Neuropsychopharmacology (2005) 30, 1711–1718

www.neuropsychopharmacology.org

Cluster B Personality Disorders are Associated with Allelic Variation of Monoamine Oxidase A Activity

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Genetic variants of the monoamine oxidase A (MAOA) have been associated with aggression-, anxiety-, and addiction-related behavior in several nonclinical and clinical populations. Here, we investigated the influence of allelic variation of MAOA activity on aggression-related personality traits and disease risk in patients with personality disorders. Personality disorders were diagnosed with the Structured Clinical Interview of DSM-IV and were allocated to cluster A, B, and C. Personality features were assessed by the revised NEO Personality Inventory and the Tridimensional Personality Questionnaire. The genotype of the *MAOA* gene-linked polymorphic region (*MAOA*-LPR) was determined in 566 patients with personality disorders and in 281 healthy controls. *MAOA* genotype was significantly associated with cluster B personality disorders ($\chi^2 = 7.77$, $p = 0.005$, df = 1) but not with cluster C personality disorders. In total, 26.0% of cluster B patients were hemi- or homozygous for the low-activity variant of the *MAOA* genotype, compared to 16.4% in the control group. Associations between *MAOA* variants and personality domains related to impulsivity and aggressiveness were inconsistent. Our findings further support the notion that allelic variation of MAOA activity contributes modestly to the balance of hyper- (impulsive-aggressive) and hyporeactive (anxious-depressive) traits.

Neuropsychopharmacology (2005) **30,** 1711–1718. doi:10.1038/sj.npp.1300737; published online 4 May 2005

Keywords: monoamine oxidase A genotype; MAOA-LPR; personality disorders; cluster B; anxiety; impulsivity

INTRODUCTION

Monoamine oxidase (MAO) is a mitochondrial enzyme that catalyzes the degradation of several biogenic amines. MAOA and MAOB are encoded by two adjacent X chromosome-linked genes and display different patterns of tissue distribution as well as substrate and inhibitor specificity (Johnston, 1968). MAOA is the prevailing isoform in the CNS and critically involved in the metabolism of monoamine neurotransmitters including serotonin and, to a lesser extent, norepinephrine, and dopamine.

The human gene encoding MAOA spans approximately 60 kb, is composed of 15 exons, and located on chromosome Xp11.3. Several polymorphisms have previously been described: a GT dinucleotide repeat polymorphism near exon 2 (*MAOA*-CA) (Black *et al*, 1991), a polymorphic region near exon 1 containing a GT microsatellite directly adjacent to an imperfectly duplicated 23-bp repeat motif (*MAOA*-VNTR) (Hinds *et al*, 1992), two functional restriction fragment length polymorphisms (*Fnu*4HI and *Eco*RV) (Lim *et al*, 1994), and the *MAOA* gene-linked polymorphic region (*MAOA*-LPR, *MAOA*-uVNTR), a functional 30-bp repetitive sequence located in the gene's transcriptional control region approximately 1.2 kb upstream of the ATG codon (Sabol *et al*, 1998; Deckert *et al*, 1999).

Six MAOA-LPR variants containing 2, 3, 3.5, 4, 5, and 6 repeats of this sequence have been identified, with the 3- and 4-repeat alleles being most common (Huang *et al*, 2004; Eley *et al*, 2003). Functional studies revealed that the *MAOA*-LPR modulates transcriptional activity of *MAOA* and ultimately enzyme activity (Sabol *et al*, 1998; Deckert *et al*, 1999; Denney *et al*, 1999). It may also influence CSF 5-HIAA concentrations gender-specifically in women (Jonsson *et al*, 2000). In consideration of the findings from *in vitro* and *in vivo* functional analyses, *MAOA*-LPR alleles have previously been dichotomized with the three-repeat variant as low-activity and longer alleles (3.5 repeats and longer) as high-activity (Deckert *et al*, 1999).

