Genetic Characteristics in Paediatric Patients with the Long QT Syndrome (LQTS) Phenotype subjected to Next Generation Sequencing (NGS)

Tavačová T (1), Kubuš P. (1), Poustková-Norambuena P. (2), Votýpka P. (2), Macek M. Jr.(2), Janoušek J. (1), Krebsová A. (3)

1. Children´s Heart Centre, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic
2. Department of Biology and Molecular Genetics, Motol University Hospital, Prague, Czech Republic
3. Cardiology Department, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

**BACKGROUND:** NGS is a new method of molecular-genetic evaluation introduced in the last years to clinical practice. We aimed to assess the genetic profile in an initial cohort of paediatric patients with the LQTS phenotype undergoing NGS at our institution.

**PATIENTS AND METHODS:** All paediatric patients phenotypically diagnosed as LQTS (N=36) who underwent molecular-genetic examination by NGS were retrospectively analysed at a single tertiary care paediatric cardiology centre. The reason for initial presentation was resuscitated cardiac arrest (N=9), arrhythmia symptoms (N=8), positive preparticipation ECG screening (N=8), other heart disease symptoms (N=7), positive family history (N=2) and incidental finding (N=2). Mean QTc interval was 510 ms. NGS used a cardiovascular gene panel that comprised 228 genes. All of the detected variants were verified by Sanger sequencing in both the patients and their first-degree relatives.

**RESULTS:** Definitely or likely pathogenic variants (sequence variant classification - class 4 and 5) were identified in 30/36 (83%) of patients. Most frequently variants were found in the KCNQ1 gene (LQT1, N=15) followed by KCNH2 gene (LQT2, N=7) and SCN5A gene (LQT3, N=4). In one case two different pathogenic variants in the KCNH2 gene with a severe clinical course were detected. Another patient had a compound heterozygosity with pathogenic variants in both the KCNQ1 and KCNH2 genes. Variants causing Andersen-Tawil syndrome (LQT7) were found in two patients and LQT12 (SNTA1 mutation) in one patient.

**CONCLUSIONS:** NGS revealed a high incidence of pathogenic or likely pathogenic LQTS variants (83%) in an initial cohort of paediatric patients with the LQTS phenotype confirming clinical utility as well as correct phenotype classification in a tertiary care paediatric cardiology centre. First degree relatives were included in the evaluation according to current guidelines to provide genetic stratification and lethal arrhythmia prevention in affected family members.