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SHORT COMMUNICATION

Genetic predictors of sick sinus syndrome

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Abstract

Sick sinus syndrome (SSS) encompasses a group of conduction disorders characterized by the inability of sinoatrial node to perform its pacemaker function. Our aim was to identify genetic predictors of SSS in a prospective cohort of patients admitted to the clinic for pacemaker implantation using single-locus and multilocus approaches. We performed genotyping for polymorphic markers of *CLCNKA* (rs10927887), *SCN10A* (rs6795970), *FNDC3B* (rs9647379), *MIR146A* (rs2910164), *SYT10* (rs7980799), *MYH6* (rs365990), and *KCNE1* (rs1805127) genes in the group of 284 patients with SSS and 243 healthy individuals. Associations between the studied loci and SSS were tested using logistic regression under recessive genetic model using sex and age as covariates. Multilocus analysis was performed using Markov chain Monte Carlo method implemented in the APSampler program. Correction for multiple testing was performed using Benjamini–Hochberg procedure. We detected an individual association between *KCNE1* rs1805127*A allele and SSS in the total study group (OR 0.43, $P_{FDR} = 0.028$) and in the subgroup of patients with 2nd or 3rd degree sinoatrial block (OR 0.17, $P_{FDR} = 0.033$), and identified seven allelic patterns associated with the disease. *SCN10A* rs6795970*T and *MIR146A* rs2910164*C alleles were present in all seven combinations associated with SSS. The highest risk of SSS was conferred by the combination *SCN10A* rs6795970*T+*FNDC3B* rs9647379*C+*MIR146A* rs2910164*C+*SYT10* rs7980799*C+*KCNE1* rs1805127*G (OR 2.98, CI 1.77–5.00, $P = 1.27 \times 10^{-5}$, $P_{FDR} = 0.022$). Our findings suggest that *KCNE1* rs1805127 polymorphism may play a role in susceptibility to sinoatrial node dysfunction, particularly presenting as 2nd or 3rd degree sinoatrial block, and the risk-modifying effect of other studied loci is better detected using multilocus approach.

Keywords Sick sinus syndrome · KCNE1 (potassium voltage-gated channel subfamily E member 1) · SCN10A (sodium voltage-gated channel alpha subunit 10) · miR-146a · FNDC3B (fibronectin type III domain 3B) · SYT10 (synaptotagmin 10) · Multilocus analysis

Introduction

Sinus node dysfunction, historically referred to as sick sinus syndrome (SSS), comprises a variety of sinus rhythm disorders, including sinus bradycardia, sinus arrest, sinoatrial block and paroxysmal tachycardias (bradycardia-tachycardia syndrome) [1]. Sinoatrial node is the physiological pacemaker of the heart primarily responsible for generating the autonomous heart beat. Various intrinsic (fibrosis, infiltrative diseases such as amyloidosis, connective tissue disorders, ion channel dysfunction, remodelling of the sinoatrial node) and extrinsic factors (autonomic dysfunction, metabolic disorders including hypothyroidism, toxins and pharmacological agents such as antiarrhythmic drugs, beta blockers, calcium channel blockers, digoxin) can impair the function of sinoatrial node. SSS is among the most common indications for permanent pacemaker implantation [1].

The true epidemiology of SSS is difficult to determine due to multifaceted character of the disorder and varying clinical spectrum, ranging from asymptomatic forms to severe manifestations of end-organ hypoperfusion, including

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congestive heart failure and stroke. The most commonly given estimate of the SSS prevalence is 1 in 600 individuals over 50 years of age and is based on the data from the Provincial Centre for Detection of Cardiovascular Diseases in Belgium [2]. The prospective study of 20,572 participants aged 45 years and older from two cohorts (CHS—cardiovascular health study and ARIC—atherosclerosis risk in communities) identified 291 (45% men, 55% women) cases of SSS (0.8 per 1000 person-year) [3]. Risk factors for SSS included advanced age, greater body mass index and height, hypertension, right bundle branch block, history of major cardiovascular event (myocardial infarction, heart failure, or stroke), and biomarkers of heart failure (N-terminal pro B-type natriuretic peptide) and kidney function (cystatin C) [3].

