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REVIEW

Molecular and genetic insights into progressive cardiac conduction disease

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Progressive cardiac conduction disease (PCCD) is often a primarily genetic disorder, with clinical and genetic overlaps with other inherited cardiac and metabolic diseases. A number of genes have been implicated in PCCD pathogenesis with or without structural heart disease or systemic manifestations. Precise genetic diagnosis contributes to risk stratification, better selection of specific therapy and allows familiar cascade screening. Cardiologists should be aware of the different phenotypes emerging from different gene-mutations and the potential risk of sudden cardiac death. Genetic forms of PCCD often overlap or coexist with other inherited heart diseases or manifest in the context of multisystem syndromes. Despite the significant advances in the knowledge of the genetic architecture of PCCD and overlapping diseases, in a measurable fraction of PCCD cases, including in familial clustering of disease, investigations of known cardiac disease-associated genes fail to reveal the underlying substrate, suggesting that new causal genes are yet to be discovered. Here, we provide insight into genetics and molecular mechanisms of PCCD and related diseases. We also highlight the phenotypic overlaps of PCCD with other inherited cardiac and metabolic diseases, present unmet challenges in clinical practice, and summarize the available therapeutic options for affected patients.

Keywords Progressive cardiac conduction disease • Atrioventricular block • Bundle branch block • Lenègre–Lev disease • Gene mutation • Genetic testing • Cardiac channelopathy • Precision medicine • Congenital atrioventricular block • Bundle branch block

Introduction

Progressive cardiac conduction disease (PCCD) is an inherited heart disease, characterized by progressive delay of impulse conduction through the His-Purkinje system with right or left bundle branch block (RBBB or LBBB), susceptibility to complete atrioventricular (AV) block, syncope, and sometimes sudden cardiac death (SCD).[1] The term PCCD encompasses disease forms with either congenital or acquired nature, which can occur with or without concomitant structural heart disease.[2,3] The classical form of PCCD has been first described as a distinct entity in 1964 by Drs Lenège and Lev, who investigated the clinical records, electrocardiograms (ECGs), and post-mortem findings in hearts of patients with isolated cardiac conduction disease.[4,5] Subsequently, the authors found that an exaggerated aging process selectively affecting the conduction tissue of the heart is responsible for the progressive deterioration of the impulse propagation through the His-Purkinje system with RBBB or LBBB, leading to complete AV block, often associated with recurrent syncope and frequently culminating with SCD. The pathophysiological basis of this primary degenerative disease are myocardial degeneration, increased collagen turnover in the myocardium and fibrosis in the conduction system, leading to conduction abnormalities at various levels. The disease is usually progressive, and currently constitutes one of the main indications for pacemaker implantation worldwide.

Recent developments in molecular biology and genetic technologies have enabled the discovery of genetic basis of some forms of familiar PCCD. Current knowledge suggests that familial PCCD in the absence of structural/congenital heart disease or a systemic disease usually results from mutations in genes encoding cardiac ion channels, involved in cardiac electrical impulse propagation, whereas PCCD in the context of structural heart disease is usually caused by mutations in genes encoding transcriptional factors, enzymes, or structural proteins (*Table 1*). However, substantial proportion of PCCD patients test negative for alterations in currently discovered PCCD-related genes, suggesting that many genes causally involved in PCCD are yet to be discovered. Here, we summarize the recent molecular and genetic advances on PCCD and discuss the broad spectrum of clinical phenotypes and diagnostic features observed in PCCD patients.

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Genetic basis of progressive cardiac conduction disease

Familial clustering of PCCD, which has been recognized for over six decades, suggested a potential genetic substrate, but the genetic basis of PCCD were uncertain until 1995, when the first chromosomal locus, mapped to the 19q13.2–13.3, was linked to this condition.[42] However, this locus has not been further investigated and the causal gene remains uncertain to date. The first PCCD susceptibility gene, reported in 1999,[29] was identified in a familial form of PCCD linked to chromosome three near the locus of the *SCN5A* gene, which encodes the cardiac sodium channel. Two different *SCN5A* mutations that cosegregated with the PCCD phenotype were identified; the affected family members had variable expression of the conduction abnormalities, RBBB, LBBB, or AV block, and the severity of conduction defects increased with age. Supporting this discovery, biophysical characterization of a Cys514Gly substitution, identified in a family with PCCD phenotype, revealed a loss-of-function of the $Na_V1.5$ (*SCN5A*) channel protein.[30] Further, disruption of the mouse cardiac sodium channel gene, Scn5a, caused intrauterine lethality in homozygotes (i.e. $Scn5a^{-/-}$ mice) with severe defects in ventricular morphogenesis, whereas heterozygotes (i.e. $Scn5a^{+/-}$ mice) convincingly recapitulated the Lenègre's disease phenotype, exhibiting normal survival, age-related lengthening of the P wave, and PR and QRS interval duration associated with myocardial rearrangements and fibrosis,[43,44] establishing the first experimental model for hereditary Lenègre–Lev disease due to *SCN5A* mutations.

During the last decade, the wide use of next-generation sequencing technologies that leverage the power of genome-scale sequencing in clinical and research setting have enabled the discovery of molecular genetic substrates underlying PCCD with or without concomitant structural heart disease. Currently, around 20 genes encoding cardiac ion channels and regulatory proteins, protein kinases, structural proteins, and transcriptional factors have been associated with different forms of PCCD, and the number of genes is expected to increase with improved diagnosis and availability of genome-wide sequencing to the affected families.

Genes associated to isolated progressive cardiac conduction disease

SCN5A

The *SCN5A* gene, which encodes the cardiac sodium channel $Na_V1.5$, remains the main ion channel gene known to be causal for familial PCCD. Among the known forms of PCCD, the molecular determinants of *SCN5A*-mediated PCCD are currently better understood. *SCN5A* encodes the voltage-gated sodium channel α subunit protein $Na_V1.5$,[45] which is expressed predominantly in the human heart. This channel mediates the inward sodium current (I_{Na}), which is responsible for the excitability and impulse conduction in the contractile myocardium (atrial and ventricular cardiomyocytes) and in the specialized conduction system (Purkinje cells and others), as well as for the late I_{NaL} current, which influences repolarization and refractoriness. *SCN5A*-mutations give rise to a spectrum of phenotypes,[46] most of which are inherited as an autosomal dominant trait, with the exception of few recessive or sporadic forms.[47–49] The pathophysiology of *SCN5A*-channelopathies remains incompletely understood, but biophysical and functional characteristics of the underlying molecular defect seem to be involved in the determination of the ultimate phenotype. Gain-of-function mutations in *SCN5A*, reflected by an increase in I_{Na}, slowed inactivation or a shift in voltage dependence of activation or inactivation, usually cause long-QT syndrome Type 3 (LQT3),[50] and less commonly early-onset, arrhythmic forms of dilated cardiomyopathy (DCM),[51] atrial fibrillation (AF),[52] and multifocal ectopic Purkinje-related premature contractions.[53] Conversely, loss-of-function mutations give rise to arrhythmogenic conditions, such as PCCD,[29,30] Brugada syndrome (BrS) Type 1,[54] idiopathic ventricular fibrillation (VF),[55] sick sinus syndrome (SSS),[47] AF, and, more rarely, ventricular tachycardia (VT),[44,56] and DCM (*Figure 1*).[57] Coexisting and overlapping phenotypes have also been reported.[58–60] Loss-of-function truncated mutations and missense mutations with >90% reduction of peak I_{Na} have been associated with significantly reduced AV and intraventricular depolarization reserve and produced more severe PCCD phenotype, than missense variants with <90% peak I_{Na} reduction.[61] Therefore, while the reported functional alterations seem to be consistent with the LQT, BrS, PCCD, and SSS phenotypes, the development of *SCN5A*-mediated DCM, AF, and overlapping phenotypes of LQT and BrS might be due to the considerable interplay of genetic factors and epigenetic influences.

