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Review

# Cardiac channelopathies: Genetic and molecular mechanisms

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ABSTRACT

Channelopathies are diseases caused by dysfunctional ion channels, due to either genetic or acquired pathological factors. Inherited cardiac arrhythmic syndromes are among the most studied human disorders involving ion channels. Since seminal observations made in 1995, thousands of mutations have been found in many of the different genes that code for cardiac ion channel subunits and proteins that regulate the cardiac ion channels. The main phenotypes observed in patients carrying these mutations are congenital long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome (SQTS) and variable types of conduction defects (CD). The goal of this review is to present an update of the main genetic and molecular mechanisms, as well as the associated phenotypes of cardiac channelopathies as of 2012.



**Contents**



*Abbreviations:* AF, atrial fibrillation; AP, action potential; BrS, Brugada syndrome; BWS, Beckwith–Wiedemann syndrome; $Ca^{2+}$, calcium; CCD, cardiac conduction disease; CNV, copy number variation; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; ECG, electrocardiogram; I, current; ICD, implantable cardioverter-defibrilator; JLNS, Jervell and Lange-Nielsen syndrome; $K^+$, potassium; LQTS, long QT syndrome; $Na^+$, sodium; QTc, corrected QT interval; RWS, Romano–Ward syndrome; SCD, sudden cardiac death; SQTS, short QT syndrome; TDP, torsades de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia.

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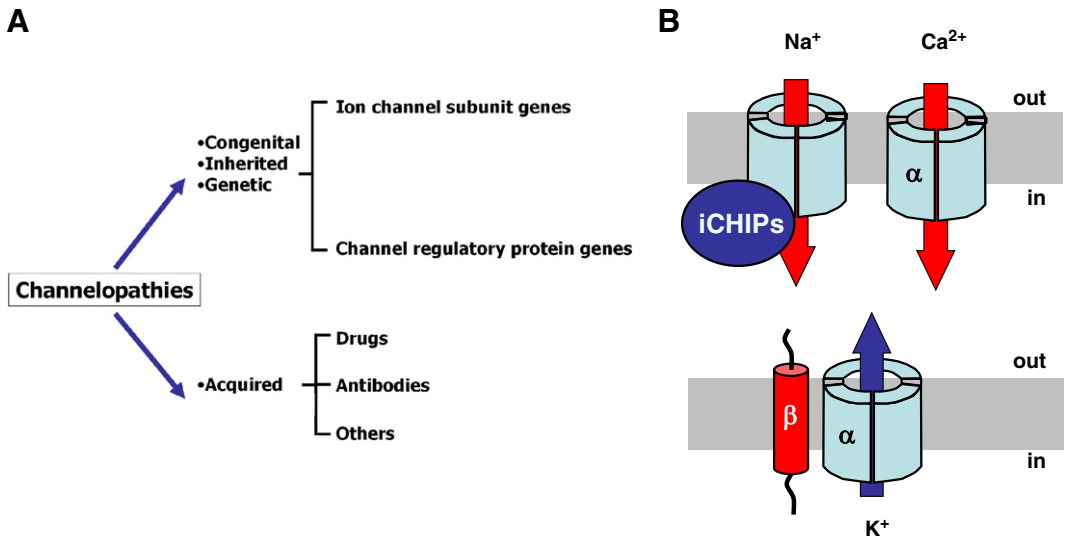


**Fig. 1.** Simplified classification of human channelopathies. (A) Two main groups of channelopathies cause human diseases. One group is caused by mutations found in the genes that encode either the pore-forming subunits of the ion channels or their regulatory subunits. These genetic channelopathies can be congenital or inherited. The second group is caused by acquired factors, such as drugs or antibodies that interact with ion channels. There may also be other unknown extrinsic factors that modulate ion channel function. (B) The mutated genes encode the alpha subunits, the pore-forming subunit of the ion channels. The regulatory beta subunits and channel interacting proteins (iCHIPs) have also been found to be mutated in cardiac channelopathies.

