Turk J Pharm Sci 13(2), 145-158, 2016

Original article

Association Between the *5-HTTLPR* Polymorphism and Response to Citalopram in Turkish Patients with Major Depressive Disorder

Zuhal UCKUN[1], Bora BASKAK[2], Hatice OZDEMIR[3], Erguvan Tugba OZEL-KIZIL[2], Halise DEVRİMCİ OZGUVEN[2], Halit Sinan SUZEN[4,*]

[1]Mersin University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Yenisehir Campus, 33169, Mersin, TURKEY, [2]Ankara University, School of Medicine, Psychiatry Department, 06590, Dikimevi, Ankara, TURKEY, [3]Kırıkkale University, Faculty of Medicine, Department of Psychiatry, Kırıkkale, TURKEY, [4]Ankara University, Faculty of Pharmacy, Department of Toxicology, Tandogan, 06100 Ankara, TURKEY

The objective of this study was to investigate the relationship between the genetic polymorphism of the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*) and the response to citalopram treatment and side effects in Turkish patients with major depressive disorder. The study involved 51 patients who received 10-40 mg/day of citalopram for 4 to 6 weeks. Clinical symptoms were evaluated by the 17-item Hamilton Depression Rating (HAMD-17) scale, Clinical Global Impression (CGI) and UKU side effect rating scale (UKU) at weeks 4 and/or 6. The *5-HTTLPRL/S* polymorphism was determined by slowdown-polymerase chain reaction method. Of the fifty-one patients, 13 (26%) were the LL genotype, 21 (41%) were the LS genotype, 17 (33%) were the SS genotype. L allele seems to be associated with better response due to odds ratio for L allele versus S allele despite statistically insignificant. In terms of CGI-Severity scale, The *LL* genotype versus the *LS* genotype had a higher risk at the week 6 (P<0.05). On the other hand, apart from this comparison, there is no significant difference in CGI-Severity and Improvement and UKU scales according to the distribution of genotypes at week 4 and/or 6. However, these findings surely need further investigation and confirmation.

Key words: *5-HTTLPR* polymorphism, Citalopram, Treatment response, Side effects

Major Depresif Bozukluğu Olan Türk Hastalarda *5-HTTLPR* Polimorfizmin ve Sitalopram Yanıtı Arasındaki İlişkisi

Bu çalışmanın amacı, serotonin transporter geni bağlantılı polimorfik bölgenin (*5-HTTLPR*) genetik polimorfizmini ve bunun majör depresif bozukluğu olan Türk hastalarda sitalopram tedavisine yanıt ve tedavinin yan etkileriyle ilişkisini araştırmaktır. Çalışma, 4 ile 6 hafta boyunca 10-40 mg/gün sitalopram kullanmış 51 hastadan oluşmuştur. Klinik belirtiler 4 ve/veya 6 haftada 17 maddelik Hamilton Depresyon Derecelendirme (HAMD-17) ölçeği, Klinik Global İzlenim (KGİ) ve UKU Yan Etki Değerlendirme ölçekleri (UKU) ile değerlendirildi. *5-HTTLPRL/S* polimorfizmi yavaşlama-polimeraz zincir reaksiyonu yöntemi ile belirlenmiştir. Elli bir hastanın, 13'ü (% 26) *LL* genotip, 21'i (% 41) *LS* genotip, 17'si (% 33) ise *SS* genotipli idi. S aleline karşı L allelin odds oranından dolayı, istatistiksel olarak anlamlı olmamasına rağmen L alleli daha iyi yanıt verme ile ilişkili görünmektedir. KGI-Şiddet ölçeği açısından, 6. haftada *LS* genotipe karşı *LL* genotipi daha yüksek riske sahipti (P<0.05). Öte yandan, bu kıyaslamının dışında 4. ve/veya 6. haftada genotip dağılımlarına göre KGİ-Şiddet ve İyileşme ve UKU ölçeklerinde önemli farklılık bulunmamaktadır. Ancak, bu bulguların daha fazla araştırılması ve doğrulanması gerekmektedir.

Anahtar kelimeler: *5-HTTLPR* polimorfizmi, Sitalopram, Tedavi yanıtı, Yan etkiler

***Correspondence:** E-mail:suzen@pharmacy.ankara.edu.tr, Tel: +90 312 2033119

INTRODUCTION

Major depressive disorder (MDD, major or unipolar depression) affects over 340 million people worldwide (1) and is an important clinical problem that has a lifetime risk in 15-20% of the general populations (2). The prevalence of MDD is twice in women than men (2) and the lifetime prevalance is 10-25% in women and 5-12% in men (3). The prevalence of MDD is on the rise. It has been predicted that MDD would be the second leading cause of death and disability by the year 2020 (4).

The selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for mild to severe MDD(5). However, approximately 30-40% of patients with depression do not sufficiently respond to treatment with SSRIs (5). Generally, it can be determined whether an antidepressant drug is effective or ineffective after 4-6 weeks of treatment (6). However, this extensive period increases the cost of treatment (7). Therefore, recently, treatment response in MDD has become a popular topic to pharmacogenetic studies.

