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Genome-wide association study of cognitive decline in schizophrenia

Ryota Hashimoto, M.D., Ph.D.[1,2,3,*], **Masashi Ikeda, M.D., Ph.D.**[3,4], **Kazutaka Ohi, M.D., Ph.D.**[2,3], **Yuka Yasuda, M.D., Ph.D.**[2,3], **Hidenaga Yamamori, M.D., Ph.D.**[2,3,5], **Motoyuki Fukumoto, M.D.**[2,3], **Satomi Umeda-Yano, Ph.D.**[3,5], **Dwight Dickinson, Ph.D.**[6], **Branko Aleksic, M.D., Ph.D.**[3,7], **Masao Iwase, M.D., Ph.D.**[2], **Hiroaki Kazui, M.D., Ph.D.**[2], **Norio Ozaki, M.D., Ph.D.**[3,7], **Daniel R. Weinberger, M.D.**[8], **Nakao Iwata, M.D., Ph.D.**[3,4], and **Masatoshi Takeda, M.D., Ph.D.**[1,2]

[1]Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Suita, Osaka, Japan

[2]Department of Psychiatry, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

[3]CREST (Core Research for Evolutionary Science and Technology), JST (Japan Science and Technology Agency), Kawaguchi, Saitama, Japan

[4]Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

[5]Department of Molecular Neuropsychiatry, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

[6]Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health, NIH, Bethesda, MD, USA

[7]Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

[8]Lieber Institute for Brain Development, Johns Hopkins University Medical Campus, Baltimore, Maryland, USA

TO THE EDITOR

Substantial evidence suggests that many patients with schizophrenia experience a decline in intellectual functioning. Approximately 50% of patients with schizophrenia show cognitive deterioration, with an IQ decline of 10 points from the premorbid IQ (1); cognitive decline in schizophrenia remains stable (2). As there is considerable inter-individual variation in the degree of decline, it appears that genetic influences play a role in determining the severity of cognitive decline in schizophrenia. We conducted a genome-wide association study (GWAS) of cognitive decline in 166 patients with schizophrenia (mean estimated premorbid

[*]Correspondence to: Ryota Hashimoto, M.D., Ph.D., Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, D3, 2-2, Yamadaoka, Suita, Osaka, 5650871, Japan, hashimor@psy.med.osaka-u.ac.jp.

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IQ (JART: Japanese Adult Reading Test): 101.2±10.0, full scale IQ (WAIS): 85.1±16.8 and difference score (subtraction of JART from full scale IQ): −16.1±13.1). We performed a multiple linear regression analysis to compare the difference score in major allele homozygous genotypes with that in minor allele carriers, with gender and years of education as covariates, using PLINK 1.07 software. Detailed information regarding the subjects and methods is provided in the "Supplementary Methods and Data" section and in Supplementary Table 1. Although we did not observe any association at a widely used benchmark for genome-wide significance ($p=5\times10^{-8}$), the strongest association was observed at rs7157599 on chromosome 14, a missense polymorphism (Asn8Ser) in the DEGS2 gene ($p=5.4\times10^{-7}$). The most significant 10 markers are shown in Table 1, and the top 200 markers are shown in Supplementary Table 2. Rs17069667 is an intronic SNP in the CSMD1 gene, which has been identified as a new risk gene for schizophrenia by a recent, large-scale GWAS (3). Associations between the 10 SNPs and the estimated premorbid IQ were not observed (all $p>0.3$); however, associations between the 10 SNPs and full scale IQ were observed in all of the SNPs (best $p=2.4\times10^{-5}$). Analysis using an additive model and analysis with age, gender, illness duration and antipsychotic dose as covariates also showed slightly reduced but remained significant association (Supplemental Table 3). Our results suggest that there are associations at the $p<1\times10^{-5}$ level between difference score in schizophrenia and four genes, one of which has been identified as a new locus for schizophrenia (CSMD1). Replication analysis using a Caucasian population (CBDB/NIMH: Clinical Brain Disorders Branch, National Institute of Mental Health) showed a directionally consistent, trend association of genotype for a proxy SNP of this SNP (rs3783332: proxy of rs7157599, $r^2=0.63$, one tailed p=0.03). Although the study should be replicated with a larger sample size, our results show that the measurement of cognitive decline in schizophrenia as a quantitative phenotype (in conjunction with GWAS) could be a gene discovery tool.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Top 10 SNPs for cognitive decline in schizophrenia

rs number	cytogenic location	Closest gene	Type of variant	M/m	MAF	difference score		current IQ	
						β	p value	β	p value
rs7157599	14q32.2	DEGS2: delta(4)-desaturase, sphingolipid 2	missense: Asn8Ser	A/G	0.245	−9.92	5.39E-07	−9.534	1.10E-04
rs1555702	10q26.3	MKI67: antigen identified by monoclonal antibody Ki-67	intergenic	T/C	0.38	−10.03	2.10E-06	−9.666	2.03E-04
rs17069667	8p23.2	CSMD1: CUB and Sushi multiple domains 1	intron	T/C	0.367	−9.43	3.33E-06	−9.137	3.43E-04
rs1219705	10q26.13	CPXM2: carboxypeptidase X (M14 family), member 2	intron	G/T	0.338	9.26	4.11E-06	10.29	2.96E-05
rs17555780	5q13.3	RGNEF: 190 kDa guanine nucleotide exchange factor	intergenic	A/G	0.204	9.07	1.27E-05	10.7	2.38E-05
rs17005024	4q21.21	BMP3: bone morphogenetic protein 3	intergenic	A/G	0.117	−11.17	1.29E-05	−10.49	9.16E-04
rs11946008	4q21.21	BMP3: bone morphogenetic protein 3	intergenic	T/A	0.121	−10.48	1.38E-05	−10.35	4.88E-04
rs7900253	10q26.13	CPXM2: carboxypeptidase X (M14 family), member 2	intron	A/G	0.333	8.72	1.47E-05	10.05	4.50E-05
rs6599627	10q26.13	CPXM2: carboxypeptidase X (M14 family), member 2	intron	T/C	0.339	8.78	1.49E-05	10.09	4.82E-05
rs9586776	13q33.2	DAOA: D-amino acid oxidase activator	intergenic	G/T	0.138	9.78	2.03E-05	9.655	6.27E-04