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REVIEW ARTICLE

Current perspectives in genetic cardiovascular disorders: from basic to clinical aspects

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Abstract We summarize recent advances in the clinical genetics of hypercholesterolemia, hypertrophic cardiomyopathy (HCM), and lethal arrhythmia, all of which are monogenic cardiovascular diseases being essential to understanding the heart and circulatory pathophysiology. Among the issues of hypercholesterolemia which play a pivotal role in development of vascular damages, familial hypercholesterolemia is the common genetic cardiovascular disease; in addition to identifying the gene mutation coding low-density lipoprotein receptor, lipid kinetics in autosomal recessive hypercholesterolemia as well as in proprotein convertase subtilisin/kexin 9 gene mutation were recently demonstrated. As for HCM, some gene mutations were identified to correlate with clinical manifestations. Additionally, a gene polymorphism of the renin–angiotensin system in development of heart failure was identified as a modifier gene. The lethal arrhythmias such as sudden death syndromes, QT prolongation, and Brugada syndrome were found to exhibit gene mutation coding potassium and/or sodium ion channels. Interestingly, functional analysis of these gene mutations helped to identify the role of each gene mutation in developing these cardiovascular disorders. We suggest considering the genetic mechanisms of cardiovascular diseases associated with hyperlipidemia, myocardial hypertrophy, or lethal arrhythmia in terms of not only clinical diagnosis but also understanding pathophysiology of each disease with therapeutic aspects.

Keywords Genetics · Hereditary diseases · Hypercholesterolemia · Hypertrophic cardiomyopathy · Lethal arrhythmias

Introduction

Recent advances in genetic analysis have made it possible to determine gene mutations for almost all hereditary diseases, irrespective of the coded gene region [1]. Therefore, the recognition, diagnosis, and suitable treatment of atherosclerosis, heart failure, and arrhythmias have become important targets for clinical genetics research in the field of cardiovascular medicine [2]. Definitive diagnosis of inheritable diseases by genetic methods could lead to tailor-made therapies using conventional medicine as well as gene silencing or targeting therapy.

Atherosclerosis develops in the presence of a lipid disorder typically represented by familial hypercholesterolemia (FH) [3]. Left ventricular hypertrophy is an independent risk factor for heart failure, and hypertrophic cardiomyopathy (HCM) is the most common genetic cause of left ventricular hypertrophy [4]. Life-threatening arrhythmias and sudden death frequently occur in inherited cardiac arrhythmia syndromes such as congenital long-QT syndrome (LQTS) [5]. In this article, we review current perspectives in genetic-related cardiovascular diseases from recent reports including our ones and provide insights into these disorders.

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Advances in hypercholesterolemia research

Large epidemiological studies have shown that coronary risk factors including hyperlipidemia, hypertension, impaired glucose tolerance, male sex, and smoking habits, are associated with the development of atherosclerosis [6]. Most coronary risk factors are associated with endothelial dysfunction, which is known to initiate atherosclerosis. Although menopausal hormone replacement therapy failed to decrease cardiovascular disease in older women [7], epidemiological data suggested that endogenous estrogen is antiatherogenic. Because aged vessels show characteristics of atherosclerosis, such as reduced number of vascular smooth muscle cells, increased collagen deposition, and fractured elastin, aging per se is a risk factor for atherosclerosis. Under these conditions, low-density lipoprotein (LDL) cholesterol, which directly accumulates in arterial walls, presents the most prominent coronary risk factor for atherosclerosis. Homozygous FH, usually defined as FH with homozygous mutation, and heterozygous FH are typical clinical models of atherosclerotic cardiovascular disease leading to premature coronary artery disease due to extreme hyper-LDL cholesterolemia. There exits the homozygous FH due to LDL receptor and other different gene mutations as double heterozygous FH. However, the most common genetic cause of FH, even in homo- and hetero-zygotes, is a mutation or defect in the LDL receptor gene associated with intracellular trafficking of LDL cholesterol (Fig. 1). Thus, homozygous FH, lacking the LDL receptor, is highly resistant to cholesterol-lowering medical therapy including HMGCoA reductase inhibitors (statins), although heterozygous FH was observed partially responding to statins [3].

