Original Article

Serotonin Transporter Polymorphism (5-HTTLPR) and Citalopram Effectiveness in Iranian Patients with Major Depressive Disorder

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Objective: Several studies have implicated the 5-HTTLPR polymorphism in treatment outcomes of selective serotonin re-uptake inhibitors in patients with major depression. The aim of this study was to examine the association between polymorphism in the serotonin transporter gene and citalopram effectiveness in Iranian patients suffering from major depressive disorder (MDD).
Methods: The sample consisted of 104 patients, with Fars ethnic background, who were diagnosed according to DSM-IV-TR criteria. Beck Depression inventory was used to evaluate the severity of the symptoms during the follow-up, and to determine clinical response of the patients at 4th and 8th week, respectively.
Results: Our results showed a correlation between the genotype and response to antidepressant drug citalopram, (odds ratios for L/S and L/L were 3.90 (95 percent CI: 1.29- 11.80) and 1.90 (95 percent CI: 0.72-5.08), respectively).
Conclusion: In conclusion, our results reveal that genetic variation of serotonin transporter is involved in clinical remission of major depressive episodes in Iranian patients after citalopram treatment.

Key words: *Major depressive disorder; 5-HTTLPR genotype; citalopram response; association study; Iran*

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Major depressive disorder (MDD) is a familial disorder, and is mostly resulted from genetic factors with a high prevalence (16.2%) (1, 2), although the effect of environmental influences is etiologically significant, antidepressant response is highly influenced by genetic constitution, but the actual genes involved have yet to be determined (3).

Depressive disorders have a large impact on social health (4). As it has been predicted that MDD would be the second leading cause of death and disability by the year 2020 (5), it became an ideal target for pharmacogenetic approaches (6). Based on many treatments which are commonly used for these patients, it can be stated that although a considerable proportion of patients benefit from the treatment, more than half will fail to respond adequately to the first antidepressants they are prescribed (7, 8). Among all choices of MDD treatment, the selective serotonin reuptake inhibitor (SSRI) antidepressants are mentioned as the first-line treatment of depression (9), but an estimated 30%-40% of patients with depression do not sufficiently respond to treatment with SSRIs (10) and the period in which treatment efficacy can be assessed is relatively long (11).

The molecular mechanism of ADs action, in particular, selective serotonin reuptake inhibitors

(SSRIs), involves the inhibition o f the serotonin transporter, and thus modulates the serotonergic activity (12). The human gene-encoding serotonin transporter (SLC6A4), is located on chromosome 17q11.1-q12 (13), which is the first candidate of approaching a genetic predictor of response to SSRIs (14). There are several functional polymorphisms in the SLC6A4 gene (The serotonin transporter gene-linked polymorphic region) (5-HTTLPR) (15). The common length polymorphism is constituted by a deletion or insertion of 44 base pairs in the regulatory region of the promoter and gives rise to short "S" and long "L" forms of the promoter region (16, 17).

The long allele is known to be associated with more efficient transcription (18), higher SLC6A4 expression, producing a gain-of-function phenotype, resilience to depressogenic effects of adversity (19), and better response to SSRI antidepressants (20).

Many studies have focused on the functional insertion-deletion promoter variant serotonin transporter-linked polymorphic region (5HTTLPR)) in the serotonin transporter gene (SLC6A4) (21). Meta-analysis suggests that s/s individuals are at a higher risk for unipolar depression but just a modest trend for bipolar depression, while other studies indicate that the s/s genotype increases the risk of bipolar depression but not unipolar depression (22). Some other meta-analysis studies showed that long-allele carriers have higher probability of response and remission than short-allele homozygotes, and on the other hand significant heterogeneity of 5-HTTLPR effect has been reported in non-European populations (23).

Whereas no effect of 5-HTTLPR on efficacy of citalopram was found in a large mixed-ethnicity sample (24), an ethnicity-sensitive re-analysis of the same sample found an effect in the expected direction among White non-Hispanic participants (25).

