No Association Between GRM3 and Japanese Methamphetamine-Induced Psychosis

Tomoko Tsunoka1,#, Taro Kishi1,*, Masashi Ikeda1,10, Tsuyoshi Kitajima1, Yoshio Yamanouchi1, Yoko Kinoshiba1, Kunihiro Kawashima1, Tomo Okochi1, Takenori Okumura1, Toshiya Inada2,3, Hiroshi Ujike2,4, Mitsuhiko Yamada2,5, Naohisa Uchimura2,6, Ichiro Sora2,7, Masaomi Iyo2,8, Norio Ozaki2,9 and Nakao Iwata1,2

1Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi 470-1192, Japan; 2Japanese Genetics Initiative for Drug Abuse, Japan; 3Department of Psychiatry, Seiwa Hospital, Institute of Neuropsychiatry, Tokyo 162-0851, Japan; 4Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan; 5National Institute of Mental Health, National Center of Neurology and Psychiatry, Ichikawa 272-0827, Japan; 6Department of Neuropsychiatry, Kurume University School of Medicine, Kurume 830-0011, Japan; 7Department of Psychobiology, Department of Neuroscience, Tohoku University Graduate School of Medicine, Sendai 980-8576, Japan; 8Department of Psychiatry, Chiba University Graduate School of Medicine, Chiba 260-8677, Japan; 9Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya 466-8850, Japan; 10Department of Psychological Medicine, School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN, United Kingdom

Abstract: Several investigations have suggested that abnormalities in glutamate neural transmission play a role in the pathophysiology of psychiatric disorders, including schizophrenia. The metabotropic glutamate 3 receptor (mGluR3) gene was reported to be associated with schizophrenia, and paranoid type schizophrenia has symptoms that are similar to those of methamphetamine-induced psychosis. This suggests that mGluR3 gene (GRM3) is a good candidate gene for the pathogenesis of methamphetamine-induced psychosis. To evaluate the association between GRM3 and methamphetamine-induced psychosis, we conducted a case-control study of Japanese samples (181 methamphetamine-induced psychosis and 232 controls).

Methods: We selected one functional SNP (rs6465084), reported to be associated with prefrontal brain functioning, for an association analysis. Written informed consent was obtained from each subject. This study was approved by the ethics committees at Fujita Health University, Nagoya University Graduate School of Medicine and each participating member of the Institute of the Japanese Genetics Initiative for Drug Abuse (JGIDA).

Results: We did not detect an association between rs6465084 in GRM3 and Japanese methamphetamine-induced psychosis.

Conclusion: Our findings suggest that rs6465084 in GRM3 does not play a major role in the pathophysiology of methamphetamine-induced psychosis in the Japanese population. However, because we did not perform an association analysis based on linkage disequilibrium (LD) or a mutation scan of GRM3, a replication study using a larger sample and based on LD may be required for conclusive results.

Keywords: GRM3, Methamphetamine-Induced Psychosis, case-control study.

1. INTRODUCTION

The glutamate hypothesis is one of the prevailing hypotheses for the pathophysiology of schizophrenia [1]. Also, a recent clinical study showed that LY379268, an agonist of metabotropic glutamate 2/3 receptor (mGluR2/3) that is involved in group II mGluR regulate glutamate neurotransmission through a presynaptic negative regulatory mechanism, has an effect on psychotic symptoms in schizophrenia almost equivalent to that of olanzapine [1].

Several investigations have suggested that metabotropic glutamate 3 receptor (mGluR3) gene has an association with schizophrenia [2-4]. Since the symptoms of methamphetamine-induced psychosis are similar to those of paranoid type schizophrenia [5], it would seem that the mGluR3 gene (GRM3) is a good candidate gene for the pathogenesis of methamphetamine-induced psychosis. To evaluate the association between GRM3 and methamphetamine-induced psychosis, we conducted a case-control study of Japanese samples (181 methamphetamine-induced psychosis patients and 232 controls). The mGluR3 gene (GRM3 OMIM *601115, 6 exons in a genomic region spanning 221.763Kb) is at 7q21. We selected rs6465084 in GRM3, which is reported to be associated with prefrontal brain functioning. Rs6465084 has been found to be associated with decreased verbal list learn-
ing and verbal fluency [3]. In addition, Egan and colleagues reported that the rs6465084 A allele predicted decreased levels of N-acetylaspartate in the prefrontal cortex in an in vivo study, and suggested that the rs6465084 A allele reduced tissue glutamate levels and synaptic abundance [3].

2. MATERIALS AND METHODS

2.1. Subjects

The subjects in the association analysis were 181 methamphetamine-induced psychosis patients (155 males and 26 females; mean age 33.3 ± 11.4) and 232 controls (187 males and 45 females; mean age 36.4 ± 11.3). All subjects were unrelated to each other, ethnically Japanese, and lived in the central area of Japan. The patients were diagnosed according to DSM-IV criteria with consensus of at least two experienced psychiatrists on the basis of unstructured interviews and a review of medical records. One hundred thirty-seven subjects with METH-induced psychosis also had dependence on drugs other than METH. Subjects with METH-induced psychosis were excluded if they had a clinical diagnosis of psychotic disorder, mood disorder, anxiety disorder or eating disorder. More detailed characterizations of these subjects have been published elsewhere [6-8]. All healthy controls were also psychiatrically screened based on unstructured interviews including current and past psychiatric history. None had severe medical complications such as cirrhosis, renal failure, heart failure or other Axis-I disorders according to DSM-IV. No structured methods were used to assess psychiatric symptoms in the controls, which included hospital staff, their families and medical students.

