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ORIGINAL PAPER

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Dysbindin gene (*DTNBP1*) and schizophrenia in Korean population

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Abstract Dysbindin gene (*DTNBP1*) has been consistently reported to be associated with schizophrenia. However data from East Asian population has been sparse and inconsistent till today. This study tried to replicate the genetic association of *DTNBP1* with schizophrenia in a large Korean sample, as well as analyzing the association of *DTNBP1* with clinical variables. Nine hundred and eight (908) patients with schizophrenia and 601 controls were investigated. The high-throughput genotyping method using pyrosequencer (Biotage AB, Sweden) was used for genotyping 4 SNPs (rs3213207, rs1011313, rs760761, and rs2619522). Haplotype analyses revealed a significant association with schizophrenia ($P < 0.0001$) with the haplotypes A-C-C-C and A-C-T-A having an eminent protective effect toward schizophrenia. The major contribution to the difference in the haplotype distribution between patients and the controls was the rs760761 (C/T) and rs2619522 (A/C) haplotypes ($P < 0.0001$). No association of *DTNBP1* with other clinical variables was found. In conclusion, the present study suggests a possible protective effect of rare *DTNBP1* variants in schizophrenia, although subsequent studies in different ethnic groups are warranted.

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Introduction

Dystrobrevin-binding-protein 1 (DTNBP1) is an evolutionary conserved protein and it has been proven to be expressed in multiple anatomical locations, including axon fibers in the corpus callosum, mossy-fiber terminal fields in the hippocampus and cerebellum, and neuropil areas of the neocortex, hippocampus, and substantia nigra in animal studies [3]. Dysbindin mRNA is also expressed in variable regions of human brain such as frontal cortex, temporal cortex, hippocampus, caudate, putamen, nucleus accumbens, amygdala and thalamus, critically associated with schizophrenia [29].

It is also worth noting that the expression of dysbindin is reduced in both the prefrontal cortex and glutamatergic terminals of hippocampal formation in schizophrenia [20, 29], which further support the role of dysbindin and the pathophysiological mechanism of schizophrenia. In addition emerging evidence suggests that dysbindin may have a possible role in the modulation of synaptic signaling and plasticity as binding snapin in presynaptic, postsynaptic and microtubule locations [23].

DTNBP1 [MIM 607145] on 6p22.3 has been currently recognized as one of the most eminent susceptibility genes for schizophrenia, evidenced by a series of independent case-control and family-based association studies in different ethnic populations, as well as it has been proven its possible role through previous multiple studies [8, 11, 19, 21, 22, 25–28], although common polymorphism or haplotype has not yet been established.

However, data from East Asian population has been sparse and inconsistent, comparing with Wes-

tern population till today [13, 19, 24, 25]. It is well known that susceptible and protective haplotypes should be sophisticated and also vary according to ethnic difference [15]. Hence we tried to replicate the genetic association of *DTNBP1* with schizophrenia in a large Korean sample as well as analyzing the association of *DTNBP1* with clinical variables.

Methods and subjects

Nine hundred and eight (908) patients with schizophrenia [female n = 448 (49.3%), mean age 33.7] and 601 controls [female n = 295 (49.1%), mean age 38.9] were recruited. There was no difference in gender (P = 0.97) and age (P = 0.26) distribution between patients and controls.

Diagnosis of schizophrenia was performed according to DSM-IV criteria [1], by two independent psychiatrists employing the structured clinical interview for DSM-IV, axis I disorders-clinician version (SCID-I-CV) [10]. All diagnostic evaluations were blind of the genotyping data.

Patients with neurological illness, autoimmune diseases, or other AXIS I psychiatric diseases were excluded. Clinical variables such as age, age of onset, family history, number of admissions, history of suicide attempts and duration of illness were collected.

All subjects were biologically unrelated, native Koreans residing in Korea. The Institutional Review Board of the Kangnam St. Mary's Hospital approved the study. Written informed was obtained from all subjects after compete description of the study.

