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COMMON VARIANTS IN *BCL9* GENE AND SCHIZOPHRENIA IN A JAPANESE POPULATION: ASSOCIATION STUDY, META-ANALYSIS AND COGNITIVE FUNCTION ANALYSIS

UOBIČAJENE VARIJANTE *BCL9* GENA I ŠIZOFRENIJA U JAPANSKOJ POPULACIJI: STUDIJA POVEZANOSTI, METAANALIZA I ANALIZA KOGNITIVNIH FUNKCIJA

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Summary

Background: Schizophrenia is a relatively common disorder, with a lifetime prevalence of about 1%. Family history is the most important risk factor for schizophrenia, consistent with a genetic contribution to its etiology. Recent human genetic studies reported that some common variants located within *BCL9* are associated with schizophrenia in the Chinese population, but not associated with bipolar disorder in the Caucasian population.
Methods: Single nucleotide variant (SNP) prioritization sample was comprised of 575 patients with schizophrenia and 564 healthy controls with no personal or family history of psychiatric illness. For SNP association analysis, we used an independent Japanese sample set (replication sample) comprising 1464 cases and 1171 controls. For the analysis of cognitive performance, we investigated 115 cases and 87 controls using Continuous Performance Test (CPT-IP) and the Wisconsin Card Sorting Test Keio version (WCST). Meta-

Kratak sadržaj

Uvod: Šizofrenija je relativno čest poremećaj, sa rasprostranjenošću od oko 1% u ukupnoj populaciji. Porodična istorija bolesti predstavlja najvažniji faktor rizika za nastanak šizofrenije, što je u skladu sa genetičkom osnovom njene etiologije. Nedavne genetičke studije pokazuju da su neke uobičajene varijante u okviru gena *BCL9* u vezi sa šizofrenijom u kineskoj populaciji, ali ne i sa bipolarnim poremećajem u populaciji belaca.
Metode: Uzorci za analizu tačkastih polimorfizama (SNP) potiču od 575 pacijenata sa šizofrenijom i 564 zdravih kontrolnih subjekata bez lične ili porodične istorije psihijatrijskih oboljenja. Za SNP analizu korišćen je nezavisni japanski set uzorak (replikacioni uzorak) koji sadrži 1464 slučaja bolesti i 1171 kontrolu. Za analizu kognitivnih funkcija, ispitivali smo 115 slučajeva bolesti i 87 kontrolnih slučajeva, korišćenjem kontinualnog testa funkcija (CPT-IP) i *Wisconsin Card Sorting* testa, Keio verzije (WCST). Metaanaliza je

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analysis was performed using a combined Japanese total sample (N=3735) and a Chinese sample from a previous study.
Results: In the replication sample set, we did not detect any association in 2 SNPs (rs672607 and rs10494252) and schizophrenia. Meta-analysis of rs672607 showed significant association (p-value 0.012, odds ratio 0.855). There was a significant ($p<0.01$) difference between the A/A and G carrier group of rs672607 in CPT mean d' ($p=0.0092$).
Conclusions: We were able to detect evidence for an association between rs672607 in BCL9 and schizophrenia in the meta-analysis of Japanese and Chinese populations. Additionally, this common variant may affect cognitive performance, as measured by the CPT-IP in schizophrenia patients.

Keywords: *BCL9*, Chinese, cognitive impairment, genome-wide association study, Japanese, meta-analysis, schizophrenia

urađena korišćenjem kombinovanog japanskog ukupnog uzorka (N=3735) i kineskog uzorka iz prethodne studije.
Rezultati: U replikacionom uzorku nije otkrivena nikakva veza između 2 SNP-a (rs672607 i rs10494252) i šizofrenije. Metaanaliza rs672607 je pokazala njegovu značajnu povezanost sa šizofrenijom (p-vrednost 0,012, 0,855 *odds ratio*). Utvrđena je značajna ($p<0,01$) razlika između A/A i G grupe nosilaca rs672607 u CPT srednjoj vrednosti d' ($p=0,0092$).
Zaključak: Dokazana je veza između rs672607 u genu BCL9 i šizofrenije u metaanalizi japanske i kineske populacije. Pored toga, ova zajednička varijanta može da utiče na kognitivne funkcije, što je utvrđeno testom CPT-IP kod šizofrenih bolesnika.

Ključne reči: *BCL9*, Kinezi, kognitivne funkcije, GWAS, Japanci, metaanaliza, šizofrenija

Introduction

Schizophrenia is a chronic, more or less enervating illness characterized by impairments in cognition, affect and behavior, all of which have a pronounced bizarre aspect (1). Delusions, which are generally bizarre, and hallucinations, generally auditory in type, typically occur during the clinical course of schizophrenia (2).

