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Review

# Inherited bradyarrhythmia: A diverse genetic background

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ABSTRACT

Bradyarrhythmia is a common heart rhythm abnormality comprising number of diseases and is associated with decreased heart rate due to the failure of action potential generation and propagation at the sinus node. Permanent pacemaker implantation is often used therapeutically to compensate for decreased heart rate and cardiac output. The vast majority of bradyarrhythmia cases are attributable either to aging or to structural abnormalities of the cardiac conduction system, caused by underlying structural heart disease. However, there is a subset of bradyarrhythmia primarily caused by genetic defects in the absence of aging or underlying structural heart disease. These include several genes that play principal roles in cardiac electrophysiology, heart development, cardioprotection, and the structural integrity of the membrane and sarcomere. Recent advances in the functional analysis of mutations using a heterologous expression system and genetically engineered animal models have provided significant insights into the underlying molecular mechanisms responsible for inherited arrhythmia. In this review, current understandings of the genetic and molecular basis of inherited bradyarrhythmia are presented.


**Contents**



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## 1. Introduction

Bradyarrhythmia is a serious electrical disorder of the heart with the potential to be life threating. The condition is caused by an electrical dissociation in the cardiac conduction system (CCS) comprising the sinus bradycardia, the sinoatrial (SA) exit block and the atrioventricular block (AVB). It often manifests as abnormally suppressed cardiac output in affected individuals, requiring permanent pacemaker implantation in order to compensate for decreased heart rate. The CCS is equipped with a sophisticated histological structure and specialized cellular function in order to maintain proper impulse generation and propagation. The mechanical burden and scars resulting from structural heart disease are a major cause of bradyarrhythmia. Accumulation of connective tissue such as collagen is almost always associated with progression of heart failure, as it promotes dissociation between electrically coupled cardiomyocytes [1]. Collagen deposition is associated with aging and underlying structural heart disease, reflected by the increased incidence and prevalence of bradyarrhythmia associated with these factors [1,2]. In the absence of underlying structural disease or aging, bradyarrhythmia may occur primarily due to genetic defects. In this review, we aim to describe the current understanding of inherited bradyarrhythmia with a focus on diverse genetic backgrounds and molecular physiology (Fig. 1 and Table 1).

## 2. Modulation mechanisms of heart rate and genetic exacerbation factors: physiological regulation of sinus rhythm

In the CCS, the sinoatrial node (SAN) is the primary pacemaker component and functions as a resource for automaticity; that is, spontaneous depolarization with regular intervals. Histologically, the SAN is intramurally embedded at the junction of the right atrium and the superior vena cava and lies along the crista terminalis [3]. The SAN displays heterogeneous cellular morphology, action potential configuration, and electrophysiological characteristics [4]. The SAN's major pacemaker site is situated at its center, however; this site may shift peripherally depending on various interventional factors such as electrolyte concentrations, autonomic nervous stimuli, and temperature [3]. The underlying mechanisms of this pacemaker shift remain undetermined, however; the pacemaker tends to shift to the site where electrical activity is least suppressed by extrinsic factors [3]. The molecular mechanisms underlying myocyte firing in the central SAN are characterized by the SAN's unique gene expression profile, with minimal expression of *KCNJ2* (inwardly rectifying K channel, Kir2.1) and *SCN5A* (cardiac Na channel, Nav1.5) and higher expression of *HCN4* (the pacemaker channel). The absence of *KCNJ2* expression allows the resting membrane potential depolarized to enable spontaneous depolarization, while the absence of *SCN5A* expression can prevent rapid upstroke of action potential. Abundant expression of the *HCN4* pacemaker channel promotes spontaneous, slow depolarization in response to phase 4 hyperpolarization. The peripheral SAN, on the other hand, partially shares the gene expression profile and electrophysiological characteristics of the atrial myocytes [3]. The major role of excitation in the peripheral SAN is the rapid transmission of the sinus impulse to surrounding atrial myocytes. An abundant expression of *SCN5A* causes fast upstroke of action potential in phase 0 and this gives rise to rapid electrical conduction in the peripheral SAN. Thus, loss-of-function mutations in *SCN5A* could result in SA exit block, an electrical conduction blockade between the central SAN and surrounding atrial myocytes [5].