Animal and human studies suggest that MAOA plays an important role in traits related to impulsivity and aggressiveness as well as in addictive behavior. Norrie disease, which is caused by X-chromosomal microdeletions

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Received 3 December 2004; revised 1 March 2005; accepted 3 March 2005
Online publication: 7 March 2005 at http://www.acnp.org/citations/NPP030705040565/default.pdf

including the MAOA gene, is associated with mental retardation, autistic behavior, motor hyperactivity, and sleep disturbances, which may, at least in part, be attributed to deficient MAO activity (Sims *et al*, 1989; Murphy *et al*, 1990). A hemizygous chain termination mutation in exon 8 of *MAOA*, resulting in an absence of MAOA enzymatic activity in cultured fibroblasts, causes mild mental retardation and episodes of impulsive aggression, arson, and hypersexual behavior, such as attempted rape and exhibitionism, in affected males from a single extended pedigree (Brunner *et al*, 1993). Male mice with a targeted inactivation of *MaoA* display elevated brain levels of serotonin and increased reactivity to stress, hyperactive startle responses, violent motions during sleep and abnormal posture, and aggressive behavior (Cases *et al*, 1995).

The *MAOA*-LPR has been linked to antisocial behavior in alcohol-dependent males (Samochowiec *et al*, 1999), and with impulsivity, hostility, and a lifetime history of aggression in a community sample of men (Manuck *et al*, 2000). In addition, the MAOA-LPR has been associated with bipolar disorders particularly in females (Ho *et al*, 2000), and with suicide in depressed males (Du *et al*, 2002), whereas other studies failed to detect association with suicidal behavior in mood disorders (Kunugi *et al*, 1999; Kirov *et al*, 1999; Syagailo *et al*, 2001; Ono *et al*, 2002). Although not consistently replicated (Craddock *et al*, 1995; Nothen *et al*, 1995), various other *MAOA* variations were found to influence addictive behavior (Parsian *et al*, 1995; Vanyukov *et al*, 1995; Hsu *et al*, 1996; Gade *et al*, 1998) and the risk for affective und anxiety disorders (Schulze *et al*, 2000; Deckert *et al*, 1999; Furlong *et al*, 1999). Finally, recent work focusing on both genetic *and* early environmental factors has begun to untangle expected complex relationships by demonstrating an interaction of *MAOA*-LPR genotype and adverse childhood environment modulating the risk for both conduct disorder and impulsive traits, antisocial behavior, aggressiveness, and violence in adulthood (Caspi *et al*, 2002; Foley *et al*, 2004; Huang *et al*, 2004). A corresponding *MAOA* genotype $\times$ environment interaction effect on aggression was recently demonstrated in rhesus macaques, in which *gene* transcription is also modulated by an analogous polymorphic repeat in the upstream regulatory region of *MAOA* (*rhMAOA-LPR)* (Newman *et al*, 2004). Detailed species comparisons revealed that the *MAOA*-LPR is differentially configured among non-human primates but absent in other mammalians (Wendland *et al*, 2005).

Based on these studies, which suggest an influence of allelic variation of MAOA activity on aggression-related traits, the *a priori* hypothesis of the present study was that there is a, presumably sex-specific, link between the low-activity 3-repeat allele and cluster B/antisocial personality disorders and the personality traits novelty seeking, neuroticism, agreeableness, and conscientiousness. Therefore, we tested (1) for differences in *MAOA*-LPR allele and genotype frequencies between patients with personality disorders and healthy controls; (2) whether personality trait differences are associated with allelic variation of MAOA activity; and (3) for sex specificity of personality disorder/- or personality trait/*MAOA*-LPR associations.

METHODS AND MATERIALS

Sample

In- and outpatients of the Department of Psychiatry and Psychotherapy, University of Wuerzburg were screened between December 2000 and August 2002. Inclusion criteria are personality disorders according the criteria of DSM-IV and age between 18 and 60 years. Exclusion criteria are medical conditions that have significantly changed previous level of functioning, and lifetime diagnosis of schizophrenia or other psychotic disorders. The controls were recruited from students of the University of Dresden. The study was approved by the Ethics Committee of the University of Wuerzburg and written informed consent was obtained from all individuals after procedures and aims of the study had been fully explained.

MAOA-LPR genotypes were analyzed in 566 patients (333 females, 233 males; mean age = 35.5 years, SD = 12.7) and 281 healthy controls (209 females and 72 males; mean age = 22.4 years, SD = 5.7). All subjects were of European origin except for six control subjects who had at least one parent from a non-European country.

