Progress in Neuro-Psychopharmacology & Biological Psychiatry 39 (2012) 57–61

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Association between glycogen synthase kinase-3β gene polymorphisms and attention deficit hyperactivity disorder in Korean children: A preliminary study

Se-Hoon Shim [a], Young Hwangbo [b], Young-Joon Kwon [c], Hwa-young Lee [c], Ji-Hoon Kim [d], Ho-Kyoung Yoon [e], Jung-A Hwang [f], Yong-Ku Kim [f,g,*]

[a] Division of Child & Adolescent Psychiatry, Department of Psychiatry, Soonchunhyang University Cheonan Hospital, 8 2Gil Soonchunhyang, Cheonan City, Choongnam Province, 330-721, South Korea
[b] Department of Preventive Medicine, Soonchunhyang University, Cheonan City, Choongnam Province, 330-721, South Korea
[c] Department of Psychiatry, Soonchunhyang University Cheonan Hospital, Cheonan City, Choongnam Province, 330-721, South Korea
[d] Division of Child & Adolescent Psychiatry, Department of Psychiatry, Pusan National University Yangsan Hospital, Yangsan City, Geumo Ro 20 Kyeongnam Province, 626-770, South Korea
[e] Department of Psychiatry, Korea University Anam Hospital, Anam Dong, Seoul, 425-020, South Korea
[f] Department of Psychiatry, Korea University Ansan Hospital, Ansan City, Gojan Dong, 516, Kyunggi Province, 425-020, South Korea
[g] Division of Brain Korea 21 Biomedical Science, Korea University, South Korea

ARTICLE INFO

Article history:
Received 7 February 2012
Received in revised form 27 April 2012
Accepted 11 May 2012
Available online 31 May 2012

Keywords:
ADHD
Attention deficit hyperactivity disorder
Glycogen synthase kinase
GSK-3β

ABSTRACT

Glycogen synthase kinase (GSK)-3β plays a key role in the phosphorylation and regulation of metabolic enzymes and many transcription factors. Recent studies have suggested the involvement of GSK-3β in the pathogenesis and treatment target of DA-associated neuropsychiatric disorders, which has led to consider GSK-beta as one of the candidate genes for those disorders. GSK-3β genes are likely to be involved in mechanisms underlying attention deficit hyperactivity disorder (ADHD). We investigated the association between −1727A/T and −50T/C SNPs of GSK-3β gene with ADHD. All ADHD subjects completed a comprehensive and standardized diagnostic test and psychological evaluation battery, including the parents' Korean version of the ADHD Rating Scale-IV (ARS). The genotype and allele frequencies of 103 ADHD patients and 173 normal controls were analyzed for −1727A/T and −50T/C SNPs of GSK-3β gene. There were statistically significant differences in the genotype distributions of the −1727A/T SNP of GSK-3β gene between the ADHD group and the control group. The frequency of the genotype AT was significantly higher in the ADHD patients.

Concerning the haplotype, there was a significant difference in the A–C haplotype frequency between the two samples. However, no differences in either the genotype distribution or in allele frequencies of −50C/T were observed between the two samples. In the parents version of K-ARS of all subjects, ANCOVA revealed that two subscales and the total score were significantly higher in the subjects with AT + TT genotypes than those with AA genotype after adjusting for age and gender. The odds ratio for the ADHD patients was 1.79, comparing the AT genotype group with the AA genotype group. Therefore, genotype AT is associated with a higher risk of ADHD. Our results suggest that the −1727A/T SNP of GSK-3β gene may affect susceptibility in ADHD.

Further investigation with a larger number of subjects is needed to validate this finding.

