

## The Serotonin System in Obsessive-Compulsive Disorder

**Obsessive-compulsive disorder (OCD) is a neurophysiological condition affecting 1-4% of the population. It is characterized by intrusive, obsessional thoughts and repetitive, compulsive behaviors. Research indicates that the serotonin system is involved in the disease pathology. Further, disease susceptibility is heritable, signifying a genetic basis for OCD symptoms. New studies reveal a polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) that appears to be associated with particular OCD symptoms. Additionally, a symptom classification system has been proposed to more specifically correlate genes with symptom categories.**

### Background

Obsessive-compulsive disorder (OCD) is one of several neurophysiological anxiety disorders. It is characterized by unwanted, intrusive thoughts known as obsessions, and ritualistic, compulsive behaviors aimed at alleviating the stress brought on by the obsessions (Heyman et al., 2006). Patients with OCD are cognizant of the irrationality of the obsessions and compulsions, and as such, OCD is classified as an “ego-dystonic condition.” Nevertheless, patients report feeling an overwhelming sense of fear and dread if prevented from carrying out the behaviors. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), the current standard for diagnosis and assessment of mental disorders, identifies three criteria that are required to assign the diagnosis of OCD. First, the thoughts and behaviors must be “severe enough to be time consuming.” Second, the patient must “recognize that the obsessions or compulsions are excessive or unreasonable.” Third, the symptoms must “cause marked distress or significant impairment.” When these criteria are met, the diagnosis of OCD can be assigned (American Psychiatric Association, 2002).

It is estimated that between one and four percent of the population experiences OCD at some point (Merlo and Storch, 2006). As the disease is both prevalent and potentially debilitating, research focusing on both the causes and treatments of OCD is warranted. Further, understanding the brain mechanism of OCD thoughts and behaviors provides intriguing epistemological insights relevant to all humans: what processes in the brain create feelings of assurance and certainty?

As OCD has been shown to be a heritable condition with a genetic component, treatments often include medicine aimed at restoring function to a level acceptable to the patient. The selective serotonin re-uptake inhibitors (SSRIs) are a category of medications used to treat a variety of mental health conditions. Little is known about the exact mechanism of SSRI action; however, it is believed that SSRIs prevent re-uptake of serotonin (5-hydroxytryptamine (5-HT)) into the neurons after release, thus delaying degradation of the neurotransmitter by stabilizing its presence in the synaptic regions. Fluoxetine (trade name Prozac) and fluvoxamine (trade name Luvox) are two of the most commonly used SSRIs, from which newer SSRI medicines are largely based (Geller et al., 2003). Studies show the SSRIs to be effective in treating OCD, with as many as 75% of patients responding to drug treatment (Thomsen 2000). The observation that medicines that act on the serotonin system help alleviate OCD symptoms, combined with evidence that SSRIs are effective in treating other anxiety disorders, lends further support to the idea that decreased serotonin availability is a causal factor in OCD.

The serotonin hypothesis provides a starting point from which to search for OCD candidate genes. The serotonin transporter gene (5-HTT) encodes the serotonin transporter protein, which is responsible for transporting serotonin out of the synapses. A

functional polymorphism in the promoter of the serotonin transporter gene (5-HTT-linked polymorphic region (5-HTTLPR)) has been identified, and was proposed as a basis for susceptibility to mental disorders (Collier et al., 1996). The long (L, 528 bp) promoter, as compared to the short (S, 484 bp) promoter, could enhance transcription of serotonin transporter mRNA, resulting in over-abundance of the protein and premature clearance of serotonin from the synapses. The promoter polymorphism has served as a starting point in association studies. Additional studies suggest that the 5-HTTLPR may be associated with only particular subcategories of OCD phenotypes, and that other genes are required to trigger initial OCD symptoms. Here we investigate the correlation between the 5-HTT polymorphism, the onset of OCD, and the relationship between genes and OCD symptom subcategories.

