Ion channelopathies: a tapped-out mine?

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The study of ion channels shifted paradigms when Keating and colleagues (3) struck silver in the Utah hills. In the early days of the molecular biological era, they were able to describe a genetic linkage between the long QT syndrome, a form of inherited sudden death associated with a particular electrocardiographic finding, and ion channel DNA mutations. They went on to describe a plausible mechanism whereby these mutations caused the disease. Since then, this mother lode has been mined in a similar manner to describe the origins of such inherited arrhythmic conditions such as Brugada syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) (5).

The mining process of identifying a mutation in affected individuals and then heterologously expressing the mutation to study the effect on the altered ion channel to develop a plausible mechanism has been played out many times. Some of the themes that have been learned in the course of finding and studying gene defects are that there are many mutations, often in several different ion channels or related proteins, that can cause the same syndrome; that mutations in the same ion channel can give more than one clinical syndrome; and that the effects of mutations are modulated by the genetic context.

The “find and express” process has become so routine that some have begun to question whether manuscripts based on it should be published or the results just catalogued (e.g., The Gene Connection for the Heart, http://www.fsm.it/cardmoc/). To address that question, it might be reasonable to ask what is the purpose of the mining process. Some possible purposes include the following: 1) identifying new mechanisms of disease, 2) developing genetic screens for affected individuals, 3) developing new therapies, and 4) understanding mechanisms of the more common acquired arrhythmic conditions. The process has been remarkable for its ability to identify the mechanisms of disease. For example, long QT syndrome results from a loss of repolarization reserve such that the cell stays in the depolarized state too long, allowing for membrane potential oscillations that cause the arrhythmia (1). Brugada syndrome seems to be related to a loss of voltage-gated sodium current, causing an abrupt shortening of the action potential duration in certain areas of the heart and current between repolarized myocytes with short action potentials and depolarized myocytes with longer action potentials (10). The current is thought to initiate the arrhythmia. In some cases such as CPVT, a defect in calcium handling has been identified, but the actual mechanism whereby this defect causes the arrhythmia is still debatable (2). The mining process has also been helpful in understanding more commonly occurring acquired arrhythmias. For example, mutations in the human ether-à-go-go-related gene potassium channel were identified as one of the causes of long QT syndrome, and it was not long before this channel was implicated in most of the cases of drug-induced long QT syndrome (7).

For all of its successes, the process has been less productive when it comes to developing genetic screening tools and developing new therapies. While genetic screening has been commercialized (e.g., Familion Testing, PGxPredict, New Haven, CT), incomplete penetrance and the lack of consistent genotype-phenotype correlations have made using the information for clinical decision making challenging. The lack of development on the treatment side has been even more disappointing. There are some leads, such as sodium channel blocking drugs for long QT type 3 (8), NAD+ for Brugada syndrome (6), and flecainide for CPVT (9), but these are just getting into clinical trials.

So is the mine tapped out, or should we just go on digging up smaller and smaller nuggets of silver? Which pieces of silver will be notable enough to publish? While we recognize publication as a motivation for investigation, it also might help to keep in mind the goals of this form of research when deciding what constitutes a publishable unit, so as to not overwhelm readers with a multitude of disjointed facts. Clearly, a primary goal of science is to learn novel information. Such is the case in the article by Huang et al. (4), published in the January issue of the American Journal of Physiology-Heart and Circulatory Physiology, where nature’s mutagenesis experiment taught us interesting new information about the structural basis of antiarrhythmic drug activity on cardiac sodium channels. Other new information that would seem worthy of publication would include the following: 1) mutations causing novel mechanisms of disease, 2) finding new proteins causing a syndrome, and 3) experiments opening new therapeutic implications. In sporadic mutations or other cases where linkage analysis alone is insufficient to establish cause and effect, it would seem that the addition of modeling (either physiologically or mathematically) accompanied by some model testing would be a desirable standard for future publications.

It is unlikely that the ion channelopathy mine is tapped out, but refining the paradigm will help direct effort toward the richest veins and make the most of future findings.

DISCLOSURES

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