooperative registry. 2) Syncope presumed to be of arrhythmic origin, but without documented arrhythmias, was the qualifying symptom in a large fraction of our symptomatic cohort, and it is always possible that the clinical impression at the time of diagnosis was wrong. 3) A single QTc value is presented for each patient and this value was not measured with a uniform method. In reality, however, each patient will have different QTc values on different ECGs. Future studies should define if the optimal QTc for risk stratification should be the QTc recorded when the heart rate is closest to 60/min or the shortest QTc recorded in a resting ECG.

Conclusions: This pooled analysis of patients with SQTS diagnosed at tertiary institutions combined with cases reported in the literature demonstrates that, among patients with congenital SQTS, a shorter QTc is associated with a higher risk of symptoms attributed to malignant ventricular arrhythmias. A QTc shorter than 320 msec appears to correlate with higher arrhythmic risk, but significant overlap exists between the QTc of patients with and without symptoms. Male patients with SQTS appear to be at higher risk.

Disclaimer: Given his role as Editor-in-Chief, Sami Viskin had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Section Editor Douglas P. Zipes, Founding Editor of *Heart Rhythm*.

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Figure legends.

Figure 1. Age distribution of symptomatic and asymptomatic patients. Individual values are plotted with the median and interquartile range. Age for symptomatic patients is the age at first symptom. Age for asymptomatic patients is the age at the latest follow-up. No significant difference was observed between groups (Mann–Whitney U test, $p = 0.7415$). Data on age at the time of first symptom are missing for 15 patients.

Figure 2. **QTc distribution of symptomatic and asymptomatic patients**. Individual values are plotted with the median and interquartile range. The QTc was significantly shorter in the symptomatic group (Mann–Whitney U test, ** $p = 0.0026$). The worst arrhythmic syncope of each patient is shown. Filled circles include patients with sudden death, cardiac arrest, and syncope with documented polymorphic ventricular tachycardia. Empty circles denote patients who had malignant syncope as their only qualifying symptom.

