Association Analysis of the Tryptophan Hydroxylase 2 Gene Polymorphisms in Patients with Methamphetamine Dependence/Psychosis

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Abstract: There is a growing evidence that serotonergic systems modulate dopaminergic neurotransmission. We analyzed the association between the variations in the brain tryptophan hydroxylase 2 (TPH2) gene, a rate limiting enzyme for serotonin biosynthesis, and methamphetamine (METH) dependence/psychosis in a Japanese population. We found ten single nucleotide polymorphisms (SNPs) and two polynucleotide polymorphisms in TPH2 gene exons and exon-intron boundaries. A total of 162 patients and 243 controls were used for the association analysis between these polymorphisms and METH dependence/psychosis. No significant differences were observed in either genotypic or allelic frequencies between METH dependent/psychotic patients and controls. A global test of differentiation among samples based on haplotype frequencies showed no significant association. With respect to latency of psychosis, prognosis of psychosis, and spontaneous relapse, we found no significant association with these SNPs. These results suggest that the TPH2 gene variants may not be a factor in vulnerability to METH dependence/psychosis.

Keywords: Single nucleotide polymorphism, SNP, variation, serotonin, human, Japanese, MAP, abuse.

INTRODUCTION

Methamphetamine (METH) is a psychomotor stimulant with high liability for abuse, and METH abuse has become a very serious social problem in Japan [1]. Chronic METH abusers have been shown to have persistent dopaminergic deficits [2, 3]. In animals, amphetamine elevates extracellular dopamine levels in the mesolimbic circuits [4, 5]. There is growing evidence that serotonergic systems modulate dopaminergic neurotransmission. For example, the mesocorticolimbic dopamine system is under inhibitory control by the serotonin system, which exerts its actions via serotonin receptor subtypes [6, 7].

Acute and chronic administration of METH markedly decreases the activity of tryptophan hydroxylase (TPH) [8, 9], the rate-limiting enzyme in the biosynthesis of serotonin [10]. TPH2 (or neuronal TPH) was identified as a second isof orm of TPH in 2003 [11, 12]. In contrast to TPH1, which is expressed predominantly in the pineal gland and the periphery, TPH2 mRNA is expressed in the raphe nuclei [11]. Since the identification of TPH2, there have been numerous association analyses between TPH2 gene variants and psychiatric diseases. For example, associations have been observed between TPH2 variants and bipolar disorder [13–18], suicidal behavior in major depression [19–21], the response to selective serotonin reuptake inhibitors (fluoxetine and/or citalopram) [22, 23] and emotional regulation in healthy subjects [24–28]. These reports indicate that polymorphic variants in the TPH2 gene may have a role in the pathophysiology of a wide range of psychiatric disorders and emotional regulation. A recent study of heroin addiction also showed an association with TPH2 variants in Hispanics and African-Americans [29].

The purpose of this study was (1) to identify novel sequence variations in all coding exons as well as exon-intron boundaries of the TPH2 gene in Japanese, and (2) to investigate whether these polymorphisms and/or haplotypes were associated with METH dependence/psychosis.

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MATERIALS AND METHODS

Subjects

One-hundred sixty-two unrelated patients with METH dependence/psychosis (130 males and 32 females; mean age 37.4±12.0 years) meeting ICD-10-DCR criteria (F15.2 and F15.5) were used as case subjects; they were outpatients or inpatients of psychiatric hospitals. The 243 control subjects (168 males and 75 females; mean age 35.4±11.5 years) were mostly medical staff members who had neither personal nor familial history of drug dependence or psychotic disorders, as verified by a clinical interview. All subjects were Japanese, born and living in the northern Kyushu, Setouchi, Chugoku, Tokai, and Kanto regions. This study was approved by the ethical committees of each institute of the Japanese Genetics Initiative for Drug Abuse (JGIDA), and all subjects provided written informed consent for the use of their DNA samples for this research [30]. After informed consent was obtained, blood samples were drawn and genomic DNA was extracted by the phenol/chloroform method.

