

## An Update on Channelopathies: From Mechanisms to Management Gregory Webster and Charles I. Berul

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## An Update on Channelopathies From Mechanisms to Management

Gregory Webster, MD; Charles I. Berul, MD

The basic science of membrane channels has set in motion striking clinical results, especially in cardiology. The clinical phenotype of cardiac channelopathies is conspicuous; sudden death or cardiac arrest may be the initial presentation. The last 2 decades have changed the face of diagnosis and treatment of inherited channelopathies for families who have a high, and often unrecognized, likelihood of sudden death.

The simple paradigm of one gene, one mutation, one disease remains true in some channelopathy diseases, but as we look deeper, the relationships increase in complexity as channel biology interrelates with membrane, intercellular, and extracellular biology. No protein acts in isolation. Genetic testing ideally identifies patients at risk, offers a window into optimal therapy, and aids in identifying those patients who are not carriers and therefore assign them to a low-risk group. However, the best-case scenario is not always the clinical scenario. The task of the clinical practitioner is to digest the flood of basic science information and use it to best serve patients.

As the prevalence of genetic testing has increased, the limitations become more important to the practicing physician. Testing may reveal a change in the patient's genome from the typical sequence, but certifying a mutation as the clinical cause of a patient's disease remains a challenge. Along with the difficult task of learning the names and nuances of the genetic products (eg, the LQT1 genotype stems from mutations in *KCNQ1*, previously known as *KVLQT1*, on chromosome 11p15.5, encoding Kv7.1, which conducts an  $I_{Ks}$  current), the practitioner must learn a new genetic vocabulary to convert a cardiac genetic test report into an informed clinical decision. The aim of this review is to summarize the scope of arrhythmia genetics and relate those mechanisms to clinical management strategies.

### Beyond Long QT Syndrome

When Keating et al<sup>1</sup> made the seminal discovery of genetic linkage for long-QT syndrome (LQTS), they changed the paradigm of inherited arrhythmias. Shortly thereafter, specific mutations in the *KCNQ1*, *KCNH2*, and *SCN5A* genes were identified as causative, supporting the pathophysiologic concept that defects in genes encoding cardiac ion channels were the basis for the clinical disorder LQTS (previously referred to as the eponyms Romano-Ward syndrome, for the

autosomal-dominant form with normal hearing, and Jervell and Lange-Nielsen syndrome, which was associated with congenital sensorineural deafness). This discovery turned out to be the cornerstone of LQTS diagnosis and treatment.<sup>2-4</sup> The study of these genetic abnormalities revealed that channel systems are more elegant and much more complicated than the channels in the membranes alone. In 2013, the science of inherited channelopathies comprises studies of the whole channel apparatus as well as the trafficking mechanisms that direct proteins to the membrane, the associated proteins that change the conformation and function of the channel, gene-gene and protein-protein interactions, and the structural framework that directs and supports proteins in the cell membrane. Recent attention has turned to the cardiac organelles, which have their own channels, trafficking proteins, and internal apparatus. Errors in any of these components and others that are yet to be discovered are the underpinnings of clinical disease. Environmental and somatic factors, as well as a multitude of confounding genetic influences, may impact the severity of disease expression. This complexity is one reason why the clinical phenotype of inherited arrhythmias is so heterogeneous, even among those with identical genetic mutations.

We first present a summary of current issues in genetic testing and then move forward to discuss cardiac channelopathies in LQTS, short QT syndrome (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy (ARVC), and other inherited arrhythmia disorders (Table 1).

### Mutations, SNPs, and the Vagaries of the Human Genome

Although the majority of the human genome is conserved between any 2 individuals, the differences in genetic code can contribute to individual differences. Genetic variations exist even in normal subjects; single nucleotide mutations are common. In a healthy control sample, the presence of a mutation does not suggest occult disease. Instead, it is tabulated as a normal variant. With sufficient effort, this creates a database of every position in the gene, some of which are known to have the same nucleotide in nearly every human (as well as in other species) studied (a highly conserved location) and some are known to have tolerance for substitutions. The list

From the Division of Cardiology, Lurie Children's Hospital, Chicago, IL (G.W.); the Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL (G.W.); the Division of Cardiology, Children's National Medical Center, Washington, D.C. (C.I.B.); and the Department of Pediatrics, George Washington University School of Medicine, Washington, D.C. (C.I.B.).

Correspondence to: Charles I. Berul, MD, Division of Cardiology, Children's National Medical Center, 111 Michigan Ave NW, Washington, DC 20010. E-mail cberul@cnmc.org

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**Table 1. Genes and General Protein Classes for Channelopathy Diseases**

Channelopathy	Gene	Protein
LQT 1	<i>KCNQ1</i>	Inwardly rectifying potassium channel, $\alpha$ -subunit ( $I_{Ks}$ )
LQT 2	<i>KCNH2</i>	Inwardly rectifying potassium channel, $\alpha$ -subunit ( $I_{Kr}$ )
LQT 3	<i>SCN5A</i>	Sodium channel, $\alpha$ -subunit
LQT 4	<i>ANK2</i>	Cellular structural protein
LQT 5	<i>KCNE1</i>	Inwardly rectifying potassium channel, $\beta$ -subunit ( $I_{Ks}$ )
LQT 6	<i>KCNE2</i>	Inwardly rectifying potassium channel, $\beta$ -subunit ( $I_{Kr}$ )
LQT 7	<i>KCNJ2</i>	Inwardly rectifying potassium channel, $\alpha$ -subunit ( $I_{K1}$ )
LQT 8	<i>CACNA1C</i>	L-type calcium channel, $\alpha$ -subunit
LQT 9	<i>CAV3</i>	Plasma membrane structural protein
LQT 10	<i>SCN4B</i>	Sodium channel, $\beta$ -subunit
LQT 11	<i>AKAP9</i>	Kinase anchoring protein
LQT 12	<i>SNTA1</i>	Syntrophin $\alpha$ 1 (affects sodium current)
LQT 13	<i>KCNJ5</i>	Inwardly rectifying potassium channel, $\alpha$ -subunit
SQT 1	<i>KCNH2</i>	Inwardly rectifying potassium channel, $\alpha$ -subunit ( $I_{Kr}$ )
SQT 2	<i>KCNQ1</i>	Inwardly rectifying potassium channel, $\alpha$ -subunit ( $I_{Ks}$ )
SQT 3	<i>KCNJ2</i>	Inwardly rectifying potassium channel, $\alpha$ -subunit ( $I_{K1}$ )
SQT 4	<i>CACNA1C</i>	L-type calcium channel, $\alpha$ -subunit
SQT 5	<i>CACNB2</i>	L-type calcium channel, $\beta$ -subunit
SQT 6	<i>CACNA2D1</i>	L-type calcium channel subunit
CPVT 1	<i>RYR2</i>	Calcium-release sarcoplasmic reticulum channel
CPVT 2	<i>CASQ2</i>	Calcium ion reservoir within sarcoplasmic reticulum
Brugada 1	<i>SCN5A</i>	Sodium channel, $\alpha$ -subunit
Brugada 2	<i>GPD1L</i>	Calcium channel, $\alpha$ -subunit
Brugada 3	<i>CACNA1C</i>	L-type calcium channel, $\alpha$ -subunit
Brugada 4	<i>CACNB2</i>	L-type calcium channel, $\beta$ -subunit
Brugada 5	<i>SCN1B</i>	Sodium channel, $\beta$ -subunit
Brugada 6	<i>KCNE3</i>	Inwardly rectifying potassium channel, $\beta$ -subunit ( $I_{Ks}$ )
Brugada 7	<i>SCN3B</i>	Sodium channel, $\beta$ -subunit
Brugada 8	<i>HCN4</i>	Hyperpolarization-activated cation channel
ARVC 1	<i>TGFB3</i>	Cellular growth factor for proliferation and differentiation
ARVC 2	<i>RYR2</i>	Calcium-release sarcoplasmic reticulum channel
ARVC 3	Unnamed; maps to 14q12-q22	
ARVC 4	Unnamed; maps to 2q32.1-q32.3	
ARVC 5	<i>TMEM43</i>	Transmembrane protein
ARVC 6	Unnamed; maps to 10p14-p12	