Schizophrenia is a relatively common disorder, with a lifetime prevalence of about 1% (3). Although the overall sex ratio is almost unbiased, males tend to have an earlier onset than females, a finding accounted for by the later age of onset in those females who lack a family history of the disease (4). Family history is the most important risk factor for schizophrenia, consistent with a genetic contribution to its etiology (5) and the heritability of schizophrenia is estimated to be 64% (6). Although genes relevant for schizophrenia or variants that may modulate risk for the disease have been identified using both linkage- and candidate-based or whole genome association studies, the genetic basis of schizophrenia is still unclear (7–10).

Recent human genetic studies reported that some B-cell CLL/lymphoma 9 gene (*BCL9*) variants are associated with schizophrenia in the Chinese population (11), but not associated with bipolar disorder in the Caucasian population (12). In addition, another study showed evidence for genetic association between common variants within *BCL9* and negative symptoms in schizophrenia patients (13). *BCL9* maps to chromosome 1q21.1 (NCBI37: 145,479,806-145,564,639), a region that was shown to be associated with schizophrenia (14). In addition, about 75% of all children with a 1q21.1 microdeletion have delayed development, particularly affecting the development of motor skills such as sitting, standing, and walking, while the intellectual disability and learning problems associated with this genetic change are usually mild (15). Furthermore, schizophrenia is significantly more common in combination with the 1q21.1 deletion syndrome, while autism is significantly more common with the 1q21.1 duplication syndrome (16).

From a biological point of view, the *BCL9* is required for efficient T-cell factor-mediated transcription in the Wnt signaling pathway (17). The Wnt signaling pathway influences neuroplasticity, cell survival, and adult neurogenesis (11), and several studies have suggested that mental disorders may involve impairments in these functions (18). As *BCL9* is indeed an attractive candidate gene for schizophrenia that has not been investigated in the Japanese population, we examined the relationship of common SNPs in *BCL9* and the risk for schizophrenia in a large Japanese case-control sample and conducted a meta-analysis between the Chinese (11) and Japanese sample set used in the current study. We also explored potential relationships between SNPs in *BCL9* and the aspects of human cognitive function.

Materials and Methods

Participants

This study was approved by the Ethics Committees of the Nagoya University Graduate School of Medicine and associated institutes and hospitals. Written informed consent was obtained from all participants. In addition, the patients' capacity to consent was confirmed by a family member when needed. Subjects with legal measure of reduced capacity were excluded. Patients were included in the study if they (1) met the DSM-IV criteria for schizophrenia, (2) were physically healthy and (3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy or known mental retardation. A general characterization and psychiatric assessment of subjects is available elsewhere (19). Controls were select-

ed from the general population. Control subjects had no history of mental disorders, based on questionnaire responses from the subjects themselves during the sample inclusion step, and based on an unstructured diagnostic interview done by an experienced psychiatrist during the blood collection step.

The JGWAS sample was comprised of 575 patients with schizophrenia (43.5±14.8 years (mean±s.d.), male 50%) and 564 healthy controls with no personal or family history of psychiatric illness (44.0±14.4 years (mean±s.d.), male 49.8%). All subjects were unrelated, living in the central area of the Honshu island of Japan and self-identified as members of the Japanese population.

For SNP association analysis, we used an independent Japanese sample set (replication sample) comprising 1464 cases (aged 45.9±14.2 years, male 54.5%) and 1171 controls (aged 48.06±14.48 years, male 47.3%). For the analysis of cognitive performance, we investigated 115 cases (aged 45.3±14.2 years, male 64.3%) and 87 controls (aged 26.3±7.7 years, male 63.2%).

SNP prioritization step

From the previous genetic study of *BCL9* in a Chinese population, we selected a SNP with the lowest p-value (rs672607 A>G, $p=1.23\times10^{-11}$). From the JGWAS data set, there were 3 SNPs (rs17160256, rs17160264 and rs10494252) with $p<0.05$ in BCL9 and +10% region. We selected only one SNP (rs10494252 A>G, $p=0.0369$) from the 3 SNPs because of high r^2 (>0.95) in the Japanese population (SNPinfo Web Server, http://snpinfo.niehs.nih.gov/snpinfo/index.html).

