UK-Russia Young Medics Conference

UK-Russia
Young Medics Association

GENETIC MARKERS OF CONNECTIVE TISSUE AND IONS CHANELS IN SICK SINUS SYNDROME

Paruyr Davtian[1]*, Naufal Zagidullin[2]

[1 2]Bashkir State Medical University; Ufa, Russia

Background. Sick sinus syndrome (SSS) is more common in elderly patients and can result from genetic and environmental factors. Over the past few years, genome-wide association studies (GWAS) have successfully identified more than a dozen genetic loci (connective tissue, cardiac signaling, regulation of atrial action potential duration, etc.), however potential mechanisms underlying of SSS heritability remains unknown.

Objectives 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

Materials. 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 (average age 62.56±14.05). 10 single nucleotide polymorphisms (SNPs) were genotyped by the real-time polymerase chain reaction (Table 1). The analysis was carried out by real-time PCR using commercial sets with fluorescent detection (FLASH / RTAS) (http://testgen.ru, Test-Gene, Russia) on a BioRad CFX96TM instrument (Bio-Rad Laboratories, Inc, USA). Detection of end-point fluorescence and discrimination of genotypes was performed according to the BioRad CFX96TM protocol using CFX Manager TM Software. Logistic regression was used to detect the association of SNPs with SSS in different models.

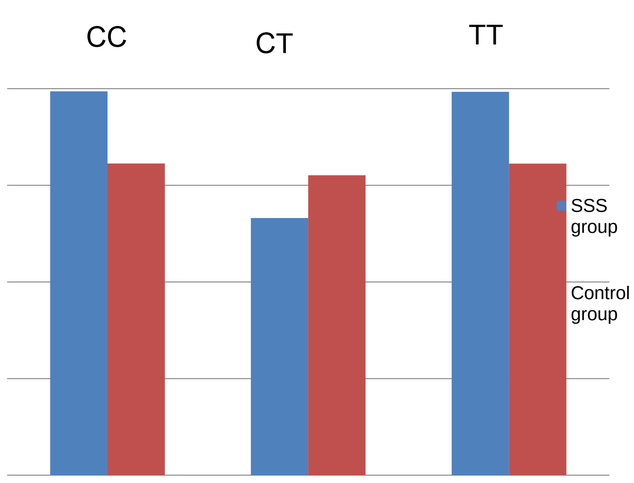
Gene polymorphic loci	Chromosome location	Gene function
KCNN3 rs13376333	1q21.3	Encodes a voltage-dependent potassium channel
KCNE1 rs1805127	21q22.12	Modulates the function of 6 transmembrane proteins forming the pore of the α-subunit Kv7.1
CLCNKA rs10927887	1p36.13	Encodes a potential-dependent chloride channel
HCN4 rs7164883	15q24.1	Encode the pacemaker f-channel
SYT10 rs7980799	14q11.2	This locus is associated with a change in heart rate
SCN10A rs6795970	3p22.2	The product of expression of this gene is the alpha subunit of type 10 voltage-dependent sodium channels, consisting of approximately 1967 amino acids
MIR146Ars2910164	5q33.3	Fibrosis regulation
MIR196A2 rs11614913	12q13.13	Fibrosis regulation
MYH6 rs365990	12p11.1	Encoding the alpha heavy chain subunit of cardiac myosin
FNDC3B rs9647379	3q26.31	Fibronectin type III domain-containing protein 3B
CHRM2 rs2350782	7q33	Associated with a different heart rate after maximum exercise

Results. Before association analysis with SSS, we verified whether observed genotype frequency distributions agreed with the Hardy-Weinberg equilibrium (HWE).

In the control group P_{H-W}=0.022 for *CHRM2* (*rs2350782*), P_{H-W}=0.081 for *SYT10* (*rs7980799*), P_{H-W}=0.18 for *MYH6* (*rs365990*), P_{H-W}=0.37 for *FNDC3B* (*rs9647379*), P_{H-W}=0.23 for *MIR146A* (*rs2910164*), P_{H-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 (χ2=2.46, P=0.118 for alleles and χ2=3.41, P=0.18 for genotypes). However, 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%) P_{adj}=0.052. Analysis, depending on the type of SSS, showed *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 P_{H-W}=0.0001 was for *HCN4* (*rs7164883*), P_{H-W}=0.49 for *SCN10A* (*rs6795970*), P_{H-W}=0.069 for *KCNE1* (*rs1805127*), P_{H-W}=1.0 for *CLCNKA* (*rs10927887*), P_{H-W}=0.0001 for *KCNN3* (*rs13376333*). *HCN4* (*rs7164883*) and *KCNN3* (*rs13376333*) with genotype distribution deviating from the HWE were excluded from the further analysis of associations. Statistically significant differences between the groups studied were found at the polymorphic locus: *KCNE1* rs1805127 (χ2 = 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) – Fig. 1.



Gene polymorphic locus	Genotypes of the allele	SSS abs. (%) (N = 284)	Control abs. (%) (N = 243)	[1]P	$P_{corr-FDR}$	OR (95% CI)
KCNN3 rs13376333	CC CT TT	170 (59.86) 83 (29.23) 31 (10.92)	166 (69.17) 49 (20.42) 25 (10.42)	0.03 0.03 0.97	- -	0.66 (0.46-0.96) 1.61 (1.07-2.42) 1.05 (0.60-1.84)

Fig. 1. KCNE1 rs1805127 polymorphism (CC, CT and TT types) analysis in patients with SSS and control group.

Discussion

Loci KCNE1 rs1805127 (OR = 1.46), KCNN3 rs13376333 (OR = 1.61), MIR196A2 rs11614913 (OR = 1.66) may be involved in SSS development. It can be assumed that the KCNN3 plays an important role in heart rhythm regulation. In our study the high risk of sinus bradycardia and sinus arrest was associated with the heterozygous genotype C/T of KCNE1 gene and the C/C genotype of the same gene was associated with the SA blockade of the 3rd degree. The polymorphic loci MIR146Ars2910164 and MIR196A2 rs11614913 were associated with development of SSS, possibly by regulating genes involved in fibrosis, since SSS usually accompanied by severe fibrosis around the sinus node, degenerative remodeling in atria, replacement of the pacemaker cells (pacemakers) and conductive fibers by connective tissue.

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-familia SSS.

Literature:
1) De Ponti R. et al. Card Electrophysiol Clin 10 (2018) 183–195.
2) KNikulina SY[1] et al. Kardiologiia. 2018 Nov 18;58(4):53-59.
3) Kusss J. et al. Circ Genom Precis Med. 2019 Jan;12(1).

Study disclosure. No conflict of interests is declared for the study team