



The Genetics and Epigenetics of Ventricular Arrhythmias in Patients Without Structural Heart Disease

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Ventricular arrhythmia without structural heart disease is an arrhythmic disorder that occurs in structurally normal heart and no transient or reversible arrhythmia factors, such as electrolyte disorders and myocardial ischemia. Ventricular arrhythmias without structural heart disease can be induced by multiple factors, including genetics and environment, which involve different genetic and epigenetic regulation. Familial genetic analysis reveals that cardiac ion-channel disorder and dysfunctional calcium handling are two major causes of this type of heart disease. Genome-wide association studies have identified some genetic susceptibility loci associated with ventricular tachycardia and ventricular fibrillation, yet relatively few loci associated with no structural heart disease. The effects of epigenetics on the ventricular arrhythmias susceptibility genes, involving non-coding RNAs, DNA methylation and other regulatory mechanisms, are gradually being revealed. This article aims to review the knowledge of ventricular arrhythmia without structural heart disease in genetics, and summarizes the current state of epigenetic regulation.

Keywords: gene, pathogenesis, non-structural ventricular arrhythmias with genome, ventricular arrhythmias, non-structural heart disease

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INTRODUCTION

The vast majority of ventricular arrhythmias occurs in structurally diseased hearts, however, a proportion of patients with ventricular tachycardia is free of cardiac structure alterations (1). Ventricular arrhythmias without structural heart disease mainly includes monomorphic ventricular tachycardia classified by location of origin, polymorphic ventricular tachycardia dominated by primary hereditary arrhythmia syndrome, and ventricular fibrillation, i.e., Brugada syndrome (BrS), congenital long QT syndrome (LQTS), short QT syndrome (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) (2, 3). The clinical presentations vary, including palpitations, vertigo, syncope, seizure-like activity and sudden cardiac death. There is no obvious cardiac structural change in patients without structural heart disease, but it may also be due to the lack of detection of pathological changes in the existing technology or focal lesions in the heart. Especially in BrS, structural abnormality has also become one of the pathogenesis, however, due to the restrictions on the acquisition of human samples, structural detection is mostly carried out in patients with severe symptoms. The prominent role of genetics in the pathogenesis of the disease remains of interest (4, 5). With the development of detection technology, we may gain a greater understanding of the mechanisms involved in this disease.

The heart has a set of well-established electrical conduction systems, and the tissues and cells coordinate with each other to make the heart contract and relax in an orderly way, and pump blood

to all parts of the body. The action potential (AP) of human ventricular myocytes is composed of depolarization and repolarization, and is subdivided into five stages, 0 and 1, 2, 3, 4 (6). The flow balance of potassium, sodium, calcium and other ions is essential for the normal beating of the heart. Cardiomyocyte depolarization induced by electrotonic coupling between adjacent cardiomyocytes drives phase 0 initiation, the sodium channel is activated, the sodium ion enters the membrane rapidly, resulting in depolarization (phase 0) (7). Subsequently, Majority of sodium channels are rapidly inactivated and L-type calcium channels are activated. At the same time, the repolarization current generated by potassium channels and $\text{Na}^+/\text{Ca}^{2+}$ exchangers, namely the instantaneous outward potassium current (I_{to}) and outward I_{NCX} reduce the membrane potential (phase 1) (8). the sodium current of slowly inactivated sodium channels, mostly inactive calcium channels current ($I_{\text{Ca,L}}$) and the sodium-potassium exchanger current operating in forward mode reach a balance with delayed rectifier potassium current (I_{K}), forming a plateau phase on ECG (phase 2). While the action potential occurs, the influx of calcium ions triggers a further release of calcium ions from the sarcoplasmic reticulum, resulting in intracellular concentration transient elevation, causing muscle contraction, namely cardiac excitation-contraction (E-C) coupling (9). Subsequently, the calcium ion channel is gradually inactivated. The ion current at this time is mainly the outward current of I_{K} and I_{K1} , and the more negative the intramembrane potential, the more rapid efflux of the potassium ion, which leads to the acceleration of the repolarization until the repolarization is completed (phase 3). The potential is stable at the resting potential level, and the ion pump pumps out the ions pumped into the cell during the action potential. The Na^+/K^+ pump can pump the Na^+ in the cell out of the cell and pump K^+ into the cell at the same time. Intracellular Ca^{2+} is transported extracellular via the $\text{Na}^+/\text{Ca}^{2+}$ exchanger and the Ca^{2+} pump (phase 4) (10). The abnormality caused by the mutation of ion channel protein coding gene will cause the disorder of electrical signal.

Triggered activity, abnormal automaticity, and re-entry are the three mechanisms of ventricular arrhythmias, in ventricular arrhythmias without structural heart disease, usually due to trigger activity (3). Triggered activity that occurs in phase 2 and early phase 3 is called early afterdepolarization (EAD), in late phase 3 and phase 4 are called delayed after-depolarization (DAD) (11). The trigger activity is generated by the membrane depolarisation induced by the I_{NCX} and/or $I_{\text{Ca,L}}$ (12, 13). Automaticity refers to the spontaneous depolarization of phase 4 membrane potential of the cells with pacemaking function, and the action potential is generated after reaching the threshold potential. Abnormal automaticity is attributed to decreased I_{K1} and/or enhanced I_{f} (mainly slow inward sodium current, causing automatic membrane depolarization) (14). Once I_{K1} is inhibited, the membrane potential cannot reach the resting potential, which may lead to the generation of abnormal inward currents, such as I_{f} , causing abnormal automaticity. Re-entry refers to a cardiac impulse that repeatedly runs and activates the cardiac muscle surrounding around the center of anatomical or functional disorders, usually the pathogenesis of structural

ventricular arrhythmias, but specific arrhythmias induced by EAD (Torsades de Pointes in LQTS) or DAD (bidirectional ventricular tachycardia in CPVT) may be caused by re-entry involving fascicles of the Purkinje system (3).

In respect to etiology, ventricular arrhythmias in patients without structural heart disease are mostly due to ion channel disorders, including various inherited arrhythmia syndromes and ventricular arrhythmias caused by unknown causes. Besides genetic studies in classical, the effects of epigenetics on ventricular arrhythmias are also being explored, which makes this part that is not yet understood gradually revealed. We searched the PubMed database using the terms “idiopathic ventricular arrhythmias”, “genetics”, “epigenetics”, and “DNA methylation” up to 2021 for articles on ventricular arrhythmias and present the genetics and epigenetics of ventricular arrhythmias in non-structural heart disease in this review. **Table 1** is a brief description.

GENETIC FACTORS OF VENTRICULAR ARRHYTHMIAS WITHOUT STRUCTURAL HEART DISEASE

The advancement of genetic technology has brought a deeper understanding of the genetic factors of the disease. It is a common Mendelian genetic phenomenon that a rare variant of a single gene has a significant impact on protein function and causes disease. However, the incomplete penetrance in the family and the frequency of pathogenic mutations in the normal population have begun to make people think that disease is not only caused by the mutation of a certain gene locus, but that the cumulative pattern of multi-site interaction can also cause the occurrence of disease. Here, we discussed the single-gene and multi-gene factors that cause ventricular arrhythmias and summarized the single gene factors in **Table 2**.

