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SODIUM CHANNEL DYSFUNCTION CAUSES INHERITED CARDIAC CONDUCTION DISEASE

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Cardiac sodium (Na) channel gene (SCN5A) mutations are known to cause repolarization abnormalities and ventricular tachyarrhythmias (VT) in Brugada and Long QT syndrome. Here, we provide the first biophysical characterization of an SCN5A mutation (G514C) associated with inherited conduction disease, but not VT. Whole-cell patch clamp studies in tsA201 cells showed a +10 mV shift in the voltage-dependence of activation, which decreases Na channel availability, and a +7 mV shift in the voltage-dependence of inactivation, which increases Na channel availability. Modeling studies in a fiber composed of endocardial, midmyocardial and epicardial cells (Luo-Rudy model) revealed that these "balanced" gating defects recapitulate the clinical phenotype. An unopposed +10 mV shift of activation (i.e., T1620M) caused severe conduction slowing and repolarization abnormalities consistent with Brugada syndrome. This change, when combined with a +7 mV shift of inactivation (i.e., G514C), resulted in conduction slowing, but no repolarization abnormalities. This inherited lesion provides a biophysical model for understanding how diverse Na channel functional behavior may evoke a spectrum of deranged cardiac excitability, from conduction disease to sudden cardiac death.