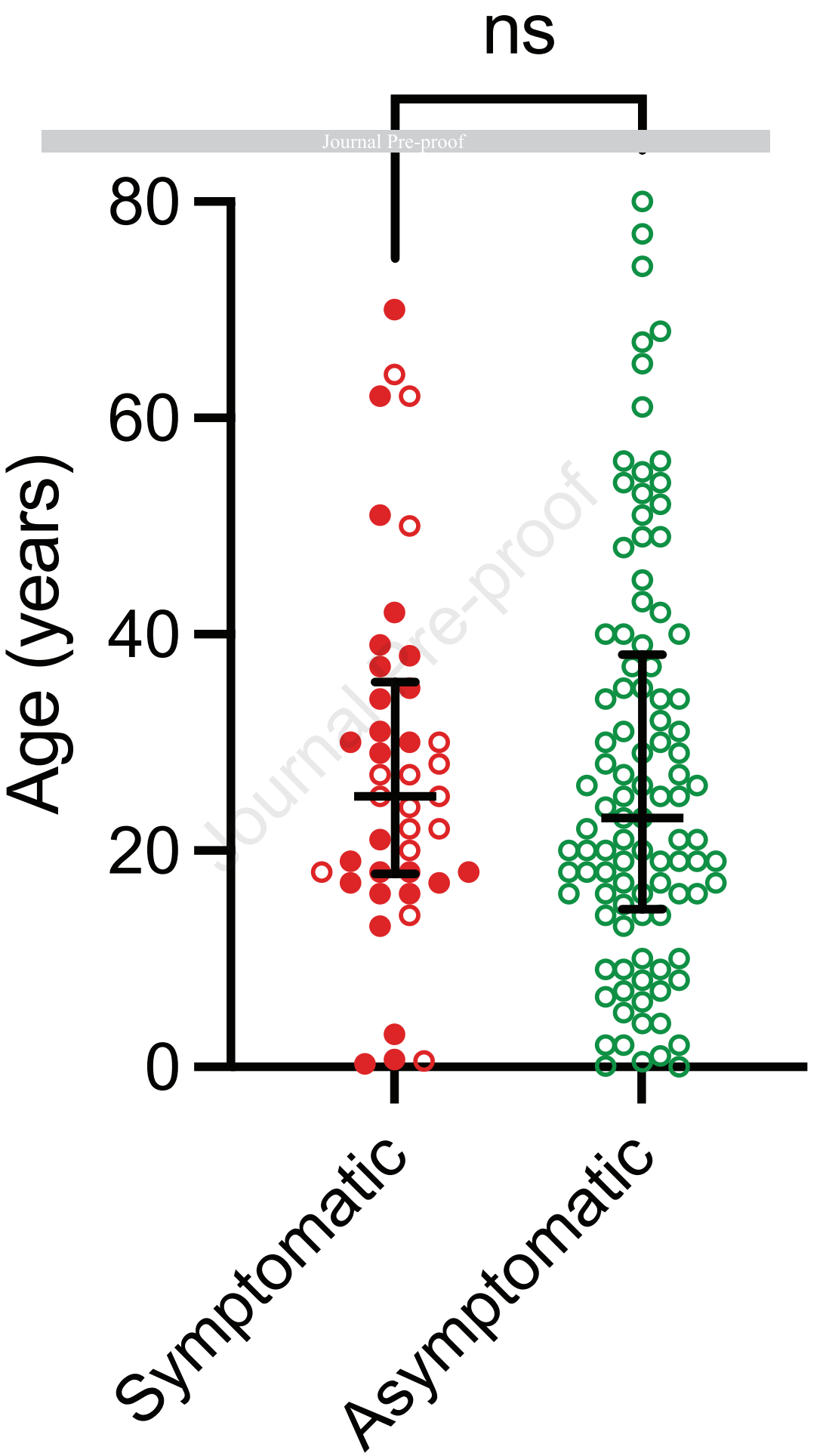
Figure 3. ROC curve analysis of QTc as a predictor of symptoms. The AUC was 0.6407 ± 0.04329 ($p = 0.0027$). The arrow indicates the optimal cutoff of <320 ms, determined by the Youden Index, which yielded a sensitivity of 62.7% and a specificity of 64.5%.