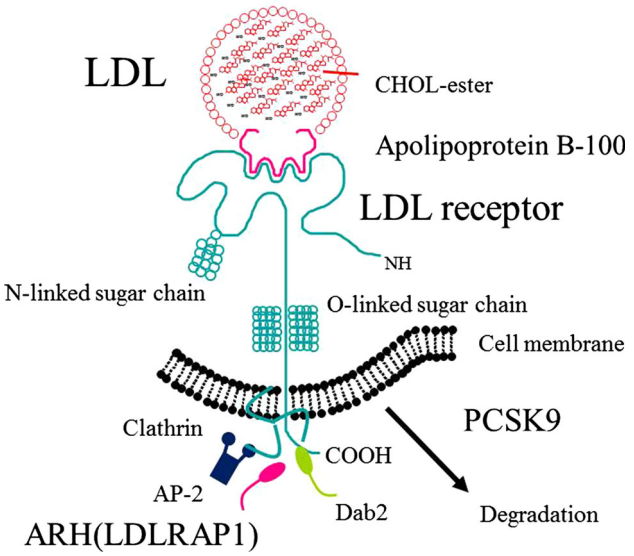

Fig. 1 Schematic illustration of the low-density lipoprotein (LDL) receptor and its associated molecules

A mutation in the apolipoprotein B-100 gene is also known to be a cause of FH. However, few FH patients with the apolipoprotein B-100 gene mutation had been detected in Japan [8, 9].

Autosomal recessive hypercholesterolemia (ARH) is a rare disorder; the reported number of patients with clinical manifestations resembling homozygous FH is approximately 70 individuals worldwide. The first ARH patient was reported in Japan [10], and we recently found the second ARH family [11]. The cause of ARH is a mutation of LDL receptor adaptor protein-1 (LDLRAP1) (Fig. 1). The clinical manifestations and severity of ARH differs from those in homozygous and heterozygous FH. Lipid reduction therapy including the use of statins is at least partially effective [12], because intracellular trafficking of very LDL via the LDL receptor without LDLRAP1 is preserved [13]. We performed a lipoprotein kinetic study in a patient with ARH and concluded that the fractional catabolic rate of LDL apolipoprotein B-100 was significantly lower and the direct removal of the very LDL remnant was significantly greater than that seen in normal controls [12, 14]. This suggests the presence of an alternate pathway of LDL cholesterol in ARH, which may be a new target of lipid-lowering therapy.

Recently, proprotein convertase subtilisin/kexin 9 (PCSK9), associated with intracellular degeneration of LDL receptor, was found as a causal gene for FH [15] (Fig. 1). We identified an E32 K mutation in the PCSK9 gene in patients with the milder FH phenotype. The frequency of PCSK9 E32 K carriers is 1.7 % in the general population; the LDL cholesterol serum level of PCSK9 E32 K carriers is significantly higher than that seen in the general population, but significantly lower than seen in individuals with the heterozygous LDL receptor gene mutation [16]. Plasma levels of PCSK9 increased following cholesterol-lowering medical therapy such as statins or fibrates, and may cancel out at least a part of the LDL cholesterol-lowering effect [17, 18], although there was no difference in increased PCSK9 levels between different statins such as pitavastatin and pravastatin [19]. Recently, treatment with anti-PCSK9 antibody was demonstrated to reduce cholesterol levels in animal as well as human trials, and further clinical trials will demonstrate its efficacy [20–28]. The S447X variant of the lipoprotein lipase gene is inversely associated with severity of coronary artery disease [29], probably due to functional loss of lipoprotein lipase associated with hyperlipoproteinemia.

Intensive genetic diagnosis sometimes reveals misdiagnosis of homozygous FH as heterozygous FH in patients with severe hypercholesterolemia without consanguinity or family history who respond to medical cholesterol-lowering therapy. For instance, an additional mutation in LDLRAP1 gene worsens the clinical manifestation such as

increases in LDL cholesterol levels and xanthomas in FH with a single LDL receptor gene mutation [30]. Interestingly, genetic diagnosis of FH reveals that the frequency of FH is higher than previously estimated [3]. Because the available intensive LDL cholesterol-lowering regimens can reduce serum levels of LDL cholesterol < 100 mg/dl [17], accurate diagnosis of FH based on genetic methods should be considered before starting therapy. Plasma LDL apheresis instead of conventional statin therapy in FH could result in regression of coronary plaques [31].