BrS Type I, a familial arrhythmia syndrome characterized by an ST segment elevation in the right precordial leads (V_1–V_2) of the ECG and high incidence of SCD, is a commonly observed phenotype among patients carrying loss-of-function *SCN5A* mutations. However, there is a significant overlap between BrS and PCCD and the two conditions may coexist, or manifest in isolated form in individuals from the same family carrying the same mutation. Nevertheless, despite the clinical and genetic overlap, these two conditions remain distinct clinical entities with differences in arrhythmic phenotype and in factors predisposing to SCD.[62] For example, programmed electrical stimulation induces VT or VF in nearly 20–33% of BrS Type 1 patients,[63] which is considered a predictor of increased risk of arrhythmic events during long-term follow-up,[64] whereas *SCN5A*-PCCD patients generally do not exhibit VT or VF in response to programmed electrical stimulation.

SCN5A-mediated PCCD has incomplete penetrance of nearly 40%, and a variable expressivity of the disease (*Figure 2*). The molecular basis of incomplete penetrance remains poorly understood, and probably includes a complex interplay of genetic, post-translational, and environmental factors. The variable expressivity of PCCD-associated *SCN5A* mutations could at least partly be caused by several *SCN5A* polymorphisms known to exert a modulatory effect on the phenotype. For example, the common polymorphism *SCN5A*-H558R restores the trafficking defect of a BrS Type 1 mutation,[65] whereas the polymorphism *SCN5A*-R1193Q mitigates the adverse effect conferred by the non-sense mutation W1421X.[66] *In vitro* experiments have suggested that a rightward shift in the voltage dependence of the mutant $Na_V1.5$ channel activation curve is a common feature for *SCN5A*-medicated PCCD.

SCN1B, SCN4B, SCN10A, and DSP

Several genes involved in $Na_V1.5$ (*SCN5A*) macromolecular complex, also contribute to the PCCD phenotype. Mutations in *SCN10A*

Table 1 Summary of progressive cardiac conduction disease susceptibility genes

Gene	Protein	Inheritance pattern	Arrhythmia and/or conduction disorder	Structural heart disease	Other organ involvement	Genotype-based risk of SCD	Disease(s)/syndrome(s)	References
BMP2	Bone morphogenetic protein 2	AD	AV block, WPW	–	Yes	Uncertain	Cognitive defects, dysmorphic features	6
CACNA1C	CaV1.2, L-type calcium channel	AD	AV block, BrS	PDA, PFO, VSD, TOF	Yes	High	Timothy syndrome	7
GJA5	Gap junction protein alpha-5 (connexin 40)	AD	BBB, AF, atrial standstill, ventricular arrhythmias	Unknown	No	High	–	8
DES	Desmin	AD, AR	AV block, BBB	RCM, DCM	Yes	High	Desminopathy	9–11
DMPK	Serine-threonine kinase	AD	BBB, AV block	HCM, DCM, MVP	Yes	High	Myotonic dystrophy Type 1	12,13
EMD	Emerin	XLR	AV block, VT/VF	DCM	Yes		Emery–Dreifuss muscular dystrophy	
GLA	Alpha galactosidase	XL	AV block	HCM, RCM, DCM	Yes	High	Fabry disease	14,15
HCN4	Pacemaker I_f channel	AD	SSS, familial bradycardia	No	No	High	SSS, BrS	16,17
KCNH2	Potassium voltage-gated channel subfamily H member 2 (HERG, I_{Kr})	AD	AVB	No	No	High	LQT2, diLQT, SQT1, SIDS	18
KCNJ2	Inward rectifier K+ channel Kir2.	AD	BBB, AV block, polymorphic VT	Bicuspidal aortic valve, aortic coarctation, pulmonary valve stenosis	Yes	High	Andersen–Tawil syndrome, SQT3, CPVT	19
KCNQ1	Potassium voltage-gated channel subfamily Q member 1	AD	AF, AV block (I, II, advanced, or III)	No	No	Yes	LQT1, SQT2, JLN (AR), familial AF3	20
LAMP2	Lysosomal-associated membrane protein 2	XLD	BBB, AV block, WPW	Glycogen storage disease, HCM/DCM/LVNC	Yes	High	Danon disease	
LMNA	Lamin A/C	AD	BBB, SSS, AV block, VT/VF	DCM	Yes	High	Emery–Dreifuss muscular dystrophy Type 2 (AD) and 3 (AR), limb-girdle muscular dystrophy, Werner's syndrome, Charcot–Marie–Tooth disease, Type 2B1 (AR)	21–23
NKX2.5	Homeobox protein NKX 2-5	AD	AV block	ASD, VSD, TOF, HLHS, subvalvular AS, pulmonary atresia	No	High	ASD, VSD, TOF, HLHS	24–26
PRKAG2	AMPK γ2 subunit	AD	BBB, AV block, WPW	Glycogen storage disease HCM/DCM	Yes	High	Glycogen storage disease	27,28
SCN5A	NaV1.5 channel	AD		DCM	No	High		29,30

Continued

Table 1 *Continued*

Gene	Protein	Inheritance pattern	Arrhythmia and/or conduction disorder	Structural heart disease	Other organ involvement	Genotype-based risk of SCD	Disease(s)/syndrome(s)	References
			BBB, SSS, AF, AV block, VT, VF				LQT3, BrS, PCCD, SSS, DCM, SIDS (AD & AR)	
SCN1B	Sodium channel subunit beta-1	AD	AF, AV block	No	Yes	High	BrS, epilepsy with febrile seizures, early infantile epileptic encephalopathy (AR)	31
TBX3	T-box transcription factor TBX3	AD	AV block, WPW	VSD	Yes	High[a]	Ulnar–mammary syndrome	32
TBX5	T-box transcription factor TBX5	AD	Sinus bradycardia, AV block, BBB	ASD	Yes	High[a]	Holt–Oram syndrome	33,34
TNNI3K	TNNI3 interacting kinase	AD	FAT, MAT, AF, frequent PAC, JET: AVNRT, VT, BBB	DCM, atrial cardiomyopathy	No	High	–	35–38
TRPM4	Transient receptor potential melastatin 4 channel	AD	AV block, BBB	No	Usually no, rarely LVNC	High	BrS	39,40
ZNF9	Zinc finger protein 9	AD	AV block (I), RBBB, LBBB	DCM	Yes	High (DM2 < DM1)	Myotonic dystrophy Type 2	41

Exceptions to the inheritance pattern for specific phenotypes are provided in brackets in the 'Disease(s)/Syndrome(s)' column.
AD, autosomal dominant; AS, aortic stenosis; ASD, atrial septal defect; AVNRT, atrioventricular nodal re-entrant tachycardia; BBB, bundle branch block; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; FAT, focal atrial tachycardia; HCM, hypertrophic cardiomyopathy; HLHS, hypoplastic left heart syndrome; JET, junctional ectopic tachycardia; JLN, Jervell and Lange–Nielsen syndrome; LBBB, left bundle branch block; LQT1, long-QT syndrome Type 1; LVNC, left ventricular noncompaction; MAT, multifocal atrial tachycardia; MVP, mitral valve prolapse; PAC, premature atrial contractions; PDA, patent ductus arteriosus; PFO, patent foramen ovale; RBBB, right bundle branch block; RCM, restrictive cardiomyopathy; SCD, sudden cardiac death; SQT1 and SQT3, short-QT syndrome Types 1 and 3, respectively; SSS, sick sinus syndrome; ToF, tetralogy of Fallot; VSD, ventricular septal defect; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolf–Parkinson–White syndrome; XLR, X-linked recessive.
[a]Shown only in experimental animal models.