The principal site of action of SSRIs is the serotonin transporter (5- hydroxytryptamine transporter, *5-HTT*, *SERT, SLC6A4*) and these drugs inhibit *5-HTT*(5). 5-HTT is a member of the family of the Na^+/Cl^--dependent membrane transporters and controls the spread of the serotonergic signal in time and space by reuptake of serotonin (5-hydroxytryptamine, 5-HT) that exerts its effects immediately after its release from the synaptic cleft (8). Thus, *5-HTT* is the first candidate of approaching a genetic predictor of response to SSRIs. The human gene-encoding serotonin transporter is located on chromosome 17q11.1-q12, spans 31 kb and consists of 14 exons. The most common polymorphisms in *5-HTT* gene are insertion/deletion and VNTR polymorphisms (8). In this study, the insertion-deletion polymorphism was investigated. The common length polymorphism, termed the *5-HTT*-linked polymorphic region (*5-HTTLPR* or *SERTPR*), is constituted by an insertion-deletion of 44 bp in the promoter region (9) and thereupon, results in a short (S, 484 bp) and long (L, 528 bp) polymorphisms. It has been shown that these alleles can alter transcription and functional capacity of *5-HTT* (9,10). S allele is known to be associated with decreased transcriptional activity of the *5-HTT* gene and lowered *5-HTT* expression (11). Polymorphisms have also been determined to play a role in the etiology and outcome of several psychiatric disorders including anxiety disorders, mood disorders, schizophrenia as well as autism (10,12-14) and some psychosomatic disorders (13).

The objective of this study was to investigate the relationship between the *5-HTTLPR* polymorphism and the response to citalopram treatment and side effects in Turkish patients with MDD.

MATERIAL AND METHOD

Subjects

The present investigation was conducted in 51 Turkish patients receiving 10-40 mg/day citalopram at the Departments of Psychiatry, Schools of Medicine, Ankara University and Kırıkkale University, Turkey. The presence of MDD was diagnosed with the structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (15). Inclusion criteria were meeting DSM-IV diagnosis of MDD, being under stable citalopram medication regimen (for at least 4 weeks). All participants were aged 18 to 65. Exclusion criteria were as follows; pregnancy, substance dependency or drug abuse, and ongoing treatment with any other antidepressant or antipsychotic, history of head trauma with loss of consciousness. The study protocol was approved by the Ethics Committee of the Ankara University and conducted in accordance with Good Clinical Practices and the Helsinki declaration. Informed written consent was obtained from each patient before participating in the study.

Blood sampling

Blood samples (10 mL) were taken from using EDTA vacutainer tubes between 08:00 and 09:00 a.m. at the 4^{th} and/or 6^{th} weeks before the daily dose of citalopram. Genomic DNA was extracted from the cell fraction immediately by use of the Wizard Genomic DNA Purification Kit (Promega, Madison, WIS, USA). DNA yields were estimated by

measuring the absorbance at 260 nm (A260). All samples were stored at -80°C until analysis.

Genotyping

The *5-HTTLPR* polymorphism was identified by slowdown-polymerase chain reaction (PCR) method according to Frey et al. (16) with minor modifications.

The primers employed were F: 5'-GGCGTTGCCGCTCTGAATGC-3', R: 5'-GAGGGACTGAGCTGGACAACCAC-3' (10). Each reaction mixture (25 µL) contained ~ 100 ng of DNA template, 10 pmol of each primer, 0.2 mM each deoxynucleotide triphosphate, 10 x PCR buffer, 2.5 mM $MgCl_2$, and 1.25 unit of Taq polymerase (Fermentase) on the MBS Satellite Thermal Cycler (Thermo, UK). Negative control reactions with no added DNA were included in each slowdown-PCR analysis to ensure the reagents used contained no contaminating DNA. The slowdown-PCR product was analyzed electrophoretically on a 2% Gamma prona agarose gel stained with ethidium bromide (500 ng/mL). Alleles were designated as short (484 bp) and long (528 bp) against a DNA marker in genotyping for the *5-HTTLPR* polymorphism.

Clinical measures

Clinical symptoms were evaluated by the 17-item Hamilton Depression Rating (HAMD-17) Scale and Clinical Global Impression Scale (CGI) was employed to assess severity of illness and global improvement of symptoms (17). Furthermore, the presence and severity of side effects was assessed by using the UKU scale which included four subscales: psychic, neurological, autonomic, and "other" (18). These evaluations were done at baseline and weeks 4 and/or 6 of treatment. Responders were defined as those subjects with a decrease in HAMD score by ≥50% from the baseline to weeks 4 and/or 6.

Statistical analysis

Allele and genotype frequencies were calculated by genotype counting method. The observed genotype frequencies of *5-HTTLPR* were compared with the expected frequencies according to Hardy–Weinberg equilibrium. The comparison of demographic and clinical data among the *5-HTTLPR* genotypes was done using chi-square test (X^2) and one-way analysis of variance test (One-Way ANOVA), as appropriate. For One-Way ANOVA test, means were compared using Duncans multiple range post hoc test. Statistical analyses were performed using SPSS for Windows 11.5 software. P value <0.05 was considered as statistically significant.

RESULTS

The *5-HTTLPR* polymorphisms analysis was conducted with 51 Turkish patients with MDD. Table 1 shows baseline characteristics of the patients according to *5-HTTLPR* polymorphisms.

Of the fiftyone patients, 86% of patients were female, whereas 14% of them were male (p>0.05) and 13 (26%) were homozygous for the *L* allele, 21 (41%) were heterozygous, and 17 (33%) were homozygous for the *S* allele.

Of the fiftyone participants, treatment response was assessed in 46 patients because 5 participants dropped out. As depicted in Table 2, 36 (78%) subjects were determined to be treatment responders (*R*+) and 10 (22%) were nonresponders (*R*-). Of the 36 *R*+ subjects and the 10 *R*- subjects, 9 (25%) and 1 (10%) had *LL* genotypes, 15 (42%) and 5 (50%) had *LS* genotypes, 12 (33%) and 4 (40%) had *SS* genotypes, respectively. *R*+ and *R*- subjects were not different in terms of polymorphisms (p>0.05). However, the results were observed that odds ratios (ORs) for *LL* + *LS* genotypes versus *SS* genotypes and *L* allele versus *S* allele were 1.333 (95% CI 0.251-6.929, p>0.05), and 1.571 (95% CI 0.506-4.987, p>0.05), respectively.