Monogenic Factors Sodium Ion Channels

Mutations in the gene encoding voltage-gated sodium channels can disrupt sodium channels, cause abnormal sodium current flow and trigger ventricular arrhythmias, due to the significant role of voltage-gated sodium channels in action potentials (15). Alterations in sodium current can cause several types of cardiac disease, including LQTS, BrS, isolated (progressive) conduction defect, atrial fibrillation, sick sinus syndrome, dilated cardiomyopathy and multifocal ectopic premature Purkinje-related complexes (15). In ventricular arrhythmias without structural heart disease, enhanced sodium currents are usually associated with LQTS, whereas diminished sodium currents are associated with BrS (15, 83). Several sodium channel-related pathogenic genes have been identified in ventricular arrhythmias without structural heart disease, including SCN5A, SCN1B, SCN2B, SCN3B, SCN4B, GPD1L, RANGRE, SCN10A, among which SCN5A is the most reported (**Table 2**). SCN5A encodes $\text{Na}_v1.5$, which is the alpha subunit of voltage-gated sodium channels. As the main functional subunit of sodium ion channels, it provides activity for the channel. $\text{Na}_v1.5$ is responsible for the

TABLE 1 | A brief description of the genetics and epigenetics of ventricular arrhythmias in non-structural heart disease.

	Causative factor	Description	References
Genetics	Monogenic factors	Among the monogenic causative factors, mutations in the sodium channel-encoding gene SCN5A, the potassium channel-encoding genes KCNQ1 and KCNH2, and the calcium channel-encoding gene RYR2 cause the majority of ventricular arrhythmias, while some cases are caused by rare variants in other ion channel and structural genes. In addition, the role of somatic mutations has been identified.	(15–18)
	Polygenic factors	The importance of polygenic factors for ventricular arrhythmias is highlighted by the heterogeneity of causative genes across patients with ventricular arrhythmias and the impact of the accumulation of mutations in multiple genes on the severity of the clinical phenotype. The concept of genetic modifier has been proposed and a recent GWAS analysis validated the link between cumulative mutational effects and the BrS clinical phenotype.	(19–22)
Epigenetics	Non-coding RNA	The research on ventricular arrhythmias without structural heart disease mainly focuses on the regulation of miRNAs on the transcription of genes encoding ion channels such as SCN5A and SCN1B. Circular RNA may serve as a marker for disease progression.	(23–25)
	DNA methylation	DNA methylation usually plays a repressive role in gene transcription. For example, SCN5A promoter hypermethylation levels enhance SCN5A expression in cardiac tissue. In addition, it plays an important regulatory role in gene imprinting.	(26, 27)
	Histone modifications	Histone modifications in the heart have mostly been studied for methylation and acetylation, which are linked to gene transcriptional activation or repression and may play a role in the formation of transmural electrophysiological gradients in the ventricle.	(28–30)
	Genomic imprinting	The methylation level of the long non-coding RNA KCNQ1OT1, which is related to a prolonged QTc interval, affects the expression of the imprinted gene KCNQ1 and may contribute to female predominance and transmission distortion in LQTS.	(31–33)
	Three-dimensional (3D) genome architecture	The ordered chromatin spatial structure allows interactions between functional elements within the topological domains to regulate gene transcription, such as the interaction of enhancers with promoters. The 3D genome architecture study offers a fresh look at the link between SNPs and ventricular arrhythmias discovered by GWAS.	(34–37)

influx of sodium ions and plays a major role during membrane depolarization, as well as the sodium current in the repolarization and refractory period. SCN5A Mutation can be divided into gain-of-function and loss-of-function mutation, leading to an increase or decrease in sodium ion influx and an acceleration or delay in channel inactivation, responsible for about 5–10% of LQTS patients and ~30% of patients with BrS, respectively (15, 16).

In addition to Nav1.5 that directly affects sodium currents, some proteins can achieve indirect regulation of sodium currents by modulating Nav1.5, have been associated with BrS and LQTS. although their clinical relevance may be limited. SCN1B, SCN2B, and SCN3B encode voltage-gated sodium channel β subunits. Mutations can decrease Nav1.5 cell surface expression and reduce sodium current, leading to BrS (38, 39, 41). SCN4B also encodes sodium channel β subunit, can cause LQTS in a minority of cases. Consistent with the molecular/electrophysiological phenotype previously displayed by LQTS, compared to wild type, the mutation L179F of SCN4B leads to an increase of late sodium current (42). GPD1L is SCN5A regulatory proteins, links redox state to cardiac excitability by PKC-dependent phosphorylation of the sodium channel (84). The GPD1L A280V mutation reduces SCN5A membrane expression, decreases inward Na⁺ current, leading to BrS (43). RANGRF (MOG1) is a co-factor of Nav1.5, which plays a potential role in the regulation of Nav1.5 expressions and trafficking. The dominant-negative mutations in RANGRF can disrupt the transport of Nav1.5 to the membrane, resulting in a reduction of I_{Na} and causing clinical manifestations

of BrS. Silencing RANGRF can reduce I_{Na} density, in addition, replacing E83D, D148Q, R150Q, and S151Q could disrupt the interaction of RANGRF with Nav1.5 and significantly impair the trafficking of Nav1.5 to the cell surface, indicating that RANGRF may play an important role in the expression of Nav1.5 channel on the cell surface (44, 45). SCN10A encodes Nav1.8, a voltage-gated sodium channel like Nav1.5. Both SCN10A and SCN5A are located on chromosome 3p22.2. Co-expression of SCN10A-WT and SCN5A can increase sodium channel current, while SCN10A mutants (R14L and R1268Q) can cause loss of Nav1.5 current function, which may be the genetic basis of BrS caused by SCN10A. However, most of the mutations associated with SCN10A are not rare variants, are relatively frequent in the population (46).

Potassium Ion Channels

The potassium ion currents associated with ventricular arrhythmias include transient outward potassium current (I_{to}), delayed rectifier potassium current (I_K), inward rectifier K⁺ current (I_{K1}), and hyperpolarization-activated currents (I_h). Dysfunction of potassium ion channels can also cause changes in ion balance, causing arrhythmia (Table 2).

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are responsible for pacing current in neurons and cardiomyocytes, in which HCN4 encode a member of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels showing slow activation and inactivation kinetics and

TABLE 2 | Genes associated with ventricular arrhythmias in non-structural heart disease.

