Haplotype Association of the MAP2K5 Gene with Antipsychotics-Induced Symptoms of Restless Legs Syndrome among Patients with Schizophrenia

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Objective Restless legs syndrome (RLS) is considered a genetic disease and, following a genome-wide association study conducted in 2007, the mitogen-activated protein kinase 5 (MAP2K5) gene has been regarded as the promising candidate gene for RLS. The present study investigated whether polymorphisms of MAP2K5 are associated with antipsychotics-induced RLS in schizophrenia.

Methods We assessed antipsychotics-induced RLS symptoms in 190 Korean schizophrenic patients using the diagnostic criteria of the International Restless Legs Syndrome Study Group. Five single-nucleotide polymorphisms (SNPs) of MAP2K5 were genotyped. We investigated genetic and haplotypic associations of these five SNPs with the risk of antipsychotics-induced RLS symptoms.

Results We divided the 190 subjects into 2 groups: 1) those with RLS symptoms (n=96) and 2) those without RLS symptoms (n=94). There were no significant intergroup differences in the distributions of the genotypes and alleles of the rs1026732, rs11635424, rs12593813, rs4489954, and rs3784709 SNPs. However, the haplotype analysis showed that the G-G-G-G-T (rs1026732-rs11635424-rs12593813-rs4489954-rs3784709) haplotype was associated with RLS symptoms (permutation p=0.033).

Conclusion These data suggest that a haplotype of MAP2K5 polymorphisms confers increased susceptibility to antipsychotics-induced RLS symptoms in schizophrenic patients.

Psychiatry Investig 2018;15(1):84-89

Key Words Restless legs syndrome, Antipsychotics, Schizophrenia, MAP2K5, Polymorphism, Haplotype.

INTRODUCTION

Restless legs syndrome (RLS) is a sleep disorder whose prevalence varies depending on the populations analyzed and methods applied. However, it is generally reported that 2–3% of the population suffers from RLS, which indicates the importance of appropriate treatment.¹ Typical clinical manifestations of RLS include uncomfortable sensations in the legs and irresistible urges to move the legs, and these symptoms aggravate or start at night and are temporarily relieved by leg movements.

Many etiologies have been reported for RLS, and they can be classified into idiopathic and secondary RLS. Secondary RLS is attributable to factors such as iron deficiency, renal failure, pregnancy, neuropathy, and certain medications, especially those involving the dopamine receptor.² Antipsychotics are common causes of secondary RLS, and it was previously found that the incidence of RLS was twofold higher in schizophrenia patients than in healthy controls, which is probably attributable to the use of antipsychotics.³,⁴ The pathophysiology of idiopathic RLS has not been fully explained before. However, it is known that genetic factors and central dopaminergic dysfunction are important causes of idiopathic RLS. Approximately half of RLS patients are known to have a family history of RLS,⁵ and nine genetic loci (2q, 4q, 9p, 12q, 14q, 16p, 17p, 19p, and 20p) for RLS have been reported based on linkage analysis.⁶-¹² In addition, two independent genome-wide association studies (GWASs) found new candidate genes such as the mitogen-activated protein kinase
Subjects. have been reported previously, prevented participation in an interview. The characteristics similar to RLS symptoms (e.g., anemia, renal failure, or peripheral neuropathy), or 3) severe psychosis or agitation that prevented participation in an interview. The characteristics of schizophrenia patients with antipsychotics-induced RLS have been reported previously, as have other findings for such subjects.

Assessment of RLS

RLS was assessed by a board-certified psychiatrist based on the diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG).

DNA analysis and genotyping

We selected the following five SNPs of MAP2K5 as candidate genes in this study: rs1026732, rs11635424, rs12593813, rs4489954, and rs3784709. These constituted five of the six SNPs that have shown significant associations in previous GWASs.

Statistical analysis

Conformity with Hardy-Weinberg equilibrium (HWE) was tested based on the $\chi^2$ test for goodness of fit; this test was also used to analyze categorical data. These statistical analyses were performed using SPSS for Windows. The cutoff for statistical significance was set at $p<0.05$; however, after applying the Bonferroni correction, the cutoff was set at $p<0.01$ in Tables 1 and 2 (since five
SNPs were genotyped in this study). The linkage disequilibrium (LD) and haplotype analyses between the RLS-symptoms group and no-RLS-symptoms group were conducted using SNPAlyze (version 7, DYNACOM, Chiba, Japan), which was established based on the expectation-maximization algorithm and the maximum-likelihood approach.

