Hereditary Cardiac Conduction Diseases

16

Rafik Tadros and Julia Cadrin-Tourigny

Abstract

Cardiac conduction diseases (CCD) are a group of electrical defects of the heart with multiple hereditary and non-hereditary etiologies. The clinical spectrum of CCD includes asymptomatic patients with incidental electrocardiographic abnormalities, as well as patients presenting with syncope and cardiac arrest. CCD can be associated with other hereditary syndromes including Brugada syndrome, cardiomyopathy and neuromuscular diseases. A comprehensive clinical evaluation of patients with CCD including a detailed family history as well as molecular diagnostics in select cases are key to establishing the correct etiology, guiding patient management and directing family screening. In this chapter, we discuss the differential diagnosis of CCD, guiding principles in cardiogenetic evaluation as well as specific genotype-phenotype correlations.

Introduction

Cardiac conduction disease (CCD) is very common in clinical practice. Its description dates back to more than a century ago. Although the co-occurrence of fainting episodes and severe bradycardia was reported by Morgagni in the eighteenth century and again later by Stokes and Adams (to whom the term Stokes-Adams attacks was dedicated) [21, 37], the first documentation of atrioventricular block (AVB) on surface electrocardiography (ECG) was achieved later [75]. Familial CCD has been first described in 1901 by Morquio, and by many others thereafter [33, 45, 46, 52].

R. Tadros, MD, PhD (✉)
Department of Medicine, Cardiovascular Genetics Center, Montreal Heart Institute, Université de Montréal, Montréal, Canada

Department of Experimental and Clinical Cardiology, Academic Medical Center, Amsterdam, Netherlands
e-mail: rafik.tadros@umontreal.ca

J. Cadrin-Tourigny, MD, MSc
Department of Medicine, Cardiovascular Genetics Center, Montreal Heart Institute, Université de Montréal, Montréal, Canada

Reflecting its numerous etiologies and electrical manifestations, the definition of CCD is highly variable. We here define it as *any persistent defect in the formation or propagation of the cardiac impulse at any level of the specialized cardiac electrical system in the absence of drug or metabolic disturbance known to affect cardiac conduction.* Unlike most cardiovascular conditions discussed in this book, CCD is primarily caused by nongenetic etiologies (Table 16.1). In many cases, CCD is *secondary* to structural heart disease (e.g., ischemic heart disease, cardiomyopathy), to a cardiac intervention (e.g., aortic valve replacement, arrhythmia ablation) or to an autoimmune process (e.g., neonatal lupus syndrome). CCD can also be *primary*, most often in the context of senile degeneration of the conduction system in an elderly patient. Primary CCD in a young patient should raise the suspicion for an inherited etiology, especially if there is a positive family history. The mechanism of CCD is either functional (decreased depolarizing currents or impaired cellular coupling) and/or associated with premature conduction system degeneration (referred to as Lenègre's disease). This chapter is focused on primary CCD in the young, which could have an inherited etiology. We review the subject in a clinically oriented manner, in a similar fashion as other chapters. A general discussion on the clinical evaluation and management

H.F. Baars et al. (eds.), *Clinical Cardiogenetics*, DOI 10.1007/978-3-319-44203-7_16

Table 16.1 Etiologies of CCD

Etiology	Definition and suggestive clinical clues
Primary CCD	
Senile progressive CCD	Progressive sinus node dysfunction, atrial arrhythmias and/or atrioventricular conduction defects typically with fascicular blocks (wide QRS). Late onset (e.g., >50 years old) Can be associated with aortic valve calcification. Can be associated with aortic valve calcification.
Hereditary (see Table 16.2)	As above but with a premature onset (e.g., <50 years old). Family history of CCD, SCD, DCM, CHD, and/or the presence of a pathogenic mutation in susceptibility genes
Idiopathic	Unexplained CCD
Secondary CCD	
Ischemic heart disease	Known coronary artery disease or the presence of risk factors for atherosclerosis. Presence of Q-waves on the ECG and the presence of wall motion abnormalities and/or scar on cardiac imaging (typically involving the septum)
Cardiomyopathy	Diagnosed with cardiac imaging. Any cardiomyopathy (most often DCM) can progressively affect the conduction system in proportion with myocardial involvement. When CCD is out of proportion with the severity of cardiomyopathy, a primary CCD should be suspected (e.g., *LMNA* mutations, see Table 16.2)
Cardiac sarcoidosis and myocarditis	Presents with CCD, ventricular arrhythmia, and/or heart failure. The presence of inflammation or scar on cardiac magnetic resonance or positron emission tomography. Diagnosis may require cardiac or extracardiac biopsy. Sarcoidosis should be suspected in all young patients with unexplained severe CCD
Neonatal lupus syndrome	Maternal lupus with transplacental passage of anti-Ro/SSA and anti-La/SSB antibodies resulting in congenital nonprogressive AVB at the level of the AV node (narrow QRS). Recurrence in siblings could mimic a hereditary etiology
Congenital heart disease	CCD commonly seen with certain CHD such as ccTGA and partial or complete AVSD. ccTGA can first present with CCD in adult life. AVSD is often associated with Down syndrome. Diagnosis requires cardiac imaging. Co-occurrence of CCD and CHD also observed in certain hereditary conditions (e.g., *NKX2-5* and *TBX5* mutations, see Table 16.2)
Iatrogenic CCD	CCD resulting from a surgical or transcatheter procedure near the conduction system. Typical examples: valvular procedures (most commonly aortic valve replacement), closure of septal defects, arrhythmia ablation, septal reduction therapy in hypertrophic cardiomyopathy
Other rare causes	Infiltrative malignancies and cardiac tumors, trauma, rheumatological disorders
Causes of transient/reversible cardiac conduction defects	
Increased vagal tone	Often seen in well-trained endurance athletes. Can also be triggered by emotion or posture in susceptible individuals (neurocardiogenic/vasovagal syncope). Presents with sinus bradycardia and different degrees of AVB with a narrow QRS
Metabolic disturbances	Examples include hyperkalemia, hypothermia, thyroid dysfunction
Drugs	Drugs affecting autonomic cardiac modulation or ion channel function. Examples include beta-blockers, calcium-channel blockers, sodium-channel blockers, digitalis, amiodarone

AV, atrioventricular; *AVB,* atrioventricular block; *AVSD,* atrioventricular septal defect; *CCD,* cardiac conduction disease; *ccTGA,* congenitally corrected transposition of the great arteries; *CHD,* congenital heart disease; *DCM,* dilated cardiomyopathy; *SCD,* sudden cardiac death

of suspected hereditary CCD will be followed by a review of the molecular genetics of the disease (section "Molecular Genetics") highlighting gene-specific aspects.

Clinical Presentation

Primary CCD is a progressive disease with variable age of onset and clinical course. During early stages, patients are generally asymptomatic, and ECG abnormalities are detected incidentally or during family screening. With the progression of disease, symptoms occur either because of *severe bradycardia* or *chronotropic incompetence* (incapacity to increase heart rate during exercise). In the *former*, patients may present with pre-syncope or syncope occurring during periods of ventricular asystole (typically >4 s), due to sinus pauses or high degrees of AVB. In the *latter*, patients could present with exercise intolerance and/or dyspnea. Rarely, patients can be symptomatic in the absence of severe bradycardia and chronotropic incompetence. This may occur because of hemodynamic consequences of electrical dyssynchrony (e.g., excessive PR prolongation causing atrioventricular (AV) dyssynchrony) or due to reentrant arrhythmia secondary to excessively slowed conduction (e.g., bundle-branch reentrant ventricular tachycardia).

