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Association between Unc-51-like autophagy activating kinase 2 gene polymorphisms and schizophrenia in the Korean population

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Abstract

Accumulating evidence indicates that the autophagy process is involved in the pathogenesis of schizophrenia. Autophagy plays a fundamental role in neuronal survival and function, and autophagy-related genes have been suggested to be associated with the pathogenesis of schizophrenia. The Unc-51-like autophagy activating kinase 2 (*ULK2*) gene has been implicated in autophagy regulation; therefore, we hypothesized that *ULK2* polymorphisms may be associated with schizophrenia susceptibility.

This study explored the association between polymorphisms of *ULK2* and schizophrenia.

Two single nucleotide polymorphisms (SNPs) (rs55730189 and rs150122) of *ULK2* were genotyped in 279 patients with schizophrenia and 403 healthy individuals using Fluidigm SNPtype assays. We analyzed the genotype distribution of 2 SNPs and haplotypes between patients with schizophrenia and control subjects.

The T allele frequency of rs55730189 showed a significant association between patients with schizophrenia and control subjects ($P = .003$). Genotype frequencies of rs55710189 were found to be significantly different between patients with schizophrenia and control subjects (odds ratio = 6.89, 95% confidence interval = 1.91–24.90, $P < .001$ in the dominant model [C/T + T/T vs C/C], OR = 6.50, 95% confidence interval = 1.83–23.01, $P < .001$ in the log-additive model (C/T vs T/T vs C/C)]. In haplotype analysis, the TT haplotype for these 2 SNPs was significantly associated with schizophrenia ($P < .001$, $\chi^2 = 12.231$).

Our findings suggest that specific *ULK2* polymorphisms may be associated with susceptibility to schizophrenia in the Korean population.

Abbreviations: CIs = confidence intervals, GWASs = genome-wide association studies, LD = linkage disequilibrium, mTOR = mammalian target of rapamycin, ORs = Odds ratios, SNPs = single nucleotide polymorphisms, ULK1 = uncoordinated 51 serine/threonine protein kinase 1, ULK2 = Unc-51-like autophagy activating kinase 2.

Keywords: autophagy, haplotype, schizophrenia, single nucleotide polymorphism, Unc-51-like autophagy activating kinase 2

1. Introduction

Schizophrenia is a mental disorder that presents with symptoms of disturbances in perception, emotion, cognition, thinking, and behavior. It is increasingly evident that autophagy contributes to schizophrenia pathogenesis. Autophagy is responsible for balancing synthesis, degradation, and recycling of cellular components.[1] Autophagy is essential for neuronal homeostasis and synaptic plasticity[2] and is imperative for neuronal survival and function. Accumulating evidence suggests that autophagy-related pathways are involved in the pathophysiological mechanisms of schizophrenia. Recently, it has been hypothesized that dysregulation of autophagy may cause cellular dysfunction associated with the pathogenesis of schizophrenia.[3] Furthermore, one study reported that the postmortem hippocampus of schizophrenia patients had decreased levels of beclin1 mRNA, a protein important for initiating autophagy.[4] This suggests that impaired autophagy in hippocampal neuronal cells contributes to the pathogenesis of schizophrenia.

Regulatory proteins modulate autophagy, either through activation or inhibition. A mammalian homolog of *Caenorhabditis elegans*, uncoordinated 51 serine/threonine protein kinase (*ULK1*), has a regulatory function in autophagy.[5] In the autophagy regulation process, the serine/threonine-protein kinase Unc-51-like autophagy activating kinase 2 (*ULK2*) has

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a redundant role in *ULK1*.[6] In mammalian forebrain development, *ULK2* is involved in neuronal development through axon guidance and neurite outgrowth.[7,8] It has been suggested that growth inhibition involving *ULK2* is implicated in apoptosis-dependent mechanisms.[9] Although *ULK2* has the potential to affect neurodevelopment, its function of *ULK2* is not entirely understood.

