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Failure to confirm an association between the *PLXNA2* gene and schizophrenia in a Japanese population

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Abstract

Plexins are receptors for multiple classes of semaphorins, either alone or in combination with neuropilins. Plexins participate in many cellular events that include axonal repulsion, axonal attraction, cell migration, axon pruning, and synaptic plasticity. *PLXNA2* maps to chromosome 1q32. Several linkage studies reported schizophrenia susceptibility loci in the 1q22–42 region. A recent study reported that intronic single nucleotide polymorphisms (SNPs) of *PLXNA2* were associated with schizophrenia in a European American population. We attempted to replicate this finding in a Japanese sample of 336 patients with schizophrenia and 304 controls. In addition, we examined 3 non-synonymous SNPs (Arg5Gln, GLn57Arg, and Ala267Thr) in *PLXNA2*. Genotyping was performed by the TaqMan allelic discrimination assay. There was no significant difference in genotype or allele distribution of either the 4 intronic SNPs or the 3 non-synonymous SNPs between patients and controls. Furthermore, haplotype-based analyses did not provide evidence for an association. These results suggest that *PLXNA2* may not play a major role in the development of schizophrenia in our Japanese sample.

Keywords: Association; Haplotype; Plexin A2; Schizophrenia; Single nucleotide polymorphism (SNP)

1. Introduction

Plexin was originally identified as a neuronal cell surface molecule that has been identified in *Xenopus* (Ohta et al., 1995; Takagi et al., 1987). To date, plexins have been identified in both invertebrate and vertebrate (Fujii et al., 2002; Kameyama et al., 1996a,b; Maestrini et al., 1996; Suto et al., 2003; Tamagnone et al., 1999; Winberg et al., 1998). Plexins were shown to act as receptors for multiple classes of semaphorins either alone or in a complex together with neuropilins (reviewed in Yazdani and Terman, 2006). Plexin A families and neuropilins form a stable complex as functional receptors for class 3 semaphorins (Takahashi et al., 1999). For example, semaphorin 3A (Sema3A) binds to neuropilin-1 (Nrp1) and activates plexin A1 (Plxna1) or plexin A2 (Plxna2) to transduce a repulsive axon guidance signal (Takahashi and Strittmatter, 2001). Many studies of plexins have concentrated on its roles in nervous development (reviewed in Kruger et al., 2005; Waimey and Cheng, 2006; Halloran and Wolman, 2006). In addition to their roles in axon guidance, semaphorin–plexin signaling has been known to play important roles in axon pruning (Liu et al., 2005; Bagri et al., 2003). Moreover, recent studies suggest that some semaphorins and their receptors might be involved in modulation of synaptic structure (Godenschwege et al., 2002; Morita et al., 2006; Bouzioukh et al., 2006; Waimey and Cheng, 2006).

Growing evidence has suggested that schizophrenia has neurodevelopmental abnormalities that might occur early in life

Abbreviations: SNP; single nucleotide polymorphism; DSM-IV; 4th edition of the Diagnostic and Statistical Manual of Mental Disorders.

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(Conrad and Scheibel, 1987; Weinberger, 1987; Murray, 1994; Waddington et al., 1998). A recent study reported that SEMA3A was increased in the cerebellum in the postmortem brains of schizophrenia patients (Eastwood et al., 2003). More recently, a genome-wide association study using 25494 single nucleotide polymorphisms (SNPs) pointed out that an intronic SNP of the *PLXNA2* gene were most consistently associated with schizophrenia in a European American population (Mah et al., 2006). These findings suggested the possibility that genetic variations of the *PLXNA2* gene confer susceptibility to schizophrenia through its effects on neurodevelopment and synaptic plasticity. To our knowledge, however, the association between the *PLXNA2* gene and schizophrenia has not yet been supported or refuted by any other study. The present study was thus aimed to examine whether there is such an association in a Japanese sample. In addition, we examined 3 additional non-synonymous polymorphisms of the *PLXNA2* gene (Arg5Gln, GLn57Arg, and Ala267Thr) for association with schizophrenia.