### **Research findings and discussion**

A recent study investigated the role of the 5-HTT polymorphism in the etiology, or onset, of obsessive-compulsive disorder (Meira-Lima et al., 2004). 79 patients with OCD were recruited and evaluated according to the diagnostic provided in DSM-IV (American Psychiatric Association, 2002). The intensity of symptoms was assessed according to the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), the standard battery of assessment for OCD severity (Goodman et al., 1989). 202 matched controls also participated in the study, and were screened to ensure there was no family history of the disease which might skew analysis of genetic association. Genomic DNA was extracted from blood lymphocytes of all individuals, and the 5-HTTLPR amplified by polymerase chain reaction. Individuals were genotyped visually by observing the resulting banding patterns on electrophoretic gels. The Meira-Lima et al. (2004) study

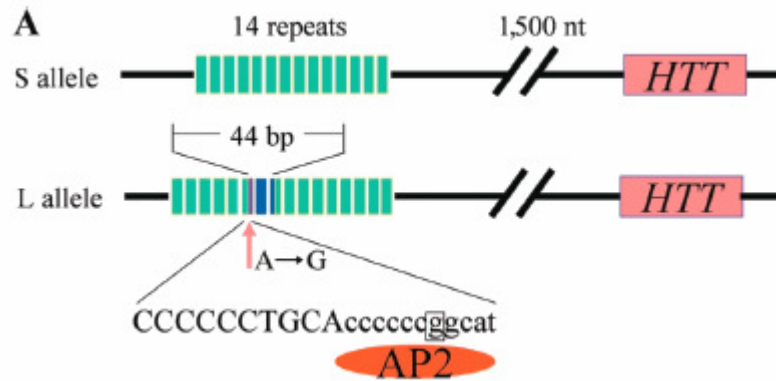
assessed both the allele frequencies and the genotype distributions of the 5-HTT polymorphism as compared to Hardy-Weinberg equilibrium values. Although a trend was observed for over-representation of the L allele in OCD patients, the divergence from equilibrium did not reach statistically significant levels (Table 1) (Meira-Lima et al., 2004).

**Table 1. Allele frequencies and genotype distributions for the 5-HTT polymorphism in OCD patients and control subjects. Adapted from Meira-Lima et al., 2004.**

<u>Group</u>	<u>L</u>	<u>S</u>	<u>p-value</u>	<u>LL</u>	<u>LS</u>	<u>SS</u>	<u>p-value</u>
OCD	60%	40%		33%	54%	13%	
Control	52%	48%	0.08	28%	47%	25%	0.10

Meira-Lima et al. (2004) did not establish a significant link between the L allele of the 5-HTT promoter and onset of OCD. They proposed that while the promoter polymorphism may not be important in the etiology of OCD, it may act to modulate the type or severity of OCD symptoms.

A second study, which could partly explain the results of Meira-Lima et al. (2004), references a third allele at the 5-HTTLPR locus. Hu et al. (2006) verified that the 5-HTT promoter contained 14 copies (in the S allele) or 16 copies (in the L allele) of a 20-23 bp imperfect repeat. However, they further classified the L allele in to  $L_A$  and  $L_G$  subtypes ; the  $L_G$  allele contains an A  $\rightarrow$  G substitution at the 6<sup>th</sup> nucleotide of the 15<sup>th</sup> repeat of the  $L_A$  allele (Figure 1).



**Figure 1. Schematic representation of S, L<sub>A</sub>, and L<sub>G</sub> alleles in the 5-HTT promoter region. The A → G substitution in the L<sub>G</sub> allele creates a binding site for AP2, a transcriptional repressor. Figure from Hu et al., 2006.**

Indeed, this distinction between the two L alleles is prudent, as the G substitution in the L<sub>G</sub> allele creates a binding site for transcription factor AP2, a suppressor of transcription. Hu et al. (2006) proposed that, since AP2 acts as a suppressor, the L<sub>G</sub> phenotype would be similar to that of the S phenotype. In fact, suppression of the 5-HTT gene appears to be dominant, and so SS and SL genotypes are often grouped together as “S” phenotypes in OCD studies.