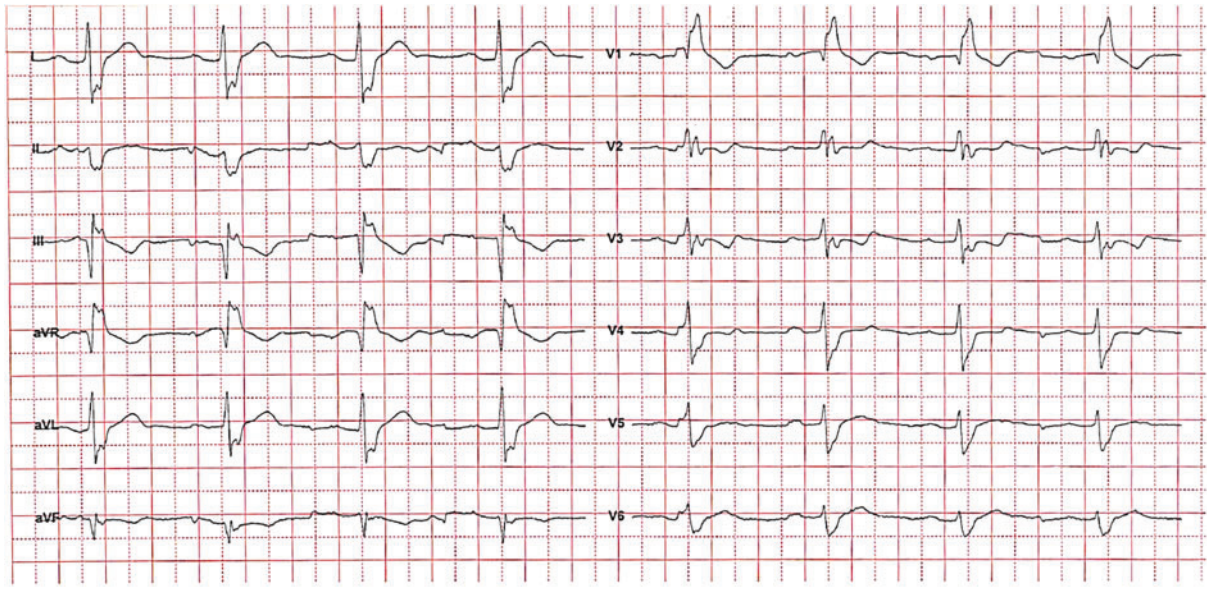

Figure 1 A 12-lead electrocardiogram recorded in a patient with PCCD and recurrent episodes of cardiac arrest (25 mm/s, 10 mm/mV). Sinus bradycardia, 51 b.p.m., first-degree atrioventricular block, right bundle branch block, and left anterior fascicular block. Left shift of electrical axis −145°. RR interval 1163 ms, PR 296 ms, QRS 200 ms, QT 480 ms, and QTc 443 ms. Molecular genetic analysis in this patient identified a pathogenic variant c.3840 + 1G>A in the *SCN5A* gene. The c.3840 + 1G>A variant is predicted to produce loss-of-function of Nav1.5. The identification of the *SCN5A* mutation confirmed that the conduction disturbances and the recurrent cardiac arrest in this patient are caused by an underlying *SCN5A*-mediated PCCD. PCCD, progressive cardiac conduction disease.

($Na_V1.8$) lead to AV conduction defects and BrS due to its interaction with the promoter of *SCN5A*.[67] Loss-of-function mutations in *SCN1B*, which encodes the beta 1 regulatory subunit of the voltage-gated cardiac sodium channel, cause BrS with conduction disease through reducing I_{Na} current density and enhancing slow inactivation of the $Na_V1.5$ channel.[31] Interestingly, different mutations in *SCN1B* have been implicated in a variety of inherited pathologies, including generalized epilepsy with febrile seizures, BrS Type 5,[68] LQT syndrome,[69] AF,[70] PCCD,[31] and sudden infant death syndrome.[68] This genetic overlap between epilepsy and arrhythmogenic diseases can confound the determination of the ultimate cause of sudden unexplained death in *SCN1B* mutation carriers. Additionally, a mutation in the *SCN4B* gene, which encodes the beta 4 regulatory subunit of $Na_V1.5$, has been linked to a familial form of LQT together with 2:1 AV block.[71]

DSP (desmoplakin) mutations have been identified in PCCD families.[72] The pathogenetic role of this gene in PCCD is unclear. Recently, it has been shown that desmosomal remodelling modifies $Na_V1.5$ and connexin expressions.[73] Further, the arrhythmogenic effects of desmosomal genes have been attributed to ion channel remodelling and dysfunction.[74,75] Therefore, it is likely that the desmoplakin mutations cause PCCD through modifying the $Na_V1.5$ current, thus mimicking *SCN5A* mutation effect.

TRPM4

Defects in the TRPM4 current have been linked to significant proportion of familial AV block and RBBB.[39] TRPM4 is a Ca^{2+}-activated non-specific channel permeable only to monovalent cations. It is expressed in atrial and ventricular tissue, in pacemaker cells, and in Purkinje fibres.[76] *TRPM4* mutations that have been identified in families with isolated PCCD were shown to cause gain-of function due to an elevated TRPM4 channel density at the cell surface secondary to impaired endocytosis and deregulation of Small Ubiquitin MOdifier conjugation (SUMOylation),[77] However, a recent experimental study of *TRPM4* mutations found that increased or decreased TRPM4 expression is caused by altered TRPM4 protein stability and half-life, suggesting an alternative pathogenetic mechanism for alteration of TRPM4 expression.[78] *TRPM4* mutations with either gain- or loss-of-function have also been linked to 6% of BrS cases with no *SCN5A* mutation,[79] further increasing the genetic overlap between these two diseases. Recently, c.858G>A variant leading to synonymous substitution p.T286T has been identified in siblings with left ventricular non-compaction (LVNC) complicated by PCCD (*Figure 3*).[40] Although the variant did not change the amino acid sequence, it led to aberrant splicing, abnormal mRNA transcription, and reduction of overall expression, culminating in loss of TRPM4 function. These observations, in the context of recently reported functional or structural association of TRPM4 and sulfonylurea receptors make the TRPM4 channel a promising target for development of novel treatments for cardiac disorders.