Genomic DNA was extracted from blood by standard methods and quantified. The high-throughput genotyping method using pyrosequencer (Biotage AB, Sweden) was used for genotyping 4 SNPs (rs3213207, rs1011313, rs760761, and rs2619522) of dysbindin gene covering a 25 Kb area, which were selected based on public database (National Center for Biotechnology Information, dbSNP, http://www.ncbi.nlm.nih.gov/SNP/) and information of previous studies [5, 11, 15, 21, 22, 26, 27]. PCR primers (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer, Daejeon, Korea) were used for the Pyrosequencing assay designed by using the Pyrosequencing Assay Design Software (Biotage AB, Sweden) (*data available upon request*). Two independent investigators (J.J.K; H·K.L.) blind to the clinical status of samples checked all genotypes independently. Samples showing ambiguous alleles were discarded if they showed the same features on repeated genotyping. The final error rate was less than 0.5% for each SNP.

Haploview 3.2 was used to generate a linkage disequilibrium map and to test for Hardy-Weinberg equilibrium [2]. Association for single markers and clinical variables were performed by the Chi-square and the Analysis of variance. Tests for associations using multi-marker haplotypes were performed using the statistics software "R" (http://www.R-project.org), which allows the analysis of quantitative traits and the inclusion of covariates; permutations (n = 10,000) were performed to estimate the global significance of the results for all haplotype analyses and to validate the expectation-maximization values. Rare haplotypes (<1%) were excluded from the analysis. Haplotype analysis result in a test for all haplotypes (Global stat., Global P) and for each haplotype (haplotype stat., haplotype P).

We calculated the power of our sample with a restricted alpha level of 0.001 (multiple-tests correction). For single marker analyses in our sample we had a power of 0.80 to detect a small effect size of w = 0.115, that corresponded to a difference of approximately 11.6% between two genotypes [odd ratio (OR) = 1.60] [7].

Results

Genotypes of all markers were in H–W equilibrium in both patients (rs3213207 P = 0.1; rs1011313 P = 0.09; rs760761 P = 0.058; rs2619522 P = 0.319) and controls (rs3213207 P = 0.402; rs1011313 P = 1.0; rs760761 P = 0.837; rs2619522 P = 0.683). All investigated loci were in strong Linkage Disequilibrium in patients, while some moderate LDs, however significant, were observed in cases (Fig. 1). Figure 2 report LD among markers as calculated in CEPH population (Utah residents with ancestry from northern and western Europe), as reported by the International HapMap Project (http://www.hapmap.org/index.html).

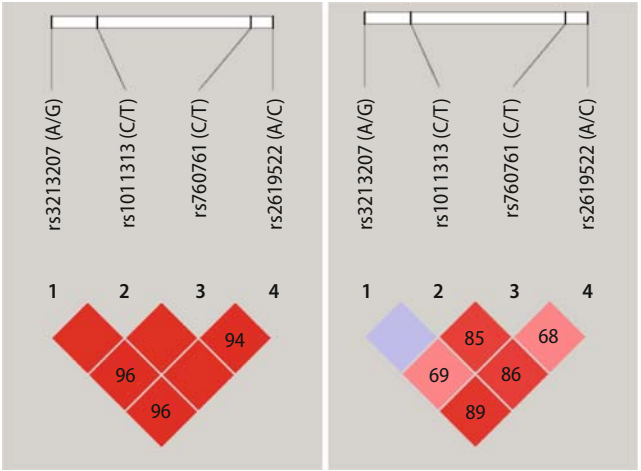

Fig. 1 Linkage disequilibrium map among *DTNBP1* markers in patients and the controls (left for patients and right for the controls). Chromosome positions, rs3213207: 15,736,081, rs1011313: 15,741,411, rs760761: 15,759,111, and rs2619522: 15,761,628

There were no differences between patients and controls in genotype and allele distributions for all tested SNPs, as shown in Table 1.

When analysing haplotypes, we found instead significant differences between patients and controls (Global-stat = 47.97, df = 7, P < 0.0001, simulated P < 0.0001) (Table 2). In fact, the A-T-C-A haplotype was more frequent in the patients group, while the rare A-C-T-A and A-C–C-C haplotypes showed prominent protective effects toward schizophrenia.

This difference remained statistically significant (Global-stat = 30.93, df = 3, P < 0.0001, simulated P < 0.0001) even when excluding rare haplotypes (frequency < 1%); the A-T-C-A haplotype maintained a small trend of association with the disease (haplotype P = 0.082).

Sliding windows analysis showed that the haplotypes rs760761 (C/T) and rs2619522 (A/C) exerted the major contributions to the difference between patients and controls (global-stat = 43.4, df = 3, P < 0.0001) (Table 3).