1. Introduction

Attention deficit-hyperactivity disorder (ADHD) is one of the most common and pervasive childhood disorders. ADHD is a neurodevelopmental disorder characterized by developmentally inappropriate inattention, hyperactivity, and impulsive behavior (American Psychiatric Association). The prevalence of ADHD in school-aged children around the world falls between 3% and 6% (Tannock, 1998), and in Korea, the disorder affects between 4% and 5% among children (Kim et al., 1999). Although its etiology is not clearly understood, a number of family and twin studies have demonstrated a strong genetic component with heritability estimates of approximately 80% (Faraone and Doyle, 2001). Glycogen synthase kinase (GSK)-3 is a serine/threonine-specific protein kinase found in the cell cytoplasm, and activation of this kinase regulates the activity of substrates via the addition of phosphoric acid to either a serine or threonine residue of the substrate (Jope and Roh, 2006). GSK-3 was initially identified as a phosphorylating and inactivating glycogen synthase that is critical to the regulation of glucose

Abbreviations: ADHD, attention deficit-hyperactivity disorder; KEDI–WISC, Korean version of the Wechsler Intelligence Scale for Children; K-ARS, Korean ADHD Rating Scale; Hyp–imp, hyperactivity–impulsivity; CPT, Continuous Performance Test; GSK, Glycogen synthase kinase; Akt, V-akt murine thymoma viral oncogene homologue; βArr2, β-arrestin-2.

* Corresponding author at: Department of Psychiatry, Korea University Ansan Hospital, Ansan City, Gojan Dong, 516, Kyunggi Province, 425-020, South Korea. Tel.: +82 31 412 5140; fax: +82 31 412 5144.
E-mail address: yongku@korea.ac.kr (Y.-K. Kim).

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doi:10.1016/j.pnpbp.2012.05.008

storage (Embi et al., 1980). There are two GSK-3 isoforms, GSK-3α and GSK-3β. GSK-3β is the most studied isoform and is important in the Wnt, the MAP kinase, and phosphatidylinositol-3 kinase pathways. GSK-3 controls functions such as metabolism, gene expression, neuroplasticity, cell survival and death, neurogenesis, and circadian rhythms in neurons through these pathways (Grimes and Jope, 2001).

One important function of GSK-3β is to phosphorylate and thus regulate the functions of many metabolic signaling structural proteins and of a large number of transcription factors. GSK-3β is a protein kinase that is highly abundant in brain tissue (Lau et al., 1999) and is involved in signal transduction cascades of multiple cellular processes, particularly neurodevelopment. Several intracellular signaling cascades converge on GSK-3β to modulate its activity, and several neurotransmitter systems, including serotonergic, dopaminergic, cholinergic, and glutamatergic systems also regulate GSK-3β. GSK-3β has been linked to bipolar disorder, depression, schizophrenia, and ADHD (Bauer et al., 2003; Beaulieu et al., 2004; Emamian et al., 2004; Gil et al., 2003; Li et al., 2004). However, the pathophysiological correlation between neurodevelopmental disorders such as ADHD and GSK-3β is not well explained to date.

The GSK-3ß gene, mapped to chromosome 3q13.3, is about 268 kb in length and includes 12 exons (Shaw et al., 1998). Russ et al. (2001) identified two common SNPs (single nucleotide polymorphisms) at positions −1727A/T and −50C/T, which are found most frequently relative to the transcriptional start site and upstream of the coding sequence. Functional studies are required to evaluate these findings, because no obvious consensus sequence is present in the predicted promoter region for known transcription factor binding sites (Russ et al., 2002).

Dopamine (DA) is a monoaminergic neurotransmitter that has been implicated in multiple brain disorders, such as Parkinson's disease, schizophrenia, ADHD, Tourette syndrome, addiction, and affective disorders (Gainetdinov and Caron, 2003). Beaulieu et al. (2004) reported the involvement of GSK-3 as an important mediator of DA and lithium action in vivo, and suggested that modulation of Akt (V-akt murine thymoma viral oncogene homolog)/GSK-3 pathway might be relevant to DA-related disorders, such as ADHD and schizophrenia. To date, although there have been a few association studies between −1727A/T and −50T/C SNPs of GSK-3β gene and DA-associated neuropsychiatric disorders, ADHD is not one of them. Based on the above findings, we hypothesized that a genetic variation in the GSK-3β gene would be associated with increased vulnerability to ADHD. The aim of the present study was to investigate associations between −1727A/T (SNP rs3755557) and −50C/T (SNP rs334558) of the GSK-3β gene and ADHD. In addition, we investigated the relationship between scores on the ADHD Rating Scale-IV according to the genotypes.