On the other hand, gender may be another important factor influencing the relationship between 5-HTTLPR genotype and antidepressant response. Ovarian steroids have a significantly strong influence on serotonin synthesis (26), expression of serotonergic receptors (27), and the transporter of serotonin (28). It seems that further studies and evidences on the potential association between 5-HTTLPR and depression or response to antidepressant drugs are needed. Our aim was to explore the association between the 5-HTTLPR polymorphism and response to an antidepressant drug (citalopram) in Iranian depressed patients.

Material and Methods

2.1 Subjects and treatment

At first we included 190 major depressant patients. Sample size was computed using this formula.

$$n = \frac{(Z_{1-\alpha/2})^2 * p * (1-p)}{d^2}$$

The subjects were selected by nonprobability method from Akhavan and Saba Treatment and Rehabilitation Clinic, Tehran, Iran. Written informed consents were taken and the study was approved by the Ethics Committee of Ethnics in the University of Social Welfare and Rehabilitation Sciences. Diagnoses were established according to the Diagnostic and Statistical Manual (DSM)-IV-TR criteria and only nonpsychotic major depressive disorder was included. An expert psychiatrist interviewed all of the patients. Diagnosis of bipolar disorder led to exclusion from the study. Patients were between 18 and 65 years of age and had to be free from psychiatric drugs at least four weeks before their entry into this study. Exclusion criteria were as follows: Lactation or pregnancy, Drug abuse (If a patient had a history of drug abuse at least four months prior to the study, he/she was excluded from the study), suicidal ideation, co-morbid severe disorders. The study consisted of one hundred and four research subjects suffering from major depressive disorder (male: 26; female: 78; 18-65 years old). Of the subjects, 25 came back to drug usage, 20 abundant their treatment, and 41 could not follow the therapeutic process systematically, and were excluded from the study.The treatment regime at level 1 aimed to evaluate outcome of treatment with the antidepressant drug citalopram (minimal dose: 20 mg/d). To reduce the risk of inadequate dosing, and to ensure that patients who progressed to the next level of the treatment were truly resistant to the level 1 treatment, the study was carried out with a desired end point after 14 weeks of treatment which is regarded as a long enough period for adjusting an optimal dosage and evaluating the corresponding effects. If deemed necessary, patients were, however, allowed to proceed into level 2 before 4 weeks of the treatment (40-60mg/d), and were included in this analysis if they had received at least 8 weeks of treatment with citalopram. Concomitant psychotropic drug that patients used was alprazolam up to 2 mg/d for sleep (Until 15 days and then tapered). In the next visit (3-4 weeks later), depression symptoms and the recovery rates were studied.

2.2. Data Collection

After examining the mental state of each patient, the severity of depression was assessed with Beck Depression inventory. Patients whose scores were above 16 were identified as having major depressive disorder. Adherence was monitored by weekly self-reports which corrected by a psychiatrist, and plasma levels of antidepressants were measured at weeks 4 and 8. Adverse effects of medication were measured using the UKU Side-Effect Rating Scale (29) and Self-Report Antidepressant Side-Effect Checklist (30). The same rater was used in the first and following ratings of each patient. Clinical response was defined as improving in clinical finding and beck scale.

2.3. HTTLPR Genotyping

To determine HTTLPR genotypes, genomic DNA was extracted from whole blood by salting out method (31) and polymerase chain reaction (PCR) amplification to generate the 487- or 523- base pair fragments corresponding to the S and L 5-HTTLPR alleles,

respectively. Amplification of genomic DNA was performed using 50 ng DNA, 0.25 mM of each primer (forward: 5′-GGC GTT GCC GCT CTG AAT C-3′ and reverse: 5′-GAG GGA CTG AGC TGG ACA ACC AC-3′) (32)

Reaction conditions were 1X PCR buffer; 1X Q-solution (Qiagen), 0.2 mM dNTPs, 2 mM MgCl2 (total concentration including from buffer); 20 ng/µl of each primer and a total of 10 ng of DNA in a 10-µl reaction. To obtain the best sharp bands, 10% DMSO was added per each reaction .

