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 HTR3A gene has recently been identified and suggested to be of functional importance.

Objective: To elucidate the possible association between the C178T polymorphism in the HTR3A 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 latter only. Both samples were genotyped with respect to the C178T polymorphism in the HTR3A gene. The A1596G polymorphism in the same gene was also investigated.

Results: A significant association between C178T genotype and the Temperament and Character Inventory factor harm avoidance was observed in sample 1 (corrected for multiple comparisons P=.04); this finding was subsequently replicated in sample 2 (P=.004) (pooled populations: P<.001). In the pooled sample, all harm avoidance subscales were found to be significantly associated with the C178T polymorphism: anticipatory worry (P<.001), fear of uncertainty (P<.001), shyness (P<.001), and fatigability and asthenia (P=.008). In addition, a significant association was found in sample 1 between the C178T polymorphism and the Karolinska Scales of Personality nonconformity factor (corrected P=.002), including the subscales of social desirability (P<.001), indirect aggression (P=.002), verbal aggression (P=.05), and irritability (P<.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 HTR3A gene may affect the personality trait of harm avoidance in women.

Arch Gen Psychiatry. 2003;60:1017-1023

Many studies have shown that interindividual variations in measures of personality are, to a great extent, heritable. Linkage between specific personality traits and several loci on different chromosomes has been suggested, and association studies have provided support for involvement of a variety of different candidate genes in this context.

Serotonergic neurotransmission has been suggested to affect a variety of aspects of personality, including harm avoidance, sensation seeking, impulsiveness, and aggression. To elucidate the possible importance of serotonin with respect to genetically determined differences in personality traits, several studies on the putative association between polymorphisms in serotonin-related genes and personality have been undertaken. To this end, Lesch and coworkers reported an association between a polymorphism in the promoter region of the serotonin transporter gene and neuroticism-related personality traits, and this association has been replicated in several (but not all) subsequent studies (eg, see Greenberg et al and Melke et al). Preliminary data also suggest that other serotonin-related genes, such as those coding for the 5-HT2C receptor and tryptophan hydroxylase, may be associated with specific personality traits in nonpatient samples.

Of the approximately 20 serotonin receptor subtypes that have been identified in the human brain so far, all are coupled to G proteins except for the 5-HT1 receptor, which is a ligand-gated ion channel. Central or peripheral 5-HT1 receptors seem to play a critical role in many serotonin-regulated physiologic processes, including vasomotor reflexes, cardiovascular con-
trol, and regulation of pain and nausea. Brain 5-HT₃ receptors have been shown to affect the activity of several other neurotransmitters, including norepinephrine, acetylcholine, γ-aminobutyric acid, and dopamine. In addition, pharmacologic studies have suggested that 5-HT₃ receptors may modulate the symptoms of eating disorders, alcoholism, psychosis, and anxiety disorders.

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). Both genes are expressed in brain areas such as the amygdala, hippocampus, and the caudate nucleus. 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. In the present study, a Swedish 238-item translation of the TCI was used. 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. 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, which has previously been widely used in studies 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.

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).

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 co-workers. The following primer pair was used for the PCR: 5′-AGCTGGCCCTTGGTGCGCCCCG-3′ and 5′-CAGATGGTCACACCAAGTCC-3′. The forward primer is modified in its 3′ end, creating the 5′ part of an AcII restriction site (CCCGC). The 3′ part of the restriction site is encoded by the more common C allele; the enzyme AcII 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. 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 30 ng genomic DNA, and 200 mM each dATP, dCTP, dGTP, and dTTP. The reaction contained 150 mM of each primer (forward: 5′-biotin-AGGCTGGCGTTGGGACATGAG-3′; reverse: 5′-AGTGTTGGGAGGAGGGCCG-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′-CTCGAGTGCTCAG-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-
sults” section), the A1596G polymorphism in exon 9 of the same gene was analyzed using Pyrosequencing as described in the previous paragraph. The following PCR primers were used: forward: 5’-biotin-TGCTGAAAGCTGCTATTCC-3’ and reverse: 5’-CCAGATGGACAGAGCATACG-3’. The sequencing primer was 5’-AGGCCAGCAGCCG-3’.

**DATA ANALYSES**

The TCI factors and subscales were analyzed using raw scores, without standardization using normative data. Associations between TCI scores for the 4 temperament 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 15 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 10,000 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) (Table 1) but no associations between genotype and the other 3 TCI factors. The association between 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 (P < .001), indirect aggression (P = .002), verbal aggression (P = .05), 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 = 10–13; sample 2: D’ = 0.46, P < 10–6). No significant associations between the A1596G polymorphism and personality traits were found in any of the 2 full 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>Sample 1 (n = 191)</th>
<th>Sample 2 (n = 175)</th>
<th>Total sample (n = 366)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n = 121</td>
<td>n = 111</td>
<td>n = 232</td>
</tr>
<tr>
<td>Novelty seeking</td>
<td></td>
<td>21.1 ± 5.0</td>
<td>20.3 ± 5.6</td>
<td>20.3 ± 5.6</td>
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<tr>
<td>Harm avoidance</td>
<td></td>
<td>15.3 ± 6.8</td>
<td>15.2 ± 5.8</td>
<td>15.2 ± 6.3</td>
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<tr>
<td>Reward dependence</td>
<td></td>
<td>15.7 ± 3.5</td>
<td>16.8 ± 3.1</td>
<td>16.8 ± 3.5</td>
</tr>
<tr>
<td>Persistence</td>
<td></td>
<td>3.7 ± 1.8</td>
<td>4.0 ± 1.8</td>
<td>4.0 ± 1.8</td>
</tr>
</tbody>
</table>