(Continued)

**Table 1. Continued**

Channelopathy	Gene	Protein
ARVC 7	Unnamed; maps to 10q22.3	
ARVC 8	<i>DSP</i>	Desmosomal protein
ARVC 9	<i>PKP2</i>	Desmosomal protein
ARVC 10	<i>DSG2</i>	Desmosomal protein
ARVC 11	<i>DSC2</i>	Calcium-dependent cell adhesion
ARVC 12	<i>JUP</i>	Desmosomal protein
WPW	<i>PRKAG2</i>	Protein kinase
PCCD	<i>NKX2.5</i>	Gene expression and regulation protein
PCCD	<i>GATA 5</i>	Transcription regulation protein
PCCD	<i>SCN5A</i>	Sodium channel, $\alpha$ -subunit
CCHS	<i>PHOX-2B</i>	Transcription regulation protein

LQT indicates long QT; SQT, short QT; CPVT, catecholaminergic polymorphic ventricular tachycardia; ARVC, arrhythmogenic right ventricular cardiomyopathy; WPW, Wolff-Parkinson-White; PCCD, progressive cardiac conduction disease; and CCHS, congenital central hypoventilation syndrome

of variations in a normal population is the background noise that accompanies genetic testing. Because we know that many normal people have sequence variations in the cardiac channelopathy genes, when we discover a new variant in a patient with a clinical phenotype, the challenge is to decide whether the mutation represents the cause of a disease (the signal we are looking for) or the normal genetic variability found in all genes (the noise).

In genes that have very little background variation in the normal population, a mutation in a person with a suspicious phenotype is likely to be the signal: a pathological mutation. In this case, the signal-to-noise ratio is high; the identification of a mutation confers a high likelihood that the mutation causes the disease. Other genes host a large amount of genetic variation in the normal population. In this case, the signal-to-noise ratio is lower, making it likely that a mutation, even in someone with disease, represents the variation that occurs in everyone. The task of the clinical practitioner is to use other clues, including the patient's clinical phenotype, the location of the mutation in the gene, the published frequency of the specific mutation in other patients with the phenotype, and the family tree of the proband to decide whether the patient's mutation represents noise or the signal for his or her disease.

One critical clue is the identity of the mutation itself. As genetic testing has become more widespread, certain mutations have been associated with significant disease repeatedly. For example, the A341V mutation in *KCNQ1* was shown in a South African population to generate an unusually severe clinical phenotype.<sup>5</sup> Subsequent research has shown that the presence of the A341V mutation carries a higher risk of severe clinical manifestations in different ethnic backgrounds as well.<sup>6</sup> In a clinically affected patient, the discovery of an A341V mutation in *KCNQ1* should be sufficient to diagnose LQTI. At a more structural level, work has been done in the LQTI genes to determine that changes in the transmembrane amino acids confer a higher risk of first cardiac events.<sup>7</sup> This is the tip of the iceberg for using genetic encoding to inform risk in cardiac channelopathies.

The discovery that certain locations, such as the coding segments governing the transmembrane region, are intolerant of change suggests that the ultrastructure of the protein matters. In many channelopathies, the functional channel is not a single protein product of the gene in question, but rather a multimer of the same gene product. The LQT1 gene, *KCNQ1*, is transcribed into a protein 4 times and those identical 4 proteins bind together to create a single channel in the membrane, accompanied by beta subunits and other proteins. Some mutations cause one or more of those proteins to fail to coassemble correctly (eg, when some of the proteins fail to traffic to the membrane). This produces fewer channels in the membrane, but all the channels that make it into the membrane are functional. This is a haploinsufficiency mutation, and it confers a  $\leq 50\%$  reduction in channel function. However, when a protein is created that successfully assembles in the membrane, but cannot function, the presence of the abnormal protein alters or shuts down the entire multimeric channel. This is a dominant negative mutation, conferring a  $>50\%$  reduction in channel function. These distinctions have an impact on clinical severity, with dominant negative mutations typically conferring a more severe impact.<sup>7</sup>

Finally, not all mutations are created equal. Some mutations do not alter the protein; the nucleotide change still encodes the same amino acid and the production of the protein carries forward, unmolested by the change. These are synonymous mutations and do not typically drive clinical disease. Nonsynonymous nucleotide substitutions alter the amino acid and either encode a different amino acid in the chain or generate a stop codon, which terminates the protein synthesis prematurely. In addition to substitutions, there are insertion and deletion mutations, some of which occur in tiny pieces, 1 to 3 bases long. Other insertions and deletions can occur over longer stretches, even adding or removing vast segments of code.

Because of the many ways that DNA may be altered, predicting the clinical phenotype from the nucleotide sequence alone is difficult. The term *variant of unknown significance* has begun to be reported in clinical genetic testing, indicating that the mutation has not been described rigorously in a physiological context and the literature cannot answer the question of whether it is a benign polymorphism or whether it may represent the patient's disease-causing mutation. As the DNA of larger normal populations is sequenced, more variants of unknown significance are found in healthy controls. In the short run, these variants add noise to the system and may make these tests even harder to interpret.

What is the consequence for the clinical cardiologist who must interpret the laboratory results for genetic testing? For a patient who presents with a marginal phenotype, a positive genetic test, indicating a genetic variant, may not mean that they have the disease. Worse, there are patients who have a clear clinical phenotype and have a mutation, but the mutation is not linked to the disease. Instead, it may just be a normal variation, inconveniently residing as a bystander in the genome of a patient with that phenotype.

The process of interpreting contemporary genetic testing is, therefore, an arduous one. When genetic test results arrive from the laboratory, it is important to identify the signal-to-noise ratio for the gene in question. If possible, the specific mutation

should be identified in the literature and any previously noted genotypic-phenotypic relationship should be reviewed. Is it a haploinsufficiency or a dominant negative mutation? The practitioner must learn the extent of physiological testing that has been performed for this mutation. If there is no physiological testing data available, then the mutation should be considered from first principles: Is it in a membrane-spanning region? On the N-terminus? On the C-terminus? Does it matter for this gene product? Finally, the mutation needs to be linked back to the patient. Is the reported mutation consistent with this patient's phenotype? Does it make sense in the context of the genotypes and phenotypes of relatives?

The list of considerations for every new patient is daunting. Nonetheless, the interpretation has consequences throughout the patient's family. The current standard of care for most genetic tests is to test the first-degree relatives of the affected patient. Once those relatives are tested, any positive tests should be identified and the first-degree relatives of those patients should be tested, in a spreading wave until no more positive tests are found or the family cannot be pursued any further. A misinterpreted test will send its ripples throughout the family and affect a much larger community than just the patient in question.

