

# Serotonin 5-HT<sub>1DB</sub> Gene's Interaction with Key Brain Regions in Obsessive-Compulsive Disorder

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## ÖZET:

Obsesif kompulsif bozuklukta 5-HT<sub>1DB</sub> geni ile anahtar beyin bölgeleri arasındaki ilişki

**Amaç:** Obsesif kompulsif bozuklukta (OKB) nöroanatomik ve genetik değişkenler arasındaki ilişkiyi inceleyen oldukça sınırlı sayıda çalışma bulunmaktadır. Bu çalışmanın amacı, 5-HT<sub>1DB</sub> gen polimorfizminin OKB'li hastalarla sağlıklı kontrollerde beyin morfolojisi üzerine olan etkilerini incelemektir.

**Metod:** Çalışmada 44 hasta ve aynı sayıda kontrol denek değerlendirildi. Deneklerin talamus ve orbito-frontal korteks (OFC) bölgelerinin manyetik rezonans görüntülemesi gerçekleştirildi. Ek olarak venöz kan örneklerinden 5-HT<sub>1B</sub> reseptör geni G861C polimorfizmi için genotipleme yapıldı.

**Bulgular:** Genotip ve tanı arasındaki ilişkinin çalışılan beyin volümleriyle ilişkili olduğunu gözlemledik. OFC bölgesinde 5-HT<sub>1DB</sub> polimorfizminin beyin morfolojisi üzerindeki etkisi hasta grubunda, kontrollere göre anlamlı olarak daha belirgindi (P<0.05). Bununla birlikte, bu polimorfizmin, talamus volümleri üzerindeki etkisi hasta ve kontrol grupları arasında anlamlı farklılık göstermedi. G alleline sahip OKB'li hastalar, C alleli taşıyanlara göre belirgin olarak daha küçük OFC volümlerine sahipti (P<0.05). Kontrol grubunda ise G ve C allel taşıyıcıları arasında morfolojik farklılık gözlenmedi.

**Tartışma:** Çalışmamız, 5-HT<sub>1DB</sub> reseptör geninin OKB'de beyin morfolojisini etkileyebileceğini ortaya koymuştur.

**Anahtar sözcükler:** 5-HT<sub>1DB</sub>, G allel, MRI, OKB, OFC, talamus

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## ABSTRACT:

Serotonin 5-HT<sub>1DB</sub> gene's interaction with key brain regions in obsessive-compulsive disorder

**Objective:** The interaction between neuroanatomical and genetic variables in obsessive-compulsive disorder (OCD) was not studied well. The aim of this study was to examine whether the 5-HT<sub>1DB</sub> gene polymorphism has an impact on brain morphology in normal subjects and patients with OCD.

**Method:** Forty-four patients and 44 healthy controls were studied. Brain volume measurements of subjects' structural MRI were performed on certain regions of interests such as orbito-frontal cortex (OFC) and thalamus. Genotyping for the 5-HT<sub>1B</sub> receptor gene G861C polymorphism was performed using venous blood samples.

**Results:** We found significant genotype-diagnosis interaction effects on brain morphology. The stronger effect of 5-HT<sub>1DB</sub> polymorphism on brain morphology in OCD patients than those in controls were determined in the OFC (P<0.05). However, the analysis showed a genotype-diagnosis interaction effect on the volume of the thalamus at a lower threshold. OCD patients with the G allele showed a significant reduction of volumes in the OFC compared to those carrying the C allele (P<0.05). Contrary to the patient group, in the control group, we found no significant morphological differences between subjects with the G allele and those with C allele.

**Discussion:** We suggest that a variation of the 5-HT<sub>1DB</sub> might be affecting brain morphology in OCD patients.