CGI-Severity & Improvement and ORs according to *5-HTTLPR* genotypes are shown in Table 3. In terms of CGI-Severity, the *LS* genotype versus the *LL* genotype had 4.44 times higher risk at week 4 although statistically insignificant. However, the *LL* genotype versus the *LS* genotype had 6.50 times higher risk at the week 6 and this comparison was statistically significant (p<0.05). *L* allele versus *S* allele had 2.70 times higher risk at week 4 and 6, inspite of

Table 1. Baseline characteristics of the patients with major depression according to *5-HTTLPR* polymorphisms

		5-HTTLPR genotypes			p value
	Total	***L/L***	***L/S***	***S/S***	
n (%)	51 (100)	13 (26)	21 (41)	17 (33)	
Gender (Female/Male)	44/7	13/0	16/5	15/2	0.140[a]
Age, years	37,3±11	32.5±8.5	42±11.5	37.3±12.9	0.129[b]
Citalopram dose, mg/day	23.75±2.50	21.5±3.75	25±6.71	24.7±8.74	0.331[b]
Smoking habit, Yes/No	26/25	7/6	12/9	7/10	0.602[a]
Education, n					0.612[a]
Primary education	13	4	6	3	
Secondary education	10	3	2	5	
High school	17	5	7	5	
College	11	1	6	4	
Employment, n					0.705[a]
Employed/Student	16	3	9	4	
Housewife	24	7	8	9	
Retired	9	2	3	4	
Unemployed	2	1	1	0	
Maritul status, n					0.932[a]
Married	37	10	16	11	
Single (Never-married)	9	2	3	4	
Divorced/Widow	5	1	2	2	
Family history, Yes/No	15/36	3/10	7/14	5/12	0.816[a]
UKU; Side effects, Yes/No	43/8	12/1	16/5	15/2	0.392[a]

Data expressed as mean ± SD, number of cases in parentheses.
[a]Chi-square, [b]One-Way ANOVA test-means were compared using Duncans multiple range post hoc test(*df=2*, *F= 2.752* for age; *df=2*, *F =1.133* for dose).

Table 2. Response to Citalopram according to *5-HTTLPR* genotypes

	Response to Citalopram[a]	
Genotype	Positive n (%)	Negative n (%)
Total	36 (78)	10 (22)
LL	9 (25)	1 (10)
LS	15 (41,7)	5 (50)
SS	12 (33.3)	4 (40)

[a]p> 0.05, Positive versus Negative.

Table 3. CGI-Severity & Improvement according to *5-HTTLPR* genotypes

Genotype

			More	Less			
			n (%)	n (%)	X^2	OR[a] (95% CI)	p
CGI-Severity	Week 4	LS	9 (35)	10(53)		1(reference)	
		LL	8(30)	2 (10)	2.876	**4.44** (0.592–40.87)	0.090
		SS	9 (35)	7 (37)	0.274	1.43 (0.307–6.76)	0.600
	Week 6	*LS*	2 (22)	13 (48)		1 (reference)	
		LL	5 (56)	5 (19)	4.001	**6.50 (0.708 – 73.765)**	**0.045***
		SS	2 (22)	9 (33)	0.115	1.44 (0.113 – 18.639)	0.735
CGI-Improvement	Week 4	*LL*	3 (15)	7 (28)		1 (reference)	
		LS	9 (45)	10 (40)	0.815	**2.10** (0.324 – 14.631)	0.367
		SS	8 (40)	8 (32)	1.008	**2.33** (0.338 – 17.401)	0.315
	Week 6	*LL*	4 (44)	6 (22)		1 (reference)	
		SS	4 (44)	7 (26)	0,029	0.86 (0.103 – 7.028)	0.864
		LS + SS	5 (56)	21 (78)	1.662	0.36 (0.054 – 2.279)	0.197

Allele

			More	Less			
			Frequency		X^2	OR (95% CI)	p
CGI-Severity	Week 4	***S***	0.33	0.57		1 (reference)	
		L	0.67	0.43	3.132	**2.70** (0.781 – 9.606)	**0.077**
	Week 6	***S***	0.33	0.57		1 (reference)	
		L	0.67	0.43	3.132	**2.70** (0.781 – 9.61)	**0.077**
CGI-Improvement	Week 4	***L***	0.38	0.48		1 (reference)	
		S	0.62	0.52	0.998	**1.54** (0.606 – 3.924)	0.318
	Week 6	***L***	0.5	0.48		1 (reference)	
		S	0.5	0.52	0.019	**1.08** (0.326 – 3.555)	0.892

			Absent	Present			
			n (%)	n (%)	X^2	OR (95% CI)	p
CGI-Improvement	Week 4	*LL*	3 (15)	7 (28)		1 (reference)	
		LS	9 (45)	10 (40)	0.815	**2.10** (0.324 – 14.631)	0.367
		SS	8 (40)	8 (32)	1.008	**2.33** (0.338 – 17.401)	0.315
	Week 6	*LL*	4 (44)	6 (22)		1 (reference)	
		SS	4 (44)	7 (26)	0,029	0.86 (0.103 – 7.028)	0.864
		LS + SS	5 (56)	21 (78)	1.662	0.36 (0.054 – 2.279)	0.197

[a]OR: Odds ratio.

*p <0.05.

statistically insignificant. On the other hand, in terms of CGI-Improvement, the *LS* genotype and the *SS* genotype versus the *LL* genotype at week 4 had 2.10 and 2.33 times higher risk, respectively, despite statistically insignificant.

