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A Prospective Study of Serotonin Transporter Gene Promoter (*5-HTT* Gene Linked Polymorphic Region) and Intron 2 (Variable Number of Tandem Repeats) Polymorphisms as Predictors of Trauma Response to Mild Physical Injury

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The aim of this study was to examine the effect of both promoter and intron polymorphisms of the serotonin transporter (*5HTT*) gene on posttraumatic stress disorder (PTSD) development. For this purpose, two polymorphisms of the *5-HTT* gene, which are found in the promoter (*5-HTT* gene-linked polymorphic region) and second intron (variable number of tandem repeats) of the gene, were analyzed in 100 patients who were admitted to the Emergency Department after a mild physical trauma. None of the *5-HTT* polymorphisms studied have an effect on PTSD development after a mild physical injury, but having L allele for *5-HTT* gene-linked polymorphic region may cause milder hyperarousal symptoms in those patients who have developed PTSD.

Introduction

Posttraumatic stress disorder (PTSD) is a disabling psychiatric disorder that causes functional limitations and diminished quality of life above and beyond the impact of injury severity and medical comorbidity (Zatzick *et al.*, 2002). Given that 50–70% of individuals have been exposed to at least one potentially traumatic event during their lifetime (Kessler *et al.*, 1995; Breslau *et al.*, 1998) and 10–40% may develop high levels of PTSD symptoms after traumatic physical injury (Blanchard *et al.*, 1996; Michaels *et al.*, 1999; Ursano *et al.*, 1999), early intervention and treatment of PTSD has become an important component of public health efforts targeting injury control and rehabilitation.

Molecular genetic studies have the potential to identify the markers of vulnerability or resilience of pathological response to trauma. To date, there are seven case–control candidate gene association studies of PTSD (Nugent *et al.*, 2008). Five of them have focused on genes of dopamine system such as dopamine receptor 2 (Comings *et al.*, 1991, 1996; Gelernter *et al.*, 1999; Young *et al.*, 2002) and dopamine transporter (Segman *et al.*, 2002), of which four found significant association. Two studies have focused on serotonin system (Lee *et al.*, 2005; Kilpatrick *et al.*, 2007) and both of them found significant association between S/S genotype of serotonin transporter promoter polymorphism and PTSD.

Although most of these molecular genetic studies have focused on dopaminergic system, there are many reasons to think that serotonergic system may be involved in the susceptibility to PTSD. Evidence for an involvement of serotonergic system in trauma response comes from both neurobiological (Broekman *et al.*, 2007; Weiss, 2007) and clinical studies (Ipser *et al.*, 2006; Opler *et al.*, 2006).

Serotonergic neurotransmission is controlled by two main mechanisms: synthesis of the transmitter regulated by the rate-limiting tryptophan hydroxylase and termination of transmission by serotonin transporter (5HTT). The magnitude and duration of serotonergic neurotransmission is determined by the synaptic action of 5HTT (Lin and Tsai, 2004). The 5HTT protein is encoded by a single gene, located on chromosome 17q11.1–q12 (Lesch *et al.*, 1994). The *5HTT* gene has two polymorphic regions with functional consequences. The first polymorphism, which is observed in the *5-HTT* gene-linked polymorphic region (5-HTTLPR), is a 44-base pair insertion (L allele) or deletion (S allele) in the 5′ regulatory promoter region. Long (L) and short (S) variants of the promoter polymorphism differentially modulate transcription of the *5HTT* gene, with the S variant being less efficient (Heils *et al.*, 1996). The second polymorphism is a 17-base pair variable number of tandem repeats (VNTR) in the second intron of the gene, which may act as a transcriptional regulator, with 12-repeat allele having stronger enhancer-like

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properties than 10-repeat allele (Ohara *et al.*, 1998; MacKenzie and Quinn, 1999).

There are only two studies about the influence of the *5-HTT* gene on susceptibility to PTSD, and both of them have examined only the 5-HTTLPR polymorphism. This study examined the effect of both 5-HTTLPR and VNTR polymorphisms of the *5-HTT* gene on PTSD development in a population exposed to mild physical trauma. We hypothesized that "lower activity" alleles (S in 5-HTTLPR and 10 in VNTR) would be associated with higher frequency of PTSD symptoms/full syndrome 6 months after exposure to physical trauma.

