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ORIGINAL INVESTIGATION

Genetic polymorphisms in the *SCN8A* gene are associated with suicidal behavior in psychiatric disorders in the Chinese population

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Abstract

Objectives. Suicidal behavior is a serious public health problem which is partly heritable. Identifying the genes and the neurobiologic pathways relevant to suicidal behavior is important for preventative strategies. One family-based study reported an association between sodium channel voltage gated type VIII alpha (*SCN8A*) and suicidal behavior. In the present study, we aimed to search for *SCN8A* polymorphisms conferring genetic susceptibility to suicide in the Chinese population. *Methods.* A total of 626 subjects was recruited for the study, including 297 suicide attempters and 329 non-attempters from Shanghai, China. We conducted a case-control association analysis of five SNPs (rs10506302, rs1601012, rs4762004, rs12581041, rs17126078) within the region of *SCN8A* gene. *Results.* we found that two genetic polymorphisms showed statistically significant differences between cases and controls (rs1601012, $P=0.004$; rs12581041, $P=0.01$). Moreover, no haplotypes were significantly associated with suicidal behavior in psychiatric disorders after the false discovery rate (FDR) correction. In the analysis of schizophrenia subgroup, three genetic polymorphisms showed statistically significant differences between cases and controls (rs10506302, $P=0.024$; rs1601012, $P=0.004$; rs12581041, $P=0.004$). *Conclusions.* Our findings suggest that the *SCN8A* gene may be involved in the susceptibility to suicidal behavior among psychiatric disorder patients in the Han Chinese population.

Key words: *Association, case–control analysis, Han Chinese, SCN8A, suicidal behavior*

Introduction

Suicidal behavior is a worldwide public health problem, and it is one of the most serious and challenging issues in China, where suicide is the fifth leading cause of death. According to data from the Chinese Ministry of Health, more than 287,000 Chinese were victims of suicide annually from 1995 to 1999 (Phillips et al. 2002; Yip et al. 2005). The basis of suicide is complex and multi-factorial. In the past decade, research has suggested that suicidal behavior is linked to genetic factors and to the interaction between genes and environment (Balazic and Marusic 2005; Marusic and Farmer 2001a,b). Evidence from family, twin, and adoption studies does suggest that genetic factors might be involved in the etiology of suicidal behavior (Roy et al. 1995; Brent et al. 2002; Souery et al. 2003). Recent studies imply that a central serotonergic system dysfunction is associated with suicide. The serotonin transporter gene (*5-HTT*) and the tryptophan hydroxylase 1 & 2 genes (*TPH1 & TPH2*), which code the rate-limiting enzyme in the biosynthesis of serotonin, have been shown to be involved in the predisposition to suicidal behavior (Tsai et al. 1999; Bondy et al. 2000; Souery et al. 2001).

The sodium channel voltage gated type VIII alpha subunit (*SCN8A*) gene located on chromosome 12q13 is abundantly expressed in the central nervous

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system (CNS) in both mice (Burgess et al. 1995) and rats (Dietrich et al. 1998). The protein encoded by *SCN8A* ($Na_v1.6$) is one of the major voltage gated sodium channels carrying sodium currents underlying action potential in mature mammalian central neurons, and consists of 1980 amino acid residues distributed among 28 exons (Trudeau et al. 2006).

Mice with mutant alleles of the *SCN8A* gene exhibit slowed nerve conduction velocity and reduced brain metabolic activity (Kearney et al. 2002). In murine Purkinje neurons lacking *SCN8A* expression, sodium currents and action potential are severely disturbed (Garcia et al. 1998; Pan and Beam 1999). Heterozyotes carrying a mutation of human *SCN8A* may exhibit impaired cognition (Trudeau et al. 2006), which could result in altered predisposition to suicidal behavior. In a recent family-based study of 77 trios of suicide attempters, Wasserman et al. (2005) reported that an intronic polymorphism, rs303802 of the *SCN8A* gene, was overtransmitted ($P=0.008$). Given the nature of the *SCN8A* gene, the simplest interpretation of the Wasserman's data is that the implicated allelic difference leads to variability in neuronal sodium currents and may affect the action potential, thereby altering the conditions for neural conduction. Ultimately, this could have cognitive/affective consequences leading to altered predisposition for suicidal behavior. As all the markers we selected to analyze were also intronic polymorphisms, a potential mechanism of the included SNPs which is similar with Wasserman's might be involved in the association of *SCN8A* gene with suicidal behavior in the Chinese population.