Genotyping and data analysis

DNA was extracted from peripheral blood according to a standard protocol (20, 21). Genotyping was performed using a fluorescence-based allelic discrimination assay (Taqman, Applied Biosystems, Foster City, CA). To exclude low-quality DNA samples or genotyping probes, data sets were filtered on the basis of SNP genotype call rate (more than 90%) or deviation from the HWE in the control sample. Subjects whose percentage of missing genotypes was >10% or who had evidence of possible DNA contamination were excluded from subsequent analyses. All allele-wise association analyses (JGWAS or replication sample set) were carried out by calculating the p-values for each candidate SNP. Significance was determined at the 0.05 level using Fisher's exact test. All p-values were two-sided. In this joint analysis, p-values were generated by Cochran-Mantel-Haenszel stratified analysis, and the Breslow-Day test was performed for evaluation of heterogeneous associations as implemented in PLINK v1.07 (22). Statistical significance was set at a nominal level ($p<0.05$) in an association study. Comprehensive Meta-Analysis Version 2 Professional version (Biostat, Inc., http://www.meta-analysis.com/index.html) was used to conduct a meta-analysis of the Japanese and Chinese sample sets in rs672607.

Neurocognitive assessment

We used the Continuous Performance Test–Identical Pairs Version Release 4.0 (CPT-IP) (New CPT.exe, Copyright 1982–2004 by Barbara A. Cornblatt, All Rights Reserved). The size of the PC monitor used for the test was 10.4 inches as each letter was at least 2.2×1.5 cm (23, 24). Stimuli were flashed on the screen at a constant rate of 1 per second, with a stimulus »on« time of 50 ms. Stimuli were four-digit numbers and were presented 150 times. In each 150-trial condition, 30 of the trials (20%) were target trials and required a response. Target trials were those on which the second of a pair of two identical stimuli appeared (23). The outcome measure was a mean d'.

The Wisconsin Card Sorting Test (WCST) (25) mainly assesses executive function including cognitive flexibility in response to feedback. We used a modified and computerized version of the test: Wisconsin Card Sorting Test (Keio Version) (KWCST) (26–28). The outcome measures were numbers of categories achieved (CA), total errors (TE), and perseverative errors of Milner (PEM) and Nelson types (PEN) in the first trial. We selected outcomes in the WCST, following a prior study, which used KWCST as a measure of cognitive function (29, 30): (1) CA, which is the number of categories for which six consecutive correct responses are achieved (eight is the maximum number of categories which can be achieved), and which is the sum measure of the level of conceptual shifts in the KWCST; (2) PEN, which is the number of incorrect responses in the same category as the immediately preceding incorrect response (maximum of 47 perseverative errors); (3) PEM, which is the number of incorrect responses in the same category as the immediately preceding correct response after the category changes; and (4) TE, which is the total number of incorrect responses.

Chlorpromazine (CPZ) equivalent doses were calculated based on the report by Inagaki et al. (31, 32). The Positive and Negative Symptom Scale (PANSS) was used to evaluate patients (33). From the sample used in the current study, we made a subset of randomly selected participants older than 18 years of age for an analysis of cognitive performance. Cognitive data analysis was done for the participants who completed both WCST and CPT-IP. We checked the effect of two SNPs (rs672607 and rs10494252) on cognitive performance measured by the CPT-IP and the WCST (115 schizophrenic patients, 87

healthy controls). IBM SPSS statistical software, version 20, was used for all analyses. We compared sex, age, education, CPZ equivalent doses, age at onset, duration of illness, positive scale, negative scale and General Psychopathology Scale between schizophrenia cases and control subjects using a Fisher's exact test, two-tailed t-test and Welch's t-test. Next, we compared d' in the CPT and CA, PEM, PEN, TE in the WCST between the case and control groups using a two-tailed t-test and Welch's test (*Table III*).

Patients' records were used to obtain relevant clinical information (e.g. age, education, CPZ equivalent doses, age at onset and duration of illness). Medication status of patients was investigated on the day when cognitive tests were conducted. Patients' medication status and positive and negative symptom scale (PANSS) (33) scores were obtained at the time of cognitive assessment.

Significance level in clinical information was set at p=0.0055 after Bonferroni correction (p=0.05/9). Significance level in five cognitive outcomes was set at p=0.01 after Bonferroni correction (p=0.05/5).

Results

In JGWAS and replication sample set, we did not detect any association in 2 SNPs (rs672607 and rs10494252) and schizophrenia (*Table I*). Joint analysis by PLINK also did not show significantly low p-value in both SNPs (*Table II*). Meta-analysis of the Japanese total sample and Chinese sample in rs672607 showed a significant association (p-value 0.012, odds ratio 0.855).

We investigated the genetic effects of rs672607 and rs10494252 on the CPT-IP and WCST. There was no significant (p<0.0055) difference in clinical information. There was a significant (p<0.01) difference between the A/A and G carrier group of rs672607 in CPT mean d' (p=0.0092) (*Table III*).

