PART V

ARRHYTHMIAS, SUDDEN DEATH, AND SYNCOPE

32 Genetics of Cardiac Arrhythmias

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Cardiac arrhythmias encompass a large and heterogeneous group of electrical abnormalities of the heart, with or without underlying structural heart disease. Cardiac arrhythmias can be innocuous, can predispose to the development of potentially lethal stroke or embolism, or can be an emergency, life-threatening condition that may result in sudden cardiac death (SCD), one of the most common causes of death in the developed countries. In the United States, for example, an estimated 300,000 to 400,000 individuals die suddenly each year, with the vast majority involving the elderly; 80% are caused by ventricular fibrillation in the context of ischemic heart disease. In comparison, SCD in the young is relatively uncommon, with an incidence between 1.3 and 8.5 per 100,000 patient-years.[1] However, tragically, thousands of otherwise healthy individuals younger than 40 years die suddenly each year without warning. Most SCD in the young can be attributed to structural cardiovascular anomalies identifiable at autopsy, but in as many as 30% to 50% of such individuals, sudden death remains unexplained following a complete autopsy and medicolegal investigation (**see Chapter 39**).

Potentially lethal and inheritable arrhythmia syndromes included under the umbrella of "cardiac channelopathies," such as congenital long-QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and related disorders, involve electrical disturbances with the propensity to produce fatal arrhythmias in the setting of a structurally normal heart. These often unassuming electrical abnormalities have the capacity to cause a potentially lethal arrhythmia to develop in the heart of an unsuspecting, otherwise healthy individual and lead to sudden and early demise.[1] In fact, it is now recognized that almost a third of autopsy-negative sudden unexplained deaths (SUDs) in the young[2] and approximately 10% of cases of sudden infant death syndrome (SIDS) stem from these genetically inherited cardiac channelopathies.[3,4]

Through molecular advances in the field of cardiovascular genetics, the underlying genetic bases responsible for many inherited cardiac arrhythmia syndromes have come to light, and the underlying genetic substrates responsible for other such syndromes are on the cusp of discovery. Over the past decade, a particular set of themes, including extreme genetic heterogeneity, reduced or incomplete penetrance, and variable expressivity, has proved to be commonplace among the cardiac channelopathies. However, for some disorders, important genotype-phenotype correlates have been recognized and have provided diagnostic, prognostic, and therapeutic impact. The clinical description, genetic basis, and genotype-phenotype correlates associated with these inherited arrhythmia syndromes are discussed in this chapter.

THE QT-OPATHIES

Long-QT Syndrome

Clinical Description and Manifestations of Long-QT Syndrome

Congenital LQTS comprises a distinct group of cardiac channelopathies characterized by delayed repolarization of the myocardium, QT prolongation (QTc >480 msec as the 50th percentile in genetically confirmed LQTS cohorts), and increased risk for syncope, seizures, and SCD in the setting of a structurally normal heart and otherwise healthy individual. The incidence of LQTS may exceed 1 in 2500 persons.[5] Individuals with LQTS may or may not manifest QT prolongation on a resting 12-lead surface electrocardiogram (ECG). This repolarization abnormality is almost always without consequence; however, triggers such as exertion, swimming, emotion, auditory stimuli (e.g., alarm clock), and the postpartum period can rarely cause the heart to become electrically unstable and result in the development of the potentially life-threatening and sometimes lethal arrhythmia of torsades de pointes (TdP) (**see Chapter 37**). Although the cardiac rhythm most often returns to normal spontaneously, with only a transient episode of syncope, 5% of individuals with untreated and unsuspected LQTS succumb to a fatal arrhythmia as their sentinel event. However, it is estimated that nearly half of the individuals experiencing SCD stemming from this very treatable arrhythmogenic disorder may have previously exhibited warning signs (i.e., exertional syncope, family history of premature sudden death) that went unrecognized.[2] LQTS may explain approximately 20% of autopsy-negative SUDs in the young and 10% of cases of SIDS.[2,3]

Genetic Basis for Long-QT Syndrome. LQTS is a genetically heterogeneous disorder largely inherited in an autosomal dominant pattern; it was previously known as Romano-Ward syndrome. Rarely, LQTS is inherited as a recessive trait first described by Jervell and Lange-Nielsen and is characterized by a severe cardiac phenotype and sensorineural hearing loss. Spontaneous/sporadic germline mutations

can account for nearly 5% to 10% of cases of LQTS. To date, hundreds of mutations have been identified in 10 LQTS susceptibility genes responsible for a nonsyndromic "classic" LQTS phenotype. In addition, two extremely rare, multisystem disorders associated with marked QT prolongation: Timothy syndrome (TS), formerly annotated as LQT8, and prolonged QU intervals (Anderson-Tawil syndrome [ATS], formerly annotated as LQT7), and a third disorder, LQT4, which is better classified as ankyrin-B syndrome, have also been described.

Approximately 75% of patients with a clinically robust diagnosis of LQTS host either loss-of-function or gain-of-function mutations in one of three major LQTS genes (**Table 32-1**)—the *KCNQ1*-encoded I_{Ks} ($K_v7.1$) potassium channel (LQT1, ≈35%; loss of function), the *KCNH2*-encoded I_{Kr} ($K_v11.1$) potassium channel (LQT2, ≈30%; loss of function), and the *SCN5A*-encoded I_{Na} ($Na_v1.5$) sodium channel (LQT3, ≈10%, gain of function)—that are responsible for orchestration of the cardiac action potential[6,7] (**Fig. 32-1**). Approximately 5% to 10% of patients have multiple mutations in these genes, and those with multiple LQTS mutations are affected at a younger age and exhibit greater expressivity[6] (**see Chapter 8**). The most recent discovery was reported in 2012 by Boczek and colleagues following whole exome sequencing,

TABLE 32-1 Summary of Heritable Arrhythmia Syndrome Susceptibility Genes

GENE	LOCUS	PROTEIN
Long-QT Syndrome		
Major LQTS Genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, $K_v7.1$)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, $K_v11.1$)
SCN5A (LQT3)	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
Minor LQTS Genes (Listed Alphabetically)		
AKAP9	7q21-q22	Yotiao
CACNA1C	12p13.3	Voltage gated L-type calcium channel ($Ca_v1.2$)
CAV3	3p25	Caveolin-3
KCNE1	21q22.1	Potassium channel beta subunit (MinK)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNJ5	11q24.3	Kir3.4 subunit of I_{KACH} channel
SCN4B	11q23.3	Sodium channel beta 4 subunit
SNTA1	20q11.2	Syntrophin-alpha 1
Andersen-Tawil Syndrome		
KCNJ2 (ATS1)	17q23	I_{K1} potassium channel (Kir2.1)
Timothy Syndrome		
CACNA1C	12p13.3	Voltage gated L-type calcium channel ($Ca_v1.2$)
Short-QT Syndrome		
KCNH2 (SQT1)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, $K_v11.1$)
KCNQ1(SQT2)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, $K_v7.1$)
KCNJ2 (SQT3)	17q23	I_{K1} potassium channel (Kir2.1)
CACNA1C (SQT4)	12p13.3	Voltage gated L-type calcium channel ($Ca_v1.2$)
CACNB2 (SQT5)	10p12	Voltage gated L-type calcium channel beta 2 subunit
CACN2D1 (SQT6)	7q21-q22	Voltage gated L-type calcium channel 2 delta 1 subunit
Catecholaminergic Polymorphic Ventricular Tachycardia		
RYR2 (CPVT1)	1q42.1-q43	Ryanodine receptor 2
CASQ2 (CPVT2)	1p13.3	Calsequestrin 2
KCNJ2 (CPVT3)	17q23	I_{K1} potassium channel (Kir2.1)
CALM1	14q32.11	Calmodulin 1
TRDN	6q22.31	Triadin
Brugada Syndrome		
SCN5A (BrS1)	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
Minor BrS Genes (listed alphabetically)		
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1–like
CACNA1C	12p13.3	Voltage gated L-type calcium channel ($Ca_v1.2$)
CACNA2D1	7q21-q22	Voltage gated L-type calcium channel 2 delta 1 subunit
CACNB2	10p12	Voltage gated L-type calcium channel beta 2 subunit
DLG1	3q29	Synapse-associated protein 97
KCND3	1p13.2	Voltage-gated potassium channel (I_{to}) subunit $K_v4.3$
KCNE3	11q13.4	Potassium channel beta subunit 3 (MiRP2)
KCNE5	Xq22.3	Potassium channel beta subunit 5
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
HCN4	15q24.1	Hyperpolarization-activated cyclic nucleotide-gated channel 4
MOG1	17p13.1	RAN guanine nucleotide release factor 1
SCN1B	19q13	Sodium channel beta 1
SCN3B	11q24.1	Sodium channel beta 3
SLMAP	3p14.3	Sarcolemma associated protein
Early Repolarization Syndrome		
CACNA1C	12p13.3	Voltage gated L-type calcium channel ($Ca_v1.2$)
CACNA2D1	7q21-q22	Voltage gated L-type calcium channel 2 delta 1 subunit
CACNB2	10p12	Voltage gated L-type calcium channel beta 2 subunit
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
Progressive Cardiac Conduction Disease		
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
TRPM4	19q13.33	Transient receptor potential cation channel, subfamily M, member 4
Sick Sinus Syndrome		
ANKB	4q25-q27	Ankyrin-B
HCN4	15q24-q25	Hyperpolarization-activated cyclic nucleotide–gated channel 4
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)

genomic triangulation, and a systems biology approach to identify a novel genetic substrate (P857R-CACNA1C) for a large 15-member (8 affected) multigenerational pedigree with autosomal dominant "classic" LQTS.[8] Functional characterization of the mutation via a whole-cell patch clamp technique revealed a gain-of-function mutation in peak $I_{Ca,L}$ consistent with prolongation of the cardiac action potential and the clinical phenotype of LQTS. Their subsequent mutational analysis of 102 unrelated patients with robust clinical evidence of LQTS has indicated that 3% to 5% of genetically elusive cases of LQTS may be attributed to *CACNA1C* mutations, thus making *CACNA1C* potentially the fifth most common genetic substrate for nonsyndromic LQTS. The majority of the mutations identified reside in the *CACNA1C*-encoded critical PEST domain of the L-type calcium channel (LTCC), which signals for rapid protein degradation. These mutations presumably result in a biogenic increase in LTCCs at the cell surface membrane.