Personality Assessment

The Structured Clinical Interview of DSM-IV personality disorders, using the DSM-IV criteria of personality disorders, has previously been demonstrated to be highly sensitive to personality and behavioral changes. In the present study, personality disorders were therefore diagnosed with the SCID-II and were allocated to cluster A, B, and C operationalized as follows: Cluster A (odd-eccentric) comprises paranoid, schizoid, and schizotypal personality disorders. Cluster B (dramatic-emotional) encompasses antisocial, borderline, histrionic, and narcissistic personality disorders. Cluster C (anxious-fearful) includes avoidant, dependent, and obsessive-compulsive personality disorders, and a category called personality disorders not otherwise specified.

It has recently been suggested that it may be less difficult to identify genes for psychopathology by searching for genes influencing personality traits (Benjamin, 1998). This view implies that there may not be genes for personality disorders but genes for behavioral dimensions and that there is both a genetic and psychopathological continuum from normal personality to personality disorder. Therefore, we also assessed personality traits by the revised NEO Personality Inventory (NEO-PI-R) (Costa and McCrae, 1997), and the Tridimensional Personality Questionnaire (TPQ) (Cloninger *et al*, 1993). The TPQ and NEO-PI-R are based on hierarchical models in which each of the proposed personality domains comprises several related subscales or facets, respectively.

The assessment of the personality disorders, including all the psychometric testing was performed by a single experienced psychiatrist. We focused statistical analyses on the case group, because we hypothesize that allelic variations influencing human behavior might more easily be detected in a sample with pronounced behavioral expression.

Genetic Analysis

Genomic DNA was extracted from EDTA blood using the QIAamp Blood Kit (Qiagen, Hilden, Germany). The *MAOA*-LPR was genotyped by PCR amplification using a modified protocol previously described by Deckert *et al* (1999). PCR fragments were amplified from genomic DNA using primers MAOAFor3 (5′-AGCCTGACCGTGGAGAAGG) and MAOARev2 (5′-GGACCTGGGCAGTTGTGC) flanking the polymorphic region located approximately 1.1 kb upstream of the ATG codon. PCR (40 s at 94°C, 40 s at 63°C, 60 s at 72°C for 35 cycles) was performed in a final volume of 25 µl containing 50 ng of genomic DNA, 10 pmol of each primer, 2.5 mM of each dNTP, 25 mM $MgCl_2$, 75 mM Tris-HCl (pH 9.0 at 25°C), 20 mM $(NH_4)_2SO_4$, 0.01% Tween-20, and 0.5 U of Taq DNA polymerase (Gibco-BRL). PCR products (258 bp/3 repeats, 276 bp/3.5 repeats, 288 bp/4 repeats, and 308 bp/5 repeats, respectively) were separated by electrophoresis on a 3% NuSieve agarose gel and visualized by ethidium bromide staining.

Statistical Analyses

For statistical analyses the *MAOA*-LPR alleles were dichotomized by functionality with the three-repeat variant as low-activity (l) and longer alleles (3.5 repeats and longer) as high-activity (h). Frequencies of the three-repeat allele were compared to those of 3.5-, four-, and five-repeat variants in patients and controls (one subject with a two-repeat allele was excluded from analyses due to the lack of data on functional consequences of the two-repeat MAOA-LPR). Hemi- or homozygous subjects for the low-activity variant (l/- and l/l) are referred to as group L, whereas males and females with at least one copy of the high-activity variant (h/-, l/h, and h/h) are referred to as group H. In women one of the two X chromosomes is inactivated but some regions frequently escape from inactivation. Based on evidence that escape from inactivation of the second X chromosome may, at least partially, compensate for the presence of a nonfunctional (and presumably also a low-activity) copy of the MAOA gene (Brunner *et al*, 1993), genotype frequencies of the L group were conservatively compared to the H group in females (Carrel and Willard, 2005).

The assumed association between the low-activity variant of the *MAOA*-LPR and Cluster B personality disorders was examined by means of χ^2 tests. To test the assumption of sex specificity, three χ^2 tests were conducted, two tests in the female group on the level of genotypes and alleles and one test in male group since in male the genotype of *MAOA*-LPR is similar to the allele-type. Since two tests were conducted on the level of alleles, the α level was adjusted to $\alpha' = \alpha/2 = 0.025$.