Several studies have identified mutations contributing to the development of familial forms of SSS, mostly confined to genes encoding ion channels—*SCN5A* [4], *HCN4* [5], *CACNA1C* [6], and structural proteins—*LMNA* [7], *MYH6* [8]. A rare variant in the *MYH6* gene was also associated with sporadic SSS in Icelandic population [9]. However, genome-wide association study (GWAS) of 903 SSS cases and 40,722 controls did not reveal an association of any individual genetic marker with SSS, although polygenic risk score for 21 loci was associated with decreased risk of SSS and pacemaker implantation [10]. In general, studies of the genetics of non-familial SSS have been rare and the evidence inconclusive. We analysed data from the prospective cohort of patients with SSS referred to the Republic Centre for Cardiology (Ufa, Republic of Bashkortostan, Russian Federation) for pacemaker implantation with a follow-up of 1–6 years. Our objective was to identify genetic predictors of the SSS risk using single-locus and multilocus analysis.

Material and methods

Study group

The study was approved by the ethics committee of the Institute of Biochemistry and Genetics of Ufa Federal Research Centre of Russian Academy of Sciences (IBG UFRC RAS) and written informed consent was obtained from each participant in accordance with Helsinki declaration (2000) outlining the principles for medical research involving human subjects. In total, 610 patients with impaired sinoatrial node function admitted to the Republic Centre for Cardiology (Ufa, Republic of Bashkortostan, Russian Federation) between 2011 and 2017 were enrolled in the study. Criteria for exclusion from the study were: unwillingness to participate, use of medications potentially affecting heart rate, acute myocardial infarction, decompensated heart failure, ejection fraction < 35%. Blood samples from 284 patients (98 men, 186 women, mean age 69.65 ± 11.04) were available for genotyping. All patients underwent full clinical examination and laboratory assessment. SSS was diagnosed by 12-lead electrocardiography (ECG), 24-h Holter monitoring using Schiller Medilog AR12 Plus recorders (Schiller Medilog, Schiller AG, Switzerland). The comparison group included 243 healthy volunteers (104 men, 139 women, mean age 62.56 ± 14.05) without history or clinical symptoms of cardiovascular disease recruited at the Republic Centre for Blood Transfusion (Ufa, Republic of Bashkortostan, Russian Federation).

Genotyping

Whole venous blood was collected into 9 ml ethylenediaminetetraacetic acid (EDTA) vacutainer tubes using standard phlebotomy technique. Total genomic DNA was isolated from 5 ml of whole venous blood using phenol–chloroform extraction. The DNA quality was evaluated by electrophoresis in 0.8% agarose gel and quantified by ultraviolet absorbance spectrophotometry analysis. The selection of single nucleotide polymorphisms (SNPs) for the analysis was based on the following criteria: known or suggested functional significance, previously reported associations with heart rate related traits, minor allele frequency > 0.05 in European population according to the Ensembl database [11]. Genotyping was performed using Taqman assays (TestGen, Moscow, Russia) on the BioRad CFX96 Real-Time PCR Detection System following standard protocols (Bio-Rad Laboratories, CA, USA). Random re-genotyping of 5% of the samples was performed to determine the genotyping accuracy, and all the newly obtained results were identical to the initial genotype calling.