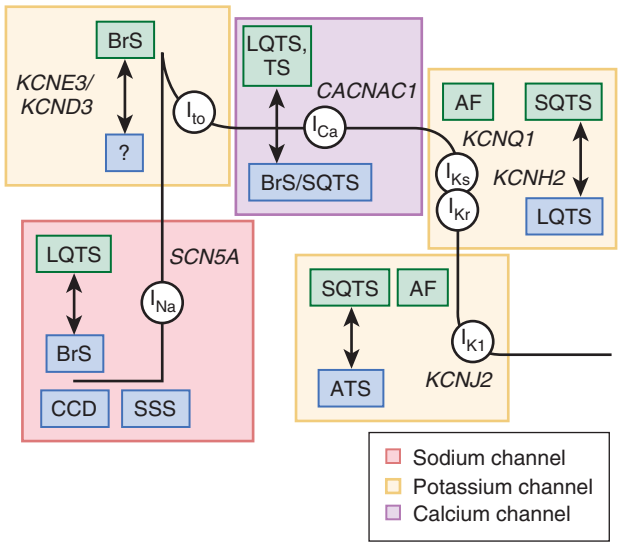

FIGURE 32-1 Cardiac action potential disorders. Illustrated are the key ion currents (*white circles*) along the ventricular cardiocyte's action potential that are associated with potentially lethal cardiac arrhythmia disorders. Disorders resulting in gain-of-function mutations are shown in *green rectangles* and those with loss-of-function mutations are shown in *blue rectangles*. For example, gain-of-function mutations in the *SCN5A*-encoding cardiac sodium channel responsible for I_{Na} lead to LQTS, and loss-of-function *SCN5A* mutations result in BrS, cardiac conduction disorder (CCD), and sick sinus syndrome (SSS). AF = atrial fibrillation.

In contrast to the rare, pathogenic LQTS-associated channel mutations present in less than 0.04% (1/2500) of persons and in 75% of clinically robust LQTS cases, comprehensive genetic testing for *KCNQ1*, *KCNH2*, and *SCN5A* in more than 1300 ostensibly healthy volunteers has revealed that approximately 4% of white individuals and up to 8% of nonwhite individuals host rare nonsynonymous genetic variants (<0.5% allelic frequency) of these specific cardiac channel genes.[12] In fact, a total of 79 distinct channel variants were detected in these healthy subjects, including 14 variants in *KCNQ1*, 28 in *KCNH2* and 37 in *SCN5A*.[12] This has enabled a case-control mutational analysis of the properties and localization of case-associated mutations relative to the compendium of presumably innocuous variants.[12] The probabilistic rather than the binary nature of genetic testing is depicted in **Figure 32-2**, which shows that rare mutations other than missense mutations (approximately 20% of the LQTS spectrum of mutations) are high-probability LQTS-associated mutations whereas the probability of pathogenicity for the most common mutation type, missense mutations (i.e., single amino acid substitutions), is strongly location dependent. For example, missense mutations localizing to the transmembrane-spanning/pore domains of the LQT1- and LQT2-associated potassium channels are high-probability disease mutations, whereas a similarly rare missense mutation that localizes to the domain I-II linker of the $Na_v1.5$ sodium channel is indeterminate, a variant of uncertain significance (VUS). Without cosegregation or functional data, such a mutation has a point estimate for probability of pathogenicity of less than 50%.

In addition to this background frequency (4% to 8%) of rare variants in health, 15 unique common polymorphisms (allelic frequency >0.5%) have been identified in the four potassium channel subunit genes (*KCNQ1*, *KCNH2*, *KCNE1*, and *KCNE2*), and 8 common polymorphisms have been identified in the sodium channel gene (*SCN5A*). Many of these rare and common polymorphisms represent innocent bystanders; however, a layer of complexity is added to the genetics of these channelopathies, and management of patients with otherwise apparently innocuous variants can modify disease. For example, the most common sodium channel variant, H558R, which has a minor allelic frequency of approximately

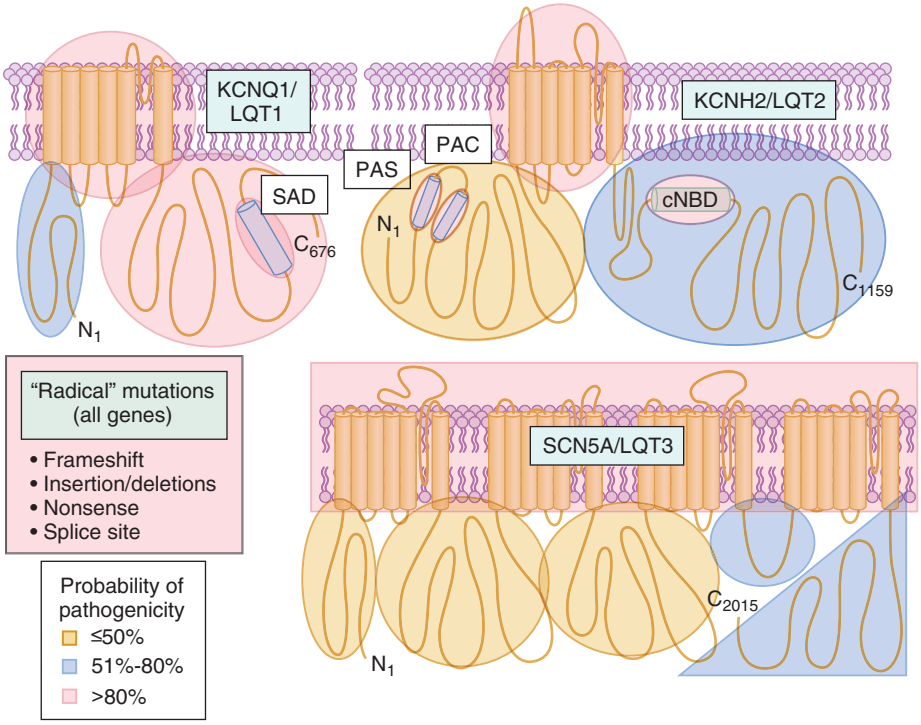

FIGURE 32-2 Probabilistic nature of LQTS genetic testing**.** Depicted are the three major ion channels involved in LQTS, with areas of probability of pathogenicity shown for mutations localizing to these respective areas. Even though "radical" mutations have greater than a 90% probability of being a true pathogenic mutation, the level of probability for missense mutations varies depending on their location for each channel protein. Missense mutations residing in *red-shaded areas* have a high probability (>80%) of being pathogenic, those in blue are possibly (51% to 80%) pathogenic, and those in *yellow-shaded areas* truly represent variants of uncertain significance (VUS, ≤50% probability) clinically. cNBD = cyclic nucleotide binding domain; PAC = PAS-associated C terminal; PAS = per (period circadian protein) arnt (aryl hydrocarbon receptor nuclear translocator protein) sim (single-minded protein); SAD = subunit assembly domain.

29% in blacks, 23% in Hispanics, 20% in whites, and 9% in Asians, can provide a modifying effect on the disease state through "intragenic complementation" (the interaction of two mutations within the same gene that produces a novel functional effect) of other *SCN5A* mutations.[13] In fact, several studies have indicated that some of these common polymorphisms may be informative clinically and relevant to the identification of those at risk for cardiac arrhythmias, particularly in the setting of TdP-inducing drugs or other environmental factors, as discussed later in this chapter.

Genotype-Phenotype Correlates in Long-QT Syndrome

The emergence of specific genotype/phenotype associations in LQTS suggest relatively gene-specific triggers, ECG patterns, and response to therapy (**Fig. 32-3**). Swimming- and exertion-induced cardiac events are strongly associated with mutations in *KCNQ1* (LQT1), whereas auditory triggers and events occurring during the postpartum period most often occur in patients with LQT2. Whereas exertion- or emotional stress–induced events are most common in LQT1, events occurring during periods of sleep or rest are most common in LQT3. In a study population of 721 LQT1 and 634 LQT2 genetically confirmed patients from the U.S. portion of the international LQTS registry, a multivariate analysis was used to assess the independent contribution of clinical and mutation-specific factors to the occurrence of a first triggered event associated with exercise, arousal, or sleep/rest.[14,15] Among the 221 symptomatic LQT1 patients, the first cardiac event was most often associated with exercise (55%), followed by sleep/rest (21%), arousal (14%), and nonspecific (10%) triggers; in contrast, the 204 symptomatic LQT2 patients most often had their first event associated with either arousal triggers (44%) or nonexercise/nonarousal triggers (43%), and only 13% of the symptomatic LQT2 patients had an exercise-triggered first event. In addition, males younger than 13 years with LQT1 had a nearly 3-fold increase in risk for exercise-triggered events, whereas females 13 years or older with LQT1 had a 3.5-fold increase in risk for sleep/rest nonarousal events. For LQT2 patients, the rate of arousal-triggered events was similar between boys and girls, but the rate of arousal-triggered events was significantly higher in women than in men (26% versus 6% at 40 years of age) after the onset of adolescence. Characteristic gene-suggestive ECG patterns have been described previously. LQT1 is associated with a broad-based T wave, LQT2 with a low-amplitude notched or biphasic T wave, and LQT3 with a long isoelectric segment followed by a narrow-based T wave.

