The Relationship between the SNAP-25 Polymorphism and Omission Errors in Korean Children with Attention Deficit Hyperactivity Disorder

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Objective: This study aimed to investigate the association between the synaptosomal-associated protein 25 kDa (SNAP-25) genotype and performance on the continuous performance test (CPT) in Korean children with attention–deficit/hyperactivity disorder (ADHD).

Methods: Eighty-seven children with ADHD (mean age, 9.23±1.99 years) participated in this study. Omission errors, commission errors, reaction time, and reaction time variability on the CPT were analyzed. The single-nucleotide polymorphism (SNP) rs3746544 (1065 T>G) of SNAP-25 was genotyped to examine the association with CPT performance.

Results: We found significantly more omission errors on the CPT among children with the TT genotype of SNAP-25 (t=2.56, p=0.012) after correcting for multiple testing.

Conclusion: Our results suggest the possible involvement of the SNAP-25 1065 T>G polymorphism in the inattention phenotype in children with ADHD. Further studies with more refined neuropsychological measures and much larger sample sizes are needed to confirm our findings.

KEY WORDS: Attention deficit disorder with hyperactivity; SNAP-25; Continuous performance test; Omission errors.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD), which is characterized primarily by symptoms of inattention, impulsivity, and hyperactivity, is the most common neurodevelopmental disorder of childhood.¹ ADHD is a complex, polygenic disorder with a heritability estimated at approximately 80%.¹ Previous genetic studies have indicated that the complex interplay of genes related to dopamine and norepinephrine regulation in the brain may be involved in the etiology of ADHD,² but the results of these studies are variable and inconsistent. One reason for the inconsistency in results is the phenotypic heterogeneity of the disorder. Several studies have measured ADHD symptoms using symptom rating scales that rely on reports by parents and teachers. The current Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) and International Statistical Classification of Diseases, 10th revision (ICD-10) criteria for the diagnosis of ADHD is based on the number of inattention and/or hyperactivity/impulsivity symptoms rather than the underlying pathophysiology. Prior studies have found that reports by parents and teachers tend to be subjective, and therefore there is a need for more objective assessments of ADHD symptoms.³ Thus, it would be highly desirable to investigate other endophenotypes that rely on objectively measured data, such as neuropsychological assessments.⁴-⁶ Under this background, the impairment of the executive attentional system or working memory,⁷ inattentiveness,³ and response inhibition deficits⁸ have been suggested as cognitive endophenotypes suitable for ADHD research.⁹ The continuous performance test (CPT)¹⁰ is one of the most frequently used measures to evaluate sustained attention, which represents the ability to maintain a tonic state of alertness over an extended period of time.¹¹ On the CPT, participants are required to detect a rare target among rapidly presented non-targets for 10 to 30 minutes. From the CPT, the number of omission errors (i.e., failing
to respond to a target), commission errors (i.e., responding to a non-target), reaction time, and reaction time variability are computed. According to a recent meta-analysis, the CPT has the largest effect size for the diagnosis of ADHD, and has been considered to be a promising endophenotype for ADHD research.

To date, prior studies on the genetic basis of CPT performance have focused on dopaminergic genes such as the dopamine D4 receptor gene (DRD4), the dopamine D5 receptor gene, and the dopamine transporter gene (DAT1), and norepinephrine transporter (NET) genes, such as G1287A genotype of the NET gene in Korean children with ADHD. Recently, genes other than those of the major catecholamine systems are gaining attention as candidate genes for ADHD. Among these candidate genes, synaptosomal-associated protein 25 (SNAP-25) is encoded by the SNAP-25 gene, which is located on chromosome 20p 11.2. SNAP-25 plays an essential role in the vesicle docking and fusion machinery, mediating the release of major neurotransmitters from the presynaptic membrane into the synaptic cleft. In addition, SNAP-25 is implicated in axonal growth and synaptic plasticity.

Polymorphisms in the SNAP-25 gene of both animal models and humans have been investigated, and the association of SNAP-25 with ADHD has been confirmed in many linkage studies. These findings have also been supported by a meta-analysis. In animal studies, the deletion of SNAP-25 in the coloboma mouse leads to 50% lower SNAP-25 mRNA and protein expression compared to wild-type mice, causing hyperactivity symptoms in this mouse strain. This finding suggests that the gene encoding SNAP-25 might be responsible for hyperkinetic behavior. In addition, normal dopaminergic transmission was restored by the transgenic rescue of SNAP-25 function. The presumed mechanism underlying the hyperactivity of these mice seems to be the possible dysregulation of the release of neurotransmitters in some brain regions. In particular, glutamate content and release as well as the utilization of dopamine in the neocortex is reduced, whereas norepinephrine concentration within the striatal structures is increased.

