Differentiation of obsessive-compulsive-, panic-, obsessive-compulsive personality-, and non-disordered individuals by variation in the promoter region of the serotonin transporter gene

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Perez, M., Brown, J.S., Vrshek-Schallhorn, S., Johnson, F., Joiner, T.E., Jr. (2005). Differentiation of obsessive-compulsive-, panic-, obsessive-compulsive personality-, and non-disordered individuals by variation in the promoter region of the serotonin transporter gene. Journal of Anxiety Disorders 20:794-806.

Abstract:

Past research investigating the role of the serotonin transporter gene in OCD has produced mixed findings. One possible reason for the mixed findings is comorbidity. In this study, non-comorbid OCD individuals were compared to non-disordered controls. A sample of panic disordered individuals was also compared to a non-disordered group. Finally, as an exploratory analysis, individuals were assessed for OCPD and their allelic frequencies were also compared to non-disordered individuals. Analyses revealed that there were higher frequencies of the s/s genotype among the OCD group when compared to non-disordered controls. There were no differences in allelic frequencies on the serotonin transporter gene between the panic disordered group, the OCPD group, and the non-disordered control group. This study found that non-comorbid OCD individuals tended to have a higher percentage of the homozygous short genotype than non-disordered individuals. The s/s genotype might serve as a contributory risk factor for OCD.

Keywords: 5-HTTLPR | obsessive-compulsive disorder | panic disorder | serotonin transporter gene | obsessive-compulsive personality disorder

Article:

1. Introduction

Numerous studies have investigated the role of the serotonin transporter gene in anxiety-related characteristics. Several studies have found a significant association between the polymorphisms of the serotonin transporter gene and anxiety. For example, Katsuragi et al. (1999) found that those with the two short allele genotype had higher Harm Avoidance scores from Cloninger's personality

theory than those with the other genotypes among a Japanese sample. Cloninger's personality theory is a biologically based model of personality with three traits, Harm Avoidance being the one that is most relevant to anxiety. A second study found that individuals with one or two short alleles had higher neurotocism scores from the NEO-PI-R personality inventory than those with two long alleles (Lesch et al., 1996). In addition, Lesch et al. found that the anxiety factor from Cattell's 16PF personality inventory was associated with serotonin transporter genotype, such that those with one or two short alleles had higher anxiety scores than those with two long alleles. A third study found that an alcoholic sample had higher frequencies of the short and heterozygous variant of the serotonin transporter gene than a control group (Mazzanti et al., 1998), and that the alcoholic group had higher harm avoidance scores than the control group. Finally, Ohara, Nagai, Suzuki, Ochiai, and Ohara (1998) found higher frequencies of the short allele of the serotonin transporter gene among anxiety disordered patients when compared to controls. From these studies, there seems to be converging evidence that anxiety-related traits are associated with the short allele variant in the serotonin transporter gene.

However, studies on particular anxiety disorders and allelic variations in the serotonin transporter gene have produced mixed findings. Specifically, there have been several studies investigating the role of the serotonin transporter gene in OCD, a few studies investigating the role of the serotonin transporter gene in panic disordered individuals, and no studies investigating the role of the serotonin transporter gene in obsessive-compulsive personality disordered (OCPD) individuals. In the OCD literature, some studies have found higher frequencies of the l/l variant in the serotonin transporter gene among OCD individuals when compared to controls (Bengel et al., 1999; Billett et al., 1997; Cavillini, Di Bella, Siliprandi, Malachiodi, & Bellodi, 2002; McDougle, Epperson, Price, & Gelernter, 1998), and several studies have found no differences between OCD and controls with regards to allelic variation in the serotonin transporter gene (Camarena et al., 2001, Frisch et al., 2000). Importantly, however, a meta-analysis that reviewed all of the literature on the polymorphisms of the serotonin transporter gene among OCD individuals found that OCD individuals tended to have higher frequencies of the s/s genotype when compared to controls (Brown & Joiner, unpublished manuscript). Brown and Joiner (unpublished manuscript) found a small effect size for this association and suggest that individual studies may not have sufficient sample size to detect differences between OCD samples and controls, but that these differences may appear when studies are aggregated meta-analytically. Given the mixed findings in this area, further studies are needed not only to replicate some of the findings, but also to investigate what might account for the discrepancies in the literature.