ULK2 encodes a protein that is similar to a serine/threonine kinase in *C. elegans*, which is involved in axonal elongation.[10]*ULK2* is located on chromosome 17p11.2, which may harbor schizophrenia susceptibility loci.[11] Several previous studies have investigated the connection between autophagy-related genes and schizophrenia. A microarray analysis in the superior temporal cortex of patients with schizophrenia showed downregulation of several genes, including *ULK2*.[10,12] Furthermore, autophagy-related stress response protein expression was upregulated in the *ULK2* heterozygous mice that exhibited behavioral deficits relevant to schizophrenia, such as impaired sensorimotor gating through dysregulation of excitatory–inhibitory balance mechanism.[13]

Considering these results, *ULK2* may contribute to impaired autophagy. Given the association between autophagy dysregulation and schizophrenia, we postulated that the *ULK2* gene may be involved in the development of schizophrenia. To date, no studies have examined the association between *ULK2* polymorphisms and schizophrenia. Our study examined the association between *ULK2* single nucleotide polymorphisms (SNPs) and schizophrenia in the Korean population.

2. Materials and methods

2.1. Participants and clinical assessment

A total of 682 subjects were recruited for the study. The 279 participants in the schizophrenia group (171 men and 108 women) had a mean (±standard deviation) age of 46.0 (±10.5 years old). There were 403 healthy individuals in the control group (189 men and 214 women), with a mean age of 48.9 (±11.0 years old). Patients with schizophrenia who were treated at Kyung Hee University Hospital in Korea participated in this study. A comprehensive diagnostic assessment, including interviews, clinical records, and family history, using the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria, was performed for all patients. Control subjects were recruited from healthy participants who visited the hospital for general health checkups. The control group comprised 403 subjects who did not have a lifetime or family history of psychiatric disorders. All participants were ethnically Korean and unrelated to each other. General psychopathology of patients was assessed using the Operational Criteria Checklist for Psychotic Illnes[14] through review of hospital records and personal interviews. We investigated the possible associations between clinical symptoms of schizophrenia and *ULK2* polymorphisms by selecting items related to persecutory delusions and auditory hallucinations, which are the main symptoms of schizophrenia. All samples were collected after each participant provided written informed consent. The study was approved by the Institutional Review Board of Kyung Hee University Hospital, Seoul, Republic of Korea.

2.2. SNP selection and genotyping

Total genomic DNA from each subject was isolated using a commercial DNA isolation kit (Roche, Indianapolis, IN). Based on the SNP database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP, build 152), 626 coding SNPs were selected from 23,324 SNPs of the *ULK2* gene. We excluded SNPs without genotype frequency data in East Asian populations, with a heterozygosity value <0.005, or those with a minor allele frequency <0.005. We selected rs55730189, rs150122, rs62636615, and rs34670978 according to our selection criteria. Of these 4 SNPs, rs62636615 and rs34670978 presented monomorphic genotypes in East Asian populations. Finally, 2 *ULK2* coding SNPs, rs55730189 (Gly752Arg) and rs150122 (Val370Met), were selected for further analysis. Using Fluidigm 192.24 Dynamic Array with EP1 (Fluidigm Incorporated, San Francisco, CA, USA), each SNP was genotyped. We used the SNPtype assay (Fluidigm Corp., CA), which employs allele-specific fluorescent (FAM or VIC) primers and a common reverse primer. Genotyping was completed using the Fluidigm SNP genotyping software to analyze the data. To obtain genotype calls, we analyzed the data using EP1 SNP Genotyping Analysis software. The software defined the genotype of each sample based on the relative fluorescence intensities.