Gene	Protein (UniProtKB)	Aliases	Functional effect	Symptom	Frequency, %	References
Sodium channel-related genes						
SCN5A	Sodium channel protein type 5 subunit alpha	Nav1.5/LQT3/VF1	$I_{Na} \uparrow$	LQTS	5–10%	(15)
			$I_{Na} \downarrow$	BrS	20–25%	(15)
SCN1B	Sodium channel subunit beta-1		$I_{Na} \downarrow$	BrS	Rare	(38)
SCN2B	Sodium channel subunit beta-2		$I_{Na} \downarrow$	BrS	Rare	(39, 40)
SCN3B	Sodium channel subunit beta-3		$I_{Na} \downarrow$	BrS	Rare	(41)
SCN4B	Sodium channel subunit beta-4	LQT10	$I_{Na} \uparrow$	LQTS	Rare	(42)
GPD1L	Glycerol-3-phosphate dehydrogenase 1-like protein	GPD1-L	$I_{Na} \downarrow$	BrS	Rare	(43)
RANGRF	Ran guanine nucleotide release factor	RANGNRF/MOG1	$I_{Na} \downarrow$	BrS	Rare	(44, 45)
SCN10A	Sodium channel protein type 10 subunit alpha	Nav1.8	$I_{Na} \downarrow$	BrS	~10%	(46)
Potassium channel-related genes						
<i>Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels</i>						
HCN4	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4		$I_f \downarrow$	IVT	Rare	(47)
<i>transient outward potassium current channels</i>						
KCND3	Potassium voltage-gated channel subfamily D member 3	Kv4.3	$I_{to} \uparrow$	BrS	Rare	(48)
KCNE3	Potassium voltage-gated channel subfamily E member 3	MIRP2/HOKPP	$I_{to} \uparrow$	BrS	Rare	(49)
KCNE5	Potassium voltage-gated channel subfamily E regulatory beta subunit 5	MIRP4	$I_{to} \uparrow$	BrS	Rare	(50)
<i>Slowly activating delayed rectifier potassium current channels</i>						
KCNQ1	Potassium voltage-gated channel subfamily KQT member 1	KVLQT1/Kv7.1/LQT1	$I_{Kr} \downarrow$	LQTS	30–35%	(51)
			$I_{Kr} \uparrow$	SQTS	Unknown	(52)
KCNE1	Potassium voltage-gated channel subfamily E member 1	MinK 2/LQT5	$I_{Kr} \downarrow$	LQTS	Rare	(53)
<i>Rapidly activating delayed rectifier potassium current channels</i>						
KCNH2	Potassium voltage-gated channel subfamily H member 2	HERG/Kv11.1/ERG-1/LQT2	$I_{Kr} \downarrow$	LQTS	25–30%	(54)
			$I_{Kr} \uparrow$	SQTS	Unknown	(55)
KCNE2	Potassium voltage-gated channel subfamily E member 2	MIRP1/LQT6	$I_{Kr} \downarrow$	LQTS	Rare	(56)
<i>Inwardly rectifying potassium (Kir) channels</i>						
Inwardly rectifying potassium channels						
KCNJ2	Inward rectifier potassium channel 2	Kir2.1/LQT7	$I_{K1} \uparrow$	SQTS	Unknown	(57)
			$I_{K1} \downarrow$	LQTS	Rare	(58)
G protein-coupled, inwardly rectifying potassium channels						
KCNJ5	G protein-activated inward rectifier potassium channel 4	Kir3.4/GIRK4/LQT13	$I_{KACH} \downarrow$	LQTS	Rare	(59)
ATP-sensitive potassium channels						
KCNJ8	ATP-sensitive inward rectifier potassium channel 8	Kir6.1	$I_{K-ATP} \uparrow$	BrS	Rare	(60)
ABCC9	ATP-binding cassette sub-family C member 9	SUR2	$I_{K-ATP} \uparrow$	BrS	Rare	(61)
Calcium channel-related genes						
CACNA1C	Voltage-dependent L-type calcium channel subunit alpha-1C	Cav1.2/LQT8	$I_{Ca,L} \uparrow$	LQTS	1–2%	(62)
			$I_{Ca,L} \downarrow$	BrS	1–2%	(63)

(Continued)

TABLE 2 | Continued

Gene	Protein (UniProtKB)	Aliases	Functional effect	Symptom	Frequency, %	References
CACNB2	Voltage-dependent L-type calcium channel subunit beta-2	CACNLB2	$I_{Ca,L} \downarrow$	BrS	1–2%	(63)
CACNA2D1	Voltage-dependent calcium channel subunit alpha-2/delta-1	CACNL2A	$I_{Ca,L} \downarrow$	BrS	Rare	(64)
RYR2	Ryanodine receptor 2	ARVC2/ARVD2	Aberrant calcium handling	CPVT	55–60%	(65)
			Aberrant calcium handling	IVF	Rare	(66)
CASQ2	Calsequestrin-2		Aberrant calcium handling	CPVT	<5%	(67)
TRDN	Triadin	TDN/TRISK/CPVT5	Aberrant calcium handling	CPVT	1–2%	(68)
CALM1~3	Calmodulin-1~3	CaMII/CaMIII/CaMIII	$I_{Ca,L} \uparrow$	LQTS	1–2%	(69)
			$I_{Ca,L} \uparrow$	LQTS	Rare	(70)
			Aberrant calcium handling	CPVT	Rare	(70)
Other related genes						
SNTA1	Alpha-1-syntrophin	LQT12/SNT1	$I_{Na} \uparrow$	LQTS	Rare	(71)
SLMAP	Sarcolemmal membrane-associated protein	SLAP	$I_{Na} \downarrow$	BrS	Rare	(72)
PKP2	Plakophilin-2	ARVD9	$I_{Na} \downarrow$	BrS	Rare	(73)
ANK2	Ankyrin-2	LQT4	Abnormal coordination of multiple functionally related ion channels and transporters	LQTS	Rare	(74)
CAV3	Caveolin-3		$I_{Na} \uparrow$, $I_{Ca,L} \uparrow$, $I_{K} \downarrow$, $I_{to} \downarrow$	LQTS	Rare	(75)
TECRL	Trans-2,3-enoyl-CoA reductase-like	TERL	Aberrant calcium handling	Mixed phenotype of CPVT and LQTS	Rare	(76)
SLC4A3	Anion exchange protein 3	AE3/SLC2C	$\Phi \uparrow$	SQTS	Unknown	(77)
TRPM4	Transient receptor potential cation channel subfamily M member 4		uncertain	BrS, LQTS	Rare	(78)
Genes specific to IVF						
DPP6	Dipeptidyl aminopeptidase-like protein 6	DPPX/DPP VI/VF2	$I_{to} \uparrow$	IVF	Unknown	(79)
IRX3	Iroquois-class homeodomain protein IRX-3	IRX-1/IRXB1	$I_{Na} \downarrow$	IVF	Unknown	(80)
Somatic mutation genes						
GNAI2	Guanine nucleotide-binding protein G(i) subunit alpha-2	GNAI2B/GIP	cAMP \uparrow	RVOT-VT	Rare	(18)
ADORA1	Adenosine receptor A1	A1AR	unknown	RVOT-VT	Rare	(81)
GNAS	Guanine nucleotide-binding protein G(s) subunit alpha isoforms short	GNAS1/NESP	$I_{Ca,L} \uparrow$	RVOT-VT	Rare	(82)

BrS, Brugada syndrome; LQTS, long QT syndrome; SQTS, short QT syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; IVF, idiopathic ventricular fibrillation; IVT, idiopathic ventricular tachycardia; RVOT-VT, right ventricular outflow tract ventricular tachycardia; \uparrow , increased and/ or enhanced; \downarrow , decreased and/ or weakened.

is the highest expressed isotype in sinoatrial node (SAN) muscle cells, necessary for cardiac pacing (85). HCN4 gene mutation was detected in patients with idiopathic ventricular arrhythmias, which resulted in the decrease of pacemaker (I_f) current (85, 86).