Aiming to investigate the genetic contribution of *SCN8A* gene to suicidal behavior in psychiatric disorders, we examined five SNPs (rs10506302, rs1601012, rs4762004, rs12581041, rs17126078) in 297 psychiatric patients who had attempted suicide and 329 psychiatric patients who had not, a case-control association strategy similar to that used by Ke and Liu (Ke et al. 2006; Liu et al. 2006).

Methods

Participants

A total of 297 psychiatric patients who had attempted suicide (SAs) (171 male and 126 female, age 46.10 ± 13.14 years) and 329 psychiatric patients who had not attempted suicide (NSAs) (217 male and 112 female, age 43.22 ± 12.27 years) were recruited for this study. The demographic and clinical characteristics of the suicide attempters and non-attempters are given in a previous study carried out by our lab (Liu et al. 2006). A total of 196 of the 297 SAs and 303 of the 329 NSAs were diagnosed as schizophrenic, accounting for 66 and 92.1% of the respective totals. The rest of the patients were suffering from anxiety disorders, organic mental disorders, personality disorders, and alcohol and drug use disorders. Sixty-seven percent of the SAs had made at least one violent attempt (Table VI). All the subjects were from Shanghai and were Han Chinese in origin. The Diagnostic and Statistical Manual of Mental Disorder, Third Revised Edition (DSM-III-R), was used as the diagnostic criterion. The clinical interviews that we used are PANSS, WMS (Wechsler Memory Scale) and WAIS-RC (Wechsler Adult Intelligence Scale-Revised in China). Two independent psychiatrists made a final diagnosis on the basis of interview data and hospital case notes. All participating subjects signed an informed consent that had been reviewed and approved by the Shanghai Ethics Committee of Human Genetic Resources. Peripheral blood samples for DNA extraction were obtained from the subjects using the phenol-chloroform method.

Genotyping

We selected the positive SNP rs303802 reported by Wasserman et al. (2005), and five other SNPs (including rs10506302, rs1601012, rs4762004, rs12581041, and rs17126078) from dbSNP (http://www.ncbi.nlm.nih.gov/SNP/) and the HapMap project database (http://www.hapmap.org) to cover the region of *SCN8A*. These six genetic polymorphisms (minor allele frequency, MAF > 0.2), all of which are intronic SNPs, spanned ~103.9 kb, with an average interval of ~17.3 kb.

The genotypes of all the SNPs were determined by the TaqMan® assay method using the ABI 7900 DNA detection system (Applied Biosystems, Foster City, California). All probes and primers were predesigned by the Assay-on-Design service of Applied Biosystems in 5-μl reactions containing 10 ng genomic DNA as well as Taqman® Universal PCR Master Mix (Applied Biosystems) reagent. Cycling conditions were 10 min at 95°C and 45 cycles of 92°C for 15 s and 60°C for 1 min.

Statistical analysis

Hardy–Weinberg equilibrium tests, allelic and genotypic distributions were analyzed/estimated on http://202.120.31.137/myanalysis.php (Shi and He 2005), a friendly platform which integrates efficient analysis tools particularly suited to association studies. The standardized measure of linkage disequilibrium (LD), denoted as "D'" was estimated at all possible pairs of SNP loci. We corrected the P values of association analysis for multiplicity using a false

discovery rate (FDR) controlling procedure (Benjamini et al. 2001). Plink was employed to execute the adjustment for age and gender factors in the genetic analysis (Purcel et al. 2007). All the *P* values in this study were two-tailed and the significance level was set at $P=0.05$. The program UNPHASED was used to estimate haplotype frequencies (Dudbridge 2003). The odds ratio (OR) and 95% confidence interval (CI) were calculated on the website http://www.hutchon.net/ConfidOR.htm. Power calculations for our sample size were calculated using the G*Power program (Faul et al. 2007).

