Association between *RELN* Gene Polymorphisms and Attention Deficit Hyperactivity Disorder in Korean Children

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Objective   Attention deficit hyperactivity disorder (ADHD) is common disorder of the school-age population. ADHD is familial and genetic studies estimate heritability at 80−90%. The aim of the present study was to investigate the association between the genetic type and alleles for *RELN* gene (rs736707, rs2229864, rs362746, rs362726, rs362691, rs1062831, rs607755, and rs2072403) in Korean children with ADHD.

Methods   The sample consisted of 180 ADHD children and 159 control children. We diagnosed ADHD according to DSM-IV. ADHD symptoms were evaluated with Conners' Parent Rating Scales and Dupaul Parent ADHD Rating Scales. Blood samples were taken from the 339 subjects, DNA was extracted from blood lymphocytes, and PCR was performed for *RELN* Polymorphism. Alleles and genotype frequencies were compared using the chi-square test. We compared the allele and genotype frequencies of *RELN* gene polymorphism in the ADHD and control groups.

Results   This study showed that there was a significant correlation among the frequencies of the rs736707 (OR=1.40, 95% CI=1.03−1.90, p=0.031) of alleles of *RELN*, but the final conclusions are not definite.

Conclusion   Follow up studies with larger patient or pure subgroups are expected. These results suggested that *RELN* might be related to ADHD symptoms.   **Psychiatry Investig 2016;13(2):210-216**

Key Words   ADHD, Polymorphism, *RELN*, Child.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common childhood neuropsychiatric disorder characterized by behavioral problems such as attention deficit, hyperactivity and impulsivity.[1] It has a prevalence of 2−7.6% among children of school age in Korea.[2,3] Family studies reported that ADHD showed a heredity as high as 80−90%,[4] and molecular genetic studies are actively carried out accordingly. Recent genetic studies on ADHD have usually been conducted on the dopamine receptors and related neurotransmitters.

Reelin is an extracellular protein that is mainly involved in nerve cell migration, appropriate brain lamination, and synapse formation in the central nervous system.[5] For humans, the reelin gene is located at chromosome 7q22.1.[6]

An animal study reported that the expression of reelin is involved in long term potentiation (LTP) and cognition.[7,8] Reelin promotes hippocampal LTP and this function requires the activity of lipoprotein receptors.[9,10] The role of Reelin in synaptic function is mediated in part through interactions between ApoER2 and N-methyl-D-aspartate (NMDA) receptors.[11] These proteins form a synaptic complex that controls Ca^{2+} entry through the NMDA receptor and thus regulate synaptic plasticity. In addition Reelin signaling is also important for the regulation of NMDA receptor subunit composition during hippocampal neuronal maturation, and NMDA receptor-mediated activity in cortical neurons.[12] Inattention and partial cognitive decline are characteristic symptoms of ADHD as well as dementia.

Many studies have reported that the abnormality of reelin

is associated with autism, schizophrenia, bipolar disorder, and lissencephaly.[13] In previous research, there have been a number of association studies on the reelin gene and autism. Serajee et al.[14] and Li et al.[15] reported the association of the rs736 707/rs362691 reelin genes with autism, and Ashley-Koch et al.[16] reported the association of rs2073559 with autism. Recently, the association between excessive transmission of the allele of RELN SNP rs362719 and bipolar disorder has been reported.[17]

Consequences of RELN mutation were first characterized in the homozygous reeler mouse which phenotypically exhibited an ataxic gait.[18-20] A number of abnormalities have been characterized in the brains of homozygous reeler mice. These include a nonfoliated cerebellum and deficits in lamination of the hippocampus and other cortical areas.[21,22] Most strikingly, in homozygous reeler mice, the cortex has been characterized as a laminar inversion of the typical inside-out pattern of development.[18] A recent analysis of neocortex of homozygous reeler mice found an even more complex pattern with evidence of a mirror-image laminar structure and rostrocaudal cell-type-specific differences in laminar phenotype.[20]

Disorganization of the hippocampus and amygdala were also observed, suggesting pervasive disruption of brain cytoarchitecture as a result of reduced Reelin expression.