The repolarization of the ventricles is spatially heterogeneous, largely dependent on the gradient of potassium current, especially I_{to} (87). Under normal circumstances, the density of I_{to} in the epicardium is higher than the endocardium and the initial repolarization of the epicardium is earlier than the endocardium, generating a transmural voltage gradient that plays an important role in synchronizing repolarization (87). Gain of function of I_{to} is related to BrS. I_{to} channel is composed of α subunit and β subunit, with the α subunit $K_v4.3$ encoded by KCND3, and the negatively regulated β -subunit MiRP2 encoded by KCNE3. It is a voltage-gated, calcium-independent potassium (K_v) current that can be quickly activated and inactivated, mainly responsible for the initial repolarization phase of the cardiac action potential (88), KCND3 mutations are known to cause BrS. The mutation KCND3 Arg431His (c.1292G>A) detected in BrS patients does not affect the mRNA and total protein expression level of $K_v4.3$, but increase the membrane protein expression of $K_v4.3$ and up-regulate the transient outward potassium current (48). Besides, at the same time, KCNE3 mutation may be the basis of the development of BrS. The co-transfection of the KCNE3 gain-of-function mutation R99H with KCND3 causes a significantly increased current intensity compared to WT KCNE3+KCND3 (49). Actually, the KCNE family encodes five isotypes in the human genome. In addition to KCNE3, KCND3 can be assembled with multiple KCNE subunits, of which KCNE5 can regulate I_{to} , showing a correlation with BrS and idiopathic ventricular fibrillation (50). KCNE5 is located on the X chromosome and when coexpressed with KCND3, the brugada-associated KCNE5 mutations upregulate I_{to} compared to the wild type (50).

There are two types of delayed rectifier K^+ current, slowly activating delayed rectifier K^+ current (I_{Ks}) and rapidly activating delayed rectifier K^+ current (I_{Kr}). Its enhancement is related to SQTS, whereas weakening is related to LQTS (89). The outward K^+ current of I_{Ks} channel is one of the main repolarizing potassium currents in the human heart, which helps to terminate cardiac action potential. The channel is composed of the pore-forming α subunit encoded by KCNQ1 (also known as $K_v7.1$ or K_vLQT1) and the β subunit encoded by KCNE1 (90, 91). Cardiac KCNQ1/KCNE1 channel mutations are the most common cause of inherited long-QT syndromes (92). Loss-of-function mutations of KCNQ1 decrease I_{Ks} current density, leading to LQTS, and there are also mutations that are gain-of-function mutations increase I_{Ks} , leading to SQTS (93, 94). Mutations in KCNE1 gene cause reduced I_{Ks} current density, manifested as loss of function, which can lead to LQTS (53). However, a recent study has indicated that QTc Interval Prolongation (>460 ms) was not observed in most people carrying KCNE1 loss-of-function mutations (95). The rapidly activating delayed rectifier potassium channel is encoded by KCNH2 and KCNE2, which produces only a small outward current during membrane depolarization, however, after the membrane is repolarized, the channel quickly recovers from the inactivation state to the open state, producing a recovery current before the slow

channel deactivation. KCNH2 gene encodes the pore-forming α subunit of voltage-gated K^+ channel $K_v11.1$, commonly referred to as Herg. Approximately 90% of LQT-associated KCNH2 mutations reduced I_{Kr} by reducing $K_v11.1$, responsible for 25–30% of LQTS cases channel synthesis or trafficking (54). Gain-of-function mutations are the genetic basis of SQTS, which increase the repolarization current activated in the early stages of AP, resulting in a shortening of the action potential and the QT interval (55). KCNE2 encodes MiRP1, an auxiliary beta-subunit. Compared with the wild-type channel, the mutant HERG/MiRP1 (V65M) channel detected in LQTS patients has a shorter current inactivation time, which may reduce the I_{Kr} current density of cardiomyocytes, weakening the cardiomyocytes' ability to repolarize sudden membrane depolarization (56). It has also been reported that overexpression of wild-type KCNE2 can rescue the phenotype caused by KCNH2 mutation, facilitating the transport of $K_v11.1$ channel protein and cell surface expression, significantly increasing the mutation current (96).

Inwardly rectifying potassium (Kir) channels allow potassium ions to move more easily into rather than out of the cell. The inwardly rectifying potassium channels gene associated with ventricular arrhythmia has KCNJ2, KCNJ5, KCNJ8, and ABCC9 (Table 2). I_{K1} plays an important role in stabilizing the resting membrane potential, regulating excitability and causing the final repolarization of atrial and ventricular action potential. Like delayed rectifier potassium channel, its enhancement is related to SQTS and reduction is related to LQTS, while ATP-sensitive potassium channel current (I_{K-ATP}) enhancement will lead to BrS. One of the molecular basis is Kir2.1, which is coded by KCNJ2. Gain-of-function KCNJ2 mutations have been found in SQTS patients, resulting in increased I_{K1} , accelerated ventricular repolarization and shortened QT interval (57, 97). There are also reports in the literature that loss-of-function mutations can cause LQTS (58). Mutations in the Inwardly rectifying potassium channels Kir2.1 encoded by KCNJ2 causing loss of function are associated with a rare clinical phenotype called Andersen-Tawil syndrome (ATS), which contains pleomorphic ventricular tachycardia (98). KCNJ5 encodes Kir3.4, a subunit of the voltage-gated potassium channel, which is controlled by G proteins and combination with Kir3.1, responsible for acetylcholine-activated potassium channel current (I_{KACH}) (59). The KCNJ5 mutation results in defects in channel trafficking and a reduction in the I_{KACH} , which is considered to be the pathogenic gene of LQTS (59). ATP-sensitive potassium channel (K_{ATP}) is one kind of inwardly rectifying channel composed of the pore forming subunits and the regulatory subunits. Kir6.1 encoded by KCNJ8 and SUR2 encoded by ABCC9 are both subunits of ATP-sensitive potassium channels (99). KCNJ8 mutation can reduce the sensitivity of K_{ATP} channels to ATP, resulting in enhanced I_{K-ATP} function, which may lead to BrS (60, 100). Gain-of-function mutation of ABCC9 has also been reported as a possible pathogenic site for BrS, however, the relevance of pathogenic requires further confirmation (61).

