

The AMPS Insider

An AMPS LLC Magazine

The AMPS Insider is a quarterly magazine dedicated to all AMPS' partners and customers. Published by AMPS, it provides news and information about AMPS' products and initiatives.

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Executive Overview

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

Editorial

In this issue of the newsletter we share an important article by Professor Peter J Schwartz and a large group of international scientists published earlier this year in the European Heart Journal: *MTMR4 variants have opposite gene-specific impact on life-threatening arrhythmic risk in type 1 and 2 long QT syndrome*.

The manuscript discusses a genetic variant which carries a life-threatening risk associated with long QT syndrome. The research effort required quantitative analysis of the repolarization segment of the ECG signal, assessing measurements such as the QT/QTc and the Tpeak-Tend intervals as well as indices of T-wave morphology. AMPS is proudly involved in this research collaboration and we are happy to share the abstract of the manuscript in our newsletter.

Professor Schwartz commented: "This study represents a major advancement in our more than 25 years of research into the role of the so-called "modifier genes"—genes that do not directly cause a disease but that can influence the expression of other genes and the severity of a condition's symptoms. Their action explains, for instance, why two siblings with the identical disease-causing mutation can experience vastly different clinical courses, with one dying while the other remains asymptomatic. In a cohort of nearly 1,200 patients, we demonstrated that a specific, relatively

common genetic variant can be protective in type 1 long QT syndrome and yet increase the risk of fatal cardiac arrhythmias in type 2 long QT syndrome. This finding enables more accurate, personalized stratification of arrhythmia risk—an approach we are already implementing for all our patients. This study is largely the result of the collaboration between our research team and the team at AMPS LLC, led by Fabio Badilini".

The abstracts follow below:

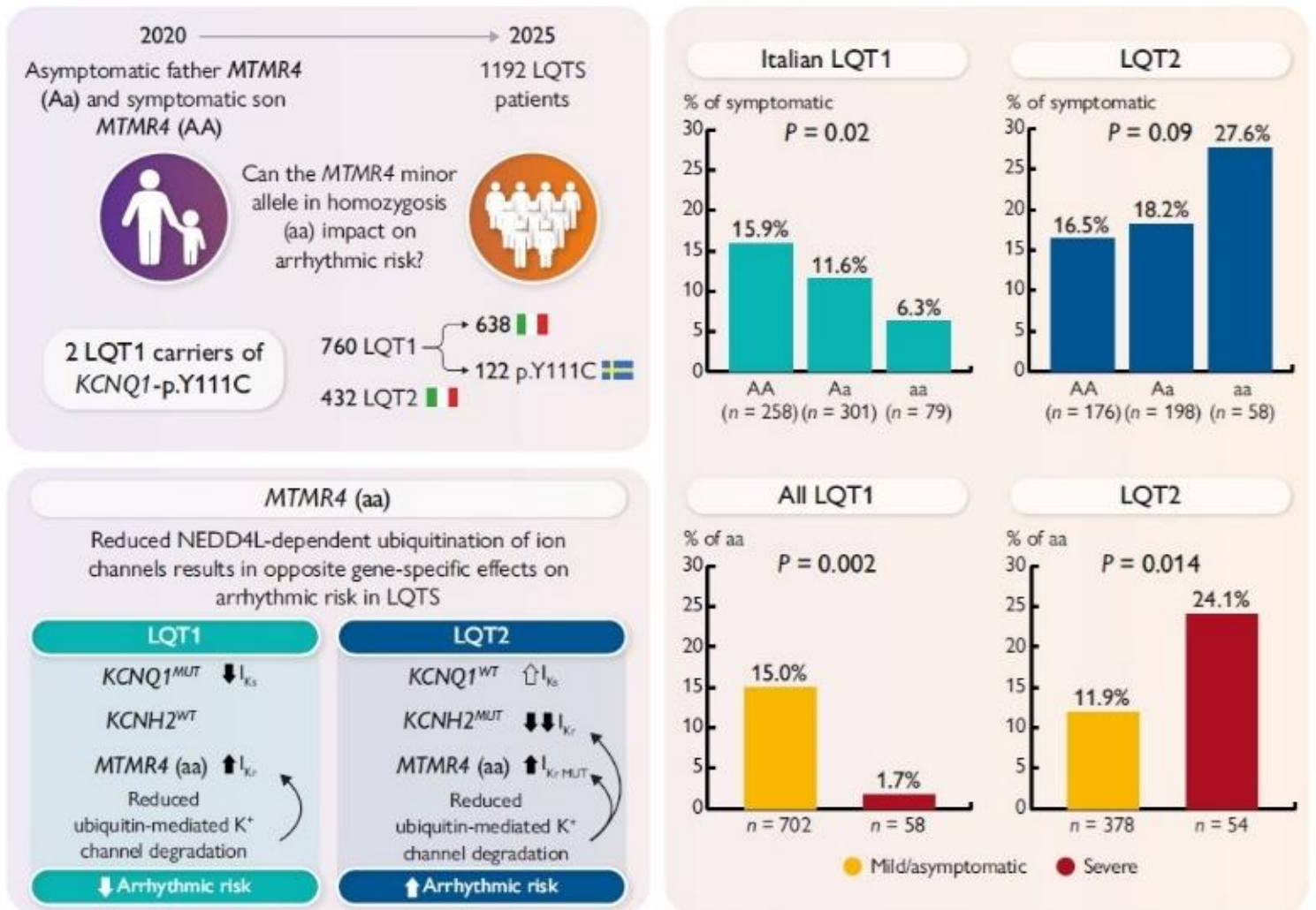
Background and Aims

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 analyzed: 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

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.

(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 homozygosity exerts a gene-specific and opposite impact on arrhythmic risk in LQTS. This finding should influence risk stratification in clinical practice.

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 homozygosis (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.

The full article, as well as other recent journal publications authored or co-authored by our staff can be found on the [AMPS website](#).

Products News

- ACG: working on version 2.3.0: adding short ECG as new resource
- CER-S:
 - working on version 4.10.0: data security improvements,
 - release of version 4.6.2: bug fixes
- Surveyor2ISHNE: release of version 1.2.0: improved handling of long records and data
- ECGSolve: release of version 2.8.0: BRAVO algorithm alignment and bug fixes
- ECGCor: working on version 1.1.0: interface and view improvements
- Abile: working on algorithm improvements, especially for single-channel ECG

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- ❖ Conversion of proprietary digital ecg files formats into the HL7 FDA xml ecg format
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