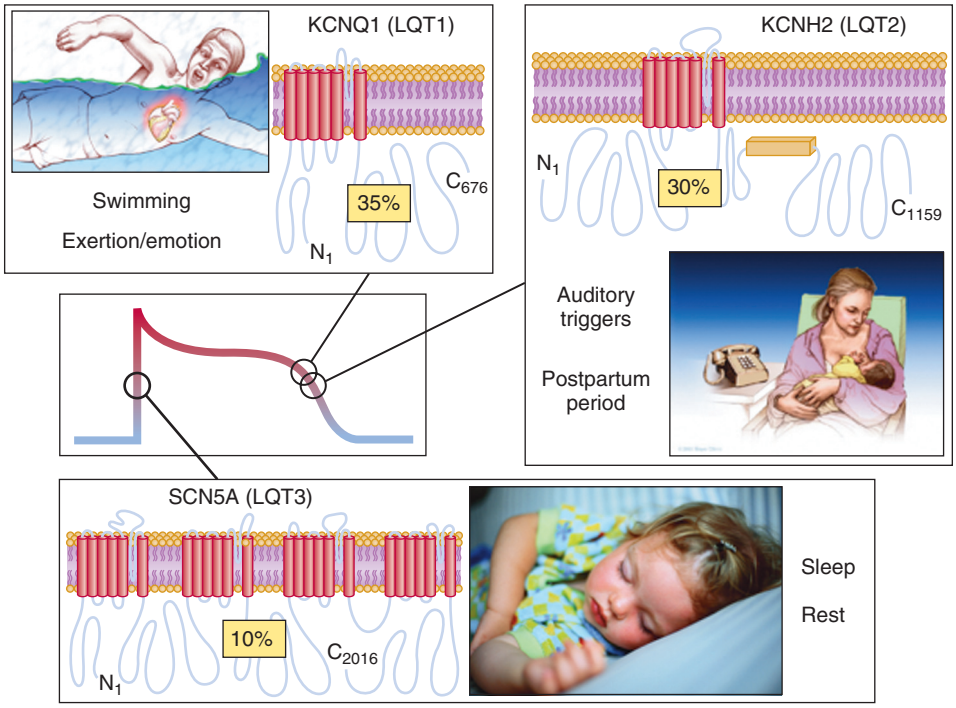

FIGURE 32-3 Genotype-phenotype correlations in LQTS. Seventy-five percent of cases of clinically strong LQTS are due to mutations in three genes (*KCNQ1*, 35%; *KCNH2*, 30%; and *SCN5A*, 10%) encoding for ion channels that are critically responsible for orchestration of the cardiac action potential. Genotype-phenotype correlations have been observed, including swimming/exertion/emotion and LQT1, auditory triggers/postpartum period and LQT2, and sleep/rest and LQT3.

However, exceptions to these relatively gene-specific T wave patterns exist, and thus due caution must be exercised when making a pre–genetic test prediction of the particular LQTS subtype involved because the most common clinical mimicker of an LQT3-appearing ECG is seen in patients with LQT1. This is key to keep in mind because importantly, the underlying genetic basis heavily influences the response to standard LQTS pharmacotherapy (beta blockers), with beta blockers being extremely protective in LQT1 patients and moderately protective in patients with LQT2 and LQT3.[16] Additionally, targeting the pathologic LQT3-associated late sodium current with agents such as mexiletine, flecainide, or ranolazine may represent a gene-specific therapeutic option for LQT3.[17,18] Attenuation in repolarization with clinically apparent shortening of the QTc has been demonstrated with such a strategy, although no evidence-based survival benefit has been shown thus far.[18] Realistically, however, at least a 30-year study may be needed for the latter. Even though the generalization that beta blocker efficacy depends on the genotype has been well accepted, the effectiveness of beta blocker therapy may be largely trigger-specific rather than dependent on genotype. In patients with either LQT1 or LQT2, beta blockade was associated with a pronounced 71% (LQT2 patients) to 78% (LQT1 patients) reduction in the risk for exercise-triggered cardiac events but had no statistically significant effect on the apparent risk for arousal- or sleep/rest-triggered events.[4,15] However, it should be noted that many symptomatic LQT1 and LQT2 patients experience a subsequent cardiac event associated with a different trigger. For example, an LQT2 patient first experiencing an arousal event or one during sleep may subsequently have an exercise-triggered event. Therefore, beta blocker therapy still remains first-line therapy even for patients experiencing a non–exercise-associated first event.

In addition, intragenotype risk stratification has been completed for the two most common subtypes of LQTS based on mutation type, mutation location, and cellular function.[19-22] Patients with LQT1 secondary to K_v7.1 missense mutations localizing to the transmembrane-spanning domains clinically have a twofold greater risk for an LQT1-triggered cardiac event than do LQT1 patients with mutations localizing to the C-terminal region. In addition, missense mutations localizing to the so-called cytoplasmic loops (C-loops) within the transmembrane-spanning domains, an area of the protein involved in the regulation of adrenergic channels, are associated with the highest rate of both exercise- and arousal-triggered events but not with an increase rate of sleep/rest-associated events.[15] C-loop K_v7.1 missense mutations were consistently associated with greater than a sixfold increase in risk for exercise-triggered events in comparison to nonmissense mutations and an almost threefold increase in comparison to N- and C-terminal missense mutations.[15]

Patients with mutations resulting in a greater degree of K_v7.1 loss of function at the cellular in vitro level (i.e., dominant negative) have a twofold greater clinical risk than that of patients with mutations that damage the biology of the K_v7.1 channel less severely (haploinsufficiency). Adding to the traditional clinical risk factors, molecular location and cellular function are independent risk factors used in the

evaluation of patients with LQTS.[20] Akin to molecular risk stratification in LQT1, patients with LQT2 secondary to K_v11.1 pore region mutations have a longer QTc and more severe clinical manifestation of the disorder and experience significantly more arrhythmia-related cardiac events occurring at a younger age than do LQT2 patients with non–pore-related mutations in K_v11.1.[23] Similarly, in a Japanese cohort of LQT2 patients, those with pore mutations had a longer QTc, and although not significant among probands, nonprobands with pore mutations experienced their first cardiac event at an earlier age than did those with a non–pore-related mutation.[21] Most recently, additional information has been gleaned suggesting that LQT2 patients with mutations involving the transmembrane pore region had the greatest risk for cardiac events, those with frameshift/nonsense mutations in any region had intermediate risk, and those with missense mutations in the C-terminus had the lowest risk for cardiac events.[22] Interestingly, LQT2 patients with mutations in the pore loop region of the K_v11.1 channel have a greater than twofold increased risk for arousal-triggered events, and LQT2 patients with non–pore loop transmembrane region mutations have an almost sevenfold increase in the risk for exercise-triggered cardiac events over patients with N-terminal/C-terminal (non-PAS domain) mutations.[24]

Incomplete penetrance and variable expressivity are the clinical hallmark features of LQTS, and it has long been thought that co-inheritance of a true disease-causing mutation and either a common or rare channel genetic variant may determine the expressed severity of the disorder. For example, coexistence of the common K897T-KCNH2 polymorphism and the A1116V-KCNH2 mutation (on opposite alleles) led to a more severe clinical course in a single Italian LQTS family. The A1116V mutation by itself produced a subclinical phenotype of mild QT prolongation and an asymptomatic course, whereas the proband hosting both variants had clinically overt disease consisting of diagnostic QT prolongation, presyncope episodes, and cardiac arrest.[25] Besides cardiac ion channels, single nucleotide polymorphisms (SNPs) of non–ion channel genes such as *NOS1AP* (the gene encoding the nitric oxide synthase 1 adapter protein), *ADRA2C* (alpha$_{2C}$-adrenergic receptor), and *ADRB1* (beta$_1$-adrenergic receptor) may modify disease severity in LQTS.[26-29]

In 2012, Amin and colleagues provided compelling evidence for a strong disease-modifying effect of a 3′ untranslated region (3′UTR), *KCNQ1* allele–specific haplotype in LQT1 mutation–positive pedigrees; the magnitude of the effect on the QTc and symptomatology goes well beyond any other currently described genetic modifiers.[30] The *KCNQ1* gene encodes for a single K_v7.1 ion channel alpha subunit. Following *KCNQ1* gene expression and post-translational modifications, four alpha subunits are assembled to create a pore-forming K_v7.1 tetrameric channel. Therefore, if a patient had a heterozygous *KCNQ1* mutation (i.e., one normal *KCNQ1* gene allele and one mutant allele), one would expect that if both the normal and mutant gene alleles were expressed in equal amounts, 1/16 of the channels would be normal homomeric tetramers and 1/16 would be mutant homomeric tetramers. The remaining channels would be hybrids containing both normal and mutant alpha subunits. One would predict that if the normal *KCNQ1* gene allele expression was somehow suppressed, there would be relatively more KCNQ1 mutant alpha subunits translated and ultimately assembled to provide more dysfunctional KCNQ1 channels and thus lead to a more severe manifestation of the disorder (**Fig. 32-4**). Simply put, far more bad (mutant) channels than good (healthy) channels would be created. The opposite would be true if the mutation containing the *KCNQ1* allele were suppressed.