Calcium Ion Channels

Voltage-gated L-type calcium channel (LTCC) is the main channel mediating influx of calcium ions into cells in repolarization stage, and in addition, NCX, an ion transport

protein, can mediate the exchange cycle of sodium ions and calcium ions with a coupling ratio of 3:1 (101). Calcium entering the cell through these two distinct mechanisms triggers the release of calcium from the sarcoplasmic reticulum. Voltage-gated L-type calcium channel consists of four subunits $\alpha 1$ subunit, auxiliary β subunit, $\alpha 2\delta$ subunit, and γ subunit. The four subunits of voltage-gated L-type calcium channels which are, respectively, coded by CACNA1C or CACNA1D, CACNB2, CACNA2D, and CACNG (102, 103). Among them, the mutant genes that have been reported to cause ventricular arrhythmia are CACNA1C, CACNB2, CACNA2D (**Table 2**). CACNA1C encodes $Ca_v1.2$ pore-forming $\alpha 1$ subunit. In general, the enhancement of $I_{Ca,L}$ is related to LQTS, on the contrary causes BrS. Timothy syndrome (TS), which manifests as severe LQTS and multiorgan dysfunction, is mainly caused by gain-of-function mutations located in CACNA1C alternative splicing exon 8 which leads to almost complete loss of voltage-related channel inactivation, resulting in maintained inward Ca^{2+} current, and prolonged Ca^{2+} current that delay cardiomyocyte repolarization (104–106). A few cases are caused by mutations within exon 9 and exon 38 of CACNA1C (107, 108). Gain-of-function mutations in CACNA1C at positions other than exon 8 can cause LQTS with non-Timothy syndrome symptoms (62, 109). The phenotype caused by the loss-of-function mutations of the cardiac L-type calcium channel $\alpha 1$ and $\beta 2b$ subunits is similar to calcium channel blockers, leading to reduced $I_{Ca,L}$, resulting in BrS (63, 110, 111). Subsequent studies identified CACNA2D1 as a novel BrS/SQTS susceptibility gene (64, 112). In addition, it is also reported that KCNE2 can affect $I_{Ca,L}$ by regulating $Ca_v1.2$ (113).

The main function of the sarcoplasmic reticulum (SR) is to store calcium in striated muscle. The genes involved in the release of calcium from the sarcoplasmic reticulum are RYR2, CASQ2, TRDN, CALM1, CALM2, and CALM3, which are pathogenic genes of CPVT (**Table 2**) (65, 114). Among them, TRDN, CALM1, CALM2, CALM3 mutations can also cause LQTS. RYR2 encodes ryanodine receptors (RyR2), responsible for the rapid release of calcium ions from the sarcoplasmic/endoplasmic reticulum (SR/ER) into the cytoplasm. RYR2 mutations may be either loss or gain of function and this may be related with different clinical phenotypes. Approximately 60% of patients with CPVT carry RYR2 mutations, and the main pathogenic mechanism of gain-of-function mutations is increased spontaneous RyR2 opening and pathological calcium release during diastole (17, 65, 115). The RyR2 mutation associated with idiopathic ventricular fibrillation confirmed as a loss-of-function mutation exhibiting Ca^{2+} release deficiency (66). However, a recent study identified a loss-of-function mutation D3291V, which markedly reduced luminal Ca^{2+} sensitivity, and blunted response to adrenergic stimulation, also exhibiting a CPVT phenotype (116). The relationship between gain-of-function or loss-of-function and the clinical phenotype still needs to be elucidated (117). The calsequestrin encoded by CASQ2 is a calcium-binding protein that regulates the amount of calcium released from the SR during excitation-contraction coupling by buffering the calcium in the SR (118, 119). Triadin (TRD) encoded by TRDN is located on the sarcoplasmic reticulum, forms a complex with

ryanodine receptors, calsequestrin and junctin, regulating the storage and release of calcium ions (120). Triadin anchors calsequestrin to junctional SR membrane and stabilizes the structure of Ca^{2+} release units (121). TRDN deficiency leads to significantly reduced protein levels of RyR2, calsequestrin, and junctin, impaired coupling efficiency between LTCC and RyR2, reduced SR calcium release and calcium-dependent inactivation of LTCC, resulting in defective cardiac excitation-contraction coupling (121, 122). Similarly, Triadin mutations are thought to result in reduced protein levels, which in turn increased calcium currents and prolonged cardiac action potentials, and increased spontaneous calcium release events caused by cellular and SR calcium overload, which is the basis of TRDN mutation leading to CPVT and LQTS (69, 123). CALM1~3 encodes Calmodulin, which is Ca^{2+} sensor, signal-transducing protein. Calmodulin binds to RyR2 and LTCC, plays a key role in the calcium-dependent inactivation of the L-type calcium channel $Ca_v1.2$ and the timely closure of the myocardial sarcoplasmic reticulum calcium release channel RyR2. Calcium binding to calmodulin inactivates the LTCC channel, namely calcium-dependent inactivation (124). The mutations associated with LQTS are mainly due to weakening of the combination of calmodulin and calcium, completely eliminating the calcium-dependent inactivation. On the other hand, the binding of calmodulin to RyR2 can inhibit the release of calcium from SR during diastole. Mutations associated with CPVT mainly lead to dysregulation of RyR2 calcium release (70, 125).

Others

The protein encoded by SNTA1 is a component of the $Na_v1.5$ channel macromolecular complex, interacting with the pore-forming α subunit (126). Gain-of-function SNTA1 mutations can affect $Na_v1.5$ gating kinetics, leading to the LQTS phenotype (71). SLMAP encodes the sarcolemmal associated protein located in T-tubules and sarcoplasmic reticulum. SLMAP mutation may cause BrS by regulating the intracellular transport of $Na_v1.5$ channel (72). PKP2 encodes Plakophilin-2, a desmosomal protein. Loss and/or changes in the Plakophilin-2 structure in the heart desmosomes can impair the interaction between myocardial cells and cause myocardial rupture, especially in response to mechanical stress (127). Mutations in PKP2 have been associated with BrS, and the deletion of PKP2 can lead to a decrease in sodium current and $Na_v1.5$ at the site of cell contact (73). Ankyrins bind to spectrins, connects the plasma membrane with the actin cytoskeleton, maintains mechanical strength and regulates the excitability of various cells. The ankyrin family contains three members: ankyrin-R, ankyrin-B and ankyrin-G, are encoded by ANK1, ANK2 and ANK3, respectively (128). Loss-of-function mutation (E1425G) in ankyrin-B (also known as ankyrin 2) can lead to dominant long QT arrhythmia (74, 129). CAV3 encodes a scaffold protein for the cavern in cardiomyocytes and participates in the separation of ion channels. CAV3 mutations are related to LQTS, which can prolong repolarization times by enhancing the late sodium current, enhancing the peak value of L-type calcium current, slowing down deactivation, reducing delayed rectifier potassium current and transient outward potassium current

(75). TECRL (TERL) is an oxidoreductase enzyme localized to the endoplasmic reticulum. Patients with TECRL pathogenic variants manifest a specialized mixed phenotype of CPVT and LQTS, which is an autosomal recessive disease. Functional experiments have shown that homozygous pathogenic variants can lead to reduced levels of RYR2 and CASQ2 proteins, and reduced calcium storage of sarcoplasmic reticulum and aberrant calcium handling (76).