Among the different polymorphisms identified for the SNAP-25 gene, the 1065 T > G single-nucleotide polymorphism (SNP) has received the most attention in prior studies of ADHD. For example, in a Korean case-controlled association study by Choi et al., the TG genotype of the 1065 T > G SNP was associated with ADHD. In addition, it was reported in a meta-analysis that the T allele of the 1065 T > G SNP is significantly associated with ADHD (odds ratio, 1.19; 95% confidence interval, 1.03-1.38). It was also reported in Mill et al. that the TT haplotype was disproportionally transmitted to ADHD offspring (p = 0.01).

However, there is sparse data in the existing literature regarding the association between SNAP-25 genotypes and neuropsychological test performance. Therefore, more studies are necessary to delineate the roles of the SNAP-25 gene in the genetic basis of the common cognitive endophenotypes of ADHD. The aim of the present study was to evaluate the association between SNAP-25 genotypes and inattentiveness symptoms as measured by the CPT in Korean children and adolescents with ADHD.

METHODS

Participants
Eighty-seven children with ADHD were recruited from the outpatient child and adolescent clinic in a university hospital in South Korea. The inclusion criteria were: (1) ADHD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria; (2) aged 6-15 years old; and (3) no history of psychostimulant or other psychiatric drug use. ADHD subjects with comorbid disorders, such as depressive disorder, anxiety disorder, tics or Tourette’s syndrome, oppositional defiant disorder, or conduct disorder were also included. The exclusion criteria were: (1) an intelligence quotient (IQ) score below 70; (2) past or current neurological disease; and (3) a diagnosis of autism spectrum disorder, learning disorder, or any psychotic spectrum disorder, including bipolar disorder. This study was approved by the Institutional Review Board of Yonsei University College of Medicine (No. 4-2011-0919), and informed consent or assent was obtained from the participants and their parents or guardians.

Diagnostic Procedures and Clinical Symptoms Assessment
The diagnosis of ADHD and comorbid disorders was established using the Korean Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL). Intellectual abilities were assessed using the Korean version of the Wechsler Intelligence Scale for Children-third edition (K-WISC-III). The severity of ADHD symptoms was assessed by the Korean
ADHD Rating Scale-IV, which was completed by both parents and teachers.

Neuropsychological Assessments: Continuous Performance Test

The Korean version of the computer-based CPT, which has been named the ADHD Diagnostic System, was administered to participants to measure neuropsychological function. On the CPT, target and non-target visual stimuli are rapidly presented at regular intervals on a computer screen, and the subject must respond as quickly as possible to target stimuli only. All the results from the CPT were automatically scored. The test duration was 10 minutes for children aged 6 to 7 years old and 15 minutes for children older than 7 years old. Subjects were measured on four indices: 1) the number of omission errors (i.e., failure to respond to a target), as an indicator of inattention; 2) the number of commission errors (i.e., response to a non-target), as an indicator of hyperactivity or impulsivity; 3) reaction time (i.e., response times for correct responses to target stimuli), as an indicator of processing speed; and 4) reaction time variability (i.e., the standard deviation [SD] of reaction time). The raw data from the four outcome variables were converted to age-adjusted T-scores, which are scaled to a mean of 50 and a SD of 10. The percentage of correct classifications on the Korean version of the computer-based CPT is 96.7% and its reliability is 0.85.

SNAP–25 (rs) Genotyping

Genomic DNA was extracted from blood lymphocytes using a genomic DNA extraction kit (Bioneer, Daejon, Korea) according to the manufacturer’s protocol. SNP identification was based on an analysis of primer extension products obtained from previously amplified genomic deoxyribonucleic acid (DNA) using a chip-based Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) mass spectrometry platform (Sequenom, Inc., San Diego, CA, USA). The procedures were performed according to the manufacturer’s standard protocol.

Oligonucleotide primers (5'- ACG TTG GAT GTT TTC CAG GTG TGA CAA CGG and 5'- ACG TTG GAT GAC CCA GCG GAT GGT GGA TTT) were used to generate polymerase chain reaction (PCR) products. Amplification of the PCR reaction was performed in a volume of 5 μL containing 1X PCR buffer (TAKARA, Shiga, Japan), 2.5 mmol/L magnesium chloride, 0.2 mmol/L each of deoxyribonucleotide triphosphate, 0.1 U HotStar Taq Polymerase (Quiagen GmbH, Hilden, Germany), 8 pmol/L of each primer, and 4.0 ng of genomic DNA. The PCR reaction consisted of denaturation at 95°C for 15 minutes followed by 45 cycles of 95°C for 20 seconds, 56°C for 30 seconds, and 72°C for 1 minutes, with a final extension at 72°C for 3 minutes.

