Abstract: P360

Mutations of the SCN5A gene in Portuguese patients with Brugada Syndrome

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Background: Brugada syndrome (BS) is an inherited disease with complex genetic substrate and incomplete penetrance. The SCN5A gene, encoding sodium channels, is most often implicated. However, pathogenic mutations are recognized in only 20-30% of patients (pts), with relevant geographic and ethnic variation.

Objective: To evaluate the prevalence of SCN5A gene mutations in Portuguese pts with BS.

Methods: Single-center prospective study of consecutive pts with BS diagnosis, defined by the presence of spontaneous or flecainide induced type 1 pattern. Direct sequencing of the SCN5A gene was performed, polymorphisms were identified and pathogenicity determined by comparison with the databases (HGMD, ClinVar and Inherited Arrhythmias Database) and in silico prediction. In all cases, family electrocardiographic screening was performed, whenever possible, to third-degree relatives.

Results:
In a population of 86 pts (median age of 45 years, 60 males), the result of the genetic study is available in 67 pts (genetic study in progress in the remaining). Of these, 11 (16.4%) had symptomatic disease, 35 (52.2%) spontaneous type 1 pattern and 12 had a family history of sudden death at an early age. In family screening, other BS cases were identified in 10 pts (14.9%).

Mutations of the SCN5A gene were identified in 17 pts (25.4%). Of these, 8 pts (11.9%) had previously described pathogenic mutations, 6 (9.0%) had predictably pathogenic mutations never described before and 3 had polymorphisms of indeterminate significance. The most frequent site of mutation was exon 28, implicated in 23% of the mutations detected. There was no association between SCN5A gene mutations and the disease phenotype, risk of events or family history.

Conclusion: This study presents the first systematic genetic evaluation in a population of Portuguese patients with BS. SCN5A gene pathogenic mutations were identified in 20.9% of the pts and an unexpected clustering of mutations in exon 28 was observed. The potential impact of this specific genotype on disease expression in Portugal should be investigated in the future.