Statistical analysis

The study data were stored and managed using IBM SPSS Statistics V22.0 (Chicago, IL, USA). Statistical analysis was performed using PLINK software v.1.07 (http://pngu.mgh.harvard.edu/purcell/plink/) [12]. All SNPs were tested for departure from Hardy–Weinberg equilibrium in the control group. Associations of the studied SNP and SSS were analysed using logistic regression analysis under recessive genetic model with sex and age as covariates. Additionally, considering that atrial fibrillation and arterial hypertension can be important confounding factors for sick sinus syndrome, the analysis was performed using sex, age, atrial fibrillation, arterial hypertension as covariates. Recessive model implies that two copies of the effect allele are required to alter the risk of the disease. Correction for multiple testing was performed using the false discovery rate (FDR) method [13]. P values of < 0.05 were considered statistically significant. Gene–gene interactions and the association between

allelic combinations of the studied loci with SSS were interrogated by APSampler 3.6.0 (the program can be accessed at http://apsampler.sourceforge.net/). APSampler (Allelic Pattern Sampler) uses a Markov chain Monte Carlo method based on Bayesian approaches to identify combinations of allelic variants of multiple loci associated with the studied trait (the detailed description has been provided earlier [14]).

Results

Clinical characteristics of the study group are detailed in Table 1. The majority of patients included in the study had sinus bradycardia (60.9%), 2nd or 3rd degree sinoatrial block (26.1%), sinoatrial arrest was detected in 12.3% of patients, while two individuals (0.7%) had tachycardia-bradycardia syndrome. Atrial fibrillation was present in one-third of the patients (34.2%), 82.7% had arterial hypertension, 15.5% had had myocardial infarction, and 10.9% suffered from type 2 diabetes.

Table 1 Clinical characteristics of the study group

Parameter	Patients	Control
N	284	243
Age (mean ± SD)	69.65 ± 11.04	62.59 ± 14.05
Sex: men/women, %	34.5/65.5	42.8/57.2
Heart rate, bpm (mean ± SD)	44.47 ± 7.23	69 ± 14.28
Ejection fraction, % (mean ± SD)	62.48 ± 6.96	NA
Sick sinus syndrome variants		
Sinus bradycardia, n (%)	173 (60.9)	0
Sinoatrial block 2nd degree, n (%)	49 (17.3)	0
Sinoatrial block 3rd degree, n (%)	25 (8.8)	0
Sinoatrial arrest, n (%)	35 (12.3)	0
Tachycardia-bradycardia syndrome, n (%)	2 (0.7)	0
Heart failure stages		
Stage A	224 (78.9)	0
Stage B	53 (18.7)	0
Stage C	1 (0.4)	0
Heart failure functional classes		
NYHA class 0	14 (4.9)	0
NYHA class I	135 (47.5)	0
NYHA class II	70 (24.6)	0
NYHA class III	65 (22.9)	0
Atrial fibrillation, n (%)	97 (34.2)	0
Arterial hypertension, n (%)	235 (82.7)	8 (3.3%)
Myocardial infarction, n (%)	44 (15.5)	0
Type 2 diabetes, n (%)	31 (10.9)	0

bpm beats per minute, *NA* not applicable, *NYHA* New York Heart Association functional classification, *SD* standard deviation

Genotyping results are summarized in Table 2. No deviation from Hardy–Weinberg equilibrium was observed for any of the studied loci. One SNP (rs1805127 at *KCNE1* gene) showed individual association with SSS (for the A allele: OR 0.42, CI_{OR} 0.23–0.76, $P_{FDR} = 0.028$, recessive model). *KCNE1* rs1805127 was also associated with SSS when the analysis was performed with atrial fibrillation and arterial hypertension as covariates (for the A allele: OR 0.44, CI_{OR} 0.25–0.77, $P_{FDR} = 0.03$, recessive model) (Table S1). Comparing the subgroups of different types of SSS (sinus bradycardia, 2nd or 3rd degree sinoatrial block, and sinoatrial arrest; type 4 was excluded from the comparison as tachycardia-bradycardia was detected only in two persons), we found that the frequency of *KCNE1* rs1805127*A allele was significantly lower in the subgroup of patients with 2nd or 3rd degree sinoatrial block than in the control group (25% vs. 35.6%, P = 0.005), and individuals carrying A allele for this polymorphism had decreased risk of SSS type 2 or 3 (OR 0.17, $P_{FDR} = 0.033$) (Table S2). No differences were observed in the distribution of the studied polymorphisms between SSS subgroups.