Most genes have a 3′UTR that produces an mRNA transcript that contains regions of cis-regulatory binding sites for small noncoding

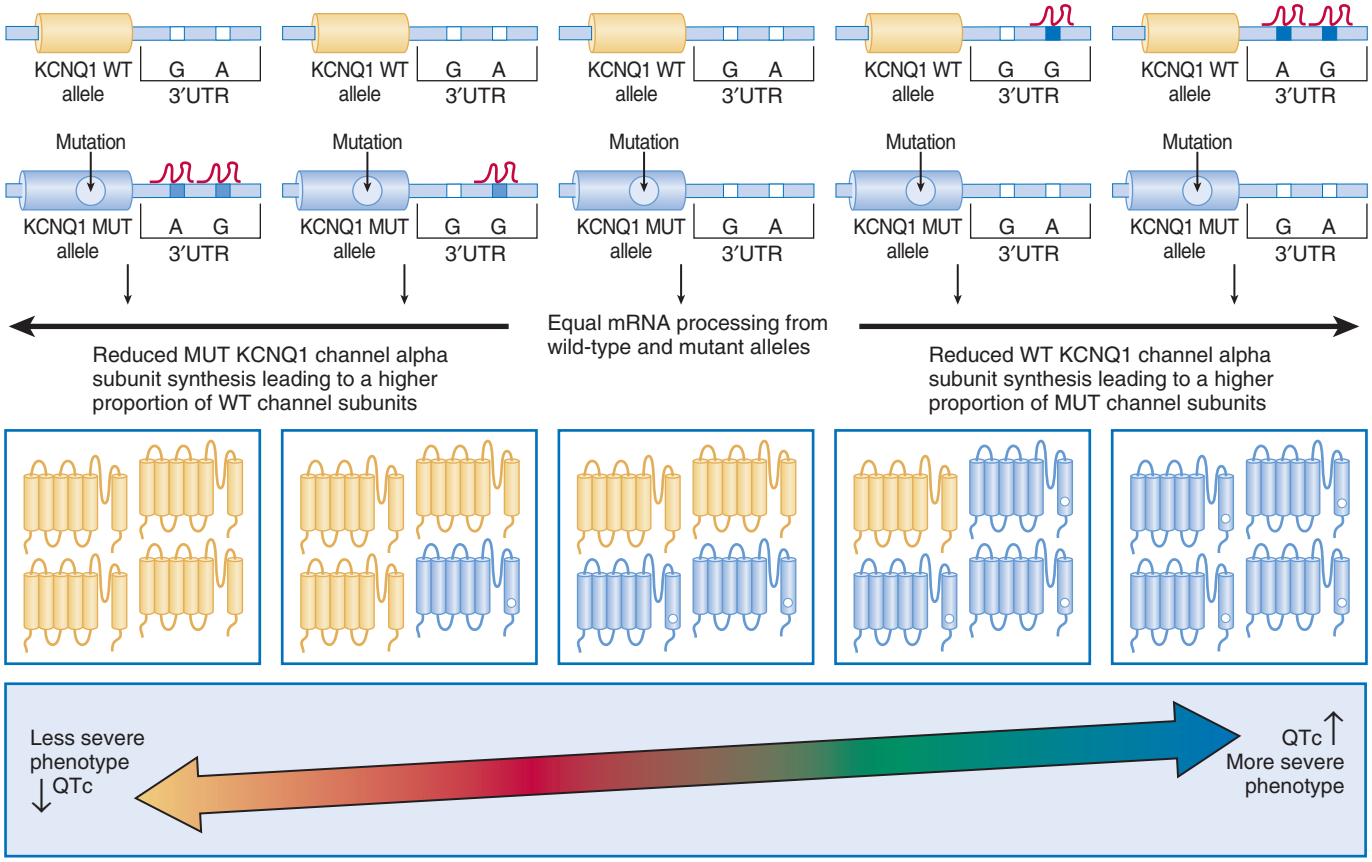

FIGURE 32-4 Hypothesized allele-specific mechanism of LQT1 disease modification by *KCNQ1* 3′UTR SNPs. Illustrated is the proposed microRNA-mediated allele-specific *KCNQ1* gene transcript–"suppressing" mechanism by the existence of naturally occurring SNPs within the *KCNQ1* 3′UTR whereby the presence of their minor alleles (A, G; *blue squares*) creates a "suppressive" haplotype by creating new microRNA (shown in *red*) binding sites that suppress expression of the *KCNQ1* gene allele in which they reside, thus altering the stoichiometric assembly of wild-type (i.e., normal, shown in *yellow*; WT) and mutant (shown in *blue*; MUT) K_v7.1 alpha subunits. *(Modified from Amin AS, Giudicessi JR, Tijsen AJ, et al: Variants in the 3′ untranslated region of the KCNQ1-encoded Kv7.1 potassium channel modify disease severity in patients with type 1 long QT syndrome in an allele-specific manner. Eur Heart J 33:714, 2012.)*

microRNA (miRNA) molecules that bind to the transcript and ultimately inhibit that gene's expression. Naturally occurring genetic variation within these 3′UTRs (miR-SNPs) can either abolish existing or create new miRNA binding sites. Amin and colleagues identified three naturally occurring SNPs (rs2519184, rs8234, and rs10798) within the *KCNQ1* 3′UTR whereby the presence of their minor alleles (A, G, G) generates a "suppressive" haplotype by creating new miRNA binding sites that suppress expression of the *KCNQ1* gene allele in which they reside.[30] In a cohort of 168 *KCNQ1* (LQT1) mutation–positive individuals from 41 families, Amin and colleagues showed that inheritance of the "suppressive" haplotype residing on the normal "healthy" allele produced a more severe LQT1 phenotype with regard to QTc and symptomatology than did inheritance of the "suppressive" haplotype residing on the same allele as the *KCNQ1* mutation (shorter QTc and fewer symptoms).[30] This intriguing discovery may not only explain a significant component of the reduced penetrance and variable expressivity that is a common feature of arrhythmia syndromes but may also represent a paradigm shift in our thinking about disease-modifying genetic drivers of mendelian disorders because one of the most important genetic determinants of disease severity in LQT1 appears to be the 3′UTR *KCNQ1* haplotype on the allele inherited from the unaffected "non-LQTS" parent.

In 2011, the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) released the first HRS/EHRA-sponsored guidelines for clinical genetic testing for LQTS and the other channelopathies and can be reviewed therein.[31]

Andersen-Tawil Syndrome

Clinical Description and Manifestations of Andersen-Tawil Syndrome

ATS, first described in 1971 in a case report by Andersen and later described by Tawil in 1994, is now recognized as a rare, multisystem disorder characterized by a triad of clinical findings, including periodic paralysis, dysmorphic features, and ventricular arrhythmias.[32] ATS is a heterogeneous disorder that is either sporadically or autosomal dominantly derived and has a high degree of variable phenotypic expression and incomplete penetrance, with as many as 20% of mutation-positive subjects being nonpenetrant.[32] The mean age at the onset of periodic paralysis has been reported to be 5 years (ranging from 8 months to 15 years) and slightly older, 13 years (range, ≈4 to 25 years), for cardiac symptoms.[32]

ECG abnormalities in ATS may include pronounced QTU prolongation, prominent U waves, and ventricular ectopy, including polymorphic ventricular tachycardia (VT), bigeminy, and bidirectional VT. Even though ventricular ectopy is common and ectopic density can be high in some patients, most patients with ATS are asymptomatic and SCD is extremely rare.[33] ATS1 was initially proposed as type 7 LQTS (LQT7) because of the observation of extreme prolongation of the QT interval; however, these measurements included the prominent U wave.[34] Accordingly, this complex clinical disorder, manifested at times with only a modest prolongation of the QT interval, is probably best considered as its own clinical entity and be referred to as ATS1 rather than as part of the LQTS regime. However, given the potential for false interpretation of the QT interval because of the prominent U wave and the probability of phenotypic expression of only cardiac-derived symptomatology (i.e., syncope, palpitations, ventricular rhythm disturbances), a considerable number of patients with ATS are conceivably misdiagnosed as having classic LQTS. Similarly, the presence of bidirectional VT, an accepted hallmark of CPVT (see later), often leads to ATS being misdiagnosed as the potentially lethal disorder CPVT. Correctly distinguishing between ATS and CPVT is critical because the treatment strategies are different.[35]

Genetic Basis for Andersen-Tawil Syndrome. To date, almost 40 unique mutations in *KCNJ2* have been described as being causative of ATS1. Mutations in *KCNJ2* account for approximately two thirds of cases of ATS, whereas the molecular basis of the residual third of ATS cases remains genetically and mechanistically elusive. However, the prevalence of *KCNJ2* mutations may be as high as 75% in patients with at least two ATS phenotypic features (i.e., typical ATS).[36] Localized to chromosome 17q23, *KCNJ2* encodes for Kir2.1, a small potassium channel alpha subunit expressed in brain, skeletal muscle, and heart that is critically responsible for the inward-rectifying cardiac I_{K1} current (see Table 32-1 and Fig. 32-1). In the heart, I_{K1} plays an important role in setting the heart's resting membrane potential, buffering extracellular potassium, and modulating the action potential waveform. Most *KCNJ2* mutations described in ATS are missense mutations that cause a loss of function of I_{K1}, either through a dominant negative effect on Kir2.1 subunit assembly or through haploinsufficiency as a result of protein trafficking defects.[37]

Genotype-Phenotype Correlates in Andersen-Tawil Syndrome

Genotype-specific ECG features of ATS are beginning to emerge. In a study by Zhang and colleagues in which T-U ECG morphology was examined, 91% of *KCNJ2* mutation–positive ATS1 patients had characteristic T-U wave patterns (including a prolonged terminal T wave downslope, a wide T-U junction, and biphasic and enlarged U waves) as opposed to none of the 61 unaffected family members or 29 genotype-negative ATS patients.[34] In a 2012 study by Kimura and associates, 88% of their *KCNJ2* mutation–positive ATS patients had an abnormal U wave.[36] Additionally, although the U wave is markedly abnormal in ATS1, it is typically normal in LQTS. Consequently, this *KCNJ2* gene–specific ECG feature of T-U morphology can be very useful in differentiating ATS1 patients from *KCNJ2* mutation–negative ATS and LQT1 to LQT3 patients and may facilitate a cost-effective approach to genetic testing of the appropriate disorder.[34] Interestingly, the topologic location of *KCNJ2* mutations may influence the phenotypic expression of ATS features. The vast majority (≈90%) of *KCNJ2* mutations reside in either the N- or C-terminus of this two-transmembrane single-pore channel. C-terminal mutations appear to be more often associated with typical ATS (more than two ATS features), dysmorphism, and periodic paralysis, whereas N-terminal mutations were more often observed in atypical ATS cases (only one ATS feature, predominately a cardiac phenotype only).[36]

Timothy Syndrome

Clinical Description and Manifestations of Timothy Syndrome

TS is an extremely rare (<30 patients described worldwide) multisystem, highly lethal arrhythmia disorder associated with both cardiac and extracardiac abnormalities. The typical cardiac manifestations of TS include fetal bradycardia and extreme prolongation of the QT interval (QTc >500 msec), often with macroscopic T wave alternans and a 2:1 atrioventricular (AV) block at birth.[38] These abnormalities frequently coincide with congenital heart defects or cardiomyopathies. The extracardiac abnormalities often consist of simple syndactyly (webbing of the toes and fingers), dysmorphic facial features, abnormal dentition, immune deficiency, severe hypoglycemia, and developmental delay (including autism).[38] Currently, most patients with TS die before reaching puberty. Although most cases of TS have been described as sporadic de novo occurrences, there have now been a few cases reported with somatic mosaicism that is associated with a less severe phenotype.[39] In such patients, for example, the *CACNA1C* mutation may be present in skeletal muscle but in only a minuscule amount or even completely absent in other types of cell in the human body (i.e., absent in heart, blood, lymphocytes, and other cell types), in which case the patient may have simple syndactyly but not an overt cardiac phenotype.