Statistical Analyses

Descriptive statistics were obtained to evaluate the demographic and clinical characteristics of the participants. Group differences in continuous demographic and clinical variables were computed using independent two-sample t-tests. Between-group comparisons on categorical variables were assessed using the χ² test or Fisher’s exact test. The allele frequency was determined, and the Hardy-Weinberg equilibrium was calculated using a goodness-of-fit χ² test. Due to the small number of participants with the SNAP–25 GG genotype, the sample was divided according to whether the rare G allele was present or not. To investigate the association between the SNAP–25 genotype and performance on the CPT, we used the SNAP–25 genotype (TT versus TG or GG) as the main predictor. Independent t-tests were used to compare the differences in the CPT measures by genotype. All statistical analyses were performed using the IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). The level of significance was set at p=0.05 (two-tailed).

RESULTS

Demographic and Clinical Characteristics

Of the 87 children with ADHD initially enrolled, 72 were boys (82.8%), and the mean age of the ADHD subjects was 9.23 years old (SD, 1.99). Thirty-nine subjects (44.8%) were diagnosed with the ADHD combined type, 40 (46.0%) with the ADHD inattentive type, and 8 (9.2%) with the ADHD hyperactive/impulsive type. The average total score on the ADHD symptom rating scale as measured by the parents was 32.19 (SD, 8.01). Table 1 reports the demographic and clinical characteristics of the participants according to their SNAP–25 genotype. We found no significant between-group differences in age, sex, IQ, comorbidity, or baseline ADHD-rating scale scores.

SNAP–25 Genetic Polymorphisms

Genotype analysis of the SNAP–25 polymorphism identified the TT genotype in 52 subjects (59.8%), the TG genotype in 31 subjects (35.6%), and the GG genotype in the remaining 4 subjects (4.6%). The genotype distribution of
Table 1. Comparison of demographic and clinical characteristics according to the SNAP-25 genotype in Korean children with ADHD

| Characteristic          | Total (n=87) | T/T (n=52) | T/G+G/G (n=35) | p value |
|-------------------------|--------------|------------|----------------|---------|
| Age (yr)                | 9.23±1.99    | 9.35±2.18  | 9.06±1.70      | 0.510   |
| Male                    | 72 (81.8)    | 44 (84.6)  | 28 (80.0)      | 0.578*  |
| FSIQ                    | 104.79±16.25 | 103.81±16.73| 106.26±15.62  | 0.575†  |
| ADHD subtype            |              |            |                |         |
| Combined                | 39 (44.3)    | 2 (35.7)   | 16 (45.7)      |         |
| Inattentive             | 40 (45.5)    | 24 (46.2)  | 16 (45.7)      | 0.982*  |
| Hyperactive/Impulsive   | 8 (9.2)      | 5 (9.6)    | 3 (8.6)        |         |
| Comorbidity             |              |            |                |         |
| Conduct disorder        | 2 (2.3)      | 1 (1.4)    | 1 (2.3)        | 1.000*  |
| ODD                     | 2 (2.3)      | 2 (3.8)    | 0 (0)          | 0.354*  |
| Depressive disorder     | 18 (20.4)    | 9 (17.3)   | 9 (25.7)       | 0.382*  |
| Anxiety disorder        | 10 (11.3)    | 7 (12.8)   | 3 (8.6)        | 0.252*  |
| Tics or Tourette’s syndrome | 8 (9.1) | 2 (3.8)    | 6 (11.4)       | 0.747*  |
| ARS baseline scores     |              |            |                |         |
| Total                   | 32.19±8.01   | 32.00±8.01 | 32.66±7.86     | 0.706†  |
| Inattentive             | 16.84±4.11   | 16.31±4.15 | 16.34±3.95     | 0.143†  |
| Hyperactive/Impulsive   | 15.42±6.37   | 15.69±6.87 | 15.03±5.61     | 0.636†  |

Values are presented as mean±standard deviation or number (%). ADHD, attention-deficit/hyperactivity disorder; FSIQ, full scale intelligence quotient; ODD, oppositional defiant disorder; MPH, methylphenidate; ARS, ADHD Rating Scale.

*Calculated by a one-way analysis of variance test. †Calculated by χ² test or Fisher’s exact test.