Defining Variants of the TPH2 Gene

Initially, 16 METH dependent/psychotic patient samples were used to identify nucleotide variants within the TPH2 gene (GenBank accession no. AC090109). Exons 1 to 11 and exon-intron boundaries were amplified by polymerase chain reaction (PCR) using a thermal cycler (Astec, Fukuoka, Japan), and the products were sequenced in both directions using BigDye terminators (Applied Biosystems, Foster City, CA) by an ABI Genetic analyzer 3100 (Applied Biosystems).

Genotyping of each polymorphism except in exon 11 was performed by PCR amplification using the relevant primers listed in Table 1 followed by sequencing using the same primers in both directions. Genotyping of polymorphisms in exon 11 was performed by PCR amplification using 9F and 11R primers followed by sequencing using 10F, 11F, and 11R primers.

Patient Subgroups

For the clinical category analysis, the patients were divided into two subgroups by three different clinical features. (A) Latency of psychosis from first METH intake: less than 3 years or more than 3 years. The course of METH psychosis varied among patients, with some patients showing psychosis sooner after the first METH intake, as previously reported [30, 31]. Because the median latency was three years, this time point was used as the cutoff in defining the two groups. (B) Duration of psychosis after the last METH intake: transient (<1 month) or prolonged (≥1 month). Some patients showed continuous psychotic symptoms even after METH discontinuation, as previously reported [30, 31]. Patients with the transient type showed a reduction of psychotic symptoms within one month after the discontinuation of METH consumption and the beginning of treatment with neuroleptics. Patients with the prolonged type showed a psychotic symptoms continued for more than one month even after the discontinuation of METH consumption and the beginning of neuroleptic treatment. (C) Spontaneous relapse: present or not. It has been well documented that once METH psychosis has developed, patients in the remission phase are liable to spontaneous relapse without reconsupmption [30, 31].

Statistical Analysis

The Hardy-Weinberg equilibrium of genotypic frequencies in each SNP was tested by the chi-square test. The level of statistical significance was set at α = 0.05. The allelic and genotypic frequencies of patients and control groups were compared using the chi-square test. Locus by locus linkage disequilibrium (LD) was evaluated by D' and r², which were calculated by the haplotype frequencies using the appropriate formula in the Excel program. A global test of differentiation among samples based on haplotype frequencies was performed using the Arlequin program available from http://anthropologie.unige.ch/arlequin [32].

Table 1. Primers Used in this Study

| Exon   | Forward | Reverse                        |
|--------|---------|--------------------------------|
| Exon 1 | 1F      | CCT TAT GTA TTT TTC ACC ACC     |
|        |         | 1R GGT GAG CAC GTA ATT GCC ACA |
| Exon 2 | 2F      | CCA CTA GAT GAC TTA GAC CAT    |
|        |         | 2R CTG ACC TAA CCT GCC AAT AGT |
| Exon 3,4 | 3F     | GTA CTT GGC ACC TTA AAG ATG    |
|        |         | 3R TGG ACC TCT GTC AGT TGG     |
| Exon 5 | 4F      | GCT CAA CTG AGC CAT TCT GCT TAC|
|        |         | 4R GTC GCA CTG GCC ATG TGG CTC ACA |
| Exon 6 | 5F      | GAT CTT TTC AGA GGC TCA TGG GCT|
|        |         | 5R CAT ACT CAT GTA GCC CAG CAG AGC |
| Exon 7 | 6F      | GTG CCG TAA GCA TCA CTT TGG ATT|
|        |         | 6R CAG ATG AGG AGT CTG ATC TCT CAG |
| Exon 8 | 7F      | GAA GCC CCA GCA TGG AGT AAC TGT|
|        |         | 7R GGC TAA GCT GAG TAA TTA TCA CAG |
| Exon 9 | 8F      | CAG GAA GGC TAA GAC TCT TAG TAG|
|        |         | 8R GTC AGT AGG ATC ACT GCT AGC TCA |
| Exon 10, 11 | 9F | CCT GCA CAC AGG AGA GTT CCA TAT |
|        |         | 9R CAT GCT GCA AAC AGA ATG TCC TCA CCA |
|        | 10F     | CAA TCC CTA CAC ACA GAG TAT TGA |
|        |         | 10R CAT TCC AAC TCG TGT GTC ACC TCA |
|        | 11F     | GAT CTA AGC CTT GCC TCT GTC TTC |
|        |         | 11R GAC ACA GAA ACA CAC GCA AGC ACT |
RESULTS

