5-HT<sub>2A</sub> SNPs and the Temperament and Character Inventory

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Abstract

Temperamental traits, the most basic part of personality, have been largely correlated with neurotransmitter systems and are under genetic control. Among serotonin candidates, the 2A receptor (5-HT<sub>2A</sub>) received considerable attention. We analyzed four SNPs (rs643627, rs594242, rs6311 and rs6313) in the 5-HT<sub>2A</sub> gene and their association with personality traits, as measured with the Temperament and Character Inventory (TCI). The sample was composed of three sub-groups: two German sub-samples, consisting of a healthy 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 sub-sample, composed of 60 mood disorder patients (35.0% males, mean age: 44.0±14.8). Controlling for sex, age and educational level, the SNPs were not strongly associated with personality dimensions. Only the rs594242 showed an association with Self-Directedness (<i>p</i>=0.003) in the German sample, while rs6313 was marginally associated with Novelty Seeking (<i>p</i>=0.01) in the Italian sample. We conclude that 5-HT<sub>2A</sub> SNPs may marginally modulate personality traits but further studies are required.

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Keywords: 5-HT<sub>2A</sub>; Character; Personality; TCI; Temperament

1. Introduction

Personality traits influence many aspects of normal and pathologic behaviours (Bienvenu and Stein, 2003; Cloninger et al., 1994; Grucza et al., 2005; Klein et al., 1993; Velting, 1999). Temperamental traits, the most basic part of personality, have been correlated with neurotransmitter systems and are under genetic control (Cloninger et al., 1994). In the last decade, a large number of studies focused on the detection of gene variants associated with specific temperament traits and numerous finding have been reported, though with conflicting results (Noblett and Coccaro, 2005; Van Gestel and Van Broeckhoven, 2003). Serotonergic genes and particularly the serotonin transporter have been extensively studied, as serotonin (5-HT) seems involved in specific temperamental traits (Carver and Miller, 2006; Ebstein, 2006; Ebstein et al., 2000; Serretti et al., 2006).

Among 5-HT candidates, the 2A receptor (5-HT<sub>2A</sub>) received considerable attention. It plays an important role in cognitive functions, like learning (Harvey, 2003) and memory (Buhot et al., 2000). It consists of 4 exons separated by 3 introns spanning over 62 kb (Chen et al., 1992) and it is located on 13q14-q21 (Sparkes et al., 1991).

In the mouse, homologous recombination knockout genes encoding various proteins involved in 5-HT neurotransmission has recently allowed further assessment of the role of the 5-HT<sub>2A</sub> receptor in the regulation of sleep (Adrien, 2004). 5-HT<sub>2A</sub><sup>−/−</sup> knockout mice exhibited more wakefulness and less slow wave sleep (SWS) than wild-types.

In humans, a large number of studies investigated the association of single-nucleotide polymorphisms (SNPs) in this
gene with a wide range of phenotypes such as psychiatric disorders, drug response and personality traits.

For what concerns psychiatric phenotypes and 5-HT2A polymorphisms, in a recent review, association studies on 5-HT2A gene and its relation with schizophrenia, mood, eating and anxiety disorders, attention-deficit hyperactivity disorders (ADHD), suicide and Alzheimer’s disease were considered, with mainly negative or conflicting results plausibly due to the small sample size (Norton and Owen, 2005). The main SNPs analysed were rs6311 (−1438 A/G) and rs6313 (102 T/C). After the publication of this review, other studies were published for each of these associations. A recent meta-analysis, conducted on 73 studies, failed to find significant association of the 5-HT2A rs6313 polymorphism with either schizophrenia or suicidal behavior. Evidence of significant association was only detected between rs6311 and suicidal behavior (Li et al., 2006). For what concerns mood disorders, a study has examined their possible association with the 5-HT2A rs6313 polymorphism and no differences were found in genotype and allele distribution between the mood disordered subjects, with and without suicide attempt history, and controls (Khait et al., 2005). Nevertheless, the relation between 5-HT2A and mood disorders is strengthened by the publication of a large number of studies on 5-HT2A and its role such as target of antidepressants (Choi et al., 2005; McMahon et al., 2006). Furthermore, negative studies were also published (Cusin et al., 2002; McMahon et al., 2006; Sato et al., 2002).