KCNH2, KCNJ2, and KCNQ1

Patients with LQT2, caused by a molecular defect in the *KCNH2* gene (I_{Kr}), can present with intermittent 2:1 AV block together with the prolonged QT interval.[18] Mutations in the *KCNJ2* gene are

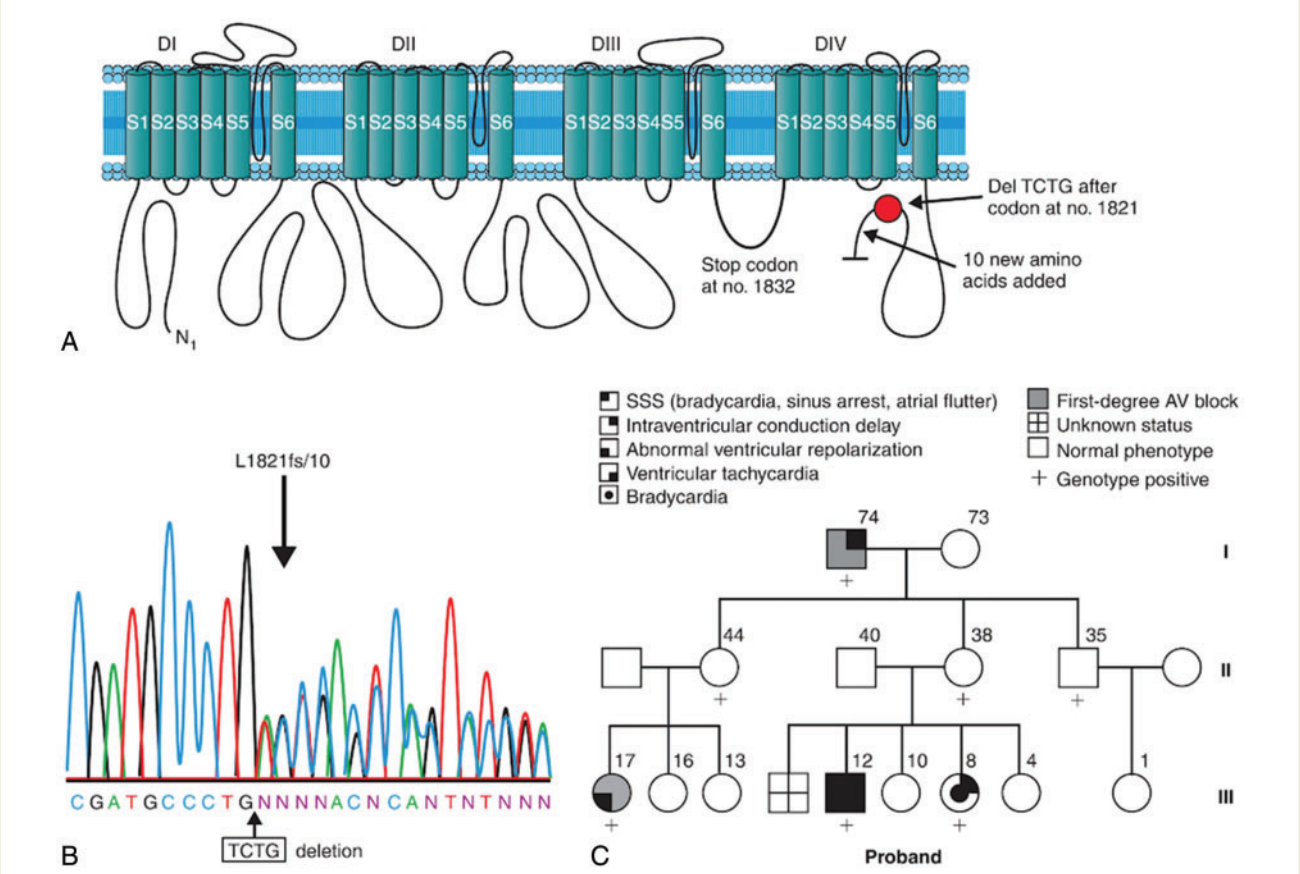

Figure 2 Example of incomplete penetrance and variable expressivity of *SCN5A*-mediated progressive cardiac conduction disease. In this particular case, a severe disruption of the channel encoded by L182fs/10-*SCN5A* yielded an electrophysiological phenotype consistent with sodium channel loss of function. (*A*) Linear topology of SCN5A showing location of the mutation L182fs/10 in the carboxyl terminus. (*B*) Sequence chromatogram for the patient. (*C*) In this family tree showing carriers and affected members, incomplete penetrance, and variable expressivity of the disease are evident. AV, atrioventricular; SSS, sick sinus syndrome. Reproduced with permission from Ref.[56]

responsible for polymorphic VT or Anderson–Tawil syndrome, which manifests with potassium-sensitive periodic paralysis, ventricular arrhythmias, and dysmorphic features. Commonly, these patients exhibit AV block, bundle branch block (BBB), or intraventricular conduction delay.[19] An S140G mutation in *KCNQ1* gene has been genetically linked in a large Chinese kindred to AF and to a slow ventricular response (<60 b.p.m.) in AF as a manifestation of AV conduction impairment.[20] Additionally, in a transgenic murine model expressing the human *KCNQ1*-S140G mutation, frequent episodes of first-, second degree, advanced-, or complete AV block have been documented, which have been successfully terminated by a K_v7.1 (*KCNQ1*)-specific blocker, HMR1556.

CACNA1C

Mutations in the *CACNA1C*, encoding the L-type calcium channel, cause a spectrum of inherited arrhythmia syndromes, including gain-of-function-mediated rare variant of long QT syndrome (LQT8), and Timothy syndrome, and loss-of-function-mediated BrS and early repolarization syndrome. Timothy syndrome is characterized by multi-organ dysfunction, including dysmorphic features, congenital heart malformations, QT interval prolongation, intermittent 2:1 AV block, and high risk of SCD.[7] Recently, a *CACNA1C*-E1115K substitution of a glutamic acid with lysine localized to the DIII-S5/S6 pore region of the channel has been identified in a 14-year-old male with idiopathic QT prolongation (486 ms), sinus bradycardia, autism spectrum disorder, variable T-wave polarity, and unexplained hyperglycaemia.[80] This rare variant, first reported in this case, has been shown to convert the calcium channel into a non-selective monovalent cation channel with marked increase in both peak and persistent inward sodium currents and outward potassium/caesium currents, a novel mechanism of calcium channelopathy. Despite the functional dysregulation, the channel's sensitivity to nifedipine block was preserved.

GJA4, GJA5, GJA1, and GJA7

Gap junctions are membrane channels that mediate the cell-to-cell movement of ions and small metabolites and play a critical role in cardiac impulse conduction. In the heart, gap junction channels electrically connect cardiomyocytes and specialized conductive tissues to co-ordinate the excitation-contraction coupling. Gap junctions are encoded by over 20 different connexins, channel forming proteins,

