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Non-familial sick sinus syndrome: search for genetic markers

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Sick sinus syndrome (SSS) can result from genetic and environmental factors. Genome-wide association studies (GWAS) have successfully identified more than a dozen genetic loci however potential mechanisms underlying of SSS heritability remains unknown. Aim of the study was to investigate whether connective tissue gens CHRM2 rs2350782, SYT10 rs7980799, MYH6 rs365990, FNDC3B rs9647379, MIR146A rs2910164, MIR196A2 rs11614913 and ion channel HCN4 rs7164883, SCN10A rs6795970, KCNE1 rs1805127, CLCNKA rs10927887, KCNN3 rs13376333 loci are involved in the pathogenesis of non-familial SSS.

Methods. In the case-control study, DNA was isolated from peripheral blood of 284 unrelated SSS patients (average age 65.65±11.04) and 243 healthy donors (62.56±14.05). 10 single nucleotide polymorphisms (SNPs) were genotyped by the real-time polymerase chain reaction. Logistic regression was used to detect the association of SNPs with SSS in different models.

Results. Before association analysis with SSS, we verified whether observed genotype frequency distributions agreed with the Hardy-Weinberg equilibrium (HWE). In the control group PH-W=0.022 for CHRM2 (rs2350782), PH-W=0.081 for SYT10 (rs7980799), PH-W=0.18 for MYH6 (rs365990), PH-W=0.37 for FNDC3B (rs9647379), PH-W=0.23 for MIR146A (rs2910164), PH-W=0.0001 for MIR196A2 (rs11614913). MIR196A2 (rs11614913) with genotype distribution deviating from the HWE was excluded from the further analysis of associations. No statistically significant differences were observed in the CHRM2 rs2350782 frequency distribution (?²=2.46, P=0.118 for alleles and ?²=3.41, P=0.18 for genotypes). But introducing variables such as sex and age into the equation of logistic regression, it was shown that the genotypes of the dominant model (T/T+T/C) are more common in the control group (36.2%) compared with SSS patients (28.9%) ?adj=0.052. FNDC3B rs9647379 C/C genotype was associated with sinus bradycardia development (P=0.05, OR=1.55). The protective effect was shown for the additive model FNDC3B rs9647379 in (P=0.014, OR=0.71). In ion channel gen analysis in the control group PH-W=0.0001 was for HCN4 (rs7164883), PH-W=0.49 for SCN10A (rs6795970), PH-W=0.069 for KCNE1 (rs1805127), PH-W=1.0 for CLCNKA (rs10927887), PH-W=0.0001 for KCNN3 (rs13376333). HCN4 (rs7164883) and KCNN3 (rs13376333) with genotype distribution deviating from the HWE were excluded from the further analysis. Statistically significant differences between the groups were found at the polymorphic locus: KCNE1 rs1805127 (?² = 8.40, P = 0.02), so the T/T genotype for this locus was statistically significantly more frequent in the control group, 15.64% vs. 8.45% in the SSS, OR = 0.50, 95% CI (0.29-0.86).

Conclusion. Among analyzed genes FNDC3B rs9647379, CHRM2 rs2350782 of connective tissue; T/T genotype of the KCNE1 rs1805127 and CLCNKA g.16351275A>G of ion channel genes polymorphism may play a significant role in the development of non-familial SSS