EDITORIAL COMMENT

The Problem, Challenge and Opportunity of Genetic Heterogeneity in Monogenic Diseases Predisposing to Sudden Death*

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The last half-decade has seen an explosion in our understanding of the molecular basis of normal and abnormal cardiac electrophysiology. Most intriguing are studies linking specific genetic defects with defined clinical syndromes (phenotypes) in diseases like the long-QT syndrome (LQTS) or the Brugada syndrome; these genotype-phenotype correlations not only point to links between subcellular phenomena and the electrical behavior of the whole heart but also suggest mechanisms in more common, "acquired" arrhythmias. In this issue of the Journal, Smits et al. (1) provide just such an example in their evaluation of a large group of patients with the Brugada syndrome.

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GENETIC HETEROGENEITY IN THE LQTS

Studies of LQTS have demonstrated genetic heterogeneity, that is, the disease phenotype can arise from mutations in any one of multiple (probably at least seven) genes (2). Important direct consequences of these genetic studies have included:

1) Identification of families with very low penetrance, that is, including individuals with disease-associated mutations, but "no" clinical phenotype (3). We and others have suggested that such individuals may, nevertheless, be at increased risk for torsades during challenge with QT-prolonging drugs (4–7). The extent to which variability in our individual genomes predisposes to unusual responses to pathophysiologic stressors or to drug challenge remains largely unexplored.

2) HERG has been identified not only as an LQTS disease gene but also as the predominant target of most drugs inducing torsades de pointes (8). This finding, in turn, has led to important changes in the way in which the pharmaceutical industry and regulatory agencies approach the problem of potential torsades toxicity by nonantiarrhythmic drugs (9). More generally, the identification of a molecular target represents an important advance in screening out undesirable actions in new drugs as they are developed.

3) It has long been recognized that individuals with the LQTS may not fit the "typical" clinical description of events with adrenergic stress or "failure to shorten the QT interval" with exercise. This phenotypic heterogeneity has now been partially resolved with the observations that the details of the clinical phenotype may be driven largely by the specific gene (or, conceivably, the specific region within that gene product) (10) affected. These findings, in turn, have important implications for evolving thinking about subtype-specific presentations in LQTS (11,12), as well as possible subtype-specific therapies, such as the preference for beta-blockade in LQT1 and the thought (as yet unconfirmed in clinical trials) that sodium channel block may play a special role in LQT3 (13,14).

GENETIC AND PHENOTYPIC HETEROGENEITY IN THE BRUGADA SYNDROME

The entity of right precordial J-point elevation, no underlying structural cardiac abnormality and "idiopathic" ventricular fibrillation (VF) (15) was recognized as a syndrome by Brugada and Brugada in the early 1990s (16). As in LQTS, affected individuals who do not display the manifest electrocardiographic features until challenge with a drug were recognized early on; in the case of the Brugada syndrome, the drug challenge required to elicit the electrocardiogram phenotype was not QT-prolonging drugs but sodium channel block (17). The recognition of the relationship between Brugada syndrome and sodium channel blockers provided an initial clue that led to identification of mutations in SCN5A—encoding the cardiac sodium channel—in individuals, and subsequently in kindreds, with the Brugada syndrome (18,19). Moreover, genetic heterogeneity has been demonstrated: kindreds in whom linkage analysis has ruled out the SCN5A locus have been identified (20). Smits et al. (1) now extend the parallels between LQTS and the Brugada syndrome by reporting phenotypic differences between 23 patients with Brugada syndrome related to mutations in the coding regions of SCN5A and 54 individuals in whom such mutations were not identified. The SCN5A-related patients had greater defects in impulse propagation (greater QRS prolongations with sodium channel blocker challenge, and longer baseline, longer PR and HV intervals) than non-SCN5A-related patients. The study is limited by the fact that we do not know what the mutations are in the non-SCN5A-related group and whether they are, in turn, all in a single locus; they could even be in regions that regulate the level of expression of SCN5A itself. Nevertheless, the findings suggest greater
defects in the function of the fast sodium channel in individuals with SCN5A coding region mutations and raise the possibility, as suggested by the authors, that, in the future, it may be possible to use clinical criteria as a first step in identifying the specific genetic locus affected. Ultimately, it may even be possible to devise gene-specific therapies, although this seems much further off and awaits identification of other disease genes in this syndrome.