Previous studies showed that high-density lipoprotein (HDL) cholesterol levels are associated with decreased frequencies of cardiovascular events [32]. Reverse cholesterol transport as well as anti-oxidant, anti-inflammatory, and anti-thrombotic effects are known to be antiatherogenic function of HDL. Statin therapy effectively increases HDL cholesterol levels and seems to be associated with regression of coronary atheroma [33, 34]. The study of genetic disorders associated with HDL, including cholesteryl ester transfer protein deficiency, first reported by our research group [35], has led to several developments in terms of genetic and functional analyses [36–38], as well as possible therapeutic implications [39, 40]. The reverse cholesterol transport-promoting concept has been a promising alternative to simple HDL-increasing therapy [41, 42], although some clinical trials have failed to demonstrate their efficacy [43, 44]. Additionally, genetic mechanisms that raise plasma HDL cholesterol do not seem to lower the risk of myocardial infarction [45]. These data challenge the concept that raising plasma HDL cholesterol will or will not uniformly translate into reductions of risk for myocardial infarction.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a heritable myocardial disorder characterized by increased ventricular wall thickness in the absence of other loading conditions, such as aortic stenosis or hypertension. Histopathologic abnormalities of HCM include myocyte hypertrophy, myocyte disarray, and increased interstitial and/or focal fibrosis. These anatomic and histopathologic findings contribute to diastolic dysfunction with impaired filling due to increased chamber stiffness, leading to elevated left ventricular end-diastolic and left atrial pressures. This condition is a slowly progressive disorder that manifests remarkably variable clinical courses from near-normal life expectancy with no symptoms to sudden cardiac death (SCD) in youth [4, 46].

The estimated prevalence of HCM in the general population is approximately 1 in 500 [47]; approximately half of the cases have a family history of HCM and the mode of inheritance is autosomal dominant. Since 1990, when a missense mutation in the β-myosin heavy chain (MYH7) gene was identified in patients with HCM [48], more than 17 disease-causing genes and several hundred mutations have been discovered [47] (Table 1). Mutations in the MYH7 and MYBPC3 genes are responsible for HCM in approximately 50 % of patients. Mutations in other sarcomere genes (TNNT2, TNNI3, TPM1, and ACTC1) account for about 10–15 % of HCM cases. Mutations in the genes that encode Z-disk-related proteins (including the genes MYOZ2, TCAP, and ANKRD1) are uncommon causes of HCM [4, 47, 49]. Collectively, the known disease-causing genes account for about two-thirds of HCM cases.

The majority of mutations are specific to a patient and the patient's family members, and different mutations are usually identified in unrelated HCM families [47]. Therefore, identifying the mutation in HCM patients requires screening for all disease-causing genes, which also requires extensive time and cost. With recently developed high-throughput DNA sequencing technologies, comprehensive genetic diagnosis in HCM may now be available [50].

Genetic testing provides opportunities to assess the relevance of the genotype in the phenotype of HCM, and numerous genotype–phenotype correlations have been identified from family studies. Clinical manifestations of HCM caused by TNNT2 gene mutations often begin near adolescence, while MYBPC3 gene mutations typically trigger HCM in middle age [47, 51]. We recently demonstrated that MYBPC3 mutation carriers developed left

Table 1 List of disease-causing gene mutations associated with hypertrophic cardiomyopathy

Classification	Protein	Gene
Sarcomere thick filament	Beta-myosin heavy chain	*MYH7*
	Regulatory myosin light chain	*MYL2*
	Essential myosin light chain	*MYL3*
	Beta-myosin heavy chain	*MYH6*
	Titin	*TTN*
Sarcomere thin filament	Cardiac troponin T	*TNNT2*
	Cardiac troponin I	*TNNI3*
	Cardiac troponin C	*TNNC1*
	Alpha-tropomyosin	*TPM1*
	Alpha-cardiac actin	*ACTC*
Intermediate filament	Cardiac myosin-binding protein C	*MYBPC3*
Z-disc	Alpha actinin 2	*ACTN2*
	Myozenin 2	*MYOZ2*
	Muscle LIM protein	*CSRP3*
	Telethonin	*TCAP*
	Vinculin/metavinculin	*VCL*
Calcium handling	Junctophilin 2	*JPH2*

ventricular systolic dysfunction less frequently than non-MYBPC3 mutation carriers [52].

