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Genetics of Sudden Cardiac Death Syndromes

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Abstract

Purpose of review—To survey recent developments in the field of genetics encompassing discovery of new candidate genes, new diagnostic strategies and new therapies for sudden cardiac death (SCD) syndromes.

Recent findings—In addition to new mutations in known SCD genes, several novel genes not previously implicated in SCD causation have been found, particularly in long QT syndrome (e.g., *KCNJ5*, *AKAP9*, *SNTA1*), idiopathic ventricular fibrillation (*DPP6*, *KCNJ8*), dilated cardiomyopathy (e.g., *NEBL*) and hypertrophic cardiomyopathy (e.g., *NEXN*). Genetic SCD animal models have provided novel insights in the cellular mechanism and pathogenesis of nearly all the major SCD syndromes, which has led to several new drug therapies for patients with genetic arrhythmia syndromes (e.g., flecainide in Catecholaminergic Polymorphic Ventricular Tachycardia). Furthermore, genetic contributions to acquired heart diseases are increasingly being recognized. For example, a 21q21 locus is strongly associated with ventricular fibrillation after myocardial infarction. Near this locus is *CXADR*, a gene encoding a viral receptor implicated in myocarditis and dilated cardiomyopathy. Finally, common variants in cardiac ion channels and proteins likely contribute to common cardiac phenotypes.

Summary—Major strides have been made uncovering new genes, mechanisms and syndromes that have significantly advanced the diagnosis and treatment of genetic SCD disorders.

Keywords

sudden cardiac death; genetics; ventricular arrhythmia; mutation

Introduction

Sudden cardiac death (SCD) remains a major public health problem in the western world with over 200,000 deaths reported annually in the USA only.(1) The underlying mechanism is ventricular tachyarrhythmia (VA) in the overwhelming majority. However, the underlying substrate varies: ischemic heart disease in 75–80% cases; idiopathic cardiomyopathy in 10–15% and 1–2% due to rare monogenic mutations in cardiac ion channels or associated proteins.(2) Even though the latter constitutes only a small portion of SCDs, their study is imperative in understanding the mechanisms of SCD. In fact, the concept of evaluating the

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molecular mechanism of a monogenic arrhythmia syndrome to provide clues in probing the mechanism and improve therapy of more commonly acquired arrhythmogenic diseases has been proposed.(3) ? For example, mutations in the RyR2 Ca^{2+} -release channel cause CPVT; acquired RyR2 dysfunction has been implicated in VA and SCD in heart failure and may contribute to the pathogenesis of other diseases like idiopathic cardiomyopathy or atrial fibrillation, with increased 'SR Ca^{2+} -leak' being the common underlying mechanism. Furthermore, common variants in SCD genes may increase arrhythmia risk associated with the 'environmental' factors (e.g., drugs, electrolytes, ischemia).(4, 5)

Newer study methods in genetics promise to enhance our understanding of disease mechanisms. For example, genome wide association studies (GWAS), a high-throughput genotyping of a large number of SNPs correlating them to a phenotype, is clearly a step forward in investigating biologic pathways of disease causation.(6) Using this technique SNP 'rs2824292' at locus 21q21 has been strongly associated with ventricular fibrillation after acute myocardial infarction, a major cause of SCD of which very little is known.(7) Interestingly, the gene closest to this SNP is *CXADR*, which encodes a viral receptor previously implicated in myocarditis and dilated cardiomyopathy and has been identified as a modulator of cardiac conduction, but not implicated in arrhythmia susceptibility.(7) However, more studies need to be done to uncover a causal relationship, if one exists.

