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Association between Genetic Polymorphism rs2952768, Close to the *METTL21A* and *CREB1* Genes, and Intellectual Ability in Healthy Subjects

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Abstract

Objective: Human intelligence, which represents a set of cognitive abilities, is assumed to be a highly heterogenic trait. The Intelligence Quotient (IQ) is the most widely used index for characterizing human intelligence in psychometric studies, and knowledge of the genes associated with IQ has continuously grown. Several previous reports indicated that IQ may be associated with addictive behaviors or the use of addictive substances, although the trend toward an association is not straightforward and depends on the substances abused. To explore the genetic factors that contribute to IQ, we conducted an association study of a genetic polymorphism, rs2952768. The rs2952768 single-nucleotide polymorphism (SNP) was recently reported to be associated with human opioid sensitivity and shown to be associated with the efficacy of opioid analgesics, severity of substance dependence, and mRNA expression levels of a neighboring gene, *CREB1*.

Methods: The present study used data from 298 biologically unrelated Japanese subjects. Psychiatrically, medically, and neurologically healthy subjects were evaluated using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Non-Patient Edition (SCID-I/NP), to exclude individuals who had substance-related disorders, who had received psychiatric medications, or who had first- or second-degree relatives with psychiatric disorders. Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0. The rs2952768 SNP close to the *METTL21A* gene was extracted from this dataset. Multiple linear regression analysis was performed to compare intellectual ability among rs2952768 SNP genotypes.

Results: A significant effect of the SNP genotype was observed on current IQ (β = -2.27, p = 0.026). The number of non-risk major C allele for drug and alcohol dependence was correlated with higher IQ scores.

Conclusion: The present results suggest that the rs2952768 SNP, which was identified as a potent SNP associated with human opioid sensitivity, is also one of the genetic factors that contribute to human intellectual ability.

Keywords: Intelligence Quotient (IQ); Opioids; Addictive substances; Substance dependence; Single-nucleotide polymorphism (SNP); Cyclic adenosine monophosphate response element binding protein 1 (*CREB1*); Methyltransferase like 21A (*METTL21A*)

Introduction

Human intelligence, which represents a set of cognitive abilities, such as thinking, remembering, reading, learning, problem solving, and using language, is assumed to be a highly heterogenic trait. Intelligence Quotient (IQ) is the most widely used index for characterizing human intelligence in psychometric studies. It can be used to assess intellectual ability in not only healthy subjects but also in patients with disorders such as schizophrenia, autism, depression, and anxiety [1–3]. Among the well-examined genes are those involved in brain functions related to mechanisms of learning and memory, and genetic variations in such genes associated with IQ have been identified [4–6]. Knowledge of the genes associated with IQ has increased. A publicly available database explores IQ-associated human genes [7], revealing that IQ-associated genes are significantly enriched in multiple signaling events, especially those related to cognitive systems.

Several previous reports suggested that IQ can affect and also be affected by addictive behaviors or the use of addictive substances. For example, people with lower IQ scores are more likely to become cigarette smokers [8,9]. In a longitudinal study that assessed marijuana's impact on IQ, current marijuana use was found to be significantly and dose-dependently correlated ($p < 0.05$) with a decline in IQ over the ages studied [10]. High childhood IQ has generally been linked to alcohol dependence and more frequent alcohol consumption [11,12]. In a study that investigated demographic profiles related to estimations

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of Wechsler Adult Intelligence Scale-Revised (WAIS-R) Full Scale IQs (DP Estimated IQs), the DP Estimated IQ was found to be significantly related to the duration of opioid addiction, and a higher estimated IQ was associated with a shorter duration [13]. However, few studies have focused on genes or their functional involvement in the mechanism of addiction in the context of investigating genes related to human intelligence or IQ scores.

To explore the genetic factors that contribute to IQ, we conducted an association study of a genetic polymorphism, rs2952768. The potent rs2952768 single-nucleotide polymorphism (SNP) was recently associated with human opioid sensitivity and shown to be associated with the efficacy of opioid analgesics, severity of substance dependence, and mRNA expression levels of a neighboring gene, *CREB1* [14].