Several studies have indicated that genetic modifiers such as polymorphisms in the renin–angiotensin–aldosterone system genes may influence the extent of left ventricular mass or left ventricular function, which could in part explain a wide spectrum of clinical expression in HCM [53]. Furthermore, HCM patients who carry more than one independent mutation may be at a higher risk for adverse clinical courses, which include development of advanced heart failure with left ventricular systolic dysfunction [54–56] (Fig. 2). Additionally, gender may have some influence on the development of ventricular hypertrophy in HCM. Because HCM is inherited in an autosomal dominant pattern, an equal ratio of males to females would be anticipated. However, previous reports of HCM cohorts have demonstrated a male predominance, with approximately 55–60 % of HCM probands [57]. It has been postulated that chromosomal or hormonal-specific factors and gender-specific single-nucleotide polymorphisms may influence the pathogenesis of hypertrophy development, which was observed in animal models [57, 58]. Although genotype–phenotype correlations may not be applied to therapy for HCM, one clinical advantage of genetic testing is gene-based preclinical diagnosis of the condition [59]. Prior to the development of genetic testing, clinicians were not able to predict whether young family members without ventricular hypertrophy would develop HCM later in life. With genetic testing, preclinical mutation carriers and non-carriers can be distinguished, which provides a relief for non-carriers and may contribute to better clinical management for the carriers [60–62].

Identification of disease-causing mutations enables researchers to generate genetically engineered animal models that harbor human HCM mutations [4, 63, 64]. From the studies of HCM animal as well as cellular models [65], molecular pathways such as transforming growth factor-beta1/Smads signals that trigger ventricular hypertrophy, fibrosis, and remodeling have been revealed [66], which could provide future therapeutic targets. There exists indirect evidence that the nonpeptide AVE0991 might attenuate myocardial hypertrophy as induced by angiotensin II through down-regulation of transforming growth factor-beta1/Smad2 expression [67]. Thus, genetic testing in HCM may contribute to gene-based accurate diagnosis, identifying "malignant" mutations in specific patients, and preclinical diagnosis in subjects who do not exhibit ventricular hypertrophy, although the clinical course of each HCM patient may not be predicted based solely on genotype.

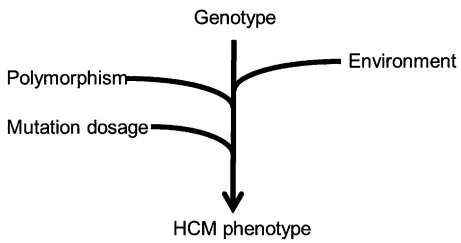

Fig. 2 Modifying factors of hypertrophic cardiomyopathy (HCM) phenotypes. Certain sarcomere gene mutations may be associated with malignant clinical courses. Polymorphisms in the renin–angiotensin–aldosterone system genes may influence HCM phenotypes. Furthermore, HCM patients who carry more than one independent mutation may exhibit severe phenotypes

Inherited cardiac arrhythmia syndrome

A line of evidence demonstrated that inherited tachycardia or bradycardia diseases are associated with monogenic gene mutations [68, 69]. LQTS is characterized by prolonged ventricular repolarization and a propensity for life-threatening ventricular tachyarrhythmias, typically torsades de pointes, resulting in syncopal attacks and sudden death [70]. Before puberty, boys with LQTS are at three to fourfold higher risk for cardiac events including syncope, aborted cardiac arrest (ACA), or SCD compared with respective females [71, 72]. In contrast, adult women in the range of 18–40 years have a significant 2.7-fold increase in the risk of ACA or SCD as compared with men [73]. LQTS can be subclassified into congenital and acquired forms. Genetic testing can identify a mutation in 50–75 % of clinically affected patients with congenital LQTS (cLQTS) [74–76], as well as some patients with acquired LQTS (aLQTS) [77–80]. Thirteen genetic forms of LQTS have been described, and the most prevalent forms are LQT1 and LQT2 associated with mutations in potassium channels, and LQT3 with a sodium channel mutation [68, 81–83] (Table 2).