For what concerns drug response, the 5-HT2A receptors are also targets for modulation of psychostimulant use (Bubar and Cunningham, 2006), in particular for hallucinogens (Nichols, 2004).

The SNPs predominantly analysed in association with personality traits to date were rs6311 and rs6313. These SNPs are in strong linkage disequilibrium (LD) being in the promoter and at the beginning of the gene, respectively. A large quantity of studies was published. In particular, platelet serotonin 2A receptor sites have been found associated with impulsivity and aggression in a Positron Emission Tomography (PET) study (Coccaro et al., 1997). Moreover, rs6311 was found to be associated with impulsive traits in alcohol dependents, measured with the Baratt Impulsiveness Scale (BIS) (Preuss et al., 2001). This was the first report on an association of a 5-HT2A promoter SNP with personality dimensions, which is partially confirmed by more recent reports on the same variant (Ni et al., 2006; Nomura, 2006). Subsequently, 5-HT2A SNPs have been found to be associated with low anxiety-related traits, which are negatively related to impulsive traits (Golimbet et al., 2004; Rybakowski et al., 2006). In addition, TCI Self-Transcendence was related to the rs6311 SNP (Ham et al., 2004). On the other hand, a considerable number of negative results have also been reported regarding the involvement of 5-HT2A in personality traits (Berggard et al., 2003; Blairy et al., 2000; Jonsson et al., 2001; Kusumi et al., 2002; Lochner et al., 2006; Tochigi et al., 2005).

The lack of unequivocal results may be due to several factors, such as sample selection for its heterogeneous composition in terms of gender, age and ethnicity, the small number of subjects in each study or the use of different personality scales. Conflicting findings may also be due to the poor gene coverage in the majority of the studies to date. With the aim to better cover the gene, we investigated several 5-HT2A SNPs (rs643627, rs594242, rs6311 and rs6313; Table 1) and their association with personality traits as measured with the TCI. We studied the first three SNPs in two sub-samples of German subjects, composed respectively of normal controls and suicide attempters with a psychiatric diagnosis. Moreover, we also investigated an independent, smaller Italian mood disorder sample for association with the rs6313 SNP, which is in strong LD with rs6311.

### 2. Materials and methods

#### 2.1. Samples

**2.1.1. German sample**

Healthy volunteers were randomly selected from the city registry (Einwohnermeldeamt) of Munich, Germany, 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 theStructured Clinical Interview for DSM-IV (SCID I and SCID II) (First et al., 1990; First et al., 1995; Wittchen et al., 1997) to evaluate their lifetime Axis I and II disorders. 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 (males/females: 123/166; 42.6% males) were included in the study. Their mean age was 45.2±14.9 years. 26.3% of the subjects had low education level, 30.1% had middle level and 43.6% had high level. The education level was rated as low (secondary school), middle (junior high school) and high (general qualification for university entrance).

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. 111 suicide attempters (males/females: 43/68; 38.7% males) were included in the study. Their mean age was 39.2±13.6 years. 30.6% of the patients had low education level, 36.9% had middle level and 32.4% had high level.

<table>
<thead>
<tr>
<th>SNP ID</th>
<th>Position*</th>
<th>Distance (bp)</th>
<th>Alleles</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs643627</td>
<td>46326612 (41430)</td>
<td>29,441</td>
<td>A/G</td>
<td>Intron</td>
</tr>
<tr>
<td>rs594242</td>
<td>46356053 (11989)</td>
<td>13,426</td>
<td>C/G</td>
<td>Intron</td>
</tr>
<tr>
<td>rs6313</td>
<td>46367941 (101)</td>
<td>1538</td>
<td>C/T</td>
<td>Coding sequence</td>
</tr>
<tr>
<td>rs6311</td>
<td>46369479 (−1437)</td>
<td>C/T</td>
<td>Promoter</td>
<td></td>
</tr>
</tbody>
</table>

* Absolute chromosomal position. The relative position to the start codon is given in parenthesis.
The current and lifetime diagnoses of mental disorders were assessed close to discharge by applying SCID I and 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 (n = 76; 68.5%), schizophrenia spectrum (n = 17; 15.3%) and borderline personality disorder (n = 18; 16.2%).