The remainder of the review focuses on new candidate genes and new developments in diagnosis and treatment of sudden cardiac death syndromes subdivided in two major categories (Table 1): Syndromes associated with structurally normal hearts (*Catecholaminergic Polymorphic Ventricular Tachycardia*, *Brugada Syndrome*, *long and short QT syndrome*, *Idiopathic Ventricular Fibrillation*) and syndromes associated with cardiomyopathic lesions (*Arrhythmogenic Right Ventricular Cardiomyopathy*, *Dilated Cardiomyopathy*, *Hypertrophic Cardiomyopathy*, *LV Non-Compaction*):

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

The number of mutations in the *RYR2*(155) and *CASQ2*(15) linked to CPVT continues to grow since they were first described almost a decade ago (<http://www.fsm.it/cardmoc/> for updated list).(8–10) Although the RyR2 binding proteins triadin and junctin have been suggested from murine models as additional candidates,(11, 12) human mutations have not yet been found. Among patients with exertional syncope, polymorphic VT and normal QTc, nearly 50% have putative *RyR2* mutations causing CPVT(13) and nearly 20% of these *RyR2* mutations are *de novo*.(13) Since sporadic cases of CPVT can be due to germ-line mosaicism in one of the parents,(13, 14) systematic genetic screening of the proband's siblings should be done even if standard methods fail to clearly detect the mutation in the parents.(14) A tiered-approach in screening for *RyR2* mutations due to clustering of known CPVT mutations in certain exons can be used to lower the cost.(13) ? It can be expected that newer technologies like the 'next-generation' gene sequencing will not only make it faster and cheaper to screen the entire *RyR2* but will also abolish the need for sequencing these 'hot regions' for mutations.

Mechanistically, CPVT is a triggered arrhythmia that occurs due to delayed after-depolarization (DAD) due to spontaneous SR Ca^{2+} -release during catecholamine surge.(15) Recent work implicates Purkinje fibers as being more arrhythmogenic than ventricular myocytes(16, 17) and may well be the source of bidirectional VT.(18) Cardiac sympathectomy has been suggested to control CPVT in patients refractory to β -blockers,(19) although relief after this surgical procedure can be temporary or of delayed onset.(20) The recent discovery that the class 1c antiarrhythmic agent flecainide directly targets the molecular defect in CPVT by virtue of blocking the *RyR2* and cardiac Na^{+} channels downstream in the β -adrenergic cascade provides a new therapeutic option for CPVT

patients refractory to β -blockers or sympathectomy.(21–24) Flecainide suppressed DADs in mutant Purkinje fibers,(16) and effectively prevented CPVT in mice and humans.(21–24) An international randomized placebo-controlled trial of flecainide in CPVT is currently open for enrollment (ClinicalTrials.gov NCT01117454).

Brugada Syndrome (BrS)

Some estimate that BrS may account for up to 50% of all SCDs in young individuals without structural heart disease.(25) ? Patients with BrS display a characteristic coved-type ST segment elevation followed by a descending negative T wave in at least one right precordial lead (V_1 to V_3), which is considered diagnostic of BrS.(25) Although nearly 300 putative ‘loss of function’ mutations in the *SCNA5* have been described,(26, 27) emerging epidemiologic data indicates that genetic background beyond *SCNA5* mutations may be required for the BrS phenotype.(28) Since *SCN5A* mutations are seen in only ~20% of all BrS patients(26, 27) this suggests that multiple molecular mechanisms culminating into loss of function of *SCNA5* may be the final common mechanism for BrS.(29) Mutations in the gene encoding glycerol-3-phosphate dehydrogenase 1-like enzyme by virtue of Na^+ current reduction has been linked to BrS.(30) Furthermore, ‘loss of function’ mutations in cardiac Ca^{2+} channel complex,(31, 32) and mutation in *KCNE3* leading to increase in the amplitude of I_{to} current(33) have also been implicated in BrS. While the genetic cause of BrS remains elusive in the remaining 70–80% patients.(26)

The class Ia anti arrhythmic agent and I_{to} current blocker quinidine seems quite effective in suppressing VA in BrS patients.(34) Particularly challenging is treatment of electrical storm in BrS patients which has been anecdotally treated with disopyrsmide,(35) orciprenaline(36) and quinine.(37)