When excluding the rare haplotypes, the C-A haplotype maintained a trend of association with the risk for schizophrenia (Global-stat = 41.33, df = 2, P < 0.0001, simulated P < 0.0001; haplotype stat = 2.5, P = 0.0135, simulated P = 0.0134).

When we compared other clinical variables such as age, age of onset, family history, number of admis-

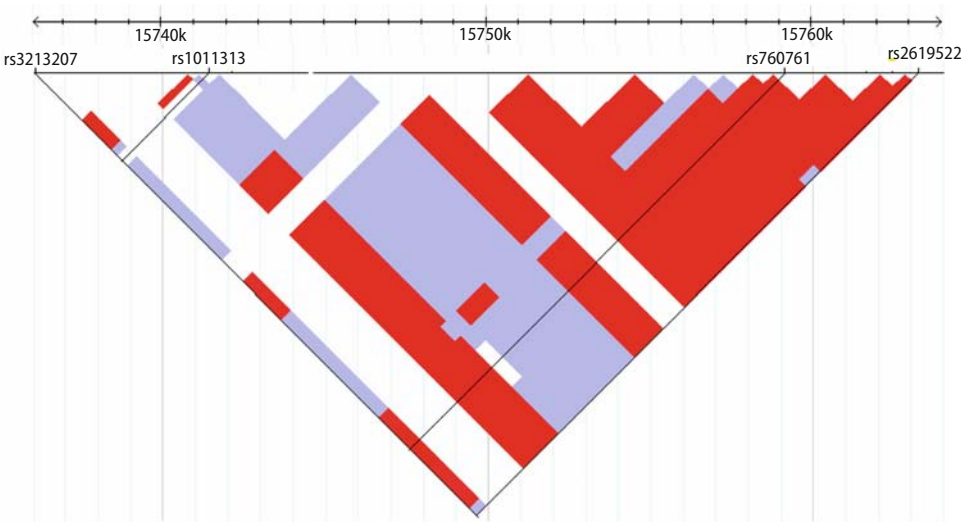

Fig. 2 Linkage disequilibrium map among *DTNBP1* markers in CEPH popoluation (Utah residents with ancestry from northern and western Europe), as reported by the International HapMap Project (http://www.hapmap.org/index.html)

Table 1 Genotype and alleles distribution in 4 *DTNBP1* markers in patients (n = 908) and the controls (n = 601)[a]

Schizophrenia			*P* values	Control		
rs3213207						
A/A 878 (96.7)	A/G30 (3.3)	G/G0 (0.0)	0.44	A/A578 (96.2)	A/G22 (3.6)	G/G1 (0.2)
A 1,786 (98.3)		G30 (1.7)	0.48	A1,178 (98.0)		G24 (2.0)
rs1011313						
C/C 543 (59.8)	C/T329 (36.2)	T/T36 (4.0)	0.27	C/C384 (63.9)	C/T194 (32.3)	T/T23 (3.8)
C 1,415 (77.9)		T401 (22.1)	0.17	C962 (80.0)		T240 (20.0)
rs760761						
C/C 750 (82.6)	C/T148 (16.3)	T/T10 (1.1)	0.59	C/C485 (80.7)	C/T110 (18.3)	T/T6 (1.0)
C 1,648 (90.7)		T168 (9.3)	0.41	C1,080 (89.9)		T122 (10.1)
rs2619522						
A/A 740 (81.5)	A/C156 (17.2)	C/C12 (1.3)	0.70	A/A481 (80.0)	A/C113 (18.8)	C/C7 (1.2)
A 1,636 (90.1)		C180 (9.9)	0.58	A1,075 (89.4)		C127 (10.6)

Data represent number and percentage
[a]Chi-Square and Fisher's exact test

Table 2 Results of 4 haplotype analysis

Haplotypes	Control frequency	Schizophrenia frequency	Stat.	*P* value	Simulated *P* value[a]
A-C-T-A	0.025	0.004	−5.2	<0.001	<0.001
A-C–C-C	0.026	0.010	−3.2	0.0012	0.0014
G-C–C-C	0.004	<0.001	−2.2	0.030	0.030
G-C-T-C	0.014	0.015	0.3	0.78	0.80
A-C–C-A	0.672	0.676	0.3	0.78	0.78
A-C-T-C	0.059	0.072	1.4	0.17	0.17
A-T-C-A	0.193	0.221	1.7	0.084	0.082

[a]10,000 simulations

Table 3 Results of two haplotypes analysis with rs760761 and rs2619522

Haplotypes	Control frequency	Schizophrenia frequency	Stat.	*P* value	Simulated *P* value[a]
T-A	0.028	0.004	−5.1	0.0001	0.0001
C–C	0.033	0.011	−3.9	0.0001	0.0003
T-C	0.073	0.088	1.4	0.17	0.16
C-A	0.867	0.896	2.5	0.014	0.013

[a]10,000 simulation

sions, suicide attempts and duration of disease, no results were observed except for small non-significant trends (Table 4).