Genetic Basis for Timothy Syndrome. In 2004, Splawski and colleagues identified the molecular basis for this highly lethal arrhythmia disorder and coined it *Timothy syndrome* after Katherine Timothy, Drs. Keating's and Splawski's study coordinator, who meticulously phenotyped these cases.[38] Remarkably, in all 13 unrelated patients from whom DNA was available, Splawski and coworkers identified the same recurrent sporadic de novo missense mutation, G406R, in the alternatively spliced exon 8A of the *CACNA1C*-encoded cardiac LTCC ($Ca_v1.2$), which is important for excitation-contraction coupling in the heart and, like the cardiac sodium channel SCN5A, mediates an

inward depolarizing current in cardiomyocytes (see Table 32-1 and Fig. 32-1).[38] Through the mechanism of alternative splicing, the human LTCC consists of two mutually exclusive isoforms, one containing exon 8A and the other containing exon 8. A year later, Splawski and coworkers described two cases of atypical TS (TS2) with similar features of TS yet without syndactyly. As with other TS cases, these two atypical cases were identified as having sporadic de novo *CACNA1C* mutations not in exon 8A but rather in exon 8. One patient hosted a mutation analogous to the classic TS mutation G406R, whereas the other hosted a G402R missense mutation.[40] All three mutations confer gain of function to the LTCCs through impaired channel inactivation[38,40] and reside very near the end of the S6 transmembrane segment of domain I in the beginning of the intracellular loop between domains I and II of the $Ca_v1.2$ alpha subunit. In 2012, Gillis and associates identified a novel *CACNA1C* mutation, A1473G, in a single patient with a prolonged QT interval, dysmorphic facial features, syndactyly, and joint contractures consistent with TS.[41] Although this mutation has not yet been functionally characterized, interestingly, its topologic position (a few amino acids away from the S6 transmembrane segment of domain IV) in the channel architecture is very similar to the position of the three original TS mutations (S6 segment of domain I).

Short-QT Syndrome

Clinical Description and Manifestations of Short-QT Syndrome

Short-QT syndrome (SQTS), first described in 2000 by Gussak and colleagues, is associated with a short QT interval (usually ≤320 msec) on a 12-lead ECG, paroxysmal atrial fibrillation, syncope, and increased risk for SCD.[42] Giustetto and coauthors analyzed the clinical features of 53 patients with SQTS from 29 families, the largest cohort studied to date, and found that 62% of the patients were symptomatic, with cardiac arrest being the most common symptom (31% of patients) and frequently the first manifestation of the disorder.[43] A fourth of the patients had a history of syncope, and almost 30% had a family history of SCD. Symptoms, including syncope or cardiac arrest, occurred most often during periods of rest or sleep. Almost a third had atrial fibrillation.[43] SCD was observed during infancy, thus suggesting a potential role for SQTS as a rare pathogenic basis for some cases of SIDS.[42]

Genetic Basis for Short-QT Syndrome. SQTS is most often inherited in an autosomal dominant manner; however, some de novo sporadic cases have been described. To date, mutations in six genes (see Table 32-1) have been implicated in the pathogenesis of SQTS, including gain-of-function mutations in the potassium channel–encoding genes *KCNH2* (SQT1), *KCNQ1* (SQT2), and *KCNJ2* (SQT3) and loss-of-function mutations in *CACNA1C* (SQT4), *CACNB2b* (SQT5), and *CACNA2D1* (SQT6), which encode for the LTCC alpha, beta, and delta subunits, respectively (see Table 32-1 and Fig. 32-1).[42,44,45] However, despite identification of these six SQTS susceptibility genes, it remains unknown what proportion of SQTS is expected to be SQT1 to SQT6 genotype positive and what proportion awaits genetic elucidation. It is estimated that more than 75% of SQTS cases remain genetically elusive.

Genotype-Phenotype Correlates in Short-QT Syndrome

Even though data are insufficient to clearly define genotype-phenotype correlations in SQTS, with probably fewer than 60 cases having been described in the literature to date, gene-specific ECG patterns are beginning to emerge. The typical ECG pattern consists of a QT interval of 320 milliseconds or less (QTc ≤340 msec) and tall, peaked T waves in the precordial leads with either no or a short ST segment. The T waves tend to be symmetric in SQT1 but asymmetric in SQT2 to SQT4. In SQT2, inverted T waves can be observed. In SQT5, a BrS-like ST elevation in the right precordial lead may be observed.[42]

Despite perhaps being premature because of a small sample size, a recent report has suggested that SQTS patients with *KCNH2* mutations have a shorter QT interval and a greater response to hydroquinidine therapy than do patients with a non-*KCNH2*–mediated SQTS.[46]

Drug-Induced Torsades de Pointes

Clinical Description and Manifestations of Drug-Induced Torsades de Pointes

Drug-induced QT prolongation and/or drug-induced torsades de pointes (DI-TdP) are a constant concern for physicians prescribing particular drugs with the capacity for producing such unwanted and potentially life-threatening side effects (**see Chapters 9 and 37**). The estimated incidence of antiarrhythmic drug–induced TdP has ranged from 1% to 8%, depending on the drug and dose.[47] DI-TdP and subsequent sudden death are rare events; however, the list of potential "QT liability" or "torsadegenic" drugs is extensive and includes not only antiarrhythmic drugs such as quinidine, sotalol, and dofetilide but also many noncardiac medications such as antipsychotics, methadone, antimicrobials, antihistamines, and the gastrointestinal stimulant cisapride (see www.qtdrugs.org for a comprehensive list).[48]

I_{Kr} Channel Blockers and the Repolarization Reserve

In addition to their intended function and their intended target of action, the vast majority of medications with a potential unwanted TdP-predisposing side effect are $I_{Kr}/K_v11.1$ channel blockers (also referred to as HERG channel blockers). In effect, QT-prolonging drugs create an "LQT2-like" phenotype through reduced repolarization efficiency and subsequent lengthening of the cardiac action potential.[49] However, I_{Kr} drug blockade alone does not appear sufficient to provide the potentially lethal TdP substrate. One particular thesis centers on the observation that cardiac repolarization relies on the interaction of several ion currents that provide some level of redundancy in protecting against extreme QT prolongation by "QT liability" drugs.[47] This so-called repolarization reserve may be reduced through anomalies in the repolarization machinery, namely, as a result of common or rare genetic variants in critical ion channels that produce subclinical loss of the repolarizing currents I_{Ks} and I_{Kr}.[47] In fact, recent studies have revealed that 10% to 15% of patients with DI-TdP host rare ion channel mutations.[50] A smaller study found potential LQTS susceptibility mutations in 40% of cases of seemingly isolated, drug-induced LQTS.[51] Moreover, functional characterization of these mutations suggested that they were somewhat "weaker" than the loss-of-function mutations associated with classic, autosomal dominant LQTS, thus furthering the multiple-hit hypothesis that underlies the "reduced repolarization reserve."

Common Ion Channel Polymorphisms and Drug-Induced Torsades de Pointes. Among the common polymorphisms of the *KCNH2*-encoding I_{Kr} potassium channel, the K897T and R1047L polymorphisms have received the most attention (**see Chapter 9**). As noted in the review by Fitzgerald and Ackerman,[48] Paavonen and associates observed that T897-KCNH2 channels exhibit slower activation kinetics with a higher degree of inactivation, an alteration expected to decrease channel function and perhaps alter drug sensitivity because several commonly used drugs that inhibit I_{Kr} channel function bind preferentially to the inactivated state of the channel. These data suggest that T897 channels may genetically "reduce the repolarization reserve" and facilitate a proarrhythmic response that may be enhanced in the setting of I_{Kr} channel–blocking drugs when compared with wild-type K897 channels. In fact, K897T appears to affect the QTc response to ibutilide in a sex-specific manner. In a study by Sun and colleagues, as noted in a review by Schullze-Bahr,[13] among 105 patients with atrial fibrillation treated with dofetilide, R1047L was overrepresented in those in whom DI-TdP developed in comparison to patients who were free of TdP. As well as these common potassium channel alpha subunit polymorphisms, three common polymorphisms (D85N-KCNE1, T8A-KCNE2, and Q9E-KCNE2) involving auxiliary beta subunits have been implicated in drug-induced susceptibility to arrhythmia.[48]

In addition to genetic variants in major repolarizing channels, variants of the major depolarizing channel $Na_v1.5$ may provide a substrate for a proarrhythmic response in the setting of I_{Kr}-blocking drugs or in patients with other risk factors for DI-TdP. The most prominent channel polymorphism conferring susceptibility to arrhythmia in an ethnic-specific manner is S1103Y-SCN5A (originally annotated as the Y1102 variant). This polymorphism, seen in 13% of black Americans but not observed in any white or Asian controls (>1000 subjects), was overrepresented in arrhythmia cases (56.5%) in comparison to controls (13%) involving black Americans (odds ratio = 8.7).[47] S1103Y has been

found to produce subtle alterations in channel kinetics in heterologous expression studies when studied under basal conditions. However, functional and modeling studies have supported the potential for QT prolongation, reactivation of calcium channels early after depolarization, and arrhythmias, particularly in the setting of concomitant exposure to I_{Kr}-blocking drugs.