Hereditary forms of CCD can be associated with other cardiac electrical or structural diseases as well as neurological disease (Table 16.2). As such, the first manifestation of disease might not be related to CCD but to the associated disease. For instance, patients with loss of function mutations in *SCN5A* can have both Brugada syndrome (BS) and CCD. In such cases, the first manifestation of disease can be

Table 16.2 Clinical characteristics of the major subtypes of hereditary CCD

Gene/disease (mutation)	Transmission	Relative frequency in CCD	Other arrhythmias	Cardiomyopathy	CHD	Risk of SCD	Typical ECG	Extracardiac features/ diseases	Management particularities
SCN5A (missense and truncating – loss of function)	AD	++	BS, LQTS, AF	+/–(mild)	–	+	Prolonged PR and QRS. Left axis deviation	–	Avoid sodium-channel blockers Treat fever
TRPM4 (missense – gain-of-function)	AD	++	-	–	–	+	RBBB, fascicular blocks	–	Usual CCD management
LMNA (missense, truncating, large deletion)	AD	++ (in CCD with DCM)	Atrial arrhythmias	++	–	++	Low voltage P-wave, prolonged PR, narrow QRS (initially)	Cardio-embolic stroke *LMNA* also linked to muscular dystrophies (EDMD and LGMD) and other diseases	ICD to be considered in presence of left ventricular dysfunction, ventricular arrhythmia or severe CCD
NKX2-5 (missense, truncating)	AD	+	AF	+/–	++	+	Various degrees of AVB, narrow QRS	–	Usual CCD management
TBX5 (missense, truncating, large deletion)	AD	+/–	AF	–	+	+/–	Various degrees of AVB, narrow QRS	Upper limb skeletal anomalies (HOS)	Usual CCD management
MD (repeat expansions in ***DMPK*** [type 1] or ***CNBP*** [type 2])	AD	++ (in CCD with muscular dystrophy	Atrial and ventricular arrhythmias	+/–	–	++	Progressive PR prolongation and fascicular blocks	Myotonia, muscle pain, muscle weakness, cataracts, GI complaints. Mild CK elevation	Low threshold for pacemaker or ICD. Consider invasive EPS. Optimal approach yet to be developed
EDMD (***EMD***, ***FHL1***, ***LMNA***)	XR AD AR	+/–	Atrial arrhythmias	+	–	+	Sinus bradycardia, atrial standstill, AVB	Contractures, humeroperoneal muscle weakness, cardio-embolic stroke. Moderate CK elevation	Low threshold for pacemaker and anticoagulation

(continued)

Table 16.2 (continued)

Gene/disease (mutation)	Transmission	Relative frequency in CCD	Other arrhythmias	Cardiomyopathy	CHD	Risk of SCD	Typical ECG	Extracardiac features/ diseases	Management particularities
LGMD type 1B (*LMNA*)	AD	+/−	Atrial arrhythmias	+	−	+	Sinus bradycardia, atrial standstill, AVB	Progressive weakness and atrophy of shoulder and pelvic girdle. Overlap with EDMD. Moderate CK elevation	Low threshold for pacemaker? Little available data
DES	AD	+/−	Atrial and ventricular arrhythmias	+	−	+	AVB, fascicular blocks	Proximal and distal muscular weakness. Mild CK elevation	Similar to *LMNA*? Little available data
HCN4 (missense, truncating)	AD	+	AF	LVNC	−	+	Sinus bradycardia	–	Usual CCD management CCD without LVNC has good prognosis
PRKAG2 (missense, truncating)	AD	+/−	WPW, AF	HCM	−	+	Ventricular preexcitation	–	Usual CCD/HCM/WPW management

AD autosomal dominant, *AF* atrial fibrillation, *AR* autosomal recessive, *AVB* atrioventricular block, *BS* Brugada syndrome, *CCD* cardiac conduction disease, *CHD* congenital heart disease, *CK* creatine kinase, *DCM* dilated cardiomyopathy, *EDMD* Emery-Dreifuss muscular dystrophy, *EPS* electrophysiological study, *GI* gastrointestinal, *HCM* hypertrophic cardiomyopathy, *HOS* Holt-Oram syndrome, *ICD* implantable cardioverter defibrillator, *LGMD* limb-girdle muscular dystrophy, *LQTS* long QT syndrome, *LVNC* left ventricular noncompaction cardiomyopathy, *MD* myotonic dystrophy, *RBBB* right bundle-branch block, *SCD* sudden cardiac death, *WPW* Wolff-Parkinson-White syndrome, *XR* X-linked recessive

ventricular arrhythmias in the context of BS. Patients with mutations in *NKX2-5* also present with atrial septal defects (ASDs), while patients with *LMNA* mutation typically develop CCD in association with dilated cardiomyopathy (DCM) in a later stage of disease development. Other genotype-phenotype correlations are summarized in Table 16.2 and further discussed below. A detailed review of symptoms, physical examination, and cardiac imaging is thus crucial in establishing a correct diagnosis and guide molecular genetic testing.

Systematic longitudinal data on the course and natural history of hereditary CCD are limited. When available, such data will be discussed below along with the specific genetic defects (section "Molecular Genetics"). By contrast, the clinical course and prognosis of conduction defects in the general population without known structural heart disease has been abundantly studied. For instance, unexplained sinus bradycardia (<50 beats/min) in healthy volunteers is not associated with adverse events during a mean follow-up of 5.4 years [74]. In a Finnish populational study of 10,685 individuals aged 30–59 years old and followed up for 30 ± 11 years, isolated first-degree AVB (2.1 % of patients) was not associated with an increased risk of adverse events [6]. Mobitz type I second-degree AVB in individuals without underlying heart disease, as often seen in athletes due to increased vagal tone, is often caused by block in the atrioventricular node and also has a benign prognosis [72]. By contrast, Mobitz type II second-degree AVB is caused by conduction block below the AV node and is associated with a bad prognosis, with a high risk of progression to complete AVB, syncope, and sudden cardiac death (SCD) [25]. The association of right bundle-branch block (RBBB) with mortality in the general population is controversial, with a recent meta-analysis showing an increased risk of mortality during follow-up (HR 1.17; 95 % confidence interval (CI): 1.03–1.33) [86]. The prognosis of left bundle-branch block (LBBB) in asymptomatic healthy individuals appears to be age-dependent. Earlier large cohort studies including patients with a mean age below 55 and a mean follow-up less than 10 years do not detect an increased adverse event rate associated with LBBB [29, 61]. By contrast, more recent studies including older patients and longer follow-up show a significant increase in high-degree AVB, cardiovascular, as well as total mortality [7, 28, 87]. Taken together, these data suggest that conduction defects in the young asymptomatic patient have a good prognosis, with the exception of Mobitz II second-degree AVB. Whether these data can be extrapolated to hereditary CCD is debatable. Since the mechanism of hereditary CCD is in part an accelerated degeneration of the conduction system, conduction defects in these patients likely occur at a higher rate than in an unselected CCD population.

Diagnosis and Differential Diagnosis

The clinical diagnosis of CCD requires the presence of a conduction abnormality on the ECG, at any single or multiple levels (Fig. 16.1). Secondary causes of CCD should be excluded (Table 16.1). An echocardiogram is indicated in all cases to assess the presence of structural heart disease, either causing or associated with CCD. Other diagnostic tests can be performed depending on patient's age, comorbidities, and clinical findings. Accumulating evidence from independent groups suggests that cardiac sarcoidosis and giant-cell myocarditis are common causes of unexplained high-degree AVB in young patients (<55–60 years) [41, 53]. In such patients, advanced cardiac imaging with cardiac magnetic resonance (CMR) or fluorodeoxyglucose (^{18}FDG) cardiac positron emission tomography should be considered in the diagnostic strategy. In endemic regions, Lyme disease, an infectious disease caused by the spirochete *Borrelia burgdorferi* should also be suspected in young patients with unexplained AVB [70]. In the presence of a clinical presentation compatible with the disease, the diagnosis is established by serologic testing. It is important to recognize this etiology in order to start an appropriate antibiotic treatment. Because AVB is most often reversible, permanent pacemaker placement is most often unnecessary.