## 1. Introduction

### *1.1. Human channelopathies*

Ion channels are essential membrane proteins found in all cell types. They permit the regulated flux of ions across the plasma membrane as well as the membrane of intracellular organelles (Hille, 2001). Since ions are charged molecules, these ionic fluxes produce electrical currents and play a major role in the determination of transmembrane electric potential differences. The cellular resting membrane potential and action potential (AP) of excitable cells largely depend on the function of these ion channels. Basic cellular and tissular processes, such as transepithelial transport, information transmission, muscle cell contraction and hormone secretion are all dependent on ion channel function. The dysfunction of ion channels, also referred to as channelopathies, has been linked to many human diseases (Ashcroft, 2006). Channelopathies are a result of either genetic mutations or acquired malfunctions of ion channels (see Fig. 1). Genetic channelopathies may be caused by mutations in the genes coding for the pore-forming subunit of the ion channels (alpha subunit) or in the genes coding for the regulatory proteins, such as the beta subunit or the enzymes that regulate alpha subunit function. Acquired channelopathies can result from drug exposure, immunoglobulins, or toxins that modify ion channel function. These compounds can inhibit or activate ion channels. It can also be proposed that alterations of the expression and/or regulation of ion channels in the context of primary disease, such as heart failure, may also be classified as secondary cardiac channelopathies.

Since ion channels are expressed in the cells of all tissues and organs of the human body, channelopathies can be at the origin of disease in virtually all fields of medicine. Channelopathies are well recognized in neuro-muscular and cardiovascular disorders since excitable cells harboring voltage-gated ion channels play primordial roles in these systems. Epilepsy, migraines, pain disorders, periodic paralysis and cardiac arrhythmias are some of the most common channelopathy phenotypes seen in these excitable tissues. One of the most prevalent channelopathies, known to be responsible for cystic fibrosis, is caused by loss-of-function of the CFTR chloride channel which disrupts the transepithelial transport of chloride ions (Guggino and Stanton, 2006). Inherited hypertension and tubular renal disorders are also caused by dysfunctional epithelial ion channels (Hubner and Jentsch, 2008).

This review article provides an update on the principal phenotypes associated with genetic cardiac channelopathies. We describe the genetic and pathophysiological mechanisms underlying these cardiac disorders. Clinical aspects, such as prevention and therapeutic strategies, will only be briefly addressed.

### *1.2. Cardiac channelopathies and their prevalence*

The genetic and molecular determinants of cardiac channelopathies were identified over 15 years ago (Priori, 2010) when it was shown that mutated genes in patients with congenital long QT syndrome (LQTS) encode ion channel subunits. Since these seminal findings (Curran et al., 1995; Wang et al., 1995a, 1996), many other inherited electrical disturbances have been linked to mutations in ion channel genes or genes that regulate their function (Fig. 1). The estimated prevalence of cardiac channelopathies in the general population remains ill-defined. Population-based clinical studies often underestimate the prevalence. The incomplete penetrance of channelopathies results in the misdiagnosis of "penetrant" cases as seizure disorders or epilepsy. In addition, many of the severe cases of channelopathies result in sudden cardiac death (SCD). On the other hand, clinical and molecular studies investigating different groups of patients are biased by inclusion criteria and external triggers, i.e. some arrhythmia-triggered drugs. Pathology-based molecular studies of SCD victims overestimate the prevalence because "survivors" with and without disease are not included.

Only a few case reports can be found in the literature from 20 years ago, and these disorders were thought to be very rare. Ten years ago a prevalence of 1:10,000 would have been judged to be an overestimation; whereas the current worldwide prevalence of all cardiac channelopathies is thought to be at least 1:2000–1:3000 per individual in the general population (Schwartz et al., 2009). Channelopathies are likely responsible for about half of sudden arrhythmic cardiac death cases (Behr et al., 2008). The most prevalent and well-known disorder in this group is congenital LQTS. The average prevalence of LQTS has been reported to be 1:2500–1:5000 per individual (Goldenberg et al., 2008; Schwartz et al., 2009; Tester et al., 2006). Much higher LQTS prevalence numbers, 0.8–1.5% of the population, have been found in some ethnic groups with founder effects (Berge et al., 2008; Brink and Schwartz, 2009; Winbo et al., 2011). The second most frequent cardiac channelopathy is Brugada syndrome (BrS) (Benito et al., 2008), for which a prevalence of about 1:10,000 has