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LOSS-OF-FUNCTION MUTATION OF THE CARDIAC CAV1.2 CHANNEL IN THE SHORT QT SYNDROME

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Short QT syndrome (SQTS) emerged as a new inherited channelopathy characterized by constantly short QT interval (QTc < 360ms) associated with atrial fibrillation, syncope episodes, and/or sudden cardiac death in patients with no underlying structural heart disease. It has been associated with a gain in function in 3 distinct potassium channels (KCNH2, KCNQ1, and KCNJ2) or a loss-of-function of a calcium channel Cav1.2. We identified a 6-year-old male proband who experienced a syncope episode and presented a QTc of 346ms. In addition, a triangular T wave was observed in V2, V3 leads. His 34-year-old mother was asymptomatic (QT: 405 ms). After a screen for ion channels, we found a variant of CACNA1C, gene encoding Cav1.2. We identified a 6-year-old male proband who experienced atrial fibrillation (VF) in the absence of gross structural abnormalities. Mutations in SCN5A, encoding the pore-forming subunit α of the cardiac voltage-gated sodium channel, are identified in about 20-30% of probands affected by Brugada syndrome (BrS). SCN5A mutations may also lead to progressive cardiac conduction defects (PCCD). The causality of SCN5A mutations in PCCD was proven by linkage analysis. In contrast, SCN5A mutations in BrS were discovered by a candidate gene approach and linkage data are still lacking.

The aim of this study was to investigate the association of SCN5A mutations and BrS in a group of large genotyped families.

Methods and Results — Families were included if at least 4 family members were carriers of the SCN5A mutation identified in the proband. Thirteen large families composed by 115 mutation-carriers were studied. The signature type I ECG was present in 54 mutation-carriers (BrS-ECG+) (47%). In 5 families, we found 7 individuals affected by BrS, but with a negative genotype (mutation-negative BrS-EGC+). Among these 7 mutation-negative BrS+ individuals, 3, belonging to 3 different families, had a spontaneous type I ECG, while 4 had a type I ECG after administration of Na+ channel blockers. EPS was performed in 5 BrS-ECG non-mutation patients. Ventricular tachyarrhythmias were inducible in 3. An ICD was implanted in these 3 patients. Mutation carriers (n=115) had, on average, longer PR and QRS intervals than non-carriers (n=148) demonstrating that these mutations exerted functional effects.

Conclusions — Our results suggest that SCN5A mutations might not be sufficient to cause BrS and that genetic background may play a powerful role in the pathophysiology of BrS. However, this study confirms the role of SCN5A mutations in PCCD. These findings add further complexity to concepts regarding the causes of BrS, and are consistent with the emerging notion that the pathophysiology of BrS includes various elements beyond mutant sodium channels.

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SCN5A MUTATIONS AND THE ROLE OF GENETIC BACKGROUND IN THE PATHOPHYSIOLOGY OF BRUGADA SYNDROME

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Background — Brugada syndrome (BrS) is an inherited arrhythmia syndrome with an increased risk of sudden death resulting from polymorphic ventricular tachycardia (VT) and/or ventricular fibrillation (VF) in the absence of gross structural abnormalities. Mutations in SCN5A, encoding the pore-forming subunit α of the cardiac voltage-gated sodium channel, are identified in about 20-30% of probands affected by Brugada syndrome (BrS). SCN5A mutations may also lead to progressive cardiac conduction defects (PCCD). The causality of SCN5A mutations in PCCD was proven by linkage analysis.

The aim of this study was to investigate the association of SCN5A mutations and BrS in a group of large genotyped families.

Methods and Results — Families were included if at least 4 family members were carriers of the SCN5A mutation identified in the proband. Thirteen large families composed by 115 mutation-carriers were studied. The signature type I ECG was present in 54 mutation-carriers (BrS-ECG+) (47%). In 5 families, we found 7 individuals affected by BrS, but with a negative genotype (mutation-negative BrS-EGC+). Among these 7 mutation-negative BrS+ individuals, 3, belonging to 3 different families, had a spontaneous type I ECG, while 4 had a type I ECG after administration of Na+ channel blockers. EPS was performed in 5 BrS-ECG non-mutation patients. Ventricular tachyarrhythmias were inducible in 3. An ICD was implanted in these 3 patients. Mutation carriers (n=115) had, on average, longer PR and QRS intervals than non-carriers (n=148) demonstrating that these mutations exerted functional effects.

Conclusions — Our results suggest that SCN5A mutations might not be sufficient to cause BrS and that genetic background may play a powerful role in the pathophysiology of BrS. However, this study confirms the role of SCN5A mutations in PCCD. These findings add further complexity to concepts regarding the causes of BrS, and are consistent with the emerging notion that the pathophysiology of BrS includes various elements beyond mutant sodium channels.