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Serotonin Transporter Gene Polymorphisms and Chronic Illness of Depression

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Clinical course of depression is variable. The serotonin transporter gene is one of the most studied genes for depression. We examined the association of serotonin transporter gene polymorphisms with chronicity and recurrent tendency of depression in Korean subjects. This cross-sectional study involved 252 patients with major depression. Patients were genotyped for s/l polymorphisms in *5-HTT* promoter region (*5-HTTLPR*), s/l variation in second intron of the *5-HTT* gene (*5-HTT VNTR* intron2). Chronicity was associated with *5-HTTLPR*. Patients with l/l had higher rate of chronicity than the other patients (l/l vs s/l or s/s; odds ratio, 4.45; 95% confidence interval, 1.59-12.46; P=0.005; logistic regression analysis). Recurrent tendency was not associated with *5-HTTLPR*. Chronicity and recurrent tendency were not associated with *5-HTT VNTR* intron2. These results suggest that chronic depression is associated with *5-HTTLPR*.

Key Words: Depression; 5-Hydroxytryptamine Transporter

Major depressive disorder is one of the most common of the serious psychiatric disorder (1). Clinical course of depressive disorder is variable. It ranges from months to years and a single episode of illness to a recurrent episode (2). About 15-18% of patients with major depressive episode could not reach to recovery in the 2 yr after onset of depressive episode. And more than 50% of patients experience a recurrence in 5 yr (3).

Chronic illness of depression has a considerable impact on social functioning, is difficult to treat and is associated with higher rates of history of suicide attempt (1, 4). And chronicity and risk of recurrence are strong predictors of the need for aggressive use of maintenance therapy. Therefore an early identification of clinical course is of great importance (5).

However, only a few factors have been shown to be associated with clinical course. Especially the genetic factors that influence the clinical course are remained unclear despite the heritability that has been shown by family studies (6, 7).

The serotonin transporter gene is one of the most studied genes for depression. Previous studies showed that polymorphisms in the serotonin transporter gene may influence antidepressant response (8, 9), neuroticism (10) and hippocampus volume (11) in depressive patients.

Although many phenotypes of serotonin transporter gene were investigated, there are few studies about clinical course. A retrospective study showed *5-HTTLPR* polymorphisms were not associated with mood disorders time course (12). However they excluded chronic depression. A population-based study of major depressive disorder showed association of *5-HTTLPR* and durations of episode (13). However no replication results were reported in an Asian population. Furthermore they estimated the duration of episodes in quantitative traits, not qualitative traits. Therefore, association between *5-HTT* gene polymorphism and chronicity was still unclear.

We examined the association of serotonin transporter gene polymorphisms with the chronic illness of depression in Korean subjects. All subjects were of unrelated Korean ancestry. Eligible patients were enrolled in the Clinical Trials Program of the Samsung Medical Center Geropsychiatry and Affective Disorder Clinics (Seoul, Korea). Entry criteria were: at least 18 yr of age, unipolar major depressive episode by DSM-IV criteria, at least 2 yr after first episode onset, agreement to informed consent. Exclusion criteria were: pregnancy, significant medical conditions, abnormal laboratory baseline values, unstable psychiatric feature (e.g., suicidal attempt), history of alcohol or drug

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dependence, seizures, neurological illness or concomitant Axis I psychiatric disorder. A total of 252 patients were enrolled. This study was approved by the Institutional Review Board of the Samsung Medical Center (IRB number 2005-09-068).

At entry, all patients received a semistructured diagnostic interview, the Samsung Psychiatric Evaluation Schedule (14) for diagnostic evaluation and clinical data collection. The SPES provides information about psychiatric symptoms, comorbid psychiatric diagnoses, and psychosocial variables (age, sex, age of onset, duration of current episode, episode number, family history and initial Hamilton Rating Scale for Depression [HAM-D]). Clinical data was collected by structured interview with patient and at least 1 family member. Psychiatric diagnoses were confirmed by a board-certified psychiatrist.

We classified the chronic illness into two categories; chronicity and recurrent tendency. Defining depressions as chronic and non-chronic is arbitrary nature of the cutoff point. Furthermore definitions of chronic depression also differ with respect to severity and pattern. The DSM-IV includes a number of categories and specifiers for chronic depression; chronic depressive episode, dysthymic disorder, major depressive episode with antecedent dysthymia and current major depression with incomplete interepisode recovery. In this study chronicity was defined as duration of current episode was not less than 24 months according to DSM-IV criteria of chronic depressive episode. We excluded another categories for chronic depression; dysthymic disorder, major depressive episode with antecedent dysthymia and current major depression with incomplete interepisode recovery.

And a cohort study showed that patients who have a history of three or more episodes has shorter inter-episode interval than those with a first time onset of unipolar major depression (15). Based on this evidence, recurrent tendency was defined as no fewer than 2 episodes in this study. We defined recurrence as occurring of another episode with interepisode recovery. The definition of depressive episode was defined as DSM-IV criteria.

Patients were genotyped for short/long (s/l) polymorphisms in *5-HTT* promoter region (*5-HTTLPR*), s/l variation in second intron of the *5-HTT* gene (*5-HTT VNTR* intron2). Genomic DNA was extracted from whole blood and *5-HTT* genotyping was performed essentially as described previously (14).

In statistical analysis, means and standard deviations of continuous variables and proportions of categorical variables were presented as descriptive statistics. The Mann-Whitney U test was used for continuous variables when they were not normally distributed and chi-square test was used for categorical variables. Hardy-Weinberg equilibrium was tested by chi-square test. Logistic regression model, with appropriate covariates (chronicity: sex, age; recurrent tendency: sex, age, age of onset), was used to evaluate the association of independent variables with the chronicity and the recurrent tendency. Result were considered significant at P value <0.05. All statistical analyses were performed using STATA 10.0 for Windows.