Long QT syndrome (LQTS)

To date, more than 700 mutations in 12 genes have been identified in ~70% of patients with LQTS. However, genetic test results for long QT syndrome can be misleading because rare variants can be non-pathogenic;(38) require a common polymorphism in the target gene(39) or a genetic modifier like *NOS1AP*(40) to display the phenotype. Furthermore, large genomic rearrangements of the canonical LQTS-susceptibility genes should be suspected in patients with a strong clinical phenotype who fail to reveal point mutations with conventional genetic testing.(41) Compound and digenic heterozygosity causing a more severe phenotype is observed in 5–10% of LQTS patients.(42) Recently, a mutation in the K^+ channel Kir3.4 resulting in a channel trafficking defect and reduction in the I_{KACH} current has been described in autosomal dominant LQTS.(43) This discovery is noteworthy since unlike in the atrium, the I_{KACH} current is generally not considered important for repolarization of the ventricle.(43) Clinically, echocardiography has been suggested as a complementary tool to QTc assessment in risk stratification of LQTS mutation carriers.(44)

Insight in pathogenesis of putative mutations causing LQTS is usually obtained from studies in heterologous cell expression system or genetic animal models. Due to their inherent limitations, the underlying mechanism by which a mutation causes LQTS may remain undetermined(45) or show discrepancy between *in vitro* and clinical phenotype.(46) To address this issue, investigators derived pluripotent stem cells from patients with LQTS-1 and directed them to differentiate into cardiac myocytes.(45) As a proof of concept, these myocytes did exhibit the abnormal biophysical and pharmacological phenotype that one would expect due to mutated I_{ks} suggesting that induced pluripotent stem-cell models can recapitulate aspects of genetic cardiac diseases and can be used as an alternative method of studying their phenotype.(45) This technique has also been utilized to study LQTS-2

syndrome where the patient-specific human induced pluripotent stem cells (iPSCs) not only accurately model the human disease but also help in individualizing drug testing.(47)?

Therapeutically, recent work suggests that the late Na⁺ current blocker ranolazine shortens QT and may be beneficial for LQT patients with Na⁺ channel mutations (LQT3).(48)

Short QT syndrome (SQTS)

SQTS is an inherited primary arrhythmogenic cardiac disorder characterized by abnormally short QT interval and a predisposition to development of atrial and ventricular tachyarrhythmias.(49) Five subtypes have been described due to gain of function mutation in genes encoding K-channels (*KCNH2*, *KCNQ1* and *KCNJ2*; types 1–3) or loss of function mutation in the gene encoding the L-type Ca channel (*CACNA1C*) or its beta-subunit *CACNB2b* (types 4–5).(49) ? The common underlying mechanism is a shortening of action potential duration which can generate a substrate for reentry.

Idiopathic Ventricular Fibrillation (IVF)

IVF – spontaneous VF without identifiable structural or electrical heart disease – may account for up to 10% of sudden death in the young.(50–52) Haplotype-sharing analysis has identified a genetic basis for IVF.(53) The shared chromosomal segment contained the *DPP6* gene, which encodes a putative regulator of the transient outward I_{to} current.(54) *DPP6* mRNA levels were increased 20-fold in hearts of human carriers in one study.(53) To date this seems to be a founder risk locus but nonetheless it suggests that an increase in *DPP6* imparts a higher risk for VF.