Analysing gene–gene interactions, we detected seven allelic patterns significantly associated with the disease (Table 3). The observed associations are likely driven by *SCN10A* rs6795970*T and *MIR146A* rs2910164*C alleles, which were present in all the identified combinations, while *FNDC3B* rs9647379*C, *SYT10* rs7980799*C, and *KCNE1* rs1805127*G alleles each appeared in four patterns. All combinations conferred increased risk of SSS (OR ranged between 2.17 and 2.98, the highest risk was contributed by the pattern containing all five alleles). Notably, the combination of *SCN10A* rs6795970*T and *MIR146A* rs2910164*C alleles alone was not significantly associated with the disease (Table 3). Two of the studied polymorphic variants, *CLCNKA* rs10927887 and *MYH6* rs365990, were not associated with SSS individually and were not featured in any of the disease-associated patterns. Performing the multilocus analysis in the SSS subgroups separately, we failed to identify any patterns significantly associated with the particular SSS types, probably due to the small sample sizes of the subgroups.

Discussion

We identified the association between *KCNE1* polymorphism and SSS, and found seven combinations of allelic variants in *SCN10A, FNDC3B, MIR146A, SYT10*, and *KCNE1* genes affecting disease risk. *KCNE1* rs1805127 variant was the only SNP included in our analysis to show an association with SSS both individually and in combination with other genetic markers. This association was independent of age, sex, and the presence of atrial fibrillation and/or arterial

Table 2 The results of the analysis of association between the studied polymorphic loci and SSS

Locus	SNP	Chr:Position	Function	P_{HWE}	Genotype	Control		Patients		OR	CI_{OR}	P value	P_{FDR}
						n	p	n	p				
CLCNKA	rs10927887	1:16351275	Missense (p.Arg83Gly)	1.000	T/T	54	22.31	61	21.86	1.00	0.65–1.55	0.985	0.985
					T/C	120	49.59	123	44.09				
					C/C	68	28.1	95	34.05				
SCN10A	rs6795970	3:38766675	Missense (p.Val1072Ala)	0.493	T/T	37	15.29	45	16.13	1.07	0.65–1.75	0.789	0.985
					T/C	108	44.63	138	49.46				
					C/C	97	40.08	96	34.41				
FNDC3B	rs9647379	3:171785168	Intron	0.369	G/G	61	25.1	52	18.64	0.74	0.48–1.15	0.184	0.615
					G/C	114	46.91	133	47.67				
					C/C	68	27.98	94	33.69				
MIR146A	rs2910164	5:159912418	Non-coding transcript exon	0.232	C/C	13	5.37	18	6.45	1.16	0.54–2.50	0.703	0.985
					C/G	72	29.75	95	34.05				
					G/G	157	64.88	166	59.5				
SYT10	rs7980799	12:33576990	Intron	0.081	A/A	32	13.17	28	10.04	0.73	0.42–1.27	0.264	0.615
					A/C	95	39.09	118	42.29				
					C/C	116	47.74	133	47.67				
MYH6	rs365990	14:23861811	Missense (p.Val1101Ala)	0.184	C/C	20	8.26	25	8.96	1.05	0.55–1.98	0.890	0.985
					C/T	85	35.12	104	37.28				
					T/T	137	56.61	150	53.76				
KCNE1	rs1805127	21:35821821	Missense (p.Ser38Gly)	0.069	A/A	38	15.64	23	8.24	**0.42**	**0.23–0.76**	**0.004**	**0.028**
					A/G	98	40.33	139	49.82				
					G/G	107	44.03	117	41.94				

Statistically significant results are shown in bold

SNP single nucleotide polymorphism, *Chr:Position* according to the data of the Genome reference consortium human build 37 (GRCh37.p13), *n* number of genotype carriers, *p* percentage of genotype carriers, *OR* odds ratio, CI_{OR} 95% confidence interval, *P value* significance level, P_{HWE} significance level for the Hardy–Weinberg equilibrium, P_{FDR} significance level corrected for multiple testing using Benjamini–Hochberg procedure