The association between *MAOA*-LPR (between subject factor) on the one hand and TPQ novelty seeking as well as NEO neuroticism, agreeableness, and conscientiousness on the other hand was tested with analyses of variance (ANOVA). The assumptions concerning these associations were regarded as four single hypotheses and therefore the alpha level was not adjusted. The domains' subscales or facets and associations with a single diagnosis of a personality disorder were analyzed *post hoc*. The adjusted α levels are mentioned in the results section. All domains and subscales/facets were age- and gender-residualized and *z*-standardized. *Post hoc* power analyses were conducted with GPOWER (Erdfelder *et al*, 1996) in order to estimate the probability of detecting present effects with the current sample. Unless stated otherwise, patients with only cluster A personality disorder ($N = 10$) and patients with personality disorders from different clusters ($N = 198$) were excluded from subsequent analyses. The former due to a limited number, the latter in order to retain transparency concerning patients' diagnoses. As measures of effect size, the ϕ-coefficient (χ^2-test) and η^2 (ANOVA) were chosen.

RESULTS

The *MAOA*-LPR genotype was significantly associated with cluster B personality disorders ($\chi^2 = 7.77$, $p = 0.005$, df = 1). In total, 26.0% of cluster B patients were hemi- or homozygous for the low-activity variant (l/- and l/l, together referred to as group L), in contrast to 16.4% of the control group (Table 1, upper panel). The effect of the association was small ($\phi = 0.12$). The comparison of allele frequencies yielded no significant difference (37% cluster B *vs* 35% controls $\chi^2 = 0.49$, $p = 0.484$, df = 1). The genotype frequencies in both the patient and control sample did not significantly deviate from the Hardy–Weinberg equilibrium (all $p > 0.12$). In the female group no differences were observed (alleles: $N = 746$, $\chi^2 = 0.00$, $p = 0.980$, df = 1; genotypes: $N = 373$, $\chi^2 = 1.14$, $p = 0.286$, df = 1). In the male group Cluster B patients had higher frequencies of the low-activity three-repeat allele but the difference did not reach significance ($N = 189$, $\chi^2 = 2.10$, $p = 0.148$, df = 1).

We next evaluated the specificity of the association by *post hoc* analyses. A comparison between genotypes of cluster C patients and controls showed no association ($N = 357$, $\chi^2 = 0.16$, $p = 0.689$, df = 1). When assigning the l/h genotype to the L group no difference in the frequency of the low-activity variant (three-repeat present) between patients and controls was detected (50 *vs* 53%, $\chi^2 = 0.35$, $p = 0.555$, df = 1). The lower panel of Table 1 depicts the allele and genotype frequencies for the cluster B personality disorder subtypes. With the exception of borderline personality disorder, a slightly higher percentage of the L genotype appeared in all personality disorder subtypes. Owing to the low number of (non-comorbid) borderline patients ($N = 10$), testing for association was not reasonable. In a *post hoc* analysis we compared *MAOA*-LPR genotypes of borderline patients with and without comorbidity *vs* controls, which increased the number of patients to $N = 118$. This analysis yielded no effect of genotype ($\chi^2 = 0.00$, $p = 0.947$, df = 1). Similar results were obtained in a separate analysis of all patients with an antisocial personality disorder ($N = 52$, $\chi^2 = 0.03$, $p = 0.867$, df = 1).

There were no significant associations between *MAOA*-LPR genotype and the personality domains TPQ novelty seeking as well as NEO neuroticism, agreeableness, and conscientiousness in patients and controls (all $p > 0.05$, $\eta^2 < 0.006$). The probability of detecting small effects ($\eta^2 = 0.01$) with the present sample of $N = 639$ and $\alpha = 0.05$ was 71 and 100% for detecting moderate effects ($\eta^2 = 0.06$). Assuming that true associations exist, the

Table 1 Allele and Genotype Frequencies of the Monoamine Oxidase A Gene-Linked Polymorphic Region (MAOA-LPR) in Patients with Cluster B Personality Disorders *vs* Controls

