A Polymorphism in the Serotonin Receptor 3A (HTR3A) Gene and Its Association With Harm Avoidance in Women

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Background: The brain neurotransmitter serotonin is known to affect various aspects of human behavior, including personality traits. Serotonin receptor type 3 is a ligand-gated channel encoded by 2 different subunit genes, HTR3A and HTR3B. A polymorphism (C178T) in the 5’ region of the HTRA gene has recently been identified and suggested to be of functional importance.

Objective: To elucidate the possible association between the C178T polymorphism in the HTRA gene and personality traits in women.

Design: Two independent samples of 35- to 45-year-old Swedish women were recruited using the population register. Sample 1 (n=195) was assessed via the Karolinska Scales of Personality and the Temperament and Character Inventory; sample 2 (n=175) was assessed using the lat-ter only. Both samples were genotyped with respect to the C178T polymorphism and the Karolinska Scales of Personality nonconformity factor (corrected P=0.002), including the subscales of social desirability (P<0.001), indirect aggression (P=0.002), verbal aggression (P=0.05), and irritability (P<0.001). Participants homozygous for the less common T allele (<4%) differed from the remaining women by displaying lower ratings on harm avoidance and nonconformity.

Conclusion: The C178T polymorphism in the HTRA gene may affect the personality trait of harm avoidance in women.

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control, and regulation of pain and nausea.10 Brain 5-HT3 receptors have been shown to affect the activity of several other neurotransmitters, including norepinephrine,20 acetylcholine,21 γ-aminobutyric acid,22 and dopamine.23,24 In addition, pharmacologic studies have suggested that 5-HT3 receptors may modulate the symptoms of eating disorders,25 alcoholism,26,27 psychosis,28 and anxiety disorders.29

The 5-HT3 ion channel is encoded by 2 different subunit genes, HTR3A and HTR3B, which map in close vicinity on chromosome 11 (11q23.1/23.2).30 Both genes are expressed in brain areas such as the amygdala, the hippocampus, and the caudate nucleus.31 Recently, a single nucleotide polymorphism (SNP), C178T, in the upstream regulatory region of the HTR3A gene was identified and proposed to be of functional importance.32 In the present study, the less common T allele was associated with symptoms of eating disorders,25 alcoholism,26,27 psychosis,28 and anxiety disorders.29

In the present study, we investigated the extent to which the C178T polymorphism is related to personality traits in 2 independent samples of women recruited from the normal population. Prompted by the results obtained regarding the C178T polymorphism, we subsequently analyzed the A1596G polymorphism in the same gene. Sample 1 was assessed via 2 personality questionnaires: the Temperament and Character Inventory (TCI) and the Karolinska Scales of Personality (KSP). Sample 2 was assessed via the TCI only.

METHODS

PARTICIPANTS

Sample 1 is a subpopulation of all women born on uneven days in 1956 and living in Göteborg; this population-based cohort was originally recruited for a study of obesity, anthropometrics, and cardiovascular risk factors, the details of which have been previously reported.33 Women with 1 or 2 parents who were probably or certainly nonwhite (n = 17) were excluded. Useful TCI and KSP questionnaires were returned by 191 and 194 women, respectively. At the time of personality assessment, the participants were 42 years old.

Sample 2 is a subgroup of a population-based cohort originally recruited for a longitudinal study on memory, personality, and aging conducted in Umeå (for details, see Nilsson et al34) in which personality was assessed using the TCI (but not the KSP). From this larger population comprising 3000 men and women of different ages, all women aged 35 to 45 years at the time of investigation (hence matching sample 1 with respect to sex and age) were selected and genotyped. Of these women, 175 returned useful TCI questionnaires.

All participants provided informed consent. The study protocols were approved by the ethics committees of Gothenburg University and Umeå University.

PERSONALITY ASSESSMENT

The TCI is a psychometric instrument based on a self-administered true-false questionnaire and designed to assess personality along 4 temperament factors—novelty seeking, harm avoidance, reward dependency, and persistence—and 3 character factors—self-directedness, cooperativeness, and self-transcendence.44 In the present study, a Swedish 238-item translation of the TCI was used.44 Whereas the 4 temperament factors are thought to be largely heritable and rooted in neurobiology, the 3 character factors are assumed to be, to a great extent, socioculturally determined and hence less likely to be associated with specific genes.44 This study explores the possible association between the studied polymorphism and the 4 temperament factors; the 3 character factors were not taken into consideration.