**RESULTS**

**Demographic and clinical characteristics of participants**

The participants were aged 39.6±9.2 years (mean±SD, range 22–66 years) and they comprised 106 (55.8%) males and 84 (44.2%) females. All participants were diagnosed as schizophrenia and 44 (23.2%) of them met the IRLSSG diagnostic criteria. The participants were classified into a group with core RLS symptoms (n=96, 50.5%) and another without core RLS symptoms (n=94, 49.5%). Since the RLS symptoms are similar to those of akathisia, 16 RLS patients could also be diagnosed as having akathisia based on the BARS. We did not exclude them from the RLS group only because they met the diagnostic criteria of akathisia. That is the reason that the antipsychotics-induced RLS and akathisia could be comorbid with each other and might share the common pathogenesis. We concluded that excluding such subjects just because they met the diagnostic criteria of akathisia could result in another bias.

The number of subjects taking one, two, and three antipsychotics was 121, 63, and 6, respectively. The five medications most frequently used as main neuroleptics were risperidone, clozapine, haloperidol, sulpiride, and olanzapine (in the order of the frequency). The range of the chlorpromazine equivalent of antipsychotics was 100 to 3400 mg/day and the mean ± standard deviation of chlorpromazine equivalent was 524.3±451.0 mg/day.

The genotype frequencies did not deviate from HWE for all six SNPs: rs102673 (χ²=0.428, p=0.5131), rs11635424 (χ²=0.268, p=0.6049), rs12593813 (χ²=0.477, p=0.4899), rs4489954 (χ²=0.177, p=0.6742), and rs3784709 (χ²=0.547, p=0.4594). The genotype frequency in the additive models did not show any statistically significant difference in the five SNPs: rs1026732 (χ²=2.158, p=0.0340), rs11635424 (χ²=2.100, p=0.350), rs12593813 (χ²=2.659, p=0.265), rs4489954 (χ²=1.579, p=0.454), and rs3784709 (χ²=1.265, p=0.531) (Table 1). There was also no

| SNP       | Genotype frequency | Genotype association analysis |
|-----------|--------------------|------------------------------|
|           | RLS symptoms (N=96) | No RLS symptom (N=94)         |
| rs1026732 | AA 50 (53.2%)       | 40 (43.0%)                   |
|           | AG 34 (36.2%)       | 43 (46.2%)                   |
|           | GG 10 (10.6%)       | 10 (10.8%)                   |
|           | Dominant            | Heterozygous                 |
|           | 1.956               | 0.66 (0.37–1.18)             |
| rs11635424| AA 42 (44.2%)       | 32 (34.8%)                   |
|           | AG 38 (40.0%)       | 46 (50.0%)                   |
|           | GG 15 (15.8%)       | 14 (15.2%)                   |
|           | Dominant            | Heterozygous                 |
|           | 1.889               | 0.67 (0.37–1.19)             |
| rs12593813| AA 41 (45.1%)       | 31 (35.6%)                   |
|           | AG 35 (38.5%)       | 44 (50.6%)                   |
|           | GG 15 (16.5%)       | 12 (13.8%)                   |
|           | Dominant            | Heterozygous                 |
|           | 1.737               | 0.67 (0.37–1.21)             |
| rs4489954 | GG 10 (10.6%)       | 9 (9.7%)                     |
|           | GT 35 (37.2%)       | 43 (46.2%)                   |
|           | TT 49 (52.1%)       | 41 (44.1%)                   |
|           | Dominant            | Heterozygous                 |
|           | 1.558               | 0.69 (0.39–1.24)             |
| rs3784709 | CC 14 (14.9%)       | 9 (9.8%)                     |
|           | CT 39 (41.5%)       | 38 (41.3%)                   |
|           | TT 41 (43.6%)       | 45 (48.9%)                   |
|           | Dominant            | Heterozygous                 |
|           | 1.121               | 0.62 (0.25–1.51)             |

RLS: restless legs syndrome, SNPs: single-nucleotide polymorphisms, MAP2K5: mitogen-activated protein kinase 5, OR: odds ratio, CI: confidence interval
statistically significant difference in dominant, recessive, and heterozygous models (Table 1). The allele frequencies of the five SNPs did not differ significantly between the two groups: rs1026732 ($\chi^2=1.152, p=0.283$), rs11635424 ($\chi^2=0.778, p=0.378$), rs12593813 ($\chi^2=0.548, p=0.459$), and rs3784709 ($\chi^2=1.138, p=0.286$) (Table 2).