Results

Genotype distributions of all the SNPs showed no significant deviations from Hardy–Weinberg equilibrium in either SAs or NSAs (Pℏ0.05). Due to assay failure, rs303802 was removed from further analysis. Between 297 SAs and 329 NSAs, two genetic polymorphisms (rs1601012 and rs12581041) showed statistically significant differences in both allele and genotype frequencies. The C allele frequency of rs1601012 was higher in SAs (89.2%) than in NSAs (83.0%; $P=0.004$, OR 1.68, 95% CI 1.18–2.40, $P=0.019$, after the FDR correction). The G allele frequency of rs12581041 was higher in SAs (64.3%) than in NSAs (56.7%; $P=0.01$, OR 1.38, 95% CI 1.08–1.76, $P=0.026$, after the FDR correction) (Table I). In addition, the significance of the two markers remained ($P < 0.05$) with adjustment for age and gender factors using the PLINK software.

LD for each pair of SNPs in SAs and NSAs is presented in Table II. The *D*'-value or r^2-value showed three markers (rs10506302, rs1601012 and rs4762004) and two markers (rs12581041 and rs17126078) to be in strong LD (Ardlie et al. 2002) respectively. We therefore assumed/estimated the haplotype distributions with these SNPs in the later analysis. Haplotypes were omitted from analysis if the estimated haplotype probabilities were less than 3% in either SA or NSA groups.

Only haplotypes with significant frequency discrepancies between suicide attempters and non-attempters (Table III) were selected for presentation. Haplotype analysis of these polymorphisms reported some significant global *p* values. Three two-SNP-based haplotypes and one three-SNP-based haplotype showed significant association with suicidal behavior in psychiatric disorders. The polymorphism which combined rs10506302 and rs1601012 was most significant giving a global $P=0.024$. As its frequency was greater in SAs than in NSAs, the haplotype C–C (rs10506302–rs1601012) was found to be strongly associated with suicide attempters ($P=0.007$, OR 1.68, 95% CI 0.65–4.35). However, none of the

Table I. Statistical analysis for SNPs.

SNP ID	Genotype frequency (%)			H-W check *P* value	*P* value	*P* value*	FDR adjusted	Allele frequency (%)		X^2	*P* value	*P* value*	FDR adjusted	Odds ratio (95% CI)
rs10506302	CC	CT	TT					C	T					
SA	210 (79.8)	48 (18.3)	5 (1.9)	0.257	0.396	0.391	0.396	468 (89.0)	58 (11.0)	1.994	0.158	0.178	0.263	0.77 (0.54–1.11)
NSA	218 (75.4)	62 (21.5)	9 (3.1)	0.088				498 (86.2)	80 (13.8)					
rs1601012	AA	AC	CC					A	C					
SA	4 (1.6)	47 (18.5)	203 (79.9)	0.506	**0.021**	**0.022**	0.051	55 (10.8)	453 (89.2)	8.364	**0.004**	**0.006**	**0.019**	1.68 (1.18–2.40)
NSA	12 (4.2)	73 (25.5)	201 (70.3)	0.113				97 (17.0)	475 (83.0)					
rs4762004	AA	AG	GG					A	G					
SA	5 (1.8)	44 (16.2)	222 (81.9)	0.118	0.203	0.236	0.254	54 (10.0)	488 (90.0)	0.111	0.739	0.721	0.739	0.93 (0.63–1.39)
NSA	1 (0.3)	52 (18.1)	235 (81.6)	0.288				54 (9.4)	522 (90.6)					
rs12581041	AA	AG	GG					A	G					
SA	29 (10.9)	131 (49.4)	105 (39.6)	0.208	**0.013**	**0.012**	0.066	189 (35.7)	341 (64.3)	6.603	**0.010**	**0.010**	**0.026**	1.38 (1.08–1.76)
NSA	56 (19.9)	132 (46.8)	94 (33.3)	0.435				244 (43.3)	320 (56.7)					
rs17126078	CC	CT	TT					C	T					
SA	37 (13.7)	134 (49.4)	100 (36.9)	0.455	0.139	0.119	0.232	208 (38.4)	334 (61.6)	1.792	0.181	0.178	0.226	1.18 (0.93–1.49)
NSA	58 (19.9)	131 (44.9)	103 (35.3)	0.167				247 (42.3)	337 (57.7)					

*P value was adjusted for age and sex using Plink. FDR, false discovery rate; CI, confidence interval; SNP, single nucleotide polymorphism.