A three-generation family history is recommended when evaluating a young patient with an unexplained cardiac conduction defect. Family history taking is detailed in Chap. 2. In the context of CCD, one should specifically assess for the presence of family history of CCD, SCD, arrhythmia, pacemaker or defibrillator implantation, heart failure or cardiomyopathy, cardiac transplantation, congenital heart disease, as well as neuromuscular disease. When assessing the inheritance pattern, one should note that CCD often accompanies many acquired diseases. For instance, ischemic or valvular heart diseases are common causes of CCD. Age is also an important factor in interpreting family history. The prevalence of CCD greatly increases with age. In a prospective cohort study of randomly selected 855 males born in 1913 [27], the prevalence of bundle-branch block increased from 1 % at the age of 50 to 17 % at 80 years old. Likewise, populational studies from the United States and Australia estimate the prevalence of permanent pacemaker therapy to be less than 0.5 % in patients below 65 years old but higher than 2 % in patients over 75 years old [16, 65]. This age-dependent prevalence is important to keep in mind when assessing the etiology of CCD in family members: In young patients, CCD is rare and more likely to be inherited, while CCD in older patients is common and more likely to be caused by senile degeneration of the conduction system. In sum, a detailed clinical review of family members with suspected CCD, including age at onset and comorbidities, is important to understand the presence and pattern of heritability and identify phenocopies.

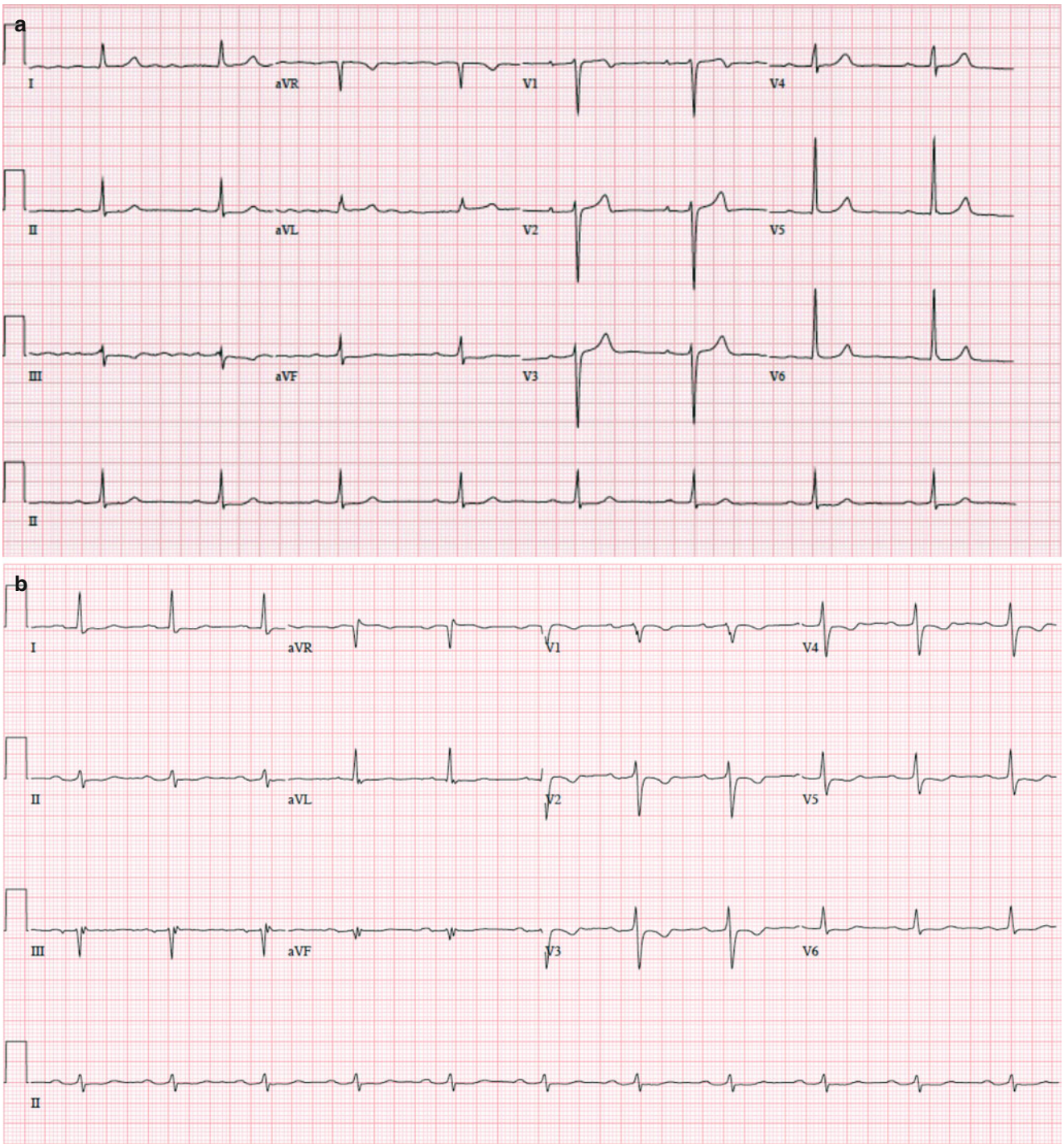

Fig. 16.1 (**a**) ECG obtained from a 50-year-old female with mild dilated cardiomyopathy (left ventricular ejection fraction, 52 %) and a truncating mutation in *LMNA* (Q410X) mutation. Note the low-voltage P-wave, prolonged PR interval, and narrow QRS, typical for *LMNA* disease. (**b**) ECG obtained from a 63-year-old female with structurally normal heart and a truncating mutation in *SCN5A* (R222X). Note the prolonged PR and QRS intervals and left-axis deviation, typical for *SCN5A* loss of function mutations

Clinical Therapy and Follow-up

The management of patients with CCD is aimed at alleviating symptoms and preventing SCD. No drug therapy is yet available. Pacemaker implantation is indicated in patients with symptomatic bradycardia as well as those at a high risk of complete AVB and SCD. Clinical guidelines on cardiac pacing are periodically updated and published [17]. With the exception of a few locus- and disease-specific management differences (e.g., *LMNA* mutations, muscular dystrophies;

discussed below), patients with suspected or established hereditary CCD are treated similarly as patients with other etiologies of CCD.

In the following situations, pacemaker implantation is recommended (Class I indication):

- Sinus node dysfunction with symptoms clearly attributed to bradycardia
- Third-degree or Mobitz II second-degree AVB, irrespective of symptoms
- Syncope with bundle-branch block and demonstration of conduction impairment below the AV node during an invasive electrophysiological study
- Alternating bundle-branch block (e.g., RBBB and LBBB), irrespective of symptoms

In the following situations, pacemaker implantation should be considered (Class IIa indication):

- Mobitz I second-degree AVB, with symptoms or invasive study showing a block below the AV node
- Syncope and demonstration of asymptomatic pauses for >6 s

Because of the progressive nature of the disease, a recent expert consensus statement on inherited arrhythmia syndromes also suggests that pacemaker implantation be considered (Class IIa) in the presence of bifascicular block with or without first-degree AVB [58].

Patients with manifest CCD as well as carriers of a pathogenic loss of function mutation in *SCN5A* should also avoid the use of medication with conduction-slowing properties, such as those listed in http://www.brugadadrugs.org [57].