Haplotype and LD analyses

The haplotype analysis (Table 3) revealed that the G-G-G-G-T (rs1026732-rs11635424-rs12593813-rs4489954-rs3784709) haplotype was associated with RLS symptoms (permutation $p=0.033$). The G-A-A-T-C haplotype was also associated with RLS symptoms (permutation $p<0.001$), but this is not included in Table 3 since it is not a common haplotype (i.e., frequency <5%). The pairwise LD values including the $D'$, $r^2$, and $p$ values for consecutive SNPs are listed in Table 4.

**DISCUSSION**

Up to 80% of the schizophrenia patients experience sleep problems and many of them suffer from RLS, which impairs their physical and mental health. Our previous study revealed that inpatient schizophrenia patients showed that the frequency of RLS was double in the schizophrenia group (21.4%) compared to healthy controls (9.3%) and RLS symptoms was associated with more severe insomnia and psychiatric symptoms. Since the antipsychotic-induced RLS in schizophrenia is considered as being more common and clinically important than before, we believe that the pharmacogenetic study on promising candidate genes in this topic has clinical and scientific merits.

This study found no significant associations between 1) the genotypes and alleles of the rs1026732, rs11635424, rs12593813, rs4489954, and rs3784709 SNPs of MAP2K5 and 2) antipsychotics-induced RLS symptoms. However, the haplotype anal-

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**Table 2.** Results of an allele association analysis between RLS symptoms in schizophrenia and five SNPs of MAP2K5

| SNP        | MAF (RLS symptoms) | MAF (no RLS symptoms) | Risk allele | Allele association analysis |
|------------|--------------------|-----------------------|-------------|-----------------------------|
| rs1026732  | 0.287              | 0.339                 | N/A         | $\chi^2=1.152, p=0.283$     |
| rs11635424 | 0.358              | 0.402                 | N/A         | $\chi^2=0.778, p=0.378$     |
| rs12593813 | 0.357              | 0.391                 | N/A         | $\chi^2=0.431, p=0.512$     |
| rs4489954  | 0.293              | 0.328                 | N/A         | $\chi^2=0.548, p=0.459$     |
| rs3784709  | 0.356              | 0.304                 | N/A         | $\chi^2=1.138, p=0.286$     |

MAF: minor allele frequency, N/A: not applicable, RLS: restless legs syndrome, SNPs: single-nucleotide polymorphisms, MAP2K5: mitogen-activated protein kinase 5, OR: odds ratio, CI: confidence interval

**Table 3.** Estimated haplotype frequencies of MAP2K5 rs1026732-rs11635424-rs12593813-rs4489954-rs3784709 and the association significance

| Haplotype (rs1026732-rs11635424-rs12593813-rs4489954-rs3784709) | Overall permutation $p$ | Haplotype frequencies | Permutation $p$ |
|---------------------------------------------------------------|-------------------------|-----------------------|---------------|
| A-A-A-T-T                                                      | 0.581                   | 0.4890                | 0.670         |
| G-G-G-G-C                                                      | 0.1726                  | 0.1920                | 0.1521        |
| G-G-G-G-T                                                      | 0.1310                  | 0.0936                | 0.1698        |
| A-A-A-T-C                                                      | 0.1270                  | 0.1188                | 0.1365        |

Only common haplotypes (frequency >5%) are listed. *significant $p$ value ($p<0.05$)

**Table 4.** Linkage disequilibrium coefficients ($D'$ and $r^2$) and $p$ values among the MAP2K5 polymorphisms

| $D'$, $r^2$, $p$ value | rs1026732 | rs11635424 | rs12593813 | rs4489954 | rs3784709 |
|------------------------|-----------|------------|------------|-----------|-----------|
| rs1026732              | -         | 0.6673, 5.139x10^-56 | 0.6804, 1.11x10^-54 | 0.9874, 5.21x10^-51 | 0.0825, 3.49x10^-8 |
| rs11635424             | 0.9545    | -          | 1.2092x10^-79 | 0.686, 4.269x10^-57 | 0.0818, 5.04x10^-8 |
| rs12593813             | 0.953     | 1          | -          | 0.6941, 6.395x10^-56 | 0.1039, 1.65x10^-9 |
| rs4489954              | 1         | 0.9693     | 0.9868     | -         | 0.0883, 6.00x10^-9 |
| rs3784709              | 0.3       | 0.3128     | 0.3561     | 0.3067    | -         |