SLC4A3 (AE3) is an electroneutral $\text{Cl}^-/\text{HCO}_3^-$ exchanger (130). Studies have found that reducing intracellular pH (pHi) could prolong QT interval; the regulation of chloride ion conductance in cardiomyocytes can also change action potential duration. In zebrafish, SLC4A3 mutations can lead to transport defects, reduce $\text{Cl}_i/\text{HCO}_3^-$ -exchange over the cell membrane, increase pHi and reduce the QT duration, which may be another development mechanism of SQTs (77). The protein encoded by TRPM4 is a transmembrane N-glycosylated ion channel, a non-selective channel activated by intracellular calcium, permeable to monovalent cations. At present, Trpm4 mutations have been detected in both BrS and LQTS cohort. Miraculously, gain-and loss-of-function variants of TRPM4 channels can cause similar phenotypes (78).

Idiopathic ventricular fibrillation is an exclusive disease that requires excluding the presence of the ventricular fibrillation substrate and specific diseases, including structural heart disease and primary arrhythmia syndrome (131). At present, most genes related to idiopathic ventricular fibrillation overlap with the pathogenic genes of hereditary ventricular arrhythmias, such as CALM1~3, RYR2, TRDN, CACNA1C, SCN5A, KCNE5 (50, 125, 132–137). However, there are also specific causative genes in the idiopathic ventricular fibrillation (138). A single-pass type II membrane protein DPP6 can promote the cell surface expression of potassium channel KCND2 and regulate its activity and gating characteristics (139–141). Haplotype analysis in both familial and sporadic cases indicated the relevance of DPP6 with idiopathic ventricular fibrillation (133, 142). Furthermore, a DPP6 mutation was detected in idiopathic ventricular fibrillation patients, which disturbs the efflux of potassium ion (79). In addition, mutations of transcription factor IRX3, specifically expressed in His bundle, have also been reported to cause idiopathic ventricular fibrillation by down-regulating SCN5A and connexin-40 mRNA (80). Although several diagnostic approaches have been proposed and pathogenic mechanisms discussed, it is far from enough for studies of idiopathic ventricular fibrillation (143). This situation may change with the development of diagnostic techniques for structural heart disease and the discovery of potential pathogenic mechanisms.

Somatic Mutations

Besides the above germline mutations, i.e., mutations carried by all cells, the effect of somatic mutations, i.e., mutations carried by only some somatic cells, on the occurrence of ventricular arrhythmias is also being investigated. Idiopathic right ventricular outflow tract ventricular tachycardia (RVOT-VT) is the most common form of ventricular arrhythmias in patients without structural heart disease. GNAI2 (f200l) and A1AR (R296C) mutations were detected in biopsy samples

collected from the origin of ventricular tachycardia in patients with adenosine insensitive RVOT tachycardia, but not in remote myocardium (18, 81). GNAI2 (F200L) increases intracellular cAMP concentrations and inhibited the inhibition of cAMP by adenosine, the effect of another mutation is unclear (81). Another study identified a cardiac somatic mutation (W234R) in GNAS (Gs-alpha, stimulatory G protein alpha-subunit) in endomyocardial biopsy samples from the origin of tachycardia in RVOT-VT patient, which was not detected in right ventricular apex biopsy samples. The mutation impairs GTP hydrolysis and increased basal intracellular cAMP levels, increasing the basal inward calcium current, and silico modeling show delayed afterdepolarizations and triggered activity (82).

Polygenic Factors

In the process of screening disease-causing genes, we often tend to pay more attention to single-gene factors, emphasizing that a gene mutation corresponds to a clinical phenotype. However, molecular genetics is developing from single-gene research to multi-gene research. The same gene mutation can give rise to multiple distinct phenotypes. The SCN5A mutation detected in a Dutch family causes two phenotypes: LQTS and BrS (144). Mutations that have been reported to be pathogenic may appear no overt phenotype when they exist in other families or individuals, in the same pedigree, mostly display incomplete clinical penetrance (145, 146). It is more common that the same phenotype is caused by a mutation in different genes, in fact, it can also be caused by the accumulation of mutations in multiple different genes, and may affect the severity of the disease. For example, the interaction between KCND3 and SCN5A, $\text{Na}_v1.5$ and $\text{K}_v4.3$ channels regulates each other's functions through trafficking and gating mechanisms (147). When screening the LQTS susceptibility gene in a Caucasian family with syncope and slightly prolonged QT interval, it was found that there is R800L mutation in SCN5A and A261V mutation in SNTA1. Family members with both mutations have the strongest clinical Phenotype (19). In a GWAS study, two significant association signals were detected in Scn10a locus (rs10428132) and near the HEY2 gene (rs9388451) in patients with BrS, and an additional signal rs11708996 was identified in SCN5A, three common variations present an unexpectedly cumulative effect on disease susceptibility. The association signal of SCN5A-SCN10A indicate that genetic polymorphisms regulating cardiac conduction also affects the susceptibility to arrhythmia (20). In addition, the concept of genetic modifiers also indicates the cooperation between multiple genes. KCNQ1 mutation A341V carriers exhibit inconsistent QT intervals, and AKAP9, encoding a scaffolding protein, variants has been shown to alter the QTc interval of the population and the risk and severity of cardiac events (21, 148). A GWAS study conducted in China investigated the relationship between the NOS1AP gene rs12143842 variant and idiopathic ventricular tachycardia. The results showed that the minor T allele of the rs12143842 SNP was significantly associated with the reduced risk of idiopathic ventricular tachycardia in the Northern Chinese cohort, indicating that SNPs can affect the susceptibility to ventricular tachycardia (149). Consistently, a recent GWAS study with polygenic risk score

analysis in BrS patients confirmed the association of mutation accumulation effects with traits (22).