Materials and Methods

This study was conducted by collaboration of the Emergency, Forensic Medicine, and Psychiatry Departments of Gazi University Hospital and the Molecular Biology Department of Hacettepe University. This study was ethically approved by the local Ethics Committee of the Medical Faculty of Gazi University.

Sample

One hundred patients who have been consecutively admitted to the Adult Emergency Department of Gazi University Hospital because of a physical trauma (vehicle/motorcycle accident, assault, stroke) were included in this study. A written informed consent was obtained from each patient. Systolic blood pressure (minimum–maximum, 80–160; mean ± standard deviation, 113.30 ± 15.16 mmHg), diastolic blood pressure (50–100, 75.05 ± 9.30 mmHg), heart rate (58–140, 91.17 ± 18.25 beats/min), respiratory rate (12–24, 18.77 ± 2.56 breaths/min), O_2 saturation (94–100, 97.18 ± 0.97%), and Glasgow coma scale (14–15, 14.95 ± 0.21) of each patient was recorded and revised trauma score was calculated; patients who had a revised trauma score other than 7.841 were excluded from this study.

Procedure

Sociodemographic information (age, gender, marital status, education level, employment status), current and past psychiatric disorders, family history of psychiatric disorder (according to the information given by the patient and family members/friends), and kind of trauma (vehicle/motor accident, assault, stroke) were recorded and peripheral venous blood samples for genetic analysis were obtained by a physician (G.K.). Their telephone numbers were recorded and a psychiatrist (A.S.), with 8 years clinical psychiatric experience, called them 6 months after their admission to the Emergency Department (to include late onset PTSD cases as well) and interviewed them using the clinician-administered PTSD scale (CAPS).

Instrument

Clinician-administered PTSD scale. This is a 17-item scale used for the assessment of current and lifetime PTSD symptoms (Blake *et al.*, 1995). The 17 symptoms cluster into three subscales: CAPS-B for reexperience, CAPS-C for avoidance/numbing, and CAPS-D for arousal. Each symptom is assessed according to frequency and intensity, and rated on a 0–4 scale. Any symptom is considered as positive, only if the total score of frequency and intensity is at least 3. A subject is diagnosed as having PTSD if there is at least one reexperience, three avoidance, and two arousal symptoms. A subject is considered positive for lifetime symptoms, if he/she had the symptoms within a certain amount of time after the traumatic event (the question was asked: Have you ever had these symptoms at least 1 month after the trauma?). A subject is considered positive for current symptoms if he/she still has these symptoms (the question was asked: Do you still have these symptoms?). The Turkish version of CAPS has Cronbach alpha of 0.91 for the whole scale, 0.78 for reexperience symptoms, 0.78 for avoidance/numbing symptom, and 0.82 for hyperarousal symptoms (Aker *et al.*, 1999).

Laboratory methods

Peripheral venous blood samples (5 mL) were collected from all subjects into ethylenediaminetetraacetic acid-treated tubes and were preserved at +4°C. Genomic DNA was extracted from peripheral blood lymphocytes according to standard phenol–chlorofom method. PCR for the 17-bp VNTR and 44-bp insertion/deletion polymorphisms were performed in total volumes of 25 μL reaction mixture containing 1×PCR Buffer (Bioron, Ludwigshafen, Germany), 10 pmol of each primer, 10% dimethyl sulfoxide (DMSO), 200 mM of each dNTP (Larova, Teltow, Germany), 10 ng DNA, and 1 U Taq polymerase (Bioron).