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 to the ethical standards laid down in the 1964 Declaration of Helsinki.

2.1.2. Italian sample

The sample was composed of 60 patients affected by bipolar disorder (n = 46) and recurrent major depression disorder (n = 14) and consecutively admitted to the Department of Neuropsychiatry at the Institute H. San Raffaele. 35.0% were males (males/females: 21:39). The mean age was 44.0 ± 10.4 years. Among patients, suicide attempters were 16 (28.6%) and subjects with a diagnosis of a personality disorder were 29 (52.7%).

The present sample is part of a larger sample that has been published for analyses of other clinical features, such as symptomatology and drug response (Serretti et al., 2001a; Serretti et al., 2002; Serretti et al., 2001b). Lifetime diagnoses were assigned by two independent psychiatrists on the basis of unstructured clinical interviews and medical records, according to DSM-IV criteria following a best estimate procedure (Leckman et al., 1982). The presence of concomitant diagnoses of mental retardation or drug dependence, together with somatic or neurological illnesses that impaired psychiatric evaluation represented exclusion criteria. Informed consent was obtained from all probands after the procedure had been fully explained to them; the probands were unrelated and of Italian descent with antecedents from all parts of the country.

2.2. Temperament and Character Inventory (TCI)

The Temperament and Character Inventory (TCI) is the tool to assess individual differences in the basic dimensions of the Cloninger biosocial model of personality (Cloninger et al., 1994). This model was based on the assumption that a part of the individual’s personality is heritable. In particular, Cloninger hypothesized that personality is composed both by traits that are heritable and stable throughout life and traits that are influenced by socio-cultural learning and mature throughout life. He defined Temperament the totality of heritable dimensions and Character the totality of non-heritable dimensions. Temperament consists of four traits, so-called Harm Avoidance (HA), Novelty Seeking (NS), Reward Dependence (RD) and Persistence (P). HA denotes the individual’s inclination to behavioral inhibition in front of potentially dangerous stimuli.
and to anticipate negative effects; NS relates to exploratory behaviours and activation in response to novel stimuli; RD concerns relational and affective skills but also dependent behaviours and activation in response to novel stimuli; RD and to anticipate negative effects; NS relates to exploratory skills, like support, collaboration, and partnership; finally, ST denotes the aptitude towards mysticism, religion and idealism.

The TCI is a battery of 240 items that has been developed to account for individual differences in both normal and abnormal behavioural patterns. In both samples, the same version of the TCI was administered, with a true–false Likert scale. The Italian version was previously validated (Fossati et al., 2001) as well as the German version (Brandstrom et al., 2003).

2.3. DNA analysis

5-HT<sub>2A</sub> rs643627, rs594242 and rs6311 were genotyped by Illumina (Illumina, Inc., San Diego, USA) through use of their Integrated BeadArray System. Additionally, 23 SNPs in genes spanning all chromosomes were genotyped as genomic controls (rs2006727; rs586726; rs724529; rs206847; rs1868155; rs2009602; rs1383628; rs876635; rs1367828; rs2076940; rs2025557; rs1993181; rs2168213; rs948184; rs2227973; rs1713449; rs2295152; rs1800404; rs1469122; rs731835; rs418251; rs725493; rs1555048). These genes have been selected based on the low a priori probability of involvement in behavioral traits and phenotypes. No association was observed for personality or diagnostic status. We supplied DNA quantified with Pico Green to be at 100 ng/μl and Illumina delivered genotypes with a quality score calculated by Illumina (Illumina, Inc., San Diego, USA) through use of their Integrated BeadArray System. Additionally, 23 SNPs in genes spanning all chromosomes were genotyped as genomic controls (rs2006727; rs586726; rs724529; rs206847; rs1868155; rs2009602; rs1383628; rs876635; rs1367828; rs2076940; rs2025557; rs1993181; rs2168213; rs948184; rs2227973; rs1713449; rs2295152; rs1800404; rs1469122; rs731835; rs418251; rs725493; rs1555048).

