The complexity of genotype-phenotype relations associated with loss-of-function sodium channel mutations and the role of in silico studies

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MUTATIONS IN GENES ENCODING the α-subunit of sodium channels are causal to a variety of diseases in several organ systems (12), including several primary arrhythmia syndromes, which are associated with mutations in SCN5a, the cardiac sodium channel gene (16). Whereas the association between, and the pathophysiological basis of, gain-of-fuction SCN5a mutations and the long QT syndrome is rather straightforward (6), the association and pathophysiological mechanisms of loss-of-function mutations are more complicated and less well understood. The associated diseases and syndromes include Brugada syndrome, familiar (progressive) conduction disease, atrial standstill, sick sinus syndrome, and various combinations thereof (12). Whereas, for some mutations, the pathophysiological mechanism is known (4, 6), including some referred to as “overlap syndromes” (7, 10, 17), it is not well understood why loss-of-function mutations in some patients lead to conduction disease, whereas in other patients it (also) leads to right precordial ST-elevation or atrial rhythm abnormalities. Other factors, among which are sex (13) and genetic factors, presumably play a role (11, 15).

In this issue of the American Journal of Physiology: Heart and Circulatory Physiology, the Maastricht group, under the guidance of Paul Volders, deals with the electrophysiological characterization of a mutation in the cardiac sodium channel (Phe2004Leu or F2004L) in a relatively small Dutch kindred with Brugada syndrome/conduction disease (5). The study comprises two sections. The first part is the description of the clinical phenotype and the cellular biophysical characterization of the mutant sodium channel, expressed in a Chinese hamster ovary (CHO) cell expression system. The second part is a computer modeling study, where changes relevant for the mutant channel have been incorporated into a strand based on Luo-Rudy elements. A mechanism is proposed for the genesis of the ST-T-wave changes observed in the index patient.

The authors of this paper are to be lauded for their attempt to bridge the gap between clinical observations, genetic identification of the mutation, biophysical characteristics of the mutant channel, and the electrophysiological mechanism of ST-segment changes in Brugada syndrome. Genotype-phenotype relations are very difficult to study in patients, especially when the mutation is related to a phenotype involving sudden cardiac death (14). Cardiac myocytes are not readily donated by the living and cannot be obtained from the dead individual. We, therefore, have to rely on extrapolation of data obtained from expression systems with the help of intricate computer simulations, except for the rare occasion when a patient undergoes cardiac transplantation (9). The extrapolation procedure of which we see an example in the paper by Bebarova et al. (5) relies, by necessity, on a cascade of assumptions. Although many of these assumptions are appropriately discussed by the authors, critical comments can be made on almost every level of the extrapolation cascade. Some of the assumptions and their related criticism are as follows.

1) The signs of the patient are typical of the syndrome. The phenotype of the patient is not that easy to interpret. Although conduction disease is apparent, also and explicitly in the F2004L patient of Dr. Schulze-Bahr (see discussion section of Ref. 5), the authors emphasize the right precordial ST-elevation, suggesting Brugada syndrome. Their basic electrophysiological data are, in fact, used in an in silico model to explain the right precordial ST-elevation (see further). The question is whether the F2004L mutation is indeed a Brugada syndrome mutation. In the small family, the penetrance of ST-elevation is very low (0% at baseline, only 2 persons have been tested with class I drugs, one of them being positive), and there is also ST-elevation in the left lateral leads (patient II-3). The tachycardia in patient II-8 is a relatively slow monomorphic right bundle-branch block ventricular tachycardia, with a very long coupling interval (not shown in the paper). All of these features do not exclude Brugada syndrome, but are not very typical either.

2) The mutation is causal to the disease. Whereas the authors are the first to associate the mutation with Brugada syndrome, F2004L has also been identified in sudden infant death syndrome (3, 18) and in adult sudden cardiac death victims (2). As these clinical disease entities have been associated with Brugada syndrome, these data are compatible with an association between F2004L and Brugada syndrome. However, the mutation is also described in control patients: 2 of 295 Caucasian and 1 of 103 Hispanic (1). The study itself does not provide strong evidence for causality either. Obviously, the family is too small for linkage analysis, and penetrance is very low. Furthermore, it is unclear how many control alleles were tested for the mutation. Based on these data, it is difficult to decide whether this variant is a rare single nucleotide polymorphism or a disease-associated variant.

3) The expression system reflects the changes in the cardiac myocyte, and a heterozygous mutation is faithfully represented by expression of only the mutant gene in CHO cells. Wang et al. (18) have observed that the F2004L exhibits increased persistent sodium current typical of long QT syndrome-associated mutations (6). In the Maastricht study, a loss of function is described with technically sound pathophysiological data, showing decreased peak and persistent Na+ current based on increased closed-state inactivation, accelerated slow inactivation, and delayed recovery from inactivation (5). The authors indicate that different cellular models (CHO cells vs. tsA201 cells) might explain the differences, but, at the same time, these differences should also shed some doubt on the value of these heterologous cell systems in explaining the pathophysiological mechanisms of these diseases. Clearly, more sophisticated cell
systems (like human stem cell-derived cell lines) are needed to resolve these issues.

4) The computer model represents the heart. The Markov model is characterized by a multitude of states that do not necessarily correspond to physical states of the ion channel. This makes the model less transparent and more difficult to understand in terms of cellular electrophysiology. In general, simpler models allow conveyance of understanding easier than more complex models (8). Another aspect is that the Luo-Rudy model consists of longitudinally coupled myocytes, a condition that does not exist in reality. Has oversimplification been coupled to overcomplication in this case?

One could say that the model tests a hypothesis that may be of general applicability for Brugada syndrome and should work for every loss-of-function sodium channel mutation. This has, however, not been tested. In addition, the most relevant patient in this family also shows left lateral ST-elevation, and this seems not to be accounted for by the model data.

5) The simulated rate-dependent ECG changes are clinically reproducible. The rate dependence of the ST-elevation, which indeed is typical for most Brugada syndrome patients, but not for all (17), has not been tested clinically. A simple exercise test would have done the job and would have further validated the modeling exercise.

Finally, the nomenclature introduced by the authors (phase 0 block) is as confusing as the term phase 2 reentry (which is not a form of reentry but a mechanism for impulse initiation) and is nothing more than classical conduction block, consistent with one of the existing hypotheses on Brugada syndrome. We prefer the traditional terminology in this case, but agree that “delayed phase 2 propagation” or “phase 2 block” may add to insight and possibly to clinical implications, as suggested by the authors. It is to be noted that the right precordial high ST-segment take-off is virtually always associated with a terminal negative T wave, which, as stated by the authors (5) and suggested previously (14), is potentially explained by significant conduction delay.

The present study (once again) launches an interesting concept for the mechanism of the right precordial ST-elevation in Brugada syndrome. Whatever criticism can be generated on these valuable attempts to understand genotype-phenotype relations in life-threatening conditions, the authors of the paper have shown us a way to obtain the much needed insights that will eventually provide us with the tools to prevent the arrhythmias and treat the patient.

REFERENCES