The KCNQ1 and KCNE1, which are also expressed in the experimental animal such as a swine [84] genes encode the α and the β subunit, respectively, of the potassium channel conducting the IKs current underlying the LQT1 and LQT5 forms. The AKAP-9 encoding Yotiao, which assembles KCNQ1, was reported to be linked to the LQT11 form. The KCNH2 and the KCNE2 genes encode the α and the β subunit, respectively, of the potassium channel conducting the IKr current underlying the LQT2 and LQT6 forms [85]. Interestingly, there exists LQTS caused by a KCNQ1 mutation associated with left ventricular non-compaction [86].

The KCNJ2 gene encodes the inward rectifier potassium current (IK1) underlying Andersen's syndrome (LQT7), with associated QT prolongation and ventricular arrhythmias. A mutation in KCNJ5 encoding the α-subunit of the

Table 2 Inherited cardiac arrhythmia and disease-associated genes

Subtype	Gene	Gene location	Protein	Protein function	Mutant protein phenotype
Long QT syndrome, LQTS					
LQT1	*KCNQ1*	11p15.5	Kv7.1	I_{Ks} α subunit	Loss-of-function, reduced I_{Ks}
LQT2	*KCNH2*	7q35–36	Kv11.1	I_{Kr} α subunit	Loss-of-function, reduced I_{Kr}
LQT3	*SCN5A*	3p21	Nav1.5	I_{Na} α subunit	Gain-of-function, increased persistent I_{Na}
LQT4	*ANK2*	4q25–27	Ankyrin-B	Targeting protein	Aberrant localization of ion transporters
LQT5	*KCNE1*	21q22	minK	I_{Ks} β subunit	Reduced I_{Ks}
LQT6	*KCNE2*	21q22	MiRP1	I_{Kr} β subunit	Reduced I_{Kr}
LQT7	*KCNJ2*	17q23.1–24.2	Kir2.1	I_{K1}α subunit	Loss-of-function, reduced I_{K1}
LQT8	*CACNA1C*	12p13.3	Cav1.2	I_{CaL} α subunit	Gain-of-function, increased I_{Ca}
LQT9	*CAV3*	3p25	Caveolin-3	Caveolae coat protein	Increased persistent I_{Na}
LQT10	*SCN4B*	11q23	Nav beta4	I_{Na} β subunit	Increased persistent I_{Na}
LQT11	*AKAP9*	7q21–22	Yotiao	Adaptor molecule	Reduced I_{Ks}
LQT12	*SNTA1*	20q11.2	Alpha1-syntrophin	Membrane molecule	Increased persistent I_{Na}
LQT13	*KCNJ5*	11q23.3–24.3	Kir3.4	I_{KACh}	Reduced $I_{K,\ ACh}$
Short QT syndrome, SQTS					
SQT1	*KCNH2*	7q35–36	Kv11.1	I_{Kr} α subunit	Gain-of-function, increased I_{Kr}
SQT2	*KCNQ1*	11p15.5	Kv7.1	I_{Ks} α subunit	Gain-of-function, increased I_{Ks}
SQT3	*KCNJ2*	17q23.1–q24.2	Kir2.1	I_{K1} α subunit	Gain-of-function, increased I_{K1}
SQT4	*CACNA1C*	12p13.3	Cav1.2	I_{CaL} α subunit	Loss-of-function, reduced I_{Ca}
SQT5	*CACNB2b*	10p12.33	I_{CaL} beta2	I_{CaL} β subunit	Loss-of-function, reduced I_{Ca}
Brugada syndrome, BrS					
BrS1	*SCN5A*	3p21	Nav1.5	I_{Na} α subunit	Loss-of-function, reduced I_{Na}
BrS2	*GPD1-L*	3p24	G3PD1L	Glycerol-3-phosphate dehydrogenase	Reduced I_{Na}
BrS3	*CACNA1C*	12p13.3	Cav1.2	I_{CaL} α subunit	Loss-of-function, reduced I_{Ca}
BrS4	*CACNB2b*	10p12.33	I_{CaL} β2b	I_{CaL} β2 subunit	Loss-of-function, reduced I_{Ca}
BrS5	*SCN1B*	19q13.1	Nav β1	I_{Na} β subunit	Reduced I_{Na}
BrS6	*KCNE3*	11q13-q14	MiRP2	I_{Ks} and I_{to} β subunit	Increased I_{to}
BrS7	*SCN3B*	11q23.3	Nav beta3	I_{Na} β subunit	Reduced I_{Na}
NC	*HCN4*	15q24.1	HCN4	I_f α subunit	Gain-of-function, increased I_f
NC	*CACNA2D1*	7q21-q22	Cavα2δ	I_{CaL} α2δ subunit	Loss-of-function, reduced I_{Ca}
NC	*MOG1*	17p13.1	MOG1	RNA guanine nucleotide release factor	Reduced I_{Na}
NC	*KCND3*	1p13.3	Kv4.3	I_{to} α subunit	Gain-of-function, increased I_{to}
NC	*KCNE5*	Xq22.3	KCNE1L	K^+ voltage-gated channel auxiliary subunit	Increased I_{to}
NC	*KCNJ8*	12p12.1	Kir6.1	$I_{K,\ ATP}$ α subunit	Gain-of-function, increased $I_{K,\ ATP}$
NC	*SCN1Bb*	19q13.1–q13.2	Navβ1B	I_{Na} β subunit	Reduced I_{Na} and increased I_{to}
NC	*SLMAP*	3p21.2–p14.3	SLMAP	Sarcolemmal membrane-associated protein	Reduced I_{Na}
Catecholaminergic polymorphic ventricular tachycardia, CPVT					
CPVT1	*RYR2*	1q42.1	RyR2α	Cardiac ryanodine receptor	Diastolic calcium release
CPVT2	*CASQ2*	1p13.3–p11	Calsequestrin	Cardiac calsequestrin	Loss-of-function, reduced I_{Ca}
NC	*KCNJ2*	17q23.1–q24.2	Kir2.1	I_{K1} α subunit	Loss-of-function, reduced I_{K1}
NC	*TRDN*	6q22	Triadin	Anchoring calsequestrin to RYR2	Impaired regulation of SR Ca^{2+} release
NC	*CALM1*	14q32.11	Calmodulin 1	Calcium-modulated protein	Compromised calcium binding

