Original Article
https://doi.org/10.9758/cpn.2017.15.3.222
Clinical Psychopharmacology and Neuroscience 2017;15(3):222-228
pISSN 1738-1088 / eISSN 2093-4327

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

Eunjoo Kim[1], Dong-Ho Song[2], Nam-Wook Kim[2], In-Jung Sohn[2], Keun-Ah Cheon[2]

[1]Department of Psychiatry and Institute of Behavioral Science in Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, [2]Division of Child and Adolescent Psychiatry, Department of Psychiatry and Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Korea

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 deficits[8)] 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

Received: August 4, 2016 / **Revised:** November 7, 2016
Accepted: November 9, 2016
Address for correspondence: Keun-Ah Cheon, MD, PhD
Division of Child and Adolescent Psychiatry, Department of Psychiatry and Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1633, Fax: +82-2-313-0891
E-mail: kacheon@yuhs.ac

to respond to a target), commission errors (i.e., responding to a non-target), reaction time, and reaction time variability are computed.[10] According to a recent meta-analysis, the CPT has the largest effect size for the diagnosis of ADHD,[12] and has been considered to be a promising endophenotype for ADHD research.[4,13,14]

To date, prior studies on the genetic basis of CPT performance have focused on dopaminergic genes such as the dopamine D4 receptor gene (*DRD4*),[15,16] the dopamine D5 receptor gene,[17] and the dopamine transporter gene (*DAT1*),[18] and norepinephrine transporter (*NET*) genes, such as G1287A genotype of the *NET* gene in Korean children with ADHD.[19] 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.[20] In addition, SNAP-25 is implicated in axonal growth and synaptic plasticity.[20,21] 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.[22-28] These findings have also been supported by a meta-analysis.[2,29] 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.[30] In addition, normal dopaminergic transmission was restored by the transgenic rescue of SNAP-25 function.[31] In a prior human study that used the transmission disequilibrium test, biased transmission of the alleles of 4 polymorphisms of *SNAP-25* (rs6039806, rs362987, rs362549, and rs362998) was found in Canadian families with ADHD.[26] 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.[20,32]

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*.,[28] 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).[2,33] It was also reported in Mill *et al.*[25] that the TT haplotype was disproportionately 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.[26] The aim of the present study was to evaluate the association between *SNAP-25* genotypes and inattention/impulsivity 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).[34] 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,[35] which was completed by both parents and teachers.

Neuropsychological Assessments: Continuous Performance Test

The Korean version of the computer-based CPT,[10] which has been named the ADHD Diagnostic System,[36] 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.[36]

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 GTC 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 χ^2 test or Fisher's exact test. The allele frequency was determined, and the Hardy-Weinberg equilibrium was calculated using a goodness-of-fit χ^2 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±stdandard deviation or number (%).
ADHD, attention-deficit/hyperactivity disorder; FSIQ, full scale intelligence quotient; ODD, oppositional defiance disorder; MPH, methylphenidate; ARS, ADHD Rating Scale.
*Calculated by a one-way analysis of variance test. †Calculated by χ^2 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±8.80	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 χ^2 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.[38] In addition to results from animal studies, previous studies in humans have found an association between *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 *SNAP-25* gene among Caucasian patients with schizophrenia who were undergoing treatment with atypical antipsychotics.[39] In addition, the rs363050 SNP of *SNAP-25* has been associated with low cognitive scores in autistic children.[40] Recent studies have also suggested the possible involvement of SNAP-25 in learning, memory, and intelligence in normal healthy control participants.[41]

However, research on the relationship between *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 *DRD4* gene and fewer commission errors and less reaction time variability on the CPT.[15] In another study, Korean ADHD subjects with the T allele of the −3081 polymorphism of the *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.[42]

There is some evidence in the literature that the *SNAP-25* genotype is associated with either ADHD or treatment response in patients with ADHD. According to the study by Choi et al.,[28] there was a significant difference between ADHD cases and controls for the 1065 polymorphism (MnlI polymorphism; rs3746544) (χ^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.[28] 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.[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.[43]