2.4. Statistical analysis

Multivariate analysis of covariance (MANCOVA) was used to test possible influence of single SNPs on TCI scores. With the aim of reducing possible sources of variance, we included in all analyses genotype and sex as main factors and education and age as covariates in the MANCOVA model. This was performed because of the influence of such variables on TCI (Cloninger et al., 1994) and unequal distribution in our study sample (Giegling et al., 2006; Rujescu et al., 2003).

Haploviz 3.2 was used to generate a LD map and to test for Hardy–Weinberg equilibrium (HWE) (Barrett et al., 2005). Tests for associations using multi-marker haplotypes were performed using the statistics software “R” (http://www.R-project.org), package “haplo.score” to compare TCI scores between haplotypes. Sex, age and education were added as covariates. Permutations (n = 10,000) were performed to estimate the global significance of the results for all haplotype analyses and to validate the expectation-maximization values.

All p values were 2-tailed, and statistical significance was conservatively set at the 0.007 level (0.05 divided by 7 TCI factors). Traditional statistical analyses were performed using “Statistica” package (StatSoft, 1995). With these parameters we had a sufficient power on the German control sample (0.80) to detect a medium effect size (d=0.45) between two main genotypes, that, as an example, corresponds to 2.3 points on NS scores (TCI) (Cohen, 1988). The other samples had lower power given the reduced sample size (data not shown).

3. Results

3.1. German sample

3.1.1. Hardy–Weinberg equilibrium and linkage disequilibrium for 5-HT<sub>2A</sub> rs643627, rs594242 and rs6311 SNPs

5-HT<sub>2A</sub> SNPs were in HWE in the whole sample (rs643627: p = 0.81; rs594242: p = 1.00; rs6311: p = 1.00), as well as separately in controls (rs643627: p = 0.43; rs594242: p = 1.00; rs6311: p = 0.88) and in suicide attempters (rs643627: p = 0.99; rs594242: p = 0.94; rs6311: p = 0.85).

### Table 3
Temperament and character dimensions stratified for 5-HT<sub>2A</sub> genotypes – German suicide sample

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Character/Temp</th>
<th>n</th>
<th>TCI Scores</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HA</td>
<td>NS</td>
</tr>
<tr>
<td>A/A</td>
<td>58.50±7.59</td>
<td>55.54±9.34</td>
<td>1.17</td>
<td>103</td>
</tr>
<tr>
<td>A/G</td>
<td>58.50±7.59</td>
<td>55.54±9.34</td>
<td>1.17</td>
<td>103</td>
</tr>
<tr>
<td>G/G</td>
<td>58.50±7.59</td>
<td>55.54±9.34</td>
<td>1.17</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>df</td>
</tr>
<tr>
<td>A/A</td>
<td>58.50±7.59</td>
<td>55.54±9.34</td>
<td>1.17</td>
<td>103</td>
</tr>
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<td>103</td>
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<tr>
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<td>58.50±7.59</td>
<td>55.54±9.34</td>
<td>1.17</td>
<td>103</td>
</tr>
</tbody>
</table>

### Table 4
Temperament and character dimensions stratified for 5-HT<sub>2A</sub> genotypes – German suicide sample

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Character/Temp</th>
<th>n</th>
<th>TCI Scores</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HA</td>
<td>NS</td>
</tr>
<tr>
<td>A/A</td>
<td>58.50±7.59</td>
<td>55.54±9.34</td>
<td>1.17</td>
<td>103</td>
</tr>
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<td>1.17</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>df</td>
</tr>
<tr>
<td>A/A</td>
<td>58.50±7.59</td>
<td>55.54±9.34</td>
<td>1.17</td>
<td>103</td>
</tr>
<tr>
<td>A/G</td>
<td>58.50±7.59</td>
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<td>1.17</td>
<td>103</td>
</tr>
<tr>
<td>G/G</td>
<td>58.50±7.59</td>
<td>55.54±9.34</td>
<td>1.17</td>
<td>103</td>
</tr>
</tbody>
</table>
Table 4
Temperament and character dimensions stratified for rs6313 genotypes – Italian patient sample