169 OCD patients (as identified by the DSM-III criteria) and 253 controls were genotyped. DNA extraction and PCR techniques were similar to those of Meira-Lima et al. (2004). However, an additional distinction between the L<sub>A</sub> and L<sub>G</sub> alleles was required; this was achieved by DNA sequencing. The L<sub>A</sub> allele was shown to significantly associate with OCD (Hu et al. 2006). Lastly, the authors needed to verify whether the increased presence of the L<sub>A</sub> polymorphism in OCD patients could be a causal factor in OCD symptoms via enhanced transcription of the serotonin transporter 5-HTT. Six cell lines were created, each containing a construct for one of the six possible

5-HTTLPR genotypes (SS, S<sub>L<sub>A</sub></sub>, S<sub>L<sub>G</sub></sub>, L<sub>A</sub>L<sub>A</sub>, L<sub>A</sub>L<sub>G</sub>, L<sub>G</sub>L<sub>G</sub>). Real-time PCR of the 5-HTT mRNA confirmed that 5-HTT expression was lowest for the SS genotype and highest for the L<sub>A</sub>L<sub>A</sub> genotype, providing evidence that the up-regulation of 5-HTT by the L<sub>A</sub> allele could be responsible for OCD symptoms (Hu et al., 2006).

The identification of a third allele in the 5-HTT promoter offers an explanation for earlier failure to associate the L allele with OCD: the L<sub>G</sub> allele does not result in increased serotonin transporter abundance. Failure to distinguish between the L<sub>A</sub> and L<sub>G</sub> alleles would thus result in a bias against the L allele as a causal factor in OCD. This study also lends support to the idea that SSRIs ameliorate OCD symptoms via preventing re-uptake or clearance of serotonin from the synapses: over-abundance of the serotonin transport protein could be compensated for by a transport-blocking medication. The researchers note, however, that the L<sub>A</sub>L<sub>A</sub> genotype alone is not sufficient to produce OCD symptoms, and recommend studies in neurobiology and serotonin transporter availability in specific brain regions (Hu et al. 2006).

Studies of 5-HTT localization in the brain have been performed. Evidence suggests that pathways in the frontal-subcortical regions of the brain are compromised in OCD. Indeed, positron emission tomography (PET) scans, which measure brain activity, have shown that OCD patients tend to have increased activity in the orbitofrontal nucleus, caudate nucleus, thalamus, and anterior cingulate gyrus. Stenger-Wenzke et al. (2004) developed a study attempting to localize 5-HTT availability in 3 specific regions: the midbrain, brainstem, and thalamus. Earlier studies on 5-HTT localization may have failed to accurately determine the exact position of the transporter. However, this study combined traditional radioligand techniques with magnetic resonance imaging (MRI)

scans, which provide anatomical information, and thus more precisely identified 5-HTT location.

10 OCD patients and 7 age-matched controls were evaluated using the DSM-IV diagnostic scale and the Y-BOCS severity scale (American Psychiatric Association, 2002; Goodman et al., 1989). Those with co-morbid psychiatric conditions or those being treated with anti-OCD medicines were removed from the study to prevent confounding of variables. Single-photon emission computerized tomography (SPECT) was used to identify a radioligand ( $[^{123}\text{I}]\text{-}2\beta\text{-carbomethoxy-}3\beta\text{-(4-idiophenyl)-tropane}$ ) which binds specifically to 5-HTT. SPECT data was then combined with MRI data to assess 5-HTT availability in three brain regions (Stenger-Wenzke et al., 2004).

5-HTT presence was significantly lower in the midbrain and brainstem of OCD patients as compared to controls, and a non-significant trend of lower 5-HTT availability was also observed in the thalamus (Table 2).

**Table 2. Mean specific-to-nondisplaceable  $[^{123}\text{I}]\text{-}2\beta\text{-carbomethoxy-}3\beta\text{-(4-idiophenyl)-tropane}$  binding in OCD as compared to control subjects. Adapted from Stenger-Wenzke et al, 2004.**

<u>Group</u>	<u>Midbrain</u>	<u>p-value</u>	<u>Brainstem</u>	<u>p-value</u>	<u>Thalamus</u>	<u>p-value</u>
OCD	3.51±0.45		2.38±0.76		4.95±0.57	
Control	4.89±1.23	<0.005	3.53±1.01	<0.05	5.48±0.87	0.15