2.3. Statistical analysis

Hardy–Weinberg equilibrium and genetic data were analyzed using SNPStats (http://bioinfo.iconcologia.net/index.php?module=Snpstats) and SPSS version 18.0 software (SPSS Inc, Chicago, IL). To assess the differences in genotype distribution between the groups, the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression analyses, controlling for age and sex as covariates. Logistic regression analysis with multiple inheritance models assuming additive inheritance and dominant and recessive inheritance models was used to correlate each SNP with susceptibility to schizophrenia. Linkage disequilibrium (LD), genetic association between SNPs and haplotypes, and schizophrenia were assessed using Haploview 4.2 (Broad Institute, Cambridge, MA). The difference in haplotype frequency was assessed using the chi-square test. Bonferroni correction was applied by multiplying P values by the number of all performed analyses (n = 6) to avoid chance findings due to multiple tests; a P-value <.008 would be required for significance ($P = .05/6$) for the 2 SNPs and for the 2 haplotypes.

3. Results

3.1. Differences in genotypic and allelic frequencies between ULK2 SNPs and schizophrenia

The distributions of the 2 *ULK2* SNP genotypes in control subjects were consistent with the Hardy–Weinberg equilibrium ($P > .05$). Table 1 summarizes the distributions of genotypic and allelic frequencies of the 2 SNPs in patients with schizophrenia and control subjects. Allele frequencies of SNP rs55730189 were significantly different between patients with schizophrenia and control subjects, reflecting a higher frequency of the T allele in patients with schizophrenia ($P = .003$). The T allele frequency of rs55730189 was higher in the schizophrenia patient group (2.5%) than in the control group (0.4%). No statistically significant difference was found in the allele frequency of rs150122 between patients with schizophrenia and the control group.

We found significant differences in the genotype frequency of rs55730189 between patients with schizophrenia and control

Table 1

Genotype and allele frequencies of *ULK2* polymorphisms in schizophrenia patients and control subjects.

			Control		Schizophrenia			
SNPs	**Model/allele**	**Genotype**	**n**	**%**	**n**	**%**	**OR (95% CI)**	***P* value**
rs55730189	Log-additive	C/C	400	99.3	266	95.3	6.50 (1.83–23.01)	**.0006**
(Gly752Arg)		C/T	3	0.7	12	4.3		
		T/T	0	0	1	0.4		
	Dominant	C/C	400	99.3	266	95.3	6.89 (1.91–24.90)	**.0007**
		C/T + T/T	3	0.7	13	4.7		
	Recessive	C/C + C/T	403	100	278	99.6	0.00 (0.00–NA)	.14
		T/T	0	0	1	0.4		
	Allele	C	803	99.6	544	97.5	1	
		T	3	0.4	14	2.5	6.89 (1.97–24.08)	**.003**
rs150122	Log-additive	T/T	271	67.2	193	69.2	0.83 (0.62–1.12)	.22
(Val370Met)		C/T	113	28.1	81	29.0		
		C/C	19	4.7	5	1.8		
	Dominant	T/T	271	67.2	193	69.2	0.91 (0.65–1.27)	.56
		C/T + C/C	132	32.8	86	30.8		
	Recessive	T/T + C/T	384	95.3	274	99.2	0.32 (0.11–0.95)	.022
		CC	19	4.7	5	1.8		
	Allele	T	655	81.3	467	84.0	1	
		C	151	18.7	89	16.0	0.83 (0.62–1.10)	.20

Bold characters indicate a significant association ($P < .008$).

CI = confidence interval, OR = odds ratio, SNP = single nucleotide polymorphism, ULK2 = Unc-51-like autophagy activating kinase 2.