Since the disease is progressive, patients with CCD should be periodically assessed with ECG and review of symptoms. Longer ECG recordings such as Holter monitoring and loop recording should be considered in symptomatic patients without ECG criteria for pacemaker implantation, to detect intermittent deterioration of the conduction abnormality. Patients reporting exercise intolerance should undergo exercise testing to detect chronotropic incompetence or exercise-induced AVB. Echocardiography should also be repeated in select patients, periodically in *LMNA, DES,* and *SCN5A* mutation carriers and whenever there is clinical suspicion of heart failure. The frequency of follow-up should be individualized, taking into account the severity of conduction anomalies, the rate of disease progression, the presence of symptoms, and the patient's age. Patients with muscular dystrophy and CCD should be monitored more closely. Patients should be advised to consult rapidly if they have a syncopal event, to assess the need for an urgent pacemaker implantation.

Molecular Diagnostics

Genetic testing should be considered in patients with primary CCD developing at a young age (<50 years old) with or without cardiomyopathy or congenital heart disease, especially in the presence of a positive family history [2]. The optimal diagnostic strategy remains unclear. As for other conditions, one should balance the desires for getting a higher yield yet avoiding the detection of variants of unknown significance. In patients with isolated CCD, sequencing of *TRPM4* and *SCN5A* is desirable. For those with associated DCM, sequencing of *LMNA, DES,* and *SCN5A* should be undertaken, while patients with CCD associated with congenital heart defects such as ASDs can be screened for mutations in *NKX2-5* and *TBX5*. Mutations in other genes have been identified in few families or isolated cases with CCD, with some supportive functional data. These genes often appear on next-generation sequencing (NGS) "arrhythmia" or "cardiac" panels. Data from the Netherlands suggest the yield of genetic testing in CCD (mostly limited to *SCN5A* sequencing) to be approximately 30 %, with a single recurrent *SCN5A* mutation (c.2582_2583delTT) accounting for most of the cases [39]. The yield of targeted genetic testing in large diverse populations and the added value of NGS remain to be explored.

Molecular Genetics

SCN5A

Mutations in *SCN5A* causing CCD were first identified by Schott [62]. The authors reported a large French family with autosomal dominant CCD presenting with first-degree AVB, LBBB, RBBB, or complete AVB requiring pacemaker implantation, in the absence of structural heart disease. Follow-up of the family showed a progressive disease. Using a targeted-linkage approach, the authors demonstrated a strong linkage to the 3p21 locus, which harbors *SCN5A*. Sequencing revealed a splice-site variant predicting skipping of exon 22. The authors also performed sequencing of *SCN5A* in an independent Dutch nuclear family with asymptomatic first-degree AVB, RBBB, and/or nonspecific intraventricular conduction delay and identified a frameshift variant predicting a premature stop codon and cosegregating with the phenotype. In sum, this study was the first to link CCD with *SCN5A*, which was earlier identified as a disease gene in long QT syndrome type 3 (LQT3) [83] and BS [20]. Similar to BS, *SCN5A* mutations causing CCD result in loss of function of Nav1.5, the major cardiac sodium channel responsible of cardiomyocyte depolarization. It is thus not uncommon for loss-of-function mutations to result in a mixed phenotype of BS and CCD, either in the same patient or in family members carrying the same variant. By contrast, LQT3 is caused by

gain of function *SCN5A* mutations, which result in impaired inactivation of Nav1.5 with increased late sodium current. Interestingly, mutations resulting in both a decrease in peak sodium current (loss of function) and increase in late current (gain of function) have been identified in families with CCD, BS, and LQT3 [59]. The 1795insD mutation is the best characterized example of such an *overlap syndrome* [56]. *SCN5A* mutations have also been observed in families with sinus node dysfunction, atrial fibrillation, as well as DCM, emphasizing the high heterogeneity of phenotypes associated with *SCN5A* [79]. Highlighting the important role of *SCN5A* and its product Nav1.5 in normal cardiac electrical function, common variants in the *SCN5A-SCN10A* locus have been associated with PR, QRS, and QT intervals as well as BS and ST-T voltages in multiple genome-wide association studies (GWAS) [4, 11, 40, 55, 66, 81].

Clinically, CCD associated with *SCN5A* mutations initially presents with a prolonged PR interval, wide QRS as well as left-axis deviation (Fig. 16.1b), which could progress to high-degree AVB. In addition to the general CCD management described in section "Clinical Therapy and Follow-up", patients with a pathogenic mutation in *SCN5A* should be counseled to avoid drugs with sodium-channel-blocking effects and should suppress fever, a potential trigger of arrhythmic events. Because of the possible overlap with other syndromes causing ventricular tachyarrhythmia, one should be attentive to investigate syncopal events appropriately, as these may sometimes be caused by malignant ventricular arrhythmia. While a standard pacemaker is usually the treatment of choice (when indicated, see above), some patients may benefit from an implantable cardioverter defibrillator (ICD), especially in overlap syndromes.

TRPM4

In 2009, mutations in *TRPM4* were identified as a cause of CCD [42]. In fact, the story behind this discovery dates back to the 1960s, when Combrink et al. [21] and later Steenkamp et al. [69] described large South African families with autosomal dominant CCD manifesting as RBBB, fascicular blocks, and SCD. Later, a large Lebanese family with a similar phenotype was reported [71]. In 1995, linkage analysis in both the South African and Lebanese families mapped the CCD phenotype to chromosome 19q13.3, which includes *TRPM4* [18, 23]. Sequencing of *TRPM4* identified two different missense mutations in these families, cosegregating with the CCD phenotype [42, 43]. Mutations were also identified in an additional large French family as well as smaller families and sporadic cases with CCD [22, 43, 68]. Based on recent data from relatively small cohorts without systematic cosegregation analysis, the estimated yield of TRPM4 testing in progressive CCD is about 15 % [22, 68]. Of note, the classic phenotype of *TRPM4*-related CCD is that of RBBB with or without fascicular block, which progresses to complete AVB, but rarely isolated LBBB.

TRPM4 encodes a Ca^{2+}-activated nonselective cation channel predominantly expressed in Purkinje fibers. The mechanism of *TRPM4*-related CCD is attenuated deSUMOylation of the protein, which results in decreased endocytosis, thus increasing channel density at the cell surface [42]. This increased cation channel density is thought to result in membrane depolarization, thus reducing the availability of Nav1.5, necessary for fast conduction in the specialized cardiac conduction system [1].

LMNA

Mutations in *LMNA* are associated with a wide spectrum of diseases, known as laminopathies. These include Hutchinson-Gilford progeria, autosomal recessive Charcot-Marie-Tooth, Emery-Dreifuss muscular dystrophy (EDMD), as well as DCM preceded by or accompanied with marked CCD. LMNA-related cardiomyopathy is a progressive disease which initially presents with CCD, typically sinus bradycardia, low-voltage P-waves, first-degree AVB, and initially a normal QRS (Fig. 16.1a). The disease is often accompanied by arrhythmia starting at an early stage (premature atrial complexes, atrial tachycardia or fibrillation, premature ventricular complexes or VT). With disease progression, the patient could present with complete AVB, malignant ventricular arrhythmia or SCD, and eventually DCM with heart failure or embolic stroke. Family data suggest that CCD typically precedes DCM by a median time interval of 7 years [19]. Patients with CCD and an LMNA mutation have a high risk of developing malignant ventricular tachyarrhythmia, even if left ventricular systolic function is preserved [3, 38]. In patients with an indication for pacemaker therapy and an *LMNA* mutation, ICD implantation should thus be considered [58], 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 mutation [76].

When no mutation is detected in *LMNA* by sequencing in a patient with a typical presentation (CCD, DCM, arrhythmia, and family history), one should consider testing for structural variants, such as a large deletion, using appropriate techniques (e.g., multiplex ligation-dependent probe amplification). Such an approach has been proven useful in some cases [36, 48, 78].