A RANGE OF FUNCTIONAL DEFECTS IN THE CARDIAC SODIUM CHANNEL

Mutations in SCN5A also cause the LQT3 subtype of LQTS, as well as isolated conduction system disease (21). Initial in vitro characterization of LQT3-related mutations demonstrated a persistent late inward current through mutant sodium channels. Because this behavior was not present in wild-type channels, it has been termed a "gain of function" (to contrast it with potassium channel defects in other forms of LQTS that largely result from a "loss of function"). However, the function that is "gained" in LQT3 is actually a mutation-imposed loss of normal fast inactivation. More recently, other LQT3-related SCN5A mutations, which do not result in persistent noninactivating current, have been identified (22), demonstrating that, rather than considering simple "gain" or "loss" of function as the mechanisms in LQTS, the derangements in protein function imposed by mutations should be considered more globally. While in vitro characterization of Brugada syndrome-related mutations is not as far advanced as in LQTS, sufficient evidence has been accumulated to implicate reduction in sodium current—through diverse mechanisms—as the underlying defect in the Brugada syndrome. These mechanisms include defective trafficking of sodium channels to the cell surface (i.e., fewer channels at the cell surface) (23), mutations that result in nonfunctional proteins (18) and mutations that generate proteins whose occupancy of an "intermediate" inactivated state is enhanced, resulting in fewer sodium channels available at normal heart rates (24,25). Indeed, the Amsterdam group (19,26) has described a large kindred with both the Brugada and LQTS phenotypes arising from a single mutation in the C-terminus of SCN5A of the sodium channel protein. The mutation, 1795insD, not only destabilizes fast inactivation but also promotes slow inactivation, thereby explaining the dual phenotype and reinforcing the idea that the terms "gain of function" or "loss of function" are incomplete descriptors, at best, of the molecular dysfunction that causes these interesting diseases. The way in which specific mutations give rise to LQTS, Brugada syndrome, conduction system disease or combinations remains an exciting area in molecular electrophysiology. One intriguing report suggests that the extent to which some Brugada syndrome mutations reduce sodium channel availability may be strongly modulated by the presence or absence, in a particular patient, of common DNA variants (polymorphisms and not disease-associated mutations) in SCN5A (27).

WHAT MIGHT THE OTHER BRUGADA SYNDROME DISEASE GENE(S) BE?

Studies of right ventricular epicardial action potentials and their response to sodium channel block have provided a nice explanation of the way in which loss of sodium channel function might translate into the Brugada phenotype (17,28). In brief, epicardial cells have a very prominent phase 1 "notch," driven by the presence of a large transient outward current (I_{TO}). The end of phase 1 can be viewed as a balance between waning inward current through sodium channels and I_{TO}. Reduction in sodium current in the Brugada syndrome is thought to disrupt this balance, driving the end of phase 1 to much more negative potentials. When this happens, phase 2 simply does not occur, and the action potential becomes very abbreviated. This effect can be heterogeneous, resulting in cells with very short action potentials adjacent to those with normal ones, the ideal breeding ground for the reentrant excitation underlying VF.

Given this framework for understanding the way in which mutations can cause the Brugada phenotype, it is, of course, tempting to speculate on what the nature of the other disease gene(s) might be. One obvious possibility is mutations that increase the transient outward current, to upset the balance between I_{TO} and I_{Na}. Lesions in other ion channel genes are also plausible. However, inspection of the genomic sequence of 3p22-25, one "non-SCN5A" chromosomal locus linked to the Brugada syndrome, does not reveal any recognized ion channel, implying that ion channels with as-yet-unrecognized structures remain to be identified or that mutations arise in other elements regulating channel function (e.g., ancillary subunits, chaperone proteins, anchoring proteins, kinases, regulatory genes or regions). It will be especially interesting to identify the mechanisms whereby non-SCN5A-related patients demonstrate the Brugada phenotype and yet appear to have much less of a problem with impulse propagation.

VARIABLE "ANTIFIBRILLATORY RESERVE"

I believe that the greatest importance of defining the molecular mechanisms in entities like LQTS or the Brugada syndrome lies not so much in the management of individual patients but in understanding the way in which sometimes subtle and sometimes not-so-subtle functional defects in individual gene products may translate into variable risk for VF. Several pieces of evidence, taken together, suggest the notion that an individual's risk for VF during "challenge" with acute myocardial ischemia may be, in part, genetically determined, in much the same way as clinical response to "challenge" with QT-prolonging drugs seems determined by multiple factors, each contributing to overall susceptibility to torsades by reducing "repolarization reserve" (29). Moreover, variants (rare mutations or common polymor-
phisms) in SCN5A and other Brugada syndrome disease genes are excellent candidates for modifying VF risk. This evidence includes: 1) manifest loss of sodium channel function in the Brugada syndrome increases risk for VF; 2) epidemiologic studies identify a family history of sudden death as an independent risk factor for sudden death (30,31); 3) the Cardiac Arrhythmia Suppression Trial demonstrated in the 1980s that treatment with sodium channel blockers in the recently injured myocardium increased sudden death risk, especially in patients at risk for recurrent ischemic episodes (32,33); and 4) in vitro studies report that the right ventricular epicardium responds to simulated ischemia in much the same way as it responds to sodium channel block, with heterogeneous abbreviation of epicardial action potentials to promote reentrant excitation (34). Testing the concept of variable “antifibrillatory reserve” will become possible as new Brugada syndrome disease genes are identified and their roles in modulating baseline electrophysiology and its response to ischemic stress are identified. Ultimately, stratification of risk for VF may extend from the clinical predictors we use now to such new genetic markers (35).

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