2. Materials and methods

2.1. Subjects

Subjects were 336 patients with schizophrenia (204 males, mean age of 44.2 years [SD 13.7]) and 304 healthy controls (99 males, mean age of 38.8 years [SD 13.4]). All subjects were biologically unrelated Japanese and recruited from the same geographical area (Western part of Tokyo Metropolitan). Consensus diagnosis by at least two psychiatrists was made for each patient according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria (American Psychiatric Association, 1994) on the basis of unstructured interviews and information from medical records. The controls were healthy volunteers recruited from hospital staffs and their associates. Control individuals were interviewed and those who had a current or past history of psychiatric treatment were not enrolled in the study. The study protocol was

Table 1
Genotype and allelic distribution of the *PLXNA2* SNPs in Japanese patients with schizophrenia and controls

dbSNP ID	Position[a]	Inter-SNP distance (bp)	Group	*N*	Genotype distribution (frequency)			Allele distribution (frequency)		Odds ratio (95% CI)	Chi-square test[b]		
											HWE (*df*=1)	GF (*df*=2)	AF (*df*=1)
rs2782948	206457877				CC	CT	TT	C	T				
	Exon 2	_	Schizophrenia	334	89 (0.27)	160 (0.48)	85 (0.25)	338 (0.51)	330 (0.49)	1.15	χ^2=0.58, *P*=0.45	*P*=0.31	*P*=0.23
	Arg5Gln		Control	303	65 (0.21)	156 (0.51)	82 (0.27)	286 (0.47)	320 (0.53)	(0.92–1.43)	χ^2=0.33 , *P*=0.57	χ^2=2.34	χ^2=1.47
rs11119014	206457721				AA	AG	GG	A	G				
	Exon 2	156	Schizophrenia	334	265 (0.79)	61 (0.18)	8 (0.02)	591 (0.88)	77 (0.12)	0.82	χ^2=3.65, *P*=0.056	*P*=0.37	*P*=0.28
	Gln57Arg		Control	301	246 (0.82)	52 (0.17)	3 (0.01)	544 (0.90)	58 (0.10)	(0.57–1.17)	χ^2=0.02, *P*=0.90	χ^2=1.99	χ^2=1.19
rs3748735	206457092				CC	CT	TT	C	T				
	Exon 2	629	Schizophrenia	334	249 (0.75)	78 (0.23)	7 (0.02)	579 (0.86)	92 (0.14)	1.06	χ^2=0.09, *P*=0.76	*P*=0.31	*P*=0.77
	Ala267Thr		Control	303	228 (0.75)	63 (0.21)	12 (0.04)	519 (0.86)	87 (0.14)	(0.77–1.45)	χ^2=7.23, *P*=0.0072	χ^2=2.33	χ^2=0.09
rs2498028	206321936				GG	GA	AA	G	A				
	Intron11	135156	Schizophrenia	335	147 (0.44)	147 (0.44)	41 (0.12)	441 (0.66)	229 (0.34)	1.00	χ^2=0.21, *P*=0.65	*P*=0.65	*P*=0.99
	_		Control	303	128 (0.42)	143 (0.47)	32 (0.11)	399 (0.66)	207 (0.34)	(0.79–1.26)	χ^2=0.73, *P*=0.39	χ^2=0.87	χ^2=0.00
rs1327175	206313757				GG	GC	CC	G	C				
	Intron12	8179	Schizophrenia	334	266 (0.80)	63 (0.19)	5 (0.01)	595 (0.89)	73 (0.11)	0.92	χ^2=0.32, *P*=0.57	*P*=0.83	*P*=0.63
	_		Control	302	244 (0.81)	55 (0.18)	3 (0.01)	543 (0.90)	61 (0.10)	(0.64–1.31)	χ^2=0.00, *P*=0.96	χ^2=0.38	χ^2=0.23
rs752016	206304300				AA	AG	GG	A	G				
	Intron12	9457	Schizophrenia	334	106 (0.32)	153 (0.46)	75 (0.22)	365 (0.55)	303 (0.45)	0.96	χ^2=1.92, *P*=0.17	*P*=0.56	*P*=0.68
	_		Control	303	94 (0.31)	150 (0.50)	59 (0.19)	338 (0.56)	268 (0.44)	(0.77–1.19)	χ^2=0.00, *P*=0.95	χ^2=1.15	χ^2=0.17
rs841865	206292532				GG	GA	AA	G	A				
	Intron14	11768	Schizophrenia	335	171 (0.51)	132 (0.39)	32 (0.10)	474 (0.71)	196 (0.29)	1.11	χ^2=0.77, *P*=0.38	*P*=0.35	*P*=0.39
			Control	302	139 (0.46)	136 (0.45)	27 (0.09)	414 (0.69)	190 (0.31)	(0.87–1.41)	χ^2=0.59, *P*=0.44	χ^2=2.08	χ^2=0.73

[a] Chromosome position was referred to dbSNP database.
[b] Without correction.