To our knowledge, no research has been reported about correlation between ADHD in youths and *RELN* gene polymorphism. Few studies have been conducted to show the correlation between *RELN* gene polymorphism and Autism. The aim of the present study was to investigate the association between the genetic type and alleles for *RELN* gene in Korean children with ADHD.

METHODS

Subjects

A questionnaire was conducted with about 16,000 elementary school students in a city whose population is about 500,000 from September 2008 and August 2010. A interview was performed randomly with the children whose Korean version of the Dupaul Attention Deficit Hyperactivity Disorder Rating Scales (K-ARS)[23] score was 19 or higher, and 180 ADHD children who consented to the genetic study were selected. For the control group, 159 children in the same area were selected by matching the sex and age of the subjects in the patient group. For both of the patient and control groups, a clinical evaluation and the DSM-IV diagnosis[1] were performed by a child psychiatrist. The number of ADHD children was 180, including 132 boys (73.3%) and 48 girls (26.7%), and the mean age was 8.67±0.84. The number of the children in the control group was 159, including 100 boys (62.9%) and

Table 1. Epidemiological characteristics between the ADHD group and the control group

Rating Scale	ADHD group (N=180) Mean±SD	Control group (N=159) Mean±SD	F or χ^2	p value
Age*	8.67±0.84	8.59±0.79	0.06	0.813
Sex (N, %)†			3.79	0.052
Female	48 (26.7%)	59 (37.1%)		
Male	132 (73.3%)	100 (62.9%)		

These data represent mean±SD, by *independent t-test, or N (%), by †chi-square test, significant p value <0.05. ADHD: attention deficit hyperactivity disorder

Table 2. SNPs considered in this study

SNP ID	Chromosome	Location	Position (coordinate)	Distance	Alleles
RELN					
rs736707	7	Intron	102917638	-57	T/C
rs2229864	7	Coding	102942940	[73/183]	C/T
rs362746	7	Coding	102966830	[70/179]	A/G
rs362726	7	Intron	102994469	-28	T/C
rs362691	7	Coding	103038396	[19/93]	G/C
rs1062831	7	Coding	103124207		A/G
rs607755	7	Intron	103177189	-3	A/G
rs2072403	7	Coding	103292224		T/C

RELN: Reelin gene; NCBI gene ID (Accession) is 1621 (NM173054 and NM005045). SNP: single nucleotide polymorphism

59 girls (37.1%), and the mean age was 8.59±0.79. There was no significant difference in the sex and age between the two groups (Table 1). Subjects were excluded from the study if there was any evidence of conduct disorder, mood disorder, anxiety disorder, Tourette's disorder, pervasive development disorder, mental retardation (IQ <70) and neurological disorders including epilepsy. Both the patient group and control group in this study underwent clinical evaluation and DSM-IV diagnosis by children psychiatrists, applying the inclusion and exclusion criteria strictly, because we will get subject group was composed of pure ADHD diagnosed subjects without major psychiatric disorder and neurological abnormality. None of the children who participated in the study has ever undergone drug treatment before the evaluation. Informed consent was obtained prior to study entry. The study was also approved by the Hospital Ethics Committee. None of the children was taking psychostimulants at the time of the study.