The study was described to subjects and written informed consent was obtained from each. This study was approved by the Ethics Committee at Fujita Health University, Nagoya University School of Medicine and and each participating member of the Institute of the Japanese Genetics Initiative for Drug Abuse (JGIDA).

2.2. SNP Selection

We selected rs6465084 in GRM3, which is reported to be associated with prefrontal brain functioning, for the following association analysis.

2.3. SNP Genotyping

SNP genotyping was done using TaqMan assays (Applied Biosystems) [9].

2.4. Statistical Analysis

Genotype deviation from the Hardy-Weinberg equilibrium (HWE) was evaluated with the chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc, Tokyo, Japan).

Marker-phenotype association analysis was used to evaluate allele- and genotype-wise association with the chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc, Tokyo, Japan). To control inflation of the type I error rate, we used Bonferroni’s correction. Power calculation was performed using a statistical program prepared by Purcell et al.

The significant level for all statistical tests was 0.05.

3. RESULTS

Rs6465084 is in HWE. We detected no association between rs6465084 in GRM3 and METH-induced psychosis in the allele/genotype-wise analysis (Table 1).

4. DISCUSSION

We performed an association study of rs6465084 in GRM3 and METH-induced psychosis in the Japanese population. Although, we recently found an association between GRM2 and METH-induced psychosis in the Japanese population [10], in the present study we detected no association between GRM3 with METH-induced psychosis.

Egan and colleagues reported that the rs6465084 A allele predicted decreased levels of N-acetylaspartate in the prefrontal cortex in an in vivo study, and suggested that the rs6465084 A allele reduced tissue glutamate levels and synaptic abundance [3]. This influence of GRM3 on prefrontal cortex and cognitive function suggests that abnormalities in glutamate neurotransmission may be involved in the pathophysiology of METH-induced psychosis. However, we did not detect an association between GRM3 and METH-induced psychosis. We designed the present study based on common disease–common variants hypothesis (CD–CV hypothesis) [11]. In addition, we selected only one SNP in GRM3. A recent study has showed an association between common diseases such as schizophrenia and rare variants. If the genetic background of METH-induced psychosis is accurately described by the common disease-rare variants hypothesis, further investigation such as medical resequencing using larger samples will be required [8, 12-17].

There are a few limitations in this study. First, the lack of association may be due to biased samples, such as small sample sizes. Second, we selected only one SNP in GRM3.

Table 1. Association Analysis of GRM3 with MAP with Psychosis

| SNP    | Phenotype a | MAF b | N   | Genotype Distribution | P-Value c |
|--------|-------------|-------|-----|-----------------------|----------|
|        |             |       |     | TT    | TC   | CC | HWE | Genotype | Allele |
| rs6465084 | Controls  | 0.0926 | 232 | 193  | 35  | 4  | 0.117 | 0.153  | 0.941  |
| A>G    | MAP with psychosis | 0.0911 | 181 | 148  | 33  | 0  | 0.177 |

a MAP with psychosis: methamphetamine use disorder with psychosis
b MAF: major allele frequency
c Hardy-Weinberg equilibrium.
To overcome these limitations, it will be necessary to conduct a replication study using gene-based association analysis and larger samples.

5. CONCLUSION

Our results suggest that rs6465084 in GRM3 does not play a role in the pathophysiology of METH-induced psychosis in the Japanese population. However, our results have limitations and replication study using gene-based association analysis and larger samples will be required.

REFERENCES

[1] Weinberger, D.R. Schizophrenia drug says goodbye to dopamine. Nat. Med. 2007, 13 (9), 1018-9.

[2] Moeller, R., Schuhmacher, A., Schulze-Rauschenbach, S., Kuhn, K.U., Rujescu, D., Rietschel, M., Zobel, A., Franke, P., Wolwer, W., Gaebel, W., Hafner, H., Wagner, M., Maier, W. Further evidence for a functional role of the glutamate receptor gene GRM3 in schizophrenia. Eur. Neuropsychopharmacol., 2008, 18, 768.

[3] Egan, M.F., Straub, R.E., Goldberg, T.E., Yakub, I., Callicott, J.H., Hariri, A.R., Mattay, V.S., Bertolino, A., Hyde, T.M., Shannon-Weicker, C., Akil, M., Crook, J., Vakkalanka, R.K., Balkissoon, R., Gibbs, R.A., Kleinman, J.E., Weinberger, D.R. Variation in GRM3 affects cognition, prefrontal glutamate, and risk for schizophrenia. Proc. Natl. Acad. Sci. U. S. A., 2004, 101, 12604.