The women in sample 1 also completed the KSP questionnaire,35 which has previously been widely used in studies36,40 examining biological correlates of personality traits. The KSP consists of 135 items that form 15 subscales. The validity and reliability of the KSP have been extensively examined, and, for several of the subscales, interindividual variations have been shown to be stable and partly heritable.41 On the basis of several factor analyses, the 15 KSP subscales have been classified into 4 factors: extraversion (comprising the subscales of impulsiveness and monotony avoidance), neuroticism (comprising the subscales of somatic anxiety, psychic anxiety, muscular tension, psychasthenia, inhibition of aggression, guilt, and socialization), nonconformity (comprising the subscales of indirect aggression, verbal aggression, irritability, and social desirability), and psychoticism (comprising the subscales of detachment and suspicion).42

MOLECULAR GENETICS

Venous blood samples were collected from all participants, and genomic DNA samples were isolated using the QIAamp DNA Blood Mini Kit (Qiagen Inc, Valencia, Calif). All polymerase chain reactions (PCRs) were performed on a GeneAmp PCR System 9700 (Applied Biosystems, Foster City, Calif).

The women in sample 1 were genotyped for the C178T polymorphism using the protocol described by Niesler and coworkers.43 The following primer pair was used for the PCR: 5′-AGCTGGCCCTTGGTGGAAGCAGG-3′ and 5′-CAGATGGTCACACAAATGTC-3′. The forward primer is modified in its 3′ end, creating the 3′ part of an Ac I restriction site (CICCGC). The 3′ part of the restriction site is encoded by the more common C allele; the enzyme Ac I thus will cleave the 175-base pair (bp) PCR product of the C alleles. The PCR products were separated on 2.5% agarose gels supplemented with ethidium bromide and visualized by ultraviolet transillumination.

The women in sample 2 were genotyped using Pyrosequencing.43 The PCR products were generated using Hotstar Taq polymerase (Qiagen Inc) in a total volume of 20 µL containing 1.5 mM magnesium chloride, approximately 50 ng genomic DNA, and 200 mM each dATP, dCTP, dGTP, and dTTP. The reaction contained 150 mM of each primer (forward: 5′-biotin-AGCTGGCCCTTGGTGGAAGCAGG-3′; reverse: 5′-AGTGTTGGGAGGAGCAAGG-3′), which amplifies a 151-bp product surrounding the C178T polymorphism. The PCR conditions comprised an initial denaturing step at 95°C for 15 minutes; 40 cycles each at 94°C for 15 seconds, 64°C for 30 seconds, and 72°C for 15 seconds; and a final extension at 72°C for 7 minutes. The polymorphism was detected using Pyrosequencing and an SNP reagent kit (PSQ 96 System; Pyrosequencing AB, Uppsala, Sweden). A total of 20 µL of PCR product was used for Pyrosequencing in accordance with the manufacturer’s instructions; 15 pmol of the sequencing primer 5′-CCCTCCGAGTGCTGAG-3′ was used to detect the corresponding polymorphism.

After the apparent association between the C178T polymorphism and personality traits had been revealed (see the “Re-
The TCI factors and subscales were analyzed using raw scores, without standardization using normative data. Associations between TCI scores for the 4 temperamental factors and C178T genotype in sample 1 were assessed using 2-sided t tests, with correction for multiple comparisons as described herein.

Sample 2 was analyzed to investigate the extent to which any associations found in sample 1 could be replicated. To this end, a 1-sided t test was performed to evaluate the possible association between C178T genotype and the TCI factor harm avoidance (recessive model; see the following paragraphs in this section). The TCI factors not displaying significant associations in sample 1 were, however, analyzed as well (2-sided t tests). Finally, the associations between the C178T polymorphism and harm avoidance, as well as its 4 subscales (anticipatory worry, fear of uncertainty, shyness, and fatigability and asthenia), were analyzed in the 2 samples pooled together using 1-sided t tests.