On the day of visiting the hospital, the child psychiatrist performed a clinical interview as well as Kovac's Children's Depression Inventory (CDI),[24,25] State Anxiety Inventory (SAIC), Trait Anxiety Inventory (TAIC)[26] and Dupaul Attention Deficit Hyperactivity Disorder Rating Sales (K-ARS),[21] computerized ADS (ADHD Diagnostic System)[27] as well as completing a questionnaire survey regarding the pregnancy, infancy, developmental history and anamnesis of the children with their parents. Subjects were included from our sample if they had a score over two standard deviations from the norm on the tests for ADS (T-score >70). ADHD had a lot of cormorbid disorders, as depressive disorder and anxiety disorder. So we excluded children with the high score of depressive symptoms and anxiety symptoms. Subjects with high anxiety scores (a Spielberger trait/state anxiety scale score >47/49) on the Korean version of Spielberger trait-state anxiety scale for children were excluded, and subjects with high depression scores (Kovacs depression inventory score >29) on Kovacs depression inventory for children were also excluded. In Cho and Lee[23] presented the score over 22 as the mild depressed state, over 26 as the middle depressed state, and over 29 as the severe depressed state in the Korean form of the Kovacs' Childhood Depression Inventory. Also Cho and Choi[24] evaluated the reliability of the Korean State Anxiety Inventory for Children, reported that the scores 39–42 indicate a little high trait anxiety, scores 43–46 indicate a considerably high trait anxiety, and scores 47 or higher indicate very high trait anxiety in TAIC scales. In addition, a professional clinical psychologist performed a comprehensive psychological test, including an intelligence test, on each subject.

DNA extraction and genotyping

DNA was extracted from leukocytes using a commercial DNA extraction kit, the Wizard Genomic DNA purification kit (Promega, Madison, WI, USA). The RELN SNP was genotyped by polymerase chain reaction (PCR) according to the protocol described by Li et al's studies[13] *RELN* rs736707, rs2229864, rs362746, rs362726, rs362691, rs1062831, rs607755, and rs2072403 were genotyped by Illumina, Inc. (San Diego, CA, USA) through the use of their Integrated Bead Array System (Table 2). We supplied Illumina with barcoded DNA microtiter plates containing the DNA quantified with Pico Green to be at 100 ng/mL and Illumina delivered genotypes with quality scores calculated by proprietary Illumina algorithms.

Statistical analysis

We performed independent t-tests for age, chi-square tests for sex, and chi-squre tests to compare the results of the control group and the ADHD group through the frequency of the genotypes and alleles. SPSS PC software (version 15.0) was used for the statistical analysis and the significance level was set to the p value being less than 0.05. The calculation revealed that a sample size of 210 subjects is required to obtain a power that is 95% or higher in the chi-square test between the control group and the patients group. Our study was conducted with 339 subjects and the power was 97.41%. This indicates that the association of the *RELN* gene polymorphism and ADHD can be sufficiently accounted for by the results in this study. However, we performed the power program analysis for the chi-squre test with 339 subjects and the result showed that the effect size was 0.46 (moderate level).

RESULTS

Demographic characteristics of the subjects

The subjects were a total of 339 children. The children in both of the ADHD group and the control group had never taken any psychostimulant in advance. There was no difference in the age (t=0.06, p=0.813) and sex (χ^2=3.79, p=0.052) between the control group and the ADHD children group (Table 2).

Comparison of the frequency of the genotypes and alleles with genetic polymorphism of *RELN* between the control group and the ADHD group

The *RELN*-rs736707 genotypes of the 159 subjects in the control group and the 180 subjects in the ADHD group were T/T alleles (37.58%:31.46%), T/C alleles (47.13%:42.70%) and C/C alleles (15.29%:25.84%), and there was a significant difference in the frequency of genotypes between the two groups (χ^2=2.24, df=2, p=0.025). The *RELN*-rs736707 allele

Table 3. Multivariate model for genotype distribution and allele frequencies of the ADHD group and the control group