**Key words:** 5-HT<sub>1DB</sub>, G allele, MRI, OCD, OFC, thalamus

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## INTRODUCTION

Obsessive-compulsive disorder (OCD) is a debilitating disorder describing as a set of recurrent obsessional ideas or compulsive actions that take up more than an hour a day or cause serious distress or impairment. The etiopathogenesis is still unclear despite a great amount of studies in which neuroanatomical, neurophysiological, genetic and neurochemical dimensions of the illness are evaluated (1-3). However, we should not overestimate some clues obtained in recent studies, especially neuroanatomic and genetic ones. The

findings from structural imaging studies have been inconsistent, with reports of increases (4), decreases (5,6) or no differences (7-11) in the volumes of key brain regions. In a recent meta-analysis, Whiteside et al. (3) reported that meta-analytic results partially support the conclusions drawn from previous narrative reviews that point to structures in the OFC, caudate nucleus, anterior cingulate, and thalamus as the key brain regions in the pathophysiology of OCD. We also focused on these key regions in two separate studies and found that the patient group had significantly smaller left and right OFC volumes and significantly greater left and right thalamus

volumes compared with healthy controls (12) and that refractoriness to the OCD may be associated with the reductions in OFC and increase in thalamic volumes and may not be due to changes in cingulate and caudate regions (13).

One of the strong contribution on the knowledge about the etiopathogenesis of OCD is recently sourced from molecular genetic studies, with candidate gene approach. In OCD, the majority of molecular genetic investigations focused on serotonergic and dopaminergic system (14). In this regard, the first protein coming into mind may be serotonin transporter (5-HTT) protein because of being the primary target of action for serotonin-reuptake inhibitors. The next step is serotonergic receptor subtypes, especially 5-HT<sub>2A</sub> and 1<sub>DB</sub>. Findings of Tot et al. (14) do not support any association of OCD and T102C and -1438 G/A polymorphisms of the 5-HT<sub>2A</sub> receptor gene but found that frequencies of the TT genotype for T102C polymorphism and the AA genotype for -1438 G/A polymorphism were significantly higher in patients with severe OCD compared to those with moderate or moderate-severe OCD. Frisch et al. (15) and Nicolini et al. (16) reported no differences with respect to genotypic and allelic distribution of the 5-HT<sub>2A</sub> receptor gene in unrelated OCD patients compared to controls. The 5-HT<sub>1DB</sub> receptor is a terminal auto-receptor involved in the regulation of 5HT release. There are few genetic investigations on 5-HT<sub>1DB</sub> gene. Mundo et al. (17,18) reported an increased transmission of the G allele of the 681G/C polymorphism. This was supported by Camarena and Nicolini (19). When the efficacy of serotonin re-uptake inhibitors (SRIs) is taken into consideration, the importance of the polymorphisms of the serotonergic genes raises in OCD. However, possible morphological changes underlying such functional impairments remain to be clarified. Moreover, there is no study evaluating genetic polymorphism and brain volumetric variables concomitantly. The aim of this study was to examine whether the 5-HT<sub>1DB</sub> gene polymorphism has an impact on brain morphology in normal subjects and patients with OCD.

## METHODS

### Subjects and clinical evaluations

We recruited 44 patients with OCD from the Department of Psychiatry at Firat University School of

Medicine. Psychiatric diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria and on the the Structured Clinical Interview for the Diagnostic Schedule for Mental Disorders-Fourth Edition (SCID-I) (20) were determined by a consensus of at least two psychiatrists (MA and SO). At the time of the study, the patients had a mean (+SD) duration of illness of 6.2±2.9 years. OCD severity was evaluated by the Yale-Brown Obsession Compulsion Scale (Y-BOCS) (21). A group of healthy controls comprising 44 volunteers were matched with patients on age, sex, education and handedness. The demographic characteristics of the 44 patients and 44 healthy normal subjects enrolled in the study is shown in Table 1. All participants were right-handed. Written informed consent was obtained from each subject. The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