The KSP factors and subscales were analyzed using T scores, which are standardized using normative data to have a mean ± SD of 50 ± 10. The grouping of the 13 subscales into 4 factors—extraversion (including impulsiveness and monotony avoidance), neuroticism (including somatic anxiety, psychic anxiety, muscular tension, psychasthenia, inhibition of aggression, guilt, and socialization), nonconformity (including indirect aggression, verbal aggression, irritability, and social desirability), and psychoticism (including detachment and suspicion)—was based on previous studies and was undertaken by calculating the mean of all items within a single factor using 100 minus the original score for scales displaying negative loading (socialization and social desirability) in relation to the other scales within that factor. For comparison of the different genotypes with respect to these summation scales, 2-sided t tests were used (with correction for multiple comparisons). For the factor displaying a significant association with genotype, that is, nonconformity, the relationships between genotype and the different subscales within that factor were analyzed using 1-sided t tests. Because sample 2 was not assessed via the KSP, we did not examine the extent to which the KSP findings obtained in sample 1 were possible to replicate.

No presumption was made regarding which variant of the studied polymorphism is recessive or dominant; hence, all analyses were undertaken in accordance with the assumption that the T allele may be either dominant (C/C vs C/T+T/T) or recessive (T/T vs C/T+C/C).

The levels of significance for all t tests undertaken with respect to TCI and KSP factors in the first sample were corrected for multiple comparisons by means of a step-down permutation procedure (comprising 100,000 permutations), automatically taking into account the correlation between the scales and between a dominant and a recessive t test. Because of the permutation, the P values are more robust to deviation from normality, and, combined with the step-down principle, this is a more powerful procedure than a Bonferroni correction. For comparison, P values adjusted using Bonferroni correction for the factors displaying significant associations with the HTR3A genotype are also presented.

Associations between the A1596G polymorphism and personality test scores were analyzed as described herein. Linkage disequilibrium coefficients between the C178T and A1596G polymorphisms were calculated. The relationship between TCI and KSP factors (and subscales) was analyzed using bivariate Pearson correlations.

### RESULTS

The genotypes of the C178T polymorphism were distributed according to the Hardy-Weinberg equilibrium in both samples (P=.12 and P=.92). The T allele was found in 19.8% of the women in sample 1 and in 20.3% in sample 2. Allele and genotype frequencies were in agreement with those of previous studies.

When sample 1 was analyzed with respect to the 4 TCI factors, comparison of the different C178T genotypes using the recessive model (T/T vs C/T+C/C) revealed a significant association between genotype and harm avoidance (P=.005 and corrected P=.04) in sample 1 and was not associated between genotype and the other 3 TCI factors. In sample 2, C178T genotype and harm avoidance was replicated in sample 2 (P=.004) (pooled populations: P<.001) (Table 1). In the pooled sample, C178T genotype was found to be associated with all harm avoidance subscales, that is, anticipatory worry (P<.001), fear of uncertainty (P<.001), shyness (P<.001), and fatigability and asthenia (P=.008).

When sample 1 was analyzed with respect to the 4 KSP factors, comparison of the different genotypes using the recessive model (T/T vs C/T+C/C) revealed a significant association between genotype and nonconformity (P=.0002; corrected P=.002) (Table 2). A subsequent analysis revealed significant associations between genotype and all subscales included in the nonconformity factor, that is, social desirability, direct aggression, verbal aggression, and irritability (P<.001, Table 2).

When the dominant model (C/C vs C/T+T/T) was applied, the groups did not differ significantly with respect to any of the personality measures investigated. Therefore, the data support the notion that the T allele is recessive at least with respect to the aspects of phenotype examined in this study.

The genotype frequencies of the A1596G polymorphism were 62.5% (A/A), 32.0% (A/G), and 5.5% (G/G) in sample 1 and 52.6% (A/A), 38.3% (A/G), and 9.1% (G/G) in sample 2. As previously reported, a high linkage disequilibrium between the C178T and A1596G polymorphisms was detected in both samples, 178C being positively associated with 1596A (sample 1: D'=0.46, P<10^-10; sample 2: D'=0.46, P<10^-10). No significant associations between the A1596G polymorphism and personality traits were found in any of the 2 samples or in the subgroup of women displaying the T/T genotype with respect to C178T (data not shown).

When the 2 different questionnaires were compared in sample 1, TCI harm avoidance was found to be strongly correlated with the KSP factors of neuroticism (R=0.74) and nonconformity (R=0.47) and with the nonconformity subscales of social desirability (R=–0.31), indirect aggression (R=0.40), and irritability (R=0.57) (P<.001 for all). However, no significant correlation was found between harm avoidance and the fourth subscale included in the nonconformity factor, verbal aggression...
As expected, other significant correlations between various TCI and KSP factors were observed as well, but these data are beyond the scope of this article and will be presented elsewhere.