Table II. Estimation of linkage disequilibrium between the five SNPs.

	rs10506302	rs1601012	rs4762004	rs12581041	rs17126078
rs10506302		**0.97**	**0.77**	0.49	0.47
rs1601012	0.81		**0.86**	0.42	0.36
rs4762004	0.42	0.42		0.12	0.13
rs12581041	0.05	0.05	0.00		**0.96**
rs17126078	0.05	0.03	0.00	0.92	

SNP, single nucleotide polymorphism.
For each pair of SNPs, *D*' values are shown above and r^2 values below the diagonal, D' > 0.7 are shown in boldface.

significant associations reported above survived the FDR correction.

According to recent studies, nearly 5% of schizophrenia patients commit suicide during their lifetime (Palmer et al. 2005), and 20–40% of patients attempt suicide during the course of schizophrenia spectrum illnesses (Radomsky et al. 1999). We therefore conducted an analysis in the schizophrenia subgroup. Three polymorphisms showed statistically significant differences in allele frequency (Table IV) between 196 SAs and 303 NSAs surviving the FDR correction (rs10506302, $P=0.024$; rs1601012, $P=0.004$; rs12581041, $P=0.004$; all $P < 0.05$ after the FDR correction). Significant difference in the global haplotype frequency (Table V) was observed at rs10506302 and rs1601012 between cases and controls ($P=0.005$). The haplotype (rs10506302–rs1601012, C–C) was found to be strongly associated with SAs because of its significantly increased frequency in SAs rather than NSAs ($P=0.003$, OR 1.05, 95% CI 0.39–2.83). Moreover, the haplotype (rs10506302–rs1601012, T–A) was found to be strongly associated with NSAs because of its significantly increased frequency in NSAs rather than SAs ($P=0.003$, OR 0.54, 95% CI 0.18–1.59). None of the haplotype significance, however, remained after controlling the FDR at level 0.05. With the adjustment for age and gender factors, no significant effects were observed on the findings in the schizophrenia subgroup.

In the power calculations using the G*Power program based on Cohen's method (Faul et al. 2007), our sample size had >90% power to detect a significant ($\alpha<0.05$) association for genotypes, alleles and haplotypes when an effect size index of 0.1 (corresponding to a "weak" gene effect) was used.

Discussion

Suicidal behavior is one of the most serious public health problems in China. It is the leading cause of death in the 15–34 age group and ranks fifth in the overall population. The mean annual suicide rate is 23 per 100 000 and a total of 287,000 suicide deaths occur every year in China. According to the World Health Organization's estimate, the annual number of suicides worldwide will be about 1.53 million by 2020, of which China will account for more than 30% (Phillips et al. 2002; Yip et al. 2005).

SCN8A encodes the α-subunit of $Na_v1.6$, which is one of the major voltage gated sodium channels in mature mammalian central neurons. In the central nervous system, $Na_v1.6$ is highly concentrated at nodes of Ranvier and is strongly expressed in the dendrites of cortical pyramidal cells and Purkinje cells. Moreover, it is the predominant sodium channel at nodes of Ranvier in both sensory and motor axons of the peripheral nervous system (Caldwell et al. 2000).

Recent research has found that mild cognitive deficits and behavioral abnormalities existed in family members who were heterozygous for the *SCN8A* mutation (Trudeau et al. 2006). Additionally, mice heterozygous for a null mutation of the *SCN8A* gene displayed increased anxiety, suggesting a critical role for *SCN8A* in emotional behavior (McKinney et al. 2008). In a recent study, Woodruff-Pak et al. deleted exon 1 of *SCN8A* in Purkinje neurons in mice and observed that they exhibited impaired learning when tested on the Morris water maze (Woodruff-Pak et al. 2006). Wasserman et al. (2005) reported that allelic differences in the *SCN8A* gene may have cognitive or affective consequences, and that this could ultimately result in altered predisposition to suicide. One of our own studies recently found an association of the *SCN8A* gene with bipolar disorder (Wang et al. 2008), but due to a lack of suicide-related information about the subjects, we were unable to pursue the analysis.