Furthermore, previously thought to be a benign and common ECG finding present in up to 5% of the population, three separate case-control studies(55–57) suggest that ‘J-point elevation’ (manifested either as terminal QRS slurring or notching, or ST-segment elevation with upper concavity and prominent T waves in infero-lateral leads) is significantly more prevalent (16–60%) in patients with IVF. Mutations in genes encoding subunits of L-type Ca²⁺ channel (*CACNA1C*, *CACNB2*, and *CACNA2D1*)(58) and a subunit of the K_{ATP} channel encoded by *KCNJ8*(59) have been implicated in this new ‘J-wave syndrome’ or ‘early repolarization syndrome’.(60)

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is an autosomal-dominant syndrome with variable penetrance in up to 50% of patients characterized by progressive myocardial atrophy with fibro-fatty replacement predominantly in the right ventricle.(61) Since the first description of mutations in plakoglobin causing ARVC in 2000,(62) many more desmosomal protein mutations have been discovered.(63) Even though mutations in the desmosomal protein plakophilin-2 (*PKP2*) are most common (25–40%) in ARVC patients,(63, 64) they may not be pathogenic in isolation, as indicated by reports of low-penetrance of some heterozygous *PKP2* mutations,(65) prevalence of certain disease-causing missense *PKP2* mutations in healthy controls,(66) and prevalence of mutations in multiple desmosomal genes in 4–42% of ARVC patients.(63, 65, 67) Additionally, a gene-dose effect is suggested by the requirement of compound or digenic heterozygosity (additional variants in the same or associated desmosomal genes, respectively) in order to manifest an ARVC phenotype(63, 65, 67) which is also significantly associated with increased likelihood of SCD and LV systolic dysfunction.(63, 64, 67) Furthermore, nonsense or frame-shift mutations in *PKP2* alone – in contrast to missense mutations – often do not result in clinical disease, which suggests a dominant-negative effect of missense mutations when compared to haplo-insufficiency associated with truncated mutations.(63, 65) Therefore, genotyping in clinical practice should include all the desmosomal proteins even if an index mutation is discovered,

especially in patients with a severe phenotype or LV dysfunction.(65, 67) The latter seems more common with mutations in desmoglein-2 (50%), plakophilin-2 (10%), and desmoplakin.(63)

Dilated Cardiomyopathy (DCM)

Familial DCM is associated with rare variants in more than 20 sarcomeric and structural proteins but known gene mutations only explain the disease in a small percentage of patients. Not surprisingly, common variants in these genes may also increase susceptibility to DCM.(68) Even though considered a separate entity, studies implicate mutations in genes associated with familial DCM in a small subset of patients with peripartum or pregnancy-associated DCM.(69, 70)

A recent new addition to the long list of DCM candidate genes is nebulin (*NEBL*), which encodes a 107 kDa protein that aligns thin filaments and connects them with the myocardial Z-disk. Novel nebulin mutations (K60N, Q128R, G202R, and A592E) were identified in patients with DCM, endocardial fibroelastosis, and cardiac failure.(71) Another is Dynamin-1-like (*Dnm1l*) gene, which is known to be critical for mitochondrial fission and has also been implicated in causing DCM by reducing levels of mitochondrial enzyme complexes and cardiac ATP depletion.(72)

Influence of common polymorphisms on DCM susceptibility was evaluated in a case-control study identifying a polymorphism (rs1739843) in intron 2 of the *HSPB7* (encoding the small heat shock protein γ Hsp, also called HspB7) being associated with susceptibility to DCM. However, the functional significance of this variant is presently unknown and needs further evaluation.(73) Furthermore, classically implicated in causing ARVC, desmosomal mutations occur in at least 5% of patients with DCM with a phenotype essentially indistinguishable from DCM patients without desmosomal mutations, except for a higher prevalence of exercise-induced ventricular ectopy.(74)

Clinically, it is not uncommon to see the degree of ischemic cardiomyopathy often out of proportion to the amount of overtly infarcted myocardium suggesting involvement of other mechanisms. One such is Prolyl Hydroxylase Domain-Containing Protein (*PHD*) prolyl hydroxylases which are oxygen-sensitive enzymes that transduce changes in oxygen availability into changes in the stability of the hypoxia-inducible factor (HIF) transcription factor, a master regulator of genes that promote survival in a low-oxygen environment.(75) Inactivation of cardiac-specific PHD and subsequent HIF activation causes structural, histological, and functional changes akin to chronic ischemic cardiomyopathy, suggesting its causal role and possible therapeutic target for pharmacological manipulation in ischemic cardiomyopathy, the leading cause of SCD from an acquired disease.(75)