EPIGENETIC FACTORS OF VENTRICULAR ARRHYTHMIAS WITHOUT STRUCTURAL HEART DISEASE

There are still a large number of cases of hereditary ventricular arrhythmias in which the causative gene has not been detected. For example, in BrS, approximately 20 pathogenic genes have been reported, but comprehensive single gene factors and polygenic factors still account for 60–80% of the causes unknown. In addition to fever, exercise, illness, and other factors, epigenetic factors have gradually attracted attention (150–152). Genetic research on diseases mainly focuses on the primary structure of DNA, i.e., when the DNA sequence changes, causing alterations in gene transcription and translation. Unlike genetics, epigenetics studies the molecules and mechanisms that maintain the state of selectable gene activity states without changing the DNA sequence and has mainly been studied in the fields of non-coding RNA expression, DNA methylation, histone modifications, genomic imprinting, and three-dimensional genome architecture (Table 1) (153).

Non-coding RNA

Non-coding RNA refers to RNA that does not encode protein, which is transcribed from the genome and does not translate into protein, but performs biological functions at the RNA level, including microRNA, circular RNA, small nuclear RNA, long non-coding RNA, etc.

MicroRNA (miRNA) is a class of conservative non-coding small RNA, primarily involved in the regulation of post-transcriptional level that can cause target mRNA degradation or repress translation by specific base pairing with target mRNA, thereby affecting the expression of target mRNA. MiR-19b has been reported to be established as a potential candidate for human LQTS, with impaired repolarization of miR-19b-deficient zebrafish, significantly prolonged action potential, showing severe bradycardia and susceptibility to arrhythmias and cardiomyopathy. MiR-19b targets multiple ion channel-related genes. SCN1B acts as the β subunit of $\text{Na}_v1.5$, directly regulated by miR-19b and is upregulated upon its loss, possibly leading to prolonged action potential duration by increasing late sodium current. Upon miR-19b reduction, both KCNE4 and KCNE1 are significantly upregulated, which may be due to the impaired cardiac repolarization caused by the inhibition of KCNQ1, resulting in reduced potassium currents, which leads to the prolongation of AP and bradycardia. In addition, the downregulation of the expression of KCNA4, KCND3, SCN12B and CACNA1C indirectly regulated by miR-19b was detected, in which KCNA4 and KCND3 mediate the I_{to} . The notch decreased during early repolarization due to damaged I_{to} , which may explain the increased potential observed in stage 1 of the miR-19b-deficient heart. However, the presence of I_{to} in zebrafish hearts remains controversial. Further, miR-19b reduction can

significantly rescue the heterozygous zebrafishes with SQTS phenotype (23).

miRNA can exist stably in a variety of body fluids, known as circulating miRNA. Circulating miRNA levels are associated with multiple diseases, and the expression profile differences significantly between normal people and disease patients, which may be a new class of disease markers. In pediatric patients without organic heart disease, miR-133 plasma levels were increased in children with ventricular tachycardia as compared with healthy controls (24). Circulating miRNA studies in patients with idiopathic ventricular tachycardia and arrhythmogenic cardiomyopathy showed that the plasma levels of miRNA-320 in idiopathic ventricular tachycardia patients were significantly higher than those in ACM patients, which may help to distinguish idiopathic ventricular tachycardia and arrhythmogenic cardiomyopathy (154). MiRNA mostly combines with the UTR region of the coding gene to regulate gene expression, so the sequence of UTR regions is of great significance for controlling the expression of ion channel genes. In fact, there have been reported mutation detection in the SCN5A UTR region and biological predictions of the combined miRNA (25, 155). Variations were also detected in the UTR region of SCN1B, but the miRNAs that may bind to SCN1B were not described in detail (156). Scientists have also tried to screen the genetic mutations of miRNA in LQTS patients to explain the cause of LQTS, but the mutation sites found failed to explain the cause of the disease in the cohort (157).

It is known that KCNH2 encoding $K_v11.1$, which is a subunit of rapid-acting inward rectifying potassium channel, actually KCNH2 intron 9 is splicing inefficient in human heart, only 1/3 of the precursor mRNA is processed into functional $K_v11.1a$ isomers and 2/3 into C-terminal truncated non-functional $K_v11.1a$ -USO isomers. The initial step of the splicing process involves the recognition of the 5' splice site by U1 small nuclear ribonucleoprotein. This recognition is mediated by complementary base pairing between the 5' splice site and U1 SnRNA (the RNA component of U1 small ribonucleoprotein) (158). A KCNH2 IVS9-2delA mutation was found in a large LQTS family that resulted in the switching of functional $K_v11.1a$ isoform to the non-functional $K_v11.1a$ -USO isoform (159). The extent of complementarity between the 5' splice site and U1 snRNA is an important determinant of splicing efficiency. Modifying the sequence of U1 snRNA can increase its complementarity to the 5' splice site of KCNH2 intron 9, significantly improve the splicing efficiency of the intron 9, increase the expression of the functional $K_v11.1a$ isoforms, and thereby increase the $K_v11.1$ current (158).

DNA Methylation

DNA methylation refers to the process where organisms transfer methyl groups to specific bases with S-adenosylmethionine as the methyl donor under DNA methyltransferase. DNA methylation is regulated at transcription levels and mainly plays an inhibitory role. The common SCN5A polymorphism H558R (rs1805124), a genetic modifier of BRS, can improve the electrocardiographic features and clinical phenotype of SCN5A mutation carriers by repairing abnormal channel gating kinetics and membrane

trafficking and improving sodium channel activity in mutant channels (160–164). In fact, studies have shown that the SCN5A polymorphism H558R can reduce the methylation level of the SCN5A promoter, increase the expression level of SCN5A in the heart tissue, and prevent the occurrence of ventricular fibrillation (26). The G allele of H558R has been linked to QTc interval prolongation, which corresponds to its function (165, 166).

DNA methylation can also play a role in gene imprinting by forming differentially methylated regions (DMRs) on genomes of different parental origins to regulate gene expression (167). For example, there is a differential methylation region within the KCNQ1 locus (KvDMR1), which regulates multiple genes, including KCNQ1, long non-coding RNA KCNQ1OT1, and CDKN1C (27). Since both KCNQ1OT1 and KCNQ1 associated with LQTS are imprinted genes, this part is detailed in the genomic imprinting section.

Histone Modifications

Nucleosome is the basic unit of chromatin composed of histones and DNA wrapped around histones. Modifications of nucleosomes control DNA packaging and regulate the entry of the transcription factor into the DNA. There are at least 15 functional histone modifications that can occur in cells, with histone methylation and demethylation, as well as acetylation and deacetylation, being the most commonly studied modifications in the heart (168).

Histone methylation can be associated with transcriptional activation or repression, while histone acetylation is usually associated with transcriptional activation (169, 170). The active trimethylation of histone H3 at lysine 4 (H3K4me3) mark plays a pivotal role in cell homeostasis in fully differentiated tissues. Decreased h3k4me3 reduces gene expression of KCHIP2, the β -subunit of the I_{to} channel, and attenuates I_{to} and sodium current, prolonging the action potential duration and resulting in increased $I_{Ca,L}$ and enhanced cardiac contractile function (28, 29). KCHIP2 is heterogeneously expressed in the human and mouse ventricular walls, and although there have been no cases of association of KCHIP2 mutations with cardiac disease, functional studies have shown that the gene defect alters repolarization gradients, eliminates fast I_{to} , and increases the susceptibility of murine ventricular cells to ventricular tachycardia (30).