In this association study, five SNPs within the *SCN8A* locus, all of which were selected from dbSNP database (http://www.ncbi.nlm.nih.gov/SNP/) and the HapMap project database (http://www.hapmap.org), were analyzed to investigate suicide behavior in psychiatric patients. The data based on 626 Han Chinese samples provides further support for the association of *SCN8A* with suicidal behavior. There were statistically significant differences of allele and genotype frequencies between

Table III. Estimated haplotype frequencies and association significance.

Haplotype*					Haplotype frequency (%)					
rs10506302	rs1601012	rs4762004	rs12581041	rs17126078	SA	NSA	X^2	*P* value	Odds ratio (95% CI)	Global *P* value
C	C				439 (89.6)	449.9 (83.9)	7.292	0.007	1.68 (0.65–4.35)	0.0243
T	A				44 (9.0)	70.9 (13.2)	4.791	0.029	1.07 (0.39–2.95)	
	A	G			23.3 (4.7)	43.3 (8.1)	4.735	0.030	0.82 (0.42–1.62)	0.0260
	C	G			430.7 (87.9)	444.6 (82.6)	5.72	0.017	1.49 (0.92–2.41)	
C	C	G			421.8 (88.6)	431.7 (83.7)	5.356	0.021	0.97 (0.23–4.04)	0.0850
			G	T	324 (63.0)	301.9 (55.9)	5.72	0.017	1.29 (1.00–1.67)	0.0438

*Haplotypes were omitted from analysis if the estimated haplotype probabilities were less than 3%.
CI, confidence interval.

Table IV. Statistical analysis for SNPs in schizophrenia.

SNP ID	Genotype frequency (%)			H-W check *P* value	p value	FDR adjusted	Allele frequency (%)		X^2	*P* value	FDR adjusted	Odds ratio (95% CI)
rs10506302	CC	CT	TT				C	T				
SA	143 (82.7)	27 (15.6)	3 (1.7)	0.209	0.096	0.120	313 (90.5)	33 (9.5)	5.075	**0.024**	**0.040**	0.61 (0.40–0.94)
NSA	196 (74.0)	60 (22.6)	9 (3.4)	0.111			452 (85.3)	78 (14.7)				
rs1601012	AA	AC	CC				A	C				
SA	3 (1.7)	31 (17.9)	139 (80.3)	0.416	**0.022**	0.055	37 (10.7)	309 (89.3)	8.160	**0.004**	**0.011**	1.80 (1.20–2.71)
NSA	11 (4.2)	71 (27.1)	180 (68.7)	0.245			93 (17.7)	431 (82.3)				
rs4762004	AA	AG	GG				A	G				
SA	3 (1.7)	26 (14.7)	148 (83.6)	0.156	0.216	0.216	32 (9.0)	322 (91.0)	0.107	0.744	0.744	1.08 (0.68–1.72)
NSA	1 (0.4)	49 (18.6)	213 (81.0)	0.300			51 (9.7)	475 (90.3)				
rs12581041	AA	AG	GG				A	G				
SA	18 (10.5)	81 (47.4)	72 (42.1)	0.494	**0.012**	0.061	117 (34.2)	225 (65.8)	8.194	**0.004**	**0.021**	1.51 (1.14–2.00)
NSA	53 (20.5)	121 (46.9)	84 (32.6)	0.438			227 (44.0)	289 (56.0)				
rs17126078	CC	CT	TT				C	T				
SA	22 (12.5)	85 (48.3)	69 (39.2)	0.595	0.090	0.150	129 (36.6)	223 (63.4)	3.460	0.063	0.079	1.30 (0.99–1.71)
NSA	55 (20.5)	120 (44.8)	93 (34.7)	0.159			230 (42.9)	306 (57.1)				

FDR, false discovery rate; CI, confidence interval; SNP, single nucleotide polymorphism.