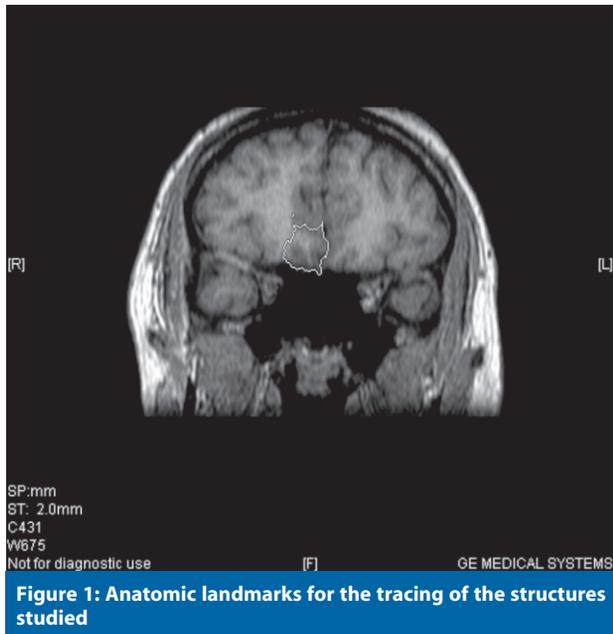
Exclusion criteria were presence of any current comorbid psychiatric disorder except depressive disorder (because of high comorbidity), current or lifetime neurologic, current medical problems, history of head injury, and alcohol/substance abuse within the 6 months preceding the study. Only one patient had current major depressive disorder. Comorbid lifetime Axis I psychiatric diagnoses were major depressive disorder (n=4), phobic disorder (n=2), and generalized anxiety disorder (n=3), and panic disorder (n=1). Exclusion criteria for the normal comparisons were any history of psychiatric illness personally or in any of their first-degree relatives.

### MRI Procedure

MRI scans were obtained with a 1.5-Tesla GE signa Excite high speed scanner (Milwaukee, USA; (repetition time [TR]=2000 ms, echo time [TE]=15.6 ms, field of view [FOV]=240 mm, flip angle=20°, bandwidth=20.8, slice thickness=2.4 mm, echo spacing=15.6 ms, 8 echoes, resolution=0.9375x0.9375x2.4 mm).

Experienced researchers (HY and MK) carried out the tracings, including the whole brain, total gray and white matter volumes, thalamus, and OFC. The tracing and measurements were done by raters who were blind to identity and diagnoses of the subjects. The boundaries of structures measured were delineated on the coronal MR images according to standard brain atlases (22-24) and were adapted from Noga et al. (25), Portas et al. (26),

Lacerda et al. (27), Sassi et al. (28), and Riffkin et al. (10). Examples of the structures of coronal slices are presented in Fig 1. All volumes were reported in cubic centimeters.



**Figure 1: Anatomic landmarks for the tracing of the structures studied**

### Genotyping

Genotyping for the 5-HT1B receptor gene G861C polymorphism was taken from the protocol described by Marziniak (29). Polymerase chain reaction (PCR) was carried out in a 25 ml volume containing 75mM Tris-HCl (pH 9.0), 20mM (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 0.01% Tween 20, 1.5mM MgCl<sub>2</sub>, 20 ng genomic DNA, 250 mM of each dNTP, 0.4 mM of the forward primer (5-GAAACAGACGCCCAACAGGAC-3), 0.4 mM of the reverse primer (5CCAGAAACCGCGAAAGAAGAT-3) and 1U Taq polymerase. Following a denaturation of 3min (95°C) PCR amplification consisted of 40 cycles at 94°C (30 s), 58°C (30s) and 72°C (30 s). After a final extension step of 7 min at 72°C, a 548 bp fragment was obtained. 17 ml of the

PCR product was incubated with 10U of the restriction enzyme, HincII, in 1XNEB3 buffer for 16 hours at 37°C. For alleles of the wild type (G at nt 861), digestion resulted in two fragments of 452 bp and 96 bp. The G-C substitution at nt 861 resulted in an additional restriction site, splitting the 452 bp into 310 bp and 142 bp fragments. The digested products were separated by agarose gel electrophoresis next to a DNA size standard.