One possibility might be comorbidity. Cavillini et al. (2002) found that only the OCD group comorbid with Tic disorders had higher frequencies of the l/l allele when compared to controls. Most of the other studies did not specify if they controlled for comorbidity. This study will use OCD individuals who do not meet criteria for any other Axis I disorder.

In the panic disorder literature, only a few studies have investigated associations between variations on the serotonin transporter gene and panic disorder. Matsushita et al. (1997) found no differences between panic disordered individuals when compared to controls on the polymorphisms of the serotonin transporter gene among a Japanese sample. Rotondo et al. (2002) investigated allelic variations in the serotonin transporter gene in a sample of Italians who had bipolar disorder comorbid with panic disorder, bipolar disorder without panic disorder, and controls. The authors found higher frequencies of the s/s variant among bipolar patients without panic disorder when compared to controls. Another study conducted by Schmidt et al. (2000) investigated the effects of the polymorphisms of the serotonin transporter gene in predicting

subjective responses to a 35% carbon dioxide challenge. These authors found that those individuals homozygous for the long allele endorsed greater fearful responses to the biological challenge when compared to individuals with the homozygous short and heterozygous alleles. Overall, further research is needed investigating variations in the serotonin transporter gene among panic disordered individuals.

Finally, there have been no studies investigating the association between the polymorphisms of the serotonin transporter gene and OCPD. OCPD is a personality disorder that is characterized by extreme rigidity, perfectionism, orderliness, attention to detail and procedures, and over scrupulosity, to the point that impairment and/or distress is marked. OCPD occurs in about 1% of community samples and 3–10% of patient samples (American Psychiatric Association, 1994). Very little is known about the etiology of OCPD, and as mentioned previously, there have been no studies investigating allelic frequencies in the serotonin transporter gene among OCPD individuals. This study will investigate if there are differences in allelic frequencies among OCPD individuals when compared to non-disordered individuals in the serotonin transporter gene.

In sum, this study will compare three samples of disordered individuals (OCD, Panic Disordered, and OCPD) to non-disordered individuals on the allelic frequencies of the serotonin transporter gene.

2. Methods

2.1. Participants and procedures

One hundred and fifty-three individuals participated in this study; most of these individuals were undergraduate university students who participated in the study to partially fulfill a requirement for their introductory psychology class. Some undergraduate students were prescreened for OCD symptomatology and those that endorsed high levels of OCD were particularly encouraged to participate. Some of the participants were volunteers from the community who had OCD, a family history of OCD or believed they had OCD but were never formally diagnosed. These volunteers were recruited via newspaper and radio announcements. These volunteers received monetary compensation for their participation. There were a total of 129 undergraduates and 24 volunteers. The sample consisted of 60 (39%) males and 93 (61%) females. Gelernter, Cubells, Kidd, Pakstis, and Kidd (1999) found that the frequencies of various alleles differ based on ethnicity and suggest that ethnicity should be taken into consideration when conducting analyses on alleles. For this reason, and because of low proportions of ethnic minority participants recruited, this study focused only on Caucasian participants.

Participants were informed that they would be answering questions about their behaviors, mood, and emotions. They were also informed that they would be donating buccal cells by swabbing the inside of their cheek with a cotton swab to provide genetic information. All participants completed written informed consents, and the project was approved by the FSU IRB. Administration was conducted on an individual basis. Upon completion of the study, participants were debriefed via a written information sheet.