Recent genome-wide association studies have associated common variants of the *NOS1AP*-encoded nitric oxide synthase 1 adapter protein with QT interval duration. NOS1AP is a regulator of neuronal nitric oxide synthase (nNOS), which regulates intracellular calcium levels and myocyte contraction through its effect on LTCCs. Common SNPs in *NOS1AP* appear to be associated with drug-induced QT prolongation and ventricular arrhythmia.[52] This association was most pronounced in patients taking amiodarone, currently one of the most common antiarrhythmic drugs. It has been hypothesized that genetic variants in *NOS1AP* that suppress expression of the gene may in turn result in increased LTCC currents and subsequent QT prolongation and that individuals with such variants may be at increased arrhythmogenic risk while taking amiodarone.[52] However, although QT prolongation is observed routinely with amiodarone, DI-TdP attributed to amiodarone is exceedingly rare.

Additionally, genetic variation or individual differences in drug elimination or metabolism may contribute to individual risk for DI-TdP. For example, patients with a genetically mediated reduction in CYP3A enzymatic activity could be vulnerable to DI-TdP in the setting of I_{Kr} blockers that depend on the cytochrome P-450 enzyme CYP3A for its metabolism.[13]

THE OTHER CHANNELOPATHIES

Catecholaminergic Polymorphic Ventricular Tachycardia

Clinical Description and Manifestations of Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a heritable arrhythmia syndrome that is classically manifested as exercise-induced syncope or sudden death, is predominately expressed in the young, and closely mimics the phenotypic byline of LQT1 but appears to be far more lethal.[53,54] Like LQT1, swimming is a potentially lethal arrhythmia-precipitating trigger in CPVT. In fact, both LQT1 and CPVT have been shown to underlie several cases of unexplained drowning or near-drowning in young healthy swimmers.[55] However, CPVT is associated with a completely normal resting ECG (perhaps bradycardia and mild U waves) and is suspected on ECGs following either exercise or catecholamine stress testing in which significant ventricular ectopy is demonstrated that occasionally includes CPVT's pathognomonic arrhythmia of bidirectional VT.

Clinically, exercise-induced syncope and a QTc less than 460 milliseconds should always prompt first consideration of and need to rule out CPVT rather than the so-called concealed or normal–QT interval LQT1. Furthermore, exercise-induced premature ventricular complexes in bigeminy are far more likely than the more specific but less sensitive finding of bidirectional VT.[56] CPVT is associated with a structurally normal heart. Once thought to be manifested only during childhood, more recent studies have suggested that age at onset can range from infancy to 40 years. The potential lethality of CPVT is illustrated by mortality rates of 30% to 50% by the age of 35 years and the presence of a positive family history of young (<40 years) SCD in more than a third of individuals with CPVT and in as many as 60% of families hosting *RyR2* mutations.[53] Moreover, approximately 15% of autopsy-negative cases of SUD in the young and some cases of SIDS have been attributed to CPVT.[2,57]

Genetic Basis for Catecholaminergic Polymorphic Ventricular Tachycardia. Perturbations in key components of intracellular calcium-induced calcium release from the sarcoplasmic reticulum serve as the pathogenic basis for CPVT (**see Chapter 33**). Inherited in an autosomal dominant fashion, mutations in the *RyR2*-encoded cardiac ryanodine receptor/calcium release channel represent the most common genetic subtype of CPVT (CPVT1); such mutations account for 60% of clinically "strong" cases of CPVT (**Fig. 32-5**; also see Table 32-1). Gain-of-function mutations in *RyR2* lead to leaky calcium release channels, which results in excessive release of calcium, particularly during sympathetic stimulation, that can precipitate calcium overload, delayed depolarizations, and ventricular arrhythmias.[53] Again, most unrelated CPVT families are found to have their own unique *RyR2* mutations, and about 5% of unrelated mutation-positive patients host multiple putative pathogenic mutations.[58]

RyR2 is one of the largest genes in the human genome, with 105 exons that transcribe/translate one of the largest cardiac ion channel proteins consisting of 4967 amino acid residues. Although there do not appear to be any specific mutation "hot spots," there are three regional hot spots or domains in which unique mutations reside (see Fig. 32-5). This observation has lent itself toward targeted genetic testing for *RyR2*

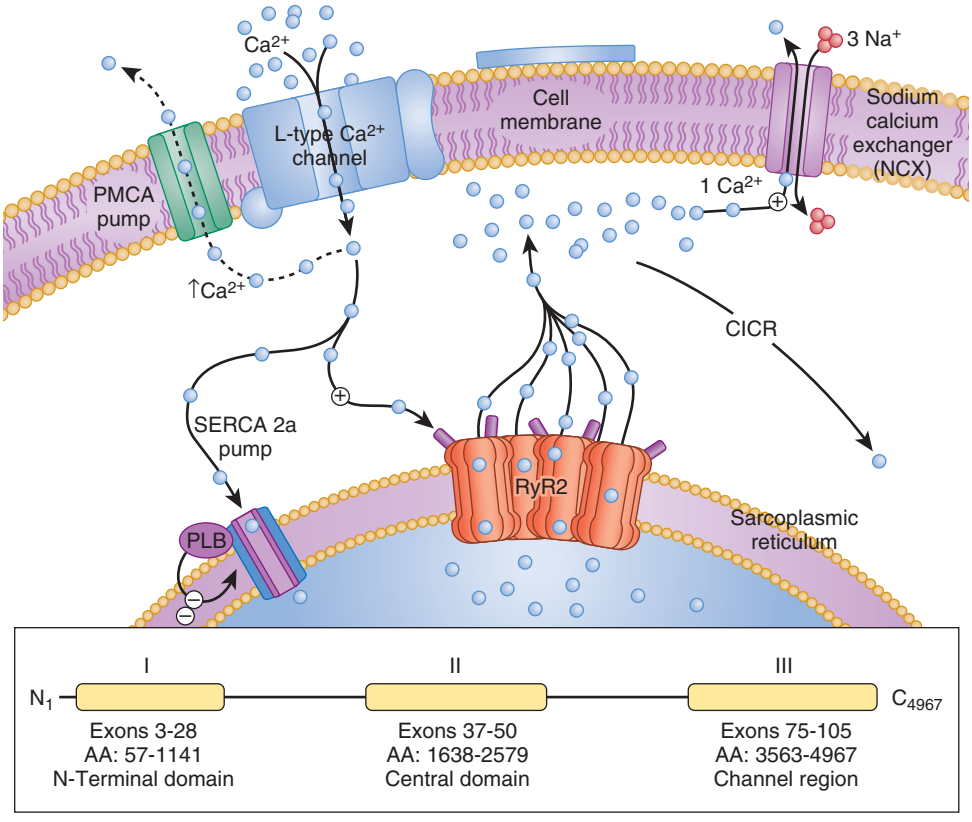

FIGURE 32-5 CPVT: a disorder of intracellular calcium handling. Perturbations in key components of the calcium-induced calcium release (CICR) mechanism responsible for cardiac excitation-contraction coupling are the pathogenic basis for CPVT. At the center of this mechanism is the *RyR2*-encoded cardiac ryanodine receptor/calcium release channel located in the membrane of the sarcoplasmic reticulum. Mutations in *RyR2* are clustered and distributed in three "hot spot" regions of this 4967–amino acid (AA) protein: domain I or the N-terminal domain (AA 57 to 1141), domain II or the central domain (AA 1638 to 2579), and domain III or the channel region (AA 3563 to 4967). PLB = phospholamban; PMCA = plasma membrane Ca^{2+}-adenosine triphosphatase (ATPase); SERCA 2a = sarcoendoplasmic reticulum Ca^{2+}-ATPase 2a.

(≈61 exons) rather than a comprehensive 105-exon scan. More than 90% of the *RyR2* mutations discovered to date represent missense mutations; however, perhaps as many as 5% of unrelated CPVT patients host large gene rearrangements consistent with large whole-exon deletions, akin to what has been observed in LQTS.[58] Even though genotype-phenotype correlations are very limited to date, a recent publication has suggested that family members hosting C-terminal (ion channel–forming domain) *RyR2* mutations may have a higher ventricular arrhythmia burden of nonsustained VT than individuals hosting N-terminal or central domain *RyR2*-localizing mutations.[59]

Strikingly, nearly a third of "possible/atypical" patients with LQTS (QTc <480 msec) and exertion-induced syncope have also been identified as *RyR2*-mutation positive.[58] In fact, it has been reported that almost 30% of patients with CPVT have been misdiagnosed as having "LQTS with normal QT intervals" or "concealed LQTS," thus indicating the critical importance of properly distinguishing between CPVT and LQTS at the clinical level because risk assessments and treatment strategies for these unique disorders may vary. Similarly, some patients in whom CPVT is diagnosed based on the presence of bidirectional VT during exercise have been identified with *KCNJ2* mutations that are associated with the rarely lethal ATS.[35] Misdiagnosis of ATS as the potentially lethal disorder CPVT may lead to more aggressive prophylactic therapy (i.e., cardioverter-defibrillator implantation) than necessary. Two autosomal recessive forms of CPVT have been identified that involve mutations in either the *CASQ2*-encoded calsequestrin-2 protein or *TRDN*-encoded triadin.[60,61] Most recently, mutations in calmodulin-1 (*CALM1*) have been implicated as a cause of autosomal dominant CPVT; a single missense mutation was identified that segregated with a CPVT phenotype in a large Swedish pedigree (see Table 32-1).[62]