Stenger-Wenzke et al. (2004) propose that the decreased 5-HTT availability seen in the midbrain and brainstem of OCD patients may be correlated to reduced levels of serotonin in these regions. However, other studies report increased 5-HTT levels in OCD

patients. The discrepancy may be explained in several ways. First, earlier studies focused on total brain 5-HTT rather than on 5-HTT levels in specific brain regions. It is possible that serotonin transporter presence is increased overall in OCD patients but deficient in certain areas. It is also possible that, while 5-HTT clears serotonin out of the synapses and results in decreased available serotonin, it may also act to transport serotonin to other areas of the brain where it is needed. In this regard, a deficit of 5-HTT could contribute to serotonin deficiency in the midbrain and brainstem, as was observed in OCD patients. However, the results of Stenger-Wenzke et al. (2004) must be treated with caution, as only 10 experimental subjects were used. A larger study, again encompassing the SPECT + MRI methodology, should provide valuable information on the availability of 5-HTT throughout the brain, and on whether or not the transporter levels and localization are genetically determined.

Another technique aimed at correlating serotonin transporter function to OCD involves classifying OCD symptoms into categories. It is likely that different phenotypes within OCD are associated with different genotypes. Rather than look for genes that are associated with OCD as a whole, it may be prudent to correlate genes with specific OCD subtypes. As such, Kim et al., (2005) attempted to establish a relationship between 5-HTTLPR and phenotype (termed "OCD symptomatologic dimensions"). Here, genotypes were classified as only L or S, with heterozygotes being classified as genotype L. 124 patients with OCD were identified by the criteria set forth in DSM-IV (American Psychiatric Association, 2002). Genomic DNA extracted from the blood was used in PCR and gel electrophoresis to genotype each individual in the study and investigate correlation between 5-HTTLPR genotype and OCD symptoms.

Symptoms were divided into 4 Dimensions or factors based on obsession-compulsion pairs that frequently occurred together (Kim et al., 2005). Dimension 1 consisted of hoarding obsessions and repeating compulsions. Contamination obsessions and cleaning compulsions were assigned to Dimension 2. Dimension 3 included aggressive obsessions and sexual compulsions, and Dimension 4 encompassed religious obsessions and bodily/somatic compulsions. The symptoms were then assigned a score of 0 (never present), 1 (previously present or currently present to a mild degree), or 2 (currently significant) in each category. Those patients with the L genotype showed significantly higher scores for Dimension 4 than did those with the S genotype (Table 3).

**Table 3. Scores for OCD Dimension 4 between OCD patients with L genotype and OCD patients with S genotype. Adapted from Kim et al. (2005).**

<u>Group</u>	<u>Dimension 4 score</u>	<u>p-value</u>
OCD L genotype	0.33 ±0.93	
OCD S genotype	-0.20 ±0.74	0.005

In this regard, while overall presence or absence of OCD could not be correlated with the 5-HTT promoter polymorphism, the polymorphism was associated with symptom subcategory for those individuals diagnosed with OCD. The Kim et al. (2005) study is valuable in demonstrating that a multidimensional classification of OCD symptoms is necessary in correlating genotypes to OCD. Broad-scale studies of OCD genes as a whole may not be feasible if OCD subcategories, rather than OCD itself, are attributed to particular genetic constitutions. Designating symptoms into Dimensions is a

logical approach. However, as demonstrated by Hu et al. (2006), the 5-HTT promoter is actually tri-allelic. Thus a repeat of the Kim et al. (2005) study, but with the additional distinction between  $L_A$  and  $L_G$  genotype, should be invaluable in associating specific genotypes with specific phenotypic subcategories.

A second study examining the relationship between 5-HTT promoter polymorphisms and OCD symptom subcategories was based on the hypothesis that some candidate genes may impact OCD phenotype more so than they impact OCD etiology. Hasler et al. (2006) developed a 4-Factor symptom subclassification system similar to that of Kim et al. (2005). Factor 1 consisted of religious obsessions and checking compulsions (similar to Kim et al. (2005) Dimension 4). Factor 2 included symmetry obsessions and repeating or counting compulsions, encompassing elements of Kim et al. (2005) Dimension 1). Factor 3, contamination obsessions and cleaning compulsions, is equivalent to the Kim et al. (2005) Dimension 2. And Factor 4, hoarding obsessions and compulsions, is similar to aspects of the Kim et al. (2005) Dimension 1.