subjects. In the log-additive model, the C/T genotype revealed an increased risk of schizophrenia [OR = 6.50, 95% CI = 1.83–23.01, $P < .001$, (C/T vs T/T vs C/C)]. The distributions of the C/C, C/T, and T/T genotypes were 95.3%, 4.3%, and 0.4% in the schizophrenia group and 99.3%, 0.7%, and 0% in the control group, respectively. There were significant differences in the genotype frequency of rs55730189 between schizophrenia patients and control groups in the dominant model [OR = 6.89, 95% CI = 1.91–24.90, $P < .001$, (C/T + T/T vs C/C)]. In the dominant model, the frequencies of genotypes containing a T allele (C/T + T/T) and those not containing a T allele (C/C) were 4.7% and 95.3%, respectively, in patients with schizophrenia compared with the values of 0.7% and 99.3%, respectively, in control subjects. These results indicate that carrying the T allele, rs55730189, significantly increases the risk of schizophrenia. However, no significant differences between the genotype frequency of rs150122 in schizophrenia patients and control subjects were observed in the recessive model after Bonferroni correction [OR = 0.32, 95% CI = 0.11–0.95, $P = .02$, (C/C vs T/T + C/T)]. The frequencies of genotypes containing a T allele (T/T + C/T) and those without a T allele (C/C) were 99.2% and 1.8% in schizophrenia patients compared with 95.3% and 4.7% in control subjects, respectively.

In addition, the genotype/allele frequencies of rs5573819 differed between men and women in our study. Sex stratification of the studied populations showed different results. There were significant differences in the genotype frequency of rs55738109 between female schizophrenia patients and female control subjects in the log-additive model [OR = 9.93, 95% CI = 1.15–85.59, $P = .007$, (C/T vs T/T vs C/C)] (Table 2). Genotype and

Table 2

Genotype and allele frequencies distributions of rs55730189 in schizophrenia patients and control subjects according to sex.

			Control		Schizophrenia			
Sex	**Model/allele**	**Genotype**	**n**	**%**	**n**	**%**	**OR (95% CI)**	***P* value**
Man	Log-additive	C/C	187	98.9	163	95.3	4.87 (1.01–23.56)	.027
		C/T	2	1.1	8	4.7		
		T/T	0	0	0	0.0		
	Allele	C	376	99.0	334	98.0	1	.06
		T	2	1.0	8	2.0	4.50 (0.95–21.35)	
Woman	Log-additive	C/C	213	99.5	103	95.4	9.93 (1.15–85.59)	**.007**
		C/T	1	0.5	4	3.7		
		T/T	0	0	1	0.9		
	Dominant	C/C	213	99.5	103	95.4	11.50 (1.30–101.57)	**.008**
		C/T + T/T	1	0.5	5	4.6		
	Recessive	C/C + C/T	214	100	107	99.1	0.00 (0.00–NA)	.14
		T/T	0	0	1	0.9		
	Allele	C	427	100	210	97.0	1	
		T	1	0	6	3.0	12.2 (1.46–101.9)	.02

Bold characters indicate a significant association ($P < .008$).

CI = confidence interval, OR = odds ratio.

allele frequency distributions of rs150122 in schizophrenia patients and control subjects according to sex showed no significant associations. These results suggest that the carriers of the T allele of rs55730189 in *ULK2* may have an increased risk of developing schizophrenia.

3.2. Genetic association of ULK2 SNPs with clinical symptoms of schizophrenia

We explored the association between SNPs and clinical symptoms of schizophrenia (persecutory delusion, auditory hallucination, and poor concentration). The allele frequencies of rs55730179 were not associated with persecutory delusion, auditory hallucination, or poor concentration ($P = .83$, .33, and .56, respectively). The genotype distribution of rs55730189 was not associated with these specific clinical symptoms when analyzed using multiple inheritance models. Allele frequency analysis of rs150122 showed no association with persecutory delusion, auditory hallucination, or poor concentration in schizophrenia patients ($P = .90$, .55, and .60, respectively). The genotype distribution of rs150122 did not differ significantly between the presence of these specific clinical symptoms in patients with schizophrenia (data not shown).

