

Genetic Screening of Familial Sinus Bradycardia

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Background: Familial sinus bradycardia (FSB) is a relatively rare phenomenon. We and others have previously shown in sporadic families that mutant hyperpolarization-activated nucleotide-gated (*HCN4*) channel, is associated with FSB. In this study we systematically screened families with SB for mutations in this channel as well as in others related to sinus node function.

Methods: Clinical evaluation and routine genetic screening of Israeli Jewish families with FSB.

Results: Twelve families with FSB were followed and screened for mutations in the *HCN4* gene. Five of them, all of Jewish Moroccan descent, demonstrated A485V mutation of the *HCN4* gene. Most of the carriers of this mutation were symptomatic. One additional family was positive for the G480R mutation. The carrier members were asymptomatic and had favorable prognosis without the need for pacemaker implantation during long-term follow-up. Six families did not have any mutations in *HCN4*. One of them was also screened for *KCNJ2*, *KCNJ12* and *SCN5A* genes. The screening revealed that only a combination of two *SCN5A* missense mutations (V1251M, V1924T) and an amino acid deletion (K1492del) in *SCN5A* resulted in clinical bradycardia with syncope and atrial tachyarrhythmias during physical exercise.

Conclusions: Genetic screening of families with FSB in Israeli Jewish population reveals a high yield of mutations in candidate genes of ion channels that participate in diastolic depolarization of SAN cells. The genotype-phenotype correlations will probably have a clinical role in risk stratification of FSB. Whether these findings apply to FSB in other populations remains to be determined