In the first sample genotyped, we found that women who were homozygous for the T allele of the C178T polymorphism in the HTR3A gene displayed lower harm avoidance than women who carried the C allele; in contrast, the groups did not differ with respect to the other TCI factors. In the second sample, the association between genotype and harm avoidance was replicated; again, no association was observed for the other factors. Analysis of the total, pooled sample revealed significant associations between C178T genotype and all of the subscales included in the harm avoidance factor.

In sample 1, women who were homozygous for the T allele displayed lower scores also with respect to the nonconformity factor of the KSP, including low scores on the subscales of irritability and indirect aggression and high scores on the subscale of social desirability. Because the second sample was not assessed via the KSP, we did not examine whether these associations could be replicated in an independent sample. Therefore, these data

### Table 1. Temperament and Character Inventory Factor Raw Scores in 2 Samples of 35- to 45-Year-Old Swedish Women Recruited From the Healthy Population, by C178T Genotype

<table>
<thead>
<tr>
<th>Variable</th>
<th>Genotype</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C/C</td>
<td>C/T</td>
<td>T/T</td>
<td>Dominant Model†</td>
<td>Recessive Model‡</td>
<td>Corrected§</td>
</tr>
<tr>
<td></td>
<td>n = 121</td>
<td>n = 64</td>
<td>n = 6</td>
<td>.72</td>
<td>.99</td>
<td>.93</td>
</tr>
<tr>
<td>Novelty seeking</td>
<td>21.1 ± 5.0</td>
<td>20.8 ± 5.1</td>
<td>21.0 ± 7.0</td>
<td>.61</td>
<td>.005</td>
<td>.04</td>
</tr>
<tr>
<td>Harm avoidance</td>
<td>15.3 ± 6.8</td>
<td>16.6 ± 6.3</td>
<td>7.8 ± 8.3</td>
<td>.48</td>
<td>.35</td>
<td>.83</td>
</tr>
<tr>
<td>Reward dependence</td>
<td>15.7 ± 3.5</td>
<td>15.2 ± 3.3</td>
<td>16.8 ± 3.5</td>
<td>.46</td>
<td>.35</td>
<td>.93</td>
</tr>
<tr>
<td>Persistence</td>
<td>3.7 ± 1.8</td>
<td>3.7 ± 1.7</td>
<td>4.3 ± 1.9</td>
<td>.68</td>
<td>.39</td>
<td>.93</td>
</tr>
<tr>
<td></td>
<td>n = 111</td>
<td>n = 57</td>
<td>n = 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novelty seeking</td>
<td>20.3 ± 5.6</td>
<td>20.2 ± 5.5</td>
<td>23.4 ± 6.9</td>
<td>NA</td>
<td>.14</td>
<td>NA</td>
</tr>
<tr>
<td>Harm avoidance</td>
<td>15.2 ± 5.8</td>
<td>14.3 ± 6.0</td>
<td>8.8 ± 3.1</td>
<td>NA</td>
<td>.004</td>
<td>NA</td>
</tr>
<tr>
<td>Reward dependence</td>
<td>16.8 ± 3.1</td>
<td>16.9 ± 3.9</td>
<td>16.0 ± 2.9</td>
<td>NA</td>
<td>.32</td>
<td>NA</td>
</tr>
<tr>
<td>Persistence</td>
<td>4.0 ± 1.8</td>
<td>4.2 ± 2.2</td>
<td>3.6 ± 1.4</td>
<td>NA</td>
<td>.51</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>n = 232</td>
<td>n = 121</td>
<td>n = 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harm avoidance (total)</td>
<td>15.2 ± 6.3</td>
<td>15.5 ± 6.3</td>
<td>8.4 ± 5.8</td>
<td>NA</td>
<td>&lt;.001</td>
<td>NA</td>
</tr>
<tr>
<td>HA1 (anticipatory worry)</td>
<td>4.5 ± 2.2</td>
<td>4.4 ± 2.1</td>
<td>2.5 ± 2.1</td>
<td>NA</td>
<td>.001</td>
<td>NA</td>
</tr>
<tr>
<td>HA2 (fear of uncertainty)</td>
<td>4.4 ± 1.5</td>
<td>4.4 ± 1.6</td>
<td>2.8 ± 1.4</td>
<td>NA</td>
<td>&lt;.001</td>
<td>NA</td>
</tr>
<tr>
<td>HA3 (shyness)</td>
<td>3.2 ± 2.1</td>
<td>3.5 ± 2.3</td>
<td>1.3 ± 2.0</td>
<td>NA</td>
<td>&lt;.001</td>
<td>NA</td>
</tr>
<tr>
<td>HA4 (fatigability and asthenia)</td>
<td>3.2 ± 2.0</td>
<td>3.1 ± 2.2</td>
<td>1.8 ± 1.4</td>
<td>NA</td>
<td>.008</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: HA, harm avoidance; NA, not applicable.
*Scores are given as mean ± SD. All t tests were 2-sided except the analyses of harm avoidance in sample 2 and in the total sample, since these were attempts to replicate the finding in sample 1.
†Significance levels of t test comparisons of the dominant model (C/C vs C/T + T/T).
‡Significance levels of t test comparisons of the recessive model (T/T vs C/T + C/C).
§Significance levels corrected for multiple comparisons using a step-down permutation procedure.