All participants filled out the Maudsley Obsessive Compulsive Inventory (MOCI), a true/false self-report questionnaire (Hodgson & Rachman, 1977). The original MOCI contained 30 items that can be used to give a total obsessionality score as well as four factor scores, checking, cleaning, slowness, and doubting-conscientiousness. An extensive amount of literature exists demonstrating the validity and reliability of the cleaning and checking subscales (Chan, 1990;

Emmelkamp, Kraaijkamp, & Van Den Hout, 1999; Hodgson & Rachman, 1977; Rachman & Hodgson, 1980; Sternberger & Burns, 1990). The checking and cleaning subscales have high test-retest reliability, moderate levels of internal consistency, and can discriminate OCD participants from non-disordered and anxious individuals (Emmelkamp et al., 1999). Consistent with previous research, reliability estimates for this sample for the cleaning subscale was .69, for the checking subscale, .77, and for the overall scale, .81. The other two factors (slowness and doubting-conscientiousness) have been problematic in terms of reliability and validity (Emmelkamp et al., 1999; Chan, 1990; Rachman & Hodgson, 1980); for this reason those subscales were not included in this study.

All participants were interviewed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders—fourth edition, patient edition, and the OCPD module from the personality disorder edition (SCID-IV and SCID-PD; American Psychiatric Press, 1994). The SCID-IV interviewing instrument is a reliable and valid tool used to determine current and lifetime Axis I diagnoses (Keel, Mitchell, Miller, Davis, & Crow, 1999; Massion et al., 2002). The SCID-PD interviewing instrument is a reliable and valid tool used to determine personality disorders (Maffei et al., 1997; Tenney, Schotte, Denys, van Megen, & Westenberg, 2003).

The diagnostic make-up of the sample is presented in Table 1. As can be seen there, 42% of the sample met criteria for an anxiety disorder. Seventeen percent of the sample met criteria for OCD. Fifty-eight percent of the sample did not meet criteria for any mood and anxiety disorder or OCPD. Rates of OCD and anxiety disorders found in this sample are not representative of a general sample. This was expected given the active soliciting of undergraduates and volunteers with anxiety-related symptoms and histories.

Table 1. Diagnostic characteristics of the sample

Psychological disorder	Current	Past
Panic disorder	11	8
Obsessive-compulsive Disorder	17	9
Obsessive-compulsive personality disorder	36	
Non-disordered	89	

Note. N = 153. It is important to note that some individuals who met criteria for OCD also met criteria for OCPD.

Breakdown in percentages of each of the main anxiety diagnoses by age and gender is presented in Table 2. There were more anxiety disorders among individuals older than 21 years of age when compared to those under the age of 21, and more anxiety disorders among females when compared to males.

2.2. Genotyping procedures

Participants donated their buccal cells by swabbing the inside of their cheeks in the presence of an experimenter. They swabbed their cheek for 30 s using a standard brush, instructions, and procedures. Swabs with buccal cells were stored in a −20 °C freezer.

DNA extraction was conducted by the QIAamp 96 DNA Swab BioRobot Kit. Polymerase chain reaction (PCR) amplification was performed on DNA extracted from the buccal cells. Primers were 5′-GGCGTTGCCGCTCTGAATTGC and 5′-GAGGGACTGAGCTGGACAADDDAD. PCR was performed in a final volume of 50 μl

Table 2. Percentages of diagnoses by age and gender

	PD (%)	OCD (%)	OCPD (%)
Age			
≤21	9	11	17
>21	33	50	58
Gender			
Males	5	5	13
Females	17	23	30

Note: PD: panic disorder; OCD: obsessive-compulsive disorder; OCPD: obsessive-compulsive personality disorder; ≤21 = 129; >21 = 24; males = 60; females = 93.

containing 10 µl of buccal DNA extract, 27 µl of water, 1.5 µl Taq DNA polymerase, 2 µl of MgCl (50 mM), 5 µl of 10×, 1 µl of dNTP, 3 µl of betaine, and .25 µl of each primer. Following an initial denaturation at 95 °C for 2 min, amplification was carried out for 35 cycles consisting of the following steps: 95 °C for 1 min, 58 °C for 1 min, 72 °C for 1 min. This was followed by an extension step of 72 °C for 5 min. PCR products were resolved on a 2% agarose gel and stained with ethidium bromide. Samples were coded so that all procedures were performed without knowledge of participant identity. The allelic distribution for this sample was 23% s/s, 72% s/l, and 5% l/l.