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HA</td>
<td>53.80±5.92</td>
<td>55.18±7.74</td>
<td>56.50±8.21</td>
<td>0.41</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>NS</td>
<td>62.40±5.82</td>
<td>57.88±4.15</td>
<td>59.45±4.95</td>
<td>4.71</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>RD</td>
<td>38.67±2.82</td>
<td>38.79±3.46</td>
<td>38.36±3.07</td>
<td>0.07</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>P</td>
<td>12.00±1.60</td>
<td>11.91±1.78</td>
<td>11.64±2.42</td>
<td>0.13</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>SD</td>
<td>71.40±7.31</td>
<td>72.00±9.30</td>
<td>67.09±8.20</td>
<td>1.36</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>C</td>
<td>69.00±6.91</td>
<td>72.97±4.43</td>
<td>70.36±4.63</td>
<td>3.38</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>ST</td>
<td>46.36±5.50</td>
<td>46.09±5.95</td>
<td>47.54±8.85</td>
<td>0.21</td>
<td>2</td>
<td>56</td>
</tr>
</tbody>
</table>

HA = Harm Avoidance, NS = Novelty Seeking, RD = Reward Dependence, P = Persistence, SD = Self-Directedness, C = Cooperativeness, ST = Self-Transcendence.

In the whole sample, rs594242 and rs6311 were in strong LD (Fig. 1), also considering separately controls and suicide attempters (data not shown), while D’ scores were lower between rs643627 and both rs594242 and rs6311.

3.1.2. 5-HT2A rs643627, rs594242 and rs6311 polymorphisms and personality traits in healthy sample

Single SNP MANCOVA results are reported in Table 2. Rs594242 showed an association with SD (main effect: \(F = 6.09; df = 2,281; p = 0.003\)). No other association was observed with other TCI factors. Rs643627 and rs6311 were not associated with TCI personality traits.

3.1.3. 5-HT2A rs643627, rs594242 and rs6311 polymorphisms and personality traits in suicide attempters

Single SNP MANCOVA results are reported in Table 3. No associations were observed between any of the three polymorphisms and TCI factors. Rs594242 and Rs6311 only showed a trend for association with C (respectively, main effect: \(F = 2.43; df = 2,103; p = 0.09\) and \(F = 2.71; df = 2,85; p = 0.07\)).

3.2. Italian sample

3.2.1. 5-HT2A rs6313 SNP and personality dimensions

Rs6313 was marginally departing from HWE in the Italian sample (\(p = 0.042\)). The SNP was marginally associated with NS (\(F = 3.42; df = 2,39; p = 0.04\); Table 4), with T/T subjects reporting higher scores for NS. None of the other personality dimensions were associated with the investigated SNP.

4. Discussion

We investigated the association of 5-HT2A SNPs (5-HT2A rs643627, rs594242, rs6311 and rs6313) with personality traits as measured with the TCI in three independent samples including healthy subjects and patients. We observed mainly negative findings, nevertheless, a marginal association between the rs594242 polymorphism and SD was found in the healthy subject German sub-sample. Interestingly a non-significant similar direction of scores was observed in the Italian sample. From a purely probabilistic calculation, the chance of the observed finding is about 3 out of 1000, however much caution should be applied given the high number of genetic investigations published in literature.

We selected several SNPs to better cover the gene; however, some genetic variance has not been captured as also demonstrated by the low LD between rs643627 and the other markers. In fact, rs643627 is located almost at the 3’ end of the gene in intron 2, and about 29 kbp downstream from rs594242, which is also located in the same intron. Rs6311 is in the promoter region further 13 kbp upstream from rs594242, an area that has been much investigated in previous studies (Blairy et al., 2000; Ni et al., 2006; Tochigi et al., 2005). Finally, rs6313, investigated in the Italian sample only, is located in the coding sequence and it is about 1.5 kbp distant from rs6311. This SNP is in almost complete LD with rs6311 in Caucasians (Ni et al., 2006).

Since rs6313 was not in HWE in the Italian sample, it is important to note that it has been observed that approximately 10% of the published studies report HWE departures; reasons may be linked to ethnic stratification of the sample, lack of random matching, spurious associations with undetected conditions, genetic drift, genotype errors, small sample size and chance (Trikalinos et al., 2006; Vogel and Motulsky, 1997). Moreover, HWE departure may bias gene–disease associations; in our sample, we carefully checked for laboratory errors with a double operator reading.