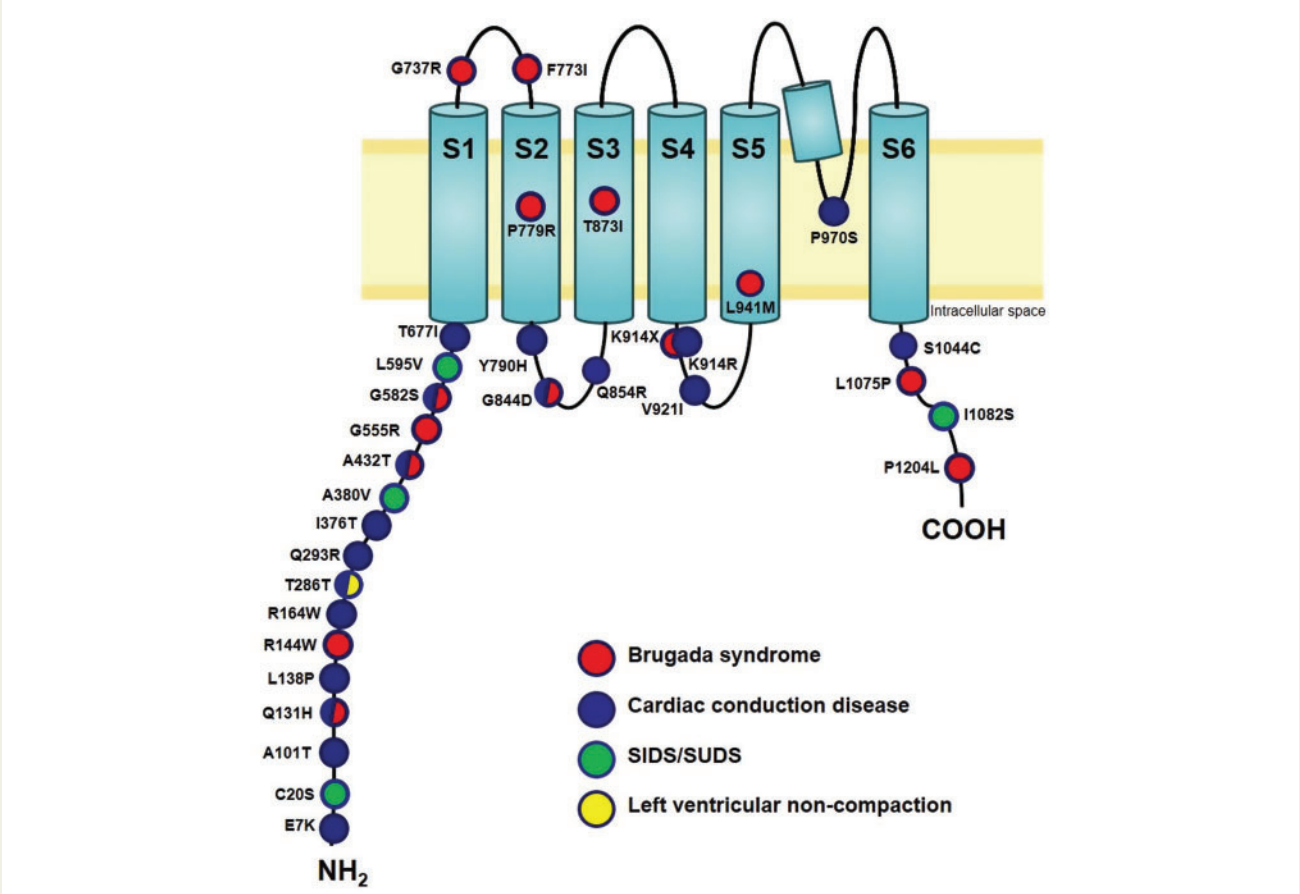

Figure 3 The predicted topology of to date reported *TRPM4* mutations and associated clinical cardiac phenotypes. SIDS, sudden infant death syndrome; SUDS, sudden unexplained death syndrome.

which serve the principal component of coupling and current conduction between adjacent myocytes.[81] There are five different connexin isotypes (Cx) expressed in the heart: Cx31.9 (gene not discovered, located on chromosome 17), Cx37 (*GJA4*), Cx40 (*GJA5*), Cx43 (*GJA1*), and Cx45 (*GJA7*), which differ in their channel properties and gating mechanisms.[82] Cx45 forms voltage-sensitive channels with very low conductance, and is mainly found in the AV node and adjoining His bundles. Cx31.9 is less investigated and is thought to contribute to AV nodal impulse conduction. Cx43 is the predominant cardiovascular connexin and is expressed in working myocytes of the atria and ventricles. Replacement of Cx43 by Cx26 in transgenic mice produced slower ventricular conduction.[83] Cx40 is expressed mainly in the atrial myocardium and His-Purkinje system, as well as in the ventricle early in development. A novel germline mutation in *GJA5* disrupting the Cx40 has been described as a cause of early-onset progressive conduction disturbances in the His-Purkinje system, slow heart rate, and malignant arrhythmias, associated with high risk of SCD.[8] Cx40-deficient mice showed AV and BBB or reduced cardiac conduction velocity and predisposition to atrial arrhythmias,[84] with a high incidence of cardiac malformations in heterozygous (18%) and homozygous (33%) animals.[85] A large number of Cx43 mutations remain clinically silent without any apparent cardiac phenotype. Rarely, there may be a specific genetic defect of connexins, but the pathogenic alterations of connexin expression are more commonly local and secondary to other cardiac pathologies.

Genetics of cardiac conduction disease with structural heart disease

Cardiac conduction disease with hypertrophic cardiomyopathy

The glycogen-storage diseases caused by *PRKAG2* or *LAMP2* mutations, mostly resemble sarcomeric hypertrophic cardiomyopathy (HCM), but are distinguished by progressive conduction impairments, namely sinus bradycardia, AV block, and ventricular pre-excitation (*Figure 4*).[86] Dilated cardiomyopathy can develop as a remodelling of initial left ventricular (LV) hypertrophy at late stages of *LAMP2* and *PRKAG2* cardiomyopathies, or may be revealed at the time of diagnosis or shortly after.[87] The determinants of phenotype progression are not well defined and might involve a variety of genetic, epigenetic, and environmental factors.

PRKAG2

The *PRKAG2* gene encodes the γ2-subunit of an AMP-activated protein kinase (AMPK), a downstream component of a kinase cascade

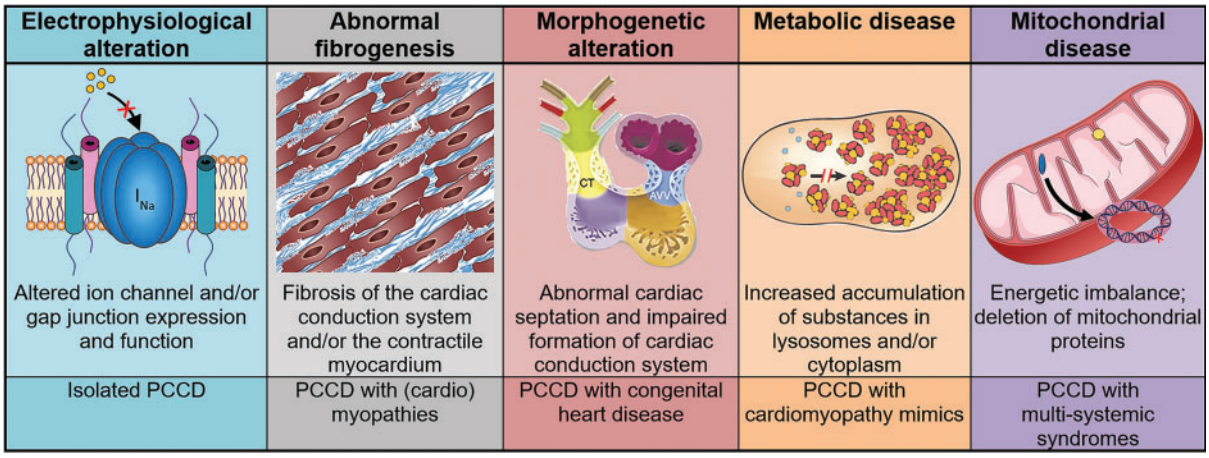

Figure 4 Main mechanisms involved in the pathogenesis of PCCD. AVV, atrioventricular valve; CT, conotruncal vale; PCCD, progressive cardiac conduction disease.