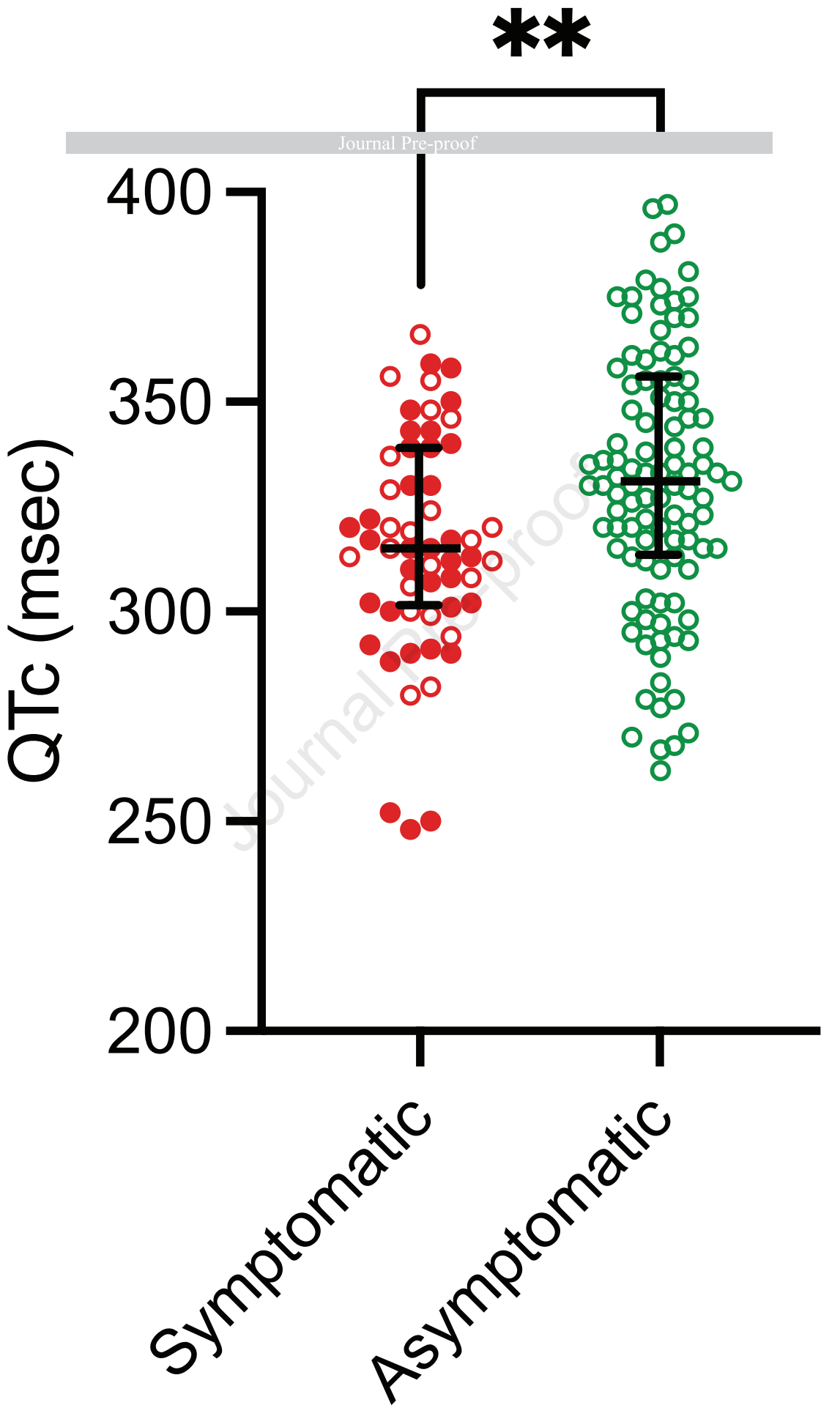
Figure 4. **Distribution of patients by QTc and the risk for symptoms**.