Table 2. Comparison of four performance measures on the CPT according to the SNAP-25 1065 T>G genotype

| CPT performance measure | 1065 T>G genotypes of SNAP 25 (mean±SD) | t | p value |
|-------------------------|----------------------------------------|---|---------|
|                         | T/T (n=52)                             | T/G+G/G (n=35) |             |         |
| Omission errors         | 66.90±37.62                            | 50.31±18.80    | 2.558       | 0.012   |
| Commission errors       | 72.77±37.24                            | 61.37±22.89    | 1.615       | 0.110   |
| Reaction time           | 54.77±16.40                            | 54.49±13.29    | 0.085       | 0.932   |
| Reaction time variability| 69.94±27.59                            | 64.60±20.85    | 0.973       | 0.333   |

CPT, continuous performance test.
The results of the χ² test are reported. The significance level was set to p<0.05.

The SNAP-25 polymorphisms were in agreement with the expected values of the Hardy-Weinberg equilibrium (p>0.05), and were similar to the previously reported reference values in a Korean ADHD population (56.8% for TT, 36.7% for TG, and 6.5% for GG) (Table 1).37)

Comparison of CPT Performance Across Genotypes
As shown in Table 2, we found a significant difference in omission errors on the visual CPT between the TT and TG+GG genotype groups (t=2.558, p=0.012). Children with ADHD possessing the TT genotype made more omission errors than those with either the TG or GG genotypes; this association remained significant after correcting for multiple test sessions (corrected p value=0.05/4 subtests=0.0125). No significant differences were found in other CPT measures between the two genotype groups (Table 2).

DISCUSSION

We found a significant association between the SNAP-25 1065 T>G genotype and omission errors on the CPT among Korean children with ADHD. Children with ADHD having the TT genotype made more omission errors on the visual CPT compared to those with the TG or GG genotype. Omission errors on the CPT are interpreted as a measure of inattention, and have been proposed as a putative endophenotype to index genetic variability in ADHD.4) Our results suggest that variations in the inattention phenotype may be related to genetic variations in the SNAP-25 gene. The association between the SNAP-25 genotype and neuropsychological measures of executive functioning, such as performance on the CPT, is consistent with prior studies that have reported a link between SNAP-25 and deficient learning and information processing in the coloboma mouse.38) These learning processes in the mouse are
somewhat similar to attention processes in humans.\textsuperscript{38} In addition to results from animal studies, previous studies in humans have found an association between \textit{SNAP-25} genotypes and cognitive variables in other neuropsychiatric disorders with impaired executive function. Specifically, an association has been found between cognitive dysfunction and the DdeI polymorphism of the \textit{SNAP-25} gene among Caucasian patients with schizophrenia who were undergoing treatment with atypical antipsychotics.\textsuperscript{39} In addition, the rs363050 SNP of \textit{SNAP-25} has been associated with low cognitive scores in autistic children.\textsuperscript{40} Recent studies have also suggested the possible involvement of \textit{SNAP-25} in learning, memory, and intelligence in normal healthy control participants.\textsuperscript{41}

However, research on the relationship between \textit{SNAP-25} polymorphisms and cognitive variables among ADHD patients is scarce in the existing literature. Most significant associations between genotypes and CPT measures that have been reported in the literature involve genes for the catecholamine system. For example, one study has reported an association between the 4-repeat allele of the \textit{DRD4} gene and fewer commission errors and less reaction time variability on the CPT.\textsuperscript{15} In another study, Korean ADHD subjects with the T allele of the –3081 polymorphism of the \textit{NET} gene exhibited a trend toward more reaction time variability on the CPT than those with the A/A genotype, whereas no differences were found between two groups with different G1287A polymorphisms.\textsuperscript{42}

There is some evidence in the literature that the \textit{SNAP-25} genotype is associated with either ADHD or treatment response in patients with ADHD. According to the study by Choi et al.,\textsuperscript{29} there was a significant difference between ADHD cases and controls for the 1065 polymorphism (MnlI polymorphism; rs3746544) (\(\chi^2 = 9.57, \) degree of freedom=2, \(p=0.008\)); there was a higher frequency of homozygotes (i.e., TT and GG) among ADHD subjects and a higher frequency of heterozygotes (TG) among control subjects.\textsuperscript{29} This result is partially consistent with our results, in that subjects with the TT genotype had more omission errors on the CPT than those with the TG or GG genotypes. When we consider more omission errors as an ADHD trait, the homozygous TT genotype seems to exert a greater effect for the ADHD trait. One possible explanation for this phenomenon is that homozygotes produce too much (i.e., over-expression) or too little (i.e., under-expression) protein for optimal biological activity, thereby disrupting neural function.\textsuperscript{28} In contrast, the G genotype may have a protective role against the development of an ADHD trait, because heterozygotes may produce just the right amount of protein for normal neural function.\textsuperscript{43}