Discussion

In this study, we investigated the association between two SNPs within *BCL9* and schizophrenia in the Japanese population. We detected a significant (p=0.012) association between *BCL9* and schizophrenia in the meta-analysis of Japanese and Chinese sample set, however, as the Chinese GWAS dataset was included in the meta-analysis, evidence for the association might be overestimated. The minor allele of rs672607 may be a common variant associated with schizophrenia in the Asian population. Thus, further studies in different populations are needed.

In addition, one of the main obstacles in the identification of genetic variants for schizophrenia is its heterogeneous diagnostic entity, which is clinically relevant, though less appropriate for etiological and genetic research. Therefore, it was of interest to focus on alternative indicators of liability, or endophenotypes. We chose the CPT-IP that is designed to assess highly heritable traits (working memory and visual sustained attention) that are shown to be impaired in schizophrenic patients (34, 35). The WCST was selected in order to evaluate executive function. We tested the association between candidate SNPs from our meta-analysis and cognitive performance meas-

Table I Association study in JGWAS and the replication sample set.

		Case N	Control N	Total N	Case[b]	Control[b]	p-value[c]	Or[d]	L95[e]	U95[e]	HWEp[f]
rs672607 A>G (Ch1, 145519964a)	JGWAS	548	552	1100	0.375	0.393	0.37	0.92	0.78	1.10	0.47
	Replication	1464	1171	2635	0.374	0.392	0.22	0.93	0.83	1.05	0.87
rs10494252 C>A (Ch1, 145483560a)	JGWAS	548	552	1100	0.190	0.226	0.04	0.80	0.65	0.99	0.06
	Replication	1464	1171	2635	0.221	0.221	1.00	1.00	0.87	1.15	0.53

a. based on NCBI 36
b. minor allele frequency
c. p-value of Fisher's exact test
d. Odds ratio
e. Lower (L95) and upper (U95) 95% confidence intervals
f. Hardy-Weinberg Equilibrium test p-value in control

Table II Joint analysis of JGWAS and the replication sample set.

	Case N	Control N	Total N	p-value[a]	OR[b]	L95[c]	U95[c]	BDp[d]
rs672607 A>G	2012	1723	3735	0.13	0.93	0.84	1.02	0.95
rs10494252 C>A	2012	1723	3735	0.26	0.94	0.83	1.05	0.08

a. p-value of Cochran–Mantel–Haenszel stratified analysis by PLINK v1.07
b. Odds ratio
c. Lower (L95) and upper (U95) 95% confidence intervals
d. p-value of Breslow-Day test

Table III Cognitive performance of two SNPs in BCL9.

	rs672607 A>G						rs10494252 C>A					
	Cases (n=110)			Controls (n=76)			Cases (n=110)			Controls (n=76)		
	A/A[a] (n=31)	G carrier (n=79)	p-value[b]	A/Aa (n=21)	G carrier (n=55)	p-value[b]	C/Ca (n=61)	A carrier (n=49)	p-value[b]	C/Ca (n=48)	A carrier (n=28)	p-value[b]
Sex (Males/Females)	21/10	49/30	0.66	13/8	36/19	0.79	37/24	33/16	0.55	26/22	23/5	0.024
Age (years)	48.2	44.8	0.25	26.6	27.2	0.76	44.4	47.5	0.25	26.2	28.4	0.24
	13.6	14.2		7.6	8.1		13.5	14.6		6.9	9.3	
Education (years)	12.1	12.1	0.94	15.6	15.3	0.66	12.2	11.9	0.53	15.4	15.4	0.96
	2.5	2.2		2.8	2.5		2.4	2.2		2.5	2.7	
CPZeq (mg/day)[c]	630.5	627.5	0.97				640.6	612.9	0.69			
	378.4	355.1					340.9	386.1				
Age at onset (years)	26.6	26.7	0.97				25.9	27.5	0.43			
	10.7	10.3					9.0	11.9				
Duration of illness (years)	21.5	18.0	0.24				18.3	19.8	0.58			
	13.9	14.0					13.4	14.8				
PANSS[d] Positive (7–49)	15.5	16.0	0.63				16.4	15.1	0.12			
	4.8	4.3					4.7	4.0				
PANSS[d] Negative (7–49)	20.0	18.5	0.19				19.8	17.8	0.05			
	5.7	5.2					5.6	4.9				
PANSS[d] General (16–112)	36.2	35.8	0.82				36.8	34.9	0.25			
	10.2	7.7					8.9	7.9				
CPT-IP[e] mean d'	0.9	1.4	0.009	2.9	2.7	0.33	1.2	1.3	0.74	2.7	2.8	0.60
	0.9	0.8		0.7	0.7		0.8	0.9		0.7	0.8	
WCST CA[f]	2.6	3.5	0.08	5.7	5.7	0.82	3.1	3.5	0.36	5.7	5.7	0.93
	2.1	2.1		0.5	0.4		2.1	2.2		0.5	0.5	
WCST PEN[g]	7.6	7.3	0.86	0.7	0.6	0.69	7.4	7.4	0.99	0.7	0.5	0.38
	5.8	7.1		1.1	0.9		6.7	6.9		1.1	0.9	
WCST PEM[h]	5.8	4.8	0.54	0.4	0.3	0.98	5.7	4.3	0.31	0.4	0.3	0.77
	5.9	7.6		0.5	0.6		8.6	4.9		0.6	0.5	
WCST TE[i]	23.1	21.3	0.44	11.0	10.8	0.74	22.2	21.2	0.60	10.7	11.0	0.63
	10.1	10.2		1.2	2.1		9.9	10.5		1.9	1.9	

