Journal of Psychiatric Research 43 (2009) 519–525

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Serotonin receptor HTR1A and HTR2C variants and personality traits in suicide attempters and controls

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ARTICLE INFO

Article history:
Received 3 December 2007
Received in revised form 23 June 2008
Accepted 25 June 2008

Keywords:
HTR1A
HTR2C
TCI
Personality
Temperament
Character
Suicide

ABSTRACT

Introduction: Serotonin has been extensively studied in relation to both personality features and suicidal behaviours.
Objective: In this study, we considered the association between the serotonin receptor 1A (HTR1A) and 2C (HTR2C) SNPs and personality traits, as measured by the Temperament and Character Inventory (TCI), in a sample of suicide patients and healthy volunteers.
Methods: The SNPs considered were, for HTR1A rs1423691, rs878567 and rs6295, and for HTR2C rs547536, rs2192372, rs6318, rs2428707, rs4272555 and rs1801412. The sample was composed of three groups: two German samples, consisting of a healthy control group of 289 subjects (42.6% males, mean age: 45.2 ± 14.9) and a psychiatric patient group of 111 suicide attempters (38.7% males, mean age: 39.2 ± 13.6), and an Italian sample, composed of 64 mood disorder patients (35.9% males, mean age: 43.0 ± 14.8). In the German samples all the SNPs were investigated, while in the Italian sample only the HTR1A rs6295 and the HTR2C rs6318 SNPs were considered.
Results: Controlling for sex, age and educational level, single markers and haplotypes were not or only marginally associated with personality dimensions.
Conclusions: Our study does not support the role of HTR1A and HTR2C gene variants on personality traits in both healthy volunteers and mood disorder patients.

1. Introduction

There is a large evidence suggesting that temperamental traits are modulated by a number of gene variants [for review of the literature, see Ebstein (2006), Noblett and Coccaro (2005), Reif and Lesch (2003), Savitz and Ramesar (2004), Serretti et al. (2007a), Van Gestel and Van Broeckhoven (2003)].

Serotonin seems particularly involved in specific temperamental traits and its candidate genes have been extensively studied (Carver and Miller, 2006; Ebstein et al., 2000; Serretti et al., 2006). Among them, both the 1A (HTR1A) and the 2C (HTR2C) receptors received considerable attention.

The HTR1A receptor gene is located on chromosome five (5q11.2-13) (Kobilka et al., 1987). A functional C-1019G variant (rs6295) in the promoter region of the gene was reported (Stahl, 1994). This polymorphism was associated with a number of psychiatric disorders, including major depression and anxiety-related traits (Lemonde et al., 2003; Rothe et al., 2004; Strobel et al., 2003). Moreover, it has been associated with antidepressant response (Lemonde et al., 2004; Serretti et al., 2004b). Finally, HTR1A involvement in suicide has been suggested (Hsiung et al., 2003; Lemonde et al., 2003; Pitchot et al., 2005; Wasserman et al., 2007).

The HTR2C receptor gene is located on the X chromosome (Xq24) (Milatovich et al., 1992) and it contains six exons and five introns spanning at least 230 kb (Xie et al., 1996). It is an interesting candidate gene for mood disorders (Serretti et al., 2004a). A presumably non-functional Cys23Ser polymorphism (rs6318) was identified (Lappalainen et al., 1995) and was found presumably related to major affective disorders (Gutierrez et al., 1996; Lerer et al., 2001; Oruc et al., 1997), particularly in females. Moreover, binding studies demonstrated increased densities of the 5-HT2 receptor sites in brains of suicide victims (Arango et al., 1990). However, a study based on two independent samples reported no significant differences in HTR2C Cys23Ser allele or genotype frequencies between victims and controls (Stefulj et al., 2004).

Strobel and collaborators investigated the role of the mentioned HTR1A polymorphism in the modulation of personality traits in a sample of healthy volunteers, using the Revised NEO Personality Inventory (NEO-PI-R) and the Temperament and Personality

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doi:10.1016/j.jpsychires.2008.06.005

Table 1
HTR1A and HTR2C SNPs considered in this study

SNP ID	Position[a]	Distance	Alleles	Role
HTR1A				
rs1423691	63287418 (5884)		C/T	3' UTR
		4329 bp		
rs878567	63291747 (1555)		C/T	3' UTR
		2574 bp		
rs6295	63294321 (−1019)		C/G	Promoter
HTR2C				
rs547536	113717336 (−150266)		A/T	Promoter
		80,693		
rs2192372	113798029 (−69573)		A/G	Intron
		73,962		
rs6318	113871991 (4389)		C/G	Coding sequence
		34,624		
rs2428707	113906615 (39013)		A/G	Intron
		83,266		
rs4272555	113989881 (122279)		C/T	Intron
		59,079		
rs1801412	114048960 (181358)		G/T	Null

[a] Absolute chromosomal position. The relative position to the start codon is given in parentheses. All data from snpper.chip.org.