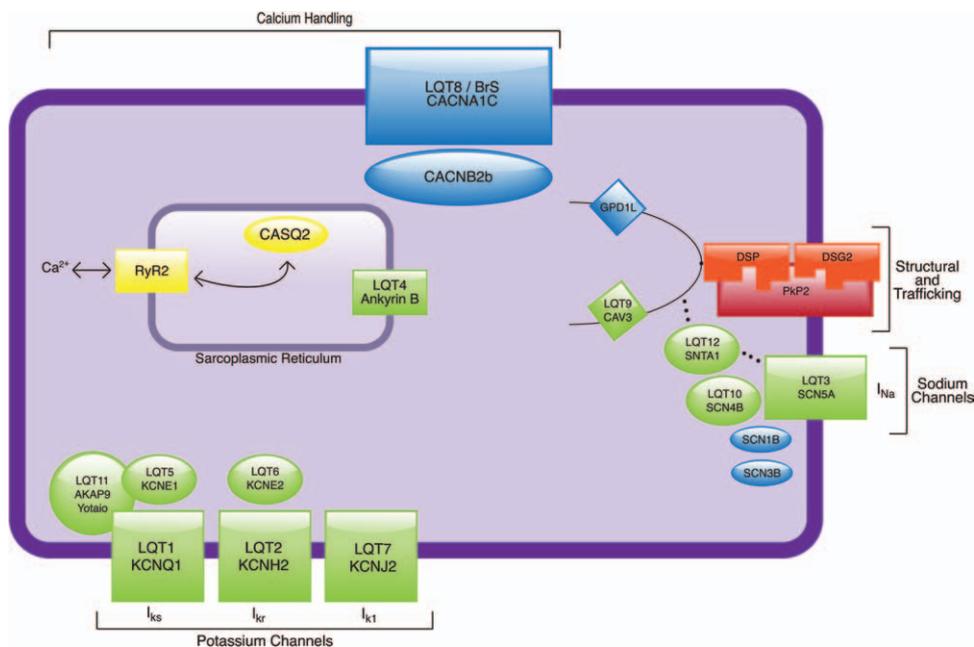
In time, genetic testing will become easier to interpret. We will know much more about the diseases in question. We will know much more about specific mutations in the human genome. For now, clinicians who order genetic tests on their patients bear the responsibility for knowing how to interpret these tests in a clinical context, and an experienced genetic counselor is invaluable. Genetic testing is only one component of the larger process of diagnosis.

Many reviews of channelopathies have been written, and the 2 most common methods of writing have been to emphasize the protein product, covering potassium channels, then sodium channels, then moving through the list of rarer channels (Figure). The second is to emphasize the clinical syndromes and review the channels as they apply to each syndrome.<sup>8-10</sup> We have chosen to emphasize clinical syndromes so we can focus on therapy, where appropriate (Table 2).

### Long QT Syndrome

The LQTS continues to be the archetype for the inherited cardiac channelopathies. The disorder manifests as an abnormal, heterogeneous pattern of repolarization in cardiac tissue that predisposes the affected patient to arrhythmias, including the stereotypical arrhythmia, torsade de pointes. To date, 13 genes have been linked to LQTS and more will be discovered; however, 3 genes represent the majority of the known cases (Table 1). Open-reading frame analysis in *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) demonstrates a mutation in approximately 75% of cases with a strong clinical phenotype.<sup>11,12</sup> *KCNQ1* mutations represent 30% to 35% of positive LQTS genetic tests, *KCNH2* mutations represent 25% to 40%, and *SCN5A* mutations represent 5% to 10%. Most commercial testing for LQTS previously relied on polymerase chain reaction–based open-reading frame analysis, which is very sensitive for point mutations but does not evaluate large gene rearrangements, duplications, or deletions. Investigations using a different probe technique on *KCNQ1*

**Figure.** Schematic representation of major channelopathy genes. The thick exterior line represents the cellular membrane. Long QT genes are green; Brugada genes are blue; arrhythmogenic right ventricular cardiomyopathy genes are red; catecholaminergic polymorphic ventricular tachycardia genes are yellow. Color coding represents the major clinical associations of each gene; however, many genes have been associated with multiple diseases. For example, *CACNA1C* is associated with Brugada syndrome but also is mutated in *LQT8*. *SCN5A* is associated with both long QT and Brugada syndromes.



and *KCNH2* recently have demonstrated phenotypic disease associated with these large-scale genetic aberrations.<sup>13–16</sup> Both probing for minor LQTS genes (LQT4–13) and searching for larger mutations likely increases the yield of genetic testing by 1% to 3%. By testing the 3 common LQTS genes and by adding minor long QT testing plus duplication/deletion/rearrangement testing, commercial genetic testing in long QT may yield a mutation in up to 80% of patients.<sup>10,15</sup>

Loss-of-function mutations in inwardly rectifying potassium channels account for most of the genetically described cases of LQTS. The first is the slowly activating delayed rectifier cardiac potassium channel, conducting an  $I_{Ks}$  current. The alpha subunit is encoded by *KCNQ1*. Four protein products from *KCNQ1* form a central channel, which complexes with a  $\beta$ -subunit, which is encoded by *KCNE1*.<sup>17,18</sup> When *KCNQ1* is the cause, the disease is categorized as LQT1. When the minor

**Table 2. Medical and Procedural Options in Inherited Cardiac Channelopathies**

		First-line therapies	Alternate therapies
LQTS	Medical	$\beta$ -Adrenergic blockers (long-acting noncardioselective)	Labetalol Nicorandil Mexiletine Verapamil
	Procedural	ICD placement*	Left cardiac sympathetic denervation Pacemaker placement
Short QT syndrome	Medical	Quinidine Sotalol Amiodarone	Propafenone
	Procedural	ICD placement*	
CPVT	Medical	Non-cardioselective $\beta$ -adrenergic blockers	Flecainide Calcium-channel blockers
	Procedural		Left cardiac sympathetic denervation ICD placement*
Brugada syndrome	Medical	Quinidine	
	Procedural	ICD placement*	
ARVC	Medical	No known mechanistic pharmacological treatment	
	Procedural	ICD placement*	

CPVT indicates catecholaminergic polymorphic ventricular tachycardia; ARVC, arrhythmogenic right ventricular cardiomyopathy; and ICD, implantable cardioverter-defibrillator.

Activity restriction is often an adjunct treatment for channelopathy diseases; see text for details.

\*ICD therapy may be a first-line procedural therapy, depending on the clinical scenario, often used after insufficiently protective medical therapy. In some cases, ICD therapy is used for protection from arrhythmia before failure of medical therapy.

subunit *KCNE1* is the problem, the disease is categorized as LQT5. In a parallel alpha/beta relationship, a voltage-gated inwardly rectifying K<sup>+</sup> channel, conducting  $I_{K_r}$ , also has a tetramer of alpha subunits (encoded by *KCNH2*), which complex with  $\beta$ -subunits (encoded by *KCNE2*).<sup>3,19</sup> Pathological mutations in *KCNH2* cause LQT2; pathological mutations in the minor subunit *KCNE2* cause LQT6. Because these mutations essentially affect the same channels, pathological mutations in *KCNE1* typically tend to behave phenotypically similar mutations in *KCNQ1*, and pathological mutations in *KCNE2* tend to behave phenotypically similar mutations in *KCNH2*, although these are generalizations and exceptions do occur.<sup>20</sup> Tawil-Anderson syndrome is the eponymous name for loss-of-function mutations in *KCNJ2* (LQT7), which encodes another inwardly rectifying K<sup>+</sup> channel (conducting  $I_{K_1}$ ) and represents only a few cases.<sup>21</sup> One family with a *KCNJ5* mutation, which is a loss-of-function mutation in an inwardly rectifying potassium channel, has been described.<sup>22</sup> These potassium channel derangements account for the majority of LQTS cases and represent long QT 1, 2, 5, 6, 7, and 13.

