Sinus Node Disease and Cardiac Conduction Disease

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Abstract

Primary sinus node disease (SND) and cardiac conduction defect (CCD) are frequent clinical entities with significant morbidity and mortality, which are major indications for the implantation of electronic pacemakers. Throughout the previous two decades, pathogenetic mechanisms underlying both disorders have been investigated in detail, and it has been demonstrated that distinct genetic defects and/or predisposing genetic constellations play important roles in a considerable number of cases. Furthermore it has been shown that both entities often are related to a broader clinical spectrum including overlapping arrhythmia syndromes and structural cardiac abnormalities, indicating that specified genetic defects are key to distinct clinical phenotypes. This book chapter summarizes the work, which most profoundly influences the current understanding of primary excitation and conduction disorders of the heart. The novel mechanistic insight into important pathogenetic aspects of these disorders may lay the groundwork for more mechanism-based, individually tailored clinical management of patients with primary SND and CCD in the future.

9.1 Sinus Node Disease

9.1.1 Clinical Aspects of Sinus Node Disease (SND)

Loss or dysfunction of sinoatrial nodal cells results in sinus node disease (SND), a term commonly used for disorders associated with failure in rate initiation or conduction from the sinoatrial node (SAN) to the atrium, comprising sinus

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bradycardia, SAN block or arrest, and bradycardia-tachycardia syndrome (Birchfield et al. 1957; Kaplan et al. 1973). In many cases, SND leads to symptoms like dizziness, fatigue, pre-syncope/syncope, or collapse, and the implantation of an electronic pacemaker is currently the only effective therapy (Jensen et al. 2014; Lamas et al. 2000). In 30–50% of all electronic pacemaker implantations, SND is the primary indication, resulting in more than 100,000 pacemakers in the USA in the year 2000, costing more than US$2 billion. With the aging of the population, the number of patients with SND will increase dramatically over the next 50 years. Based on a recent population study, it was calculated that there were approximately 78,000 incident cases of SND in 2012 in the USA, and this number would increase to almost 172,000 per year by 2060 resulting in a major public health burden (Jensen et al. 2014).

In the majority of the cases, SND is a primary "idiopathic" disorder which occurs clearly age-dependent and equally among gender and was found to be associated with risk factors like greater body mass index, height, N-terminal pro-B type natriuretic peptide, cystatin C, and additional cardiovascular disease (Jensen et al. 2014).

Furthermore, primary SND has been related to inherited forms, and specified genes have been linked to SND and shown to be mutated in affected family members (Choudhury et al. 2015). Interestingly, abnormalities of SAN function are particularly common in heart failure and cardiomyopathies (structural, ischemic, or inflammatory) indicating a genetic and/or mechanistic link between electrical and structural dysfunction (Sanders et al. 2004a, b; Zicha et al. 2005). In addition, there are secondary causes of SND like drug intake, myocardial infarction/ischemia, or heart surgery (Monfredi and Boyett 2015). In particular mentionable is the association of SND with the generation of atrial tachyarrhythmias, mostly atrial fibrillation (AF), as these tachycardias affect around 50% of patients with SND (Gomes et al. 1981), leading to the term "bradycardia-tachycardia syndrome." Clinical data suggest that both conditions lay the groundwork for the development and perpetuation of each other (Sairaku et al. 2012).

Many genetic and epigenetic factors constitute the clinical phenotype of primary SND, which represents a complex and heterogenous disease entity. The following sections will provide a comprehensive overview of the different factors that contribute to the clinical development of SND.

9.1.2 The Sinoatrial Node

The sinoatrial node (SAN) is a complex and heterogeneous tissue, which constitutes the primary pacemaker of the heart (Dobrzynski et al. 2005). It is located at the entrance of the *superior* vena cava to the right atrium and is thought to consist of $<$10,000 highly specialized cells, capable of automatically depolarizing, and by this pace ~5 billion working cardiomyocytes downstream of the SAN (Cho 2015). Automaticity is modulated by the central nervous system via sympathetic and parasympathetic stimulation and thus can be adapted to the physiological needs of the body. Interestingly, at embryonic stages, early myocardial cells possess the

capability to spontaneous excitation (Yasui et al. 2001; Schweizer et al. 2009). Later, at postnatal stages, automaticity is restricted to specialized cells of the sinoatrial node (SAN) and the conduction system, while tissue of the working type myocardium remains quiescent if not activated by the neighboring cell (Kurata et al. 2005).