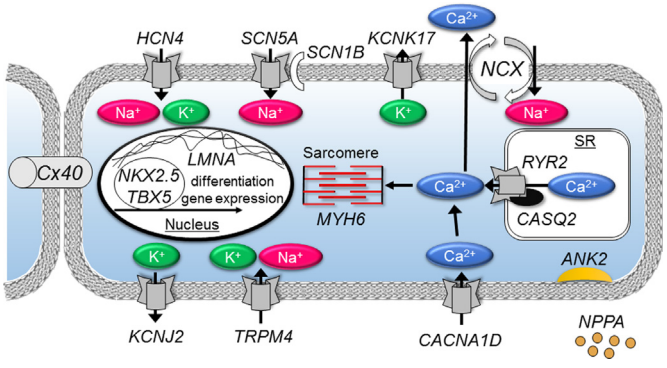


**Fig. 1.** Molecular modules involved in inherited bradyarrhythmia. Abnormalities in multiple pathways involving membrane ion channels, SR ion channels, sarcomere components, cardiac hormones, and membrane anchor proteins are associated with inherited bradyarrhythmia.

The mechanism of cyclic activation in voltage-gated ion channels involves the action of the pacemaker current on the cell membrane and is known as a membrane clock. Recently, a growing body of evidence has implicated the involvement of additional complementary mechanisms in this process, in particular, the rhythmic spontaneous release of $Ca^{2+}$ by the sarcoplasmic reticulum (SR), which is referred to as a calcium clock. The calcium clock functions collaboratively with the membrane clock to form a unified, automatic system, known as a coupled-clock pacemaker system [6]. Genetic defects in the genes involved in membrane and calcium clocks can potentially cause SA disorders.

### 2.1. HCN4

In mammals, the hyperpolarized-activated cyclic nucleotide-gated channel (HCN) family is comprised of four distinct genes, *HCN1*, *2*, *3* and *4*; that are expressed in a wide variety of excitable cells (*HCN4* is predominantly expressed in the central SAN) [7]. *HCN4* slowly becomes permeable for $K^+$ and $Na^+$ in response to hyperpolarization, thus giving rise to slow diastolic depolarization resulting in automaticity [7]. Since the first description of an *HCN4* mutation in familial sick sinus syndrome (SSS) [8], twenty-two further mutations have been reported. Patch-clamp analysis of these mutations using a heterologous expression system with *Xenopus oocytes* or cultured cell lines have shown that reduced peak current densities or a hyperpolarizing shift of the voltage-dependence of activation are the major causes of disease [9,10]. Indeed, these loss-of-function properties decrease the slope of diastolic depolarization, resulting in sinus bradycardia. Some *HCN4* mutations disrupt the cyclic-nucleotide binding domain (cNBD) to which cyclic nucleotide cAMP and cGMP bind directly in response to β-adrenergic stimuli [8,9,11]. However, the molecular mechanisms of *HCN4* mutations are not yet fully elucidated; for example, G482R has been reported in multiple families associated with sinus bradycardia and left ventricular noncompaction cardiomyopathy [7,12]; however, the molecular mechanism underlying left ventricular noncompaction remains unknown.

### 2.2. SCN5A

The cardiac Na channel α subunit Nav1.5 encoded by *SCN5A* is associated with auxiliary β-subunits Navβ1 and Navβ3 [13]. Activation of the sodium channel initiates a rapid influx of $Na^+$, giving rise to the phase 0 upstroke of cardiac action potential, which in turn triggers depolarization of neighboring cardiomyocytes [13]. As this $Na^+$ influx determines the slope and amplitude of phase 0, mutations in *SCN5A* may affect cardiac conduction velocity. The genetic defects in *SCN5A* are associated with multiple diverse inherited arrhythmias referred to as cardiac sodium channelopathy and include type-3 long QT

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