Currently, the functional significance of the *SNAP-25* 1065 T > G polymorphism is unknown. However, it is assumed that this polymorphism does not influence the encoding of protein variants or SNAP-25 expression directly, because this SNP is located in the 3' untranslated region of the *SNAP-25* genes.[22] Based on the results of the current study, the 1065 T > G polymorphism may modulate the expression of *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 SNAP-25. In addition, there exists the possibility that this SNP represents an important site for mRNA stability and translational efficiency.[44] Taken together, it is plausible that the 1065 T > G polymorphism plays a role in the expression and regulation of the *SNAP-25* gene, and may enhance susceptibility to ADHD.

Other studies have reported that the *SNAP-25* gene modifies the release of neurotransmitters.[31] There is some evidence that genetic variation may lead to lower levels of SNAP-25 through transcriptional regulation, which would ultimately lead to the decreased exocytosis of several neurotransmitters, including dopamine.[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 *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 *SANP-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 *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.[46] Further studies are needed to explore the relationship between the *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,[28] 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.[47,48] 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.[36]

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.

■ Acknowledgments

This work was supported by research grants funded by the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (Grant numbers: HI12C0021 [A120029] and HI12C0245 [A120296]). We thank the participants who volunteered their time for this study.

REFERENCES

1. Biederman J, Faraone SV. *Attention-deficit hyperactivity disorder. Lancet 2005;366:237-248.*
2. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, *et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1313-1323.*
3. Heiser P, Friedel S, Dempfle A, Konrad K, Smidt J, Grabarkiewicz J, *et al. Molecular genetic aspects of attention-deficit/hyperactivity disorder. Neurosci Biobehav Rev 2004;28:625-641.*
4. Doyle AE, Faraone SV, Seidman LJ, Willcutt EG, Nigg JT, Waldman ID, *et al. Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD? J Child Psychol Psychiatry 2005;46:774-803.*
5. Doyle AE, Willcutt EG, Seidman LJ, Biederman J, Chouinard VA, Silva J, *et al. Attention-deficit/hyperactivity disorder endophenotypes. Biol Psychiatry 2005;57:1324-1335.*
6. Castellanos FX, Tannock R. *Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 2002;3:617-628.*
7. Fan J, Wu Y, Fossella JA, Posner MI. *Assessing the heritability of attentional networks. BMC Neurosci 2001;2:14.*
8. Aron AR, Poldrack RA. *The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1285-1292.*
9. Jucaite A, Fernell E, Halldin C, Forssberg H, Farde L. *Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: association between striatal dopamine markers and motor hyperactivity. Biol Psychiatry 2005;57:229-238.*
10. Greenberg LM, Waldman ID. *Developmental normative data on the test of variables of attention (T.O.V.A.). J Child Psychol Psychiatry 1993;34:1019-1030.*
11. Huang-Pollock CL, Karalunas SL, Tam H, Moore AN. *Evaluating vigilance deficits in ADHD: a meta-analysis of CPT performance. J Abnorm Psychol 2012;121:360-371.*
12. Frazier TW, Demaree HA, Youngstrom EA. *Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. Neuropsychology 2004;18:543-555.*
13. Kollins SH, Anastopoulos AD, Lachiewicz AM, FitzGerald D, Morrissey-Kane E, Garrett ME, *et al. SNPs in dopamine D2 receptor gene (DRD2) and norepinephrine transporter gene (NET) are associated with continuous performance task (CPT) phenotypes in ADHD children and their families. Am J Med Genet B Neuropsychiatr Genet 2008;147B:1580-1588.*
14. Hervey AS, Epstein JN, Curry JF. *Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychology 2004;18:485-503.*
15. Kim B, Koo MS, Jun JY, Park IH, Oh DY, Cheon KA. *Association between dopamine D4 receptor gene polymorphism and scores on a continuous performance test in Korean children with attention deficit hyperactivity disorder. Psychiatry Investig 2009;6:216-221.*
16. Manor I, Tyano S, Eisenberg J, Bachner-Melman R, Kotler M, Ebstein RP. *The short DRD4 repeats confer risk to attention deficit hyperactivity disorder in a family-based design and impair performance on a continuous performance test (TOVA). Mol Psychiatry 2002;7:790-794.*
17. Manor I, Corbex M, Eisenberg J, Gritsenkso I, Bachner-Melman R, Tyano S, *et al. Association of the dopamine D5*