that has multiple cellular targets but is particularly essential to the cellular energetic metabolism. *PRKAG2*-mediated disease manifests with pseudohypertrophy of right and left ventricles, mimicking HCM, which is usually accompanied by Wolff–Parkinson–White (WPW) syndrome and conduction defects,[27] extracardiac manifestations such as a skeletal myopathy, consistent with a systemic metabolic storage disease.[88] It can be further distinguished from sarcomeric HCM by the absence of myocyte and myofibrillar disarray and by the presence of pronounced amylopectin vacuole formation in cardiomyocytes. In fact, the ventricular pre-excitation in *PRKAG2* disease results from disruption of annulus fibrosus by glycogen-filled myocytes, distinct from the muscular-appearing bypass tracts observed in typical WPW syndrome. Clinically, *PRKAG2* disease should be suspected in the presence of massive LV wall thickening (>30 mm) in combination with advanced AV block. A mouse model of PRKAG2 disease has been generated, which has recapitulated the human phenotype typical for the disease.[86] The *PRKAG2*-disease course often leads to progressive conduction impairment, requiring pacemaker implantation.[88] Apart from the typical phenotype, RBBB, sinus bradycardia, and short PR interval in absence of WPW or obvious structural heart disease has been reported in two large families.[28]

A novel form of genetic WPW syndrome has been linked to the genetic locus of the *BMP2* gene,[6] which encodes bone morphogenetic protein 2, a member of the transforming growth factor-beta family that affects the formation of the annulus fibrosus. Deletion of the *BMP2* region within 20p12.3 leads to prolonged AV conduction on atrial pacing, variable dysmorphisms, and neurocognitive delay.

Untreated patients with *PRKAG2* cardiomyopathy have a poor prognosis. However, recent studies suggested that the PRKAG2 phenotype is reversible and treatments targeting the reduction of glycogen storage by transgene regulation are associated with potential improvement of cardiac function. Furthermore, transgenic suppression during early postnatal period has been shown to modulate the disease course by preventing the development of accessory electrical pathways but not the cardiomyopathy or conduction system degeneration, providing insights into mechanisms of PRKAG2 disease.[89]

LAMP2

LAMP2 mutations produce Danon disease (glycogen storage disease Type IIb), a rare X-linked dominant disorder caused by lysosomal-associated membrane protein 2 (LAMP2) deficiency. Danon disease manifests as progressive muscular dystrophy (skeletal vacuolar myopathy), variable intellectual disability, and peripheral pigmentary retinopathy, and cardiomyopathy—commonly diffuse and marked LV hypertrophy associated with accessory pathways difficult to ablate; less commonly, patients exhibit a DCM, or rarely LVNC phenotype.[21–23] Affected females develop isolated cardiomyopathy in adulthood, whereas males present with severe and progressive cardiomyopathy, myopathy, and mental retardation before 20 years.[23] LAMP2 functions in lysosomal enzyme targeting chaperone-mediated autophagy, and lysosomal biogenesis. Many aspects of the *LAMP2* cardiomyopathy pathophysiology remain uncertain. The outcome in affected males is usually fatal due to terminal heart failure, and cardiac transplantation is the only effective treatment.[90]

GLA

Fabry disease is an X-linked lysosomal storage disorder caused by a mutation in the *GLA* gene, which leads to deficiency of α-galactosidase A enzyme.[91] It affects multiple organ systems, including the heart, nervous system, the gastrointestinal system, and kidneys. Females present signs and symptoms of Fabry disease usually later in life and present with milder phenotypes than their affected male relatives. Fabry disease affects an estimated one in 40 000 to 60 000 males; the prevalence in females is unknown. Milder, late-onset forms confined to the heart or the kidneys are thought to be more common than classic early-onset disease.

Cardiac involvement in Fabry disease is considered the main determinant of outcome and clinically manifests in the form of myocardial hypertrophy, mimicking HCM, with or without restrictive physiology pattern.[92] The main ECG abnormalities include ST-depressions or elevation and T-wave inversion commonly in V5 and V6, which fit well with the region of late gadolinium enhancement, hinting myocardial

fibrosis.[93] Prolonged PR interval without a delta wave is observed in nearly 40% of males with Fabry disease.[14] With increasing age, progressive prolongation of the PR interval, and a broadening of the QRS may be observed. Premature conduction disease in Fabry patients may be related to the autonomic dysfunction or cardiac conduction tissue degeneration resulting from accumulation of glycosphingolipid, apoptosis, and vacuolization.[14]

Patients often present atrial and ventricular arrhythmias. Resting bradycardia and chronotropic incompetence are very frequent.[15] Permanent pacemaker implantation is often required due to bradyarrhythmias resulting from sinus node disease or AV block. In a recent systematic review, about 75% of deaths in Fabry disease patients were due to cardiovascular problems, around 60% being SCD events.[94] Male gender, older age (>40 years in males), left ventricular hypertrophy, non-sustained VT and presence of late gadolinium enhancement on cardiac magnetic resonance imaging (MRI) were shown to be risk factors associated with ventricular arrhythmias and SCD.[94] In patients who meet these criteria, implantable cardioverter-defibrillator (ICD) implantation is warranted to protect from SCD.

Cardiac conduction disease and dilated cardiomyopathy

LMNA

Mutations in *LMNA* are associated with the development of multisystem disease, often referred to as laminopathies, including PCCD, atrial and ventricular arrhythmias, DCM with or without PCCD, and a variety of neuromuscular lipodystrophy and progeria-type disorders including Emery–Dreifuss muscular dystrophy.[95] Cardiac involvement in laminopathies prevails with mutations upstream of the nuclear localization signal. Previously, non-missense mutations were considered to have worse prognosis, but a recently performed combined analysis of the literature suggests that some missense mutations can be as harmful as non-missense ones.[96] It has been suggested that haploinsufficiency is the disease mechanism in patients carrying truncating *LMNA* mutations, whereas *LMNA* missense mutations have been proposed to act through a dominant negative pathway.[97–99] Interestingly, the clinical findings indicate that the poor prognosis and high risk of SCD in *LMNA* mutation carriers may be associated with high amount of expressed mutant proteins. A recent study of a missense mutation suggested that mutant lamin proteins might accumulate and form intra-nuclear aggregates and thereby exhibit a dominant negative effect.[100] These findings may assist in counselling and risk assessment of *LMNA* families.

Lamins A and C constitute the main structural proteins of the inner nuclear envelope. The two isoforms are produced by alternative splicing of *LMNA*, differing only in the structure of their carboxyl terminus.[101] They are expressed in almost all differentiated tissues, including the myocardium and fibroblasts. In addition to their structural and supportive function of the nucleus, these proteins are believed to influence regulation of gene expression through an interaction with transcription factors, DNA, and chromatin.[101] In a *LMNA* cardiomyopathy model, microtubule instability led to the abnormal trafficking of Cx43 towards the lateral plasma membrane, triggered abnormal electrical communication between adjacent cardiomyocytes, and induced cardiac conduction defects.[102] Stabilization of the microtubule network by paclitaxel, a microtubule-stabilizing agent successfully used as an anticancer medication, suppressed these events and improved cardiac conduction, suggesting a novel viable therapeutic approach for patients with laminopathies. Of note, the mechanism underlying microtubule instability caused by *LMNA* mutations remains to be elucidated.