As for other findings, rs594242 and rs6311 showed a trend for association with C (\(p = 0.09\) and \(p = 0.07\), respectively). These are novel and marginal results, so replication studies are clearly necessary.

Interestingly, rs6313 was marginally associated with NS (\(p = 0.01\)) in the Italian mood disorder sample. T/T subjects reported higher scores in NS than the others. However, this result is not in line with findings of two previously published studies. In a healthy subject sample, rs6313 heterozygotes scored lower on the State–Trait Anxiety Expression Inventory (STAI) scale of Anxiety and had a lower score on the Minnesota Multiphasic Personality Inventory (MMPI) scale of Social Introversive, which is correlated with the TCI HA dimension. For what concerns TCI, rs6313 heterozygotes had significantly lower scores in HA than homozygous schizophrenics (Golimbet et al., 2004). In a second study in borderline personality disorder patients and controls, there was no association between the C allele of rs6313 and higher extraversion scores (Ni et al., in press). No other studies on the association of rs6313 with personality traits are published to date, consequently further studies are required.

The results of the present investigation are mainly negative, considering the weakness of the p values, nevertheless, it is however possible to hypothesize a link between impulsivity and 5-HT2A SNPs, that should be more deeply dissected. In a recent study carried out on the same German sample, C/C homozygotes for the functional rs6311 SNP reported more anger- and aggression-related behaviours. In particular, regarding the State–Trait Anger Expression Inventory (STAXI), C/C homozygotes had higher scores on Trait Anger and Angry Reaction and lower scores on Anger Out subscales and regarding the Questionnaire for Measuring Factors of Aggression (FAF) C-allele carriers...
showed less Aggression Inhibition (Giegling et al., 2006). Since we have previously observed (data not published) a positive correlation between NS and the Anger Out subscale and a negative one between NS and Aggression Inhibition, also the rs6311 could be related to NS. Consequently all SNPs analyzed in this study should be considered in future research.

The present study has relevant strengths: the number of the polymorphisms considered, two of which scarcely studied in literature; the sample, large and composed of control subjects in the German group. Also the fact that the two samples are made up of subjects from two different ethnic groups is relevant. Actually, ethnic origin is a frequent cause of stratification bias, but our sample was composed of subjects mainly from Germany and the North of Italy with local antecedents for at least two generations. The German population is considered genetically homogeneous (Cavalli Sforza, 1994). North Italy is also characterized by a substantial genetic homogeneity (Barbujani and Sokal, 1991a; Barbujani and Sokal, 1991b; Gasparini et al., 1997). Finally, a collaborative paper presenting 5-HT2C genotypes from different countries reported similar frequencies for Italy and Germany (Lerer et al., 2001).

Nevertheless, limitations are also present: the difference in the polymorphisms investigated in Italians and Germans; the dissimilarity of the psychiatric diagnoses between the two samples; the lack of the control sample among Italian subjects; and the difference in terms of gender ratio and mean age among controls and the clinical samples. Moreover, candidate gene studies like the present are highly likely to produce false positive findings (Sullivan, in press). A number of clinical factors influence TCI scores, among them sex and age in particular. In a recent meta-analysis on gender differences in the TCI temperament dimensions, women scored higher in RD and HA. There were no differences in NS or in P (Miettunen et al., 2007). In another work distribution by age and sex of the dimensions of the TCI were assessed cross-culturally for samples in Sweden, Germany and the USA (Brandstrom et al., 2001). Significant effects of age, sex and culture in univariate and multivariate comparisons on the distribution by age and sex of the dimensions of the TCI were reported. Also genetic analyses revealed cross-cultural, univariate and multivariate comparisons on the personality dimensions were found. Also genetic analyses revealed gender specific differences (Samochowiec et al., 2004). Consequently, we put gender, age and education as covariants. Another question could be the validity problems arising from the administration of the TCI to schizophrenia spectrum patients. A few studies were published in literature on the temperamental profile of schizophrenic patients (Ekland et al., 2004; Guillem et al., 2002), consequently future investigations are required.

In conclusion, we observed a minor effect of 5-HT2A variants on personality scores in both patients and controls; a false-positive finding is possible but further analyses may be worthwhile.

References

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