Hypertrophic Cardiomyopathy (HCM)

Familial HCM is usually caused by mutations in genes encoding sarcomeric proteins. Among them, mutations in β -myosin heavy, cardiac myosin-binding protein C, cardiac troponin I, and cardiac troponin T account for nearly 50% of reported cases.

Recently, missense mutations that cause defective interaction between Nexilin and α -actin have been described in HCM.(76) Nexilin (*NXN*) is a cardiac Z-disc protein that has a crucial function to protect cardiac Z-discs from forces generated within the sarcomere.(76) Pathologic hypertrophy in HCM is associated with α -MHC downregulation and β -MHC induction representing a fetal state of MHC expression. Brg1, a chromatin-remodelling protein, has a critical role in regulating cardiac growth, differentiation and gene expression and is reactivated by cardiac stresses to induce this pathologic MHC shift.(77) Preventing Brg1 re-expression decreases hypertrophy and reverses this pathologic MHC switch

suggesting it to be a potential therapeutic target for cardiac hypertrophy and failure.(77) Amidst general cardiac hypertrophy, myocyte enhancer factor-2 mediated focal myocyte necrosis and scarring may lead to heterogeneous scarring that predisposes to VA.(78) These show that novel structural genes (*NXN*) and pathogenic mechanisms in causation of HCM, a common cause of SCD continue to be discovered, re-emphasizing the importance of future research in this area.

Increased myocardial collagen synthesis in HCM mutation carriers often antedates overt clinical hypertrophy and may identify persons at risk for arrhythmias, sudden death, or heart failure even before manifestation of overt myocardial fibrosis, a hallmark of HCM and a likely substrate for VA and heart failure.(79) Mechanistically, non-myocyte activation of Tgf- β signaling is pivotal for increased fibrosis in HCM.(80) Therefore, prophylactic pharmacologic inhibition of Tgf- β cascade may prevent fibrosis and heart failure and warrants further study in patients with sarcomeric gene mutations.(80)

Another independent mechanism for VA risk in HCM appears to be the increased myofilament Ca^{2+} sensitivity caused by several mutations in troponin T or I. Even in absence of cardiac remodeling, increased myofilament Ca^{2+} sensitization reduces effective refractory period, greater beat to beat variability of APD and increased dispersion of ventricular conduction velocities at fast heart rates in mice.(81) This observation has potential therapeutic implications and should be explored further.

Left Ventricular Non-Compaction (LVNC)

LVNC – a rare disorder characterized by multiple deep trabeculations within the LV myocardium – is increasingly being recognized as a cause of VA and SCD in young patients.(82) Overlapping genetic predisposition to LVNC, HCM and dilated CM, suggesting a continuum of disease associated with sarcomeric gene mutations has been proposed.(83) Interestingly, distal chromosome deletion at 22q11.2(84) and 1p36(85, 86) while previously associated with atrial and ventricular septal defects, have been more recently described in patients with LVNC.

Conclusion

Genetic testing does not only impact care of inherited SCD syndrome patients but benefits also their often asymptomatic, disease carrying relatives by institution of prophylactic treatment.(87) At the other end of the spectrum, postmortem screening for cardiac channelopathies in SCD victims has been advocated; newer technologies are emerging to accomplish this more effectively.(88, 89) Furthermore, discovery of novel SCD syndromes (e.g., IVF) provides the opportunity to decipher the genetic contribution to relatively well characterized clinical ECG phenotypes (e.g., J-wave).(57, 90, 91) Finally, new discoveries in genetics enable a better understanding of fundamental mechanisms of SCD that may lead to better treatments in the future.(3)