For genotyping of the 44-bp insertion/deletion polymorphism, the 5-HTTLPR region was amplified using the primers HTTLPR5′-ATGCCAGCACCTAACCCCTAATGT-3′ (forward) plus HTTLPR5′-GGACCGCAAGGTGGGCGGGA-3′ (reverse) (Steiger *et al.*, 2007) which generates a 419- and 375-bp product for the L and S alleles, respectively. The VNTR region in the second intron of the *5HTT* gene was amplified using the primers 5-HTTVNTR5′-GTCAGTATCACAGGCT GCGAG-3′ (forward) plus HTTVNTR5-TGTTCCTAGTCT TACGCCAGTG-3′ (reverse) (Li *et al.*, 1997). The *5-HTT* had three alleles that were 250, 267, and 300 bp and corresponded to 9, 10, and 12 repeats, respectively. The PCR program for both reactions consisted of one denaturing cycle at 94°C for 3 min, 35 cycles of 94°C for 30 s, 60°C for 30 s, 72°C for 45 s, and final 5 min extension at 72°C. Amplification products were electrophoresed on 2.5% agarose gel (Sigma–Aldrich, Steinheim, Germany) and visualized with ultraviolet light after ethidium bromide staining.

Statistical analysis

Statistical analysis of all the obtained data was made using SPSS version 15.0 (SPSS Inc., Chicago, IL). Chi-square analysis was performed to find the statistical differences with respect to all variables between patients with and without lifetime PTSD according to CAPS scores. Kruskal–Wallis and Mann–Whitney *U* tests were used to assess the association between scores of CAPS subscales and sociodemographic features, current and psychiatric history, family history of psychiatric disorder, trauma subtype, both genotypes, and four alleles in the patients with lifetime PTSD diagnosis. Exploratory analysis, including variables which were found to have statistically significant effect on CAPS scores, was per-

formed using multivariate linear regression analysis with enter modeling. A p-value smaller than 0.05 was considered statistically significant.

Results

Fourteen patients could not be reached by telephone after 6 months, and the blood samples of nine patients were unfit for genetic analysis. This resulted in 77 patients for further analysis.

The patients were grouped according to their genotypes of both polymorphisms; LL, SL, and SS for 5-HTTLPR polymorphism and 12.12, 12.10, and 10.10 for VNTR polymorphism. Moreover, they were also grouped with respect to the existence of S and L alleles, as well as 12 and 10 alleles. For the 5-HTTLPR polymorphism, the SL genotype was the most frequently found one (60%, $n = 54$). About 24.4% ($n = 22$) of the patients had the LL genotype and 15.6% ($n = 14$) had the SS genotype. The L allele was more common than the S allele, with a ratio of 3:1. For the VNTR polymorphism, the 12.12 genotype had the highest frequency of 58.9% ($n = 53$), whereas the 10.10 genotype was second with 22.2% ($n = 20$) and the 12.10 genotype was the most rarely found genotype with 18.9% ($n = 17$). The 12 allele was more common than 10 allele, with a ratio of 3:1.

The results of CAPS scores of the patients who could be reached by the telephone after 6 months were as follows: when clinically significant positive symptoms were considered, 23.3% ($n = 20$) of the patients had current and 50.0% ($n = 43$) had lifetime reexperiencing symptoms, 14.0% ($n = 12$) of the patients had current and 32.6% ($n = 28$) had lifetime avoidance symptoms, 15.1% ($n = 13$) of the patients had current and 39.5% ($n = 34$) had lifetime hyperarousal symptoms, and 10.5% ($n = 9$) of the patients had current and 34.9% ($n = 30$) had lifetime PTSD symptoms.

For further analysis, only lifetime PTSD was considered because the number of patients with current PTSD was too low for statistical analysis. Comparison of patients with and without lifetime PTSD is summarized in Table 1.

Kruskal–Wallis and Mann–Whitney U tests were used to find the possible variables that may have an effect on the severity of PTSD symptoms in patients who had developed PTSD. Gender, occupational status, marital status, psychiatric history, as well as 5-HTTLPR and VNTR genotypes had no significant association with scores from any of the PTSD symptom clusters. Educational level (those with less than 8 years of education had significantly higher scores on lifetime reexperiencing symptoms [mean = 3.59, $p = 0.03$], lifetime [mean = 4.71, $p = 0.04$] and current [mean = 2.24, $p = 0.04$] avoidance symptoms, lifetime [mean = 12.94, $p = 0.01$] and current [mean = 6.65, $p = 0.01$] PTSD score), current psychiatric illness (those who did not have a current psychiatric illness had significantly higher scores on lifetime reexperiencing symptoms [mean = 3.44, $p = 0.01$] and lifetime PTSD [mean = 12.11, $p = 0.03$]), family history for psychiatric disorder (those who had a family history of psychiatric disorder had significantly higher scores on current hyperarousal symptoms [mean = 4.00, $p = 0.01$] and current PTSD [mean = 12.33, $p = 0.04$]), and the type of trauma (those who had a stroke had significantly higher levels of current reexperiencing symptoms [mean = 2.00], current hyperarousal symptoms [mean = 2.78, $p = 0.01$], and current PTSD [mean = 8.33, $p = 0.04$]) were found to have a statistically significant effect on the severity of PTSD symptoms and syndrome.