### Statistical Analysis

All statistical tests were conducted by using SPSS for Windows 10.0 (SPSS, Chicago, IL). Analysis of covariance (ANCOVA), chi-square, and partial correlation analyses were used for the statistical comparisons. Genotype frequencies were investigated using Chi-square analysis to test for Hardy-Weinberg equilibrium. Statistical significance was defined as  $P < 0.05$  by a two-tailed test.

## RESULTS

Patients and controls did not differ with regard to demographic variables including age, gender composition, educational level, and intracranial volume (ICV) ( $P > 0.05$ ) (Table 1). Also, as can be seen in Table 1, the mean (+SD) Y-BOCS scores were  $22.3 \pm 5.3$  and  $5.8 \pm 2.4$  in the patient and control groups, respectively ( $P < 0.0001$ ). While there was no difference between the groups in total brain volume and total gray matter volumes, those with OCD had significantly smaller OFC ( $P = 0.020$ ) and larger thalamus ( $P = 0.038$ ) and total white matter volumes ( $P = 0.033$ ).

The genotypic distribution was as follow: 28/44 OCD patients (63.6%) and 22/44 controls (50.0%) were GG homozygotes; 14/44 patients (31.8%) and 15/44 controls

**Table 1: Clinical and demographic characteristics of the OCD patients and healthy individuals**

Item	Patients group	Control group	p
Number	44	44	
Age (years)	$32.1 \pm 5.5$	$30.3 \pm 4.27$	$> 0.05$
Gender (Female/Male)	27/17	24/20	$> 0.05$
Education High school			$> 0.05$
High school	26	28	
Elementary school	8	9	
First school	10	7	
Total Y-BOCS Score	$22.2 \pm 4.0$	$5.4 \pm 2.1$	$< 0.0001$
Length of illness (months)	$6.4 \pm 2.9$	-	
Handedness (right/left)	41/3	43/1	$> 0.05$

**Table 2: Interaction between the volumes of the structures and genotypic differences in patients with OCD versus controls subjects\* #**

Structure	OCD Patients (n=40)				Healthy Controls (n=40)			
	G Carriers (GG, GC) C Carriers (CC)	Genotype	GenotypeXSide	GenotypeXdiagnosis	G Carriers (GG, GC) C Carriers (CC)	Genotype	GenotypeXSide	GenotypeXdiagnosis
OFC Volumes								
Left	11.79 ± 1.35	4.94	1.56	0.83	15.59 ± 2.48	0.83	0.68	8.05
Right	11.53 ± 1.20	0.69	0.88	0.64	14.93 ± 1.88	0.64	0.52	0.97
Thalamus Volumes								
>0.05								
Left	6.14 ± 0.78				5.12 ± 0.74			
Right	5.77 ± 1.08				4.87 ± 0.42			

\* Volumes are in cm<sup>3</sup>.  
# Data are given mean±SD.

(34.1%) were GC heterozygotes; and 2/44 patients (4.6%) and 7/44 controls (15.9%) were CC homozygotes (P=0.41). Allelic distribution for the genotype groups did not differ significantly from Hardy–Weinberg equilibrium.

In Table 2, comparison of the relative volumetric data between the G allele and C allele of the patients and controls was demonstrated. Interaction between genotype and diagnosis for OFC and thalamus was also evaluated. We found significant genotype-diagnosis interaction effects on brain morphology. The stronger effect of 5-HT<sub>1DB</sub> polymorphism on brain morphology in OCD patients than those in controls were determined in the OFC (P=0.0079). However, the analysis showed a genotype-diagnosis interaction effect on the volume of the thalamus at statistically insignificant level (P>0.05). The interaction between genotype and being OCD led to us evaluate the effects of genotypes on OFC and thalamus in the OCD and control groups separately. OCD patients with the G allele showed a significant reduction of volumes in the OFC when compared to those carrying the C allele (P=0.021). Contrary to the patient group, in the control group, we found no significant morphological differences between persons with the G allele and those with C allele. ANCOVA revealed that no significant main effect of genotype-by-side interaction for the OFC and thalamus in both groups (P>0.05).