3. Results

There was no significant difference between the past and current OCD groups in allelic variation [$X2(2) = 2.69$, $p = .26$]. Since there were no significant differences between the current and past OCD groups, and because the goal was to assess the relation of the serotonin transporter gene to OCD (whether current or not), these groups were combined in the subsequent analyses. Similar to OCD, there was no difference on allelic variation between the past and current panic disordered individuals [$X2(1) = .06$, $p = .80$]. Accordingly, analyses were conducted with current and past panic disordered groups combined.

3.1. Panic disorder versus non-disordered individuals

In order to compare the polymorphisms of the serotonin transporter gene among panic disordered individuals without OCD and non-disordered controls, a chi-square analysis was computed. The genotype variable was coded as 1 = s/s, 2 = s/l and 3 = l/l. A second variable was coded as 1 = non-disordered individuals and 2 = panic disordered individuals without OCD. This chi-square was not significant [$X2(2) = 2.54$, $p = .30$] (Table 3).

3.2. OCD versus non-disordered individuals

Similar to the previous analysis, a chi-square was computed comparing individuals with non-comorbid OCD and non-disordered controls on the allelic frequencies of the serotonin transporter gene. The OCD variable was coded as 1 = non-disordered individuals and 2 = non-comorbid OCD individuals. The genotype variable was coded as 1 = s/s and 2 = s/l and 3 = l/l. This chi-square was significant [$X2(2) = 11.19$, $p < .01$]. As can be seen in Table 4, the OCD group had a higher percentage of s/s genotypes (29%) than the non-disordered group (15%). In addition, the non-

disordered group had a higher percentage of individuals with the s/l genotype (81%) than the OCD group (58%). Since the chi-square was significant, Cramer's phi was calculated and was significant ($\varphi c = .34$, $p < .01$). It is important to note that unlike the correlations in parametric statistics, Cramer's phi ranges from 0 to +1.00, and the sign does not represent a positive or negative association.

Table 3. Chi-square observed and expected counts for panic versus non-disordered individuals

	Genotype on serotonin transporter gene			Total
	s/s	s/l	l/l	
Non-disordered = 1 and Panic disorder = 2				
1.00				
Count	18	66	3	87
Expected count	20.5	63.2	3.3	87.0
2.00				
Count	7	11	1	19
Expected count	4.5	13.8	.7	19.0
Total				
Count	25	77	4	106
Expected count	25.0	77.0	4.0	106.0

3.3. OCPD versus non-disordered individuals

A chi-square was computed to test if there were differences in allelic frequencies among OCPD and non-OCPD individuals. It is important to note that some OCD individuals met criteria for OCPD and therefore were excluded from this analysis. A chi-square was computed and was not significant [$X2(2) = 2.90$; $p = .24$]. The observed and expected counts can be seen in Table 5.

Table 4. Chi-square observed and expected counts for OCD versus non-disordered

	Genotype on serotonin transporter gene			Total
	s/s	s/l	l/l	
OCD dx and non-disordered				
Non-disordered				
Count	20	64	3	87
Expected count	21.6	60.8	4.6	87.0
OCD				
Count	8	15	3	26
Expected count	6.4	18.2	1.4	26.0
Total				
Count	28	79	6	113
Expected count	28.0	79.0	6.0	113.0

3.4. OCPD and OCD versus non-disordered individuals

A chi-square was computed to test if there were differences in allelic frequencies among individuals that had either OCD and/or OCPD when compared to non-disordered control. The chi-square was not significant [X2(2) = .77; p = .68].