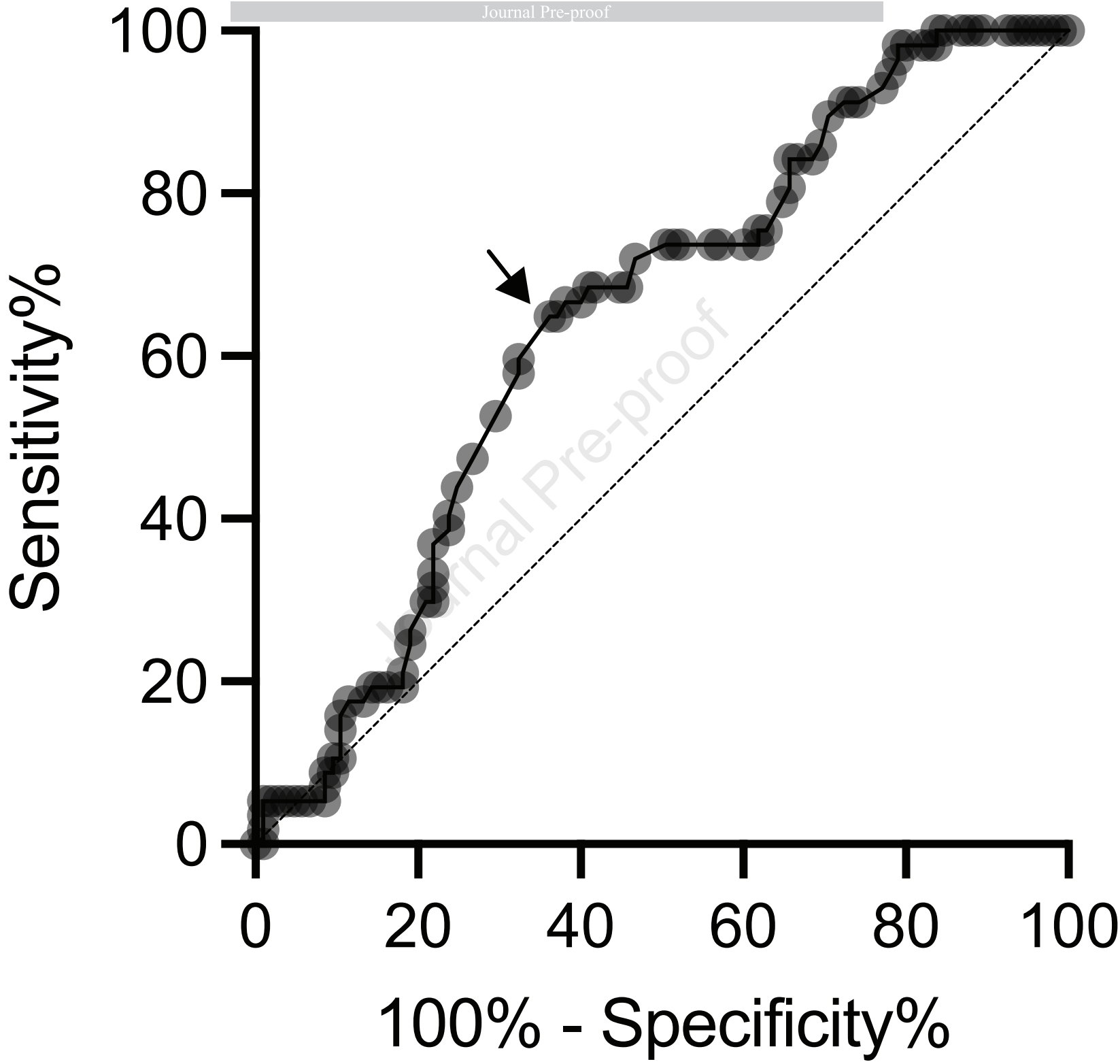
Table 1. Genetic results of genotype-positive patients.

