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## GENETICS OF THE LONG QT SYNDROME

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Long QT syndrome (LQTS) is one of the first cardiovascular diseases that has been recognized as a primarily inherited disease and quickly got a broad spectrum of causative genes [1]. LQTS's relatively high population prevalence (approximately 1:2500), well-recognized ECG pattern, and clear genotype-phenotype correlations were the impetus for the introduction of genetic testing for LQTS into clinical practice. Being one of the first genetic syndromes in the cardiovascular field, LQTS continues to prove its pioneering role in cardiogenetics, bringing on the stage the problem of "variants of unknown clinical significance" and focusing the attention on the growing number of new LQTS susceptibility genes only occasionally described in connection with the disease without segregation analysis and functional studies though [2]. As a result, LQTS first underwent an evolution which later was repeated by many other genetic cardiovascular disorders, such as Brugada syndrome, arrhythmogenic cardiomyopathy, and dilated cardiomyopathy. This evolution included the quick identification of the broad spectrum of disease-associated genes using NGS technologies, defining the genotype-phenotype correlations, recognition of the polygenic impact on the disease phenotype, the renaissance of single nucleotide polymorphisms (SNPs), and analysis of their role in modifying the disease manifestation. The recent achievements of structural biology, molecular electrophysiology, and pharmacogenetics are exploited to narrow the spectrum of all found causative genes to the functionally proven for further safe usage in clinical genetics.

Apart from the most frequent forms of LQTS - LQTS types 1, 2, 3 together with recessive and rare malignant conditions such as Jervell and Lange-Nielsen syndrome, Timothy syndrome, and Andersen-Tawil syndrome, a vast majority of genes associated with LQTS often had very scarce evidence and only single case reports. For many of these genes, e.g., *AKAP9*, *ANK2*, *CAV3*, *KCNE1*, *KCNE2*,

*SCN4B*, *SNTA1*, later on, the doubts have been raised, leading to the reappraisal of defined causative genes for LQTS [3]. Currently, only *KCNQ1*, *KCNH2*, *SCN5A* are considered as causal genes for typical LQTS, and another four genes (*CALM1*, *CALM2*, *CALM3*, *TRDN*) were reported as definitive for LQTS with atypical features, including neonatal atrioventricular block. While for *CACNA1C*, the level of evidence is moderate, other genes are considered as having limited evidence as causative for LQTS. In parallel, growing evidence appeared regarding the role of common genetic variants (SNPs) in LQTS-associated genes as important modulators of disease phenotypic variability. Thus, previously reported LQTS-associated genes *KCNE1* and *KCNE2* were recognized as the significant contributors of acquired LQTS, and the role of common genetic determinants of *NOS1AP*, *KCNQ1*, and *KLF12* genes in the development of acquired LQTS prolongation is confirmed now [4].

Since LQTS mainly manifests in childhood, most of the patients reported with genetic testing are children. In our country, inherited LQTS in adult patients was unrecognized for a long time, and LQTS diagnosis was not commonly accepted. Therefore, there are only few papers published on the genetic spectrum of adult patients with LQTS. The research paper published in the current Journal issue [5] represents one of them, providing clinical and genetic information on 24 adult patients with LQTS. Overall, this study confirms worldwide data on the approximate rate of positive genotyping around 60-70% and supports the data on the prevalence of *KCNQ1* and *KCNQ2* pathogenic variants among patients with LQTS. Importantly, the authors also demonstrated the low frequency of *CACNA1C* and other variants among patients with LQTS raising criticism regarding including these genes in clinical testing [6]. Together with recently published papers on the role of rare genetic variants in LQTS, this study can lead to the reappraisal of the clinical inter-

pretations of the earlier reported genes and their use in target panels for genetic testing.

Currently, our knowledge on LQTS genetics, electrophysiology, and structural biology, together with data on SNPs impact, demand new clinical concepts regarding

diagnostic and treatment approaches in patients with inherited and acquired disease. Therefore, the paper presented in this issue is well in line with the most contemporary view of LQTS genetics and supports modern trends in the cardiovascular genetic field.

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