Characteristics	Control		ADHD		OR	95% CI	χ^2	p
	N	%	N	%				
RELN−rs736707 (T/C)								
Genotype					2.02	1.09−3.73	2.24	0.025
TT	59	37.58	56	31.46				
TC	74	47.13	76	42.70				
CC	24	15.29	46	25.84				
Allele					1.40	1.03−1.90	2.15	0.031
T	192	61.15	188	52.81				
C	122	38.85	168	47.19				
RELN−rs2229864 (C/T)								
Genotype					1.13	0.49−2.61	0.29	0.770
CC	97	61.39	109	61.24				
CT	50	31.65	55	30.90				
TT	11	6.96	14	7.87				
Allele					1.04	0.73−1.48	0.20	0.840
C	244	77.22	273	76.69				
T	72	22.78	83	23.31				
RELN−rs362746 (A/G)								
Genotype					1.13	0.72−1.78	0.52	0.600
AA	101	63.92	108	60.67				
AG	53	33.54	64	35.96				
GG	4	2.53	6	3.37				
Allele					1.14	0.79−1.66	0.70	0.486
A	255	80.70	280	78.65				
G	61	19.30	76	21.35				
RELN−rs362726 (T/C)								
Genotype					0.90	0.53−1.51	-0.41	0.682
TT	41	25.95	48	26.97				
TC	79	50.00	83	46.63				
CC	38	24.05	47	26.40				
Allele					1.03	0.76−1.39	0.17	0.863
T	161	50.95	179	50.28				
C	155	49.05	177	49.72				
RELN−rs362691 (G/C)								
Genotype					1.40	0.82−2.40	1.22	0.221
GG	129	81.65	135	75.84				
GC	28	17.72	41	23.03				
CC	1	0.63	2	1.12				
Allele					1.39	0.86−2.25	1.34	0.18
G	286	90.51	311	87.36				
C	11	9.49	45	12.64				
RELN−rs1062831 (A/G)								
Genotype					0.68	0.32−1.42	-1.03	0.301
AA	74	46.84	82	46.07				
AG	64	40.51	81	45.51				
GG	20	12.66	15	8.43				

Table 3. Multivariate model for genotype distribution and allele frequencies of the ADHD group and the control group (continued)

Characteristics	Control		ADHD		OR	95% CI	χ^2	p
	N	%	N	%				
Allele					0.93	0.67−1.28	-0.45	0.650
A	212	67.09	245	68.82				
G	104	32.91	111	31.18				
RELN−rs607755 (A/G)								
Genotype					0.82	0.44−1.50	-0.65	0.514
AA	58	36.71	71	39.89				
AG	69	43.67	76	42.70				
GG	31	19.62	31	17.42				
Allele					0.90	0.66−1.22	-0.69	0.487
A	185	58.54	218	61.24				
G	131	41.46	138	38.76				
RELN−rs2072403 (T/C)								
Genotype					2.83	0.30−27.62	0.90	0.370
TT	119	75.32	126	70.79				
TC	38	24.05	49	27.53				
CC	1	0.63	3	1.69				
Allele								
T	276	87.34	301	84.55	1.27	0.82−1.96	1.08	0.278
C	40	12.66	55	15.45				

These data represent N (%) by chi-square test, significant p value <0.05. RELN: Reelin gene; NCBI gene ID (Accession) is 1621 (NM173054 and NM005045). ADHD: attention deficit hyperactivity disorder

of the 159 subjects in the control group and the 180 subjects in the ADHD group were T alleles (61.15%:52.81%) and C alleles (38.85%:47.19%), and there was a significant difference in the frequency of allele between the two groups (χ^2=2.15, df=1, p=0.031) (Table 3).

Odds ratio of the genotypes and alleles with genetic polymorphism of *RELN* between the control group and the ADHD group

For the *RELN*-rs736707 genotypes, the odds ratio was significant at 2.02 (confidence interval: 1.09−3.73, p=0.025). Also for the *RELN*-rs736707 allele, the odds ratio was significant at 1.40 (confidence interval: 1.03−1.90, p=0.031) (Table 3).

