Sudden unexplained death in young people: A family matter

Oscar Campuzano[1–3], Georgia Sarquella-Brugada[3–5], Ramon Brugada[1–3, 6]

[1]Cardiovascular Genetics Center, Institut d'Investigació Biomèdica de Girona (IDIBGI-CERCA), Parc Hospitalari Martí i Julià, Salt, Spain
[2]Centro de Investigación Biomédica en Red. Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain
[3]Medical Science Department, School of Medicine, University of Girona, Girona, Spain
[4]Pediatric Arrhythmias, Inherited Cardiac Diseases and Sudden Death Unit, Cardiology Department, Sant Joan de Déu Hospital de Barcelona, Barcelona, Spain
[5]Arrítmies Pediàtriques, Cardiologia Genètica i Mort Sobtada, Malalties Cardiovasculars en el Desenvolupament, Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain
[6]Cardiology Service, Hospital Josep Trueta, University of Girona, Girona, Spain

Related article
by Chmielewski et al.

Correspondence to:
Oscar Campuzano, BSc, MSc, PhD, Medical Science Department, School of Medicine, University of Girona, Emili Grahit 77, 17003, Girona (Catalunya), Spain
phone: +34 972 41 96 16,
e-mail: oscar@brugada.org

DOI: 10.33963/v.phj.99975

Received:
March 21, 2024

Accepted:
March 21, 2024

Early publication date:
March 25, 2024

The Trans-Tasman Response AGAinst sudden Death in the Young team (TRAGADY), the Royal College of Pathologists of Australia, and the National Heart Foundation of New Zealand proposed the first standardized protocol focused on performing an autopsy in young people who died suddenly and without a conclusive cause of decease (named Sudden Unexplained Death, SUD) (www.rcpa.edu.au/getattachment/b72c2a4c-0e36-4656-8704-f2e8a7b7bc20/Guidelines-on-Autopsy-Practice.aspx). In this first guide, properly informing relatives about SUD implications for their survival was strongly emphasized as most cases of SUD in the young population are due to inherited arrhythmogenic syndromes (IAS), including cardiac channelopathies and cardiomyopathies [1, 2]. These entities are caused by pathogenic alterations in gene encoding cardiac ion channels or associated proteins as well as desmosomal, sarcomeric, and cytoskeletal proteins of the myocyte. Current clinical and genetic guidelines recommend performing a post-mortem genetic analysis (called molecular autopsy) in those SUD cases where a highly suspected cause of death is IAS [3, 4]. Owing to the genetic origin of IAS, relatives can be carriers of the same pathogenic alteration, so genetic analysis of family members is highly recommended [5].

A molecular autopsy is a fundamental tool helping to unravel genetic alterations, clarify the cause of SUD, and therefore, facilitate early identification of genetic carriers. The first manifestation of an IAS may be SUD, thus identifying genetic carriers at risk allows for adoption of preventive personalized therapies [3, 4]. Nowadays, use of massive sequencing technologies (called, next generation sequencing) allows wide-ranging genetic analysis [6]. Despite recent advances, genetic diagnosis in some SUD cases remains uncertain mainly because of identifying rare variants classified as variants of unknown significance (VUS) according to the current American College of Medical Genetics and Genomics recommendations [7]. These recommendations include a list of items based on available data at the moment of the analysis. In consequence, modification of data may also alter the previous classification of a genetic variant. In recent years, several studies recommend performing a periodic re-analysis/re-interpretation of rare variants, especially those previously classified as VUS by the American College of Medical Genetics and Genomics [8–10]. This is especially relevant in SUD cases because a large number of variants remains ambiguous [11]. For this reason, molecular autopsy and familial assessment are crucial in unraveling causes of unexpected deaths in young people.

In this issue of the journal, Chmielewski et al. [12], report on clinical and genetic screening in a cohort of 65 young SUD cases from 39 families, including 87 relatives. After a comprehensive analysis of all collected data (situation of death, genetic analysis, familial assessment), definite diagnosis was identified in 44%, mainly cardiomyopathies, followed by cardiac channelopathies. In 18% of cases,