HEY2 is a BrS susceptibility gene, which can not only affect the expression of SCN5A and the formation of the cardiac conduction system but also regulate the expression of transmural potassium channels such as Kcnp2 and KCND2, altering the peak and density of I_{to} and I_{Na} and affecting transmural electrophysiological gradients (20). Studies have shown that H3K4me3 and active H3K27ac (histone H3 acetylated lysine 27) can regulate the ventricular differential transcription of the HEY2 gene by binding to the promoter or enhancer of HEY2, affecting ventricular myocyte depolarization and repolarization (168).

Genomic Imprinting

Genomic imprinting refers to the phenomenon that gene expression has parental selectivity in tissues or cells, and only a specific parental allele is expressed, and the other parental allele are not expressed or rarely expressed. Paternal genes are

not expressed as paternal imprinting, and maternal imprinting is the same (171). The KCNQ1 gene, which is an imprinted gene, exists in clusters with other imprinted genes, called imprinted domains. Imprinted domains are regulated by shared regulatory elements (long non-coding RNA and DMR) (171). KCNQ1OT1 is a long non-coding RNA located in the KCNQ1 locus, with a promoter located within the KvDMR1. Affected by differential methylation of the promoter region this gene only expresses the paternal allele, while the maternal allele is silent (172). Unlike KCNQ1OT1, KCNQ1 is biallelic expression in adult tissues and fetal heart, although it shows maternal expression in other fetal tissues and the coding of paternal gene is repressed (27). The main reason is that KCNQ1OT1 can regulate the spatiotemporal expression of KCNQ1 by coordinating chromatin conformation changes and histone modifications, which makes LQTS caused by KCNQ1 mutation not show obvious maternal predisposition, but an autosomal dominant manner (173, 174). Even so, there are still reports that LQTS exhibits female predominance and transmission distortion, i.e., the LQTS allele is more maternally than paternally derived, especially in patients with LQTS due to KCNQ1 mutations, which may be associated with genomic imprinting (31, 32). A study investigating the methylation state of KCNQ1OT1 in a group of patients with symptomatic QTc prolongation found that the rs11023840 AA genotype of KCNQ1OT1 increased the methylation level of KCNQ1OT1 promoter, which was associated with prolonged QTc interval, supporting the role of differential methylation/imprinting of KCNQ1OT1 in symptomatic prolonged QTc risk (33). However, another study showed that different degrees of potassium channel dysfunction caused by variations in different parental origins may also lead to transmission distortion (175). Although inconclusive, there is no doubt that genetic imprinting plays an important role in the pathogenesis of LQTS.

Arsenic trioxide (As₂O₃, ATO) is a reagent for the treatment of acute promyelocytic leukemia with adverse effects, including the induction of LQTS. Studies have shown that ATO induces a decrease in the transcription level of long non-coding RNA KCNQ1OT1 in the KCNQ1 locus, while KCNQ1OT1 silencing can inhibit the expression of KCNQ1, thus prolonging action potential duration *in vitro* and causing LQTS *in vivo* (176). It has also been reported that miRNA is also involved in ATO-induced QT prolongation, with ATO-induced miR-133 and miR-1 dysregulation acting as the basis of As₂O₃-induced cardiac electrical disorder. In guinea pigs, ERG protein expression was inhibited by miR-133 while the expression of Kir2.1 channel protein was downregulated by miR-1, resulting in the decrease of rapidly activating delayed rectifier potassium current and inward rectifier potassium current, thereby inducing the prolongation of QT (177).

Three-Dimensional Genome Architecture

With the development of chromosome conformation capture technologies and fluorescence *in situ* hybridization imaging technologies, the role of 3D genome architecture in gene regulation has gradually emerged (178, 179). The genomic DNA in the nucleus is folded into an ordered chromatin spatial

structure that allows elements with a long linear distance can also interact, such as the loop structure formed between enhancer and promoter (180). Among them, CTCF and cohesin complexes assemble three-dimensional chromatin loops in the genome and play a crucial role in regulating the transcriptional patterns of genes (181, 182). CTCF and cohesins are abundantly enriched at topological domain boundaries and localize to CTCF sites, limiting the interaction of functional elements within topological domains (34, 183). Although the association of CTCF binding site variants with ventricular arrhythmias in non-structural heart disease has not been reported, however, CTCF knockout has been reported to cause disorder in the expression of RYR2, KCND2/KCNQ1/SCN5A/CACNB1 and other genes in the ventricle, leads to heart failure, suggesting an association with ventricular arrhythmias (35, 36). Besides, DNA sequence changes that affect the formation of the normal 3D structure of the genome have also been confirmed to be involved in the occurrence and development of the disease (184). Studies have shown that the enhancer (ENHA) in SCN10A interacts with SCN5A promoter, which is necessary for the expression of SCN5A *in vivo* (185). The major allele G of the common variant locus rs6801957 in SCN10A located within this enhancer region establishes a conserved T-box transcription factor binding site to promote enhancer activity, while the risk allele significantly reduces the expression of SCN5A (186). This largely explains the association of this variant site with QRS prolongation in the GWAS study and common variants in SCN10A with BrS (20, 187). In turn, the results of GWAS can also guide the discovery of functional element regions within the loci (188, 189). The analysis of common variants associated with LQTS in the KCNH2 locus identified a conserved cardiac cis-acting element that acts as enhancer and regulates KCNH2 expression through physical proximity to the KCNH2 promoter (37). In fact, GWAS

studies have identified a large number of SNPs associated with heart disease, however, the mechanisms of most of the SNPs involved in the occurrence of the disease have not been revealed (190). Marking of regulatory element regions such as enhancers of known disease-causing genes can characterize some variants of unknown significance and provide a theoretical basis for deciphering genetic variation (191). In conclusion, studies of 3D genome architecture provide a new perspective for us to understand the potential mechanism between these SNPs and diseases, as well as a better understanding of the pathogenic mechanism of diseases.

SUMMARY

This article summarizes the genetic and epigenetic factors of ventricular arrhythmia in patients without structural heart disease and introduces the genes that may cause ventricular arrhythmias and their possible pathogenic mechanisms. However, there are still a large number of cases of ventricular arrhythmias without structural heart disease whose causes have not been clarified. Further research and exploration are needed, and the development of high-throughput patch clamping and other related technologies will undoubtedly play an important role. In addition, emerging disciplines such as optogenetics are also developing steadily, which will drive us to have a deeper understanding of the pathogenesis of ventricular arrhythmias.

AUTHOR CONTRIBUTIONS

XT: conceptualization, writing, and supervision. MW: data curation and writing. Both authors contributed to the article and approved the submitted version.

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