Currently, the functional significance of the \textit{SNAP-25} 1065 T \textgreater{} G polymorphism is unknown. However, it is assumed that this polymorphism does not influence the encoding of protein variants or \textit{SNAP-25} expression directly, because this SNP is located in the 3’ untranslated region of the \textit{SNAP-25} genes.\textsuperscript{23} Based on the results of the current study, the 1065 T \textgreater{} G polymorphism may modulate the expression of \textit{SNAP-25}. The association found in this study may also indicate a linkage disequilibrium with a functionally relevant variation in the coding or regulatory region of \textit{SNAP-25}. In addition, there exists the possibility that this SNP represents an important site for mRNA stability and translational efficiency.\textsuperscript{44} Taken together, it is plausible that the 1065 T \textgreater{} G polymorphism plays a role in the expression and regulation of the \textit{SNAP-25} gene, and may enhance susceptibility to ADHD.

Other studies have reported that the \textit{SNAP-25} gene modifies the release of neurotransmitters.\textsuperscript{31} There is some evidence that genetic variation may lead to lower levels of \textit{SNAP-25} through transcriptional regulation, which would ultimately lead to the decreased exocytosis of several neurotransmitters, including dopamine.\textsuperscript{45} In our study, individuals with the TT allele presumably have relatively fewer available synaptic catecholamine neurotransmitters, and thus perform more poorly on neuropsychological measures of executive function than do individuals with the TG or GG allele.

In this study, the \textit{SNAP-25} polymorphism was only associated with omission errors, but not with other measures of the CPT, such as commission error or response time variability. It is possible that different genes may be implicated in different intermediate phenotypes, and our results suggest that \textit{SNAP-25} variants may be closely linked to the intermediate phenotype of inattention. The findings from our study are in contrast to what might be expected from the coloboma mouse model, in which it would be hypothesized that the \textit{SNAP-25} polymorphism contributes to the hyperactivity phenotype. However, inattention, which is a hallmark characteristic of ADHD in humans, cannot be directly examined in the coloboma mouse model. The investigation of cognitive phenotypes is therefore a significant limitation of ADHD animal models.\textsuperscript{46} Further studies are needed to explore the relationship between the \textit{SNAP-25} genotype and ADHD behavioral phenotypes in both animal models and humans.

There were several limitations to our study. First, our sample size was small, which limits the statistical power to
detect significant group differences. Further studies using a larger sample size are necessary to replicate our findings. Second, we did not compare SNAP-25 polymorphisms in subjects with ADHD and those in control subjects. Although the frequency of SNAP-25 polymorphisms in our study was similar to those reported in previous studies with Korean ADHD and control subjects, lack of control group presents some methodological limitations, and our results should be interpreted with caution. Third, incomplete genetic coverage is another limitation. In our study, only one well-known polymorphism, rs3746544 (1065 T > G) of SNAP-25, in previous studies of childhood ADHD has been examined, but it is unlikely that only one polymorphism influences inattention phenotype as measured by the CPT. Accordingly, it is possible that our results may be affected by other risk mutations of SNAP-25. Therefore, our findings need to be confirmed by further large-scale studies using tagged SNPs, which cover the entire gene region of SNAP-25, in a more comprehensive gene set. Fourth, demographic and clinical variables that may affect CPT results, such as age, IQ, and comorbidities were not controlled in this study. However, clinical variables are not likely to have affected our results, because these variables were not significantly different between the SNAP-25 genotype groups. Fifth, the use of the CPT as a clinical test for ADHD is controversial. The inattention phenotype observed in subjects with ADHD is a complex phenomenon involving several brain areas. In contrast, the CPT involves simple visual stimuli, and results from older subjects and those with high IQs have suggested the difficulty of discrimination on the CPT. However, the CPT produces relatively consistent results compared with other objective neuropsychological test measures. In addition, the CPT is widely used in both the clinical and research setting due to its proven reliability and validity and standardization in Korean population.

Despite these limitations, to the best of our knowledge, our study offers the first comparative analysis of CPT performance according to the SNAP-25 1065 T > G genotype in Korean children with ADHD. Further studies with more refined neuropsychological measures and larger sample sizes are needed to confirm our findings.

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