A special case of LQTS, the Jervell and Lange-Nielsen syndrome, is typically expressed as marked QT prolongation with congenital sensorineural hearing loss. The syndrome usually is inherited in an autosomal recessive fashion and depends on either 2 homozygous mutations or 2 compound heterozygous mutations in either *KCNQ1* or *KCNE1*. The phenotype tends to present at younger age and be severe, especially in patients affected in *KCNQ1*, in those with QTc >550 ms, and in male patients. Implantable cardioverter-defibrillator (ICD) therapy is typically considered early in the course of the disease.<sup>23</sup>

The other major player in LQTS is a gain-of-function mutation in a sodium channel, encoded by *SCN5A*. In this case, the multimeric cardiac sodium channel interacts with a  $\beta$  subunit, encoded by *SCN4B*. Mutations in *SCN5A* produce LQT3 and mutations in *SCN4B* produce LQT10. Other  $\beta$ -subunit mutations associated with *SCN5A* have been described but have not yet been designated with unique long-QT numbers.<sup>24</sup> By permitting ongoing flux of the sodium current throughout repolarization, defects in the sodium channel cause prolongation of the cardiac action potential. In an example of channel-associated proteins that do not themselves encode transmembrane channels, *SNTA1* encodes syntrophin- $\alpha 1$ , a protein that causes LQT12. *SNTA1* is linked to a calcium-ATP synthase subtype and associates with the *SCN5A* cardiac sodium channel.<sup>25</sup> *CAV3* encodes calveolin-3, which is a structural protein that causes LQT9 and is involved in maintaining the plasma membrane and providing localization of ion channels. It induces late sodium current, similar to channel gain-of-function mutations.<sup>24,26</sup> These proteins are not sodium channels, but they affect sodium channel trafficking and function.

Potassium genes and sodium genes account for most of the long-QT genotypes, leaving LQT 4, 8, 10, and 11 at large. One is a calcium channel (LQT8, or Timothy syndrome, encoded by *CACNA1C*). Failure of the calcium channel to close properly may be responsible for after-depolarizations during repolarization and induce long-QT arrhythmias.<sup>27</sup>

We now return briefly to the fascinating proteins that behave as channelopathies but are not strictly channel forming. LQT4 is caused by mutation of a membrane adaptor protein,

ankyrin-B, at transverse-tubule and sarcoplasmic reticulum sites. Ankyrin-B binds with a sodium/potassium ATPase, a sodium/calcium exchanger, and inositol-1,4,5-triphosphate receptors. With a loss-of-function mutation in the ankyrin-B protein, targeting of proteins to the transverse tubules is reduced. Alterations in calcium ion signaling have been linked to ankyrin-B mutations and may be the cause of arrhythmias in LQT4 as well as other cardiac arrhythmias, including bradycardia and CPVT.<sup>28</sup>

Although the clinical mutation is rare, the Yotai protein (LQT11) is encoded by *AKAP9* and has a particularly interesting story of discovery. The defective gene in LQT1, *KCNQ1*, encodes the  $\alpha$  subunits of the channel that conducts  $I_{K_s}$  current, and the LQT5 gene, *KCNE1*, produces a beta subunit. Marx et al<sup>29</sup> described a molecular mechanism modulating the interaction of the 2 subunits and linking them to the adrenergic pathway via a kinase anchoring protein. Having demonstrated that a kinase anchoring protein existed that was required to create a functional  $I_{K_s}$  current, they searched for mutations in a protein that could produce the phenotype. After screening 500 families with LQTS, they found the protein, naming it Yotai. This demonstrated that the molecular models that come from basic science research may yet yield further candidate genes for channelopathy discovery in LQTS and elsewhere.<sup>29-31</sup>

The genetic underpinnings of LQTS still are expanding. Genetic modifiers recently have been described that do not represent the primary mutation but that can affect the QTc interval.<sup>32</sup> Epigenetic phenomena are the subject of ongoing research. Although effects of epigenetics have been described in the extracardiac transcription of *KCNQ1*, differential expression in cardiac tissue has not yet been demonstrated.<sup>33</sup>

In part, LQTS is a paradigm for channelopathy research because these investigations have expanded and informed therapy. Genetic identification of at-risk patients allows for early evaluation for phenotypic expression, offering a presymptomatic treatment window and possibly altering patients' lives and decreasing mortality. Several large studies have shown that lifelong  $\beta$ -blocker therapy reduces fatal cardiac events in LQTS.<sup>34,35</sup> Although study populations have differed and there is a correlation between genotype and  $\beta$ -blocker efficacy,  $\beta$ -blocker therapy overall is associated with a 42% to 78% reduction of aborted cardiac arrest or sudden cardiac death.<sup>36-38</sup> It is important to recognize that, although this is a marked reduction in events, patients taking  $\beta$ -blockers still have risk of sudden death. In a large study directed at the impact of  $\beta$ -blocker therapy, the mean number of cardiac events before initiation of  $\beta$ -blocker therapy was 0.97 events per patient per year and decreased to 0.31 cardiac events per patient per year after the initiation of therapy.<sup>39</sup> While the study has some limitations, practitioners can counsel families that taking  $\beta$ -blockers significantly reduces morbidity and mortality in LQTS.

Of the 3 common LQTS variants,  $\beta$ -blocker therapy seems to be most efficacious in LQT1 and may be somewhat less effective in LQT3. Sodium-channel blockers such as mexiletine frequently have been used in patients with *SCN5A* mutations; however, mexiletine is a clinically challenging drug to administer, with dosing 3 times daily and side effects in some patients. In patients with known LQT3, the combination of mexiletine with a noncardioselective  $\beta$ -blocker such

as propranolol (which also has some sodium-channel blocking effect), seems to be the most effective pharmacological therapy. The mechanism for protection with  $\beta$ -blockers is not fully elucidated; however, investigators have noted the effects on L-type calcium channels, QTc duration, and repolarization dispersion in addition to  $\beta$ -adrenergic blockade.<sup>39,40</sup> Other medical therapies are also available, including sodium-channel blockade, calcium-channel blockade, and potassium-channel opening agents, but these have been incompletely investigated in humans. Oral potassium supplements have been tried, but in the face of normal renal function, the additional dietary potassium load typically is excreted without clinically significant increases in serum potassium levels. Potassium-sparing diuretics, such as spironolactone, have been used in combination with dietary potassium in attempts to counteract the potassium-channel dysfunction caused by genetic mutation, but these small series demonstrated modest, if any, clinical efficacy.<sup>41</sup> Pharmacogenomic therapy may eventually be used to customize individual treatment strategies. In addition, registry studies have described patients in whom phenotypic expression can provide risk stratification. The group at highest risk includes patients with a QTc greater than 500 ms, prior syncope, and (especially in young patients) male sex.<sup>37,42</sup>

Triggered activity may induce torsade de pointes.<sup>43,44</sup> An electric pause can precipitate heterogeneity in repolarization and cause the subsequent QT interval to prolong. A premature beat during the vulnerable portion of repolarization may precipitate ventricular tachycardia. Pacemakers can be implanted to avoid long pauses. Patients with LQT2 and LQT3, who may be especially susceptible to pause-dependent phenomena, may particularly benefit from pacing. The data for pacemakers, however, is limited to older studies on small numbers of patients.<sup>45,46</sup> The largest series to date concludes that combined pacemaker and  $\beta$ -blocker therapy may be beneficial, but it notes a cardiac event rate of 24% in this group and suggests that back-up defibrillation may be necessary.<sup>47</sup> The most recent consensus guidelines state that "permanent pacing is indicated for sustained pause-dependent VT [ventricular tachycardia], with or without QT prolongation."<sup>48</sup> Although the guidelines recommend pacemakers, most clinicians often choose an ICD when a device is used in patients with LQTS to allow pacing as well as defibrillation, if needed.