The spontaneous excitation originates from the center of the SAN and is then propagated from the leading pacemaker site to the periphery, where it connects the SAN to the atrial muscle of the crista terminalis and right atrial free wall (Boyett et al. 2000, 2006). The SAN center has little electrical coupling to protect it from the inhibitory hyperpolarizing influence of surrounding cardiac muscle and is characterized by unique ionic currents appropriate for pacemaking. By contrast, the SAN periphery, although capable of spontaneous depolarization, achieves to drive the surrounding atrial muscle by a large inward sodium current (consequently, an action potential with a rapid upstroke) to generate sufficient depolarizing current and pronounced electrical coupling to deliver current to the atrial muscle (Boyett et al. 2000; Fedorov et al. 2010). Thus, molecular mechanisms underlying specified excitation and conduction are crucial for proper pacemaking and constitute critical pathomechanistic components in SND.

9.1.3 Sinoatrial Node Remodeling

SND was originally attributed to idiopathic fibrosis, cell atrophy, or ischemia. However, whether chronic ischemia is a cause of SND remains unresolved as postmortem studies could not establish a definite association of the grade of SAN artery disease with symptomatic SND (Evans and Shaw 1977; Shaw et al. 1987). Recent evidence is accumulating that changes in the electrophysiology of the SAN, known as electrical remodeling, may contribute importantly to SND (Choudhury et al. 2015). In this context, patterns of SAN remodeling between different predisposing diseases/states, i.e., heart failure, aging, diabetes, atrial fibrillation, and endurance sports, are diverse but are suspected to lay a molecular groundwork for the common end point of sinus node disease (Choudhury et al. 2015) (Fig. 9.1). The following examples highlight this view: with respect to age-related changes, various studies demonstrated remodeling processes of the SAN, going along with a specific footprint of ion-channel downregulation, including hallmark pacemaker channels HCN1, HCN4, Cav1.2, and Nav1.5 (Hao et al. 2011; Tellez et al. 2011; Larson et al. 2013) (Table 9.1).

Furthermore, endurance training is associated with marked sinus bradycardia. Athletes more often show symptomatic SND and AF later in life, compared to control groups (Baldesberger et al. 2008). Originally, bradycardia was considered a result of high vagal tone, in terms of a neural response to exercise, thought to be fully reversible after cessation of excessive training. However "intrinsic heart rate," investigated by complete pharmacological vagal blockade has been shown to be lower in trained individuals (Boyett et al. 2013). Recently a study in rodents demonstrated downregulation of *HCN4* and *TBX3* in trained animals (D'Souza et al. 2014). Furthermore it was shown by the same group that miR-423-5p contributes to training-induced bradycardia by targeting *HCN4* (D'Souza et al. 2017). These

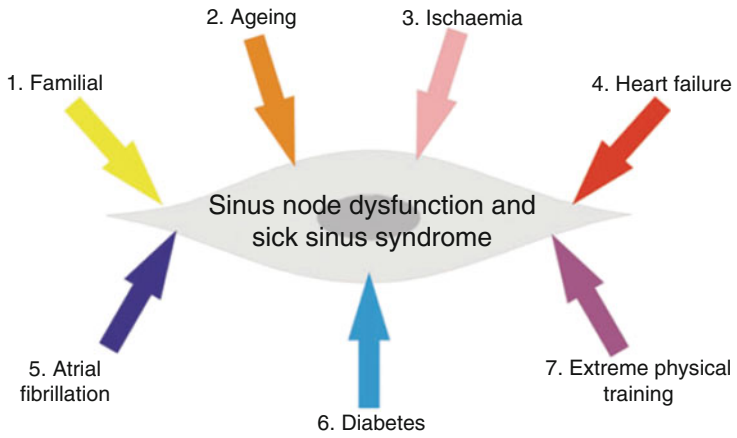

Fig. 9.1 Illustration of the most important etiologies of SND (modified from Monfredi et al. 2010)

Table 9.1 Genes and mechanisms involved in electrical remodeling of the SAN in different causes of SND. The inherited genes are mutations found in patients affected by familial SND, while data on other causes of electrical remodeling were observed in animal models. Downward arrows mean downregulation (modified from Choudhury et al. 2015)