Brugada Syndrome

Clinical Description and Manifestations of Brugada Syndrome

BrS is an heritable arrhythmia syndrome characterized by an ECG pattern consisting of coved-type ST-segment elevation (≥2 mm) followed by a negative T wave in the right precordial leads V_1 through V_3 (often referred to as a type 1 Brugada ECG pattern) and increased risk for sudden death resulting from episodes of polymorphic ventricular tachyarrhythmias.[63,64] The penetrance and expressivity of the disorder are highly variable and range from life-long asymptomatic individuals to SCD during the first year of life. BrS is generally considered a disorder that involves young male adults, perhaps greatest in Southeast Asian males, with arrhythmogenic manifestations first arising at an average age of 40 years and sudden death typically occurring during sleep.[65,66] In fact, sudden unexplained nocturnal death in young males is endemic in Southeast Asia and is now considered phenotypically, genetically, and functionally the same disorder as BrS.[64] However, BrS has also been demonstrated in children and infants.[67] In a 2007 population study of 30 children (<16 years of age) affected by BrS from 26 families, fever was the most common precipitating factor for arrhythmic cardiac events, including syncope and SCD.[67]

Genetic Basis for Brugada Syndrome. BrS is inherited as an autosomal dominant trait; however, more than half of BrS cases may be sporadic. Approximately 20% to 30% of BrS cases stem from loss-of-function mutations in the *SCN5A*-encoded cardiac sodium channel (see Table 32-1 and Fig. 32-1) and are classified as Brugada syndrome type 1 (BrS1). In 2010, an international compendium of *SCN5A* mutations in patients referred for BrS genetic testing reported almost 300 distinct mutations in 438 of 2111 (21%) unrelated patients, and the mutation detection yield ranged from 11% to 28% across nine centers.[68] The yield of mutation detection may be significantly higher with familial forms than with sporadic cases. Schulze-Bahr and coworkers identified *SCN5A* mutations in 38% of their familial BrS cases as opposed to none in 27 sporadic cases ($P = 0.001$).[69] Most of the mutations were missense (66%), followed by frameshift (13%), nonsense, (11%), splice site (7%), and in-frame deletions/insertions (3%). Approximately 3% of genotype-positive patients host multiple putative pathogenic *SCN5A* mutations, and like the genotype-phenotype observations in LQTS,[6] patients hosting multiple *SCN5A* mutations tend to be younger at diagnosis (29.7 ± 16 years) than those with a single mutation (39.2 ± 14.4 years).[68] Again, as with LQTS, there is no particular mutational hot spot, with almost 80% of the BrS-related *SCN5A* mutations occurring as "private" single-family mutations. However, almost 10% of the 438 unrelated, *SCN5A* mutation–positive patients hosted one of four mutations: E1784K (14 patients), F861WfsX90 (11 patients), D356N (8 patients), and G1408R (7 patients).[68] Interestingly, the most commonly occurring BrS1 mutation, E1784K, has also been reported to be the most commonly seen LQT3-associated *SCN5A* mutation, thus illustrating how the same exact DNA alteration in a given gene can lead to two distinct cardiac arrhythmia syndromes, most likely as a result of other environmental or genetic modifying factors. In fact, E1784K represents the quintessential example of a cardiac sodium channel mutation with the capacity to provide a mixed clinical phenotype of LQT3, BrS, and conduction disorders.[70]

In addition to pathogenic mutations in *SCN5A*, common polymorphisms may have a modifying effect on the disorder. As noted in the review by Antzelevitch and Nof,[71] Bezzina and colleagues described an Asian-specific haplotype of six *SCN5A* promoter polymorphisms in nearly complete linkage disequilibrium that occurred with an allelic frequency of 22% and was comparatively absent in whites and blacks. These promoter region polymorphisms may modulate the variability in cardiac conduction and in part contribute to the higher prevalence of BrS observed in the Asian population. Brugada and coauthors provided data supporting the common polymorphism H558R as a modulator of the BrS phenotype, with the minor allele R558 providing a less severe clinical course in their 75 genotyped patients with BrS.[64] Patients homozygous for H558 had a longer QRS complex duration in lead II, higher J point elevation in lead V_2, and a higher "aVR sign" and tended to have more symptoms than H558R heterozygotes or R558 homozygotes.[64]

Mutations have now been discovered in 13 BrS susceptibility genes in addition to *SCN5A* (see Table 32-1). Mechanistically, either decreases in the inward sodium or calcium currents or increases in the outward $K_v4.3$ potassium current produce the BrS phenotype through perturbation of either the respective channel alpha subunits or channel-interacting proteins (see Fig. 32-1).[65] For example, mutations in the glycerol-3-phosphate dehydrogenase 1–like protein encoded by *GPD1L* affect trafficking of the sodium channel to the plasma membrane, thus reducing the overall sodium current and giving rise to the BrS phenotype,[72] whereas mutations involving the LTCC alpha and beta subunits encoded by the *CACNA1C* and *CACNB2b* genes, respectively, were implicated in approximately 10% of BrS cases.[73] However, on closer examination of this seminal discovery, a tight link between calcium channel–mediated disease and the clinical phenotype of BrS with a concomitant short QT interval is evident, with 50% of patients with BrS/short QT interval hosting a mutation in the LTCC subunit. In fact, in 2012, Crotti and colleagues performed the first comprehensive mutational analysis of a large cohort of unrelated patients with BrS, and although they identified *SCN5A* mutations in 16% of the cohort, only 1.5% of the BrS cases had a mutation in one of the LTCC subunit genes in the absence of a short QT interval.[74] Importantly, the genetic cause of more than two thirds of clinically diagnosed cases of BrS remains elusive, thus suggesting a high degree of genetic heterogeneity for this disorder. This degree of genetic elusiveness also begs the question of whether most BrS is a genetically heterogeneous monogenic disorder or in fact a congenital heart defect/developmental disorder involving the epicardial right ventricular outflow tract.[75]

Genotype-Phenotype Correlates in Brugada Syndrome

Because most BrS cases are genetically elusive, genotype-phenotype correlations in BrS have not been analyzed to the same degree as in LQTS. *SCN5A* mutations are associated with a higher incidence of conduction abnormalities in patients with BrS, and the presence of a long PQ interval may be indicative of *SCN5A*-mediated BrS1, whereas the presence of a short QT interval (QTc <350 msec) may be indicative of LTCC-mediated BrS pathology. In fact, Crotti and coauthors reported that although fewer than 10% of patients with a PQ interval of less than 200 milliseconds had a positive *SCN5A* genetic test, the yield was almost 40% in patients with a PQ interval of 200 milliseconds or more.[74] Interestingly, young males with BrS (<20 years, 83%) had a significantly higher *SCN5A* mutation detection rate than did males aged 20 to 40 years (21%) and those older than 40 years (11%, $P < 0.0001$).[74] In addition, patients with BrS1 and nonsense, frameshift, or premature truncation–causing mutations exhibited a more severe phenotype.[76] Unlike genetic testing for LQTS, in which the triad of diagnostic, prognostic, and therapeutic impact has been fulfilled, genetic testing for BrS is currently limited by its lower yield (25% for BrS versus 75% for LQTS) and relative absence of a therapeutic contribution from knowledge of the genotype.[31,77]

Early Repolarization Syndrome

Clinical Description and Manifestations of Early Repolarization Syndrome

The early repolarization (ER) pattern is characterized by the ECG finding of elevation (≥1 mm above baseline) of the QRS-ST junction (the so-called J point) manifested as either QRS slurring (at the transition of the QRS to the ST segment) or notching (a positive deflection inscribed on the terminal S wave), ST-segment elevation with upper concavity, and prominent T waves in two or more contiguous leads.[78] The prevalence of the ER pattern in the general population has been reported to range from less than 1% to 13%, depending on age, sex, race, and the criteria for J point elevation.[78] This ECG phenomenon has long been considered an innocuous variant in healthy individuals. However, Haissaguerre and colleagues noted that J point elevation (≥1 mm above baseline) on inferolateral ECG leads was significantly overrepresented (31%) and greater in magnitude in 206 case subjects who experienced cardiac arrest secondary to idiopathic ventricular fibrillation (IVF) than in 412 controls (5%, $P < 0.001$) matched for age, sex, race, and level of physical activity.[79] Patients with ER were more often males and had a personal history of syncope or cardiac arrest during sleep than did those without an ER pattern.[79] Similarly, Rosso and associates saw an overrepresentation of J point elevation in their 45 patients with IVF in comparison to controls (45% versus 13%, $P = 0.001$), with the same observation of a male preponderance in those with ER.[80]

In a community-based general population of 10,864 middle-aged (30 to 59 years old, 52% male) Finnish subjects, Tikkanen and colleagues identified 630 subjects overall (5.8%) with a J point elevation of at least 0.1 mV.[81] The overall prevalence of the ER pattern was reduced to just 0.33% when considering a J point elevation of 0.2 mV or higher. After a 30-year follow-up with the endpoint being cardiac death, Tikkanen and colleagues noted that when compared with subjects without a J point elevation, subjects with ER (J point ≥0.1 mV) in the inferior leads had an increased risk for both cardiac death (adjusted relative risk [ARR] = 1.28; 95% confidence interval [CI] = 1.04 to 1.59; $P = 0.03$) and arrhythmias (ARR = 1.43; 95% CI = 1.06 to 1.94; $P = 0.03$) and that this risk was further elevated (cardiac death ARR = 2.98; 95% CI = 1.85 to 4.92; $P < 0.001$; arrhythmia ARR = 2.92; 95% CI = 1.45 to 5.89; $P < 0.001$) with increasing elevation (≥0.2 mV) of the J point. However, an ER pattern localizing to only the lateral leads did not show a statistically significant association with increased risk for arrhythmic cardiac death.[81] Obviously, the vexing clinical conundrum with respect to this inferolateral early repolarization syndrome (ERS) is that of distinguishing potentially lethal ERS from the all too often observed juvenile ER pattern seen in healthy subjects, particularly healthy athletes.