Materials and Methods

Subjects

The data from 298 healthy subjects (40.9% male [122/176]; mean age ± SD: 36.8 ± 12.4 years) were used in the present study. The subjects were all biologically unrelated and Japanese. The subjects were recruited through local advertisements at Osaka University. Psychiatrically, medically, and neurologically healthy subjects were evaluated using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), Non-Patient Edition (SCID-I/NP), to exclude individuals who had substance-related disorders, who had received psychiatric medications, or who had first- or second-degree relatives with psychiatric disorders. Additionally, subjects were excluded from the study if they had neurological or medical conditions that could potentially affect their central nervous system, such as atypical headaches, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, thyroid disease, active cancer, cerebrovascular disease, epilepsy, seizures, or mental retardation. Written informed consent was obtained from all of the subjects after the procedures were explained. This study was performed in accordance with the World Medical Association's Declaration of Helsinki and approved by the Osaka University Research Ethics Committee.

Measurement of intellectual ability

Current low IQ may or may not be a determinant of drug and alcohol dependence or the use of addictive substances, and the tendency toward an association may be different between abused substances [8-13]. Based on our evidence that a genetic variant close to the methyltransferase like 21A (*METTL21A*) gene, rs2952768, is related to the severity of drug and alcohol dependence, we investigated the association between the rs2952768 genotype for drug and alcohol dependence and current IQ in healthy Japanese subjects. To assess current intellectual ability, we used verbal IQ from the Japanese version of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III) [15]. The subjects were assessed by trained clinical psychologists to obtain verbal IQ scores on the WAIS-III.

Single-nucleotide polymorphism genotyping

Venous blood was collected from the subjects, and genomic DNA was extracted from whole blood according to standard procedures. Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) as previously described [16]. The rs2952768 SNP close to the *METTL21A* gene was extracted from this dataset. No deviation from Hardy-Weinberg equilibrium (HWE) in the examined SNP was detected ($p = 0.10$).

Statistical analysis

Differences in clinical characteristics between the genotype groups were analyzed using the χ^2 tests for categorical variables and Kruskal-Wallis test for continuous variables using PASW Statistics 18.0 software (SPSS Japan, Tokyo, Japan). Deviation from HWE was tested using the χ^2 test for goodness-of-fit using SNPAlyze 5.1.1 Pro software (DYNACOM, Yokohama, Japan). Multiple linear regression analysis was performed to compare intellectual ability among rs2952768 SNP genotypes (the number of major alleles: 0, 1, or 2) using PASW software. Intellectual ability may be influenced by sex and years of education, and these variables were corrected for as covariates. We did not include age as a covariate because IQ score was already corrected for age. All p values were two tailed, and statistical significance was defined as $p < 0.05$.

Results

Influence of the rs2952768 genotype on current intellectual ability

Demographic variables, mean age, sex, and years of education are shown in Table 1. The mean age and years of education did not differ significantly between the genotype groups ($p > 0.59$), whereas the sex ratio differed significantly between groups ($p = 0.015$). We examined the possible effect of the rs2952768 genotype on intellectual ability. A significant effect of the SNP genotype was observed on current IQ ($\beta = -2.27$, $p = 0.026$). The number of C allele was correlated with higher IQ scores (Figure 1).

	Total	C/C	T/C	T/T	
Variables	(*N* = 298)	(*N* = 45)	(*N* = 123)	(*N* = 130)	*p* (*H*)
Age (years)	36.8 ± 12.4	36.3 ± 13.6	37.0 ± 11.7	36.8 ± 12.6	0.83 (0.38)
Sex (male/female)	122/176	11/34	60/63	51/79	**0.015 (8.35)**[a]
Education (years)	14.9 ± 2.3	15.0 ± 2.3	14.8 ± 2.3	15.0 ± 2.3	0.59 (1.06)

Means ± SD are shown. $p < 0.05$ is in boldface and underlined [a]χ^2 test.

Table 1: Demographic variables for subjects included in this study.