Table V. Estimated haplotype frequencies and association significance in schizophrenia.

Haplotype*					Haplotype frequency (%)					
rs10506302	rs1601012	rs4762004	rs12581041	rs17126078	SA	NSA	X^2	*P* value	Odds ratio (95% CI)	Global *P* value
C	C				299 (90.1)	407.9 (83.3)	8.599	0.003	1.05 (0.39–2.83)	0.005
T	A				26 (7.8)	68.9 (14.1)	8.635	0.003	0.54 (0.18–1.59)	
	A	G			16.2 (4.9)	41.3 (8.4)	4.207	0.040	0.91 (0.43–1.94)	0.024
	C	G			292.8 (88.2)	401.7 (82.0)	6.2	0.013	1.69 (0.98–2.92)	
C	C	G			286.9 (89.1)	390.7 (83.1)	6.33	0.012	0.55 (0.12–2.57)	0.018
T	A	A			14.9 (4.6)	38.8 (8.3)	4.556	0.032	0.29 (0.05–1.53)	
T	A	G			10.1 (3.1)	28.2 (6.0)	4.231	0.040	0.27 (0.05–1.46)	
			G	T	214 (64.9)	270.9 (55.1)	8.109	0.004	1.41 (1.05–1.90)	0.019

*Haplotypes were omitted from analysis if the estimated haplotype probabilities were less than 3%.
CI, confidence interval.

Table VI. Demographic and clinical characteristics of the subjects.

	SA (*n*=297)	NSA (*n*=329)
Male	171	217
Female	126	112
Age±SD	46.10±13.14	43.22±12.27
Family history, No. (%)	77 (25.9)	98 (29.8)
Schizophrenia, No. (%)	196 (66)	303 (92.1)
At least once violent SA, No. (%)	199 (67)	
SA once, No. (%)	172 (57.9)	
SA twice, No. (%)	62 (20.9)	
SA thrice and more, No. (%)	63 (21.2)	

SA, suicide attempts; NSA, nonsuicide attempts.

SAs and NSAs at rs1601012 and rs12581041 surviving the FDR correction. We found that the C allele of rs1601012 and the G allele of rs12581041 showed higher frequencies in cases than in controls indicating that both might be risk alleles for suicidal behavior in psychiatric disorders. In the further analysis of schizophrenia subgroup, significant difference in allele frequency was observed between cases and controls at rs10506302, rs1601012 and rs12581041, supporting the recent reports about high risk for suicidal behavior in patients with schizophrenia.

Haplotypes constructed from closely located markers will typically increase the statistical power for association with the disease. Thus, a haplotype analysis was performed in genetic polymorphisms which showed strong LD (D'>0.7), involving three markers (rs10506302, rs1601012 and rs4762004) and two markers (rs12581041 and rs17126078) respectively. Three two-SNP-based haplotypes showed significant global association with suicidal behavior (Table III). In the association study of schizophrenia subgroup, the most significant window spanned rs10506302 and rs1601012 giving a global p=0.005. And the most significant haplotype was C–C (rs10506302–rs1601012, P=0.007) with a higher frequency in SAs (89.6%) than in NSAs (83.9%), which is consistent with the finding in the schizophrenia subgroup (C–C, rs10506302–rs1601012, P=0.003). However, all of the haplotype significance vanished when we applied the FDR corrections, indicating that no haplotypes within the *SCN8A* gene showed significant association with suicidal behavior.

Wasserman et al. (2005), using transmission disequilibrium (TDT) analysis, found that rs303802, situated in the *SCN8A* gene, was overtransmitted (P=0.008) in 77 trios (suicide attempters and both their parents), indicating that *SCN8A* may be a potential susceptibility gene in suicide attempters of Caucasian origin. Due to the assay failure of