Key Points

- Novel gene discoveries have been made in many SCD syndromes
- New genetic SCD animal models have provided novel mechanistic insights of nearly all the major SCD syndromes, which has led to new drug therapies for patients with genetic SCD syndromes
- New studies identify genetic contributions to arrhythmia risk after myocardial infarction

- Common variants in cardiac ion channels and proteins likely contribute to common cardiac phenotypes

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Table 1

Phenotype, genotype and underlying arrhythmia mechanisms of familial sudden cardiac death syndromes. Genes in bold are discussed more extensively in the text.

	Sudden Cardiac Death Syndrome	Phenotype	Disease Gene	Arrhythmia Mechanism
Structurally normal heart	Catecholaminergic Polymorphic Ventricular Tachycardia	Catecholaminergic polymorphic VT, Atrial and ventricular arrhythmia, bradycardia	RYR2 CASQ2	DAD-mediated automaticity, premature calcium release from sarcoplasmic reticulum
	Brugada syndrome	ST-segment elevation in V1–V3, RBBB, structurally normal heart, VA	SCN5A, CACNA1C, CACNB2, GPD1L, CNE3, SCN1B, SCN3B, CACNA2D1, KCNE3	Slow conduction in RV, loss of action potential dome in epicardial cells
	Long QT syndrome	Long QT interval, Torsades-de-Pointes VT	KCNQ1 (type 1 LQTS), KCNH2 (type 2 LQTS) SCN5A (type 3 LQTS), KCNE1 (type 5 LQTS) KCNE2 (type 6 LQTS), KCNJ2 (type 7 LQTS) CACNA1C (type 8 LQTS; Timothy syndrome) CAV3 (type 9 LQTS), SCN4B (type 10 LQTS), KCNJ5 , AKAP9, SNTA1, ANK2	Action potential prolongation, EADs
	Short QT syndrome	Short QT	KNCQ1, KCNH2, KCNJ2, CACNA1C, CACNB2	Short AP, reentry and VF
	Idiopathic Ventricular Fibrillation	Normal QT duration, VF	DPP6 , KCNJ8	Unknown
Cardiomyopathic lesions	Arrhythmogenic Right Ventricular Dysplasia/ cardiomyopathy	Fibro-fatty infiltration and RV systolic dysfunction and VA	PKP2, DSP, JUP, DSG2, DSC2, DES, RYR2, TGFB3, TMEM43	Re-entrant and DAD-mediated automaticity
	Dilated cardiomyopathy	Dilated LV and systolic dysfunction	ACTC, DES, SGCD, MYH7, TNNT2, TPM1, TTN, VCL, MYBPC, MLP/ CSRP3, ACTN2, PLN, ZASP/LBD3, MYH6, ABCC, LMNA, DMD, TAZ/ G4.5, TNNI3, NEBL , DNM1L	Cytoskeletal and sarcomeric protein dysfunction, re-entrant VT, EAD, DAD
	Hypertrophic cardiomyopathy	LV hypertrophy	MYH7, MYBPC3, TNNT2, TNNI3, TNNC1, ACTC1, TPM1, MYL3, MYL2, TTN, CSRP3, TCAP, NEXN , ACADVL, ACTN2, ANKRD1, FHL, FXN, GAA, HRAS, KRAS, LAMP2, LDB3, MYH6, MYH16, MYOZ2,	Sarcomeric protein dysfunction, myofibrillar disarray; re-entrant VT, EAD, DAD

	Sudden Cardiac Death Syndrome	Phenotype	Disease Gene	Arrhythmia Mechanism
			PTPN11, PRKAG2, RAF1, SOS1, TAZ, TTR, VCL	
	LV non-compaction	trabeculations and intertrabecular recesses in LV	LDB3, TAZ, DTNA, LMNA, MYH7, TNNT2, TPM1	unknown