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REVIEW ARTICLE

Cardiac channelopathies: The role of sodium channel mutations☆

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KEYWORDS
Mutations;
Sodium channels;
Heart diseases;
Heart arrhythmias;
Sudden cardiac death

Abstract
Introduction and objectives: The importance of sodium channels for the normal electrical activity of the heart is emphasized by the fact that mutations (inherited or de novo) in genes that encode for these channels or their associated proteins cause arrhythmogenic syndromes such as the Brugada syndrome and the long QT syndrome (LQTS). The aim of this study is to conduct a review of the literature on the mutations in the sodium channel complex responsible for heart disease and the implications of a close relationship between genetics and the clinical aspects of the main cardiac channelopathies, namely at the level of diagnosis, risk stratification, prognosis, screening of family members and treatment.
Methods: The online Pubmed® database was used to search for articles published in this field in indexed journals. The *MeSH database* was used to define the following query: ''Mutation [Mesh] AND Sodium Channels [Mesh] AND Heart Diseases [Mesh]'', and articles published in the last 15 years, written in English or Portuguese and referring to research in human beings were included.
Conclusions: In the past few years, significant advances have been made to clarify the genetic and molecular basis of these syndromes. A greater understanding of the underlying pathophysiological mechanisms showed the importance of the relationship between genotype and phenotype and led to progress in the clinical approach to these patients. However, it is still necessary to improve diagnostic capacity, optimize risk stratification, and develop new specific treatments according to the genotype-phenotype binomial.

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PALAVRAS-CHAVE
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Canalopatias cardíacas: o papel das mutações nos canais de sódio

Resumo
Introdução e objetivos: A importância dos canais de sódio para a normal atividade elétrica do coração é enfatizada pelo facto de as mutações (hereditárias ou de novo) nos genes que codificam esses canais ou as proteínas a esses associadas provocarem síndromes arritmogénicas como a síndrome de Brugada e a síndrome do QT longo. O objetivo deste trabalho é proceder a uma revisão bibliográfica sobre as mutações no complexo dos canais de sódio responsáveis por doença cardíaca e as implicações da relação estrita entre a genética e a clínica das principais canalopatias cardíacas, nomeadamente no nível do diagnóstico, da estratificação do risco, do prognóstico, do rastreio de parentes e terapêutica.
Métodos: Foi usada a base de dados online Pubmed® para pesquisar os artigos publicados nessa área, em revistas indexadas. Recorreu-se à *MeSH Database* para definir a seguinte *query*: ''Mutation [Mesh] AND Sodium Channels [Mesh] AND Heart Diseases [Mesh]'' e incluíram-se artigos publicados nos últimos 15 anos, escritos em inglês ou português e referentes à investigação em humanos.
Conclusões: Nos últimos anos, grandes avanços foram feitos no esclarecimento da base genética e molecular dessas síndromes. A maior compreensão dos mecanismos fisiopatológicos subjacentes demonstrou a importância da relação entre o genótipo e o fenótipo e permitiu efetuar progressos na abordagem clínica desses pacientes. Todavia, é ainda necessário melhorar a capacidade de diagnóstico, aprimorar a estratificação do risco e desenvolver novas terapêuticas específicas de acordo com o binómio genótipo-fenótipo.

List of abbreviations

AF	atrial fibrillation
AP	action potential
BrS	Brugada syndrome
Ca^{2+}	calcium ion
CAV3	caveolin-3
CCD	cardiac conduction disease
CPVT	catecholaminergic polymorphic ventricular tachycardia
DCM	dilated cardiomyopathy
ECG	electrocardiogram
EPS	electrophysiological study
HR	heart rate
I_{Ca}	calcium current
I_K	potassium current
I_{Na}	sodium current
$I_{Na\ late}$	late, persistent or sustained sodium current
$I_{Na\ peak}$	peak sodium current
K^+	potassium ion
LQTS	long QT syndrome
LQTS1	long QT syndrome type 1
LQTS2	long QT syndrome type 2
LQTS3	long QT syndrome type 3
ms	milliseconds
Na^+	sodium ion
NaC	sodium channels
PVS	programmed ventricular stimulation
PVT	polymorphic ventricular tachycardia
QTc	QT interval corrected for heart rate
SCD	sudden cardiac death
SD	sudden death
SNP	single nucleotide polymorphism
SNTA1	syntrophin
SQTS	short QT syndrome
TdP	Torsade de pointes
VF	ventricular fibrillation
VT	ventricular tachycardia

Introduction

Cardiac channelopathies constitute a heterogeneous group of inherited cardiac diseases caused by mutations in genes that encode for the ion channels expressed in the heart (involved in Na^+ [I_{Na}], K^+ [I_K] and Ca^{2+} [I_{Ca}] currents) and/or the proteins that regulate their function.[1–3] These mutations result in different phenotypes according to the abnormalities induced in the sodium current and in other ion currents, leading to a greater likelihood of occurrence of syncope, seizures and arrhythmias, although most of the time there are no underlying structural heart defects.[4] This shows the importance of ion channels, namely sodium channels (NaC), in the genesis and propagation of the action potential (AP), and consequently in heart excitability.[2,3,5–7]