CCD Associated with Congenital Heart Defects: *NKX2-5* and *TBX5*

In 1998, Schott identified one missense and two nonsense variants in ***NKX2-5*** in four families affected with an

autosomal dominant form of congenital heart defects, mostly (27 of 33 cases) secundum ASDs but also a few with other defects with or without ASD [63]. All affected individuals had CCD manifesting as various degrees of AVB. Invasive electrophysiological studies performed in three patients revealed that the site of conduction delay was the AV node, and patients who were later followed up show progressive CCD. *NKX2-5* encodes a transcription factor involved in cardiac morphogenesis, specifically in septation during development and is also important for normal function of the AV node in postnatal life. Other groups also reported mutations in *NKX2-5* in smaller families with a similar phenotype, reproducing the original findings [67].

Holt-Oram syndrome (HOS) is an autosomal dominant disease affecting the heart and hand (heart and hand syndrome) and is caused by mutations in the transcription factor ***TBX5*** in >70 % of cases [9, 49]. Virtually all affected individuals have skeletal anomalies involving the radius, carpal, or hand bones, sometimes only seen on radiography. Most patients also have a congenital heart defect, typically a secundum ASD or VSD, but more severe lesions have been reported. Patients with the syndrome are also at risk for severe progressive CCD requiring pacemaker implantation, regardless of the presence of a structural defect. The exact prevalence of CCD in HOS has not been reported. Likewise, the prevalence of pathogenic *TBX5* mutations in suspected hereditary CCD is unknown. Both missense and truncating *TBX5* variants have been associated with HOS. The mutation type and the location of missense variants have been suggested as predicting the phenotype [10]. In the presence of a typical HOS and absence of mutation using sequencing, one should also consider testing for large deletions, which have been previously reported [15]. *TBX5* is critical for normal cardiac development in prenatal life, while its control of *SCN5A* expression makes it important in regulating cardiac conduction in postnatal life [5]. In addition to its involvement in HOS, GWAS identified common variations in the *TBX5* locus associated with both PR and QRS durations, again highlighting its role in normal cardiac conduction [24, 40, 66].

CCD Associated with Muscular Dystrophies: An Overview

Muscular dystrophies are a group of clinically and genetically heterogeneous inherited skeletal muscle diseases that often also affect the heart [34]. The prevalence, type, and severity of cardiac involvement depend on the specific muscular dystrophy. In the X-linked recessive *Duchenne and Becker dystrophies* caused by mutations in dystrophin (*DMD*), DCM is the predominant cardiac phenotype and CCD is infrequent. By contrast, the autosomal dominant *myotonic dystrophies* caused by repeat expansions in *DMPK* (type 1) or *CNBP* (type 2), CCD is very common and progressive while DCM is uncommon. In myotonic dystrophy type I (Steinert's disease), the majority of patients develop CCD. When CCD is severe (defined as nonsinus rhythm, PR >240 ms, QRS >120 ms, or second- or third-degree AVB), it is associated with an increased risk of SCD [35]. Interestingly, the number of CTG repeats in *DMPK* and the severity of the muscular phenotype are predictors of severe CCD. Because SCD is responsible for 30 % of mortality and that CCD is thought to play a major role in the mechanism of SCD, the threshold for pacemaker implantation should be low in patients affected with this disease. While the presence of second- or third-degree AVB is a clear indication for pacemaker implantation, the optimal approach for risk stratification and prophylactic device implantation in other patients remains unclear. Some experts suggest the use of an invasive electrophysiological study. A large nonrandomized study showed that an invasive electrophysiological study-guided device implant strategy was associated with increased survival, when compared to a conservative noninvasive strategy, after adjusting for baseline differences or matching using propensity scores [82]. Because of a risk of ventricular arrhythmia-mediated SCD, ICD implantation should also be considered instead of a standard pacemaker [12]. *EDMD* is a rare disease inherited as either X-linked recessive (caused by mutations in *EMD* or *FHL1*) or autosomal dominant or recessive (mutations in *LMNA*). EDMD is associated with CCD presenting with sinus bradycardia, atrial standstill, and AVB. Patients are also at risk of DCM and atrial arrhythmias with cardio-embolic stroke [14]. Both autosomal dominant and X-linked recessive EDMD forms are at risk, but *LMNA* mutation carriers are believed to be at a higher risk to have a cardiac involvement [13]. *LMNA* mutations can also cause autosomal dominant *limb girdle muscular dystrophy* (LGMD) type IB with a high prevalence of cardiac involvement (CCD and DCM). Other autosomal dominant and autosomal recessive subtypes of LGMD can be associated with DCM at various degrees but rarely with CCD. Other types of muscular dystrophies are rarely seen in the context of CCD or DCM.

Myofibrillar myopathy is another genetically heterogeneous neuromuscular disease associated with CCD with or without DCM. Its most common form observed in cardiogenetics is the autosomal dominant desmin-related myopathy. The latter is caused by mutation in *DES* and is characterized by isolated cardiac involvement (25 %), isolated neurological involvement (25 %), or both (50 %) [77]. Cardiac disease consists of cardiomyopathy (mainly DCM), CCD, supraventricular arrhythmias, as well as ventricular arrhythmias including a few cases of SCD despite a pacemaker. Considering the potential risk of SCD from ventricular arrhythmias, some clinicians suggest the use of an ICD in *DES* mutation carriers with a pacemaker indication [77]. Mitochondrial disease caused by mitochondrial DNA deletion can also present with both a neuromuscular defect and CCD with or without cardiomyopathy.

The *Kearns-Sayre syndrome* is the classic example, where rapidly progressive AVB is observed.

Management of patients with neuromuscular disease and CCD can be challenging given the limited available literature and the associated muscular morbidity. Given the increased risk of SCD in many of these diseases, clinical practice guidelines suggest a more aggressive approach than with other CCD patients. For instance, permanent pacemaker implantation may be considered for myotonic dystrophy and limb-girdle muscular dystrophy, with any degree of AV block (including first-degree AV block) or bifascicular block, with or without symptoms [26]. Such an aggressive approach based on little clinical data does not make a consensus among experts [17].

Other CCD Genes

Loss-of-function mutations in ***HCN4***, which encodes the major pacemaker channel protein in humans, have been identified in patients and families with sinus node dysfunction, sometimes in association with paroxysmal atrial fibrillation [50, 64]. The severity of the phenotype is highly variable and sometimes benign with isolated asymptomatic sinus bradycardia in a whole family [54]. Recently, loss-of-function mutations were identified in four families with sinus bradycardia in combination with left ventricular noncompaction cardiomyopathy [51] and mild aortic dilatation [80]. Of interest, a gain-of-function mutation in *HCN4* was identified in a familial form of inappropriate sinus tachycardia [8].

The cardiac voltage-gated sodium channel (Nav1.5) is part of a protein complex composed of the α-subunit (encoded by *SCN5A*), as well as β-subunits (e.g., *SCN1B*) and ancillary proteins. Following the association of *SCN5A* with CCD and BS, a candidate gene-sequencing study identified mutations in ***SCN1B*** in three small pedigrees affected by CCD with or without BS [84]. The investigators performed functional studies showing that coexpression of *SCN5A* with the mutant *SCN1B* resulted in a decreased sodium current as compared to coexpression of both wild-type proteins. Although these functional data are supportive, the lack of robust human genetic data (three small pedigrees and lack of convincing validation studies) makes one question the role of *SCN1B* in CCD.