Comparison of mean scores of patients with lifetime PTSD according to both genotypes and different alleles is presented in Table 2.

A multivariate linear regression model was performed for significant variables of symptom clusters of patients with lifetime PTSD and the results are presented in Table 3.

Discussion

We believe that there are three major findings in this study. First, we did not find any significant association between development of PTSD and any of genotypes and alleles of both *5-HTT* polymorphisms. The previous two studies performed to investigate the association between 5-HTLPR polymorphism and development of PTSD have both found a significantly higher frequency of S allele in patients with PTSD. The first one investigated 5-HTTLPR polymorphism in Korean patients with PTSD and normal controls (control participants were not necessarily trauma exposed) and found that the frequency of the S/S genotype was significantly higher in patients with PTSD than in normal controls (Lee *et al.*, 2005). The second one used an epidemiologic sampling strategy to examine whether 5-HTTLPR polymorphism moderated the risk of developing PTSD in 589 adults exposed to the 2004 Florida hurricanes, and the authors found that the S allele increased risk of posthurricane PTSD only under the conditions of high hurricane exposure and low social support (Kilpatrick *et al.*, 2007). These studies did not focus on VNTR polymorphism. The reasons for this discrepancy between this and previous studies' results may be caused by the differences between sample characteristics and instruments used to evaluate PTSD.

The second major result of this study was that both polymorphisms had a significant effect on the severity of some specific symptoms in patients who had developed PTSD. The "higher activity" allele of 5-HTLPR polymorphism (L allele) (Heils *et al.*, 1996) caused significantly milder hyperarousal symptoms, whereas the "higher activity" allele of the VNTR polymorphism (12 allele) (Ohara *et al.*, 1998; MacKenzie and Quinn, 1999) was significantly associated with more severe avoidance symptoms. Yet, one may assume that the decreasing effect of the L allele was stronger than the increasing effect of the 12 allele, because the L allele kept its significance even after the other variables were controlled.

The L allele's effect was on severity of hyperarousal symptoms. Key brain areas involved in hyperarousal responses are anterior cingulate cortex, medial prefrontal cortex, amygdala, and thalamus (Lanius *et al.*, 2006), which are rich in serotonergic neurons. It has been proposed that the failure of prefrontal cortex in its inhibition of stimuli from reaching the amygdala may cause a hyperresponsive amygdala, and an overactive amygdala may be responsible for hyperarousal symptoms (Shin *et al.*, 2006). Hypoactivation of these serotonergic neurons in the ascending serotonin pathway, originating in the dorsal raphe nucleus and innervating the amygdala and frontal cortex, caused by the lower activity allele may result in more severe hyperarousal symptoms, at least in this sample.

Table 1. Comparison of Patients with and without Lifetime Posttraumatic Stress Disorder