Discussion

The present study supports previous findings that suggested an association of certain haplotypes of *DTNBP1* with schizophrenia. The protective haplotypes we observed (rs760701 T-rs2619522 A) are in partial agreement with previous studies [8, 11, 19, 21, 22, 26].

Several replication studies have reported confirmation of an association to DTNBP1 in independent samples; however, reported risk alleles and haplotypes differs between studies, and comparison among studies has been confounded because different marker sets were employed by each group. Many studies [8, 11, 19, 21, 25, 26] reported the rs1011313 C variant, analyzed in different blocks, associated with Schizophrenia,

Table 4 *DTNBP1* markers stratified for demographic and clinical data

	N (%)	*N* (%)	*N* (%)	*P*	*N* (%)	*N* (%)	*P*
Rs3213207	A/A	A/G	G/G		A	G	
Males	687 (49.8)	33(66.0)	1 (100)	0.039	1,407 (50.1)	35 (67.3)	0.013
Females	691 (50.2)	17 (34.0)	0 (0)		1,399 (49.9)	17 (32.7)	
Rs1011313	C/C	C/T	T/T		C	T	
Males	457 (51.8)	238 (48.3)	26 (47.3)	0.39	1,152 (51.1)	290 (48.1)	0.19
Females	424 (48.2)	255 (51.7)	29 (52.7)		1,103 (48.9)	313 (51.9)	
Rs760761	C/C	C/T	T/T		C	T	
Males	575 (49.5)	137 (54.4)	9 (60)	0.28	1,287 (50)	155 (55)	0.11
Females	587 (50.5)	115 (45.6)	6 (40)		1,289 (50)	127 (45)	
Rs2619522	A/A	A/C	C/C		A	C	
Males	1,138 (49.4)	282 (54.4)	22 (61.1)	0.050	1,279 (49.9)	163 (55.25)	0.08
Females	1,166 (50.6)	236 (45.6)	14 (38.9		1,284 (50.1)	132 (44.75)	
	Mean ± St.dev.	Mean ± St.dev.	Mean ± St.dev.	*P*	Mean ± St.dev.	Mean ± St.dev.	*P*
Age							
Rs3213207	A/A38.6 ± 12.9	A/G38.6 ± 13.6	G/G40 ± 0	0.99	A38.6 ± 12.9	G38.6 ± 13.3	1.00
Rs1011313	C/C38.8 ± 12.9	C/T38.2 ± 13.0	T/T38.5 ± 12.6	0.73	C38.7 ± 12.9	T38.3 ± 12.9	0.51
Rs760761	C/C38.6 ± 12.8	C/T38.5 ± 13.1	T/T44.3 ± 17.5	0.22	C38.6 ± 12.8	T39.1 ± 13.6	0.49
Rs2619522	A/A38.7 ± 12.9	A/C38.0 ± 12.7	C/C43.1 ± 15.6	0.06	A38.6 ± 12.8	C38.6 ± 13.2	0.95
Onset age							
Rs3213207	A/A24.7 ± 7.4	A/G23.5 ± 10.0	G/G23.3 ± 12.4	0.72	A24.7 ± 7.4	G23.5 ± 10.0	0.57
Rs1011313	C/C24.2 ± 7.1	C/T25.2 ± 7.8	T/T27.2 ± 7.9	0.16	C24.4 ± 7.3	T25.6 ± 7.8	0.07
Rs760761	C/C24.9 ± 7.4	C/T23.3 ± 6.6	T/T28.2 ± 15.5	0.17	C24.8 ± 7.4	T24.0 ± 8.3	0.40
Rs2619522	A/A24.8 ± 7.5	A/C23.8 ± 6.6	C/C31.0 ± 16.4	0.15	A24.7 ± 7.4	C24.6 ± 8.1	0.91