DISCUSSION

This study is a case-controlled study in which the frequency of the genotypes and alleles of *RELN* were compared between the ADHD children and the control group in Korea. The correlation between the genotypes and alleles of eight candidate *RELN* SNPs was investigated. This study showed that there was a significant correlation between the frequencies of the *RELN*-rs736707. This study showed that there was a significant correlation between the frequencies of the

RELN-rs736707 and ADHD, this result is reported for the first time in child ADHD studies.

Li et al.[13] reported the association between rs5906883 genetic polymorphism of the *RELN* gene and Autism was reported first in Asia. But no association has been reported about correlation between ADHD and *RELN* gene polymorphism. In this study, the correlation between ADHD and *RELN*-rs736707 genetic polymorphism was found in this study firstly.

Combining the results about the correlation between the *RELN* rs736707 and ADHD, it can be understood that the failure of *RELN* regulation may cause the changes in neurodevelopmental process and may be correlated with the vulnerability of various psychiatric diseases including ADHD and movement disorder. These receptors can affect the NMDA-mediating action, which is related with the symptoms found in the children with ADHD. This study also suggests that the failure to regulate the RELN expression causes changes in the synaptogenesis and neural migration and the structural development of the brain regions related with nerve activity, attention and impulsivity. Recently, a very large study by Plessen et al.[28] involving children and adolescents with ADHD reported an increased volume of the hippocampus bilaterally in those with the disorder. The hippocampus is known to be

involved in attentional processes such as visuospatial working memory[29] and in modulating executive functions.[30] Disturbances in these functional domains belong to core symptoms of ADHD.[24] In the same study, the authors reported indirect evidence of a reduced size of the basolateral amygdala complex in children and adolescents with ADHD. The finding of altered amygdala and hippocampus volumes in ADHD is of particular interest for adult patients with ADHD because affective symptoms, emotional instability and impulsivity often dominate the clinical picture in this age group compared with hyperactivity and inattentiveness, which often play a minor role. Based on previous findings in children with ADHD described by Plessen et al.,[26] we suspected that abnormality of the amygdala and the hippocampus have the association RELN polymorphism abnormality. Hence, the correlation between the *RELN* gene and ADHD should be carefully handled and the result of our study should be verified in the future study with a large number of independent samples.

The limitations of this study are as follows: first, the number of subject children was small. The subjects of this study were 180 ADHD children and 159 children in the control group. Second, the results of this study may not be generalized for the cases of other racial or ethnic groups since the frequency of alleles can vary due to local or racial differences. The distribution of the allele frequency in the ADHD patient children and parents group in this study was also different from that of other countries. Third, only a few SNPs were investigated in this study among the many genes related with the various ADHD phenotypes. Although it is clear that not just one genetic factor causes the increased ADHD vulnerability, we did not consider the interaction with other risk factors.

Despite the methodological limitations described before, this study has several advantages. First, the patient group and the control group were matched so that there was no difference in the frequency of sex and age. The prevalence of ADHD is higher among males and in adolescence; thus, the sex and age characteristics can have a great effect. Considering this, our study was evaluated by matching the age and sex of the patient group and the control group with each other. Second, this study used population-based samples. Previous studies in Korea were hardly considered to represent the general population because the subjects were usually ADHD children who visited hospitals for their clinical symptoms. In this study, the subjects in the risk group were selected by the questionnaire survey from the whole population in a region and the patient and control samples were obtained by random contact. Thus, the subjects in this study may be more appropriate to the characteristics of general population than those of the study performed with the patients who visited hospitals. Third, both the patient group and control group in this study underwent clinical evaluation and DSM-IV diagnosis by children psychiatrists, applying the inclusion and exclusion criteria strictly, and thus the patient group was composed of pure ADHD diagnosed subjects.

We expect that different allele distribution results may be produced from future studies on the quantitative correlation of the ADHD performance in the pure ADHD group from which co-existing diseases are excluded, the patients group composed of only boys or girls, the subtype groups such as hyperactivity dominant group and attention deficiency dominant group, and the drug response group.

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