Cause of SND	Ion channels and genes involved
Familial/inherited	HCN4, SCN5A, RYR2, CASQ2, ANKB, MYH6, CACNA1D
	KCNQ1, CASQ2, GIRK1, GIRK4
Aging	↓Nav1.5, ↓Cx43, ↓RYR2, ↓HCN1, ↓HCN4
Heart failure	↓HCN4
Exercise training	↓HCN4, ↓TBX3
Atrial tachyarrhythmia	↓HCN2, ↓HCN4

data suggest electrical remodeling of the SAN as a key mechanism for exercise-induced bradycardia rather than high vagal tone, pointing to molecular changes associated with endurance sports that may aggravate in a subset of patients leading to SND later in life.

9.1.4 Sinus Node Disease and Atrial Tachyarrhythmias

Regarding known genetic pathomechanisms of SND, it is interesting to note that most disease genes for SND also associate with AF. As SND is increasingly recognized not simply to be a disease of the SAN but also including the conduction system and the atrial myocardium (Sanders et al. 2004a, b), electrical and structural remodeling of these structures lay the groundwork for the development of AF as well (Monfredi and Boyett 2015). Concomitant bradycardia further facilitates the development of AF through an increased probability of atrial ectopic activity and a greater

dispersion of refractoriness, which both are established pathomechanisms of AF (Amasyali et al. 2014). The other way around, AF and other supraventricular tachycardias are known to compromise the SAN by the fast rate leading to SAN remodeling and dysfunction. In this context, it has been reported that atrial tachyarrhythmias cause alterations of Ca^{2+} cycling, as well as reduced I_f and I_{Ks} currents due to downregulation of HCN2, HCN4, and minK channels within the SAN, respectively (Yeh et al. 2009). Thus, it becomes obvious that bradycardia and atrial tachyarrhythmias in SND are not incoherent processes; rather they are the result of the same underlying pathomechanisms and reinforce each other (Monfredi and Boyett 2015). Therefore treating the one might co-effect the other, although limited data exist upon this relationship.

9.1.5 Genetic Findings of Familial Sinus Node Disease

Primary sinus node dysfunction has been related to inherited, familial forms of the disease (Spellberg 1971). Several genes have been associated with the disorder (Table 9.2). "Loss-of-function" mutations within those genes were related to either congenital SND or to phenotypes that developed throughout life with variable penetrance in families. The findings facilitated not only novel insight into SAN pathophysiology but also uncovered SND as a primary Mendelian disorder in a subset of cases. Among the genes associated with the syndrome, loss-of-function mutations of the *SCN5A* gene underlying the cardiac sodium channel alpha subunit are an established pathomechanism (OMIM sick sinus syndrome 1; Benson et al. 2003). Based on electrophysiological studies and computational modeling, mutated channels were demonstrated to cause either abnormally slow pacemaking or to produce sinus exit block (Butters et al. 2010). In addition, *SCN5A* mutations associate with multiple arrhythmic disorders including Brugada syndrome, long QT syndrome, and dilated cardiomyopathy (Remme 2013), but little is known about the mechanisms underlying phenotypic specification. However, the possibility of multiple overlapping symptoms, also summarized as "sodium channel disease," requires particular attention in the management of such patients.

Furthermore, mutations in *HCN4* underlying a significant proportion of the pacemaker current I_f in the SAN have been demonstrated to cause hereditary SND (OMIM sick sinus syndrome 2). Although initially linked to rather asymptomatic sinus bradycardia (Milanesi et al. 2006; Nof et al. 2007; Schweizer et al. 2010), a significant number of *HCN4* mutations were associated with symptomatic bradycardia requiring pacemaker implantation (Schulze-Bahr et al. 2003; Duhme et al. 2013; Schweizer et al. 2014). Moreover, *HCN4* loss-of-function mutations were shown to facilitate bradycardia-tachycardia syndrome and atrial fibrillation, indicating that I_f-channel dysfunction also contributes to the development of atrial tachyarrhythmias and in particular AF (Ellinor et al. 2012; Duhme et al. 2013; Macri et al. 2014). Recently, the phenotypic spectrum of *HCN4* mutations was expanded to a combined electromechanical phenotype of sinus bradycardia and noncompaction cardiomyopathy (Schweizer et al. 2014; Milano et al. 2014), and it