**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>
<th>Sample 1 (n = 191)</th>
<th>Sample 2 (n = 175)</th>
<th>Total sample (n = 366)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n = 121</td>
<td>n = 111</td>
<td>n = 232</td>
</tr>
<tr>
<td>Extraversion</td>
<td></td>
<td>51.5 ± 7.5</td>
<td>52.6 ± 8.2</td>
<td>52.6 ± 8.2</td>
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<tr>
<td>Neuroticism</td>
<td></td>
<td>47.9 ± 7.4</td>
<td>49.6 ± 7.2</td>
<td>49.6 ± 7.2</td>
</tr>
<tr>
<td>Psychoticism</td>
<td></td>
<td>48.0 ± 8.7</td>
<td>48.7 ± 10.1</td>
<td>48.7 ± 10.1</td>
</tr>
<tr>
<td>Conformity</td>
<td></td>
<td>50.0 ± 7.5</td>
<td>52.1 ± 5.2</td>
<td>52.1 ± 5.2</td>
</tr>
<tr>
<td>Social desirability</td>
<td></td>
<td>47.2 ± 8.8</td>
<td>46.4 ± 6.6</td>
<td>46.4 ± 6.6</td>
</tr>
<tr>
<td>Indirect aggression</td>
<td></td>
<td>53.4 ± 11.5</td>
<td>55.6 ± 9.5</td>
<td>55.6 ± 9.5</td>
</tr>
<tr>
<td>Verbal aggression</td>
<td></td>
<td>48.1 ± 9.2</td>
<td>51.7 ± 9.3</td>
<td>51.7 ± 9.3</td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td>45.6 ± 9.0</td>
<td>47.5 ± 7.7</td>
<td>47.5 ± 7.7</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.

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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 by the observation that harm avoidance scores are reduced by treatment with selective serotonin reuptake inhibitors in patients with generalized anxiety disorder. Depression, and obsessive-compulsive disorder. Whereas the results of studies regarding the possible association between harm avoidance and polymorphisms in the serotonin transporter gene are partly conflicting, studies investigating the possible relationship between harm avoidance and polymorphisms in genes coding for the 5-HT2A and 5-HT1C receptors have yielded negative results. Our data support the notion that harm avoidance may be affected by serotonin and suggest that this effect may partly be mediated by 5-HT3 receptors. Whether such an effect of 5-HT3 receptors is exerted during development of the central nervous system or whether it is permanently exerted within the developed brain cannot be established by means of association studies.

The observation in sample 1 of an association between the C178T polymorphism and KSP subscales related to irritability and indirect aggression is in line with previous studies suggesting that modulation of aggressive behavior is one of the most prominent physiologic roles of brain serotonergic neurons. An effect of serotonin on irritability in humans gains support from studies demonstrating an association between traits related to hostility or anger and serotonin-related biological markers. and by the observations that irritability and dysphoria may be increased by tryptophan depletion and reduced by treatment with serotonin reuptake inhibitors. Data on the possible role of 5-HT3 receptors in this context are as yet sparse, but there is preliminary support for the notion that some aspects of aggressive behavior in animals may be modulated by 5-HT3 agonists and antagonists.

Previous studies have shown that sex and age may affect the outcome of questionnaire-based personality assessments; the possibility of observing associations between a personality trait and a gene is probably better if the studied individuals are of the same sex and of similar age. In this context, a strength of sample 1 is that all of the participants are not only of the same sex (women) but also were born in the same year (being 42 years old when examined). The second sample also comprised women only, and it was selected to match the first sample as closely as possible with respect to age. Whereas our results support the notion that the C178T polymorphism is associated with harm avoidance and nonconformity in women aged 35 to 45 years, the possible relationship between this polymorphism and personality traits in men, and in younger and older women, should be the subject of future studies.

Although the C178T polymorphism on the basis of in vitro studies has been suggested to affect receptor expression, the possibility that the apparent association between this SNP and harm avoidance is due to the C178T being in 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 2 populations. 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.

Genotypic 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\textsuperscript{1-8} 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-HT\textsubscript{3} 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.

Submitted for publication September 3, 2002; final revision received December 27, 2002; accepted March 6, 2003.

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This study was supported by grants from the Swedish Medical Research Council (grants 8668, 251, and 10412); Lundbeck’s Foundation (Goteborg, Sweden); Thuring’s Foundation (Stockholm, Sweden); and Lundbeck’s Foundation (Helsingborg, Sweden).

This study was presented in part at the 43rd annual meeting of the Scandinavian College of Neuro-Psychopharmacology; April 9–12, 2002; Juan les-Pins, France; and at the World Congress on Psychiatric Genetics; October 9–13, 2002; Brussels, Belgium.

We thank Lisa Ekselfius, PhD, and J. Petter Gustavsson, PhD, for valuable comments regarding the Karolinska Scales of Personality and Inger Oscarsson, Gunilla Bourghardt, Monika Montell, and Anna Nilsson for skillful technical assistance.

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