Clinical and Genetic Diagnosis for Brugada Syndrome

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Brugada syndrome (BrS) is characterized by specific ST-segment elevation in the right precordial electrocardiographic leads known as the type-1 or coved-type Brugada ECG and associated with a high risk of sudden cardiac death due to VF without structural heart diseases. Recent HRS/EHRA/APHRS expert consensus statement on the diagnosis and management proposed that BrS is definitively diagnosed when a type 1 ST-segment elevation is observed either spontaneously or after intravenous administration of a sodium channel blocking agent in at least ONE right precordial lead (V1 and V2), wherever it is placed in a standard or a higher intercostal space (up to the 2nd intercostal space). Only one-third of affected patients can be genotyped mainly in the sodium channel gene, *SCN5A*, therefore, genotype-phenotype relationships in clinical studies have been limited. Two genomic regions, the *SCN10A* at 3p22.2 and the *HEY2* at 6q22.32, has been identified, which displayed significant association with BrS in a genome-wide association study (GWAS) including 383 individuals with BrS and 1,115 ancestry-matched controls. Antzelevitch's group also identified 17 *SCN10A* mutations in 25 (yield; 16.7%) out of 150 patients of their Brugada cohort. *SCN10A* is expressed in the working myocardium and the specialized conduction system, indicating a possible role for Nav1.8 in cardiac electrical function. Overall, the yield for detection of a Brugada genotype has reached approximately 50%. *HEY2* is involved in patterning Nav1.5 (*SCN5A*) expression across the ventricular wall. Loss of *HEY2* is suggested to affect the transmural expression gradient of sodium channel implicated in BrS.