A molecular genetic diagnosis in Brugada syndrome (BrS) can facilitate effective family screening for a condition in which death is potentially preventable. Yet, for the asymptomatic individual, a molecular genetic diagnosis of BrS brings a considerable psychological and social burden, as well as interaction with a medical community that is uncertain of best management. We must, therefore, be as sure as we can that a genetic change found in any given individual truly underlies his/her condition. Most such changes identified to date in the SCN5A gene, and other rarer genes linked to BrS,1 have largely been unique to each family, with limited supporting in vitro evidence of their effect on the cardiac sodium channel. Since genetic variants appear in healthy controls, there is a risk that a rare genetic variant in a patient could be misclassified as a “mutation” that underlies his/her clinical diagnosis.

Kapplinger et al2 have started to tackle this problem by producing a compendium of 293 mutations seen in the SCN5A gene in a cohort of 2111 suspected BrS patients. This team of international researchers must be congratulated for contributing their data to one paper like this, which is worth more than the sum of its parts. The paper shows the significance of both the position and the nature of variants worth more than the sum of parts. The paper shows the importance, however, is the clinical value that is given to the label of “mutation.”

Kapplinger et al2 have classified “rare variants” as those appearing at a frequency of less than 0.5% in their study group, but rare variants that appear only in patients are termed “mutations.” While such nomenclature is designed to be helpful to the non-geneticist, it may be taken to imply a difference between the two that may be unjustified. “Mutation” and “rare variant” describe the same phenomenon: a permanent heritable change in the nucleotide sequence occurring very uncommonly. While these and other researchers grapple to define which mutations are truly disease causing, clinicians must remember that receiving a label of “mutation” does not of itself define pathogenicity. Kapplinger et al2 report that rare variants in the SCN5A gene occur in 21% of patients and in 2%–5% of healthy controls. The suggestion is that excluding the latter from the former reveals the functionally critical mutations. However, the level of uncertainty regarding this suggestion is increased by the lack of phenotype data for the cohort, including ethnicity, mode of presentation, and, critically, electrocardiogram evidence, which was not always available for each patient.

Therefore, when can the physician be sure that a “mutation” is truly disease causing? The best way to do this is to see that overt disease and nondisease cosegregate with genetic status in a family. Such evidence is, however, particularly hard to obtain in BrS, where many genetic carriers may have no sign of disease and even pharmacological challenge is not 100% predictive.3 However, some mutations can be viewed as almost certainly pathological. These mutations comprise nonsense mutations, where the protein is truncated at the mutation site, and splice-site, frameshift, insertion, and deletion mutations, where the protein is usually completely altered after the mutation site.

Rare variants detected in healthy controls by Kapplinger et al2 were all of the missense type, which are simple “spelling mistakes” in the genetic code that alter an amino acid. Missense mutations also occurred in two-thirds of patients. Of concern is that most of them were only detected once, so there is a lower level of confidence in their pathogenicity compared with those that have recurred in several families, such as E1784K (also the commonest mutation linked to long QT type 3)4 and D356N. Missense variants located in the transmembrane and pore-forming segments of the protein encoded by the SCN5A gene were seen mostly in patients, whereas those located in the linking regions were mostly in controls. However, position is not everything; for example, E1784K is not in the transmembrane region and R376H occurs in four BrS patients, yet R376C occurs in a white control subject. Interestingly, R376H is a conservative amino acid change, but R376C is nonconservative and possibly could be considered more damaging.

This impressive collaborative effort advances our understanding of the importance of position and nature of genetic variants in the SCN5A gene in BrS. Yet it remains the duty of the physician to be sceptical of most novel missense mutations reported in their patients, since most are actually unclassified rare variants. Clinicians should regard mutations as having...
levels of probability of pathogenicity, such as can now be applied with more confidence to long QT syndrome variants. Increasing this level of confidence based on a battery of in vitro, in silico, and clinical data remains the next challenge to build upon the study of Kapplinger et al.

References