Review

Eur J Pediatr. 2024 Sep 23.

.

Cardiac channelopathies in pediatrics: a genetic update

Estefanía Martínez-Barrios[#1,2], Oscar Campuzano[#3,4,5], Andrea Greco[1,2], José Cruzalegui[1,2], Georgia Sarquella-Brugada[6,7,8,9]

Affiliations

[1]Arrhythmias, Inherited Cardiac Diseases and Sudden Death Unit, Hospital Sant Joan de Déu, Esplugues de Llobregat, 08950, Barcelona, Catalonia, Spain.
[2]Malalties Cardiovasculars en El Desenvolupament, Institut de Recerca Sant Joan de Déu (IRSJD), Arrítmies Pediàtriques, Cardiologia Genètica I Mort Sobtada, Esplugues de Llobregat, 08950, Barcelona, Spain.
[3]Centro de Investigación Biomédica en Red, Enfermedades Cardiovasculares (CIBERCV), 28029, Madrid, Spain.
[4]Institut d'Investigació Biomèdiques de Girona (IDIBGI-CERCA), 17190, Salt, Spain.
[5]Medical Science Department, School of Medicine, Universitat de Girona, 17003, Girona, Spain.
[6]Arrhythmias, Inherited Cardiac Diseases and Sudden Death Unit, Hospital Sant Joan de Déu, Esplugues de Llobregat, 08950, Barcelona, Catalonia, Spain. georgia.sarquella@sjd.es.
[7]Malalties Cardiovasculars en El Desenvolupament, Institut de Recerca Sant Joan de Déu (IRSJD), Arrítmies Pediàtriques, Cardiologia Genètica I Mort Sobtada, Esplugues de Llobregat, 08950, Barcelona, Spain. georgia.sarquella@sjd.es.
[8]Medical Science Department, School of Medicine, Universitat de Girona, 17003, Girona, Spain. georgia.sarquella@sjd.es.
[9]Pediatric Department, School of Medicine, Universitat de Barcelona, 08036, Barcelona, Spain. georgia.sarquella@sjd.es.
[#]Contributed equally.

PMID: 39307882 DOI: 10.1007/s00431-024-05757-3

Abstract

Cardiac channelopathies are a group of inherited syndromes that can cause malignant arrhythmias and sudden cardiac death, particularly in the pediatric population. Today, a 12-lead electrocardiogram is the most effective tool to diagnose these diseases. Incomplete penetrance and variable expressivity are hallmarks of these syndromes. Some of these malignant entities may remain hidden and only a trigger such as exercise, emotions or fever can unmask the electrical pattern to diagnose the disease. Sudden cardiac death may be the first manifestation of any of these syndromes. The use of complementary tests that allow early diagnosis is strongly recommended, among which we find: pharmacological provocations, exercise tests, and genetic analysis. Genetic testing makes it possible to unravel the origin of the disease, and also identify family members who carry the harmful genetic defect and are therefore at risk. One of the main challenges in this area is the large number of genetic variants of uncertain significance, which prevent effective translation into clinical practice. Early identification of the pediatric population at risk and adequate risk stratification are crucial to adopting personalized preventive measures that reduce the risk of lethal episodes in this population. What is Known: • In the pediatric population, malignant arrhythmias leading to sudden cardiac death are mainly caused by inherited syndromes. • A conclusive genetic diagnosis unravels the origin of the syndrome and allows cascade screening to identify relatives carrying the genetic alteration. What is New: • The use of sequencing technologies allows a broad genetic analysis, helping to unravel new genetic alterations causing inherited arrhythmogenic syndromes. • A periodic reanalysis of genetic variants that currently have an ambiguous role will help discern those that are truly pathogenic.

Keywords: Arrhythmias; Genetics; Pediatrics; Sudden cardiac death.