Questionnaire (TPQ). Carriers of the G allele exhibited higher Neuroticism and Harm Avoidance scores than carriers of the C variant (Strobel et al., 2003).

Moreover, a PET study investigating the relationship between serotonin HTR1A receptor density and personality traits (Borg et al., 2003) found that the binding potential correlated inversely with scores of Self-Transcendence (ST), in particular the subscale for Spiritual Acceptance (ST3). Recently, we tested the involvement of the HTR1A rs6295 SNP in this trait in a sample of 40 remitted mood disorder patients. Subjects with the C/C genotype showed significantly lower scores at the total ST and at the subscales of Transpersonal Identification (ST2) and ST3 (Lorenzi et al., 2005).

For what concerns HTR2C, in a healthy volunteer sample Reward Dependence (RD) and Persistence scores were significantly lower among rs6318 ser variant carriers (Ebstein et al., 1997). Furthermore, a significant interaction between the dopamine receptor D4 exon III repeat polymorphism (DRD4) and HTR2C on RD was found: the effect of the HTR2C polymorphism was more marked in carriers of the DRD4 long variant. Nevertheless, in another study HTR2C was not associated with RD, but a significant interaction effect of DRD4 and HTR2C receptor polymorphisms on RD was observed in accordance to Ebstein's report (Kuhn et al., 1999). Finally, another study failed to detect the association between the rs6318 polymorphism and personality traits evaluated using the NEO-PI-R and the State-Trait Anxiety Inventory (STAI) in healthy Japanese subjects (Tochigi et al., 2006).

In this study, we investigated possible associations between personality traits and a panel of markers in both HTR1A and HTR2C receptors in a German sample of suicide attempters and controls and in an Italian sample of mood disorder patients. In the German sample the HTR1A rs1423691, rs878567 and rs6295 SNPs, and the HTR2C rs547536, rs2192372, rs6318, rs2428707, rs4272555 and rs1801412 SNPs were investigated (see Table 1). In the Italian sample the HTR1A rs6295 and the HTR2C rs6318 SNPs were investigated.

2. Materials and methods

2.1. Samples

2.1.1. German sample

Healthy volunteers were randomly selected from the city registry of Munich, and contacted by mail. To exclude subjects with neuropsychiatric disorders we conducted further screenings before the volunteers were enrolled in the study. First, subjects who responded were initially screened by phone. Detailed medical and psychiatric histories were assessed by using systematic forms. Second, they were invited to a comprehensive interview including the Structured Clinical Interview for DSM-IV (SCID I and SCID II) (First et al., 1990, 1995; Wittchen et al., 1997). Subjects with relevant somatic diseases or a lifetime history of any Axis I or II disorders or suicidal behavior were excluded. Finally, 289 healthy subjects were included in the study (Table 2).

The patient group consisted of suicide attempters. The attempters were consecutively referred to general psychiatric wards of the Department of Psychiatry, Ludwig-Maximilians-University of Munich, Germany. One hundred and eleven suicide attempters were included in the study (Table 2). The same sample was recently reported by us not supporting the notion that HTR1A and HTR2C gene variants are major contributors to suicide-, anger-, or aggression-related behaviours (Serretti et al., 2007b).

Systematic information on suicide attempts was collected by repeated interviews with patients and all available medical records. The suicide attempts were classified as violent (hanging, stabbing, shooting, jump from buildings or in front of vehicles, severe deliberate car accident, electricity, fire) or non-violent (illicit or prescription drugs, rather superficial wrist manipulations, gas suffocation and drowning) according to the methods used and the severity of the attempt. The German version of the Intent Score Scale (Pierce, 1981) was used to define impulsive and non-impulsive suicidal behaviour.

The current and lifetime diagnoses of mental disorders were assessed close to discharge by applying SCID I and SCID II. Patients with mental disorders due to a general medical condition or with dementia were excluded. DSM-IV lifetime diagnoses of mental disorders among the patients were affective spectrum, schizophrenia spectrum and borderline personality disorder (Table 3).

Written informed consent was obtained from all subjects after a detailed and extensive description of the study. The study was approved by the local ethics committee and carried out in accordance

Table 2
Socio-demographic features of German controls and suicide attempters [the education level was rated as low (secondary school), middle (junior high school) and high (general qualification for university entrance)]

Socio-demographic features	Controls (n = 289)	Suicide attempters (n = 111)	Statistic	d.f.	p
Gender					
Males	123 (42.56%)	43 (38.74%)	$\chi^2 = 0.34$	1	0.56
Females	166 (57.44%)	68 (61.26%)			
Age	45.22 ± 14.89	39.20 ± 13.65	$t = 3.70$	398	0.0001
Education level					
Low	76 (26.30%)	34 (30.63%)	$\chi^2 = 4.19$	2	0.12
Middle	87 (30.10%)	41 (36.94%)			
High	126 (43.60%)	36 (32.43%)			