NC no consensus

acetylcholine-sensitive potassium current (IK-ACh) channel was reported to be responsible for LQT13.

The SCN5A gene encodes the protein of the cardiac sodium channel underlying the LQT3 form [87] (Fig. 3). The CAV3 encoding caveolin-3 and SCN4B encoding Navβ4, an auxiliary subunit of the cardiac sodium channel, are also reported to be associated with the LQT9 and LQT10 forms. The SNTA1 encoding a cytoskeletal protein syntrophin-α1 interacts with the cardiac sodium channel underlying the LQT12 form. A mutation in the CACNA1C gene results in an increase in Cav1.2 current, QT prolongation, and a phenotype that is characterized by syndactyly in both hands and feet and multiorgan dysfunction (Timothy's syndrome) (Fig. 3). LQT4 is caused by mutations in the ankyrin B gene that produces a protein that functions as a membrane of versatile membrane adapters.

Life-threatening cardiac events tend to occur under specific circumstances in a gene-specific manner. Syncope or sudden death in LQT1 patients is triggered by emotional or physical stress such as diving and swimming. LQT1 patients tend to have an optimal response to β-blockers compared to another forms of LQTS. Interestingly, C-loop missense mutations in the KCNQ1 channel present a high risk for life-threatening events and have a pronounced benefit of treatment with β-blockades [88]. It is known that effectiveness is not equal for different β-blockers. A recent study shows that propranolol has a significantly better QTc-shortening effect compared to metoprolol and nadolol [89]. In addition, symptomatic LQTS patients treated with metoprolol are four times more likely to have breakthrough cardiac events than those treated with propranolol and nadolol [89]. Emotion and noise have been noted to cause cardiac symptoms more frequently in LQT2. LQT2 patients are particularly sensitive to sudden noise, such as a telephone or alarm clock ring, but β-blockers have been found to reduce cardiac events in patients with LQT2. Increased extracellular potassium concentration has been reported to shorten the QT interval in LQT2 patients. Patients with LQT3 have the highest risk of events when at rest or asleep and a relatively low risk of events during arousal. Sodium-channel blockers such as mexiletine may normalize the QTc interval in patients with LQT3.