### DISCUSSION

This volumetric MRI study investigated the effect of the 5-HT<sub>1DB</sub> receptor 861G/C polymorphism on the OFC and thalamus in the patients with OCD and healthy controls. Before discussing the interaction between 5-HT<sub>1DB</sub> receptor gene and morphological changes, despite very small sample, according to the results from here, the G861C polymorphism of the 5HT<sub>1DB</sub> receptor gene seems to be specifically implicated in the pathogenesis of OCD, with the G variant conferring an increased risk of developing the disorder, as also supported by other investigations (17,18). We found a significant genotype-diagnosis interaction effects on brain morphology. The stronger effect of 5-HT<sub>1DB</sub> polymorphism on brain morphology in OCD patients than those in controls were detected in the OFC and at a lower threshold in the thalamus.

OCD patients with the G allele showed a significant

volume reduction in the OFC when compared to those carrying the C allele. Contrary to the patient group, in the control group, we found no significant morphological differences between persons with the G allele and those with C allele. Consequently, our results suggest that some of the morphological alterations in key brain regions of OCD mentioned above may be linked to the 861G/C polymorphism of the 5-HT<sub>1DB</sub> receptor gene. The 5-HT<sub>1DB</sub> receptor, a terminal auto-receptor, is involved in the regulation of serotonin release. The acute administration of ligands of the 5-HT<sub>1DB</sub> receptor (e.g., mCPP [methyl chloro phenyl piperazine], sumatriptan) triggers a transient worsening of OCD symptoms (30-32). On the other hand, the chronic administration of sumatriptan was demonstrated to improve symptoms in some OCD cases that are resistant to conventional pharmacotherapy (33). In fact, in a previous study, we reported that reductions in OFC and increase in thalamic volumes may be associated with refractoriness of OCD and may not be due to changes in cingulate and caudate regions (13). Therefore, the investigations on 5HT<sub>1DB</sub> receptor can lead to the development of new therapeutic strategies and help us to better understand the pathogenesis of OCD and refractory OCD. One of the variants of the G861C polymorphism could be inducing different mRNA secondary structure, thereby causing volumetric change in key brain regions in OCD. It would be naive to explain the morphological changes in OCD by the effects of one single nucleotide polymorphism of the

5HT<sub>1DB</sub> receptor gene. Beyond G861C polymorphism, we think other polymorphisms of OCD susceptibility genes such as other serotonergic genes and genotype–genotype interaction may also associate with individual brain morphology. Probably, more than one gene contribute the occurrence of OCD and each gene has a relatively small effect in increasing the risk for the disorder. Further studies are needed to evaluate other OCD susceptibility genes regarding how to effect on the brain morphology and clarify how polymorphisms of these genes affect the phenotypes of OCD.

Several important limitations should be emphasized for the present study. First of all, the number of participants is relatively small, and thus these findings should be considered preliminary until replicated in larger populations. Second, as also mentioned above, it is a handicap examining a single polymorphism in relationship to multiple phenotypic traits, which may raise the likelihood of false positives. Lastly, it would be important to evaluate potential gene-environment interactions in future investigations.

In summary, this is a preliminary study investigating genetic contributions of the 5-HT<sub>1DB</sub> receptor gene polymorphism to OFC and thalamus volumes in OCD. We suggest that a variation of the 5-HT<sub>1DB</sub> may be affecting brain morphology in OCD patients. Hopefully, our study would stimulate further research about on the influence of functional genetics on the brain structure in patients with OCD.

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