The fast propagation of the electrical impulse in the His-Purkinje system depends on the availability of Nav1.5 and also high-conductance gap junctional channels. In a 6-year-old boy with CCD (LBBB and second-degree AVB) who later died suddenly, Makita et al. [47] identified a missense variant in ***GJA5***, which encodes the high-conductance gap junctional channel subunit connexin40. The variant was also present in his mother with documented CCD (LBBB) who later had a SCD, as well as in his 4-year-old sister with a QRS duration at the upper limit of normal. Expression of the mutant proteins showed a reduction in junctional conductance compared to wild-type connexin40. Somatic *GJA5* mutations in left atrial DNA have also been previously identified in patients with atrial fibrillation [31], although this finding was not reproduced in a larger cohort [60] (see Chap. 15 for discussion).

Recently, using linkage analysis and whole-exome sequencing, two groups identified missense variants in ***TNNI3K*** in families with supraventricular tachyarrhythmia and CCD, sometimes associated with DCM [73, 85]. *TNNI3K* encodes for the Troponin I-interacting kinase, a cardiac-specific kinase that was previously implicated in atrioventricular conduction in mice [44]. The pathophysiological mechanism implicating *TNNI3K* in arrhythmogenesis is an area of active investigation.

In 2001, Gollob identified missense mutations in ***PRKAG2*** in families with CCD and ventricular preexcitation with or without cardiac hypertrophy [30, 32]. Multiple families with mutations in *PRKAG2* and an identical phenotype have been identified since then. Sequencing of this gene should be performed in the presence of CCD in association with ventricular preexcitation and/or cardiac hypertrophy. *PRKAG2* encodes the gamma2 regulatory subunit of AMP-activated protein kinase, which is part of the AMP-activated protein kinase complex involved in cardiomyocyte metabolism and energetics.

Family Screening

Given the limited long-term data available on familial CCD, it is difficult to recommend a detailed family screening and follow-up algorithm. Instead, the clinician should adapt the follow-up plan to each patient and family. Below are some points for guidance depending on whether a pathogenic variant is identified and whether the disease is familial or sporadic.

When a pathogenic mutation is identified in the proband, cascade screening using mutation analysis in family members is recommended [2]. Mutation carriers should have a complete baseline cardiological evaluation, consisting of a review of symptoms, physical evaluation, ECG, and echocardiography. Exercise testing, Holter monitoring, or loop recoding are suggested if the patient reports any intermittent symptom. Given the progressive nature of the disease, mutation carriers need to be periodically evaluated (e.g., every 1–3 years) depending on age and the extent of ECG abnormalities, if present. Follow-up evaluation should include a review of symptoms and ECG. For patients with *LMNA* mutations, repeating the echocardiogram every 1–2 years is suggested. Patients should be advised to seek urgent medical attention if they present a syncopal event. Family members

that do not carry the mutation can be reassured, unless the pathogenicity of the variant is questionable. A baseline ECG is encouraged, while a more extensive evaluation should be performed if symptoms develop.

In genetically elusive unexplained CCD in a young patient without a clear familial disease, a baseline ECG should be performed in first-degree relatives. If the proband also has structural heart disease, an echocardiogram should also be performed in first-degree relatives. If the baseline evaluation is normal, the patient can be discharged from cardiological care and instructed to consult if symptoms develop (e.g., presyncope, syncope, exercise intolerance). If the baseline evaluation is abnormal, the patient should be treated accordingly and periodically followed up.

In genetically elusive CCD with a clear familial disease, advanced genetic testing (e.g., whole-exome sequencing, large-sequencing gene panel, and targeted deletion assays) with appropriate cosegregation analysis should be considered, recognizing that the yield is likely to be low. Clinical screening of first-degree relatives should be performed as above. However, if the baseline evaluation is normal, it is probably prudent to follow-up the patients periodically for a long term, unless the disease onset in affected family members is at a young age.

Summary and Take-Home Messages

- Cardiac conduction disease (CCD) is a clinically heterogeneous disorder involving genetic and nongenetic etiologies.
- A genetic etiology and genetic testing should be considered in the presence of a family history of CCD, cardiomyopathy, or congenital heart disease as well as in young patients (<50 years old) with unexplained severe sporadic CCD.
- Isolated CCD can be caused by mutations in *SCN5A* or *TRPM4*.
- CCD in association with dilated cardiomyopathy (DCM) can be caused by *LMNA* and *DES* mutations. Patients with such mutations and severe CCD are also at risk of ventricular arrhythmia. Implantable cardioverter defibrillator (ICD) therapy should be considered in such cases.
- CCD in association with congenital heart disease can be caused by mutations in *NKX2-5* and *TBX5*. The latter is invariably associated with upper limb skeletal anomalies (Holt-Oram syndrome).
- CCD in association with ventricular preexcitation or unexplained cardiac hypertrophy is suggestive for mutations in *PRKAG2*.
- CCD can accompany some muscular dystrophies (e.g., myotonic dystrophy, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy type IB). In these cases, aggressive therapy with a pacemaker or ICD can be considered in early stages.
- Device therapy is the only available treatment for hereditary CCD. The decision to implant a device usually follows the same principles as with other causes of CCD, with the exceptions mentioned above.
- Family screening with genetic testing and/or phenotypic testing is recommended in established or suspected hereditary CCD.

References

1. Abriel H, Syam N, Sottas V, Amarouch MY, Rougier JS. TRPM4 channels in the cardiovascular system: physiology, pathophysiology, and pharmacology. Biochem Pharmacol. 2012;84(7):873–81.
2. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace. 2011;13(8):1077–109.
3. Anselme F, Moubarak G, Savoure A, Godin B, Borz B, Drouin-Garraud V, et al. Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders. Heart Rhythm. 2013;10(10):1492–8.
4. Arking DE, Pulit SL, Crotti L, van der Harst P, Munroe PB, Koopmann TT, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. Nat Genet. 2014;46(8):826–36.
5. Arnolds DE, Liu F, Fahrenbach JP, Kim GH, Schillinger KJ, Smemo S, et al. TBX5 drives Scn5a expression to regulate cardiac conduction system function. J Clin Invest. 2012;122(7):2509–18.
6. Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA, et al. Prognostic significance of prolonged PR interval in the general population. Eur Heart J. 2014;35(2):123–9.
7. Badheka AO, Singh V, Patel NJ, Deshmukh A, Shah N, Chothani A, et al. QRS duration on electrocardiography and cardiovascular mortality (from the National Health and Nutrition Examination Survey-III). Am J Cardiol. 2013;112(5):671–7.
8. Baruscotti M, Bucchi A, Milanesi R, Paina M, Barbuti A, Gnecchi-Ruscone T, et al. A gain-of-function mutation in the cardiac pacemaker HCN4 channel increasing cAMP sensitivity is associated with familial Inappropriate Sinus Tachycardia. Eur Heart J. 2015.
9. Basson CT, Bachinsky DR, Lin RC, Levi T, Elkins JA, Soults J, et al. Mutations in human TBX5 [corrected] cause limb and cardiac malformation in Holt-Oram syndrome. Nat Genet. 1997;15(1):30–5.
10. Basson CT, Huang T, Lin RC, Bachinsky DR, Weremowicz S, Vaglio A, et al. Different TBX5 interactions in heart and limb defined by Holt-Oram syndrome mutations. Proc Natl Acad Sci U S A. 1999;96(6):2919–24.
11. Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud JB, Simonet F, et al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet. 2013;45(9):1044–9.
12. Bhakta D, Shen C, Kron J, Epstein AE, Pascuzzi RM, Groh WJ. Pacemaker and implantable cardioverter-defibrillator use in a US myotonic dystrophy type 1 population. J Cardiovasc Electrophysiol. 2011;22(12):1369–75.
13. Bonne G, Leturcq F, Ben YR. Emery-Dreifuss Muscular Dystrophy. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews(R). Seattle (WA); 1993.