Table 3 Allelic combinations associated with SSS

SCN10A rs6795970	*FNDC3B* rs9647379	*MIR146A* rs2910164	*SYT10* rs7980799	*KCNE1* rs1805127	Control (%)	Patients (%)	*P* value	P_{FDR}	Odds ratio	CI_{OR}
T	C	C	C	G	**9.09**	**22.94**	$\mathbf{1.27\times10^{-5}}$	**0.022**	**2.98**	**1.77–5.00**
T	C	C	C		**10.33**	**24.37**	$\mathbf{1.81\times10^{-5}}$	**0.016**	**2.80**	**1.70–4.59**
T	C	C		G	**11.16**	**24.73**	$\mathbf{4.21\times10^{-5}}$	**0.019**	**2.62**	**1.61–4.24**
T	C	C			**12.81**	**26.52**	$\mathbf{6.37\times10^{-5}}$	**0.019**	**2.46**	**1.55–3.90**
T		C	C	G	**12.40**	**24.73**	$\mathbf{2.25\times10^{-4}}$	**0.044**	**2.32**	**1.45–3.71**
T		C		G	**14.46**	**27.24**	$\mathbf{2.5\times10^{-4}}$	**0.044**	**2.21**	**1.42–3.45**
T		C	C		**14.46**	**26.88**	$\mathbf{3.5\times10^{-4}}$	**0.047**	**2.17**	**1.39–3.39**
T		C			17.36	29.75	6.29×10^{-4}	0.055	2.02	1.32–3.07

The statistically significant results are shown in bold

P_{FDR} significance level corrected for multiple testing using Benjamini–Hochberg procedure, CI_{OR} 95% confidence interval

hypertension. Notably, when the analysis was performed separately with different SSS types, *KCNE1* rs1805127 was associated with 2nd or 3rd degree sinoatrial block, but not with sinus bradycardia or sinoatrial arrest. Our findings may indicate that the association between rs1805127 and SSS observed in the total study group is driven by the association between rs1805127 and sinoatrial exit block.

KCNE1 gene is located on chromosome 21 (21q22.12) and encodes a 129 amino acid transmembrane protein KCNE1 (potassium voltage-gated channel subfamily E member 1) that coassembles with KCNQ1 (potassium voltage-gated channel, KQT-like subfamily member 1) forming the slowly activating delayed rectifier potassium (IKs) current in the heart that controls repolarization phase of cardiac action potential. The entire protein coding sequence of the *KCNE1* gene is restricted to the exon 3 which harbours the rs1805127 (c.112A > G) polymorphism that results in serine to glycine substitution at amino acid position 38 (p.Ser38Gly). Several authors have reported that rs1805127*G allele was associated with atrial fibrillation, but other studies failed to reproduce this association [15]. Family-based association study has demonstrated that *KCNE1* rs1805127 variant accounted for ~ 2.2% of the total QTc interval variance in healthy subjects from six kibbutz settlements in Northern Israel [16]. Men who carried rs1805127*A allele were found to have longer mean heart-rate-corrected QT (QTc), while no such effect was observed in women [16]. Haplotype containing rs2236609*G and rs1805127*A alleles of the *KCNE1* gene was associated with two-fold increase in risk of QTc interval prolongation in the French population [17]. *KCNE1* rs1805127 polymorphism was linked to congenital deafness and QTc prolongation [18]. Genome-wide association studies identified association signals for electrocardiographic traits, including QT interval, in the *KCNE1* gene region (rs727957, rs1805128, rs12626657), but neither of them showed any linkage disequilibrium (LD) with the rs1805127 variant. *KCNE1* rs1805127*A allele was shown to result in weaker augmentation of KCNH2 and KCNQ1 channel currents than C allele, which may contribute to impaired channel function in cardiomyocytes [19]. Consistently, *KCNE1* rs1805127*A carriers had prolonged QT intervals, particularly during bradycardia [19]. *KCNE1* missense mutations (S74L and D76N) have been previously shown to reduce slow delayed rectifier potassium current (IKs), and have been linked to delayed cardiac repolarization, prolonged QT syndrome and an increased risk of atrial fibrillation [20]. Other *KCNE1* mutations (G25V and G60D) are associated with early-onset familial atrial fibrillation due to increase in potassium current. Gain-of-function mutations of the IKs channel (that could also apply to rs1805127 polymorphism) are expected to increase the repolarising potassium currents which could abbreviate the cardiac action potential duration in sinoatrial node as well as the effective refractory period in cardiomyocytes.