Given the propensity toward ventricular tachyarrhythmias in LQTS, even without an indication for bradycardia pacing, the placement of an ICD has become common for the perceived higher-risk subgroup of patients with LQTS (but certainly not for all patients with LQTS). Current guidelines recommend ICD placement for selected patients with recurrent syncope despite drug therapy, sustained ventricular arrhythmias, or sudden cardiac arrest (secondary prevention). In addition, the guidelines recommend consideration of ICD therapy for primary prevention in patients with risk factors for sudden cardiac death.<sup>48</sup>

Extensive experience is now available for ICDs in this disease. Several groups have found that ICDs were safe and effective in the population, with few acute complications.<sup>49,50</sup> As clinical experience with the disease increased, it became clear that minimally symptomatic patients were at a lower risk for cardiac events than the population of highly symptomatic

patients who were identified initially. As ICD therapy became more widespread, the long-term consequences of device therapy became clearer. In children, the group with highest risk of device-related complications, reintervention was required in up to 48% of patients.<sup>51</sup> With battery changes, most patients eventually will require some reintervention. A cost-effectiveness analysis has been performed on ICDs in LQTS; it suggests that, for an appropriately selected high-risk population, ICD therapy is cost-effective.<sup>52</sup>

In a retrospective review of the European experience with ICDs in LQTS, Schwartz and colleagues<sup>53</sup> reported a mean of 1.1 appropriate cardiac shocks per patient per year, with 63 of 228 patients (27%) receiving appropriate shocks and only 8% receiving inappropriate shocks. They found that patients who had a cardiac event while taking pharmacological therapy before ICD placement were more likely to receive appropriate shocks than those who had an event off therapy. In addition, patients with appropriate shocks had a longer mean QTc value (more frequently >500 ms), and were significantly younger at the time of implantation. Neither sex nor family history were associated with a higher likelihood of receiving ICD therapy. When deciding which risk factors should be considered before ICD placement, many practitioners lend important weight to corrected QT interval (especially longer than 500 ms), sex (more adult women with LQTS receive devices), personal history of syncope, and genotype (especially *SCN5A*). For a period of time, patients were being implanted with ICD devices only on the strength of having an *SCN5A* mutation, and it was not always clear that it was a pathogenic mutation. With physician education and experience, the time course of the data in the study by Schwartz et al suggests that this is becoming a less frequent practice, which is appropriate as we gain greater clinical experience with this disease. Asymptomatic patients with *SCN5A* mutations of unproven clinical significance should not receive ICDs in the absence of additional risk factors.

ICDs have known risks, including lead fracture, dislodgement, infection, inappropriate discharge, and electrical storm. Studies of adults and children have suggested that there can be psychosocial sequelae of ICD placement in some patients.<sup>54,55</sup> Devices may require multiple replacements, particularly when implanted in younger patients who are more likely to require reintervention for lead revision/extraction/replacement, generation replacements, or both. Careful consideration of the risks versus benefits of ICD therapy is required on a case-by-case basis. Automated external defibrillators have been recommended for families with LQTS as a noninvasive means of providing prompt defibrillation, but this obviously necessitates that an observer be nearby and able to use the automated external defibrillator promptly.

Left cardiac sympathetic denervation is a process in which the lower half of the left stellate ganglion as well as the thoracic ganglia of T2–T4 are ablated.<sup>56,57</sup> Decreasing adrenergic stimulation from the left cardiac sympathetic network is hypothesized to have multiple antiarrhythmic effects, including a reduction in the release of cardiac norepinephrine, an increase in the ventricular fibrillation threshold, and suppression of ventricular arrhythmias. The procedure remains relevant in the post-ICD era as a useful adjunct to other therapies.

It may decrease VT events and thus decrease the frequency of ICD discharges, which may be painful or sufficiently frequent as to be debilitating. In a study of 174 patients after left cardiac sympathetic denervation, frequency of cardiac events per patient decreased by 91%.<sup>58</sup> The procedure carries relatively low risks of Horner syndrome and surgical morbidity. A minimally invasive approach using videoscope-assisted thorascopic surgery for left cardiac sympathetic denervation is feasible and has been shown by several groups to be safe.<sup>59,60</sup> In experienced hands, left cardiac sympathetic denervation can be efficacious and removes the variable of compliance, which is an important factor in long-term therapy, particularly in young patients.

### Short QT Syndrome

SQTS is a rare condition, described only within the last 11 years as an ultrashort-QT interval (<320 ms) with peaked T waves in the precordial leads, often with early repolarization on the ECG.<sup>61</sup> SQTS presents symptomatically with recurrent syncope, sudden cardiac death, and atrial fibrillation.<sup>62-64</sup> Mutations have been found in the potassium handling genes, substantially overlapping with known LQTS genes, including *KCNH2*, *KCNQ1*, and *KCNJ2*. Mutations in the *CACNA1C* and *CACNB2* genes, which encode  $\alpha$ - and  $\beta$ -subunits of the L-type calcium channels, have been described as well.<sup>65</sup> The physiological mechanism of these defects is the inverse of what occurs in LQTS, leading to abnormally rapid repolarization. Thus far, pharmacological treatment options to normalize the QT interval have been limited to QT-prolonging medications such as quinidine, which often comes with significant gastrointestinal side effects. Sotalol, amiodarone, and propafenone empirically have been tried clinically, but no literature about efficacy is available. ICD placement in high-risk cases is currently the standard of care; however, as we understand more about the underlying genetics and mechanism of SQTS, further options may become available for this very rare condition.

### Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is characterized by a structurally normal heart with myocardial substrate that is highly disposed to ventricular arrhythmias, typically triggered by adrenergic stimulation, especially physical exertion or emotional stress. Patients with CPVT have an entirely normal-appearing ECG at rest, but exertion may provoke ventricular ectopy, characteristically in a bidirectional or polymorphic pattern. Thus far, only 2 genetic variants have been identified that cause CPVT, both of which involve calcium handling. Mutations in a cardiac calcium-release channel (ryanodine receptor, isoform 2 [RyR2], encoded by *RYR2*) and in a sarcoplasmic reticulum (SR) protein (calsequestrin, isoform 2, encoded by *CASQ2*) cause CPVT. Technically, CPVT is not truly a cardiac channelopathy, but given the phenotypic and therapeutic overlap with LQTS and SQTS, it makes sense to discuss this inherited arrhythmia as a second cousin.

CPVT originally was described by Reid and colleagues<sup>66</sup> in a single case report. Like other channelopathies, from that first case report, a whole genetic understanding has grown. The first protein identified was in the ryanodine receptor, followed

by an understanding of the role of mutations in the calsequestrin gene.<sup>67-69</sup>

Cardiac excitation-contraction coupling is mediated by an influx of calcium into the cellular cytoplasm, initiating a complex conformational change in the myofilaments, causing them to course past one another, producing cellular contraction (and myocardial contraction when performed in concert across the cellular syncytium). This process begins in response to the initiation of a cellular action potential. The change in transmembrane charge activates a voltage-dependent L-type calcium channel, which produces a small influx of calcium from the external milieu to the intracellular cytoplasm. This quantity of calcium is insufficient to bind a significant amount of troponin C, but the calcium ions also bind a cytosolic sensor for the RyR2 protein, located in the SR, the major storehouse of intracellular calcium. Calcium-induced activation of RyR2 opens the RyR2 channel and floods the cytoplasm with calcium, which binds to troponin C and initiates contraction. During relaxation, calcium is returned to the SR via an ATPase pump or expelled outward from the cell using a  $\text{Na}^+$ / $\text{Ca}^{++}$  exchanger. The role of the SR as the major calcium store is prone to derangements. Spontaneous calcium release can occur, especially in settings of calcium overload in the SR ( $\beta$ -adrenergic stimulation, rapid pacing, digitalis toxicity).<sup>70</sup> Spontaneous calcium release from the SR increases cytoplasmic calcium, which runs down its gradient through the  $\text{Na}^+$ / $\text{Ca}^{++}$  exchanger. The unequal exchange of charge across the membrane causes transient inward depolarization current, called delayed after-depolarizations. If the amplitude of the delayed after-depolarizations is sufficiently high to reach the action potential trigger, the cell undergoes its full response to a threshold depolarization ahead of the rest of the myocardium's schedule, which can cause triggered arrhythmias.

