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Association between obsessive–compulsive disorder and a variable number of tandem repeats polymorphism in intron 2 of the serotonin transporter gene

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Abstract

Background: Pharmacological studies indicate a dysregulation of the serotonergic system in obsessive–compulsive disorder (OCD). A variable number tandem repeats (VNTR) polymorphism with three alleles (Stin2.9, Stin2.10, Stin2.12) has been described in intron 2 of the serotonin transporter (5-HTT) gene. This polymorphism has been associated with unipolar depression, bipolar disorder, schizophrenia, and anxiety disorders including OCD.

Methods: The association between OCD and the polymorphism is examined in 97 OCD patients, 578 psychiatric controls and 406 healthy controls, all Spanish Caucasians.

Results: Genotype frequencies for the polymorphism were significantly different in OCD patients, psychiatric patients and controls. There was a significant excess of 12/12 and 12/10 genotypes in OCD patients compared to psychiatric patients and controls.

Conclusions: Our results indicate a possible association between the Stin2.12 allele of the VNTR polymorphism and OCD.

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Keywords: Genetic polymorphism; Intron 2; Obsessive-compulsive disorder; Serotonin transporter; Variable number tandem repeats

1. Introduction

Pharmacological studies indicated a dysregulation of the serotonergic system in obsessive–compulsive disorder (OCD). Selective serotonin reuptake inhibitors (SSRIs) are effective in

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the treatment of OCD, and relapse is common when SSRIs are discontinued (McDougle et al., 1993). It is reported that addition of the serotonin releaser fenfluramine to serotonin reuptake inhibitors is sometimes beneficial for treatment-resistant OCD patients (Hollander and Liebowitz, 1988), while administration of *meta*-chlorophenyl-piperazine (mCPP), a serotonin 2C receptor agonist, can induce the emergence of symptoms in OCD patients (Zohar et al., 1987).

Family studies have suggested that genetic factors increase individual susceptibility to OCD, but the nature of this predisposition is unclear (Pauls and Alsobrook, 1999). The most studied gene in OCD is probably the serotonin transporter (5-HTT) gene (Baca-Garcia et al., 2005). A polymorphism has been described in intron 2 of the serotonin transporter (5-HTT) gene, which consists of a variable number of tandem repeats (VNTR) with multiple repeated copies of a 16–17 bp element

Abbreviations: VNTR, Variable number of tandem repeats; 5-HTT, Serotonin transporter; OCD, Obsessive–compulsive disorder; SSRIs, Selective serotonin reuptake inhibitors; mCPP, *meta*-chlorophenyl-piperazine; 5-HTTLPR, Serotonin transporter promoter polymorphism; Y-BOCS, Yale Brown Obsessive–Compulsive Scale; PCR, Polymerase chain reaction; SPSS, Statistical Package for Social Sciences; DAT1, Dopamine transporter gene; COMT, Catechol-*O*-methyltransferase; MAO, Monoamine oxydase; HWE, Hardy–Weinberg equilibrium.

	Genotypes ^{a, b} (%)						
	N	9/9	9/10	9/12	10/10	10/12	12/12
Healhty controls	406 (100.0)	1 (0.2)	4 (1.0)	5 (1.2)	50 (12.3)	170 (41.9)	176 (43.3)
Psychiatric controls	578 (100.0)	2 (0.3)	6 (1.0)	7 (1.2)	72 (12.5)	240 (41.5)	251 (43.4)
OCD patients	97 (100.0)	0 (0)	0 (0)	0 (0)	4 (4.1)	46 (47.4)	47 (48.5)

Distribution of the genotypes of the VNTR polymorphism in the intron 2 of the 5-HTT gene in OCD patients, psychiatric controls and healthy controls

^a All subjects: χ^2 Linear-by-Linear Association=2.038; *d.f.*=1; *p*=0.153.

Table 1

^b Comparison of genotype frequencies in OCD patients and healthy controls: χ^2 Linear-by-Linear Association=4.947; df = 1; p = 0.026.