153 OCD subjects were evaluated with the DSM-IV and Y-BOCS tests (American Psychiatric Association, 2002; Goodman et al., 1989). Symptoms in each of the 4 Factor categories were assigned a score of 0 (never present) or 1 (had occurred at some point). Genotypes (LL, LS, SS) were identified based on gel electrophoresis of PCR performed on the 5-HTTLPR region isolated from blood lymphocyte DNA. Genotype distributions were then compared to Factor scores for each of the 4 Factors identified (Hasler et al., 2006).

Gender, symptom severity as determined by the Y-BOCS test (Goodman et al., 1989) and age of onset of OCD were not associated with the 5-HTT promoter

polymorphism. The SS genotype, however, was present significantly more in those patients with Factor 2 symptoms than those without Factor 2 symptoms (Table 4) (Hasler et al., 2006).

**Table 4. 5-HTTLPR genotype distribution as compared to OCD factor score. Adapted from Hasler et al., 2006.**

<u>Group</u>	<u>Factor 2 = 0</u>	<u>Factor 2 &lt; 0</u>	<u>p-value</u>
OCD LL genotype	25.9%	41.2%	
OCD LS genotype	49.4%	48.5%	
OCD SS genotype	24.7%	0.3%	0.03

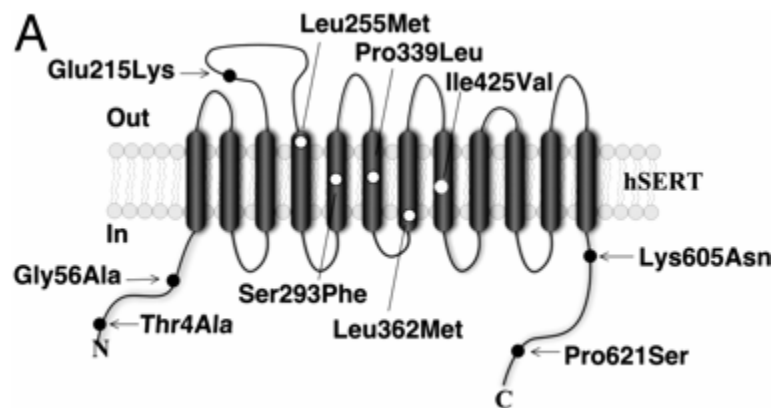
Even more specifically, the SS genotype was particularly correlated with the repeating compulsions classified under Factor 2.

The studies of both Kim et al. (2005) and Hasler et al. (2006) point to the link between phenotypic/symptomatological heterogeneity and genotypic heterogeneity. For example, Hasler et al. (2006) writes, "We may conclude that the possible modifier effect of the 5-HTTLPR polymorphism on Factor 2 might be specific." Thus the value of treating genes as modifiers of OCD symptoms rather than as candidates for OCD susceptibility is that this technique allows a more classified view of the disorder, leading to more targeted and specific treatments depending on the responsible genotypes.

It becomes clear that a large-scale association study, which both develops a standardized set of symptom Dimensions or Factors and takes in to account the tri-allelic nature of 5-HTTLPR, is necessary before we can be certain of which genotypes are associated with which type of OCD symptoms.

In addition to associating phenotype subtypes with promoter polymorphisms, it is also probable that variations in the coding sequence of 5-HTT itself create functional variants. Serotonin transporter can be regulated by G-protein coupled receptors, protein kinases and other regulatory proteins. Genetic variation could alter binding sites for the transport protein, resulting in modified regulation or an altered serotonergic pathway.

Prasad et al. (2005) identified 10 5-HTT coding variants in both extra- and inter-membrane domains (Figure 2).



**Figure 2. Locations of 5-HTT coding variants. Figure from Prasad et al. (2005).**

The variants consisted of 1 bp substitutions (single nucleotide polymorphisms) that created single, functional amino acid changes. DNA constructs containing each SNP were created by cloning cDNA for each variant into mammalian expression vectors, followed by transfection into HeLa cells. Cells were allowed to culture for 36 hours before the serotonin transport assays were performed. To ensure that the assay measured only the differences in transport activity, researchers first verified that each variant was producing the same level of 5-HTT protein (Prasad et al., 2005).