a variant with a definite deleterious role was identified and a VUS was identified in 2 SUD cases; the remaining subjects had a negative genetic diagnosis. Familial assessment identified 3 families with a definite diagnosis and affected relatives received guidance on personalized therapeutic preventive measures. Unfortunately, a comprehensive autopsy was not performed in SUD cases, which, from our point of view, is a crucial task to identify any macroscopic and/or microscopic alteration in the heart, especially in cardiomyopathies. The autopsy is a crucial point in disclosing the cause of SUD and may help to interpret genetic variants, especially those classified as VUS. For this reason, the yield of the genetic testing has little effectiveness in families without the disease phenotype. The number of genes with a definitive association with any IAS is limited to no more than 10 in cardiac channelopathies and 25 in cardiomyopathies [3, 4]. Therefore, increasing the knowledge about the number of causative genes in IAS and obtaining forensic data could help to raise the percentage of cases with a definite diagnosis. Despite this limitation, molecular autopsy and familial genotype-phenotype analysis may help to identify relatives at risk and save lives.

Article information

Conflict of interest: None declared.

Funding: This work was supported by Obra Social "La Caixa Foundation" (LCF/PR/GN16/50290001 and LCF/PR/GN19/50320002). Co-funded by Instituto de Salud Carlos III (FIS PI21/00094). CIBERCV is an initiative of the ISCIII, Spanish Ministry of Economy and Competitiveness. IDIBGI is a "CERCA Programme / Generalitat de Catalunya". The funders played no role in the study design, data collection, data analysis, interpretation, or writing of the report.

REFERENCES

1. Svane J, Lynge TH, Hansen CJ, et al. Witnessed and unwitnessed sudden cardiac death: a nationwide study of persons aged 1-35 years. Europace. 2021; 23(6): 898–906, doi: 10.1093/europace/euab017, indexed in Pubmed: 33595080.
2. Lynge TH, Risgaard B, Banner J, et al. Nationwide burden of sudden cardiac death: A study of 54,028 deaths in Denmark. Heart Rhythm. 2021; 18(10): 1657–1665, doi: 10.1016/j.hrthm.2021.05.005, indexed in Pubmed: 33965606.
3. Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the State of Genetic Testing for Cardiac Diseases. Heart Rhythm. 2022; 19(7): e1–e60, doi: 10.1016/j.hrthm.2022.03.1225, indexed in Pubmed: 35390533.
4. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 2023; 44(37): 3503–3626, doi: 10.1093/eurheartj/ehad194, indexed in Pubmed: 37622657.
5. Stiles MK, Wilde AAM, Abrams DJ, et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. Heart Rhythm. 2021; 18(1): e1–e50, doi: 10.1016/j.hrthm.2020.10.010, indexed in Pubmed: 33091602.
6. Adams DR, Eng CM, Adams DR, et al. Next-generation sequencing to diagnose suspected genetic disorders. N Engl J Med. 2018; 379(14): 1353–1362, doi: 10.1056/NEJMra1711801, indexed in Pubmed: 30281996.
7. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015; 17(5): 405–424, doi: 10.1038/gim.2015.30, indexed in Pubmed: 25741868.
8. Martínez-Barrios E, Sarquella-Brugada G, Pérez-Serra A, et al. Reanalysis and reclassification of rare genetic variants associated with inherited arrhythmogenic syndromes. EBioMedicine. 2020; 54(2): 102732, doi: 10.1016/j.ebiom.2020.102732, indexed in Pubmed: 32268277.
9. Vallverdú-Prats M, Alcalde M, Sarquella-Brugada G, et al. Rare variants associated with arrhythmogenic cardiomyopathy: Reclassification five years later. J Pers Med. 2021; 11(3), doi: 10.3390/jpm11030162, indexed in Pubmed: 33652588.
10. Sarquella-Brugada G, Fernandez-Falgueras A, Cesar S, et al. Clinical impact of rare variants associated with inherited channelopathies: a 5-year update. Hum Genet. 2022; 141(10): 1579–1589, doi: 10.1007/s00439-021-02370-4, indexed in Pubmed: 34546463.
11. Martinez-Barrios E, Sarquella-Brugada G, Perez-Serra A, et al. Reevaluation of ambiguous genetic variants in sudden unexplained deaths of a young cohort. Int J Legal Med. 2023; 137(2): 345–351, doi: 10.1007/s00414-023-02951-0, indexed in Pubmed: 36693943.
12. Chmielewski P, Świerczewski M, Foss-Nieradko B, et al. Clinical and genetic yield of familial screening after sudden unexplained death at young age. Pol Heart J. 2024; 82(4): 382–390, doi: 10.33963/v.phj.99617, indexed in Pubmed: 38493454.