Clinical and demographic characteristics are shown in Table 1. There were no major differences between patients with chronicity and the other patients with sex, age, age of onset, initial HAM-D scores and first degree family history. There were no notable differences between patients with recurrent tendency and the other patients with sex, age and initial HAM-D. But patients with recurrent tendency showed earlier age of onset (43.3 vs 53.0, P<0.001) and higher rate of first degree family history. (30.3% vs 18.3%, P=0.027)

Among the subjects, 19.3% of subjects had chronicity and 39.3% of subjects had recurrent tendency. Only 8% of patients with recurrent tendency had chronicity and 22% of patients with chronicity had recurrent tendency.

The *5-HTTLPR* and the *5-HTT VNTR* intron2 genotypes were distributed according to the Hardy-Weinberg equilibrium. Chro-

Table 1. Characteristics of study patients and distribution according to genotypes

Characteristics/Genotypes	Overall	Chronicity (Duration of Current Episode)			Recurrent Tendency (Number of Episode)		
		≥24 months	<24 months	*P* value	≥3	<3	*P* value
Total†	252			0.67			0.22
Male	56	9	47		18	38	
Female	196	27	169		81	115	
Age* (yr)	62.5 (54.5-69)	59 (51.5-66.5)	63 (55-69)	0.24	64 (55-71)	61 (54-68)	0.26
Age of Onset* (yr)	52 (40-60)	45 (38.5-58)	52 (40-60)	0.27	43 (30-55)	55 (45-61)	<10-4
Initial HAM-D*	20 (17-24)	20 (18-23)	20 (17-24)	0.68	20 (17-23)	20 (17-24)	0.23
% 1st degree family history†	23.02%	16.67%	24.07%	0.33	30.30%	18.30%	0.027
5-HTTLPR‡				0.005			0.29
l/l	18	7	11	[OR]=4.45	9	9	[OR]=1.79
s/l plus s/s	234	29	205	(95% CI: 1.59-12.46)	90	144	(95% CI: 0.60-5.28)
5-HTT VNTR intron2‡				0.48			0.32
l/l	206	28	178	[OR]=0.73	77	129	[OR]=0.68
s/l plus s/s	46	38	8	(95% CI: 0.31-1.74)	22	24	(95% CI: 0.32-1.45)

*The Mann-Whitney U test was used; Value is median (interquartile); †The χ^2 test was used; ‡Logistic regression analysis was used.
HAM-D, hamilton rating scale for depression score; 5-HTTLPR, serotonin transporter gene-linked polymorphic region; 5-HTT, serotonin transporter; OR, odds ratio; CI, confidence interval; VNTR, variable number of tandem repeats.

nicity was associated with *5-HTTLPR*. Patients with l/l had higher rate of chronic depression than the other patients (l/l vs s/l plus s/s; Odds ratio, 4.45; 95% confidence interval, 1.59-12.46; *P*=0.005). We calculated that the sample size gives 81% power at the 0.05 level of significance. However, chronicity was not associated with *5-HTT VNTR* intron2. Recurrent tendency was not associated with *5-HTTLPR* and *5-HTT VNTR* intron2 (Table 1). The study was not powered to detect significant associations with recurrent tendency and polymorphisms.

In this study we investigated possible genetic predictors of chronicity and recurrent tendency of depression. The result indicate that chronic depression is associated with *5-HTTLPR*. However, recurrent tendency was not associated with *5-HTTLPR*. Chronicity and recurrent tendency were not associated with *5-HTT VNTR* intron2. To the best of our knowledge, this is the first study of the association between the polymorphisms of serotonin transporter and episode duration in Asian subjects.

In the previous study that was conducted in American population, individuals with 1 or 2 short alleles (s/l or s/s) had episodes that were about 20 weeks shorter (13). It was similar with the result of our study. Contrast with pharmacogenetic studies it showed that the association of episode duration and *5-HTTLPR* has no ethnic difference (9, 16). Studies of *5-HTTLPR* reported that in white populations, depressed patients with the short allele genotype (s/s) generally show a smaller response to selective serotonin reuptake inhibitors than those with a long allele (l/l and s/l). However, studies in Korean and Japanese population report an association in the opposite direction (8, 17). It suggests the possibility of different mechanism of genetic influence to chronicity and drug response.

In our data only 8% of patients with recurrent tendency had chronicity and 22% of patients with chronicity had recurrent tendency. Moreover, *5-HTTLPR* was associated with chronicity and has no association with recurrent tendency. This inconsistent result between chronicity and recurrent tendency suggests the genetic difference of chronic depression and recurrent depression. However, our study was not powered to detect significant associations with recurrent tendency and polymorphisms. The further genetic investigations were needed to reveal the relationship between chronic depression and recurrent depression.

The major limitation of our study is its retrospective approach of clinical course. Recall bias could affect detection of past episode and duration of illness. Lack of adequate clinical information is notable limitation. Our study did not include the whole clinical course. The past episode durations and the natural course of current episode were not assessed. And past medication and antidepressant response history were not included in the analysis. In addition, we have little consideration on psychosocial factors despite its influence on mental illness (18). Another limitation is the generalizability of study finding. Our participants were mostly elderly, and most had late-onset illness. Despite these limitations, this study demonstrates the significant association of genetic factor and chronicity of depression.

In conclusion, we examined the association of serotonin transporter gene polymorphisms with the chronicity and the recurrent tendency of depression in Korean subjects. These results suggest that chronic depression is associated with *5-HTTLPR*. Confirmation of this preliminary finding would help to predict the clinical course of depression by genetic evaluation.

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