Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans.

Abstract:
Brugada syndrome is a genetic disease associated with sudden cardiac death that is characterized by ventricular fibrillation and right precordial ST segment elevation on ECG. Loss-of-function mutations in SCN5A, which encodes the predominant cardiac sodium channel alpha subunit NaV1.5, can cause Brugada syndrome and cardiac conduction disease. However, SCN5A mutations are not detected in the majority of patients with these syndromes, suggesting that other genes can cause or modify presentation of these disorders. Here, we investigated SCN1B, which encodes the function-modifying sodium channel beta1 subunit, in 282 probands with Brugada syndrome and in 44 patients with conduction disease, none of whom had SCN5A mutations. We identified 3 mutations segregating with arrhythmia in 3 kindreds. Two of these mutations were located in a newly described alternately processed transcript, beta1B. Both the canonical and alternately processed transcripts were expressed in the human heart and were expressed to a greater degree in Purkinje fibers than in heart muscle, consistent with the clinical presentation of conduction disease. Sodium current was lower when NaV1.5 was coexpressed with mutant...
beta1 or beta1B subunits than when it was coexpressed with WT subunits. These findings implicate SCN1B as a disease gene for human arrhythmia susceptibility.