References

1. Sarquella-Brugada G, Garcia-Algar O, Zambrano MD et al (2021) Early identification of prolonged QT interval for prevention of sudden infant death. Front Pediatr 9:704580 - DOI - PubMed - PMC
2. Sarquella-Brugada G, Campuzano O, Brugada J (2020) Paediatric arrhythmology: the challenge of the 21st century. An Pediatr (Barc) 92(1):1–2 - DOI
3. Janzen ML, Davies B, Laksman ZWM et al (2023) Management of inherited arrhythmia syndromes: A HiRO consensus handbook on process of care. CJC Open 5(4):268–284 - DOI - PubMed - PMC
4. Hayesmoore JB, Bhuiyan ZA, Coviello DA et al (2023) EMQN: recommendations for genetic testing in inherited cardiomyopathies and arrhythmias. Eur J Hum Genet 31(9):1003–1009 - DOI - PubMed - PMC
5. Wilde AAM, Semsarian C, Marquez MF et al (2022) 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
6. Coll M, Perez-Serra A, Mates J et al (2017) Incomplete penetrance and variable expressivity: hallmarks in channelopathies associated with sudden cardiac death. Biology 7(1)
7. Campuzano O, Sarquella-Brugada G, Arbelo E et al (2020) Genetic variants as sudden-death risk markers in inherited arrhythmogenic syndromes: personalized genetic interpretation. J Clin Med 9(6)
8. Campuzano O, Sarquella-Brugada G, Fernandez-Falgueras A et al (2020) Reanalysis and reclassification of rare genetic variants associated with inherited arrhythmogenic syndromes. EBioMedicine 54:102732 - DOI - PubMed - PMC
9. Richards S, Aziz N, Bale S et al (2015) 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 17(5):405–424 - DOI - PubMed - PMC
10. Martinez-Barrios E, Cesar S, Cruzalegui J et al (2022) Clinical genetics of inherited arrhythmogenic disease in the pediatric population. Biomedicines 10(1)
11. Landstrom AP, Chahal AA, Ackerman MJ et al (2023) Interpreting incidentally identified variants in genes associated with heritable cardiovascular disease: a scientific statement from the American Heart Association. Circulation genomic and precision medicine 16(2):e000092 - DOI - PubMed
12. Kline J, Costantini O (2019) Inherited cardiac arrhythmias and channelopathies. Med Clin North Am 103(5):809–820 - DOI - PubMed
13. Specterman MJ, Behr ER (2023) Cardiogenetics: the role of genetic testing for inherited arrhythmia syndromes and sudden death. Heart 109(6):434–441 - DOI - PubMed
14. Moras E, Gandhi K, Narasimhan B et al (2023) Genetic and molecular mechanisms in Brugada syndrome. Cells 12(13)
15. Schwartz PJ, Sala L (2023) The impact of genetics on the long QT syndrome: myth or reality? Curr Opin Cardiol 38(3):149–156 - PubMed
16. Krahn AD, Laksman Z, Sy RW et al (2022) Congenital long QT syndrome. JACC Clinical electrophysiology 8(5):687–706 - DOI - PubMed
17. Abbas M, Miles C, Behr E et al (2022) Catecholaminergic polymorphic ventricular tachycardia. Arrhythmia & electrophysiology review 11:e20 - DOI
18. Durkie M (2024) ACGS best practice guidelines for variant classification in rare disease 2024 ACGS
19. Gudmundsson S, Singer-Berk M, Watts NA et al (2022) Variant interpretation using population databases: Lessons from gnomAD. Hum Mutat 43(8):1012–1030 - DOI - PubMed
20. Yadav D, Patil-Takbhate B, Khandagale A et al (2023) Next-Generation sequencing transforming clinical practice and precision medicine. Clin Chim Acta 551:117568 - DOI - PubMed
21. Foreman J, Perrett D, Mazaika E, Hunt SE, Ware JS, Firth HV (2023) DECIPHER: improving genetic diagnosis through dynamic integration of genomic and clinical data. Annu Rev Genomics Hum Genet 24:151–176 - DOI - PubMed - PMC
22. Martinez-Barrios E, Sarquella-Brugada G, Perez-Serra A et al (2023) Reevaluation of ambiguous genetic variants in sudden unexplained deaths of a young cohort. Int J Legal Med 137(2):345–351 - DOI - PubMed - PMC