polymorphism rs303802, we were unable to perform a direct replication of Wasserman et al.'s work. Nevertheless, since rs12581041 is in strong LD with rs303802 being separated by only 0.7 kb, based on HapMap data, and as the correlated major alleles of both polymorphisms were implicated with a similar phenotype, we concluded that our results were sufficiently consistent with the Wasserman findings. A possible interpretation of our results is that the implicated difference of genetic polymorphisms within the *SCN8A* gene induces variability in neuronal sodium currents, and may alter the conditions for neural conduction through affecting the action potential. Thus, this could finally have cognitive/affective consequences resulting in altered predisposition for suicidal behavior. In addition, genetic variation in the *SCN8A* gene might contribute to unbalanced analysis of incoming information in periods of physical and emotional stress, which in turn could increase the risk of suicidal behavior (Wasserman et al. 2005). However, the genetic contributions to suicidal behavior unlike single gene disorders are generally considered to be associated with a series of susceptibility loci, influencing but not determining overall suicide risk. Genetic, environmental and biochemical influences are all thought to be contributing factors for suicide. Both biological and social etiologic factors may contribute to the complexity of the suicidal behavior phenotype, which poses a major challenge for association studies (Balazic and Marusic 2005; Marusic and Farmer 2001a,b).

Limitations

There were some limitations in our research. First, the two positive polymorphisms (rs1601012 and rs12581041) may not be involved in a direct effect on suicidal behavior. Second, the five SNPs we selected could not cover the whole region of *SCN8A*, thus more markers in ethnic groups other than Asian or Caucasian ethnicity needs to be investigated. Moreover, we focused mainly on the suicidal behavior among schizophrenia patients in the study. Particular attention has been paid to the question whether the same genetic basis for suicidal behavior exists between schizophrenia patients and other psychiatry disorder patients, and further research needs to be undertaken for this deduction.

Conclusions

In summary, we firstly investigate the relevance of *SCN8A* to suicidal behavior in the Han Chinese population, and our study provides consistent evidence that *SCN8A* might play a potential role in the susceptibility to suicide among psychiatric disorders. Studies to date have been based on subjects of Asian or Caucasian ethnicity, hence further research in other ethnic groups needs to be undertaken. Replicating studies with larger samples and with more markers will be necessary to clarify the apparent relationship of *SCN8A* to suicidal behavior.

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Statement of interest

None to declare.

References

Ardlie KG, Kruglyak L, Seielstad M. 2002. Patterns of linkage disequilibrium in the human genome. Nat Rev Genet 3:299–309.

Balazic J, Marusic A. 2005. The completed suicide as interplay of genes and environment. Forensic Sci Int 147(Suppl):S1–3.

Benjamini Y, Drai D, Elmei G, Kafkafi N, Golani I. 2001. Controlling the false discovery rate in behavior genetics research. Behav Brain Res 125:279–284.

Bondy B, Erfurth A, de Jonge S, Kruger M, Meyer H. 2000. Possible association of the short allele of the serotonin transporter promoter gene polymorphism (5-HTTLPR) with violent suicide. Mol Psychiatry 5:193–195.

Brent DA, Oquendo M, Birmaher B, Greenhill L, Kolko D, Stanley B, et al. 2002. Familial pathways to early-onset suicide attempt: risk for suicidal behavior in offspring of mood-disordered suicide attempters. Arch Gen Psychiatry 59:801–807.

Burgess DL, Kohrman DC, Galt J, Plummer NW, Jones JM, Spear B, et al. 1995. Mutation of a new sodium channel gene, *SCN8A*, in the mouse mutant 'motor endplate disease'. Nat Genet 10:461–465.

Caldwell JH, Schaller KL, Lasher RS, Peles E, Levinson SR. 2000. Sodium channel Na(v)1.6 is localized at nodes of ranvier, dendrites, and synapses. Proc Natl Acad Sci USA 97:5616–5620.

Dietrich PS, McGivern JG, Delgado SG, Koch BD, Eglen RM, Hunter JC, et al. 1998. Functional analysis of a voltage-gated sodium channel and its splice variant from rat dorsal root ganglia. J Neurochem 70:2262–2272.

Dudbridge F. 2003. Pedigree disequilibrium tests for multilocus haplotypes. Genet Epidemiol 25:115–121.

Faul F, Erdfelder E, Lang AG, Buchner A. 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39: 175–191.

Garcia KD, Sprunger LK, Meisler MH, Beam KG. 1998. The sodium channel *SCN8A* is the major contributor to the postnatal developmental increase of sodium current density in spinal motoneurons. J Neurosci 18:5234–5239.