Cycling conditions were 95◦C for 3 min; 35 cycles at 94◦C for 1 min, 58◦C for 1 min, 72◦C for 45 s, 72◦C for 5 min, and hold on 4◦C. The labeled PCR products were separated on 2% agarose gel to differentiate the L (523bp) and S (487bp) variants. Plasma levels of citalopram were quantified using HPLC. The analysis was performed on a Knaver HPLC system (Smart model), consisting a UV detector and an injector with 100µl loop. Chromatographic separation was achieved isocratically at room temperature on a Spherisorb ODS2 column (250 mm×4mm, 5µm particle size (LKB, Bromma, Sweden). THE plasma level of all the patient's citalopram were in the therapeutic range (30-130 ng/ml).

Researchers who were blind to the clinical scores of depression performed quantification of plasma levels and genotyping. The clinician-rated 21 items of Beck Depression inventory was used to measure the treatment response at each treatment visit and at the end of the treatment period of up to 12 weeks.

In the categorized outcome definition, remitters were defined as having a Beck score ≥10 at endpoint of the level 1 treatment, whereas non-remitters still had a score ≤10 at the last visit as long as they were not classified as intolerant of the medication. In a parallel analysis, response was defined as a 50% reduction of Beck score at the last treatment visit and non-response as less than a 40% reduction. In order to minimize the risk for misclassification, individuals who received scores between these ranges or had less than 6 weeks of treatment were excluded from the respective analysis. After such exclusions, a total of 104 individuals were eligible for the treatment-response study when response was the outcome.

Clinicians were blind to the plasma levels and genotype of each patient till the end of the study.

2.4. Statistical Analysis

At first, we used chi-square to test the significance of association between sex, genotype and treatment. Then, we used logistic regression to model the relationship between the odds of treatment and sex and genotype. Two independent variables were entered into a logistic model simultaneously to assess the predictive ability of each variable while controlling for all other variables. The interaction term between sex and genotype was dropped from the model because it was not statistically significant. The results are presented as the odds ratios and the 95% CI's. The Hosmer and Lemeshow test was used in this model to evaluate the significance of improved port with introduction of additional variables. SPSS software Package, version 15, was used to analyze the data.

Result

Of the one hundred and four participants, 36 (34.6%) were homozygous for the L allele (L/L genotype), 34 (32.7%) were heterozygous (L/S genotype), and 34 patients (32.7%) were homozygous for the S allele (S/S genotype).

Table 1: Characteristics of the 65 analytical samples by sex, Genotype and Treatment

	Positive response to Citalopram		
Variable	No	%	**p-value**
Sex			
Women	43	55.1	
Men	22	84.6	0.007
Genotype			
S/S	16	47.1	
L/S	26	78.8	0.027
L/L	23	62.2	

Table 2: Overall response of patients compare with their genotype

Response to Citalopram	**Genotype: L/L or L/S**	**Genotype: S/S**
Positive	49 (70%)	16 (47.1%)
Negative	21 (30%)	18 (52.9%)

Table 3: Adjusted odds ratios for treatment [b], in the logistic analysis

Variable	OR[c]	95% CI[d]
Sex		
Women	1.00	
Men	4.22	1.29-13.76
Genotype		
S/S	1.00	
L/S	3.90	1.29-11.80
L/L	1.90	0.72-5.08

[a] Adjusted for another variable in the table.
[b] Refers to participants with a treatment-yes.
[c] Odds ratio.
[c] Confidence interval

According to our study, carriers of the L allele, either homozygous of L/L or heterozygous of L/S, had a better and faster response to the treatment with citalopram. On the other hand, gender should also be considered when examining the genetic effects of 5-HTTLPR on psychological outcomes (33). Significant main effects in participants treated with citalopram qualified the interaction effects especially in men. We found a statistically significant association between sex and treatment; citalopram response odds ratio was 4.22 (95 percent CI: 1.29-13.76) for men compared with women (table3).