Table 5. Chi-square observed and expected counts for OCPD versus non-disordered

	Genotype on serotonin transporter gene			Total
	s/s	s/l	l/l	
Non-disordered = 1 and OCPD = 2				
1.00				
Count	20	64	3	87
Expected count	17.4	66.3	3.3	87.0
2.00				
Count	1	16	1	18
Expected count	3.6	13.7	.7	18.0
Total				
Count	21	80	4	105
Expected count	21.0	80.0	4.0	105.0

3.5. Genotype differences in cleaning and checking subscales

To test if there were differences in symptom severity across the allelic variations of the serotonin transporter gene among OCD individuals, a one-way ANOVA was created with the genotype variable as the independent variable and the MOCI total, cleaning and checking subscales from the MOCI as the dependent variable. The genotype variable was coded as 1 = s/s, 2 = s/l, and 3 = l/l. There were no significant differences between the allelic variants of the serotonin transporter gene on the MOCI total [F(2, 21) = .02; p = n.s.], the cleaning subscale [F(2, 21) = .61; p = n.s.], and the checking subscale [F(2, 22) = .72; p = n.s.]. Given the previous findings that OCD individuals had higher frequencies of the s/s genotype, a t-test was used to compare the s/s genotype group versus the s/l and l/l genotype groups on the MOCI total, cleaning, and checking subscales. Again, no significant differences were found [MOCI Total t(22) = −.12; p = n.s.; Cleaning Subscale t(22) = .39; p = n.s.; Checking Subscale t(23) = −.52; p = n.s.].

4. Discussion

Overall this study found that individuals with non-comorbid OCD had higher frequencies of the s/s genotype than non-disordered individuals. Consistent with past research, individuals with panic disorder did not have higher frequencies of short alleles in the serotonin transporter gene when compared to non-disordered individuals. There were also no significant differences in allelic variation between the OCPD group and the non-disordered group.

The main finding in this study was that the OCD individuals had a higher frequency of the homozygous short genotype than the non-disordered group. These findings are important for several reasons. First, the previous literature on OCD and the serotonin transporter gene had mixed findings. The current findings are consistent with the depression and other anxiety-disorders literatures that have found higher frequencies of the homozygous short allele among depressed and

anxiety disordered when compared to non-disordered individuals (Katsuragi et al., 1999, Lesch et al., 1996, Mazzanti et al., 1998) and consistent with the meta-analysis that found a significant association between the s/s variant of the serotonin transporter gene and OCD (Brown & Joiner, unpublished manuscript). Second, past research has found that individuals with the s/s genotype on the serotonin transporter gene have a poor response to SSRIs when compared to individuals with the same disorder who have s/l or l/l alleles on the serotonin transporter gene (Perlis et al., 2003, Rausch et al., 2002). The poor response to treatment might in part be due to higher occurrences of side effects for individuals with the s/s genotype (Perlis et al., 2003). Given that our results and those of Brown and Joiner (unpublished manuscript) indicated that the s/s genotype may be fairly common in OCD people, treatments other than SSRIs assume importance, especially including exposure with response prevention, which is the most effective OCD treatment overall (Franklin & Foa, 1998). Finally, a possible conceptual implication to these findings is that etiologically, if OCD individuals have higher frequencies of the homozygous short genotype, then the s/s genotype may serve as a contributory risk factor for OCD, as well as to depression, suicidal behavior, and some anxiety-related personality traits. The different outcomes (i.e., OCD, depression, suicidality, etc.) might be determined by the influence of other genes and environmental factors.

But why are these discrepant findings among different studies? One possible explanation might be comorbidity. Cavillini et al. (2002) studied allelic variations on the serotonin transporter gene among OCD and non-disordered individuals, but controlled for Tic disorders, which tend to be highly comorbid with OCD. When they controlled for Tic disorders, they found that only the comorbid group (OCD + Tic) had higher frequencies of the homozygous long genotype. Most of the studies looking at the association between OCD and the serotonin transporter gene have not controlled for Tic disorders or for other comorbidities (Bengel et al., 1999, Billett et al., 1997). In this study, none of the OCD individuals had a Tic or other disorders. Thus, comorbidity might explain some of the previous, varied findings.