	Alleles							Genotypes		
	3	3.5	4	5	3 (l, %)	3.5+4+5 (h, %)		l/-+l/l (L group, %)	h/-+l/h+h/h (H group, %)	
Cluster B (N = 281)										
Males	48	1	67	1	48 (41)	69 (59)	$p = 0.148$			
Females	118	1	203	6	118 (36)	210 (64)	$p = 0.980$	25 (15)	139 (85)	$p = 0.286$
Total	166	2	270	7	166 (37)	279 (63)	$p = 0.484$	73 (26)	208 (74)	$p = 0.005$
Controls (N = 281)										
Males	22	0	50	0	22 (31)	50 (69)				
Females	150	3	260	5	150 (36)	268 (64)		24 (11)	185 (89)	
Total	172	3	310	5	172 (35)	318 (65)		46 (16)	235 (84)	
Cluster B subtypes										
Histrionic (N = 203)										
Males	31	1	37	1	31 (44)	39 (56)	$p = 0.091$			
Females	100	1	160	5	100 (38)	166 (62)	$p = 0.651$	22 (17)	111 (83)	$p = 0.181$
Total	131	2	197	6	131 (39)	205 (61)	$p = 0.255$	53 (26)	150 (74)	$p = 0.009$
Narcissistic (N = 55)										
Males	14	0	26	0	14 (35)	26 (65)	$p = 0.629$			
Females	12	0	17	1	12 (40)	18 (60)	$p = 0.650$	2 (13)	13 (87)	$p = 0.540$
Total	26	0	43	1	26 (37)	44 (63)	$p = 0.738$	16 (29)	39 (71)	$p = 0.026$
Borderline (N = 15)										
Males	2	0	0	0	2 (100)	0 (0)				
Females	4	0	22	0	4 (15)	22 (85)		0 (0)	13 (100)	
Total	6	0	22	0	6 (21)	22 (79)		2 (13)	13 (87)	
Antisocial (N = 8)										
Males	1	0	4	0	1 (20)	4 (80)				
Females	2	0	4	0	2 (33)	4 (67)		1 (33)	2 (67)	
Total	3	0	8	0	3 (27)	8 (73)		2 (25)	6 (75)	

Hemi- or homozygous subjects for the low-activity variant (l/- and l/l) are referred to as group L, whereas males and females with at least one copy of the high-activity variant (h/-, l/h, and h/h) are referred to as group H. The MAOA-LPR genotype was significantly associated with cluster B personality disorders ($\chi^2 = 7.77$, $p = 0.005$, df = 1).

probability of finding them in this study was sufficient. Increasing power for small effects to 83% by including all subjects with comorbid personality disorders yielded similar results ($N = 847$, all $p > 0.08$, $\eta^2 < 0.004$). *Post hoc* analyses at adjusted α levels of $\alpha = 0.013$ for the four TPQ novelty seeking subscales and $\alpha = 0.008$ for the six facets of NEO neuroticism, agreeableness, and conscientiousness also yielded no significant associations (all $p > 0.03$, $\eta^2 < 0.008$).

Post hoc analyses of association for personality disorders subtypes were conducted for the histrionic subtype ($N = 203$), narcissistic subtype ($N = 55$), and controls ($N = 281$). The group sizes of the remaining two subtypes did not suffice for analysis. Thus, three tests per personality domain were conducted, and therefore the α level was adjusted to $\alpha = 0.017$. In the histrionic subtype group, patients with *MAOA*-LPR genotypes of the L group had lower levels of novelty seeking ($p = 0.005$, $\eta^2 = 0.039$) (Figure 1a) and higher scores of conscientiousness ($p = 0.009$, $\eta^2 = 0.033$) (Figure 1b). No effect was observed in the remaining two personality domains, neuroticism, and agreeableness (all $p > 0.61$, $\eta^2 < 0.002$).

In patients with narcissistic subtype, carriers of L genotypes showed lower scores of agreeableness compared to patients of the H group ($p = 0.002$, $\eta^2 = 0.16$) (Figure 2), no association was detected with the other three personality domains (all $p > 0.56$, $\eta^2 < 0.007$). In the control group, no significant associations between personality domains and *MAOA*-LPR were observed (all $p > 0.36$, $\eta^2 < 0.004$).