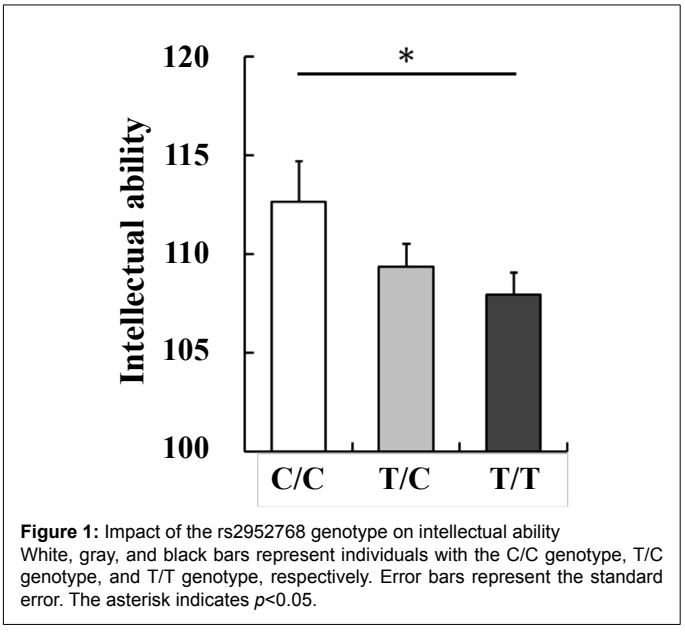

Figure 1: Impact of the rs2952768 genotype on intellectual ability
White, gray, and black bars represent individuals with the C/C genotype, T/C genotype, and T/T genotype, respectively. Error bars represent the standard error. The asterisk indicates $p<0.05$.

Discussion

We conducted an association study between verbal IQ and the rs2952768 SNP, which was recently identified as a potent SNP associated with opioid sensitivity that affects both the efficacy of opioid analgesics and liability to severe substance dependence. A significant effect of the SNP genotype was observed on current IQ (β = -2.27, p = 0.026), and the number of non-risk major C allele for severe drug and alcohol dependence was correlated with higher IQ scores (Figure 1), suggesting that the rs2952768 SNP is one of the genetic factors that contribute to human intellectual ability.

Several previous reports suggested associations between IQ score and addictive behaviors or the use of addictive substances, but the trend toward an association is not straightforward or easily understood [8-13]. Several reports indicated that people with lower IQ scores are more likely to become cigarette smokers [8,9]. Another report found that higher estimated IQ was significantly related to a shorter duration of opioid addiction [13]. High childhood IQ generally has been linked with alcohol dependence and more frequent alcohol consumption, and a 1 SD (15-point) increase in IQ score was found to be associated with an increased risk of illegal drug use in women, such as the use of cannabis, cocaine, amphetamines, amyl nitrate, and "magic mushrooms" [11,12]. The outcome in the present study that the number of non-risk major C allele for substance dependence in the rs2952768 SNP was correlated with higher IQ scores (Figure 1) is seemingly consistent with the results reported by Chastain et al. [13]. Although the rs2952768 SNP was identified as an opioid sensitivity-related SNP, the association was also found in the same direction with the severity of substance dependence, including alcohol dependence, methamphetamine dependence, and eating disorder [14]. Much more studies will be required to make definitive conclusions about the correlations or causal associations between IQ and the use of various addictive substances and vulnerability to or severity of dependence, since the fundamentally important pre-condition, the relationship of rs2952768 with severe drug dependence, has not been well-established.

In our previous study, the homozygote of the non-risk C allele for severe drug and alcohol dependence of the rs2952768 SNP was significantly associated with the elevated expression of a neighboring gene, cyclic adenosine monophosphate response element binding protein 1 (*CREB1*), which encodes a transcription factor that is a member of the leucine zipper family of DNA binding proteins. CREB plays various roles as a transcription factor in many cells, including neuronal cells, and it is also involved in the molecular mechanisms that couple synaptic activity to long-term changes in neuronal plasticity, which is thought to underlie learning and memory [17]. Therefore, the elevated expression of the *CREB1* gene may promote the transcription levels of some target genes related to both human intellectual ability and addiction, leading to alterations in the neural mechanisms that are involved in both increasing intelligence and decreasing the rewarding effects of addictive substances. However, such speculative statements should be avoided before much more extensive studies are conducted in the future, and the precise mechanism by which elevated *CREB1* expression generally affects human opioid sensitivity requires further study.

The *CREB1* and *METTL21A* genes are both located within a linkage disequilibrium block that spans 2q33.3–2q34 [14]. Although these genes were not contained in the publicly available database that explores IQ-associated human genes [7], the chromosomal region 2q33 was included in the linkage regions, indicating that this region may be an IQ-associated region. Furthermore, chromosomal abnormalities, such as duplication and deletion of 2q33.3–2q34, were reported in patients with developmental delay and mental retardation [18,19], the severity of which may be related to IQ [20]. Despite the fact that the responsible genes within this region for IQ should be further clarified in future studies, these previous reports support the results of the present study, in which SNPs in this region may be associated with intellectual ability.