MAP2K5: mitogen-activated protein kinase 5
yasis showed that a haplotype of the MAP2K5 polymorphisms confers increased susceptibility to antipsychotics-induced RLS symptoms in schizophrenic patients. The rs1026732-rs11635424-rs12593813-rs4489954-rs3784709 haplotype analysis showed a significant association of G-G-G-G-T and G-A-A-T-C with a low risk of developing antipsychotics-induced RLS symptoms. To the best of our knowledge, this is the first report of positive findings in a haplotype analysis of MAP2K5 with RLS; note that previous studies of MEIS1 have also shown positive findings in haplotype analyses.14,15

Schizophrenia patients frequently suffer from side effects of neuroleptic-induced RLS, but the pathophysiology is not fully understood. Nevertheless, we assumed that the etiology of neuroleptic-induced RLS could be similar to that of idiopathic RLS. Since idiopathic RLS has shown novel and strongly significant findings in GWASs and replication studies,14,34,35 we aimed to replicate in our sample the significant association of MAP2K5, a promising candidate gene, with antipsychotics-induced RLS symptoms.

MAP2K5 is a dual specificity protein kinase that belongs to the MAP kinase family and activates MAPK7/extracellular-signal-regulated kinase 5 (ERK5), interacting therewith.40 MAP2K5 and ERK5 are expressed abundantly in heart and skeletal muscles, and the MAP2K5/ERK5 MAP kinase cascade is critical at the early stage of muscle cell differentiation and is known to be important in the neuroprotection of dopaminergic neurons.14,37,38 Impairment of the dopamine system is believed to be one of the important etiologies of RLS, and dopaminergic D2/D3 agonists have been used as treatments of idiopathic RLS.41 In addition, MAP kinases regulate LBX1 and, since LBX1 is expressed in a subset of dorsal horn interneurons of the developing spinal cord, MAP kinases are likely to be involved in the modulation of pain and sensory inputs.42

Winkelman et al.14 conducted a GWAS of 500,568 SNPs using an Affymetrix 500K array set and reported in 2007 that SNPs of MAP2K5 are closely associated with RLS. However, some subsequent replication studies of MAP2K5 have resulted in different conclusions. Yang et al.35 performed a family-based and population-based case-control study involving a US population, and selected only the rs1026732 polymorphism, which had been found to have the most significant association with RLS in the previous GWAS. Winkelman et al.41 also performed an enlarged GWAS involving 922 RLS patients and 1,526 control cases, and conducted a replication study with independent case-control samples in order to confirm the previous research and identify risk loci, and reported a significant result for the rs1259813 SNP of MAP2K5. Another study involving 244 RLS patients (including 123 patients with a family history) and a control group of 497 subjects examined 11 candidate SNPs, and found no association in MAP2K5 and an insignificant trend in rs6494696 (p=0.05) in familial RLS patients.42 The patients in that study with a family history showed a stronger association than sporadic RLS patients in cases of MEIS1 and BTBD9, which was attributed to environmental and genetic factors in sporadic RLS.42 A recent Korean replication study of idiopathic RLS also found no significant relationship.43 These diverse research results may have due to differences in the method used to diagnose RLS and thus differences in RLS phenotypes40 and racial differences in genotype and allele frequencies. Racial differences are important in MAP2K5, since RLS-associated alleles are significantly less frequent in Asians40 and the minor allele of the European ancestry is opposite to that of Asians (Chinese and Japanese) in rs1026732 (refer to dbSNP: http://www.ncbi.nlm.nih.gov/projects/SNP/). In addition, the present study may have been affected by many factors other than genetic ones since it adopted antipsychotics-induced RLS as its phenotype.

This study had several limitations. First, the sample was relatively small for investigating genetic associations, especially considering current genetic research trends. Second, various types of antipsychotics were taken by the subjects. It will be necessary to perform a similar study of subjects taking identical or consistent antipsychotics in order to fully understand the association between promising candidate genes such as MAP2K5 and antipsychotics-induced RLS. Moreover, future studies are also needed to evaluate the association between RLS and other candidate genes for primary RLS such as GLO1 and DNAH8. Such studies will provide a better understanding of the etiologies of antipsychotics-induced and idiopathic RLS, and also help clinicians to select the safest antipsychotics for different patients.

Acknowledgments

This study was supported by the Otsuka schizophrenia research fund for the young investigator of the Korean Society for Schizophrenia Research.

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