Disease penetrance is low (= 25 %) in some families with cLQTS [90], and QT duration appears normal in about 30 % of LQTS mutation carriers [91]. Electrophysiological studies to date show that channel function varies with different mutations and mutation sites. The pore region of the hERG channel, which was encoded by the KCNH2 gene, provides an aqueous pathway for potassium ions. Most mutations involving this region are missense mutations with dominant-negative effects on IKr, and subjects with pore mutations exhibit a severe clinical course. In contrast, most mutations in the non-pore region of the KCNH2 gene are known to not exhibit dominant-negative effects, resulting in mild clinical phenotypes [92]. However, we recently identified a novel mutation of KCNH2 T473P in the non-pore region in patients with the congenital or acquired form of LQTS, which result in protein trafficking defects and exhibit dominant negative effects with severe phenotype [93]. These mutations seem to be concentrated in the region between S2 and S2-S3 linker of the hERG channel and may cause severe clinical course in affected patients [94]. In patients with LQTS caused by a mutation leading to mild dysfunction of a cardiac ion channel, marked QT prolongation or torsade de pointes may appear only upon the addition of a stressor such as a drug, or under conditions such as hypokalemia or bradycardia [95]. Up to 40 % of aLQTS patients with torsades de pointes carry mutations in KCNQ1, KCNH2, KCNE1, KCNE2, KCNE3, and SCN5A [77–80].

Previous study reported that the K^+ channel regulator 1 (KCR1) protected KCNH2 current from drug block [96, 97]. Another study showed that the I447 V variant of KCR1 occurred less frequently in patients with drug-induced torsade de pointes compared to controls, and this variant was more effective at protecting KCNH2 against dofetilide inhibition in a heterologous expression study [98]. We identified a KCR1 genetic variant (E33D) in a patient who suffered ventricular fibrillation and QT prolongation; this variant diminished the ability of KCR1 to protect KCNH2 from inhibition by commonly used therapeutic agents and constitutes a risk factor for aLQTS [99] (Fig. 3).

Congenital short QT syndrome (SQT) is a hereditary disease characterized by a shorter than normal QT interval (< 350 ms), ventricular and atrial arrhythmias, and SCD [100, 101]. Some patients with SQTS develop lethal arrhythmias within the first year of life, and this syndrome is thought to be one of the causes of sudden infant death syndrome. Five ion channel genes were reported to be responsible for SQTS [102] (Table 2). In heterologous expression systems, mutations in KCNH2 (SQT1), KCNQ1 (SQT2), and KCNJ2 (SQT3) genes showed an increase in the potassium currents involved, resulting in short QT intervals. In contrast, mutations in the CACNA1C (SQT4) and CACNB2b (SQT5) showed loss of function of Calcium channels [102].

Brugada syndrome (BrS) is a channelopathy associated with conduction delay and ST-segment elevation of the right precordial leads with or without right bundle branch block in the absence of structural disease, characterized by syncope and premature sudden death due to ventricular fibrillation [103]. The ECG abnormality can be manifested by administration of channel blocker or by environmental influences, including fever or large meals. BrS affects men more commonly and severely than women. Previous study

