The gene SCN5A encodes the α subunit protein NaV1 which forms the pore through which flows most Na current (iNa) in the heart. In addition to the α subunit the SCN5A-macromolecular complex (MMC) is composed of up to four β subunits and many more channel interacting proteins (ChIPs) which interact directly with SCN5A or through intermediary adapter proteins. Mutations in SCN5A have been implicated to cause inherited arrhythmias such as LQTS type 3 (LQT3) by increasing late iNa, and Brugada syndrome (BrS) type 1 and other arrhythmia syndromes by decreasing peak iNa. More recently mutations in as many as 8 different proteins of the MMC have been implicated as causes of LQTS and BrS. Among these are the gene CAV3 encoding caveolin 3 as a cause of LQTS (LQT9), and SCN5A encoding syntrophin α1 as a cause of LQTS (LQT12). This presentation will discuss how mutations found in LQT9 and LQT12 patients increased late iNa by a mechanism involving increased direct nitrosylation of SCN5A. The delineation of these pathways has implications for basic research by yielding insights into the regulation of cardiac electrogensis, and implications for clinical research by suggesting new candidate genes for genotyping inherited arrhythmia and by suggesting therapeutic targets for arrhythmia therapy.

Keywords: Brugada syndrome, sodium channel