### Table 2. Karolinska Scales of Personality Factor and Nonconformity Subscale T Scores in Sample 1, by C178T Genotype

<table>
<thead>
<tr>
<th>Factor</th>
<th>Genotype</th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C/C</td>
<td>C/T</td>
<td>T/T</td>
<td>Dominant Model†</td>
<td>Recessive Model‡</td>
<td>Corrected§</td>
</tr>
<tr>
<td>Extraversion</td>
<td>51.5 ± 7.5 (n = 122)</td>
<td>52.6 ± 8.2 (n = 63)</td>
<td>56.8 ± 11.8 (n = 6)</td>
<td>.21</td>
<td>.13</td>
<td>.57</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>47.9 ± 7.4 (n = 114)</td>
<td>49.6 ± 7.2 (n = 58)</td>
<td>44.6 ± 8.4 (n = 5)</td>
<td>.25</td>
<td>.25</td>
<td>.66</td>
</tr>
<tr>
<td>Psychoticism</td>
<td>48.0 ± 8.7 (n = 119)</td>
<td>48.7 ± 10.1 (n = 63)</td>
<td>44.3 ± 14.2 (n = 6)</td>
<td>.73</td>
<td>.32</td>
<td>.66</td>
</tr>
<tr>
<td>Nonconformity</td>
<td>50.0 ± 7.5 (n = 119)</td>
<td>52.1 ± 5.2 (n = 62)</td>
<td>39.8 ± 7.1 (n = 6)</td>
<td>.31</td>
<td>.0002</td>
<td>.002</td>
</tr>
<tr>
<td>Social desirability</td>
<td>47.2 ± 8.8</td>
<td>46.4 ± 6.6</td>
<td>59.0 ± 12.9</td>
<td>NA</td>
<td>&lt;.001</td>
<td>NA</td>
</tr>
<tr>
<td>Indirect aggression</td>
<td>53.4 ± 11.5</td>
<td>55.6 ± 9.5</td>
<td>40.6 ± 14.3</td>
<td>NA</td>
<td>.002</td>
<td>NA</td>
</tr>
<tr>
<td>Verbal aggression</td>
<td>48.1 ± 9.2</td>
<td>51.7 ± 9.3</td>
<td>42.9 ± 7.9</td>
<td>NA</td>
<td>.05</td>
<td>NA</td>
</tr>
<tr>
<td>Irritability</td>
<td>45.6 ± 9.0</td>
<td>47.5 ± 7.7</td>
<td>33.7 ± 8.6</td>
<td>NA</td>
<td>&lt;.001</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
*Scores are given as mean ± SD. Scores are standardized using normative data to have a mean ± SD of 50 ± 10. All t tests were 2-sided except the analyses of the nonconformity subscales, which were 1-sided.
†Significance levels of t test comparisons of the dominant model (C/C vs C/T + T/T).
‡Significance levels of t test comparisons of the recessive model (T/T vs C/T + C/C).
§Significance levels corrected for multiple comparisons using a step-down permutation procedure.

(R = 0.10; P = .16). As expected, other significant correlations between various TCI and KSP factors were observed as well, but these data are beyond the scope of this article and will be presented elsewhere.

In the first sample genotyped, we found that women who were homozygous for the T allele of the C178T polymorphism in the HTR3A gene displayed lower harm avoidance than women who carried the C allele; in contrast, the groups did not differ with respect to the other TCI factors. In the second sample, the association between genotype and harm avoidance was replicated; again, no association was observed for the other factors. Analysis of the total, pooled sample revealed significant associations between C178T genotype and all of the subcales included in the harm avoidance factor.
should be interpreted with caution, the apparent association between the studied HTR3A polymorphism and TCI harm avoidance being the major finding of this study.