Table 4 has shown UKU side effect rating subscale and ORs according to *5-HTTLPR* promoter polymorphism. The presence and severity of side effects was assessed by using the UKU scale which included four subscales: psychic, neurological, autonomic, and "other" (18) at the end of the 4th week of pharmacological treatment. As depicted in Table 4, the *LL* genotype and the *LS* genotype versus the SS genotype had 3.21 times and 2.32 times higher risk for UKU psychic subscale, respectively. For UKU autonomic subscale, patients with the SS genotype versus the *LL* genotype had 2.80 times higher risk. For UKU "other" subscale, patients with the *LL* genotype versus the SS genotype had 2.00 times higher risk. However, these comparisons were statistically insignificant ($p>0.05$).

DISCUSSION

Baseline characteristics of the patients with major depression

In the present study, we assessed baseline characteristics of the patients with major depression according to *5-HTTLPR* polymorphisms as depicted in Table 1. Age, gender and marital status are found to be associated with depression as a result of epidemiological studies in different countries (19). The risk of MDD is generally higher in women than men (2,3,19). Furthermore, the proportion of major depression is significantly higher in individuals who are divorced or separated compared to the married individuals (19). The results of major depression related to age may be inconsistent. According to some studies, the prevalence of major depression decrease with age (19). Whereas, other studies found that major depression is increased with age (19). In this study, education level, marital and employment status were comparable among different polymorphism groups and this enables a clear discussion of our results.

Correlation between 5-HTTLPR genotypes and response to citalopram treatment

Much recent research has focused on identifying genetic predictors of treatment response. The variability in interindividual pharmacological response give rise to different problems of efficacy and safety, especially in psychopharmacotherapy (20). Therefore, genetic factors seem to be biomarkers of responses to treatment (21).

To the best of our knowledge, the study was the first to investigate the association between *5-HTTLPR* promoter polymorphism and response to citalopram treatment in Turkish population.

It has been reached predictive information that subjects having *L* allele might have better response to citalopram treatment than those having *S* allele because odds ratio for *L* allele versus *S* allele was 1.571 in spite of statistically insignificance. Our results were in accordance with most of the studies in Caucasian – and not Oriental – populations (Table 5). Significant associations between the long variant and good treatment response have been reported in most of studies performed in Caucasian populations. On the other hand, the *SS* genotypes were reported to be more likely to respond in the studies performed in Oriental populations. However, findings in both inter-ethnicity and intra-ethnicity have not always been consistent as shown in Table 5. There are several possible explanations for this discrepancy. First, the frequencies of *L* and *S* alleles are different between Caucasian and Oriental populations. The frequencies of the *LL* genotype and the SS genotype in Caucasian are 29–43% (47) and 21.6 to 28.3% (48), respectively while those in Oriental populations are 1–13% (47), 55.6 and 60.0% (48), respectively. The *L* allele is present ~55% in Caucasians and ~ 25% in Oriental populations, respectively (40). The *S* allele is present in 42% in Caucasians and 79% in Oriental populations, respectively (49). Secondly, other polymorphisms in the *5-HTT* gene or other relevant genes may be possible factors and and were not assessed in the present study. Finally, the interactions between *5-HTTLPR* genotype and the other genes, drug plasma concentration, life events and gender may be

Table 4. UKU side effect rating subscale and OR value according to *5-HTTLPR* promoter polymorphism

GENOTYPE						ALLELE				
	Genotype	Yes, n (%)	No n (%)	OR[a] (%95 CI)	p value	Allele	Frequency Yes	Frequency No	OR (%95 CI)	p value
UKU Psychic subscale	*SS*	7 (24)	10 (45)	1 (reference)		**UKU Psychic subscale**				
	LS	13 (45)	8 (36)	**2.32** (0.522 – 10.674)	0.203	*S*	0.47	0.64	1 (reference)	
	LL	9 (31)	4 (18)	**3.21** (0.558 – 19.904)	0.127	*L*	0.53	0.36	**2.01** (0.836 – 4.861)	**0.086**
	LL + LS	22 (76)	12 (55)	**2.62** (0.682 – 10.334)	0.110					
UKU Autonomic subscale	*LL*	6 (21)	7 (30)	1 (reference)		**UKU Autonomic subscale**				
	LS	10 (36)	11 (48)	1.06 (0.213 -5.302)	0.934					
	SS	12 (43)	5 (22)	**2.80** (0.490 – 17.004)	0.176	*L*	0.39	0.54	1 (reference)	
	LS + SS	22 (79)	16 (70)	1.60 (0.382 – 6.826)	0.463	*S*	0.61	0.46	**1.25** (0.549 – 2.834)	0.566
UKU "Other" subscale	*SS*	9 (33)	8 (33)	1 (reference)		**UKU "Other" subscale**				
	LS	9 (33)	12 (50)	0.67 (0.150 – 2.910)	0.536					
	LL	9 (33)	4 (17)	**2.00**(0.348 – 12.023)	0.367	*S*	0.50	0.58	1 (reference)	
	LL + LS	18 (67)	16 (67)	1.00 (0.266 – 3.749)	1.00	*L*	0.50	0.42	**1.40** (0.594 – 3.308)	0.399

[a]OR: Odds ratio

possible factors (50). As a result, it may be concluded that *5-HTTLPR* may be a biomarker of response to antidepressant in Caucasians, but it does not appear to play a main role in Oriental populations.