To identify polymorphisms in the TPH2 gene, all coding exons (1 to 11) and exon-intron boundaries were analyzed using genomic DNA from 16 Japanese METH-dependent/psychotic subjects. Ten single nucleotide polymorphisms (SNPs) and two insertion / deletion polymorphisms were identified. One polymorphism, Exon11+(C3)500(C2), was novel (Table 2). Two SNPs, rs7305115 (Exon7+A131G) and rs4290270 (Exon9+A57T), were synonymous mutations and Eon2+C18A was a non-synonymous mutation. Three linkage disequilibrium (LD) regions were found, rs11178998 (Exon1-A42G) to rs41265611 (IVS1+60 (I/D)), rs11179003 (IVS4+C4821T) to rs10879348 (IVS6+G144A), and rs4760816 (IVS6+C6106T) to rs7305115 (Exon7+A131G), in the sense that all genotypic patterns in all 16 samples analyzed were the same. Each one of the SNPs was chosen and a total of nine SNPs were genotyped for further analysis. LD mapping was analyzed by using SNPs having minor allele frequencies of over 10% in both samples (Table 4). LD was observed from rs17110566 (IVS6+G152A) to rs17110747 (Exon11+G654A) and from rs4290270 (Exon9+A57T) to rs41317114 (IVS11+G128C) (Fig. 1 and Table 3).

Association analyses were performed on these nine polymorphic positions using 162 METH dependent/psychotic patients and 243 controls. Genotypic frequencies in these

Table 2. TPH2 Gene Variants Found in the Japanese Population

| Position | Location | rs Number | SNP Name | Variation | Function |
|----------|----------|-----------|----------|-----------|----------|
| 30029    | 5' side  | rs11178998| Exon1-A42G| A/G       |          |
| 30241    | Intron 1 | rs41265611| IVS1+60(ID)| TCT/del   |          |
| 32694    | Exon 2   | Exon2+C18A| C/A     | nonsynonymous (Ser41Tyr) |
| 40601    | Intron 4 | rs11179003| IVS4+C4821T| C/T       |          |
| 63953    | Intron 6 | rs10879348| IVS6+G144A| G/A       |          |
| 63961    | Intron 6 | rs17110566| IVS6+G152A| G/A       |          |
| 69915    | Intron 6 | rs4760816 | IVS6+C6106T| C/T       |          |
| 70176    | Exon 7   | rs7305115 | Exon7+A131G| A/G       | synonymous (Pro312Pro) |
| 113549   | Exon 9   | rs4290270 | Exon9+A57T| A/T       | synonymous (Ala375Ala) |
| 123114   | Exon 11  | Exon11+(C3)500(C2) | C3/C2 |
| 123268   | Exon 11  | rs17110747| Exon11+G654A| G/A       |          |
| 123663   | 3' side  | rs41317114| IVS11+G128C| G/C       |          |

1) Position: nucleotide position number in the NCBI nucleotide database under accession number AC090109. 2) rs number: NCBI SNP database. 3) This SNP was reported as C2755A [14].