Kearney JA, Buchner DA, De Haan G, Adamska M, Levin SI, Furay AR, et al. 2002. Molecular and pathological effects of a modifier gene on deficiency of the sodium channel *SCN8A* (Na(v)1.6). Hum Mol Genet 11:2765–2775.

Ke L, Qi ZY, Ping Y, Ren CY. 2006. Effect of SNP at position 40237 in exon 7 of the TPH2 gene on susceptibility to suicide. Brain Res 1122:24–26.

Liu X, Li H, Qin W, He G, Li D, Shen Y, et al. 2006. Association of TPH1 with suicidal behaviour and psychiatric disorders in the Chinese population. J Med Genet 43:e4.

Marusic A, Farmer A. 2001a. Genetic risk factors as possible causes of the variation in European suicide rates. Br J Psychiatry 179:194–196.

Marusic A, Farmer A. 2001b. Toward a new classification of risk factors for suicide behavior. Crisis 22:43–46.

McKinney BC, Chow CY, Meisler MH, Murphy GG. 2008. Exaggerated emotional behavior in mice heterozygous null for the sodium channel *SCN8A* (Nav1.6). Genes Brain Behav 7:629–638.

Palmer BA, Pankratz VS, Bostwick JM. 2005. The lifetime risk of suicide in schizophrenia: a reexamination. Arch Gen Psychiatry 62:247–253.

Pan F, Beam KG. 1999. The absence of resurgent sodium current in mouse spinal neurons. Brain Res 849:162–168.

Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. 2007. PLINK: a tool set for whole-genome association and population-based linkage analysis. Am J Hum Genet 81:559–575.

Phillips MR, Li X, Zhang Y. 2002. Suicide rates in China, 1995–99. Lancet 359:835–840.

Radomsky ED, Haas GL, Mann JJ, Sweeney JA. 1999. Suicidal behavior in patients with schizophrenia and other psychotic disorders. Am J Psychiatry 156:1590–1595.

Roy A, Segal NL, Sarchiapone M. 1995. Attempted suicide among living co-twins of twin suicide victims. Am J Psychiatry 152:1075–1076.

Shi YY, He L. 2005. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 73: 49–62.

Souery D, Van Gestel S, Massat I, Blairy S, Adolfsson R, Blackwood D, et al. 2001. Tryptophan hydroxylase polymorphism and suicidality in unipolar and bipolar affective disorders: a multicenter association study. Biol Psychiatry 49:405–409.

Souery D, Oswald P, Linkowski P, Mendlewicz J. 2003. Molecular genetics in the analysis of suicide. Ann Med 35:191–196.

Trudeau MM, Dalton JC, Day JW, Ranum LP, Meisler MH. 2006. Heterozygosity for a protein truncation mutation of sodium channel *SCN8A* in a patient with cerebellar atrophy, ataxia, and mental retardation. J Med Genet 43:527–530.

Tsai SJ, Hong CJ, Wang YC. 1999. Tryptophan hydroxylase gene polymorphism (A218C) and suicidal behaviors. Neuroreport 10:3773–3775.

Wang Y, Zhang J, Li X, Ji J, Yang F, Wan C, et al. 2008. *SCN8A* as a novel candidate gene associated with bipolar disorder in the Han Chinese population. Prog Neuropsychopharmacol Biol Psychiatry 32:1902–1904.

Wasserman D, Geijer T, Rozanov V, Wasserman J. 2005. Suicide attempt and basic mechanisms in neural conduction: relationships to the *SCN8A* and VAMP4 genes. Am J Med Genet B Neuropsychiatr Genet 133B:116–119.

Woodruff-Pak DS, Green JT, Levin SI, Meisler MH. 2006. Inactivation of sodium channel *SCN8A* (Na-sub(v)1.6) in Purkinje neurons impairs learning in Morris water maze and delay but not trace eyeblink classical conditioning. Behav Neurosci 120:229–240.

Yip PS, Liu KY, Hu J, Song XM. 2005. Suicide rates in China during a decade of rapid social changes. Soc Psychiatry Psychiatr Epidemiol 40:792–798.