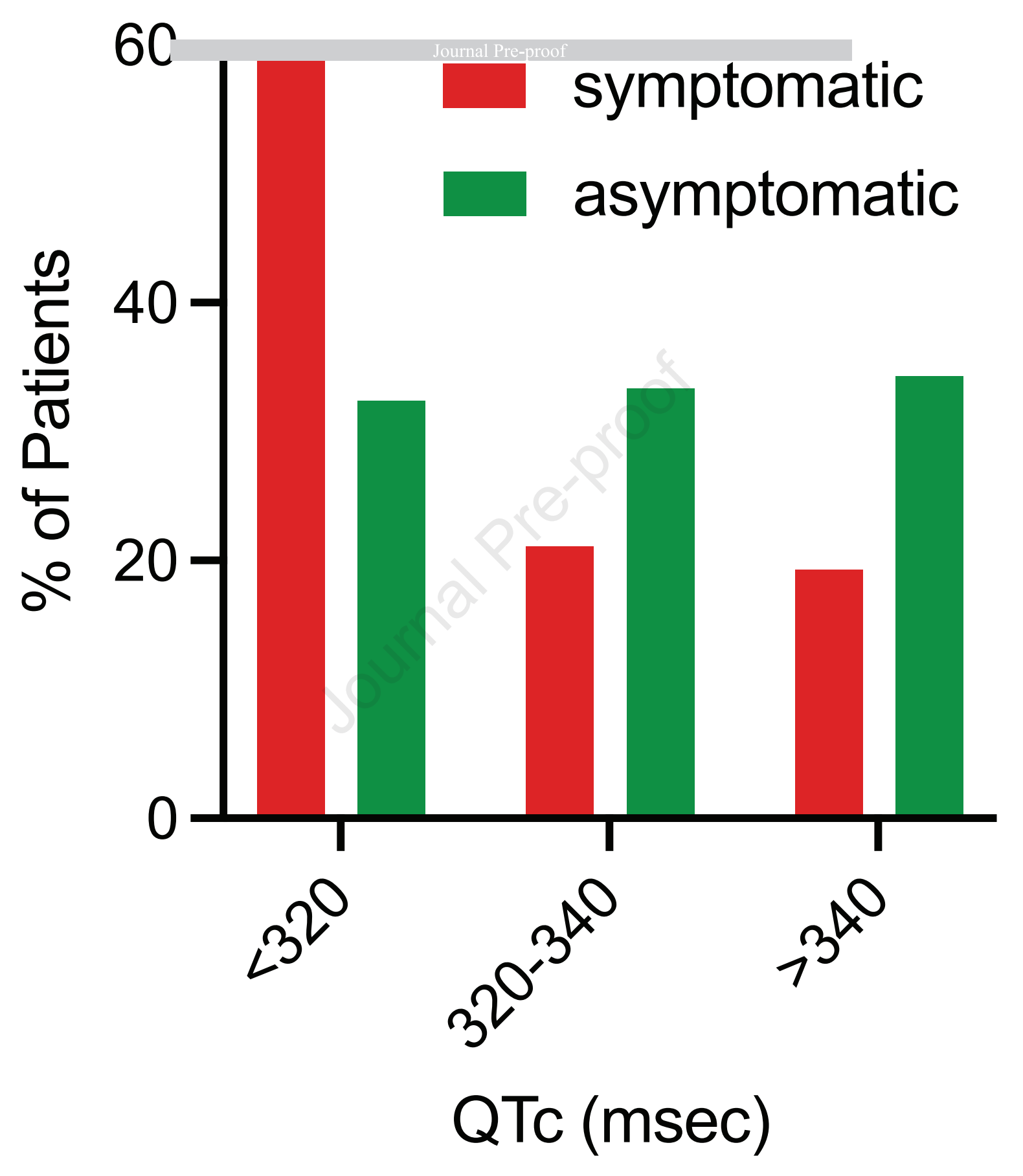
Culprit gene	Reported mutations(s)	Accession	Number of cases	ACMG classification	Allele frequency
KCNH2	E50D	NM_000238.4:c.150G>T	1	LP	6.85e-7
	I560T	NM_000238.4:c.1679T>C	1	LP	0
	N588K	NM_000238.4:c.1764C>A	11	P	0
	T618I	NM_000238.4:c.1853C>T	1	P	0
	R1135H	NM_000238.4:c.3404G>A	3	VUS	2.1e-6
KCNQ1	V307L	NM_000218.3:c.919G>T	1	LP	0
	V141M	NM_000218.3:c.421G>A	13	P	0
KCNJ2	D172N	NM_000891.3:c.514G>A	2	P	0
	M301K	NM_000891.3:c.902T>A	1	P	0
	K346T	NM_000891.3:c.1037A>C	2	VUS	0
SLC4A3	R343H*	NM_005070.4:c.1028G>A	21	P	6.8e-7
	F347S	NM_005070.4:c.1040T>C	4	LP	0
	G359V*	NM_005070.4:c.1076G>T	2	LP	0
	P428R**	NM_005070.4:c.1283C>G	1	VUS	0
	R573C	NM_005070.4:c.1717C>T	1	LP	0
	R925H	NM_005070.4:c.2774G>A	2	VUS	2.1e-6
	R1016G	NM_005070.4: c.3046C>G	11	LP	0
	A1068V**	NM_005070.4:c.3203C>T	1	VUS	3.4e-6
	P1069H	NM_005070.4:c.3206C>A	3	LP	0