SCN10A rs6795970 and *MIR146A* rs2910164 variants were core elements of the allelic combinations associated with SSS according to the results of the multilocus analysis (Table 3). SCN10A (sodium voltage-gated channel alpha subunit 10) is responsible for the initial depolarization phase of action potential. It exhibits more depolarized activation potential and slower inactivation kinetics than other sodium channels, and can therefore continue to operate when other Na^+ channels fail to respond to stimuli. *SCN10A* gene is located on chromosome 3 (3p22.2) and is mainly expressed in peripheral neurons, especially nociceptive neurons. *SCN10A* expression has been reported in intracardiac neurons, cardiomyocytes, and in the specialized conduction system; however, recent study demonstrated the lack of *SCN10A* expression in cardiac tissue [21]. The rs6795970 polymorphism (c.3218 T > C) is located in exon 17 of the *SCN10A* gene and causes substitution of valine to alanine in 1073 amino acid position. Genome-wide studies have implicated rs6795970 in various cardiovascular traits, including QRS duration, PR interval, heart rate response

to recovery post exercise. Notably, rs6795970 is located in a tightly linked cluster of variants (rs6801957, rs7433306, rs6790396, rs6800541, rs10428132, rs7428232, rs6599250, rs7433723, rs6599251, rs6599255, rs6798015) associated with a plethora of electrocardiographic traits according to GWAS. One of these SNPs, rs6801957, is located within an enhancer of *SCN5A* gene encoding sodium channel that is critical for cardiac conduction [22]. The rs6801957 variant is in strong LD with rs6795970 ($r^2 = 0.96$), which may explain the observed associations between rs6795970 and cardiac arrhythmias.

The rs2910164 polymorphism is a G to C substitution at position 60 in the passenger strand of the precursor of miR-146a that is expressed in cardiac cells and regulates immune response and inflammation by targeting multiple genes involved in inflammatory signalling pathways, including tumor necrosis factor receptor-associated factor 6 (*TRAF6)*, interleukin 1 receptor associated kinase 1 and 2 (*IRAK1*, *IRAK2)*, MYD88 innate immune signal transduction adaptor (*MYD88*), signal transducer and activator of transcription 1 (*STAT1*), caspase recruitment domain family member 10 (*CARD10*), and Toll-like receptor 4 (*TLR4*). The rare rs2910164*C allele causes mispairing within the pre-miR-146a hairpin and leads to the decrease of mature miR-146-a level via altering the efficiency of transcription factors binding. An association was detected between rs2910164*C/C genotype and lower heart rate variability in factory workers exposed to polycyclic aromatic hydrocarbons [23]. Our results show that rs2910164*C allele was present in all the combinations associated with SSS (Table 3).

The rs9647379, rs7980799, and rs365990 were among 21 loci associated with heart rate according to the GWAS performed in 41,625 individuals (903 SSS cases, 40,722 controls) [10]. The rs9647379 polymorphism is located in intron 1 of fibronectin type III domain 3B (*FNDC3B*) gene and was previously identified by GWAS as associated with heart rate [10]. Furthermore, rs9647379 was implicated by GWAS in anthropometric and metabolic traits, including waist-hip ratio and appendicular lean mass. *FNDC3B* is expressed in heart tissue, it activates TGFβ signaling that plays crucial role in fibroblast activation and fibrosis [24]. It may explain the association between *FNDC3B* and SSS, since degenerative fibrosis is one of the major pathophysiological mechanisms in sinoatrial node dysfunction.