while in our sample this variant was included in the four-markers blocks being more frequent in controls than in cases. Nevertheless, the rs1011313 T variant has been also reported as included in risk haplotype blocks in other populations [22, 27]. A number of studies [8, 11, 19, 21, 22, 26, 27] reported the rs760761 T and the rs2619522 A variants in blocks associated with Schizophrenia, while in our sample these variants were not different in cases and controls. Finally, as regards rs3213207, inconsistent results have been reported [8, 19, 22, 25, 27, 28]. To our knowledge, only few studies have been performed on Asiatic populations. Numakawa et al. [19] found the G-C rs3213207-rs1011313 haplotype significantly associated with Schizophrenia. This finding is in partial agreement with our result: indeed, we found the opposite rs3213207 A variant being protective against Schizophrenia, though combined with the rs760761 marker. On the other hand, rs3213207, rs760761 and rs2619522 were not found associated with Schizophrenia on a Korean sample [13] and a study on Japanese sample reported quite opposite results [25]. Inconsistency among studies has been already discussed [18].

However, it has been suggested that unidentified sequence variants in regulatory regions of *DTNBP1* may alter expression of the gene [4, 5]. Moreover, functional effect of *DTNBP1* on schizophrenia and genetic analyses with accurate schizophrenia phenotyping should be used in further studies [5].

All the markers investigated in this study showed strong LDs, except for rs3213207 due to its low informativeness. LD values were not different in patient and control groups and they were similar to previous studies. The most common haplotype of the present study consisted of the common alleles of each SNP (A-C–C-A), which was similar to previous investigations in Caucasian population [9, 16]. However, rs760701 and rs2619522 were in *strong* LD in patients (0.96) while only *moderate* in controls (0.69). Given that all patients were Korean (of Korean descendents), collected in the area of Seoul, no population background biases can had reliably influenced results, while differences in samples size may better explain this relatively small discrepancy. On the other hand, differences in LDs can influence genetic associations. Nevertheless, given the significance of the association, the small LDs' difference is not sufficient to completely explain the finding.

Fanous and colleagues [9] suggested negative symptoms to be associated with high-risk haplotypes of *DTNBP1*. Considering DTNBP1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia [20], it could be related with cognitive deficit or negative symptoms of schizophrenia. More detailed analyses for clinical association of *DTNBP1* in schizophrenia is warranted.

The major limitations of the lack of genomic control which is liable for stratification bias, however Korean population is considered genetically homogenous [6] and in our sample we were able to detect risk factors of about 2 with very conservative alpha levels. Further, the protective haplotypes sum up to 6.4% in controls and 1.5% in patients, therefore the variance explained by the present association is very low, but this is in line with the supposed minor effect of liability genes in complex disorders [14]. Never-

theless, the low frequency of significant haplotypes may increase the risk of false positives.

Single markers frequencies were not different between cases and controls, while only combined allelic variants (haplotypes) showed different distributions in the two groups. It is likely that the analysis of markers in strong linkage disequilibrium increases the probability to detect differences of stratification.

Little is known about the functional significance of markers investigated in the present sample. To our knowledge only one study tested whether sequence variations in the dysbindin gene would affect mRNA levels [29]. Authors found the hCV3114520 (rs11558324) polymorphism in Exon 1 to influence cortical mRNA levels, while rs760761 was not found associated to mRNA levels; other variants have been never investigated. However, it is likely a strong LD between these markers; indeed Gornick et al. [12] reported a D' value of 0.74 between the markers, though LD was not significant ($P > 0.01$) in their sample.

Multiple testing may lead to false positive findings, and this should be considered in the present paper where 4 SNPs were tested, however they should not be considered independent given the LD between them and previous findings on the gene make this analysis not completely exploratory; furthermore, we set a conservative alpha-level in order to limit the problem of multiple testing. Moreover, we investigated only a small part of the DTNBP1 gene, 25 Kb, and the possible functional effects of the polymorphisms are not known. Therefore associations based on haplotypes in the absence of any demonstrated function associated with the risk haplotypes is to be considered with caution. However, it has been recently suggested that haplotypes including some of the markers analysed in the present study reduce DTNBP1 expression [4]. We are also aware that *P*-values can be inflated through genotyping error [17], however genotypes were blindly checked by two independent and experienced molecular biologists.

In conclusion, the present study suggests a possible protective effect of rare dysbindin gene variants in schizophrenia. Subsequent association study in different ethnic groups is warranted.

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