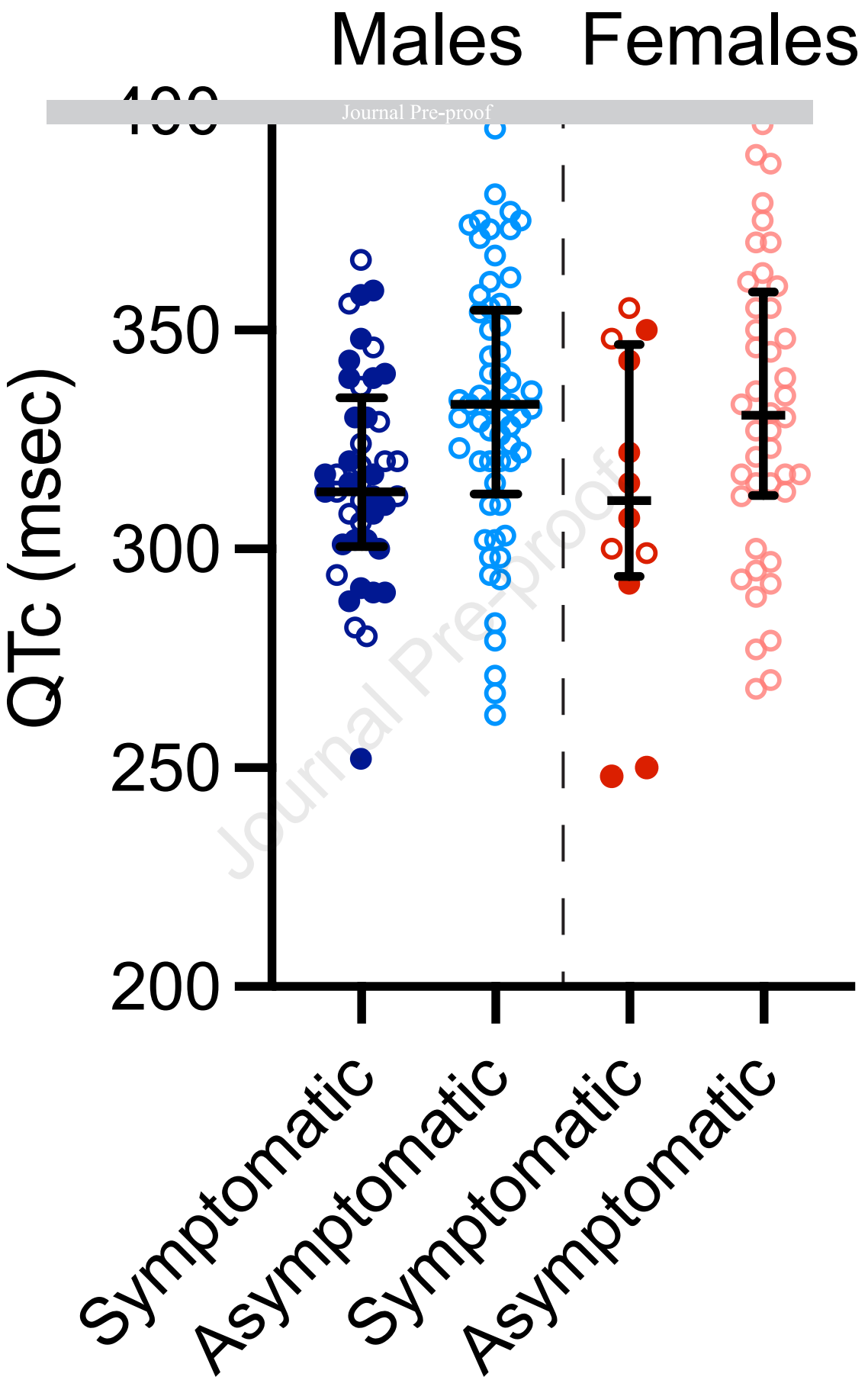
All variants are described according to HGVS standards. The following canonical transcripts were used: *KCNH2* (NM_000238.4), *KCNQ1* (NM_000218.3), *KCNJ2* (NM_000891.3), and *SLC4A3* (NM_005070.4). Allele frequencies were obtained from gnomAD v4 exomes. ACMG Classifications (P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance; LB, Likely Benign; B, Benign) were cross-referenced with ClinVar and predicted using Genebe (ACMG 2015 criteria). * *SLC4A3* R343H, G359V and R925H are reported in some literature as R370H, G386V, and R952H, respectively, based on alternative transcript numbering. **Novel variants reported in this study.











Supplementary Figure 1. **Distribution of QTc by symptoms and gender**. Individual values are plotted with the median and interquartile range. QTc was significantly shorter in symptomatic compared with asymptomatic males (Mann–Whitney U test, $p = 0.0137$), whereas no significant difference was observed between symptomatic and asymptomatic females ($p = 0.0813$), or between symptomatic males vs symptomatic females ($p=0.6519$).