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Clinical and genetic yield of familiar screening after sudden death of young patients.

Authors:
A Podgorska¹, B Foss-Nieradko², EK Biernacka³, M Franaszczyk⁴, M Stepień-Wojno², J Poninska⁴, E Michalak², P Chmielewski², R Baranowski⁵, R Ploski⁶, A Lutynska⁴, ZT Bilinska², ¹Institute of Cardiology in Anin, Department of Medical Biology - Warsaw - Poland, ²Institute of Cardiology in Anin, Unit for Screening Studies in Inherited Cardiovascular Diseases - Warsaw - Poland, ³Institute of Cardiology in Anin, Department of Congenital Heart Diseases - Warsaw - Poland, ⁴Institute of Cardiology in Anin, Department of Medical Biology - Warsaw - Poland, ⁵Institute of Cardiology in Anin, Department of Arrhythmia - Warsaw - Poland, ⁶Medical University of Warsaw, Department of Medical Genetics - Warsaw - Poland,

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Background:
In Europe, approximately 9000 patients under the age of 45 die suddenly every year. In this group the predominant reasons of sudden death (SD) are channelopathies, cardiomyopathies, myocarditis and substance abuse. The main challenge is the identification of the cause of an unexpected death, especially when the autopsy was not done routinely.

Objective:
The aim of the study was to investigate the value of clinical and genetic screening in relatives of subjects who died suddenly under the age of 45.

Methods:
In the years 2017-2018 we evaluated 53 relatives (41 1st degree) of 25 young SD subjects. Clinical screening included a review of medical history, clinical examination, ECG, transthoracic echocardiogram, 24-hour EKG Holter monitoring, stress test and, cardiac MRI, provocative drug tests, if necessary. Standard diagnostic criteria were used according to currently available ESC guidelines. The most affected 1st degree relative of the SD victim was named as proband.

DNA samples from 25 probands were examined by next generation sequencing (NGS) using a custom panel which included 174 genes associated with 17 cardiac diseases-TruSight Cardio (TSC) panel. Variants identified with NGS were followed-up in probands and other relatives with Sanger sequencing.

Baseline analysis of NGS results was based on searching for genetic variants with very low frequency (<0.001) with high bioinformatic prediction scores with special regard to phenotypically consistent genes. The frequencies of variants were compared with the GnomAD database, Phase 3 of 1000 Genomes, NHLBI GO Exome Sequencing Project (ESP) 6500. For the bioinformatic prediction scores we used data summarized in VarSome database. The clinical significance of the variants was based on ClinVar database.

Results:
Based on comprehensive clinical evaluation of relatives the diagnosis was made in 16/25 (64%) families, namely long QT syndrome (n=7/16; 43.75%), hypertrophic cardiomyopathy (n=5/16; 31.25%), Brugada syndrome (1/16; 6.25%), arrhythmogenic right ventricular cardiomyopathy (n=1/16; 6.25%), thoracic aortic aneurysm (n=1/16; 6.25%) and complete heart block (n=1/16; 6.25%). In 9/25 families (36%) exams showed minor abnormalities, but definite diagnosis could not be made.

We found pathogenic variants in 11/25 (44%) probands. We identified 9 variants in a subgroup of probands with diagnosis (frameshift in MYBPC3 and PKP2, missense variants in KCNQ1, SCN3B, SCN5A, MYH7, TPM1, SCN2B, KCNH2 genes) and 2 variants in a subgroup of probands without diagnosis (frameshift in TTN gene and a missense in KCNH2 gene).
Conclusion:
This study shows that clinical and genetic familial screening after sudden death of young patients may be effective, helps in identifying individuals at risk and allows to implement an adequate treatment to prevent subsequent sudden death.