To our knowledge, the possible relationship between KSP and TCI ratings has never before been examined in a population of normal women. Individuals with a low harm avoidance rating have previously been described as being “confident, relaxed, optimistic, carefree, uninhibited, outgoing, and energetic”; moreover, it has been shown that low harm avoidance is associated with “positive emotionality” and “positive self-esteem.” The observation that women who were homozygous for the T allele of the C178T polymorphism displayed low harm avoidance, therefore, is in line with the observation that they also displayed low ratings on the KSP nonconformity subscales of irritability and indirect aggression and a high rating on the subscale of social desirability. Also, the observation that these subscales within the KSP nonconformity factor correlated with TCI harm avoidance is not surprising.

In line with a previous study of men, the TCI factor of harm avoidance also displayed a positive correlation with several neuroticism-related KSP subscales. Despite this, the C178T polymorphism was not significantly associated with the KSP factor of neuroticism. Participants displaying the T/T genotype, however, displayed lower ratings with respect to 2 of 7 KSP neuroticism subscales (muscular tension and psychasthenia), but these differences were not significant after correction for multiple comparisons (data not shown). Our data thus suggest that the studied polymorphism is associated primarily with aspects of harm avoidance not mirrored by the KSP neuroticism factor but more closely related to the KSP nonconformity factor, such as irritability and social desirability. However, irritability is indeed regarded by some researchers as part of the KSP neuroticism factor rather than belonging to the nonconformity factor.

It has previously been suggested by Cloninger and coworkers that harm avoidance is related to brain serotonergic neurotransmission. Support for this theory has been provided by studies showing an association between serotonin-related biological markers and harm avoidance and KSP nonconformity scores—those homozygous for the T allele of the C178T polymorphism on the basis of linkage disequilibrium with other polymorphisms within this gene, or in nearby genes, should not be ignored. However, as yet no other common polymorphisms that are likely to be of functional importance have been identified within the HTR3A gene. The only common polymorphism apart from the C178T that has been identified so far in this gene is the silent A1596G SNP in exon 9. Prompted by the observation of an association between the C178T polymorphism and harm avoidance, we also analyzed the A1596G polymorphism in these participants with respect to TCI harm avoidance scores. The finding that this polymorphism displayed high linkage disequilibrium with the C178T polymorphism but no association with personality traits is in line with the notion that the observed association between C178T and harm avoidance may be due to an effect of this polymorphism on receptor function.

The genotype group that differed from the rest of the participants with respect to TCI harm avoidance scores and KSP nonconformity scores—those homozygous for the less common T allele—constituted less than 4% of the women investigated. Therefore, the results obtained do not suggest that the studied polymorphism is a major determinant of interindividual variations in personality traits in the general population.

Women carrying the uncommon T/T genotype, differing from most participants with respect to personal-
ity, reported low TCI harm avoidance and low KSP non-conformity; in contrast, most previous studies of associations between gene polymorphisms and personality traits seem to have aimed at identifying alleles or genotypes associated with high scores on personality traits predisposing for—or correlating with—psychiatric disorders. Self-report questionnaires such as the TCI and the KSP, however, are constructed to detect extreme variants at both ends of the scale; needless to say, there are no reasons to assume that extreme variants that are not associated with psychiatric illness but that are on the opposite end of the scale would be determined by genetic factors to a lesser extent than variants that are associated with reduced well-being.

To summarize, to the best of our knowledge, this is the first study investigating the possible effect of the C177T polymorphism in the HTR3A gene on personality; the results, therefore, should be interpreted with caution until replicated by other researchers, especially since the subgroups deviating from the rest were so small. An obvious strength of this study, however, is that the association between the C177T polymorphism and the TCI factor of harm avoidance was observed in 2 independent samples, reinforcing the assumption that this association is actual and not merely due to chance. The association between the KSP factor of nonconformity and the studied polymorphism seemed robust and survived correction for multiple comparisons, but because KSP was assessed in 1 of the 2 populations only, this observation has not yet been replicated and should be regarded as preliminary. The T/T genotype displaying aberrant personality scores is rare and hence cannot be a major determinant of variations in personality traits in the general population; the finding that an uncommon variant of the 5-HT3 receptor gene may be associated with personality should, however, encourage further studies regarding the possible effect of this receptor on the regulation of human behavior.

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