Genetic Basis for Early Repolarization Syndrome. The inclination for a genetic basis for ERS stems from Haissaguerre and colleagues' observation that 16% of their patients with IVF and an ER pattern had a family history of SUD.[79] The first gene to be implicated in ERS was described by Haissaguere and associates, who reported finding a rare, functionally uncharacterized, missense mutation (S422L) in the *KCNJ8*-encoding pore-forming subunit Kir6.1 of the adenosine triphosphate–sensitive potassium channel in a 14-year-old girl with IVF.[82] Since then, this same mutation has been described in additional cases of BrS and ERS and has been shown to have a gain of function in electrophysiologic phenotype.[83,84] In 2010, Burashnikov and colleagues implicated the LTCC alpha-1 (*CACNA1C*), beta-2 (*CACNB2b*), and alpha-2-delta (*CACNA2D1*) subunit–encoding genes in the pathogenesis of ERS with their identification of mutations in 4 of 24 (16.7%) ERS index cases[85]; however, not all these genetic variants have been characterized functionally, and some may represent a rare VUS.

Progressive Cardiac Conduction Disease

Clinical Description and Manifestations of Progressive Cardiac Conduction Disease

Cardiac conduction disease (CCD) causes a potentially life-threatening alteration in normal impulse propagation through the cardiac conduction system. CCD can be a result of a number of physiologic mechanisms ranging from acquired to congenital, with or without structural heart disease. Progressive cardiac conduction disease (PCCD), also known as Lev-Lenègre disease, is one of the most common cardiac conduction disturbances in the absence of structural heart disease and is characterized by a progressive (age-related) alteration in impulse propagation through the His-Purkinje system, with right or left bundle branch block and widening of the QRS complex leading to complete AV block, syncope, and occasionally sudden death.[66]

Genetic Basis for Progressive Cardiac Conduction Disease. As noted in a review by Raun and associates,[66] Schott and coworkers further expanded the spectrum of loss-of-function *SCN5A* disease in 1999 with the inclusion of familial PCCD. They identified a splice site *SCN5A* mutation (c.3963+2 T>C) associated with an autosomal dominant inheritance pattern in a large French family. Since then, investigators have identified more than 30 PCCD-associated mutations in *SCN5A*; additionally, mutations in *SCN1B* can cause BrS with conduction disease. These mutations result in a loss-of-function phenotype through reduced current density and enhanced slow inactivation of the channel. As with most loss-of-function *SCN5A* diseases, the phenotypic expression of PCCD can be complex and is often accompanied by a concomitant BrS or BrS-like phenotype. In fact, Probst and coworkers showed that PCCD is the prevailing phenotype in BrS-associated *SCN5A* mutation carriers, in whom the penetrance of conduction defects was 76%.[67]

In 2009, Meregalli and colleagues demonstrated that the *SCN5A* mutation type can have a profound effect on the severity of PCCD and BrS.[76] Studying 147 individuals hosting one of 32 different *SCN5A* mutations, Meregalli and coworkers found that patients with either a premature truncation mutation (M_T, i.e., nonsense or frameshift) or a severe loss-of-function missense mutation ($M_{inactive}$, >90% reduction in peak I_{Na}) had a significantly longer PR interval than did patients with missense mutations causing less impairment of the sodium current (M_{active}, ≤90% reduction). Furthermore, patients with a truncation mutation had significantly more episodes of syncope than did those with an "active" mutation (M_{active}).[76] These data suggest that mutations with more deleterious loss of sodium current produce a more severe phenotype of syncope and conduction defect, thus providing the first evidence for intragenotype risk stratification associated with *SCN5A* loss-of-function disease.

Most recently, gain-of-function mutations (E7K, R164W, A432T, and G844D) in the *TRPM4*-encoded transient receptor potential melastatin type 4 ion channel have been implicated as a cause of autosomal dominant isolated CCD and progressive familial heart block type 1 (PFHB1) following linkage analysis and subsequent mutational analysis of *TRPM4* in four different large multigenerational pedigrees, thus identifying an essential role for calcium-activated nonselective cation channel activity in the cardiac conduction system.[86,87]

When CCD is associated with a concomitant LQTS phenotype, the QRS interval is usually narrow and the conduction defect is commonly an intermittent 2:1 AV block. Patients with LQT2, TS1, or ATS1 may also have dysfunctional AV conduction.

Sick Sinus Syndrome

Clinical Description and Manifestations of Sick Sinus Syndrome

Sinus node dysfunction (SND) or sick sinus syndrome (SSS) manifested as inappropriate sinus bradycardia, sinus arrest, atrial standstill, tachycardia-bradycardia syndrome, or chronotropic incompetence is the principal reason for pacemaker implantation and has been attributed to dysfunction of the sinoatrial (SA) node[37,66] (**see Chapter 37**). SSS commonly occurs in the elderly (1 in 600 cardiac patients >65 years) with acquired cardiac conditions, including cardiomyopathy, congestive heart failure, ischemic heart disease, or metabolic diseases. However, a significant number of patients have no identifiable cardiac anomalies or cardiac conditions underlying their sinus node dysfunction ("idiopathic SND"), which can occur at any age, including in utero.[37] Additionally, familial forms of idiopathic SND consistent with autosomal dominant inheritance with reduced penetrance and recessive forms with complete penetrance have been reported.[66]

Genetic Basis for Sick Sinus Syndrome. Mutational analysis of small cohorts and case reports of patients with idiopathic SSS have thus far implicated three genes: *SCN5A*, *HCN4*, and *ANKB* (see Table 32-1). To date, 15 SSS-associated mutations have been reported in *SCN5A*.[66,88]

The mutations produced either nonfunctional sodium channels through loss of expression or channels with mild to severe loss of function through an altered biophysical mechanism of the channel.[88] As noted in a review by Raun and associates,[66] in 2003, basing their work on previous observations of arrhythmias and conduction disturbances, Benson and colleagues examined *SCN5A* as a candidate gene for congenital SSS in 10 pediatric patients from seven families in whom SSS was diagnosed during the first decade of life. They identified compound heterozygote mutations (T220I + R1623X, P1298L + G1408R, and delF1617 + R1632H) in five individuals from three of the seven families, thus implicating *SCN5A* in autosomal recessive SSS. Not surprisingly, many of the *SCN5A*-positive patients displayed a mixed phenotype consisting of SSS, BrS, and/or CCD. The expressivity of the mixed phenotype can be highly variable within affected families. In 2007, the case of a 12-year-old boy with SSS, CCD, and recurrent VT was presented. The patient was identified with an L1821fsX10 frameshift mutation that displayed a unique channel phenotype of 90% reduced current density (consistent with BrS/SSS/CCD), yet an increase in the late sodium current relative to the peak current (consistent with LQT3) in the channels that are expressed. As illustrated by this family, in which the mutation was present in six asymptomatic family members and two displayed only mild ECG phenotypes, this disorder is often associated with incomplete or low penetrance.

Two loss-of-function mutations in the hyperpolarization-activated cyclic nucleotide–gated channel 4 gene *HCN4* have been identified in two cases of idiopathic SND. The *HCN4* gene encodes the so-called I_f or pacemaker current and plays a key role in automaticity of the sinus node. In one study, a heterozygous single nucleotide deletion (c.1631delC) creating a frameshift mutation (P544fsX30) with early truncation of the protein was identified in a patient with idiopathic SND, and in a second study, another patient with idiopathic SND had a missense mutation (D553N) that results in abnormal trafficking of the pacemaker channel.[89] Interestingly, although the frameshift mutation identified in a 66-year-old woman produced a mild phenotype associated with sinus rhythm during exercise, the D553N missense mutation identified in a 43-year-old woman was associated with severe bradycardia, recurrent syncope, QT prolongation, and polymorphic VT (TdP), thus suggesting the potential for lethality in *HCN4*-mediated disease.[89] Whether the preliminary 10% to 15% yield of defective *HCN4*-encoded pacemaker channels in idiopathic SND derived from the two small cohorts is durable will require further studies involving much larger cohorts.

In 2008, Le Scouarnec and coauthors reported the genetic and molecular mechanism involving *ANK2* (also known as *ANKB*)-encoded ankyrin-B in two large families with highly penetrant and severe SND.[90] Ankyrin-B is essential for normal membrane organization of the ion channels and transporters in cardiocytes within the SA node and is required for proper physiologic cardiac pacing. Dysfunction of the ankyrin-B–based trafficking pathway causes abnormal electrical activity in the SA node and SND.[90] Similar to the sodium channel, variants in *ANK2* cause a variety of cardiac dysfunctions.

CONCLUSIONS

This relatively new discipline of the heritable arrhythmia syndromes/cardiac channelopathies has exploded over the past decade. The pathogenic insights into the molecular underpinnings for nearly all these syndromes have matured through the entire continuum of research from discovery, translation, and most recently, incorporation into clinical practice. This bench-to-bedside maturation now requires learned interpretation of the available genetic tests for these syndromes and a clear understanding of the diagnostic, prognostic, and therapeutic implications associated with genetic testing for these channelopathies.

FUTURE PERSPECTIVES

The emergence of next-generation sequencing platforms and systems biology bioinformatics algorithms is providing new tools to efficiently interrogate an individual's entire genome or exome (entire amino acid–encoding region of the genome) in a single reaction. This highly proficient technology effectively provides a list of every single nucleotide substitution and small insertion/deletion (common or rare, benign or pathogenic) for every gene in a patient's genome and is crucial for the current and next phase of new gene discovery within even small currently genotype-negative pedigrees. It is through the current advanced sequencing technologies and systems biology bioinformatics algorithms and those on the horizon that we will soon be able to close the genetic gap in our understanding of these potentially lethal yet highly treatable cardiac arrhythmia syndromes.

In addition, recent advances in cellular programming have provided new avenues for understanding the cause of complex diseases. The biomedical promise of human induced pluripotent stem cell–generated cardiomyocytes derived from the patient's own skin biopsy specimen (fibroblast) is enormous and may hold significant promise in cardiac research involving disease models, personalized drug development, and key questions about the reduced penetrance and variable expressivity that is common in these cardiac channelopathies.

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