(Lesch et al., 1994). Three alleles have been described, containing 9 (Stin 2.9), 10 (Stin 2.10), and 12 (Stin 2.12) copies of this repetitive element. Several studies have examined the relationships between the number of repeats of the VNTR polymorphism and susceptibility to psychiatric disorders. Some authors have reported an association between the Stin2.9 allele and unipolar depression (Ogilvie et al., 1996; Battersby et al., 1996), and bipolar disorder (Battersby et al., 1996). In a recent meta-analysis, Fan and Sklar (2005) found highly significant evidence for association between the Stin2.12 allele and schizophrenia. Collier et al. (1996) found an association between the Stin.2.12 allele and bipolar disorder (but not unipolar depression). Collier et al.'s results (1996) were replicated by several groups (Kunugi et al., 1997; Rees et al., 1997; Kirov et al., 1999), but other case-control studies (Bellivier et al., 1997; Gutierrez et al., 1998; Hoehe et al., 1998) and a meta-analysis (Furlong et al., 1998) did not replicate the association between the allele 12 and bipolar disorder. Evans et al. (1997) found an association between anxiety and the short alleles (Stin 2.9 and Stin 2.10) of the VNTR intron 2 polymorphism in patients with self-harming behaviors. Ohara et al. (1999) found a significant excess of the Stin2.12 allele in patients with anxiety disorders compared to healthy controls and in the subgroup of OCD patients (N=15) compared to controls. Concerning function, different alleles (copy number variations) of the VNTR have been shown to have differential regulatory effect on transcription in vitro (Fiskerstrand et al., 1999) and in vivo (MacKenzie and Quinn, 1999), and more recent data (Lovejoy et al., 2003) indicate that there is an additional layer of transcriptional regulation based on the primary sequence of the VNTR. It has been suggested that there is possible combined effect of serotonin transporter promoter (5-HTTLPR) and VNTR polymorphisms on 5-HTT gene expression (Hranilovic et al., 2004).

This study assesses the association between OCD and the serotonin transporter intron 2 polymorphism in a Spanish Caucasian sample.

2. Methods

2.1. Patient population and assessment instruments

The Mini International Neuropsychiatric Interview version 4.4 (Sheehan et al., 1998), a brief structured interview, provided the DSM-IV diagnosis for the psychiatric patients including 97 OCD patients and 578 psychiatric controls with other diagnoses excluding OCD (27.7% substance abuse; 30.7% psychoses;

42.5% unipolar depression; 7.5% eating disorders; 23.4% anxiety disorders; 13.3% personality disorders;) from three general hospitals in Madrid, Spain. OCD symptoms and severity were ascertained with the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989). As nonpsychiatric controls, 406 healthy blood donors were recruited at Ramon y Cajal hospital in Madrid, Spain. Subjects were Spanish Caucasians who are relatively homogenous from the genetic point of view (Cavalli-Sforza et al., 1994). A structured interview was used to inquire about personal and family history of psychiatric disorders, treatment or admissions. Controls with history of psychiatric disorders, treatments, or admissions were removed from the study. The General Health Questionnaire-12 (GHQ-12) (Rajmil et al., 1998) was used to screen for psychopathology in controls, and those with scores above the cut off point were excluded from the study. After complete description of the study to the subjects, written informed consent was obtained. The research was prospectively reviewed and approved by a duly constituted ethics committee.

2.2. Genotyping

Genomic DNA was extracted from peripheral blood samples. Polymerase chain reaction (PCR) amplification of the VNTR polymorphism was carried out with the following primers: Forward: 5'-GTCAGTATCACAGGCTGCGAG-3'; Reverse: 5'-TGTTCCTAGTCTTACGCCAGTG according to Battersby et al. (1996).

2.3. Data analysis

The Statistical Package for Social Sciences (SPSS) (version 12.0) was used for the statistical analyses. Genotype frequencies of the VNTR polymorphism of intron 2 of the 5-HTT gene were compared among OCD patients, psychiatric controls and healthy controls using χ^2 Tests (Table 1). In a second step, we grouped the genotypes in two subgroups (allele 12 carriers [12/12, 12/10, and 12/9], and non-carriers [9/9, 9/10, 10/10]) and compared their distribution in OCD patients, psychiatric patients and controls.