3.3. Haplotype analyses

Associations of haplotypes consisting of rs55730189 and rs150122 with schizophrenia were assessed. We tested LD between rs55730189 and rs150122 SNPs ($|D'| = 1.0$, $r^2 = 0.003$). The 2 loci showed strong LD. Haplotype analysis revealed that the TT haplotype ($P < .001$, $\chi^2 = 12.231$) was significantly associated with schizophrenia (Table 3). The distributions of the CT, CC, and TT haplotypes were 0.811, 0.176, and 0.012, respectively. The frequency of the TT haplotype was significantly higher in patients with schizophrenia than in the control group (0.025 vs 0.004). This result indicates that the T allele of rs55730189 and rs150122 contributes to an increased risk of schizophrenia.

4. Discussion

In the present study, we explored the potential associations between coding *ULK2* polymorphisms and schizophrenia in the Korean population. The T allele and T allele carrier genotypes of rs55730189 were associated with schizophrenia when compared to that in control subjects. Haplotype analysis showed that the TT haplotypes for rs55730189 and rs150122 were associated with a higher risk of schizophrenia.

Dysregulated autophagy is associated with several neurodegenerative disorders in mammals.[10] Recently, impaired autophagy was identified as a major factor contributing to the pathogenesis of neurodegenerative disorders.[15] In addition to their role in neurodegeneration, several studies reported a significant role of autophagy pathways in schizophrenia pathogenesis. Medications treating various psychiatric illnesses have been suggested to function, in part, through autophagy induction.[3] Autophagy dysfunction interferes with neuronal cell biology, and may induce psychiatric symptoms.[16] Another study has shown that downregulation of autophagy-related genes in patients with schizophrenia could be reversed by antipsychotic drugs that induce autophagy activity.[17] Although the exact mechanism of autophagy-related pathways in schizophrenia remains unclear, this evidence suggests an important role of autophagy in the pathogenesis of schizophrenia.

Among the autophagy-related genes, *ULK2*-related autophagy dysfunction has been suggested to cause several diseases. Overexpression of *ULK2* inhibits the proliferation of nonsmall cell lung cancer cells and enhances chemo-sensitivity to cisplatin.[18]*ULK2* inhibits astrocyte transformation in vitro and tumor growth.[9] Increasing evidence indicates that *ULK2* may play an important role in the pathophysiology of neuropsychiatric diseases, including schizophrenia. In zebrafish, *ULK2* appears to promote the branching of dendrites in habenular nuclei.[19] Habenular activation in dopaminergic and serotonergic networks appears to play a role in negative feedback from external sources observed in schizophrenia and depression.[20,21] Although autophagy has been suggested to be related to schizophrenia, there are no reports on the association between *ULK2* variants and schizophrenia. However, a recent study showed that rare variants of *ULK1* may be involved in schizophrenia susceptibility in a Swedish population.[22] Furthermore, unc-51-like kinase 4 deletion was reported to be genetically linked to schizophrenia and was associated with a decrease in cell proliferation and migration in a mouse model.[23] Interestingly, both autophagy and disruption of the mammalian target of rapamycin (mTOR) signaling system have been suggested to be related to the pathophysiology of schizophrenia.[4] Autophagy induction is regulated by the activity of mTOR kinase,[24] and *ULK1/2* activity is regulated by mTOR kinase.[25] Although the role of *ULK2* in schizophrenia is not well known, this growing evidence suggests that *ULK2* is involved in the pathogenesis of schizophrenia by impairing autophagy via mTOR signaling. Thus, we hypothesized that *ULK2* may contribute to the development of schizophrenia via autophagy-related pathology.

To date, genome-wide association studies (GWASs) have identified over 200 risk loci that are significantly associated with schizophrenia.[26] However, the association of *ULK2* SNPs in schizophrenia GWASs has not yet been elucidated. No study has examined the association between *ULK2* polymorphisms and

Table 3

Haplotype distribution of *ULK2* polymorphisms between schizophrenia patients and control subjects.