In this study, we also investigated the relationship between the *5-HTTLPR* genotypes and CGI-Severity&Improvement. Interestingly, our results suggested that patients with the *LL* genotype or *L* allele had higher disease severity than patients with the *SS* genotype or *S* allele. Furthermore, the *LS* and/or *SS* genotypes hadin favour for CGI-improvement than the *LL* genotype. However, there is no significant difference in either CGI-severity or CGI-improvement according to the distribution of genotypes at week 4 and 6 except that the comparison of *LL* genotype to the *LS* genotype at the week 6 in terms of CGI-Severity scale ($P<0.05$).

The association between the 5-HTTLPR polymorphism and side effects

Side effects are among primary reason to incompliance in SSRI treatment. The present study, 84% of patients had side effects but the remaining 16% had not. 57, 55 and 53% of patients had side effects in terms of psychic, autonomic and "other" subscale, respectively. The most frequently reported psychic side effects were sleepiness/sedation (38%), increased duration of sleep (28%) and reduced duration of sleep (17%). The most common autonomic side effects were nause/vomiting (39.3%), palpitations/tachycardia (28.5%), increased tendency to sweating (25%) and constipation (18%). Furthermore, headache (37%) and sexual dysfunction (increased sexual desire plus diminished sexual desire) (37%) were the most often declared side effects among "other" subscale. These results are in accordance with those of previous studies related to the frequent of side effects during SSRIs (51, 52).

Our findings suggested that patients with the *LL* genotype and the *LS* genotype versus the *SS* genotype had a higher risk for psychic side effects. For UKU "other" subscale, the *LL* genotype versus the *SS* genotype had a higher risk. Whereas, for autonomic side effects, the *SS* genotype versus the *LL* genotype were under a higher risk. Nevertheless, comparison of the subjects with the *LL* genotype and those with the *LS* and *SS* genotypes revealed no significant differences in the UKU side effect rating subscale at week 4.

Side effects can be related to stimulation of different serotonin receptors. For instance, the 5HT2 receptors are thought to have a role in mood, anxiety, sexual function, sleep, eating behavior (53). Moreover, the 5HT3 receptors are involved in nause, vomiting, appetite and GI motility (53). The *5-HTTLPR* polymorphism may moderate some of SSRI-induced side effects caused by increased serotonin levels and stimulation of serotonin receptors. However, this hypothesis that the *5-HTTLPR* genotype plays a certain role in inducing side effects during SSRI treatment is unclear (52).

The main limitation of our study was the small sample size. The amount of patients with variant alleles, female/male ratio, etc. were not high and socio demographic features were comparable among different polymorphism groups. Nevertheless, our findings are in accordance with some of previous studies findings in Caucasians. Moreover, the study provides valuable information because the study was the first to investigate the association between *5-HTTLPR* promoter polymorphism and response to citalopram treatment in Turkish population.

CONCLUSION

Consequently, our findings suggest that *L* allele tend for better response due to acceptable odds ratio values for *L* allele versus S allele despite statistically insignificant. Moreover, there is no significant difference in CGI and UKU according to the distribution of genotypes at week 4 and/or 6 except that the comparison of *LL* genotype to the *LS* genotype at the week 6 in terms of CGI-Severity scale ($P<0.05$). However, larger study populations are definetely required to confirm these findings.

ACKNOWLEDGEMENT

This work was supported by The Scientific and Technological Research Council of Turkey under Project 109S147.

Table 5. Summary of some of pharmacogenetic studies of *5-HTTLPR* polymorphisms in Caucasian and Oriental populations

Reference	n (Female/Male)	Mean age (years)	Drug	Dose (mg/day)	Inclusion criteria	Location	Population	Results
Caucasian or Mainly Caucasian								
Smeraldi et al. (22)	53 (37/16)	49.0	Fluvoxamine	100-300	[a]MDD + BP	Italy	Not specified	*LL* and *LS* genotype subjects were more likely to respond compared to *SS* genotype subjects (p=0.017)
Pollock et al. (23)	51 (not reported)	72.0 Whole group	Paroxetine	20-30	MDD	USA	Not specified	*LL* genotype associated with faster response in elderly (p=0.028)
Zanardi et al. (24)	58 (43/15)	47.7	Paroxetine	40	MDD + BP	Italy	Italian	*LL* and *LS* genotype associated with more favourable and faster response compared to *SS* genotype subjects (p<0.001)
Zanardi et al. (25)	88 (63/25)	52.0	Fluvoxamine	100-300	MDD + BP	Italy	Italian	*L* allele subjects were more likely to respond
Rausch et al. (26)	51 (not reported)	Not reported	Fluoxetine	0-40	MDD	USA	Not specified	*LL* genotype associated with response (p=0.001)
Joyce et al. (27)	86 (not reported)	31.8 Whole group	Fluoxetine	10-80	MDD+ BPII[a]	New Zealand	Not specified	*SS* genotype associated with slower response
Arias et al. (28)	131 (100/31)	40.0	Citalopram	20-40	MDD	Spain	Spanish	*SS* genotype was significantly more frequent in no remission group (p=0.013)
Perlis et al. (29)	37 (not reported)	Not reported	Fluoxetine	20-60	**M**MDD**D**	USA	Caucasian	Higher rate of insomnia and agitation in *S/S* subjects compared to *L/S* and *L/L*
Murphy et al. (30)	122 (64/57)	72.2	Paroxetine	20-40	MDD	USA	Mixed, 89% white	*L* allele subjects show a better response and less side effects
Serreti et al. (31)	220 (145/75)	50.6	Fluvoxamine Paroxetine	0-300 for FLUV[a] 0-40 for PAR[a]	MDD+BP	Italy	Italian	*SS* genotype associated with a poor response (p<0.034)
Durham et al. (32)	106 (59/47)	69.5	Sertraline	50-100	MDD	USA	Mixed, 95% white	*LL* genotype associated with faster response in elderly
Kirchheiner et al. (33)	77 (55/22)	44.0	Various SSRI	Common doses	MDD+ BP	Germany	Caucasian	No association
Bozina et al. (34)	130 (61/69)	45.0	Paroxetine	20	MDD	Croatia	Croatian	*LL* genotype associated with response
Ruhe et al. (35)	42 (27/15)	42.5	Paroxetine	10-20	MDD	Netherlands	69% Caucasian	*LL* genotype associated with response
Maron et al. (36)	135 92/43	31.3	Escitalopram	10-20	MDD	Estonia	96% Estonian	No association with response, but *S* alleleassociated with increased risk for side effects.
Huezo-Diaz et al. (37)	450 (278/172)	43.0	Escitalopram	10-30	MDD	Europe	White European	*LL* genotype associated with response
Dogan et al. (38)	64 (not reported)	37.0	Sertraline	50-100	MDD	Turkey	Turkish	No association
Yuksel et al. (39)	30 (17/13)	36.8	Venlafaxine	75-300	MDD	Turkey	Turkish	No association
The present study	**46 (40/6)**	**39.0**	**Citalopram**	**10-40**	**MDD**	**Turkey**	**Turkish**	***L* allele trend for better response due to odds ratio for *L* allele versus *S* allele despite statistically insignificant**