3. Results

The statistical power for the sample was 99% for finding medium-sized effects (15% difference in the proportions of allele 12 carriers [12/12, 12/10, and 12/9]). The proportion of males was slightly higher in the healthy control group (59.1%)

than in the psychiatric control group (40.0%) and in OCD patients (44.3%) ($\chi^2 = 35.5$; *d.f.*=2; *p*<0.001). There were no significant differences in the distribution of genotypes in men and women (χ^2 =4.661; *d.f.*=5; *p*=0.459). These differences remained non significant after grouping the genotypes into two subgroups (allele 12 carriers [12/12, 12/10, and 12/9], and noncarriers [9/9, 9/10, 10/10]) (Fisher's exact test p=0.553). The mean ages in each group were: healthy controls (mean=36.2, 95% C.I. 35.0–37.3) psychiatric controls (mean=40.3, 95% C. I. 39.1-41.5), and OCD patients (mean=39.7, 95% C.I. 31.9-47.5). There were no significant differences in the mean ages of individuals with different genotypes (ANOVA F=1.058; d.f.=5: p=0.382). These differences remained non significant after grouping the genotypes into two subgroups of allele 12 carriers and non-carriers (Student's t test=0.001; d.f.=933; p=0.999). Patients had mean scores of 22.7 (S.D.=6.5) in Y-BOCS global scale; 11.3 (S.D.=3.4) in the Obsessions subscale, and 11.6 (S. D.=4.2) in the Compulsions subscale. Genotype frequencies were in Hardy-Weinberg equilibrium (HWE) in OCD patients $(\chi^2=3.157; d.f.=3; p=0.360)$ and psychiatric patients $(\chi^2 = 1.822; d.f. = 3, p = 0.610)$. Genotype frequencies were not in HWE in healthy controls ($\chi^2 = 12.956$; *d.f.*=3; *p*=0.004). Since this is a self-selected sample of blood donors, we cannot rule out that this may mean that the genotype has something to do with being a blood donor. The genotype may plausibly be associated with certain personality traits.

Genotype frequencies for the VNTR polymorphism in intron 2 of the 5-HTT gene were significantly different in OCD patients compared to psychiatric patients and in OCD patients compared to controls (Table 1). However, genotype frequencies were not significantly different in psychiatric patients compared to controls. OCD patients had an excess of the 12/12 and 12/10 genotypes. After grouping the genotypes into two subgroups (allele 12 carriers [12/12, 12/10, and 12/ 9], and non-carriers [9/9, 9/10, 10/10]), the differences were significant when comparing OCD patients (93/97 allele 12 carriers [95.9%]) versus healthy controls (351/406 allele 12 carriers [86.5%]) (Fisher exact test p=0.008) and OCD patients versus psychiatric patients (498/578 allele 12 carriers [86.2%]) and controls ($\chi^2 = 7,274$; *d.f.*=2; *p*=0.026). We applied Bonferroni correction for multiple testing (0.05/2 tests=0.025). Thus, significant p values were lowered to p= 0.025. We have calculated the Odds Ratio (O.R.) for the risk of being a psychiatric patient (excluding OCD) versus being a control (O.R.=0.975; 95% C.I.=0.674-1.411) for the allele 12-carrying genotypes [12/12, 12/10, and 12/9]. We have also calculated the Odds Ratio (O.R.) for being a control versus being an OCD patient (O.R.=3.643; 95% C.I.=1.287-10.312) and for being a psychiatric patient (excluding OCD) versus being an OCD patient (O.R. = 3.735; 95% C.I. = 1.336-10.444) for the allele 12 non-carrying genotypes.

4. Discussion

The short alleles (Stin2.9 and Stin 2.10) of the VNTR polymorphism in the intron 2 of the 5-HTT gene have been associated with anxiety symptoms (Evans et al., 1997), bipolar

disorder (Battersby et al., 1996), and unipolar depression (Ogilvie et al., 1996; Battersby et al., 1996;). The Stin2.12 allele has been associated with bipolar disorder (Collier et al., 1996) and anxiety disorders including OCD (Ohara et al., 1999). Alternatively, the VNTR polymorphism may be in linkage disequilibrium with the real factor associated with OCD.