Table 9.2 Genes linked to human SND

Causative gene	Mechanism mutation	Rhythm disorder	Additional phenotype	Reference
SCN5A	Loss-of-function	SB, SA block, SArr, CD, AF, BrS	DCM	Benson et al. (2003), Remme (2013) and Haas et al. (2015)
	Gain-of-function	LQT-3, SB	–	Makita et al. (2008)
HCN4	Loss-of-function	SB, CI, AVB, AF, APC, VPC	NCCM, MVP, DAA	Schulze-Bahr et al. (2003), Schweizer et al. (2010, 2014), Vermeer et al. (2016)
	Gain-of-function	IST	–	Baruscotti et al. (2017)
MYH6	Loss-of-function	SB, AVB, SSS	DCM, HCM	Holm et al. (2011)
ANK2	Loss-of-function	SB, AF, CD, LQT-4	–	Le Scouarnec et al. (2008)
CACNA1D	Loss-of-function	SB, AVB (autosomal recessive)	Inner ear deafness	Baig et al. (2011)
GNB2	Loss-of-function	SB, AVB	–	Stallmeyer et al. (2017)
GNB5	Loss-of-function	SB	Eye, gastric, and neural disease	Lodder et al. (2016)
KCNE2	Loss-of-function	SB, LQT-6	–	Nawathe et al. (2013)
KCNQ1	Loss-of-function	SB, AF, LQT-1	–	Henrion et al. (2012)
	Gain-of-function	SB, SQT, AF	–	Ki et al. (2014))
RYR2	Loss-of-function	SB, CPVT, ARVC	NCCM, HCM	Postma et al. (2005)
CASQ2	Loss-of-function	SB, CPVT (autosomal recessive)	HCM	Postma et al. (2002)
GIRK1	Unknown	SB, SA block	–	Holmegard et al. (2010)
GIRK4	Unknown	SB, SA block	–	Holmegard et al. (2010)

AF atrial fibrillation, *APC* atrial premature contraction, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *BrS* Brugada syndrome, *CD* conduction defect, *CPVT* catecholaminergic polymorphic ventricular tachycardia, *DAA* dilatation of the ascending aorta, *DCM* dilated cardiomyopathy, *HCM* hypertrophic cardiomyopathy, *IST* idiopathic sinus tachycardia, *LQT* long QT syndrome, *NCCM* noncompaction cardiomyopathy, *SA-block* sinoatrial block, *SArr* sinus arrest, *SB* sinus bradycardia, *SQT* short QT syndrome, *SSS* sick sinus syndrome, *VPC* ventricular premature contraction

was shown that defects of the mitral valve and dilation of the ascending aorta also form part of this symptom complex (Vermeer et al. 2016). A very recent work identified HCN4 "gain-of-function" to be associated with inappropriate sinus tachycardia in a familial trait (Baruscotti et al. 2017), providing a novel molecular mechanism underlying this previously unresolved disorder.

Furthermore, the non-ion channel genes *MYH6* have been demonstrated to contribute to SND in humans as well (OMIM sick sinus syndrome 3; Holm et al. 2011). *MYH6* was shown to be importantly involved in SND pathogenesis, as a common missense variant (allelic frequency 0.38% in Icelanders) increases the lifetime risk of developing SND to ~50%, although pathomechanisms remained unresolved yet (Holm et al. 2011).

Other genes have been associated with combined phenotypes of SND together with additional cardiac (i.e., *KCNQ1* and *ANK2* mutations linked to long QT syndrome) or noncardiac (i.e., *CACNA1D* mutations associate with deafness) symptoms (Ki et al. 2014; Le Scouarnec et al. 2008; Baig et al. 2011), in agreement with the view that rhythm genes often are crucial for other physiological processes as well (Akhirome and Jay 2015). Accordingly, dysfunction of calcium-handling proteins (RYR2, Postma et al. 2005 and CASQ2, Postma et al. 2002) has been reported to cause sinus bradycardia in addition to catecholaminergic polymorphic ventricular tachycardia (CPVT) and various structural phenotypes (hypertrophic cardiomyopathy, noncompaction cardiomyopathy). Apart from the clinical scenario, experimental animal models suggested various ion channel and transcriptional/regulatory proteins to be implicated in SND, although the clinical relevance of these mechanisms needs to be determined.