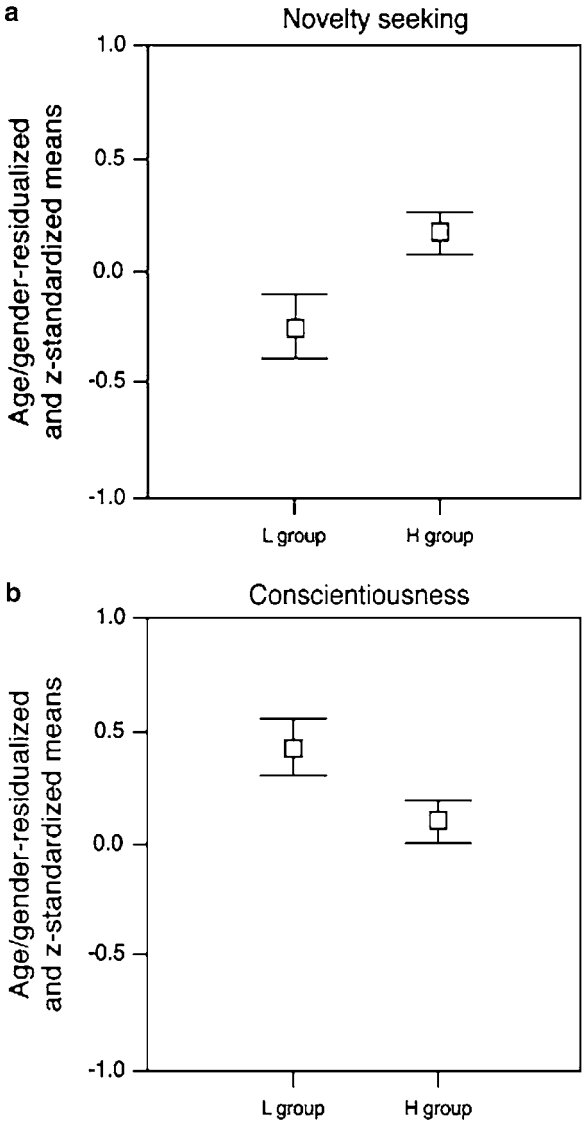

Figure 1 Means and standard error bars of novelty seeking (a) and conscientiousness (b) for carriers of the low activity ($N = 53$) and the high activity ($N = 150$) variant of the MAOA gene-linked polymorphic region (MAOA-LPR) in patients with histrionic personality disorders.

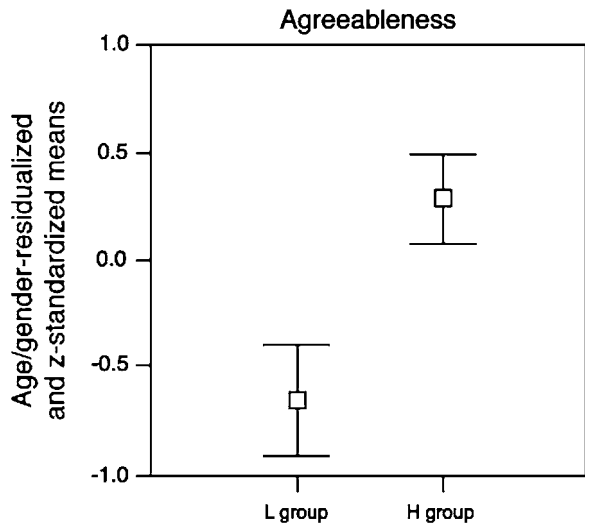

Figure 2 Means and standard error bars of agreeableness for carriers of the low activity ($N = 16$) and the high activity ($N = 39$) variant of the MAOA gene-linked polymorphic region (MAOA-LPR) in patients with narcissistic personality disorders.

DISCUSSION

Our results show an association between hemi- and homozygosity for the low-activity variant of *MAOA*-LPR and cluster B personality disorders. The proportion of subjects with the low-activity variant was ~10% higher in the patients group compared to controls. Since the gender-specific analyses revealed no significant effects, the results of the present study do not allow a conclusive interpretation of the *MAOA*-LPR/cluster B personality disorder association as a genotype–phenotype correlation that fits with the biological characteristics of x-linked traits. While the power to detect effects in the separated groups was reduced due to gender-based subdivision of the sample, a possible explanation for the observed smaller effect in female (4%) compared to male (10%) may be the conservative allocation of females heterozygous for the MAOA-LPR l variant to the high-activity H group.

There are a few limitations inherent to our study concerning intergroup differences, which may have influenced the results. The cohort encompasses considerably more females than males, both in the group of patients with cluster B personality disorders as well as in the controls and the mean age of patients with personality disorders is slight lower (22.4 *vs* 35.5 years, respectively). Since personality disorders are defined as conditions persisting throughout the life span, it seem unlikely that personality disorders will develop at an older age in the control group. The proportion of respective cluster A, B, and C personality disorders would have been different in a cohort with an equal or exceeding number of male subjects, possibly leading to other findings and conclusions. Further studies with increased sample size as well as additional work in the non-human primate model will have to address these questions.