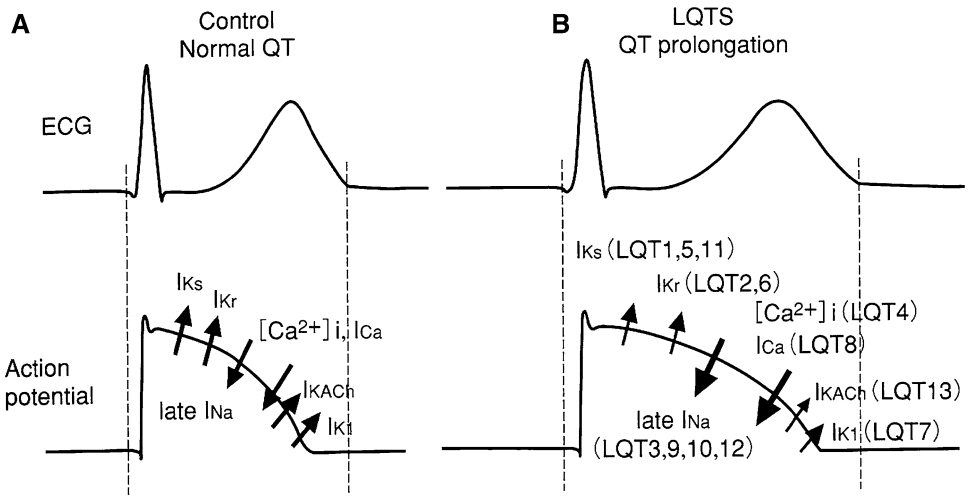

Fig. 3 Schematic illustration of ion channels related to QT formation in normal (**a**) and in QT prolongation (**b**)

for a series of 384 patients with BrS showed that men were predominant (70.8 %) and had experienced syncope or aborted SCD more frequently than woman, as well as a greater event rate in follow-up [104].

At least 15 genes were reported to be linked to BrS [81, 105–113] (Table 2). There is no consensus on the relation between BrS types 8 and higher and responsible genes, probably because some associated mutations are not universally considered pathogenic. Mutations of SCN5A are reported to account for 18–30 % of clinically diagnosed BrS patients at present, and these mutations cause loss of function in the sodium current (BrS1). Less commonly, BrS may result from mutations in CACNA1C (BrS2) and CACNB2b (BrS3) through a reduction in the L-type calcium current, or from GPD1-L (BrS4), SCN1B (BrS5), or SCN3B (BrS7) causing a loss of sodium channel function. The KCNE3 mutation identified in the BrS family reduces the inhibitory effect of KCNE3 on the Kv4.3 channel, resulting in an increase in transient outward current (BrS6). Symptomatic patients with VF or syncope had higher recurrence rates of cardiac events compared to asymptomatic patients [114, 115], and therefore the symptomatic patients should be considered to receive an ICD for secondary and primary prevention of SCD. Risk stratification in asymptomatic patients is still controversial. Recent studies showed that a family history of SCD and the presence of early repolarization were predictors of a poor outcome in this patient group [115, 116].

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a familial disease characterized by stress-induced ventricular arrhythmias that result in syncope and sudden death in children or young adults [117]. The resting ECG is unremarkable: therefore, the diagnosis is mostly based on symptoms and on the detection of stress-induced arrhythmias during exercise stress test or continuous ECG recording. Three genes were reported to be responsible for CPVT. Mutations in the RYR2 gene, encoding the cardiac ryanodine receptor, account for autosomal dominant disease [118, 119]. In addition, mutations in the cardiac calsequestrin gene CASQ2 account for a small number of autosomal recessive cases [120]. In addition, mutations in KCNJ2 associated with Anderson syndrome, TRDN encoding triadin, which links RYR2 with calsequestrin, or CALM1, encoding the calcium-modulated protein calmodulin 1 may underlie the minority of cases [121–123] (Table 2). Under these conditions, calcium channel inhibition by verapamil rectified abnormal calcium handling in CPVT myocytes and prevented ventricular arrhythmias [124], however, the effect of verapamil is still controversial. Recent studies showed that flecainide reduced exercise-induced ventricular arrhythmias in patients with CPVT not controlled by conventional drug therapy [125, 126]. Therefore, flecainide in addition to β-blocker therapy including carvedilol should be considered for these CPVT patients.

Recently, fibroblasts derived from patients with LQTS were reprogrammed and the induced pluripotent stem (iPS) cells were directed to differentiate into cardiac myocytes. The patient-derived cells showed the electrophysiological properties of the disorder [127, 128]. Application of iPS cell-derived cardiomyocytes to study inherited cardiovascular diseases will enable us to understand the molecular mechanisms of human disease in more detail, although it is still controversial whether iPS cell-derived cells can represent mature ones in terms of channel expression [129].

Conclusions

We reviewed the current perspectives in cardiovascular genetic diseases such as FH, HCM, and hereditary arrhythmic syndrome, all of which are major fields of

cardiovascular research. Functional analysis of disease-causing gene mutations will give us new insight into the mechanism of each disease, while development of newer technology for gene analysis may identify additional novel gene mutations.

Conflict of interest None.

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