9.2 Isolated and Progressive Cardiac Conduction Defects

9.2.1 Clinical Aspects and Classification of Cardiac Conduction Defect

Cardiac conduction defect (CCD) as failure in the propagation of the cardiac impulse along the specialized electrical system is a primary disorder, if not explained by other pathophysiological states like congenital, ischemic or structural heart disease, infection, drug intake, or disturbed metabolic states. Isolated cardiac conduction defect (ICCD) constitutes a heterogeneous group of disease-causing mechanisms resulting in potentially life-threatening heart block.

Usually patients present with exercise intolerance and/or dyspnea due to compromised AV conduction, which later results in pre-syncope or syncope due to periods of ventricular asystole caused by high-grade AV block. At disease onset, patients are mostly asymptomatic and only rarely show hemodynamic disturbance due to prolonged AV conduction.

The disorder was first described in 1964 by Lenegre and Lev and thus carries the synonym Morbus Lev-Lenegre (Lev 1964; Lenegre 1964). Both authors independently reported from patients with diseased cardiac conduction that is AV block or

left and/or right bundle branch block resulting in symptoms like dizziness, syncope, and sudden cardiac death. Postmortem investigations revealed distinct fibrosis of the cardiac conduction system, providing the initial pathogenetic hypothesis of the disease mechanism. Further, it was shown that the disorder progressed in an age-related manner (Probst et al. 2003). With respect to its pathophysiological mechanisms, two forms of primary CCD are distinguished: a senile form with late onset (age $>$ 50 years), pointing to age-related fibrotic degeneration and remodeling of the conduction system similar to the SAN, and a hereditary form, which more often has an early onset (age $<$ 50 years) and goes along with a family history of CCD, sudden cardiac death, congenital heart disease, and/or cardiomyopathy originating from an underlying pathogenic mutation in susceptibility genes. As the mechanism of hereditary CCD is in part an accelerated degeneration of the conduction system, progress of degeneration might occur much faster in such patients compared to others affected by the senile form of the disease.

9.2.2 Genetic Findings of CCD

The identification of mutations in the depolarizing cardiac ion channel gene *SCN5A* in patients affected by CCD, for the first time, offered a plausible explanation for the inheritance of this idiopathic disorder (Schott et al. 1999; Tan et al. 2001). Since then ICCD has been associated with multiple different *SCN5A* mutations (OMIM progressive cardiac conduction defect 1a), which constitutes the most important disease gene for the disorder. More recently, mutations in other genes have been reported but are less frequently identified among patients with ICCD than *SCN5A* mutations. Recent data suggested the yield of genetic testing in CCD to ~37%, with a single recurrent SCN5A mutation (c.2582_2583delTT) being the predominant genetic hit (Hofman et al. 2013). However, this single center study was confined to mutation scanning of single genes. Thus, genetic distribution among larger populations using modern sequencing techniques remains to be explored.

Clinically, patients carrying *SCN5A* mutations usually present with bradycardia, a prolonged PR interval, wide QRS, and left-axis deviation. Generally, it is important to note that patients with a pathogenic mutation in *SCN5A* should be advised to avoid drugs with sodium-channel-blocking effects (please refer to https://www.brugadadrugs.org/). With respect to the possibility of an overlap syndrome associated with "sodium channel disease," some patients requiring pacemaker therapy may benefit from an implantable cardioverter defibrillator (ICD), which should be carefully evaluated prior implantation.

Another important disease gene linked to isolated CCD is *TRPM4* (OMIM progressive cardiac conduction defect 1b), which encodes a Ca^{2+}-sensitive unselective cation channel that is highly expressed in the Purkinje system. Critical mutations in *TRPM4* linked to CCD were shown to cause attenuated deSUMOylation of the TRPM4 channel resulting in increased expression at the cytoplasmic membrane (Kruse et al. 2009; Liu et al. 2010). Consequently, TRPM4 gain-of-function results

in membrane depolarization, which reduces availability of Nav1.5 and therefore leads to conduction disturbance. Mutations segregated with multiple families and clinical phenotype are typically characterized by a right bundle branch block that progresses to complete heart block. Based on recent studies with small cohorts, the estimated yield of *TRPM4* mutations in progressive CCD is up to 15% (Stallmeyer et al. 2012; Daumy et al. 2016).