Table 5 continued

Oriental or Mainly Oriental

Reference	n (Female/Male)	Mean age (years)	Drug	Dose (mg/day)	Inclusion criteria	Location	Population	Results
Kim et al. (6)	120 (42/78)	54.2	Paroxetine, Fluoxetine	20-60 for PAR[a] 20-50 for FLUX[a]	MDD+BPI[a], II+Dysthymia	Korea	Korean	*SS* genotype subjects were more likely to respond (p=0.007)
Yoshida et al. (40)	54 (32/22)	51.2	Fluvoxamine	50-200	MDD+BP	Japan	Japanese	*SS* genotype subjects were more likely to respond (p=0.010)
Yu et al. (41)	121 (51/70)	44.7	Fluoxetine	20-60	MDD	China	Chinese	*LL* genotype subjects were more likely to respond (p=0.013)
Kato et al. (42)	81 (45/36)	44.8	Fluvoxamin Paroxetine	50-150 for FLUV[a] 20-40 for PAR	MDD	Japan	Japanese	*L* allele subjects were more likely to respond (p=0.015)
Hong et al. (43)	224 (131/93)	44	Fluoxetine	20-40	MDD	Taiwan	Chinese	*LL* genotype subjects were more likely to respond (p<0.001)
Kim et al. (44)	119 (86/33)	59.9	Fluoxetine, sertraline	20-50 for FLUX 20-60 for SERT[a]	MDD	Korea	Korean	*SS* genotype subjects were more likely to respond (p=0.006)
Ng et al. (45)	35 (18/17)	41.6	Sertraline	25-200	MDD	Australia& Malaysia	67% Chinese, 33%Australian	No association
Yoshimura et al. (46)	60 (38/22)	42	Paroxetine	20-40	MDD	Japan	Japanese	No association

[a] MDD-Major depressive disorder; BP-bipolar; BPI-Bipolar I; BPII-Bipolar II; FLUV-Fluvoxamin; PAR-Paroxetine; FLUX-fluoxetine, SERT-Sertraline.