	PTSD (–) n *(%)*	*PTSD (+)* n *(%)*	*df*	*OR*	χ^2	p-*Value*
Gender						
Female	12 (25)	18 (62.1)	1	0.203	10.446	0.002[a]
Male	36 (75)	11 (37.9)				
Education						
≤8 years	24 (50)	17 (58.6)	1	0.705	0.54	0.4
>8 years	24 (50)	12 (41.4)				
Employment status						
Unemployed/retired	9 (18.8)	18 (62.1)	1	0.141	14.899	0.000[a,b]
Working/student	39 (81.3)	11 (37.9)				
Marital status						
Single/divorced	23 (47.9)	9 (31.0)	1	2.044	2.121	0.1
Married	25 (52.1)	20 (69.0)				
Past PD						
No	45 (93.8)	23 (79.3)	1	3.913	3.652	0.07[a]
Yes[c]	3 (6.2)	6 (20.7)				
Current PD						
No	47 (97.9)	27 (93.1)	1	3.481	1.119	0.5[a]
Yes[d]	1 (2.1)	2 (6.9)				
Family history of PD						
No	43 (89.6)	26 (89.7)	1	0.992	0	1.0[a]
Yes[e]	5 (10.4)	3 (10.3)				
Trauma						
Vehicle accident	26 (54.2)	20 (69.0)	1	0.531	2.121	0.1[a]
Stroke/hack	22 (45.8)	9 (31.0)				
5-HTTLPR genotype						
LL	13 (27.1)	5 (17.2)	2	1.613[f]	1.535	0.4
SL	29 (60.4)	18 (62.1)		1.611[g]		
SS	6 (12.5)	6 (20.7)		2.600[h]		
S allele						
–	13 (27.1)	5 (17.2)	1	1.782	0.978	0.4[a]
+	35 (72.9)	24 (82.8)				
L allele						
–	6 (12.5)	6 (20.7)	1	0.547	0.922	0.3[a]
+	42 (87.5)	23 (79.3)				
Variable number of tandem repeats genotype						
12.12	28 (58.3)	17 (58.6)	2	0.915[f]	0.034	0.9
12.10	9 (18.8)	5 (17.2)		1.145[g]		
10.10	11 (22.9)	7 (24.1)		1.048[h]		
12 allele						
–	11 (22.9)	7 (24.1)	1	0.934	0.007	1.0[a]
+	37 (77.1)	22 (75.9)				
10 allele						
–	28 (58.3)	17 (58.6)	1	0.988	0.001	1.0[a]
+	20 (41.7)	12 (41.4)				
Risk factors						
–/–	31 (64.6)	16 (55.2)	1	1.481	0.673	0.4[a]
–/+	17 (35.4)	13 (44.8)				

[a]Fisher exact test was performed.
[b]Statistically significant for $p < 0.05$.
[c]Anxiety disorder (4), depression (3), undefined (2).
[d]Anxiety disorder (2), attention deficient hyperactivity disorder (1).
[e]Undefined (6), depression (2), schizophrenia (1).
[f]OR between first and second rows.
[g]OR between second and third rows.
[h]OR between first and third rows.
–/–, absence of SS and 10.10; –/+, presence of SS or 10.10; PTSD, posttraumatic stress disorder; PD, psychiatric disorder.

The third major result of this study was that having S allele of the 5-HTTLPR polymorphism was significantly related to more severe PTSD syndrome, although this significance was lost after the other possible variables were controlled. The result that the allele may cause lower activity of one of the genes and regulate serotonergic neurotransmission, which may be related to more severe PTSD symptoms, is important because of the relationship between trauma response and a hypoactive serotonergic system. Moderate stress causes serotonin release to the frontal cortex and diminishes dysphoria

Table 2. Comparison of Mean Scores of Patients with Lifetime Posttraumatic Stress Disorder According to Both Genotypes and Four Alleles

	5-HTTLPR genotype			*S allele*	*L allele*	*Variable number of tandem repeats genotype*			*12 allele*	*10 allele*	*Risk factors*	
	LL	*SL*	*SS*	+	+	*12.12*	*12.1*	*10.1*	+	+	−/−	−/+
RES-L	2.8	3.39	3.5	3.42	3.26	3.29	3.8	3	3.41	3.33	3.38	3.23
RES-C	0.6	1.5	0.67	1.29	1.3	1.06	2	0.86	1.27	1.33	1.5	0.77
AS-L	3.2	4.39	4.38	4.5	4.13	4.59	4.6	3.29	4.59[a]	3.83	4.5	4
AS-C	1.4	2.11	0.83	1.79	1.96	1.59	2.6	1.43	1.82	1.92	2.19	1.15
HAS-L	3.6	3.94	5.33	4.29	3.87[b]	4.18	4.8	3.71	4.32	4.17	3.94	4.46
HAS-C	0.6	1.67	1	1.5	1.43	1.35	2.6	0.43	1.64	1.33	1.88	0.69[a]
PTSD-L	9.6	11.78	13.67	12.25[b]	11.3	12	13.2	10.29	12.27	11.5	11.75	11.85
PTSD-C	3.4	5.61	2.67	4.88	5.13	4.24	7.6	3.43	5	5.17	5.88	3.08