Mutations in *LMNA* are associated with a broad phenotypic spectrum, known as laminopathies, including Hutchinson-Gilford progeria, autosomal recessive Charcot-Marie-Tooth syndrome, and Emery-Dreifuss muscular dystrophy. Importantly, mutations in *LMNA* are linked to dilated cardiomyopathy. Disease onset is typically preceded by marked CCD (Brodt et al. 2013). Carriers of *LMNA* mutations have a considerable risk of malignant ventricular arrhythmias, even with preserved left ventricular ejection fraction (Kumar et al. 2016). Thus, on the basis of a pacemaker indication, ICD implantation should be considered (Priori et al. 2013), especially in the presence of additional risk factors such as male sex, nonsustained VT, left ventricular ejection fraction <45%, and the presence of a non-missense *LMNA* mutation (van Rijsingen et al. 2012).

NKX2–5 encodes a transcription factor involved in cardiomyogenesis and formation of cardiac structure, as well as development of the conduction system. Accordingly mutations in *NKX2–5* were found to cause congenital heart defects with autosomal dominant inheritance. Mostly, CCD characterized by different degrees of AV block was reported to be accompanied by ostium secundum atrial septal defects (ASD) (Schott et al. 1998; Stallmeyer et al. 2010).

Furthermore CCD is an essential symptom of Holt-Oram syndrome (HOS), an autosomal dominant.

disease, which is caused by mutations in the transcription factor *TBX5*. Affected individuals have skeletal anomalies involving the radius, carpal, or hand bones. In addition, patients display congenital heart defects, typically a secundum ASD or ventricular septal defect (VSD). Progressive CCD also forms part of the symptom complex often requiring pacemaker implantation. With respect to the disease mechanism of CCD, TBX5 is critical for normal cardiac development in prenatal life, while it controls SCN5A expression making it important in regulating cardiac conduction in postnatal life (Arnolds et al. 2012). Accordingly, genome-wide association studies (GWAS) identified common variations of *TBX5* associated with both PR and QRS durations, again underlining its relevance for cardiac conduction (Sotoodehnia et al. 2010).

Moreover, muscular dystrophies commonly involve the cardiac muscle as well and can cause CCD (Groh 2012). Among the muscular dystrophies with frequent involvement of the conduction system, the autosomal dominant myotonic dystrophies caused by repeat expansions in *DMPK* (type 1) or *CNBP* (type 2) are most prevalent. In particular in myotonic dystrophy type I (also called Steinert's disease), the majority of patients develop CCP, which is the major cause of sudden death (Groh et al. 2008). Thus, pacemaker implantation should be considered at low threshold.

Other neuromuscular disorders associated with CCD are Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy type IB, and myofibrillar myopathy (Groh 2012). The most common form with cardiac involvement is the autosomal dominant desmin-related myopathy, which commonly associates with DCM and CCD but also causes supraventricular and ventricular arrhythmias (van Spaendonck-Zwarts et al. 2011). Given the increased risk of SCD in many neuromuscular disorders, clinical guidelines suggest a more aggressive approach than with other CCD patients, including a lower threshold to implant an ICD in patients with pacemaker indication. Other genes that have been described in association with familial CCD are the sodium channel β-subunit gene *SCN1B* (Watanabe et al. 2008), *GJA5* encoding the gap junction protein Cx40 (Makita et al. 2012), and *PRKAG2*. The latter is involved in hypertrophic cardiomyopathy and the WPW syndrome as well (Gollob et al. 2001a, b).

Taken together, many factors determine the clinical phenotype of SND and CCD, representing complex and heterogeneous disorders. There is growing evidence that genetic disposition plays an important role in the pathogenesis of SND and CCD, and mutations in specified genes have been shown to cause hereditary forms in a subset of cases. Particularly, certain genetic defects were linked to distinct clinical profiles, which may pave the way for better diagnosis and surveillance of patients in the future. Thus, evidence of a genetic form of SND and/or CCD may have the potential to improve clinical stratification of patients as genetic changes can underlie specified clinical pathways that may also point to overlapping cardiac phenotypes or syndromic comorbidity.

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Compliance with Ethical Standards

Conflict of Interest Dr. Schweizer indicates no potential conflicts of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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