Fig. (1). Location and linkage disequilibrium mapping of the TPH2 gene polymorphisms. All the coding exons and their regions were taken from the NCBI database under accession number AC090109. Red ovals indicate the polymorphic positions, solid black lines the analyzed regions, and solid red lines the LD block.
Table 3. Linkage Disequilibrium Mapping of the TPH2 Gene

| SNP                | rs17110566 (IVS6+G152A) | rs4760816 (IVS6+C6106T) | rs4290270 (Exon9+A57T) | rs17110747 (Exon11+G654A) | rs41317114 (IVS11+G128C) |
|--------------------|-------------------------|-------------------------|------------------------|---------------------------|--------------------------|
| rs17110566         | 0.9392                  | 0.6138                  | 0.8581                 | 0.0348                    | 0.9399                   |
| rs4760816          | 0.9724                  | 0.7301                  | 0.9253                 | 0.0092                    |                          |
| rs4290270          | 0.5262                  | 0.5881                  | 0.9284                 | 0.6051                    |                          |
| rs17110747         | 0.8437                  | 0.7885                  | 0.9774                 |                          | 0.9399                   |
| rs41317114         | 0.0111                  | 0.2179                  | 0.6284                 | 0.9123                    |                          |

D' and r² values for Control samples are shown in the upper right and lower left, respectively.

Table 4. Genotypic and Allelic Distribution of the TPH2 gene SNPs in the METH Dependent/Psychotic Patients and the Control Groups

| SNP                  | Group | Genotype (%) | P     | Allele (%) | P   |
|----------------------|-------|--------------|-------|------------|-----|
| rs11178998 (Exon1-A42G) | METH  | A/A 130 (80%) | 0.102 | A 289 (89%) | 0.617 |
|                      |       | A/G 29 (18%)  |       | G 35 (11%)  |     |
|                      |       | G/G 3 (2%)    |       |            |     |
|                      | Control| 197 (81%)    |       | 440 (91%)  | 46 (9%) |
|                      |       | 46 (19%)     |       |            |     |
|                      |       | 0 (0%)       |       |            |     |
| rs17110566 (IVS6+G152A) | METH  | G/G 123 (76%) | 0.552 | G 281 (87%) | 0.406 |
|                      |       | G/A 35 (22%)  |       | A 43 (13%)  |     |
|                      |       | A/A 4 (2%)    |       |            |     |
|                      | Control| 173 (71%)    |       | 410 (84%)  | 76 (16%) |
|                      |       | 64 (26%)     |       |            |     |
|                      |       | 6 (2%)       |       |            |     |
| rs4760816 (IVS6+C6106T) | METH  | C/C 28 (17%)  | 0.314 | C 141 (44%) | 0.200 |
|                      |       | C/T 85 (52%)  |       | T 183 (56%) |     |
|                      |       | T/T 49 (30%)  |       |            |     |
|                      | Control| 57 (23%)     |       | 235 (48%)  | 251 (52%) |
|                      |       | 121 (50%)    |       |            |     |
|                      |       | 65 (27%)     |       |            |     |
| rs4290270 (Exon9+A57T)  | METH  | A/A 29 (18%)  | 0.840 | A 138 (43%) | 0.777 |
|                      |       | A/T 80 (49%)  |       | T 186 (57%) |     |
|                      |       | T/T 53 (33%)  |       |            |     |
|                      | Control| 49 (20%)     |       | 213 (44%)  | 273 (56%) |
|                      |       | 115 (47%)    |       |            |     |
|                      |       | 79 (33%)     |       |            |     |
| Exon11+(C3)500(C2) | METH  | C3/C3 159 (98%) | 0.357 | C3 321 (99%) | 0.357 |
|                      |       | C3/C2 3 (2%)  |       | C2 3 (1%)   |     |
|                      |       | C2/C2        |       |            |     |
|                      | Control| 242 (100%)   |       | 485 (100%) | 1 (0%) |
|                      |       | 1 (0%)       |       |            |     |
|                      |       | 0 (0%)       |       |            |     |
| rs17110747 (Exon11+G654A) | METH  | G/G 92 (57%)  | 0.956 | G 247 (76%) | 0.888 |
|                      |       | G/A 63 (39%)  |       | A 77 (24%)  |     |
|                      |       | A/A 7 (4%)    |       |            |     |
|                      | Control| 136 (56%)    |       | 367 (76%)  | 119 (24%) |
|                      |       | 95 (39%)     |       |            |     |
|                      |       | 12 (5%)      |       |            |     |
| rs41317114 (IVS11+G128C) | METH  | G/G 119 (73%) | 0.719 | G 276 (85%) | 0.462 |
|                      |       | G/C 38 (23%)  |       | C 48 (15%)  |     |
|                      |       | C/C 5 (3%)    |       |            |     |
|                      | Control| 187 (77%)    |       | 424 (87%)  | 62 (13%) |
|                      |       | 50 (21%)     |       |            |     |
|                      |       | 6 (2%)       |       |            |     |
Table 5. Genotypic Distribution of the TPH2 Gene SNPs in Clinically Subcategorized METH Subjects