The ryanodine receptor is responsible for much of this calcium efflux from the SR during a normal cardiac impulse because of calcium overload in the SR. Mutations in the *RyR2* gene in CPVT cluster to 4 primary domains the gene. These domains are highly conserved across species and *RyR2* mutations tend to have autosomal dominant transmission.<sup>9</sup> The mechanisms for enhanced calcium release during SR overload in mutated *RyR2* channels is incompletely elucidated; however, mutations seem to alter the threshold for calcium activation of the channel and lower the threshold at which calcium-overload calcium release is triggered.<sup>71-73</sup>

The *CASQ2* gene causes a much less common autosomal recessive form of CPVT.<sup>74,75</sup> Only 12 variants have been identified to date (<http://www.fsm.it/cardmoc/>). The function of *CASQ2* has not been fully clarified, but it plays a role in buffering calcium and reducing cytoplasmic calcium overload.<sup>76</sup> It thus localizes calcium in the SR, lowers concentration of free calcium, and allows greater uptake by calcium-ATPases. *CASQ2* and *RyR2* mutations produce a phenotype that has thus far been clinically indistinguishable in both humans and mice,<sup>77</sup> suggesting that *CASQ2* and *RyR2* share a common end pathway of calcium handling in the cell.<sup>78</sup>

Clinical therapy for CPVT traditionally has relied on high-dose noncardioselective  $\beta$ -adrenergic blockade. In addition to blunting whole-body adrenergic tone,  $\beta$ -blockers modulate the heart rate-dependent overload of calcium in cells and may

directly reduce L-type calcium channel current. Calcium channel blockers have been used and have been shown in small studies to partially protect patients from exertion-induced arrhythmic events.<sup>79</sup> The sodium-channel blocking drug flecainide inhibits *RyR2* activity and reduces spontaneous SR calcium release.<sup>80</sup> It also seems to have significant antiarrhythmic effects in *CASQ2* models and small clinical series, suggesting that the effects of flecainide, the role of *CASQ2* in CPVT, or both are still incompletely understood.

Some patients with CPVT may require combination medical therapy, with high-dose  $\beta$ -blockers plus flecainide, verapamil, or both. There continues to be a significant rate of cardiac events among patients with CPVT, even despite medication therapy. Therefore, use of nonpharmacological therapies, such as left cardiac sympathetic denervation, implantation of an ICD, or both, may be warranted for medically refractory cases (Table 2). In one study, 50% of patients with CPVT with ICDs had appropriate discharges over 2 years of follow-up. Because of the catecholaminergic nature of this disease, the risk of arrhythmic storm is of particular concern.<sup>81</sup> Vigilant programming of ICDs and discussions to minimize medication noncompliance are vital because even an inappropriate shock can trigger electrical storm with multiple shocks.<sup>82</sup> A minimally invasive left cardiac sympathetic denervation has been reported by several groups to be effective for selected patients with CPVT, although the numbers treated with this technique are still small.<sup>59,60,83,84</sup> As was suggested earlier, the label "channelopathy" encompasses a number of diseases, not all of which are strictly due to channel mutations. Exceptions exist where non-channel-forming proteins cause LQTS. CPVT is primarily manifest through mutations in *RyR2* and has a strong mechanistic link to channel defects; however, *CASQ2* encodes a channel-related protein and not the channel itself.

### Brugada Syndrome

Brugada syndrome is another example of a channelopathy in which the channel itself is only part of the phenotypic profile. Loss-of-function mutations in the *SCN5A* sodium channel were the first and best-understood genetic cause of Brugada syndrome, but they account for only 20% of phenotypic disease. In addition to *SCN5A*, the Brugada phenotype has been associated with mutations in the sodium channel  $\beta$ -subunits, encoded by *SCN1B* and *SCN3B*; the potassium channel encoded by *KCNE3*; and the  $\alpha$ - and  $\beta$ -subunits of the L-type calcium channel (*CACNA1C* and *CACNB2B*).<sup>85,86</sup> Mutations in *GPD1L* create an abnormal trafficking protein that seems to inhibit appropriate expression of sodium channels in the cell membrane.<sup>87</sup>

Nonetheless, typical channelopathy genetics are absent in some cases. A single, coherent mechanism for sudden death in Brugada syndrome has not yet become widely accepted. One hypothesis has been that unequal transient outward current in the subepicardium and subendocardium during repolarization creates heterogeneity and prolongation of myocardial repolarization with susceptibility to arrhythmia due to phase 2 re-entry. Although this could be related to loss of function in the sodium channel, it fails to explain the augmentation of the Brugada ECG pattern by most class IA and IC drugs except the class IA drug quinidine. In addition, the subendocardium

to subepicardium gradient that has been hypothesized has not been demonstrated during cardiac surgery, when the human heart is accessible to recording studies.<sup>88</sup>

Brugada syndrome is recognized clinically by a characteristic ECG appearance, including right precordial ST elevation and intermittent right bundle-branch block, along with a propensity toward arrhythmic syncope and sudden cardiac death.<sup>89</sup> It is transmitted most commonly in an autosomal dominant inheritance with variable penetrance and variable expressivity, and the phenotype is much more common in men. Risk stratification is based on clinical findings, with prior cardiac arrest, recurrent syncope, or arrhythmia being the biggest risk factors. The characteristic ECG pattern may be manifest (called spontaneous appearance) or elicited by pharmacological challenge using sodium-channel blockers, such as ajmaline (not available in United States), procainamide, or flecainide. The second Consensus Conference on Brugada Syndrome recognized 3 types of ECG findings. A type 1 ECG, with a coved ST-segment elevation  $\geq 0.2$  mV and negative T-wave deflection in  $>1$  lead from  $V_1$  to  $V_3$  (with or without the presence of a sodium-channel blocker) is considered diagnostic when there is also documented ventricular fibrillation, polymorphic VT, a family history of coved ECG waves or sudden cardiac death at an age  $<45$  years, syncope, or nocturnal agonal respiration. The role of invasive studies of ventricular stimulation is controversial, even as published in consensus statements.<sup>90-92</sup> Although some experts use the results of electrophysiological studies to decide on treatment plans, others base clinical parameters for risk stratification and medical decision making regarding ICD placement. The presence of the spontaneous ECG pattern portends higher risk for arrhythmic syncope and sudden cardiac death. Type 2 and type 3 ECG patterns are not diagnostic of Brugada syndrome but may convert to type 1 ECGs with sodium-channel blockade. Modifying the placement of the right precordial leads to the second intercostal space may increase the sensitivity of the ECG for a type 1 pattern, and we use this modification in our practice when a standard ECG is inconclusive.

A few investigators have suggested that structural heart disease is part of the expression of the Brugada phenotype. This hypothesis has been advanced in other diseases, such as arrhythmogenic right ventricular cardiomyopathy and Chagas disease. In the case of Brugada syndrome, the channelopathy component is hypothesized to produce a substrate that is susceptible to arrhythmia as structural heart disease progresses.<sup>93</sup> This implies that in some patients, the channel may be abnormal, but without myocardial substrate, the electric disorder of the channel may be insufficient to manifest clinical disease. Structural abnormalities have been seen in some victims with a Brugada ECG pattern who have experienced sudden death, and biopsies have revealed lymphocytic infiltration and abnormal cardiomyocytes.<sup>94-97</sup> A cohesive theory that unifies the discrepant data in Brugada syndrome, linking the clinical presentation, the family trees, the response to medications, and potential structural findings, is still not available.