14. Boriani G, Gallina M, Merlini L, Bonne G, Toniolo D, Amati S, et al. Clinical relevance of atrial fibrillation/flutter, stroke, pacemaker implant, and heart failure in Emery-Dreifuss muscular dystrophy: a long-term longitudinal study. Stroke. 2003;34(4):901–8.
15. Borozdin W. Bravo Ferrer Acosta AM, Bamshad MJ, Botzenhart EM, Froster UG, Lemke J, et al. Expanding the spectrum of TBX5 mutations in Holt-Oram syndrome: detection of two intragenic deletions by quantitative real time PCR, and report of eight novel point mutations. Hum Mutat. 2006;27(9):975–6.
16. Bradshaw PJ, Stobie P, Knuiman MW, Briffa TG, Hobbs MS. Trends in the incidence and prevalence of cardiac pacemaker insertions in an ageing population. Open Heart. 2014;1(1):e000177.
17. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013;34(29):2281–329.
18. Brink PA, Ferreira A, Moolman JC, Weymar HW, van der Merwe PL, Corfield VA. Gene for progressive familial heart block type I maps to chromosome 19q13. Circulation. 1995;91(6):1633–40.
19. Brodt C, Siegfried JD, Hofmeyer M, Martel J, Rampersaud E, Li D, et al. Temporal relationship of conduction system disease and ventricular dysfunction in LMNA cardiomyopathy. J Card Fail. 2013;19(4):233–9.
20. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature. 1998;392(6673):293–6.
21. Combrink JM, Davis WH, Snyman HW. Familial bundle branch block. Am Heart J. 1962;64:397–400.
22. Daumy X, Amarouch MY, Lindenbaum P, Bonnaud S, Charpentier E, Bianchi B, et al. Targeted resequencing identifies TRPM4 as a major gene predisposing to progressive familial heart block type I. Int J Cardiol. 2016;207:349–58.
23. de Meeus A, Stephan E, Debrus S, Jean MK, Loiselet J, Weissenbach J, et al. An isolated cardiac conduction disease maps to chromosome 19q. Circ Res. 1995;77(4):735–40.
24. den Hoed M, Eijgelsheim M, Esko T, Brundel BJ, Peal DS, Evans DM, et al. Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders. Nat Genet. 2013;45(6):621–31.
25. Dhingra RC, Denes P, Wu D, Chuquimia R, Rosen KM. The significance of second degree atrioventricular block and bundle branch block. Observations regarding site and type of block. Circulation. 1974;49(4):638–46.
26. Epstein AE, DiMarco JP, Ellenbogen KA, Estes 3rd NA, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61(3):e6–75.
27. Eriksson P, Hansson PO, Eriksson H, Dellborg M. Bundle-branch block in a general male population: the study of men born 1913. Circulation. 1998;98(22):2494–500.
28. Eriksson P, Wilhelmsen L, Rosengren A. Bundle-branch block in middle-aged men: risk of complications and death over 28 years. The Primary Prevention Study in Goteborg, Sweden. Eur Heart J. 2005;26(21):2300–6.
29. Fahy GJ, Pinski SL, Miller DP, McCabe N, Pye C, Walsh MJ, et al. Natural history of isolated bundle branch block. Am J Cardiol. 1996;77(14):1185–90.
30. Gollob MH, Green MS, Tang AS, Gollob T, Karibe A, Ali Hassan AS, et al. Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. N Engl J Med. 2001a;344(24):1823–31.
31. Gollob MH, Jones DL, Krahn AD, Danis L, Gong XQ, Shao Q, et al. Somatic mutations in the connexin 40 gene (GJA5) in atrial fibrillation. N Engl J Med. 2006;354(25):2677–88.
32. Gollob MH, Seger JJ, Gollob TN, Tapscott T, Gonzales O, Bachinski L, et al. Novel PRKAG2 mutation responsible for the genetic syndrome of ventricular preexcitation and conduction system disease with childhood onset and absence of cardiac hypertrophy. Circulation. 2001b;104(25):3030–3.
33. Gourraud JB, Kyndt F, Fouchard S, Rendu E, Jaafar P, Gully C, et al. Identification of a strong genetic background for progressive cardiac conduction defect by epidemiological approach. Heart. 2012;98(17):1305–10.
34. Groh WJ. Arrhythmias in the muscular dystrophies. Heart Rhythm. 2012;9(11):1890–5.
35. Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E, et al. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. N Engl J Med. 2008;358(25):2688–97.
36. Gupta P, Bilinska ZT, Sylvius N, Boudreau E, Veinot JP, Labib S, et al. Genetic and ultrastructural studies in dilated cardiomyopathy patients: a large deletion in the lamin A/C gene is associated with cardiomyocyte nuclear envelope disruption. Basic Res Cardiol. 2010;105(3):365–77.
37. Harbison J, Newton JL, Seifer C, Kenny RA. Stokes Adams attacks and cardiovascular syncope. Lancet. 2002;359(9301):158–60.
38. Hasselberg NE, Edvardsen T, Petri H, Berge KE, Leren TP, Bundgaard H, et al. Risk prediction of ventricular arrhythmias and myocardial function in Lamin A/C mutation positive subjects. Europace. 2014;16(4):563–71.
39. Hofman N, Tan HL, Alders M, Kolder I, de Haij S, Mannens MM, et al. Yield of molecular and clinical testing for arrhythmia syndromes: report of 15 years' experience. Circulation. 2013;128(14):1513–21.
40. Holm H, Gudbjartsson DF, Arnar DO, Thorleifsson G, Thorgeirsson G, Stefansdottir H, et al. Several common variants modulate heart rate, PR interval and QRS duration. Nat Genet. 2010;42(2):117–22.
41. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. Circ Arrhythm Electrophysiol. 2011;4(3):303–9.
42. Kruse M, Schulze-Bahr E, Corfield V, Beckmann A, Stallmeyer B, Kurtbay G, et al. Impaired endocytosis of the ion channel TRPM4 is associated with human progressive familial heart block type I. J Clin Invest. 2009;119(9):2737–44.
43. Liu H, El Zein L, Kruse M, Guinamard R, Beckmann A, Bozio A, et al. Gain-of-function mutations in TRPM4 cause autosomal dominant isolated cardiac conduction disease. Circ Cardiovasc Genet. 2010;3(4):374–85.
44. Lodder EM, Scicluna BP, Milano A, Sun AY, Tang H, Remme CA, et al. Dissection of a quantitative trait locus for PR interval duration identifies Tnni3k as a novel modulator of cardiac conduction. PLoS Genet. 2012;8(12):e1003113.
45. Lynch HT, Mohiuddin S, Sketch MH, Krush AJ, Carter S, Runco V. Hereditary progressive atrioventricular conduction defect. A new syndrome? JAMA. 1973;225(12):1465–70.
46. Lynch RJ, Engle MA. Familial congenital complete heart block. Its occurrence in 2 children with another genetically determined anomaly. Am J Dis Child. 1961;102:210–7.
47. Makita N, Seki A, Sumitomo N, Chkourko H, Fukuhara S, Watanabe H, et al. A connexin40 mutation associated with a malignant variant of progressive familial heart block type I. Circ Arrhythm Electrophysiol. 2012;5(1):163–72.
48. Marsman RF, Bardai A, Postma AV, Res JC, Koopmann TT, Beekman L, et al. A complex double deletion in LMNA underlies progressive cardiac conduction disease, atrial arrhythmias, and sudden death. Circ Cardiovasc Genet. 2011;4(3):280–7.
49. McDermott DA, Fong JC, Basson CT. Holt-Oram syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al. editors. GeneReviews(R). Seattle (WA); 1993.