An association was observed between L/S and treatment. Using S/S as the reference group, treatment odds ratios for L/S and L/L were 3.90 (95 percent CI: 1.29- 11.80) and 1.90 (95 percent CI: 0.72-5.08), respectively (table 3).

Among patients treated with citalopram, those homozygous for the short allele had significantly worse outcome than long-allele carriers, and this effect of the 5-HTTLPR genotype was more considerable among males treated with citalopram but was absent among females treated with citalopram (Table 1). Odds ratio for males' genotype ((L/L or L/S) / SS) is equal to 0.074 with 95% confidence interval (0.006, 0.911), whereas odds ratio for females' genotype ((L/L or L/S) / SS) was equal to 0.516, with 95% confidence interval (0.201, 1.327).

Obviously, there is a huge difference between female's and male's genotype in response to antidepressant treatment .

As it is shown in table 2, overall response of individuals with the L/L genotype and L/S genotype (70%), confirming a dominant effect of the L allele compared with the response of homozygotes of the S allele (47.1%). The statistical analyses proved the strong correlation between the presence of the L allele and better response to antidepressant drug citalopram, (P =0.023, and Pearson Chi-Square test statistic=5.139).

Discussion

There has been much recent interest in the use of genetic variants for the prediction of response to medication treatments (34), which is so important for the psychopharmacologic treatment of psychiatric disorders (20) .

In this study of Iranian sample population for the SLC6A4 promoter polymorphism, we observed that specifically male carriers of the 5-HTTLPR long allele showed a better response to citalopram treatment than male short-allele homozygotes (P = 0.047), whereas such affect is absent among women (P= 0.167). Our study indicated a significant interaction between the 5-HTTLPR, drug and gender.

The finding of this study is consistent with that of previous reports of gender specific genetic influences on serotonergic function (35) that might indicate a biological interaction between the serotonergic system and ovarian hormones. Through the oestrogen alpha receptor, oestrogens stimulate the production of the 5-HT receptor that is involved in the regulation of serotonin release and is down regulated in response to serotonin reuptake inhibitors (27). Oestrogens also increase the expression of the serotonin transporter.

It is possible that the impact of the less functional short 5-HTTLPR allele is moderated by the oestrogen-induced stimulatory effect on serotonin transporter expression in hormonally active women. Although this evidence shows biological plausibility to the observed 5-HTTLPR-gender interaction, this finding requires replication in an independent sample.

Therefore, overall, the study revealed a significant correlation between carrying the L allele and better response to citalopram treatment that confirms the previous Western reports (36-39), and one meta-analysis (23), whereas it is in contrasts with a Korean study (40) and some other meta-analysis (24, 41) .

We believe that there would be several possible explanations for this discrepancy. First, most of the previous studies were gender independent, so the number of female individuals who showed poorer response to treatment with the antidepressant drug, citalopram, might modulate the results. Second, the 5-HTTLPR polymorphism may be in linkage disequilibrium with a functional variant that affects SSRI response, and the extent of this linkage disequilibrium would be different in each of that ethnic populations. Thus, the association between 5HTTLPR genetic variants and SSRI treatment response may be ethnicity-dependent (42). Thirdly, this discrepancy may have resulted from differences in severity of MDD or subtypes for MDD populations enrolled in various studies, and as compared with the European American

population, the L allele frequency in Chinese (42, 43) or Korean (40) populations was much lower.

On the other hand, we believe that therapeutic antidepressant effect may involve the interaction of many different genes. Therefore, a single gene may play only a relative role, and not be strongly associated with antidepressant response. Thus, analysis of the interactions of multiple genes implicated in the pharmacokinetics of SSRIs is suggested to be mentioned in future pharmacogenetic study of antidepressants, although It is unlikely that the 5-HTTLPR polymorphism alone will be clinically useful in predicting response to antidepressants in people with depression (44).

In summary, in this study it was revealed that for Iranian population, male patients bearing the 5HTTLPR L/L or L/S genotype have a superior response to SSRI treatment than S allele-carriers, supporting Western reports.

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