| SNP                        | Groups                | Subgroup           | N  | Genotype | P     |
|----------------------------|-----------------------|--------------------|----|----------|-------|
| rs17110566 (IVS6+G152A)   | Control               |                    | 243| G        |       |
|                            |                       |                    |    | G/A      | A     |
|                            | METH                  | Latency of Psychosis | <3 years | 64 | 53  | 10  | 1 | 0.172 |
|                            |                       |                    |    | ≥3 years | 67  | 47  | 18  | 2 | 0.966 |
|                            |                       | Prognosis of Psychosis | Transient (<1 month) | 87 | 67  | 17  | 3 | 0.421 |
|                            |                       |                    |    | Prolonged (≥1 month) | 52  | 38  | 13  | 1 | 0.951 |
|                            |                       | Spontaneous Relapse | Not present | 101 | 78  | 21  | 2 | 0.517 |
|                            |                       |                    |    | Present  | 56  | 42  | 12  | 2 | 0.694 |
| rs4760816 (IVS6+C6106T)   | Control               |                    | 243| C        |       |
|                            |                       |                    |    | C/T      | T     |
|                            | METH                  | Latency of Psychosis | <3 years | 64 | 13  | 35  | 16 | 0.771 |
|                            |                       |                    |    | ≥3 years | 67  | 9   | 35  | 23 | 0.165 |
|                            |                       | Prognosis of Psychosis | Transient (<1 month) | 87 | 15  | 39  | 33 | 0.125 |
|                            |                       |                    |    | Prolonged (≥1 month) | 52  | 7   | 34  | 11 | 0.107 |
|                            |                       | Spontaneous Relapse | Not present | 101 | 19  | 51  | 31 | 0.577 |
|                            |                       |                    |    | Present  | 56  | 8   | 30  | 18 | 0.306 |
| rs4290270 (Exon9+A57T)    | Control               |                    | 243| A        |       |
|                            |                       |                    |    | A/T      | T     |
|                            | METH                  | Latency of Psychosis | <3 years | 64 | 8   | 35  | 21 | 0.338 |
|                            |                       |                    |    | ≥3 years | 67  | 13  | 32  | 22 | 0.990 |
|                            |                       | Prognosis of Psychosis | Transient (<1 month) | 87 | 16  | 37  | 34 | 0.541 |
|                            |                       |                    |    | Prolonged (≥1 month) | 52  | 6   | 34  | 12 | 0.058 |
|                            |                       | Spontaneous Relapse | Not present | 101 | 17  | 52  | 32 | 0.712 |
|                            |                       |                    |    | Present  | 56  | 10  | 27  | 19 | 0.923 |
| rs17110747 (Exon11+G654A) | Control               |                    | 243| G        |       |
|                            |                       |                    |    | G/A      | A     |
|                            | METH                  | Latency of Psychosis | <3 years | 64 | 35  | 28  | 1  | 0.438 |
|                            |                       |                    |    | ≥3 years | 67  | 37  | 26  | 4  | 0.947 |
|                            |                       | Prognosis of Psychosis | Transient (<1 month) | 87 | 52  | 31  | 4  | 0.827 |
|                            |                       |                    |    | Prolonged (≥1 month) | 52  | 26  | 25  | 1  | 0.366 |
|                            |                       | Spontaneous Relapse | Not present | 101 | 57  | 41  | 3  | 0.712 |
|                            |                       |                    |    | Present  | 56  | 32  | 21  | 3  | 0.970 |
| rs41317114 (IVS11+G128C) | Control               |                    | 243| G        |       |
|                            |                       |                    |    | G/C      | C     |
|                            | METH                  | Latency of Psychosis | <3 years | 64 | 49  | 15  | 0  | 0.411 |
|                            |                       |                    |    | ≥3 years | 67  | 48  | 16  | 3  | 0.552 |
|                            |                       | Prognosis of Psychosis | Transient (<1 month) | 87 | 65  | 19  | 3  | 0.852 |
|                            |                       |                    |    | Prolonged (≥1 month) | 52  | 38  | 13  | 1  | 0.767 |
|                            |                       | Spontaneous Relapse | Not present | 101 | 77  | 21  | 3  | 0.966 |
|                            |                       |                    |    | Present  | 56  | 38  | 17  | 1  | 0.282 |