receptor with attention deficit hyperactivity disorder (ADHD) and scores on a continuous performance test (TOVA). Am J Med Genet B Neuropsychiatr Genet 2004;127B:73-77.
18. Loo SK, Specter E, Smolen A, Hopfer C, Teale PD, Reite ML. *Functional effects of the DAT1 polymorphism on EEG measures in ADHD. J Am Acad Child Adolesc Psychiatry 2003;42:986-993.*
19. Song DH, Jhung K, Song J, Cheon KA. *The 1287 G/A polymorphism of the norepinephrine transporter gene (NET) is involved in commission errors in Korean children with attention deficit hyperactivity disorder. Behav Brain Funct 2011;7:12.*
20. Jones MD, Williams ME, Hess EJ. *Abnormal presynaptic catecholamine regulation in a hyperactive SNAP-25-deficient mouse mutant. Pharmacol Biochem Behav 2001; 68:669-676.*
21. Osen-Sand A, Catsicas M, Staple JK, Jones KA, Ayala G, Knowles J, *et al. Inhibition of axonal growth by SNAP-25 antisense oligonucleotides in vitro and in vivo. Nature 1993;364:445-448.*
22. Barr CL, Feng Y, Wigg K, Bloom S, Roberts W, Malone M, *et al. Identification of DNA variants in the SNAP-25 gene and linkage study of these polymorphisms and attention-deficit hyperactivity disorder. Mol Psychiatry 2000;5:405-409.*
23. Brophy K, Hawi Z, Kirley A, Fitzgerald M, Gill M. *Synaptosomal-associated protein 25 (SNAP-25) and attention deficit hyperactivity disorder (ADHD): evidence of linkage and association in the Irish population. Mol Psychiatry 2002;7:913-917.*
24. Mill J, Curran S, Kent L, Gould A, Huckett L, Richards S, *et al. Association study of a SNAP-25 microsatellite and attention deficit hyperactivity disorder. Am J Med Genet 2002;114:269-271.*
25. Mill J, Richards S, Knight J, Curran S, Taylor E, Asherson P. *Haplotype analysis of SNAP-25 suggests a role in the aetiology of ADHD. Mol Psychiatry 2004;9:801-810.*
26. Feng Y, Crosbie J, Wigg K, Pathare T, Ickowicz A, Schachar R, *et al. The SNAP25 gene as a susceptibility gene contributing to attention-deficit hyperactivity disorder. Mol Psychiatry 2005;10:998-1005, 973.*
27. Kustanovich V, Merriman B, McGough J, McCracken JT, Smalley SL, Nelson SF. *Biased paternal transmission of SNAP-25 risk alleles in attention-deficit hyperactivity disorder. Mol Psychiatry 2003;8:309-315.*
28. Choi TK, Lee HS, Kim JW, Park TW, Song DH, Yook KW, *et al. Support for the MnlI polymorphism of SNAP25; a Korean ADHD case-control study. Mol Psychiatry 2007;12:224-226.*
29. Liu YS, Dai X, Wu W, Yuan FF, Gu X, Chen JG, *et al. The association of SNAP25 gene polymorphisms in attention deficit/hyperactivity disorder: a systematic review and meta-analysis. Mol Neurobiol 2017;54:2189-2200.*
30. Corradini I, Verderio C, Sala M, Wilson MC, Matteoli M. *SNAP-25 in neuropsychiatric disorders. Ann N Y Acad Sci 2009;1152:93-99.*
31. Steffensen SC, Henriksen SJ, Wilson MC. *Transgenic rescue of SNAP-25 restores dopamine-modulated synaptic transmission in the coloboma mutant. Brain Res 1999;847: 186-195.*
32. Raber J, Mehta PP, Kreifeldt M, Parsons LH, Weiss F, Bloom FE, *et al. Coloboma hyperactive mutant mice exhibit regional and transmitter-specific deficits in neurotransmission. J Neurochem 1997;68:176-186.*