DES

Desmin is a muscle-specific intermediate filament protein, which connects and anchors different cell structures, such as desmosomes, mitochondria, and Z-bands to the cytoskeleton.[103] Missense mutations in *DES* disrupt the cytoplasmic desmin meshwork and lead to accumulation of abnormal desmin aggregation within the cytoplasm,[104] culminating in a variety of cardiomyopathy phenotypes with arrhythmias and conduction disorders, as well as isolated and combined skeletal myopathies. About 75% of patients with *DES* mutations present cardiac symptoms and only 22% of them have an isolated cardiac phenotype.[105] Most commonly, cardiac involvement in desminopathies is in the form a restrictive cardiomyopathy or DCM leading to heart failure, frequently accompanied with severe conduction disease requiring pacemaker implantation or, in some cases, ventricular arrhythmias necessitating ICD implantation.[9,10] Cardiac arrhythmias are the predominant cause of death in desminopathies.[105] Atrioventricular block of different severity is the most common conduction abnormality observed in *DES* mutation carriers, but isolated LBBB with progression to complete AV block and asystole has also been described.[11] Clemen *et al.*[106] showed that in an experimental model of *DES*-p. R349P knock-in mice, mutant desmin results in altered subcellular distribution and turnover of desmin itself and of desmin-interacting proteins, leading to increased mechanical vulnerability of muscle fibres. Clinically, these mice manifested skeletal muscle weakness, DCM, as well as cardiac arrhythmias and conduction defects, recapitulating the phenotype observed in patients with *DES*-R350P mutation, the human ortholog of murine R349P.[106] Currently, the molecular determinants of the incomplete penetrance and clinical heterogeneity of desmin mutation-associated phenotypes are unknown, and additional research is necessary to identify the potential contribution of further genetic, epigenetic, and environmental factors in modulating the clinical phenotype.

TNNI3K

TNNI3K encodes for the cardiac troponin-I interacting MAP kinase (TNNI3K), a functional serine/threonine/tyrosine kinase with a cardiac-restricted expression pattern, and with particularly high transcriptional levels in the interventricular septum and apex.[35,107] TNNI3K plays a key role in cardiac morphogenesis and sarcomere organization.[107] Rare variants in *TNNI3K* have been identified in families with infra-Hisian cardiac conduction disease (in >75%), DCM or signs of congestive heart failure (in 25%) and signs of atrial cardiomyopathy or supraventricular arrhythmias (in 90%), mainly atrial of AV junctional arrhythmias.[35,36] Both gain-of-function and loss-of-function mechanisms leading to either increased (p.Glu768Lys)[36] or decreased kinase activity (p.Gly526Asp, splicing variant c.333 + 2T>C)[37,38] have been described as potential mechanisms of conduction disease, electrical instability, myofilament loss, and ultimately DCM, but identification of TNNI3K interacting partners and phosphorylation targets is necessary for better understanding of the underlying mechanisms of this disease.

Cardiac conduction disease and left ventricular non-compaction

HCN4

The *HCN4* gene is responsible for the pacemaker current (I_f), and thus has a central role in slow diastolic depolarization (automaticity) of the sinus node. *HCN4* mutations have been associated with diverse phenotypes, primarily reflecting impaired sinus node function,[16] including SSS, sinus bradycardia, inappropriate sinus tachycardia, but have also been linked to early-onset AF, AV block, LVNC, idiopathic VT, VF, dilation of the aorta, and mood and anxiety disorders.[17] In other forms of LVNC, cardiac conduction disturbances are uncommon.[108]

Cardiac conduction disease and congenital heart disease

NKX2.5, *TBX3* and *TBX5* encode transcriptional factors that regulate cardiac morphogenesis. Mutations in these genes have been linked to inherited forms of conduction system disease associated with atrial or ventricular septal defects. The molecular pathway unifying these transcription factors in the pathogenesis of cardiac conduction disease is thought to be their down-regulation of Cx40 and Cx43.

NKX2.5

The *Nkx2.5* homeobox gene encodes a transcription factor critical to the postnatal conduction system maturation and maintenance. Loss-of-function *NKX2.5* mutations cause a loss of DNA-binding activity and result in hypoplasia of the AV node, His bundle, and Purkinje system.[109] Clinically, *NKX2.5* mutations produce familial atrial septal defects, progressive AV block and other conduction abnormalities at different levels, with associated high risk of SCD.[24–26] Experimental studies in animal models revealed that Nkx2.5 can act as an activator as well as repressor of Cx43.[110]

TBX3 and TBX5

Mutations in the T-box transcription factor genes *TBX3* and *TBX5*, regulators of cardiac morphogenesis, cause congenital anomalies in patients with ulnar–mammary syndrome, or Holt–Oram syndrome, respectively. Patients with *TBX5* mutations exhibit congenital heart disease, particularly secundum-type atrial septal defects, associated with progressive AV block, and radial ray deformities of the upper limb.[33,34] Infrequently, patients with Holt–Oram syndrome have structurally normal hearts, and exhibit only AV conduction defects with subtle hand deformities. In *Tbx5* heterozygous knockout mice *Tbx5* haploinsufficiency markedly decreased Cx40 mRNA transcription in the heart, indicating that Tbx5 is a critical regulator of Cx40 expression.[111] Deletion of *Tbx5* from the mature murine AV bundle and bundle branches resulted in loss of fast conduction, arrhythmias, and SCD.[112] Experimental evidence suggests that disruption of Tbx3 function in the heart causes sinus pauses and bradycardia due to sino-atrial node dysfunction, and pre-excitation and AV block due to abnormalities in the AV junction.[32] Surviving *Tbx3* mutant mice conferred increased risk for SCD.

Cardiac conduction disease and myotonic dystrophies

DMPK and ZNF9

Myotonic dystrophy (DM) is an autosomal dominant disease, and the most common form of adult onset muscular dystrophy. DM1, the more common type, results from expansion of a cathepsin G (CTG) trinucleotide repeat in the myotonic dystrophy protein kinase gene (*DMPK*) that culminates in production of RNA aggregates within cells.[113] Normally, there are between 4 and 37 CTG repeats; 37–50 CTG repeats are considered a 'pre-mutation', and expansion beyond 50 repeats are considered pathogenic. Notably, *DMPK* alleles with >37 repeats are unstable and additional trinucleotide repeats may be inserted during cell division, leading to further expansion of CTG repeats and associated earlier disease onset and increased severity in each subsequent generation. In DM2, a CCTG repeat is expanded within intron 1 of the zinc finger protein 9 (*ZNF9*) gene. DM1 is a multisystemic disease; common manifestations include myotonia, progressive muscle weakness due to skeletal muscle atrophy, profound fatigue, cardiac disease, cataracts, diabetes mellitus, intellectual disability, hypogammaglobulinaemia, and mental retardation.[113]

Cardiac disease in DM1 is due to progressive myocardial fibrosis that results in LV hypertrophy and dilatation, systolic dysfunction, mitral valve prolapse, regional wall motion abnormalities, and left atrial dilatation.[114] Atrial tachyarrhythmias are the most common electrical abnormalities. Conduction disturbances at any level are present in 30–75% of DM1 patients,[12] and progressive conduction disease constitutes the second most common cause of death among patients with DM1.[13] Up to 40% of patients present with first-degree AV block, followed in order of frequency by left anterior fascicular block, LBBB, RBBB, QT-interval prolongation, ST-T abnormalities, and electrical axis deviation.[114] In transgenic mouse model, it has been clearly demonstrated that cardiac conduction defects in DM1 result from RNA toxicity-induced overexpression of the cardiac transcriptional factor Nkx2.5 and consequent down-regulation of Cx40 and Cx43.[115] DM2 is less investigated, but up to 35% of patients may exhibit prolonged PR interval with or without LBBB or RBBB.[41] Presence of Q waves in the absence of a history of myocardial infarction is also possible due to depolarization abnormalities. Furthermore, late potentials can be observed, resulting from delayed activation of the His-Purkinje system, rather than propagation of action potentials through focal islands of fibrosis.[113] Late potentials are considered predictors of ventricular arrhythmias. Though both DM1 and DM2 confer high risk, SCD seems to be more common in DM1 patients, while progressive DCM is more frequently observed in DM2 patients.[116]

Genetic testing is the 'gold standard' for diagnosis of DM. Although the management of DM is primarily symptomatic, precision in diagnosis allows to anticipate multiple other manifestations that may develop over time and to assist with appropriate clinical monitoring. In DM1 patients with normal ECG at diagnosis, ECG screening every 6–12 months is recommended due to the slow but progressive and unpredictable nature of conduction abnormalities in DM1.[114] Genetic counselling and predictive genetic testing should be offered to family members because of the high risk of transmission.

