To the Editor:

This issue of J Hum Growth Dev contains an excellent review by Pérez-Riera et al describing one of the most involved ion channel gene named SCN5A that encode the cardiac sodium channel linked to different inherited cardiac arrhythmias (ICA) phenotypes or/and syndromes. The genetic bases of mutation in the SCN5A gene has been implicated in ICA phenotypes and their functional impact may lead to a significant loss (reduction) or gain (increasing) of the sodium channels mutants compared with the wild type.

Sodium channelopathies are recently delineated, emerging as a group of ICA disorders grouped by genetically determined defects in ion-channel function. ICA disorders are characterized by a prominent genetic and phenotypic heterogeneity that can make them challenging to understand. This systematic review by Pérez-Riera et al (1) attempts to understand the role of the sodium channel mutations of these disorders according to their clinical manifestations (i.e., Long QT Syndrome, Brugada Syndrome and others), within the context of what is presently known and their molecular and genetic basis. The review is intended to assist clinicians and scientists in enhancing their clinical and genetic diagnostic knowledge.

The functional genomics in vitro studies are part of the new process to be translated into potential treatments to restore the dysfunction cardiac electrophysiology linked within mutations in the SCN5A gene. The new generation of DNA sequencing methods has now discovered hundreds of new mutations in different sodium channels genes that can lead different phenotypes of channelopathies; and the majority are located in the SCN5A gene showing low expression in the adult heart system. Our group and others found new mutations in the β3 subunits associated with Brugada syndrome and cardiac conduction disease with a significant reduction in the peak sodium current by the co-interaction with the mutant β subunits and SCN5A channels.

Pérez-Riera et al; described in this review that different mutations in SCN5A may lead a large spectrum of different arrhythmia phenotypes. For this reason, it is very important to develop new innovative studies in pharmacogenomics to determine the best treatment options to be
used as specific antiarrhythmic drugs (AAD) in all different ICA phenotypes or syndromes. The majority of the AAD agents that act as blockers have receptor sites on the alpha subunits in the sodium channel protein structure. (4) There are some ADD that shown a positive result by rescuing the loss of function in some SCN5A mutations. For example, the I1660V mutation that produced a significant reduction in sodium current can be treated by using some sodium channel blockers that can rescue the I1660V mutant sodium current (mexiletine, ranolazine, ajmaline, quinidine). Mexiletine has proved to be the most effective. (5) In the modeling site of sodium channels; the L325R mutation showed in cardiac action potential experiments in patients with reduced sodium channels and fever; conditions that could prematurely shorten the action potential, suggesting that a dominant negative phenomenon may underlie BrS triggered by fever. (6) On the other hand, some other AAD are used to unmask other diseases such as BrS.

We are very grateful to read the integration of the basic and translational description of this review by Perez-Riera et al; which contributes to knowledge translation in this fascinating area of science.
REFERENCES