The change in the  $I_{to}$  current and normalization of the Brugada ECG pattern with quinidine has led some to recommend this drug as a treatment modality.<sup>98,99</sup> Fever has been shown to be a trigger for clinical events, particularly in younger

patients with Brugada syndrome, and therefore prompt treatment with antipyretics is an important adjunctive therapy. The role of electrophysiology study for risk stratification and catheter ablation of ventricular ectopic foci is controversial and not uniformly accepted. Our own clinical management strategy typically does not include electrophysiological testing for risk stratification in asymptomatic Brugada syndrome. ICD therapy has been the mainstay of treatment for patients who are thought to have a high-risk substrate, particularly those with cardiac arrest, ventricular tachycardia, or arrhythmic syncope. Having only a Brugada pattern on ECG without symptoms is not a high-risk indicator and likely does not warrant universal use of an ICD as primary prevention. Patients with Brugada syndrome who have ICDs do receive appropriate shocks, many of which are presumed to be potentially life-saving. Review of ICD stored electrograms reveal ventricular fibrillation, typically preceded by premature ventricular beats, occurring in approximately 30% to 40% of patients with Brugada syndrome who have an ICD. Several studies comparing the efficacy of ICD versus medical therapy (or no treatment) revealed decreased mortality in the groups with ICDs, as well as relatively frequent appropriate shocks.<sup>100,101</sup> The second Consensus Conference on Brugada Syndrome recommended an ICD for patients with spontaneous ECG pattern and aborted sudden cardiac death (class I), symptomatic patients without clear etiology (class I), and asymptomatic patients with either a positive malignant family history, a positive electrophysiology study, or both (class IIa). If the Brugada ECG pattern is elicited only with sodium-channel blockade, ICD is recommended for aborted sudden cardiac death (class I), symptomatic patients without extracardiac cause (class IIa), and asymptomatic patients with both a positive family history and positive electrophysiology study (class IIb).<sup>90</sup> In a large, French, multicenter study of 220 patients with Brugada syndrome and an ICD, only 8% received appropriate shocks over an average of 3 years of follow-up, and the authors observed a 28% complication rate, including 20% inappropriate shocks. This retrospective report highlights several downsides of ICD implantation for Brugada syndrome, including inappropriate shocks due to T-wave oversensing and supra-ventricular arrhythmias.<sup>102</sup> A similar study of children with Brugada syndrome and ICDs illuminated the importance of fever as a clinical trigger and demonstrated relatively frequent appropriate and inappropriate shocks in this unique cohort of pediatric Brugada syndrome.<sup>102</sup> Further genetic etiologies will provide better mechanistic explanations; new environmental and somatic influences will likely be identified. These discoveries eventually will lead to improved risk stratification and therapy options, as recently seen for other channelopathies.

### Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC (also called ARVD, when dysplasia is the noun of choice, or AVC, to denote that the left ventricle is sometimes also involved in the disease process) is the bridge between the sudden death channelopathies and the genetic cardiomyopathies. Although ARVC is not strictly an ion channelopathy, syncope, ventricular arrhythmias, and sudden cardiac death are the hallmark clinical presentations. Either or both of the

ventricles can be involved in the disease, but the right ventricle most typically dominates. The disease may initially present with arrhythmia and gradually progress to increasingly prominent morphological changes, stereotypically involving fibrofatty infiltration of the ventricle(s). Defects in the cardiac ryanodine receptor (*RyR2*) have been linked with a subset of the disease called ARVC2. ARVC2 may represent a variant of CPVT rather than a subset of CPVT or ARVC; however, at this time, ARVC2 remains classified with the other ARVC presentations and is the only genetic link to ARVC that directly encodes a transmembrane channel (Table 1).

Nonetheless, the contribution of desmosomal proteins to cell-to-cell signaling renders ARVC a close relative of the channelopathies, with overlapping phenotypes. Hence, more explanation in this context is worthwhile, especially given the arrhythmia phenotype of the disease. Desmosomal proteins have been identified as the primary cause of the ARVC derangement. Desmosomes are cellular complexes that primarily serve to link intermediate filaments to the plasma membrane and, in turn, create strong, durable intercellular linkages (intercellular cardiac glue) that allow transmission of force through the cardiac syncytium. Desmosomes provide a tight linking function at the biochemical level as well. There are 14 described ARVC mutations, including 2 named diseases (Naxos disease and Carvajal syndrome). The remainder are named ARVC1 through ARVC12. The histological and gross pathological hallmark of ARVC is fibrofatty replacement of the myocardium, but arrhythmias may precede histological evidence of disease. In advanced cases, interstitial fibrofatty infiltrate may provide a macro-re-entrant circuit for VT, the presence of VT before the development of circuit substrates suggests that there is another mechanism for some clinical arrhythmias in ARVC. Gap junction remodeling due to abnormal cellular adhesion may cause a conduction delay and electric instability, thus creating a cellular substrate for arrhythmia vulnerability.

Three primary desmosomal proteins have been identified in 40% of ARVC cases: *PKP2* encodes plakophilin 2, *DSP* encodes desmoplakin, and *DSG2* encodes desmoglein 2.<sup>103–106</sup> *PKP2* is the most common gene mutation identified in ARVC. In an intriguing look into the 60% of patients in whom genetic mutations have not yet been described, transforming growth factor  $\beta$ -3 has been shown to be linked to ARVC, suggesting that the complicated interaction of cell-to-cell adhesions and communication is governed (and pathologically deranged) in ways that are not yet fully understood.

Recent work has demonstrated that genetic testing for ARVC is associated with a low signal-to-noise ratio. When both ARVC cases and healthy controls were sampled, 43% of cases with an ARVC phenotype had mutations versus 16% of controls.<sup>107</sup> Cases had a higher likelihood of in-frame and frame-shift insertions, deletions, splice junction, and nonsense mutations. These are frequently more disruptive than point mutations, underscoring the point that the results of genetic testing cannot be analyzed only in a binary fashion of mutation present or mutation absent.

No mechanistic therapy is yet available for ARVC. There is intriguing evidence that the disease progresses in fits and starts,<sup>108–110</sup> which may suggest that environmental factors

play a role in disease progression and that blunting of these environmental factors might slow the progression of disease. Exercise may exacerbate the progression of disease, hypothesized to be due to increased forces and wall stress in genetically susceptible ventricles because of the desmosomal mutations. For now, ICD therapy is still the final end point of treatment, with the goal of offering protection against life-threatening arrhythmias for those with the highest risk profile. Determining which patient needs an ICD and the optimal timing of initial ICD implantation remains a difficult clinical decision, particularly for young patients with asymptomatic ARVC. A unique challenge of ICD therapy in ARVC is that the disease is often progressive, leading to loss of myocardium and therefore difficulties in ventricular R-wave sensing over time. Cardiac transplantation may be necessary in severe disease with intractable arrhythmias or heart failure, when large portions of myocardium are replaced with fibrofatty infiltration.

### Other Channelopathies

ARVC leads naturally into a discussion of cardiomyopathies, some of which seem to be caused by channel derangements. *SCN5A* mutations have been shown in patients with dilated cardiomyopathy.<sup>111</sup> Sodium channel current density has been shown to be reduced in mouse models of Duchenne muscular dystrophy.<sup>112</sup> Given that there are links between voltage-gated channels and localization of membrane structural proteins, further links are likely to be found in the wide array of clinical cardiomyopathies.<sup>113</sup>

Atrial fibrillation presents the greatest clinical arrhythmia burden in the practices of cardiologists who predominantly care for adult patients. There are genetic implications of atrial fibrillation that continue to be recognized, and reviews of the subject have been printed in several locations. A discussion of atrial fibrillation is outside the scope of this review.