Haplotype			Control		Schizophrenia			
rs55730189	rs150122	Frequency	+	−	+	−	Chi square	*P* value
C	T	0.811	652	154	455	103	0.073	.7864
C	C	0.176	151	655	89.4	469	1.681	.1947
T	T	0.012	3	803	14	544	12.231	**<.0001**

Haplotype is comprised of rs55730189 and rs150122.

ULK2 = Unc-51-like autophagy activating kinase 2.

Bold characters represent statistically significant values ($p < 0.008$).

schizophrenia. Lang et al[27] investigated multiple schizophrenia cases with copy number variation abnormalities specific to *ULK* family genes. According to the study, deletions spanning exons 21 to 34 of the Unc-51-like kinase 4 gene were present in 4 out of 3391 schizophrenia patients but not in 3181 controls, and 1 additional genomic duplication involving the 5'-half of the *ULK2* gene was present in the patient group and partial duplications of the 3'-half of *ULK1* gene were found in 2 patients, suggesting that the *ULK* gene family is associated with schizophrenia.

Moreover, the allelic frequencies of rs55730819 and rs150122 showed ethnic differences. The frequencies of the minor allele T of rs55730189 and the minor allele C of rs150122 were 0.00002 and 0.03, respectively, in Europeans. In East Asia, the minor allele frequency of the 2 SNPs was relatively high compared to that in the European population, which is the main ancestry of the largest GWASs. The frequencies of the T allele of rs55730189 and the C allele of rs150122 were 0.02 and 0.2 in East Asian, respectively. In our study, it were 0.004 for rs55730189 and 0.19, rs150122. The allelic frequencies of the 2 SNPs may differ between Asian populations. Furthermore, the minor allele frequency of rs55730189 in Koreans was 0.017, according to gnoMAD v.2.1. In our study, the minor allele frequency of rs55730189 was 0.004 in the control group and 0.025 in the schizophrenia group. The small size of our population could be a limitation and could induce false-positive results. Further investigation in collaboration with other psychiatric centers to increase population size may be needed to validate our results. In addition, considering the diverse differences in allelic frequency in different ethnic populations, performing GWASs in various populations will provide new insights into the pathogenesis of schizophrenia.

In the present study, we found that the coding SNPs rs55730189 and rs150122 of *ULK2* and their haplotypes were significantly associated with schizophrenia. Specifically, the T allele and the T allele carrier genotype of rs55730189 may confer susceptibility to schizophrenia. Our 2 SNPs were the result of a missense mutation, glycine to arginine and valine to methionine, respectively. Missense mutations often induce protein functions. To predict the functional significance of the 2 SNPs, we used complementary algorithms: sorting intolerant from tolerant (http://sift.bii.a-star.edu.sg/) and polymorphism phenotyping (http://genetics.bwh.harvard.edu/pph/) and uploaded the SNP accession numbers of 2 SNPs into variant effect predictor (http://www.ensembl.org/Tools/VEP). We found that rs55730189 has deleterious effects on the structure and function of *ULK2* protein, and this mutation was predicted to be possibly damaging, with a score of 0.943 (sensitivity: 0.80; specificity: 0.95). Thus, the mutation in the rs55730189 SNP might have a putative functional role.

Our study has a limitation regarding the lack of assessment of other putative functional SNPs within *ULK2*. In addition, the relatively small sample size was insufficient for finding associations between rare SNPs and schizophrenia. This is the first study to demonstrate the significant association between *ULK2* polymorphisms and schizophrenia. Further investigations should be performed to explore the clinical implications of *ULK2* polymorphisms and the underlying mechanisms of schizophrenia.

5. Conclusions

In the present study, we demonstrated that polymorphisms in *ULK2* and their haplotypes were significantly associated with schizophrenia in the Korean population. We found that missense mutation of rs55730189 in *ULK2* appears to increase susceptibility to schizophrenia. These results suggest that T alleles and the TT haplotype of rs55730189 might be associated with susceptibility to schizophrenia. Future studies are needed to determine the role of *ULK2* variants in the pathophysiology of schizophrenia.

Author contributions

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