Based on the *in vitro* transport assay, 5 of the 5-HTT variants (Thr4Ala, Gly56Ala, Ser293Phe, Leu362Met, and Ile425Val) demonstrated enhanced transport activity of serotonin (Prasad et al., 2005). It is interesting to note that these SNP variants affect both extra- and inter- membrane regions of the protein, indicating that transport activity can be impacted via more than one method. Pro339Leu, a variation that occurs in an inter- membrane region, resulted in a protein that displayed reduced serotonin uptake in the assay. To further show that the assay specifically measured serotonin transport activity,  $V_{\max}$  and  $K_m$  were also calculated. For example, the  $V_{\max}$  of the Pro339Leu variant was significantly reduced as compared to the  $V_{\max}$  of the control 5-HTT proteins.

This study was successful in demonstrating that polymorphisms in the 5-HTT coding region produce functional variants of the serotonin transport protein, and that these variants account for differences in the protein's serotonin transport activity. For example, the Pro339Leu variant presented a change in transport activity consistent with a protein that is improperly folded, and which may be rerouted to degradative pathways. If this is the case, then the 5-HTT protein would display reduced uptake of serotonin, which was confirmed in the study (Prasad et al., 2005). The authors also proposed that since the observed changes in protein activity are genetically encoded, they are likely expressed early in development. Susceptibility to mental health conditions would thus begin in early childhood, and early treatments could potentially compensate for the serotonin transport differences which affect psychology later in life. This study is significant in correlating genetic variation to changes in protein activity, and may provide a basis for

ascertaining the exact mechanism of the serotonergic dysfunction seen in obsessive-compulsive disorder.

### **Future of the field**

Study of the causes of and treatments for OCD has progressed rapidly, from first viewing the condition as an environmentally-based neurosis, to treating OCD as a medical disease with genetic components, to developing methods for correlating genetic variation to symptom subtype.

Early genetic studies attempted to search for associations between genetic polymorphisms and the disease as a whole. However, investigation has shown that it is likely a combination of factors, including a particular constitution of multiple genes, that contribute to the onset of OCD. At the same time, researchers are beginning to focus less on the genetic cause of OCD, and more on the correlation between specific polymorphisms with particular facets of OCD symptoms. Discrepancies in classification of symptoms between researchers can lead to conflicting results about which genotypes are associated with which phenotypes. As such, a standardized symptom subclassification system is necessary. A purely statistical evaluation based on interviews with OCD patients may reveal which obsessions and compulsions tend to be present in unison, and thus which symptoms can be properly classified together as subtypes of the condition.

Although the SSRI medicines are often quite effective at alleviating OCD symptoms, many unpleasant side effects are reported. There is also the possibility of the brain developing a tolerance for the prevention of serotonin re-uptake, such that the medication dose must be consistently increased throughout a patient's life. As little is

known about how the SSRI medicines function mechanistically, research is needed on their mode of action and on the serotonergic pathway in general. If 5-HTT polymorphisms can be correlated with specific transport dysfunctions, tailored medications more specific than the SSRIs may be used to target only that region of the serotonin transporter that is disrupted. Furthermore, gene therapy is a possibility once more is known about the various genetic causes of OCD and of OCD phenotypes.

An emerging trend in neuroscience is the study of the correlation between cognitive therapy and brain physiology. Reports indicate that psychotherapy can result in brain restructuring and physiological change (Schwartz, 1998; Linden, 2006). Less than ten years ago, the scientific community was quite resistant to studies of free will, consciousness and the effect of mental training/learning on impacting physiological change. Some scientists are now beginning to consider the brain as an open system rather than an entirely genetically pre-determined processor. A mechanism for how psychotherapy can alter brain circuitry has not been proposed; however, several studies do report changes in brain activity, including changes in glucose metabolism, in patients who undertook cognitive therapy without medication. While OCD has been shown to have genetic causes, it may be possible to alter brain physiology without medical treatment, in much the same way that traditional medical diseases with genetic components (high blood pressure, obesity) can often be moderated through lifestyle changes without medication. An ideal treatment for OCD may involve a combination of personalized medications tailored to an individual's genetic constitution, in addition to cognitive therapy aimed at lessening OCD symptoms and improving the individual's quality of life.

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