a. Results shown as mean and standard deviation (absolute number for row »sex«)
b. P-value of Student's t-test (p-value of Fisher exact test for row »Sex«/p-value of Welch's t test for row WCST PEN)
c. Chlorpromazine equivalent dose
d. Positive and negative syndrome scale
e. Continuous performance test–identical pairs version
f. Wisconsin card sorting test categories achieved
g. Wisconsin card sorting test perseverative errors – Nelson's type
h. Wisconsin card sorting test perseverative errors – Milner's type
i. Wisconsin card sorting test total errors

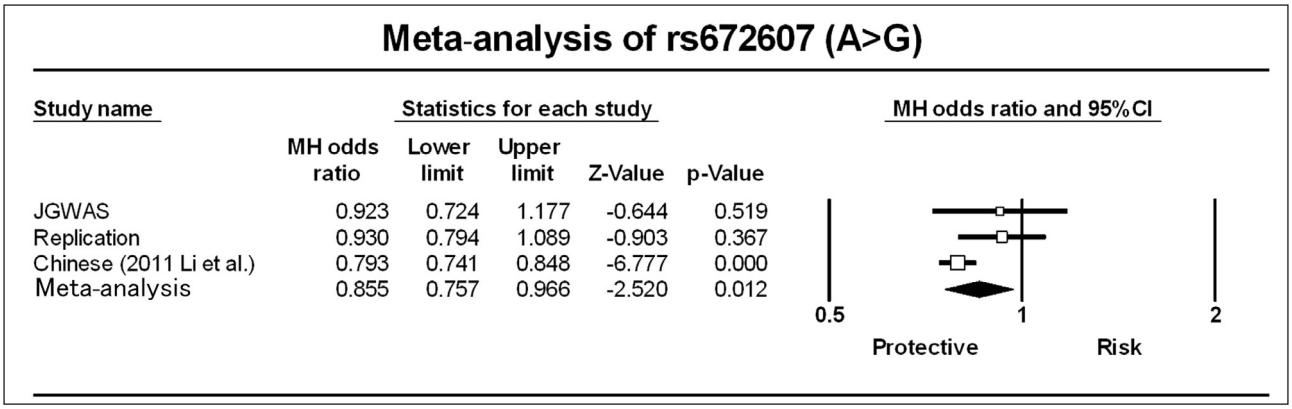

Figure 1 Meta-analysis of the Japanese and Chinese sample set in rs672607. MH: Cochran–Mantel–Haenszel test; lower limit: 95% confidence intervals; upper limit: 95% confidence intervals.

ured by the CPT and WCST. In the CPT-IP, the group with the minor allele of rs672607 (protective allele, odds ratio= 0.855 in our meta-analysis of Japanese and Chinese sample sets) showed significantly impaired working memory in schizophrenia patients.

Several caveats should be noted. Firstly, we did not include a systematic genome-wide mutation scan in either the 5 flanking region or exon regions to search for novel functional variants that may exist within the BCL9 locus, but had not been registered in the databases of common variants. Secondly, our phenotypic diagnosis is not based on structured interviews, and the control samples are significantly younger than the case samples. Thirdly, the sample sizes of cognitive tests were relatively small and the results of cognitive tests may be biased.

As a conclusion, we were able to detect evidence for an association between rs672607 in BCL9 and schizophrenia in the meta-analysis of Japanese and Chinese populations. Additionally, this common variant may affect cognitive performance, as measured by the CPT-IP in schizophrenia patients. Further studies using the sample collected in a non-Asian population are needed.

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Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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