33. Gizer IR, Ficks C, Waldman ID. *Candidate gene studies of ADHD: a meta-analytic review. Hum Genet 2009;126:51-90.*
34. Kim YS, Cheon KA, Kim BN, Chang SA, Yoo HJ, Kim JW, *et al. The reliability and validity of kiddie-schedule for affective disorders and schizophrenia-present and lifetime version- Korean version (K-SADS-PL-K). Yonsei Med J 2004;45:81-89.*
35. So YK, Noh JS, Kim YS, Ko SG, Koh YJ. *The reliability and validity of Korean parent and teacher ADHD rating scale. J Korean Neuropsychiatr Assoc 2002;41:283-289.*
36. Shin MS, Cho S, Chun SY, Hong KE. *A study of the development and standardization of ADHD diagnostic system. Korean J Child Adolesc Psychiatr 2000;11:91-99.*
37. Song J, Kim SW, Hong HJ, Lee MG, Lee BW, Choi TK, *et al. Association of SNAP-25, SLC6A2, and LPHN3 with OROS methylphenidate treatment response in attention-deficit/hyperactivity disorder. Clin Neuropharmacol 2014; 37:136-141.*
38. Heyser CJ, Wilson MC, Gold LH. *Coloboma hyperactive mutant exhibits delayed neurobehavioral developmental milestones. Brain Res Dev Brain Res 1995;89:264-269.*
39. Spellmann I, Müller N, Musil R, Zill P, Douhet A, Dehning S, *et al. Associations of SNAP-25 polymorphisms with cognitive dysfunctions in Caucasian patients with schizophrenia during a brief trail of treatment with atypical antipsychotics. Eur Arch Psychiatry Clin Neurosci 2008;258:335-344.*
40. Braida D, Guerini FR, Ponzoni L, Corradini I, De Astis S, Pattini L, *et al. Association between SNAP-25 gene polymorphisms and cognition in autism: functional consequences and potential therapeutic strategies. Transl Psychiatry 2015;5:e500.*
41. Gosso MF, de Geus EJ, van Belzen MJ, Polderman TJ, Heutink P, Boomsma DI, *et al. The SNAP-25 gene is associated with cognitive ability: evidence from a family-based study in two independent Dutch cohorts. Mol Psychiatry 2006;11:878-886.*
42. Cho SC, Kim JW, Kim BN, Hwang JW, Park M, Kim SA, *et al. No evidence of an association between norepinephrine transporter gene polymorphisms and attention deficit hyperactivity disorder: a family-based and case-control association study in a Korean sample. Neuropsychobiology 2008;57:131-138.*
43. Comings DE, MacMurray JP. *Molecular heterosis: a review. Mol Genet Metab 2000;71:19-31.*
44. Hughes TA. *Regulation of gene expression by alternative untranslated regions. Trends Genet 2006;22:119-122.*
45. Kim JW, Biederman J, Arbeitman L, Fagerness J, Doyle AE, Petty C, *et al. Investigation of variation in SNAP-25 and ADHD and relationship to co-morbid major depressive disorder. Am J Med Genet B Neuropsychiatr Genet 2007;144B:781-790.*
46. Davids E, Zhang K, Tarazi FI, Baldessarini RJ. *Animal models of attention-deficit hyperactivity disorder. Brain Res Brain Res Rev 2003;42:1-21.*
47. Dulcan M. *Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry 1997;36(10 Suppl):85S-121S.*
48. Corkum PV, Siegel LS. *Is the Continuous Performance Task a valuable research tool for use with children with attention-deficit-hyperactivity disorder? J Child Psychol Psychiatry 1993;34:1217-1239.*