Considerable evidence indicates that genetic variation associated with low MAOA activity modulates aggression and impulsive violence in humans (Shih *et al*, 1999). Males with a hemizygous chain termination mutation in *MAOA*, but not heterozygous females due to the compensatory effect of a MAOA copy on the other X chromosome, exhibit markedly disturbed monoamine metabolism, mild mental retardation, and episodes of impulsive aggression (Brunner *et al*, 1993). Although inhibition of MAOA in adults leads to antidepressant effects but not to aggression-related behavior, the deviant behavior in MAOA-deficient men is likely due to neuroadaptive changes resulting from altered monoamine metabolism during early development of the brain. The behavioral consequences of targeted inactivation of *MAOA* further supports the notion that the aggressive phenotype is a consequence of the null mutation in the human MAOA gene (Cases *et al*, 1995; Seif and De Maeyer, 1999). MAOA-deficient mice display elevated brain concentrations of serotonin and increased reactivity to stress,

hyperactive startle responses, and abnormal posture, and aggressive behavior. Enhanced male aggressiveness was demonstrated by the observation of increased injury between male cage-mates as well as by the resident-intruder paradigm.

The substantial heterogeneity of both genetic and environmental determinants has increasingly encouraged the pursuit of dimensional approaches to behavioral genetics and the focus on gene variants with a significant impact on neurocircuit functionality, associated with quantitative traits, might be a rational strategy (Plomin *et al*, 1994; Reif and Lesch, 2003). This view suggests that it may be less difficult to identify genes for psychopathology by searching for genes influencing personality, and that complex traits are not attributable to single genes necessary or sufficient to cause a disorder (Benjamin, 1998).

An association between genotypes of the *MAOA*-LPR and two of three dimensions of the Barrat Impulsiveness Scale has previously been reported by Manuck *et al* (2000). Carriers of the low-activity variants of the *MAOA*-LPR scored modestly, but significantly, lower on a composite measure of dispositional aggressiveness and impulsivity than individuals with high-activity alleles in a community sample of 110 male participants (Manuck *et al*, 2000).

Eley *et al* (2003) recently reported higher neuroticism scores in males carrying a high-activity of MAOA variant. Neuroticism is a normally distributed quantitative anxiety-related trait, which is consistently associated with an increased risk for anxiety disorders and depression. In agreement with the evidence for a role of MAOA activity in panic disorder (Deckert *et al*, 1998), these findings further support the notion that the *MAOA*-LPR contributes modestly to the balance of the dimension of over- (antisocial) and underreactive (anxious-depressive) via several neurotransmitter systems in interaction with environmental factors (Schmidt *et al*, 2000). It may therefore be hypothesized that this dysbalance may also be involved in pathogenesis of Cluster B personality disorders. However, there were no associations with anxiety- and depression-related symptoms, with personality traits that predispose to anxiety or with personality traits related to antisocial behavior in a general population sample of 850 Caucasian Australians (Jorm *et al*, 2000). The allelic variations of MAOA activity did also not have a large impact on the expression of personality characteristics in a Swedish population neither in men nor in women (Garpenstrand *et al*, 2002).

The present study in general failed to demonstrate an association between allelic variation of MAOA activity and aggression-related personality traits in patients with personality disorders. Several significant associations in subgroups were, however, not entirely consistent with our *a priori* hypothesis. While in patients with narcissistic personality disorders, carriers of the low-activity genotype showed lower scores in NEO agreeableness, which is related to antisocial behavior, in histrionic patients the low-activity genotype of *MAOA*-LPR was associated with low TPQ novelty seeking and high NEO conscientiousness, and therefore with nonimpulsive and nonaggressive traits or behavior. Low NEO agreeableness, a personality dimension related to an antagonistic interpersonal style has been reported to be one of the strongest predictor of aggression (Gleason *et al*, 2004). Low NEO conscientiousness and high TPQ novelty seeking are considered to represent personality dimensions related to impulsivity. Moreover, a meta-analytic examination of the relationship between several structural models of personality and antisocial behavior revealed consistent, moderately large effects, particularly a correlation between NEO neuroticism and antisocial behavior (Miller and Lynam, 2001).