REFERENCES

1. Slattery DA, Hudson AL, Nutt DJ, Invited review: the evolution of antidepressant mechanisms, Fundam Clin Pharmacol 18 (1), 1-21, 2004.
2. Albert PR, Lemonde S, 5-HT1A receptors, gene repression, and depression: guilt by association, Neuroscientist 10(6), 575-593, 2004.
3. Kessler RC, Mcgonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS, Life-time and 12-month prevalence of DSM-III-R psychiatric disorders in the United States, AMA 51, 8-19, 1994.
4. Murray CJ, Lopez AD, Evidence-based health policy-lessons from the global burden of disease study, Science 274(5288), 740-743, 1996.
5. Sahraian S, Babashams M, Reza-Soltani P, Najmabadi H, Kahrizi K, Gorgani SH, Serotonin transporter polymorphism (*5-HTTLPR*) and citalopram effectiveness in Iranian patients with major depressive disorder, Iran J Psychiatry 8(2), 86-91, 2013.
6. Kim DK, Lim SW, Lee S, Sohn SE, Kim S, Hahn CG, Carroll BJ, Serotonin transporter gene polymorphism and antidepressant response, Neuroreport 11(1), 215-219, 2000.
7. Smits KM, Smits LJ, Schouten JS, Peeters FP, Prins MH, Does pretreatment testing for serotonin transporter polymorphisms lead to earlier effects of drug treatment in patients with major depression? A decision-analytic model, Clin Ther 29(4), 691-702, 2007.
8. Serreti A, Benedetti F, Zanardi R, Smeraldi E, The influence of serotonin transporter promoter polymorphism (SERTPR) and other polymorphisms of the serotonin pathway on the efficacy of antidepressant treatments, Prog Neuropsychopharmacol Biol Psychiatry 29(6), 1074-1084, 2005.
9. Heils A, Teufel A, Petri S, Stöber G, Riederer P, Bengel D, Lesch KP, Allelic variation of human serotonin transporter gene expression, J Neurochem 66(6), 2621-2624, 1996.
10. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL, Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region, Science 274(5292), 1527-1531, 1996.
11. Lanctôt KL, Rapoport MJ, Chan F, Rajaram RD, Strauss J, Sicard T, McCullagh S, Feinstein A, Kiss A, Kennedy JL, Bassett AS, Herrmann N, Genetic predictors of response to treatment with citalopram in depression secondary to traumatic brain injury, Brain Inj 24(7-8), 959-969, 2010. doi: 10.3109/02699051003789229.
12. Klauck SB, Poustka F, Benner A, Lesch KP, Poustka A, Serotonin trasnporter (5-HTT) gene variants associated with autism, Hum Mol Genet 6(13), 2233 – 2238, 1997.
13. Erdal ME, Herken H, Barlas O, Erdal N, Serotonin transporter gen polimorfizmi, Klinik Psikiyatri 3, 192-196, 2000.
14. Flattern NL, Blakely RD, Modified structure of the human serotonin transporter promoter, Mol Psychiatry 5(1),110 -115, 2000.
15. First MB, Spitzer RL, Gibbon M, Williams JBW, Structured clinical interview for DSM-IV Axis I disorders (SCID-I), Clinical Version, American Psychiatric Press, Inc., Washington D.C., 1997.
16. Frey UH, Bachmann HS, Peters J, Siffert W, PCR-amplification of GC-rich regions: 'slowdown PCR', Nat Protoc 3(7), 1312-1317, 2008.
17. Guy W, ECDEU Assessment Manual for Psychopharmacology-Revised DHEW Publ No (ADM), Rockville, MD, NIMH,76-338, 1976.
18. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K, The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients, Acta Psychiatr Scand Suppl 334,1-100, 1987.
19. Kessler RC, Bromet EJ, The epidemiology of depression across cultures, Annu Rev Public Health 34, 119–138, 2013. doi:10.1146/annurev-publhealth-031912-114409.
20. Uckun Z, Baskak B, Ozel-Kizil ET, Ozdemir H, Devrimci Ozguven H, Suzen HS, The impact of CYP2C19 polymorphisms on citalopram metabolism in patients with major depressive disorder, J Clin Pharm Ther 2015 Sep 7. doi: 10.1111/jcpt.12320
21. Margoob MA, Mushtaq D, Murtza I, Mushtaq H, Ali A, Serotonin transporter gene polymorphism and treatment response to serotonin reuptake inhibitor (escitalopram) in depression: An open pilot study, Indian J Psychiatry 50(1), 47-50, 2008. doi: 10.4103/0019-5545.39759.
22. Smeraldi E, Zanardi R, Benedetti F, Di Bela D, Perez J, Catalona M, Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoksamine, Mol Psychiatry 3(6), 508-511, 1998.
23. Pollock BG, Ferrell RE, Mulsant BH, Mazumdar S, Miller M, Sweet RA, Davis S, Kishner MA, Houck PR, Stack JA, Reynolds CH, Kupfer DJ, Allelic variation in the

serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression, Neuropsychopharmacol 23(5), 587-590, 2000.
24. Zanardi R, Benedetti F, Di Bela D, Catalano M, Smeraldi E, Efficacy of paroxetine in depresseion is influenced by a functional polymorphism within the promoter of the serotonin transporter gene, J Clin Psychopharmacol 20(1), 105-107, 2000.
25. Zanardi R, Serretti A, Rossini D, Franchini L, Cusin C, Lattuada E, Dotoli D, Smeraldi E, Factors affecting fluvoxamine antidepressant activity: influence of pindolol and 5-HTTLPR in delusional and nondelusional depression, Biol Psychiatry 50(5), 323–330, 2001.
26. Rausch JL, Johnson ME, Fei YJ, Li JQ, Shendarkar N, Hobby HM, Ganapathy V, Leibach FH, Initial conditions of serotonin transporter kinetics and genotype: influence on SSRI treatment trial outcome, Biol Psychiatry 51(9), 723–732, 2002.
27. Joyce PR, Mulder RT, Luty SE, McKenzie JM, Miller AL, Rogers GR, Kennedy MA, Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G protein beta3 subunit as predictors of response to fluoxetine and nortriptyline, Int J Neuropsychopharmacol 6(4), 339–346, 2003.
28. Arias B, Catalan R, Gasto C, Guiterrez B, Fananas L, 5-HTTLPR polymorphism of the serotonin trasnporter gene predicts non-remission in major depression patients treated with citalopram in a 12 weeka follow up study, J Clin Psychopharmacol 23(6),563-567, 2003.
29. Perlis RH, Mischoulon D, Smoller JW, Wan YJ, Lamon-Fava S, Lin KM, Rosenbaum JF, Fava M, Serotonin transporter polymorphism and adverse effects with fluxetine treatment, Biol Psychiatry 54(9), 879 – 883, 2003.
30. Murphy JR, GM, Hollander SB, Rodrigues HE, Kremer C, Schatzberg AF, Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression, Arch Gen Psychiatry 61(11), 1163–1169, 2004.
31. Serretti A, Cusin C, Rossini D, Artioli P, Dotoli D, Zanardi R, Further evidence of a combined effect of SERTPR and TPH on SSRIs response in mood disorders, Am J Med Genet B Neuropsychiatr Genet 129B(1), 36–40, 2004.
32. Durham LK, Webb SM, Milos PM, Clary CM, Seymour AB, The serotonin transporter polymorphism, 5HTTLPR, is associated with a faster response time to sertraline in an elderly population with major depressive disorder, Psychopharmacology (Berl) 174(4), 525–529, 2004.
33. Kirchheiner J, Nickchen K, Sasse J, Bauer M, Roots I, Brockmöller J, A 40-basepair VNTR polymorphism in the dopamine transporter (DAT1) gene and the rapid response to antidepressant treatment, Pharmacogenomics J 7(1), 48–55, 2007, Epub 2006 May 9.
34. Bozina N, Peles AM, Sagud M, Bilusic H, Jakovljevic M, Association study of paroxetine therapeutic response with SERT gene polymorphisms in patients with major depressive disorder, World J Biol Psychiatry 9(3), 190–197, 2008.
35. Ruhe HG, Ooteman W, Booij J, Michel MC, Moeton M, Baas F, Schene AH, Serotonin transporter gene promoter polymorphisms modify the association between paroxetine serotonin transporter occupancy and clinical response in major depressive disorder, Pharmacogenet Genomics 19(1), 67–76, 2009.
36. Maron E, Tammiste A, Kallassalu K, Eller T, Vasar V, Nutt DJ, Metspalu A, Serotonin transporter promoter region polymorphisms do not influence treatment response to escitalopram in patients with major depression, Eur Neuropsychopharmacol 19(6), 451–456, 2009.
37. Huezo-Diaz P, Uher R, Smith R, Rietschel M, Henigsberg N, Marusic A, Mors O, Maier W, Hauser J, Souery D, Placentino A, Zobel A, Larsen ER, Czerski PM, Gupta B, Hoda F, Perroud N, Farmer A, Craig I, Aitchison KJ, McGuffin P, Moderation of antidepressant response by the serotonin transporter gene, Br J Psychiatry 195(1), 30–38, 2009.
38. Dogan O, Yuksel N, Ergun MA, Yilmaz A Ilhan MN, Karslioglu HE, Koc A, Menevse A, Serotonin transporter gene polymorphisms and sertraline response in major depression patients, Genet Test 12(2), 225–231, 2008.
39. Yüksel N, Dogan O, Ergun MA, Ersin Karslioglu H, Koc A, Yilmaz A, Ilhan MN, Menevse A, Correlation between SERT polymorphisms and Venlafaxine response in major depression patients, Genes&Genomics 32, 217-223, 2010.
40. Yoshida K, Ito K, Sato K, Takahashi H, Kamata M, Higuchi H, Shimizu T, Itoh K, Inoue K, Tezuka T, Suzuki T, Ohkubo T, Sugawara K, Otani K, Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients, Prog Neuropsychopharmacol Biol Psychiatry 26(2), 383–386, 2002.