50. Milanesi R, Baruscotti M, Gnecchi-Ruscone T, DiFrancesco D. Familial sinus bradycardia associated with a mutation in the cardiac pacemaker channel. N Engl J Med. 2006;354(2):151–7.
51. Milano A, Vermeer AM, Lodder EM, Barc J, Verkerk AO, Postma AV, et al. HCN4 mutations in multiple families with bradycardia and left ventricular noncompaction cardiomyopathy. J Am Coll Cardiol. 2014;64(8):745–56.
52. Morquio L. Sur une maladie infantile caractérisée par des modifications permanentes du pouls, des attaques syncopales et épileptiformes. Arch Med Enfants. 1901;4:467–75.
53. Nery PB, Beanlands RS, Nair GM, Green M, Yang J, McArdle BA, et al. Atrioventricular block as the initial manifestation of cardiac sarcoidosis in middle-aged adults. J Cardiovasc Electrophysiol. 2014;25(8):875–81.
54. Nof E, Luria D, Brass D, Marek D, Lahat H, Reznik-Wolf H, et al. Point mutation in the HCN4 cardiac ion channel pore affecting synthesis, trafficking, and functional expression is associated with familial asymptomatic sinus bradycardia. Circulation. 2007;116(5):463–70.
55. Pfeufer A, van Noord C, Marciante KD, Arking DE, Larson MG, Smith AV, et al. Genome-wide association study of PR interval. Nat Genet. 2010;42(2):153–9.
56. Postema PG, Van den Berg M, Van Tintelen JP, Van den Heuvel F, Grundeken M, Hofman N, et al. Founder mutations in the Netherlands: SCN5a 1795insD, the first described arrhythmia overlap syndrome and one of the largest and best characterised families worldwide. Neth Hear J. 2009a;17(11):422–8.
57. Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (http://www.brugadadrugs.org/). Heart Rhythm. 2009b;6(9):1335–41.
58. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace. 2013;15(10):1389–406.
59. Remme CA, Verkerk AO, Nuyens D, van Ginneken AC, van Brunschot S, Belterman CN, et al. Overlap syndrome of cardiac sodium channel disease in mice carrying the equivalent mutation of human SCN5A-1795insD. Circulation. 2006;114(24):2584–94.
60. Roberts JD, Longoria J, Poon A, Gollob MH, Dewland TA, Kwok PY, et al. Targeted deep sequencing reveals no definitive evidence for somatic mosaicism in atrial fibrillation. Circ Cardiovasc Genet. 2015;8(1):50–7.
61. Rotman M, Triebwasser JH. A clinical and follow-up study of right and left bundle branch block. Circulation. 1975;51(3):477–84.
62. Schott JJ, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M, et al. Cardiac conduction defects associate with mutations in SCN5A. Nat Genet. 1999;23(1):20–1.
63. Schott JJ, Benson DW, Basson CT, Pease W, Silberbach GM, Moak JP, et al. Congenital heart disease caused by mutations in the transcription factor NKX2-5. Science. 1998;281(5373):108–11.
64. Schulze-Bahr E, Neu A, Friederich P, Kaupp UB, Breithardt G, Pongs O, et al. Pacemaker channel dysfunction in a patient with sinus node disease. J Clin Invest. 2003;111(10):1537–45.
65. Silverman BG, Gross TP, Kaczmarek RG, Hamilton P, Hamburger S. The epidemiology of pacemaker implantation in the United States. Public Health Rep. 1995;110(1):42–6.
66. Sotoodehnia N, Isaacs A, de Bakker PI, Dorr M, Newton-Cheh C, Nolte IM, et al. Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction. Nat Genet. 2010;42(12):1068–76.
67. Stallmeyer B, Fenge H, Nowak-Gottl U, Schulze-Bahr E. Mutational spectrum in the cardiac transcription factor gene NKX2.5 (CSX) associated with congenital heart disease. Clin Genet. 2010;78(6):533–40.
68. Stallmeyer B, Zumhagen S, Denjoy I, Duthoit G, Hebert JL, Ferrer X, et al. Mutational spectrum in the Ca(2+)–activated cation channel gene TRPM4 in patients with cardiac conductance disturbances. Hum Mutat. 2012;33(1):109–17.
69. Steenkamp WF. Familial trifascicular block. Am Heart J. 1972;84(6):758–60.
70. Steere AC, Batsford WP, Weinberg M, Alexander J, Berger HJ, Wolfson S, et al. Lyme carditis: cardiac abnormalities of Lyme disease. Ann Intern Med. 1980;93(1):8–16.
71. Stephan E. Hereditary bundle branch system defect: survey of a family with four affected generations. Am Heart J. 1978;95(1):89–95.
72. Strasberg B, Amat YLF, Dhingra RC, Palileo E, Swiryn S, Bauernfeind R, et al. Natural history of chronic second-degree atrioventricular nodal block. Circulation. 1981;63(5):1043–9.
73. Theis JL, Zimmermann MT, Larsen BT, Rybakova IN, Long PA, Evans JM, et al. TNNI3K mutation in familial syndrome of conduction system disease, atrial tachyarrhythmia and dilated cardiomyopathy. Hum Mol Genet. 2014;23(21):5793–804.
74. Tresch DD, Fleg JL. Unexplained sinus bradycardia: clinical significance and long-term prognosis in apparently healthy persons older than 40 years. Am J Cardiol. 1986;58(10):1009–13.
75. van den Heuvel GCJ. Die ziekte van Stokes-Adams en een geval van aangeboren hartblok 1908.
76. van Rijsingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, et al. Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. J Am Coll Cardiol. 2012;59(5):493–500.
77. van Spaendonck-Zwarts KY, van Hessem L, Jongbloed JD, de Walle HE, Capetanaki Y, van der Kooi AJ, et al. Desmin-related myopathy. Clin Genet. 2011;80(4):354–66.
78. van Tintelen JP, Tio RA, Kerstjens-Frederikse WS, van Berlo JH, Boven LG, et al. Severe myocardial fibrosis caused by a deletion of the 5′ end of the lamin A/C gene. J Am Coll Cardiol. 2007;49(25):2430–9.
79. Veerman CC, Wilde AA, Lodder EM. The cardiac sodium channel gene SCN5A and its gene product NaV1.5: role in physiology and pathophysiology. Gene. 2015;573(2):177–87.
80. Vermeer AM, Lodder EM, Thomas D, Duijkers FA, Marcelis C, van Gorselen EO, et al. Dilation of the aorta ascendens forms part of the clinical spectrum of HCN4 mutations. J Am Coll Cardiol. 2016;67(19):2313–5.
81. Verweij N, Mateo Leach I, Isaacs A, Arking DE, Bis JC, Pers TH, et al. Twenty-eight genetic loci associated with ST-T wave amplitudes of the electrocardiogram. Hum Mol Genet. 2016. (http://hmg.oxfordjournals.org/content/early/2016/03/23/hmg.ddw058.full)
82. Wahbi K, Meune C, Porcher R, Becane HM, Lazarus A, Laforet P, et al. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. JAMA. 2012;307(12):1292–301.
83. Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell. 1995;80(5):805–11.
84. Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott JJ, et al. Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. J Clin Invest. 2008;118(6):2260–8.
85. Xi Y, Honeywell C, Zhang D, Schwartzentruber J, Beaulieu CL, Tetreault M, et al. Whole exome sequencing identifies the TNNI3K gene as a cause of familial conduction system disease and congenital junctional ectopic tachycardia. Int J Cardiol. 2015;185:114–6.
86. Xiong Y, Wang L, Liu W, Hankey GJ, Xu B, Wang S. The prognostic significance of right bundle branch block: a meta-analysis of prospective cohort studies. Clin Cardiol. 2015;38(10):604–13.
87. Zhang ZM, Rautaharju PM, Soliman EZ, Manson JE, Cain ME, Martin LW, et al. Mortality risk associated with bundle branch blocks and related repolarization abnormalities (from the Women's Health Initiative [WHI]). Am J Cardiol. 2012;110(10):1489–95.