One of the reasons why the relationship between the *MAOA*-LPR and impulsive-aggressive or antisocial behavior remains controversial may be the difference in the assessment of the phenotype (eg self-rating, standardized interview, best estimate diagnosis). While there was a negative association with aggressiveness, impulsivity, and anger-related personality traits in previous studies on diverse clinical, forensic, and nonpatient populations, no significant differences were observed when personality traits were diagnosed by various instruments including the Temperament and Character Inventory, the revised NEO Personality Inventory, and the Karolinska Scales of Personality (Garpenstrand *et al*, 2002). *MAOA*-LPR genotype frequencies did also not differ on measures of the Buss–Durkee Hostility Inventory (hostility), the Behavioral Inhibition System/Behavioral Activation System scales, and the revised Eysenck Personality Questionnaire (Manuck *et al*, 2000; Jorm *et al*, 2000).

Previous studies may have been confounded by their focus on a limited aspect of psychopathology, and their results could be influenced by the substantial comorbidity of personality disorders or an underlying, but not evaluated, neurobehavioral dimension of individual differences contributing to the risk for these disorders. Nevertheless, our findings correspond to a recent Swedish study, in which a male criminal population Cluster A and B personality disorder had significantly lower platelet MAO activity than controls (Longato-Stadler *et al*, 2002). Although the monoamine metabolism in platelets primarily is due to MAOB activity, our results confirm the sensitivity of Structured Clinical Interview of DSM-IV personality disorders, in detecting hypothesis-driven genetic influences in personality disorders and behavioral changes.

There is increasing evidence for an interaction between genetic and environmental determinants. Childhood maltreatment appears to modulate the genetic risk for antisocial behavior, aggressiveness, and violence in adulthood that is conveyed by allelic MAOA deficiency (Caspi *et al*, 2002). It is concluded that the existence of significant stressors in the environment of individuals carrying the low-activity MAOA-LPR variant is necessary to further tip the balance towards the development of psychopathology. The low-activity variant of the *MAOA*-LPR was also shown to be associated with a history of early abuse below 15 years of age in males, but not females, and to increase impulsive traits in adulthood in the group of abused subjects indicating a complex gene $\times$ environment interaction (Huang *et al*, 2004). Likewise, low MAOA activity was found to increase the risk for conduct disorder only in the presence of adverse childhood environment (Foley *et al*, 2004). Similar to findings in human populations, aggressive behavior in non-human primates is increased in the presence of both low MAOA enzymatic activity as well as early exposure to a range of social behaviors that includes

aggression. We have recently confirmed the relevance of genotype × environment interaction in the sensitization process to aggression in rhesus monkeys, suggesting that the behavioral expression of allelic variation of MAOA activity is sensitive to social experiences early in development and that its functional outcome may depend upon the social context (Newman *et al*, 2004). The relevance of such environmental stressors acting on an extended neural circuitry in facilitating the influences of allelic variation of MAOA activity on behavior is underscored by the absence of consistent genotype effects on traits of impulsivity and aggression. Rather, our current results along with those previously reported indicate that the *MAOA*-LPR represents a classical susceptibility factor and, as such, will be of critical importance in understanding the etiology of personality disorders. Further studies will be needed to investigate the interactions of *MAOA*-LPR and the different aspects of 'environment' in clinical and nonclinical samples. A critical role in modifying the influence of genes that convey the risk for complex behavioral disorders may be one's early experience, particularly during infancy and early childhood. Together with findings in mice with targeted inactivation of genes of the serotonergic pathway (Lesch, 2005; Lesch *et al*, 2003), associations of personality traits and the *MAOA*-LPR low-activity variant may thus reflect a complex interrelationship of neurodevelopmental adaptive processes and environmental contributions.

In conclusion, our results further support the notion that allelic variation of MAOA activity contributes modestly to the balance of hyper- (impulsive-aggressive) and hypo-reactive (anxious-depressive) traits and that differential gene effects in conjunction with environmental factors may be operative in distinct normal and clinical population. This dysbalance together with gene × environment interactions are likely to influence the risk for cluster B personality disorders.

ACKNOWLEDGEMENTS

We thank G Ortega and N Steigerwald for excellent technical assistance. The work was supported by the Deutsche Forschungsgemeinschaft (SFB 581; KFO 125/1-1), and the European Commission (NEWMOOD LSHM-CT-2003-503474).

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