Mitochondrial disease and cardiac conduction disease

Cardiac conduction defects are detected in 10–40% of the patients with mitochondrial disorders.[117] Most commonly, conduction disease is observed in patients with Kearns–Sayre syndrome (in 80% of cases), which involves large-scale mitochondrial DNA deletions, and manifests as complete AV block, chronic progressive external

ophthalmoplegia, ataxia, and pigmentary retinal degeneration. Conduction defects typically involve the distal His bundle, bundle branches, and infranodal conduction. Dilated cardiomyopathy may also develop. Because of the unpredictable progression to complete AV block and the mortality of up to 20% associated with it, patients with Kearns–Sayre syndrome and their family members should be routinely evaluated with an ECG for conduction disease.

Management of inherited forms of cardiac conduction disease

Currently, irrespective of its cause, the only effective treatment for PCCD is implantation of an implantable pacemaker.[118] Although pacemakers improve the survival and reduce the morbidity, these devices are subject to several limitations, including their lack of sensitivity to autonomic regulation of the heart rate, potential provocation of ventricular remodelling by imposing an abnormal activation sequence, and technical challenges, such as the limited battery life and the need for multiple invasive replacement procedures. Additionally, long-term pacemaker system-related complications are not rare. Hence, existing pharmacological and device therapies for PCCD patients are far from being optimal and a search for novel treatment strategies is highly desirable.

The genotype-based assessment of the risk of SCD is an essential determinant of clinical management strategy. Unfortunately, due to the limited awareness of this rare entity among clinicians and the restricted access to next-generation sequencing technologies, many cases and even familial forms of unexplained PCCD remain insufficiently genetically investigated. Currently, genotype-phenotype correlations in PCCD are not well established. An important observation has been the higher SCD risk in some forms, which cannot be suspected by the phenotype alone, but may be diagnosed only by genetic testing. So far, mutations in *SCN5A, DES,* and *LMNA* genes have been associated with higher risk of SCD. It is essential to remember that otherwise unexplained His-Purkinje disease, particularly in young individuals (<40 years), has a high likelihood of being related to an underlying high-risk *SCN5A* mutation. Genetic testing in these subjects should be part of the clinical evaluation, as upon identification of a loss-of-function *SCN5A* mutation, drugs with sodium channel blocking properties (amongst others class I antiarrhythmic medications, propranolol, tricyclic antidepressants, and certain anticonvulsants) should be avoided and ICD implantation should be considered. Considering the clinical and genetic overlap with BrS and idiopathic VF, patients with *SCN5A*-mediated PCCD should receive active treatment of fever with antipyretics to avoid fever-induced ventricular arrhythmias, typical for BrS.[119] Isoproterenol may be effective for prevention of recurrent ventricular arrhythmias and improvement of cardiac conduction disease in high-risk patients with *SCN5A*-mediated PCCD. When the molecular defect is identified, extension of targeted-genetic screening to appropriate family members allows identification and prospective follow-up of asymptomatic mutation carriers.[119] Additionally, carrier status allows performing clinical evaluation targeting the various *SCN5A* phenotypes, which in turn, might enable timely diagnosis and decision making in early disease stages.

Molecular diagnosis is also part of other disease forms. Patients with *LMNA* disease have a very high risk of malignant arrhythmias in all disease stages, including when the LV ejection fraction is >35%, and may suffer SCD despite pacemaker implantation.[120] For this reason, ICD implantation in these patients is often preferred. A risk stratification scheme has been developed to identify high-risk patients, who would benefit most from ICD implantation in early disease stages.[121] *LAMP2*-mediated disease is usually fatal in young males, whereas females commonly present in mild disease form, but may have rapid progression of disease to a terminal stage, requiring cardiac transplantation. Certain *DES* mutations can lead to severe cardiac phenotype with high incidence of ventricular arrhythmias, conduction defects, progressive cardiomyopathy, and death[105]; therefore, when a high-risk *DES* mutation is identified, ICD implantation should be considered to prevent SCD from tachyarrhythmias. In other pleiotropic genes, an association with high risk of SCD has been reported for other gene-associated phenotypes, but not specifically for cardiac conduction defects. However, this knowledge is rapidly evolving and should be updated regularly since many PCCD-associated genes are rarely involved and the evidence might change upon publication of new series. Additional clinical implications of the molecular diagnosis in cardiac conduction disease are important for patients with Fabry disease. Therapeutic options in these patients include enzyme replacement therapy (agalsidase alfa or beta, i.v.) and chaperone therapy (migalastat, *per os*), but their potential impact on progression/reversal of conduction abnormalities or mortality is unknown.

The 2012 ACCF/AHA/HRS updated guidelines for device-based therapy for cardiac rhythm abnormalities suggested consideration of permanent pacemaker placement for neuromuscular diseases or Kearns–Sayre syndrome with any degree of AV block, with or without symptoms, because of unpredictable progression of AV conduction disease.[122] Recent evidence suggests that ICD should be preferred over a pacemaker in Kearns–Sayer syndrome given that proper pacing may suppress early after depolarizations associated with a QT prolongation due to bradycardia, but these patients remain at risk for dying suddenly from polymorphic VT or VF caused by delayed after depolarization via an increasing intracellular Ca concentration due to mitochondrial dysfunction.[123] Selection of MRI-compatible pacemaker is recommended in patients with structural heart disease, to allow for continuous monitoring of the disease progression.[124] In case an MRI-incompatible pacemaker has been implanted, serial echocardiograms are recommended for monitoring of disease progression.

Future directions

Currently, the therapeutic potential of selective and orally bioavailable TNNI3K inhibitors is being explored at biological experiments and may help develop a novel therapy targeting gain-of-function *TNNI3K* disease.[125] The progress of efficient, cardiac-specific gene transfer technologies have placed PCCD well within reach of gene-based therapies. Gene transfer approach to convert normally quiescent myocytes into pacemaker cells exhibiting spontaneous depolarization by switching on their pluripotent state has been successfully performed in animals.[126] The main molecular target for this 'inducible pacemaking' are the T-box transcription factors TBX3[127] and TBX18,[128] regulators of the cardiac conduction system during early

development. An attractive feature of TBX-based technologies for biological pacemaking is their presumed ability to produce long-term effects after the target gene expression has vanished. It has also been experimentally shown that genetically modified bone marrow-derived human mesenchymal stem cells express functional cardiac pacemaker channels *in vitro* and *in vivo*[129] and can repair conduction block in cardiomyocyte cultures.[130] Despite these impressive achievements in preclinical level, these novel methods face many challenges and obstacles. Upon launch of further investigations, that facilitate the crossing of the bridge between bench side research and clinical application, these methods may revolutionize our ability to combat malignant PCCD phenotypes.

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