[a]$p < 0.05$.
[b]$p = 0.05$.
RES, reexperiencing symptoms; AS, avoidance symptoms; HAS, hyperarousal symptoms; L, lifetime; C, current; −/−, absence of SS and 10.10; −/+, presence of SS or 10.10.

and anxiety (Bremner, 2006). However, severe stress or trauma can lead to excessive serotonin activation in many regions of brain (Kaehler *et al.*, 2000) and cause serotonin depletion if the trauma is chronic or becomes chronic by reexperiencing symptoms and intrusive memories (Matsumoto *et al.*, 2005). Reduced availability of serotonin then leads to diminished ability of the central nervous system to dampen emotional responses to later stressors, increasing one's proneness to dysphoric states. Serotonin depletion may also contribute to the symptoms of hyperarousal (e.g., hypervigilance, impulsivity, and irritability) that are seen in PTSD (Weiss, 2007). Evidence of serotonin depletion in PTSD comes not only from studies about beneficial treatment effects of serotonergic antidepressants, but also from results of some neurobiological studies, including decreased serum concentrations of serotonin (Maes *et al.*, 1999), decreased density of platelet serotonin uptake sites (Spivak *et al.*, 1999), and a blunted prolactin response to D-fenfluramine (indicative of central serotonin hypoactivity) (Davis *et al.*, 1999).

Our results need to be interpreted cautiously because they come from a small sample and consists of people who were exposed to only mild physical trauma. Diagnostic data for PTSD were obtained from structured interviews over the telephone rather than from in-person clinical interviews. In addition, other psychiatric disorders, such as anxiety and depression, which are also related to serotonergic system, might have a significant effect on the development of PTSD and we did not evaluate these disorders. Despite these limitations, we believe that this study is of importance, because to our knowledge this is the first study conducted in a prospective design to investigate the VNTR polymorphism of serotonin transporter gene as a predictor of trauma response, and also the first study to investigate gene-by-environment interaction in a Turkish population. However, our results

Table 3. A Multivariate Linear Regression Model for Predictors of Severity of Current and Lifetime Posttraumatic Stress Disorder Symptoms in Patients with Lifetime Posttraumatic Stress Disorder

	Coefficient, β *(significance,* p*)*							
	RES-L	*RES-C*	*AS-L*	*AS-C*	*HAS-L*	*HAS-C*	*PTSD-L*	*PTSD-C*
Education (>8, ≤8)	0.35 (0.02)[a]	–[b]	0.30 (0.09)	0.36 (0.05)	–	–	–	0.39 (0.00)[c]
Current PD (+/–)	0.54 (0.00)[c]	–	–	–	–	0.43 (0.00)[c]	0.33 (0.04)[a]	–
Family history of PD (–/+)	–	–	–	–	–	0.40 (0.01)[c]	–	0.38 (0.01)[a]
Trauma type (VHA/stroke)	–	0.34 (0.07)	–	–	–	–	–	0.32 (0.03)[a]
S allele (–/+)	–	–	–	–	–	–	0.19 (0.24)	–
L allele (+/–)	–	–	–	–	0.37 (0.04)[a]	–	–	–
12 allele (–/+)	–	–	0.34 (0.06)	–	–	–	–	–
Risk factors (–/+ or –/–)	–	–	–	–	–	0.88 (0.38)	–	–

[a]Statistically significant for $p < 0.05$.
[b]–, not included in multivariate linear regression model.
[c]Statistically significant for $p < 0.01$.
VHA, vehicle accident; –/–, absence of SS and 10.10; –/+, presence of SS or 10.10.

ought to be carefully interpreted, because of the limitations stated earlier, and further study is needed.

Disclosure Statement

No competing financial interests exist.

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