Another possibility that might explain the discrepant findings in the literature is that OCD has only been analyzed as a dichotomous diagnostic classification. Following the DSM-IV classification system, individuals can have obsessions, obsessions and compulsions, or just compulsions. However, none of the literature has analyzed the allelic frequencies based on these three groups, perhaps due to small sample size. In addition, analyzing OCD based on the content of the obsession might prove more useful when looking across genotypic groups. For example, there might be allelic differences among those who have hoarding obsessions and compulsions, versus those who have somatic obsessions and compulsions. In this study, differences on the MOCI and its subscales were analyzed across the allelic variants on the serotonin transporter gene among OCD individuals and no differences were found. However, Cavillini et al. (2002) factor analyzed OCD individuals' scores on the Yale-Brown Obsessive-Compulsive Scale and found that only the factor containing counting and repeating rituals was associated with the homozygous long genotype, raising the possibility that some symptoms are associated with distinct genotypes. Further investigation into OCD as a spectrum disorder might prove beneficial when looking at allelic variation on the serotonin transporter gene. Future studies may want to investigate other symptom dimensions that were not emphasized in this study. This might be an excellent avenue for genetics to improve the classification system of OCD.

Based on these findings, the homozygous short genotype on the serotonin transporter gene is not a necessary or sufficient cause of OCD but might be a contributory cause of OCD for several reasons. First, it is not necessary to have the homozygous short genotype in order to have OCD.

There are individuals with OCD who do not have the homozygous short genotype. Second, the homozygous short genotype is not sufficient to cause OCD because there are individuals who have the homozygous short genotype that do not have OCD. However, there is a higher frequency of individuals with OCD with the homozygous short genotype; this suggests that having the short genotype on the serotonin transporter gene does contribute to having OCD. This contributory effect might occur within a multigenic model that leads to OCD.

An interesting finding in this study was the lack of differences between OCPD and non-disordered individuals on the serotonin transporter gene, even when OCPD was combined with the OCD group. To date, very little is known about the etiology of OCPD. This is the first study to investigate allelic variations on the serotonin transporter gene and OCPD. In part, the lack of differences between OCPD and non-disordered individuals is not surprising. One issue is that OCPD has significant problems with the diagnostic efficiency of its criteria (Grilo, 2004). For example, Farmer and Chapman (2002) found that among a community sample, OCPD criteria had poor sensitivity, internal consistency and positive predictive power (α ranged from .50 to .55). This could explain the lack of findings in this study. Another possibility might be that OCPD has a different etiology than OCD. Further research replicating these findings are called for.

Several important limitations exist which should be considered when reviewing these findings. First, there was a small number of participants carrying the l/l genotype. The sample may not of been representative simply due to chance. Regardless of the reason for the small number of individuals carrying the l/l allele, this limitation may have hindered the ability to find significant differences in allelic frequencies across the disordered and non-disordered groups. Despite this limitation, there were still significant differences in allelic frequencies between the OCD group and the non-disordered group. Although the OCD group was non-comorbid, comorbidity among the panic disordered and OCPD group may have obscured our findings. It is possible that if comorbidity with non-OCD disorders had been assessed and/or controlled for, differences between panic, OCPD and non-disordered groups may have emerged. Finally, a larger sample of individuals with various forms of psychopathology would have strengthened the results of this study.

In conclusion, an extensive amount of research is still necessary in investigating the role of the serotonin transporter gene in OCD individuals. This study found that non-comorbid OCD individuals tended to have a higher percentage of the homozygous short genotype than non-disordered individuals, despite the low sampling of participants with the homozygous long genotype. This finding has significant clinical and conceptual implications. These findings, in connection with meta-analytic findings (Brown & Joiner, unpublished manuscript), suggest an association between OCD and allelic variations on the serotonin transporter gene.

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