In conclusion, we identified a significant effect of the SNP genotype on current IQ, and the number of non-risk major C allele for drug and alcohol dependence was correlated with higher IQ scores. Although we should not over-interpret the present finding and the precise underlying mechanisms remain to be clarified in future studies, the results of the present study suggest that this SNP may be one of the genetic factors that contribute to human intellectual ability.

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References

1. Mortensen EL, Sørensen HJ, Jensen HH, Reinisch JM, Mednick SA (2005) IQ and mental disorder in young men. Br J Psychiatry 187: 407-415.
2. Koenen KC, Moffitt TE, Roberts AL, Martin LT, Kubzansky L, et al. (2009) Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. Am J Psychiatry 166: 50-57.
3. Kalbfleisch ML, Loughan AR (2012) Impact of IQ discrepancy on executive function in high-functioning autism: insight into twice exceptionality. J Autism Dev Disord 42: 390-400.
4. Ohi K, Hashimoto R, Yasuda Y, Fukumoto M, Nemoto K, et al. (2013) The *AKT1* gene is associated with attention and brain morphology in schizophrenia. World J Biol Psychiatry 14: 100-113.
5. Hashimoto R, Ohi K, Yasuda Y, Fukumoto M, Yamamori H, et al. (2013) The *KCNH2* gene is associated with neurocognition and the risk of schizophrenia. World J Biol Psychiatry 14: 114-120.
6. Ohi K, Hashimoto R, Yasuda Y, Fukumoto M, Yamamori H, et al. (2013) Influence of the *NRGN* gene on intellectual ability in schizophrenia. J Hum Genet 58: 700-705.
7. Kong L, Cheng L, Fan LY, Zhao M, Qu H (2013) IQdb: an intelligence quotient score-associated gene resource for human intelligence. Database (Oxford) 2013: bat063.
8. Hemmingsson T, Kriebel D, Melin B, Allebeck P, Lundberg I (2008) How does IQ affect onset of smoking and cessation of smoking--linking the Swedish 1969 conscription cohort to the Swedish survey of living conditions. Psychosom Med 70: 805-810.
9. Weiser M, Zarka S, Werbeloff N, Kravitz E, Lubin G (2010) Cognitive test scores in male adolescent cigarette smokers compared to non-smokers: a population-based study. Addiction 105: 358-363.
10. Fried P, Watkinson B, James D, Gray R (2002) Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults. CMAJ 166: 887-891.
11. Batty GD, Deary IJ, Schoon I, Emslie C, Hunt K, et al. (2008) Childhood mental ability and adult alcohol intake and alcohol problems: the 1970 British cohort study. Am J Public Health 98: 2237-2243.
12. White JW, Gale CR, Batty GD (2012) Intelligence quotient in childhood and the risk of illegal drug use in middle-age: the 1958 National Child Development Survey. Ann Epidemiol 22: 654-657.
13. Chastain RL, Lehman WE, Joe GW (1986) Estimated intelligence and long-term outcomes of opioid addicts. Am J Drug Alcohol Abuse 12: 331-340.

14. Nishizawa D, Fukuda K2, Kasai S1, Hasegawa J1, Aoki Y3, et al. (2014) Genome-wide association study identifies a potent locus associated with human opioid sensitivity. Mol Psychiatry 19: 55-62.

15. Wechsler D (1997) WAIS-III: Wechsler Adult Intelligence Scale. (3rdedn), Psychological Corporation, San Antonio, TX.

16. Hashimoto R, Ikeda M, Ohi K, Yasuda Y, Yamamori H, et al. (2013) Genome-wide association study of cognitive decline in schizophrenia. Am J Psychiatry 170: 683-684.

17. Sakamoto K, Karelina K, Obrietan K (2011) CREB: a multifaceted regulator of neuronal plasticity and protection. J Neurochem 116: 1-9.

18. Usui D, Shimada S, Shimojima K, Sugawara M, Kawasaki H, et al. (2013) Interstitial duplication of 2q32.1-q33.3 in a patient with epilepsy, developmental delay, and autistic behavior. Am J Med Genet A 161A: 1078-1084.

19. Bisgaard AM, Kirchhoff M, Tümer Z, Jepsen B, Brøndum-Nielsen K, et al. (2006) Additional chromosomal abnormalities in patients with a previously detected abnormal karyotype, mental retardation, and dysmorphic features. Am J Med Genet A 140: 2180-2187.

20. Battaglia A, Bianchini E, Carey JC (1999) Diagnostic yield of the comprehensive assessment of developmental delay/mental retardation in an institute of child neuropsychiatry. Am J Med Genet 82: 60-66.