The rs7980799 SNP is located in the intron of *SYT10* gene encoding synaptotagmin 10, membrane-trafficking protein involved in Ca2+-dependent release of neurotransmitters. It is structurally distinct from other members of synaptotagmin gene family and has been suggested to play a role in modulating neurotransmitter release in response to excitotoxic neuronal activation. *SYT10* rs7980799 has been associated with heart rate variability; it is also in LD with other variants extensively implicated by GWAS in heart rate (rs9888363, $r^2 = 0.924$); heart rate variability (rs1384598, $r^2 = 0.669$); heart rate response to recovery post exercise (rs1343676, $r^2 = 0.653$; rs6488162, $r^2 = 0.862$; rs1384590, $r^2 = 0.351$); heart rate variability and response to exercise (rs1351682, $r^2 = 0.669$). A recent functional study showed that mutations in *SYT10* may affect the odds of sinoatrial pauses [25].

An association of the rs365990 variant with heart rate was initially discovered in an Icelandic population [9]. This polymorphism is located in exon 25 of the alpha myosin heavy chain (*MYH6*) gene and results in valine to alanine substitution at position 1101 (p.Val101Ala). According to GWAS data, rs365990 was associated with resting heart rate and blood pressure traits. *MYH6* gene harbours other loci associated with electrocardiographic traits and in LD with rs365990: rs422068 (atrial fibrillation, resting heart rate, $r^2 = 0.944$), rs452036 (P-wave duration, resting heart rate, $r^2 = 0.927$), rs445754 (P-wave terminal force, $r^2 = 0.538$), rs432256 (heart rate, $r^2 = 0.363$). *MYH6* rs365990 did not show any association with SSS in our study, neither individually, nor as a part of allelic combinations with other SNPs. Previously, rs365990*C allele was associated with decreased risk of SSS together with 21 other loci according to the study performed for 903 cases and 40,722 controls [10]. Therefore, it is likely that detecting the effect of rs365990 on SSS requires larger sample size as well as including in the analysis other loci.

Rs10927887 is located in *CLCNKA* (chloride voltage-gated channel Ka) gene and leads to arginine to glycine substitution in 83 amino acid position (p.Arg83Gly). The allele 83Gly was associated with decreased functional expression of the renal chloride channel, increased risk of heart failure [26], and reduced glomerular filtration rate [27]. It is linked ($r^2 = 0.825$) to ECG-associated rs1763604. In our study, we did not detect an association between *CLCNKA* rs10927887 in either single-locus or multilocus analysis. The absense of association may be due to the limitations of the study design that include relatively small size of the study group, which may result in small genetic effects remaining undetected, and lack of validation of the obtained results in an independent sample.

Conclusion

Our results indicate that *KCNE1* rs1805127 may be independently associated with sick sinus syndrome, and that association may be driven by the association between rs1805127 and sinoatrial exit block. Multilocus approach has shown an advantage in detecting the combined effect of common genetic variants on disease risk.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11033-021-06517-4.

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Author contributions YT analysed the data and wrote the paper; MB, LA, TN, EB, AP, VP, IS collected data, performed the clinical assessments and genetic experiments; NZ conceived and designed the study.

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Data availability Data available on request due to privacy/ethical restrictions.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The study was approved by the ethics committee of the Institute of Biochemistry and Genetics of Ufa Federal Research Centre of Russian Academy of Sciences (IBG UFRC RAS).

Consent to participate Written informed consent to take part in the study was obtained from each participant in accordance with Helsinki declaration (2000) outlining the principles for medical research involving human subjects.

Consent for publication All authors read and approved the final manuscript.

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