41. Yu YW, Tsai SJ, Chen TJ, Lin CH, Hong CJ, Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders, Mol Psychiatry 7(10), 1115-1119, 2002.
42. Kato M, Fukuda T, Wakeno M, Fukuda K, Okugawa G, Ikenaga Y, Yamashita, M, Takekita Y, Nobuhara K, Azuma J, Kinoshita T, Effects of the serotonin type 2A, 3A and 3B receptor and the serotonin transporter genes on paroxetine and fluvoxamine efficacy and adverse drug reactions in depressed Japanese patients, Neuropsychobiology 53(1), 186-195, 2006.
43. Hong CJ, Chen TJ, Yu YW, Tsai SJ, Response to fluoxetine and serotonin 1A receptor (C-1019G) polymorphism in Taiwan Chinese major depressive disorder, Pharmacogenomics J 6(1), 27–33, 2006.
44. Kim H, Lim SW, Kim S, Kim JW, Chang YH, Carroll BJ, Kim DK, Monoamine transporter gene polymorphisms and antidepressant response in Koreans with late-life depression, JAMA 296(13), 1609-1618, 2006.
45. Ng CH, Easteal S, Tan S, Schweitzer I, Ho BK, Aziz S, Serotonin transporter polymorphisms and clinical response to sertraline across ethnicities, Prog Neuropsychopharmacol Biol Psychiatry 30(5), 953–957, 2006.
46. Yoshimura R, Umene-Nakano W, Suzuki A, Ueda N, Miyamoto K, Ikenouchi-Sugita A, Hori H, Otani K, Nakamura J, Rapid response to paroxetine is associated with plasma paroxetine levels at 4 but not 8 weeks of treatment, and is independent of serotonin transporter promoter polymorphism in Japanese depressed patients, Hum Psychopharmacol 24(6), 489–494, 2009.
47. Goldman N, Glei DA, Lin YH, Weinstein M, The serotonin transporter polymorphism (5-HTTLPR): allelic variation and links with depressive symptoms, Depress Anxiety 27, 260–269, 2010.
48. Smits KM, Smits LJ, Schouten JS, Stelma FF, Nelemans P, Prins MH, Influence of SERTPR and STin2 in the serotonin transporter gene on the effect of selective serotonin reuptake inhibitors in depression: a systematic review, Mol Psychiatry 9, 433–441, 2004.
49. Kunugi H, Hattori M, Kato T, Tatsumi M, Sakai T, Sasaki T, Hirose T, Nanko S, Serotonin transporter gene polymorphisms: ethnic difference and possible association with bipolar affective disorder, Mol Psychiatry 2, 457–462, 1997.
50. Porcelli S, Fabbri C, Serretti A, Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy, Eur Neuropsychopharmacol 22(4), 239-258, 2012.
51. Ferguson JM, SSRI Antidepressant Medications: Adverse effects and tolerability, Prim Care Companion J Clin Psychiatry 3(1), 22-27, 2001.
52. Smits K, Smits L, Peeters F, Schouten J, Janssen R, Smeets H, van Os J, Prins M, Serotonin transporter polymorphisms and the occurrence of adverse events during treatment with selective serotonin reuptake inhibitors, Int Clin Psychopharmacol 22(3), 137-143, 2007.
53. Stahl SM, Mechanism of action of serotonin selective reuptake inhibitors, Serotonin receptors and pathways mediate therapeutic effects and side effects, J Affect Disord 51(3), 215-235, 1998.

Received: 08.10.2015
Accepted: 24.12.2015