[4] Sartorius, L.J., Weinberger, D.R., Hyde, T.M., Harrison, P.J., Kleinman, J.E., Lipska, B.K. Expression of a GRM3 splice variant is increased in the dorsolateral prefrontal cortex of individuals carrying a schizophrenia risk SNP. Neuropsychopharmacology, 2008, 33(11), 2626-34.

[5] Sato, M., Chen, C.C., Akiyama, K., Otsuki, S. Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. Biol. Psychiatry, 1983, 18(4), 429-40.

[6] Kishi, T., Ikeda, M., Kitajima, T., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Inada, T., Harano, M., Komiyama, T., Hori, T., Yamada, M., Iyo, M., Sora, I., Sekine, Y., Ozaki, N., Ujike, H., Iwata, N. Alpha4 and beta2 subunits of neuronal nicotinic acetylcholine receptor genes are not associated with methamphetamine-use disorder in the Japanese population. Ann. N. Y. Acad. Sci., 2008, 1139, 70.

[7] Kishi, T., Ikeda, M., Kitajima, T., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Okochi, T., Tsukada, T., Okumura, T., Inada, T., Ujike, H., Yamada, M., Uchimura, N., Sora, I., Iyo, M., Ozaki, N., Iwata, N. A functional polymorphism in estrogen receptor alpha gene is associated with Japanese methamphetamine induced psychosis. Prog. Neuro-psychopharmacol. Biol. Psychiatry, 2009, 33, 895.

[8] Kishi, T., Tsunoka, T., Ikeda, M., Kitajima, T., Kawashima, K., Okochi, T., Okumura, T., Yamanouchi, Y., Kinoshita, Y., Ujike, H., Inada, T., Yamada, M., Uchimura, N., Sora, I., Iyo, M., Ozaki, N., Iwata, N. Serotonin 1A receptor gene is associated with Japanese methamphetamine-induced psychosis patients. Neuropsychopharmacology, 2010, 58, 452.

[9] Tsunoka, T., Kishi, T., Ikeda, M., Kitajima, T., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Okochi, T., Okumura, T., Inada, T., Ozaki, N., Iwata, N. Association analysis of group II metabotropic glutamate receptor genes (GRM2 and GRM3) with mood disorders and fluvoxamine response in a Japanese population. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2009, 33, 875.

[10] Tsunoka, T., Kishi, T., Kitajima, T., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Okochi, T., Okumura, T., Inada, T., Ujike, H., Yamada, M., Uchimura, N., Sora, I., Iyo, M., Ozaki, N., Iwata, N. Association analysis of GRM2 and HTR2A with methamphetamine-induced psychosis and schizophrenia in the Japanese population. Prog. Neuro-Psychopharmacol. Biol. Psychiatry, 2010, 34, 639.

[11] Chakravarti, A. Population genetics--making sense out of sequence. Nat. Genet., 1999, 21(1 Suppl), 56-60.

[12] Kishi, T., Kitajima, T., Ikeda, M., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Okochi, T., Ozaki, N., Iwata, N. Orphan nuclear receptor Rev-erb alpha gene (NR1D1) and fluvoxamine response in major depressive disorder in the Japanese population. Neuropsychobiology, 2009, 59, 234.

[13] Kishi, T., Kitajima, T., Ikeda, M., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Okochi, T., Okumura, T., Tsukada, T., Ozaki, N., Iwata, N. CLOCK may predict the response to fluvoxamine treatment in Japanese major depressive disorder patients. Neuromol. Med., 2009, 11, 53.

[14] Kishi, T., Kitajima, T., Ikeda, M., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Okochi, T., Okumura, T., Tsukada, T., Inada, T., Ozaki, N., Iwata, N. Association study of clock gene (CLOCK) and schizophrenia and mood disorders in the Japanese population. Eur. Arch. Psychiatry Clin. Neurosci., 2009, 259, 293.

[15] Kishi, T., Kitajima, T., Tsunoka, T., Ikeda, M., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Okochi, T., Okumura, T., Inada, T., Ozaki, N., Iwata, N. Genetic association analysis of serotonin 2A receptor gene (HTR2A) with bipolar disorder and major depressive disorder in the Japanese population. Neurosci. Res., 2009, 64, 231.

[16] Kishi, T., Kitajima, T., Ikeda, M., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Okochi, T., Ozaki, N., Iwata, N. Association analysis of nuclear receptor Rev-erb alpha gene (NR1D1) with mood disorders in the Japanese population. Neurosci. Res., 2008, 62, 211.

[17] Kishi, T., Yoshimura, R., Okochi, T., Fukuo, Y., Kitajima, T., Okumura, T., Tsunoka, T., Kawashima, K., Yamanouchi, Y., Kinoshita, Y., Umene-Nakano, W., Naitoh, H., Nakamura, J., Ozaki, N., Iwata, N. Association analysis of SIGMAR1 with major depressive disorder and SSRI response. Neuropsychopharmacology, 2010, 58, 1168.