The relationship between the VNTR polymorphism in intron 2 of the 5-HTT gene and anxiety disorders is probably very complex. First, there are ethnic variations in genotype and allele frequencies of this polymorphism, with higher rates of Stin2.12 alleles reported in Japanese compared to Caucasian samples (Ohara et al., 1999). Furthermore, the SNP-based and haplotype based approaches have been criticized in favor of a gene-based approach, which is less susceptible to erroneous findings due to genetic differences between populations (Neale and Sham, 2004; Hemmings and Stein, 2006). Second, the function of the VNTR polymorphism remains uncertain, and it may act in a synergistic way with other polymorphisms to contribute to the development of disease. Allele-dependent (based on copy number variations) differential enhancer activity of the VNTR polymorphism was demonstrated as different levels of gene expression in embryonic stem cells (Fiskerstrand et al., 1999) and in mouse embryo (MacKenzie and Quinn, 1999). Lovejoy et al. (2003) demonstrated that variations in the sequence of individual repeat elements within the VNTR are also capable of differential transcriptional regulatory properties. It has been suggested that there is weak individual influence, but possible combined effect, of serotonin transporter promoter (5-HTTLPR) and VNTR polymorphisms on 5-HTT gene expression (Hranilovic et al., 2004). It would be interesting to genotype 5-HTTLPR in the whole sample and perform a haplotype analysis. Unfortunately we cannot obtain this data in the whole sample.

There are other polymorphisms in the 5-HTT gene that may be contributing to the effects we have observed. One functional polymorphism in the promoter region (5-HTTLPR) has been studied extensively in OCD. There are two allelic variants, a long (1) variant and a short (s) variant. The "1" allele has 2 to 3 times higher basal transcriptional activity (Lesch and Hiels, 2001) and has been associated with higher levels of 5-HTT in platelets and brain (Little et al., 1998; Heinz et al., 2000; Greenberg et al., 1999;). Most studies have been negative (Camarena et al., 2001; Cavallini et al., 2002; Di Bella et al., 2002; Kim et al., 2005; Kinnear et al., 2000; Frisch et al., 2000; Walitza et al., 2004; Chabane et al., 2004;), except for the ones by McDougle et al. (1998) and Bengel et al. (1999), who reported an association with the l-allele. Denys et al. (2006) reported an association of the s-allele with female OCD patients. Hu et al. (2006) have recently reported that the 5-HTTLPR polymorphism is functionally triallelic. A common single-base substitution (A->G) occurs in the L allele. The L_G allele has a similar effect on expression as the S allele, while the L_A allele (gain of function allele) is the highest expressing genotype. An uncommon 5-HTT variant, Ile425Val (Ozaki et al., 2003) which leads to gain of function (Kilic et al., 2003) has been linked to treatment-resistant OCD, anorexia nervosa, and Asperger syndrome (Ozaki et al., 2003).

Other candidate genes that have been studied in OCD are serotonin receptor genes (5-HT2A, 5-HT2C, and 5-HT1D β), the tryptophan hydroxylase gene, genes related to dopaminergic neurotransmission (dopamine transporter gene –DAT1– and dopamine receptor genes), and genes related to the metabolism of neurotransmitters (catechol-*O*-methyltransferase –COMT– and monoamine oxydase–MAO–) (Kim and Kim, 2006).

Finally, we must note that in the present study genotype frequencies were not in HWE healthy controls. Some authors have expressed the concern that associations may be spurious in genetic case-control studies if the distribution of genotypes in the healthy controls group deviates from HWE. Prior studies have estimated that there are significant deviations from HWE in healthy controls in approximately 10% of gene disease association studies (Trikalinos et al., 2006). These deviations may be due to genotyping error, selection, chance, inbreeding, nonrandom mating, differential survival of marker carriers, genetic drifting, population stratification, or combinations of these reasons (Trikalinos et al., 2006). We hypothesized that in the present study the significant deviation from HWE in healthy controls may be explained because the genotype may be associated with certain personality traits that may have something to do with being a blood donor.

5. Conclusion

Our results support the hypothesis that there is a significant excess of allele 12 in OCD patients.

This is consistent with the findings of Ohara et al. (1999), who reported an association between the Stin2.12 allele and anxiety disorders, including OCD, in a Japanese sample. However, since many other studies have failed to replicate these results and other authors have reported an association between the Stin2.9 and Stin2.10 alleles and symptoms of anxiety (Evans et al., 1997), further research is required to clarify the relationship between the VNTR polymorphism in intron 2 of the 5-HTT gene and anxiety disorders.

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