2. Methods

2.1. Subjects

The present study included 103 children with ADHD, consisting of 81 boys and 22 girls. All subjects have visited the Department of Child and Adolescent Psychiatry of Soonchunhyang University Cheonan Hospital in Korea and agreed to participate in the study. Individuals with a full-scale IQ of lower than 70, neurological disorders, seizure disorders, pervasive developmental disorders, tic disorders, bipolar mood disorders, or psychotic disorders were excluded. All ADHD subjects were drug-naive at the time of recruitment, and ADHD tests (including the CPT) were administered before treatment with medication.

The demographic and clinical characteristics of the ADHD probands and the controls are presented in Table 1. The control group included 173 healthy children, consisting of 82 boys and 91 girls who were all recruited from the same primary school in Korea. All of the control subjects were also free of any major medical and psychiatric problems. Control subjects with scores higher than 18 on the Korean version of the ADHD Rating' Scale (K-ARS) and those who were mentally handicapped were excluded. The control subjects were all physically healthy, well adjusted academically, and showed no signs of psychiatric or developmental problems. Parents of all subjects provided written informed consent for the assessment and participation of their children in this study. The study protocol was approved by the Ethics Committee of Soonchunhyang University Cheonan Hospital.

2.2. Clinical assessments

The diagnostic assessments of psychiatric disorders, including ADHD, were carried out according to the DSM-IV criteria, with the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present (K-SADS-PL-K), and the Lifetime—Korean Version (K-SADS-PL-K) used for ADHD subjects (Kim et al., 2004). The K-SADS-PL-K interviews were performed with all ADHD subjects and either one or both parents. The interviews were carried out by clinically experienced child/adolescent psychiatrists. All of the ADHD subjects completed a comprehensive and standardized battery of psychological tests, including the Korean Educational Development Institute—Wechsler Intelligence Scale for Children (Park et al., 1991) and the ARS (DuPaul, 1991). The ARS is a behavior-rating scale consisting of 18 items: 9 inattention items and 9 hyperactive/impulsivity items. The Korean versions of the ARS (K-ARS) parent and teacher forms are known to be highly valid and reliable (So et al., 2002).

2.3. Neuropsychological measurements

A computerized Continuous Performance Test (CPT) (Greenberg and Waldman, 1993) was used to measure the inattention, impulsivity, and sustained attention deficits of the ADHD children. The Korean version of the CPT was standardized, and its validity and reliability have been well established (Shin et al., 2000). A visual stimulus was presented for 100 ms every 2 s, with the subjects being required to respond to a square containing a triangle (target) and not respond to a square containing a circle or square (non-target). The four major variables recorded were: (1) omission errors

Table 1
Demographic and psychometric variables in the study subjects.

		ADHD	Normal controls
		(n = 103)	(n = 173)
Sex (male/female)[a]		81/22	82/91
Age (years)			
Mean ± SE[a]		8.91 ± 0.23	9.54 ± 0.10
(range)		(5–14)	(7–12)
Clinical features			
KEDI–WISC	Verbal IQ	102.81 ± 1.37	
	(range)	(72–127)	
	Performance IQ	100.52 ± 1.43	
	Total IQ	102.00 ± 1.29	
K-ARS subscale score	Inattention score[a]	13.92 ± 0.59	4.64 ± 0.17
	Hyp-imp score[a]	12.50 ± 0.54	3.62 ± 0.15
	Total score[a]	26.58 ± 0.97	8.26 ± 0.28
CPT	Omission error	73.08 ± 2.45	
	Commission error	75.08 ± 2.23	
	Response time	52.41 ± 1.66	
	Response variability	82.45 ± 2.67	
ADHD subtypes (DSM-IV), %	Combined	70.87	
	Inattentive	8.74	
	Hyp–imp	7.77	
	NOS	12.62	

Note: ADHD = attention deficit-hyperactivity disorder; KEDI–WISC = Korean version of the Wechsler Intelligence Scale for Children; K-ARS = Korean ADHD Rating Scale; Hyp–imp = hyperactivity–impulsivity; CPT = Continuous Performance Test; NOS = not otherwise specified.

[a] $p < .01$.