N: Number of samples.
P: Significance values between the METH subjects and the controls.
SNPs were within the Hardy-Weinberg expectations. No significant differences were found in the allelic or genotypic frequencies of these SNPs between the METH dependent-psychotic patients and the controls (Table 4). Since the minor allele frequency of the Exon11+(C3)500(C2) SNP was less than 1% in controls, this SNP was excluded from the haplotype analysis. No significant difference (P=0.448) was observed in a differentiation test between all pairs of samples based on haplotype frequencies by the Arlequin program.

Subcategory analyses were conducted on the clinical parameters (latency of psychosis, prognosis of psychosis, and spontaneous relapse). SNPs having minor allele frequencies of over 10% in both samples were used for this analysis: rs17110566 (IVS6+G152A), rs4760816 (IVS6+C6106T), rs4290270 (Exon9+G57T), rs17110747 (Exon11+G654A), and IVS11+G129C. No significant associations with clinical parameters were observed (Table 5).

**DISCUSSION**

We analyzed the TPH2 gene polymorphisms in a Japanese population and found ten SNPs and two insertion/deletion variants, among which one variant was novel. However, we failed to identify any variants or haplotypes in the TPH2 gene examined in this study which were associated with METH dependence/psychosis.

Exon2+C18A is a nonsynonymous SNP and the corresponding amino acid is changed from Ser to Tyr at peptide position 41 (S41Y). This SNP was reported as C2755A by Lin and colleagues in a Han Chinese population [14]. They transfected plasmids containing full-length TPH2 protein–encoding sequences with two alternative alleles into SH-SY5Y cells and found that the amount of serotonin in SH-SY5Y cells expressing the 41Y allele was about 36% lower than in cells expressing the 41S allele. Despite the strong scientific rationale for studying polymorphisms in the TPH2 gene in METH dependence/psychosis, we could not identify any variants or haplotypes associated with the phenotype. These results were comparable to those for cocaine use. Both cocaine and METH increase extracellular dopamine in the brain, and increased dopamine in the nucleus accumbens is thought to underlie the reinforcing effects of drugs of abuse [5, 33]. The association of cocaine dependence in subjects of African descent with TPH2 SNPs was analyzed by Dahl and colleagues, but they failed to identify any SNPs that were associated with the cocaine-dependent phenotype [34]. The disparity between these results and the previously reported results for heroin addiction [29] suggest that the TPH2 gene has little effect in psychostimulants with the characteristics of indirect dopaminergic agonists.

Our results indicate that the TPH2 gene variations may not be vulnerability factors in METH dependence/psychosis, and indeed that they are likely to make a small or no contribution to the development of METH dependence/psychosis.

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