Inherited forms of Wolff-Parkinson-White syndrome, with or without cardiac hypertrophy, have been described as being attributable to mutations in protein kinase genes such as *PRKAG2*.<sup>114</sup> These autosomal-dominant inherited disorders have been shown to be treatable in a way similar to sporadic Wolff-Parkinson-White syndrome, using medications and catheter ablation. Often there are multiple accessory pathways and associated conduction system disease. A mouse model of *PRKAG2*-mediated Wolff-Parkinson-White syndrome has been developed, which recapitulates many of the clinical findings seen in this rare disorder.<sup>115</sup>

Progressive cardiac conduction disease pulls together a heterogeneous group of presentations for diseases of conduction at any level in the cardiac conduction system when not secondary to acquired structural disease. In some cases, these rhythm disorders are associated with congenital heart disease, such as the association of atrial septal defect with atrial arrhythmias and atrioventricular nodal conduction in *NKX2.5* and *GATA4*.<sup>116–118</sup> In others, when the rhythm defects occur in isolation, the sodium channel encoded by *SCN5A* and its  $\beta$ -subunit (*SCN1B*) are implicated more frequently.<sup>119–121</sup> A calcium-activated cation channel (encoded by *TRPM4*) has been described in patients with idiopathic conduction disease. For all of these genetic mutations, few treatments are available

and pacemaker implantation according to clinical guidelines typically is provided.

There are rarer diseases that suggest that the known channelopathies are only the tip of a larger iceberg of clinically relevant diseases. In congenital central hypoventilation syndrome, the primary genetic mutation is in the paired-like homeobox 2B (*PHOX-2B*) gene, which does not encode a channel (it encodes a homeodomain transcription factor). The clinical presentation is central alveolar hypoventilation often with autonomic nervous system dysregulation. Some patients develop severe symptomatic bradycardia with long cardiac pauses. Genotype is highly predictive of the need for pacemaker implantation: the 20/26 and 20/27 genotypes had a much higher rate of implantation in one clinical study.<sup>122</sup> In a mouse model of this disease, mice bearing the *PHOX-2B* mutation fail to express potassium channels in the retrotrapezoid region of the brain stem. The mice who fail to express potassium channels are insensitive to hypoxia and hypercapnia; they hypoventilate and die young.<sup>123</sup> This reintroduces the question of defining channelopathies. If a genetic syndrome does not encode a channel-forming protein and its product does seem to directly or indirectly bind channel proteins, but it nonetheless affects channel transcription, is it a channelopathy? In our view, a channelopathy is a disease that affects channel function and, by doing so, compromises the patient's clinical status. When this happens indirectly, through other mechanisms, it is fascinating — and still is a channelopathy.

### Counseling Families With Channelopathies about Sports Participation

Each disease described here has its own list of medications and interventions that may modify the course of the disease. Careful attention to diagnosis, risk stratification, and subsequent treatment is at the heart of therapy for these patients. However, sports activity has been an area of modifiable risk that ties together all of these diseases. It is unfortunate that few or no data are available about the extent to which modifying athletic participation actually modifies risk.<sup>124</sup> The most recent formal guidelines are from the 36th Bethesda Conference, which considers LQTS, SQTS, CPVT, and Brugada syndrome separately.<sup>125</sup> In patients with SQTS, CPVT, and Brugada syndrome, restriction to a limited number of 1A sports is thought to be prudent on the basis of expert recommendation. These 1A sports have become well known: they include billiards, bowling, cricket, curling, golf and riflery and exclude a number of sports that some practitioners think are performed at similar levels in most people. Other sports in the table clearly require higher levels of exertion, but no data are available that suggest that they actually raise the risk of sudden death. The Bethesda Conference guidelines are more specific for LQTS, excluding asymptomatic patients with short baseline QTc intervals from significant restrictions. Other guidelines are available, including guidelines written specifically for young patients with genetic cardiovascular disease; however, all of these are based primarily on expert consensus.<sup>126</sup>

The stakes are high. Despite whether channelopathies are causative, many deaths have occurred during exercise in patients with channelopathies, some in high-profile situations. Before an event, restriction from sports often feels like

a heavy burden to patients and families. After a tragic event, the knowledge that modifying activity might have prevented the outcome may be even more devastating. As physicians are aware, there have been successful lawsuits brought to bear in these circumstances.

In addition to the immediate risk of sudden death with activity, there is a background risk of higher rates of early cardiovascular disease in sedentary members of the population. Especially in children, we recognize that exclusion from essentially all sports has important developmental and social consequences that are not easily measured.

Many practitioners have struggled with sports recommendations. A survey of practitioners whose patients had ICDs showed that 71% of practitioners have patients who participate in sports, regardless of recommendations.<sup>127</sup> In this survey, ICD shocks were common, even if injuries to the patient or the device were uncommon. Many prominent practitioners in the field have pointed out the dearth of data about the efficacy of sports restriction and have been working to enlarge our understanding of what can be permitted.<sup>124</sup> There is unlikely to be one blanket convention for all channelopathies. For example, as mentioned earlier for ARVC, there is a plausible hypothesis that mechanical stress may impact the cellular junctions. For patients who have proven ARVC, we typically recommend sports restriction to mild cardiovascular sports for weight management with a low static component, but we involve the patients and their families in the discussion.

In our practice, we see many young patients with a strong desire to live active athletic lives. No one recommendation fits all of these families. We do our best to educate them about the current guidelines, emphasizing that these guidelines represent the best consensus of the field. We talk about the consequences of being wrong and the consequences of having a life-threatening event or permanently altering the level of the patient's activity. We encourage families to reach out to other members of our practice who have experienced sports restrictions. We work on coping skills. However, with the knowledge that families do not always follow sports recommendations, we attempt to create an activity profile for every individual that they can live with. We do not insist that the profile fit the current guidelines for every family. In some families, the decision is largely to follow the guidelines. In other families, patients participate in much higher-intensity sports with the knowledge that there is risk involved. We help them modify their choices to be more permissive or restrictive as they come back and see us during follow-up.

We encourage patients to participate and thrive in casual sports, especially physical education in school-aged children and social activities such as shooting hoops and playing catch. We discuss the difference between casual activity and aggressive sports and encourage each person to recognize when casual basketball becomes a high-level sports activity. The patients often have to be the ones to see the line and pull themselves out of the activity. It is fortunate that tragic events during sports remain rare, even in this population.

### Conclusions

Cardiac channelopathies are a highly diverse group of diseases, some of which adhere strongly to the appealing idea

of a monogenetic mutation in which a disruption of a single cardiac channel, or even a single protein moiety, can alter cellular mechanics and impart a disease phenotype. From this model of one mutation—one disease, tailored therapies can be developed to alter the cellular consequences of an abnormal protein. Other channelopathy diseases have been shown to be much more complicated, inextricably tied to the complex, highly regulated environment of cellular physiology. Multiple mutations in related proteins likely are required for some of these derangements to manifest clinically. The extracellular environment and external cues matter: the gene-versus-environment argument is likely to play out further at the cellular scale within the world of channelopathies. The definition of what a channel is and which diseases belong in the company of channelopathies is not yet settled, especially as it becomes clear that few, if any, channels exist without a complicated protein support structure. To us, channelopathies are those diseases related to channel function, gathering all of the varying mechanisms under one umbrella, knowing that some diseases can be shared between channelopathies and other classification schemes.

For clinicians, understanding how these genetic diseases present and when to use testing to look for genetic derangements requires understanding clinical medicine in a new light. Guidelines recently have been reported to help guide the practitioners caring for patients with inherited cardiac diseases.<sup>128</sup> Understanding the strengths and limitations of genetic testing, understanding signal-to-noise ratios in individual diseases, and learning genotypic/phenotypic correlations represents a new challenge in practicing clinical medicine. Armed with an imperfect basic science background, we are nonetheless at the front line of explaining it to our patients. Learning this new language fortunately produces clinical rewards.

Research into the genetic underpinnings of channelopathies is likely to continue to inform clinical medicine, broadening our ability to care for patients, outlining new therapies, and allowing us to stratify risk among patients and their families.

### Disclosures

None.

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KEY WORDS: arrhythmia ■ Brugada syndrome ■ catecholaminergic polymorphic ventricular tachycardia ■ genetic heart disease ■ long QT syndrome