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A monoamine oxidase B gene variant and short-term antidepressant treatment response

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Abstract

Genetic differences among patients suffering from Major Depression are likely to contribute to interindividual differences in medication treatment response. Thus, the identification of gene variants affecting drug response is needed in order to be able to predict response to psychopharmacological drugs. This study analyzed a possible association of the common A644G single nucleotide polymorphism (SNP) within intron 13 of the monoamine oxidase B (MAOB) gene with antidepressant treatment response. The study population consisted of $n=102$ patients with major depression (criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-IV) participating in a randomized double-blind controlled clinical trial, conducted at 50 centers in Germany, comparing the efficacy of mirtazapine and paroxetine during 6 weeks of treatment. Overall, female patients homozygous for the A-allele had a significantly faster and more pronounced antidepressant treatment response than AG/GG-carriers. In paroxetine-treated females these differences remained statistically significant. In mirtazapine-treated females homozygous for the A-allele compared to AG/GG-carriers, HAMD-17 scores during the study period were constantly and markedly lower, but not statistically different. In males, we found no association between the MAOB A644G intron 13 SNP and antidepressant treatment response. Our data provide first suggestive evidence that the MAOB A644G SNP is involved in the outcome of treatment with mirtazapine or paroxetine in females with major depression. To confirm the role of the MAOB A644G gene variant in antidepressant treatment response, independent replications are needed. If replicated, the MAOB A644G polymorphism could be considered useful for prospective confirmatory pharmacogenetic trials in patients with major depression.

Keywords: Major depression; MAOB; Mirtazapine; Paroxetine; Polymorphism; Treatment outcome

Abbreviations: **5-HT**, serotonin; **5-HTT**, serotonin transporter; **ANOVA**, analysis of variance; **bp**, base-pair; **CEU-CEPH**, Utah residents with ancestry from northern and western Europe; **CGI**, Clinical Global Impressions Scale; **CI**, 95%-confidence interval; **COMT**, catechol-*O*-methyltransferase (gene); **DA**, dopamine; **DNA**, Deoxyribonucleic acid; **DSM-IV**, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; **HAMD-17**, Hamilton Rating Scale for Depression, 17-item version; **HTTLPR**, Serotonin transporter gene-linked polymorphic region; **ITT**, intention-to-treat; **LD**, linkage disequilibrium; **MADRS**, Montgomery–Asberg Depression Rating Scale; **MAOA**, monoamine oxidase A (gene); **MAO-A**, monoamine oxidase A (enzyme); **MAOB**, monoamine oxidase B (gene); **MAO-B**, monoamine oxidase B (enzyme); **MD**, Major Depression; **MDE**, major depressive episode; **M.I.N.I.**, Mini-International Neuropsychiatric Interview; **MMRM**, mixed-effects model repeated measures; **mRNA**, messenger Ribonucleic Acid; **n**, number; **NE**, Norepinephrine; **OR**, Odds Ratio; **PCR**, Polymerase chain reaction; **PD**, Parkinson's disease; **SNP**, single nucleotide polymorphism; **SPSS**, Statistical Package for the Social Sciences; **SSRI**, selective serotonin reuptake inhibitor.

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1. Introduction

Genetic differences among patients suffering from Major Depression (MD) are likely to contribute to interindividual differences in medication treatment response. Thus, the identification of gene variants affecting drug response is needed in order to predict response to psychopharmacological drugs.

Paroxetine belongs to the group of selective serotonin reuptake inhibitors (SSRI). It enhances serotonergic neurotransmission through inhibition of the serotonin transporter (5-HTT), thereby decreasing the reuptake and raising the concentration of synaptic serotonin (5-HT). The majority of pharmacogenetic studies concerning the treatment response to paroxetine and other SSRIs in MD have focused on the common 44 bp-insertion/deletion polymorphism located in the promoter region of the serotonin transporter (HTTLPR), where the long allele has been shown to have a higher transcription activity than the short allele (Heils et al., 1996; Lesch et al., 1996). Numerous studies suggested a less favorable response to SSRI treatment in patients with the s/s genotype compared to carriers of the s/l or the l/l genotype (Serretti et al., 2005a; Smits et al., 2004). Recently, this view has been challenged by an analysis in a large clinical sample that found no association between multiple tagging markers of the 5-HTT gene (SLC6A4) including the ins/del promoter polymorphism and citalopram response (Kraft et al., 2007). The results for other genes have been even less convincing (Kirchheiner et al., 2004; Serretti et al., 2005b), demonstrating the persistent need of new candidate genes for antidepressant treatment response.

The antidepressant effect of mirtazapine is believed to be a result of the enhancement of central serotonergic and noradrenergic neurotransmission. Direct inhibition of presynaptic α_2-receptors results in increased norepinephrine (NE) release that, in turn, enhances 5-HT release *via* stimulation of α_1-receptors on serotonergic cells. Enhanced 5-HT release is also mediated by direct inhibition of the inhibitory α_2-receptors located on 5-HT terminals. This enhanced 5-HT release is only mediated by 5-HT_1 receptors, because mirtazapine inhibits 5-HT_2 and 5-HT_3 receptors (Anttila and Leinonen, 2001; de Boer, 1996). Pharmacogenetic studies on mirtazapine treatment response in mood disorders are still scarce. Murphy et al. (2004) showed a small effect of the serotonin transporter gene promoter polymorphism (5-HTTLPR) on mirtazapine efficacy in geriatric major depression. Our previous reports indicated associations between the catechol-O-methyltransferase (COMT) Val/Met (Szegedi et al., 2005) and the monoamino-oxidase A (MAOA) Fnu4H1 (Tadic et al., 2007) polymorphisms with mirtazapine treatment response in major depression.

Monoamine oxidases (MAOs) are flavin-containing mitochondrial enzymes catalyzing the oxidative deamination of a number of monoamines in the brain and peripheral tissues, including 5-HT, histamine and the catecholamines dopamine (DA), NE and epinephrine (Shih et al., 1999; Tipton et al., 2004). The two forms of the enzyme (MAO-A and MAO-B) differ in molecular weight, substrate affinities and immunological properties. DA, NE and epinephrine are common substrates for both enzymes, MAO-A has higher affinity to 5-HT (Youdim et al., 2006). In brain, MAO-A is expressed at highest levels in catecholaminergic neurons, whereas highest levels of MAO-B are found in astrocytes and serotonergic neurons (Thorpe et al., 1987; Westlund et al., 1988). Physiologically, MAO-A seems to play a major role in the degradation of 5-HT. The main function of MAO-B in serotonergic neurons might be the elimination of foreign amines, thereby minimizing their access to synaptic vesicles and, in summary, contributing to the purity of synaptic 5-HT (Youdim et al., 2006). The gene encoding MAO-B is located on the X-chromosome (Xp11.4-p11.23) (Hsu et al., 1989) and contains an A644G (rs1799836) SNP in intron 13 (Kurth et al., 1993). Although this A→G substitution does not change protein sequence, it was associated with varying enzyme activity: *in vitro*, the G allele was associated with higher enzyme activity (Costa-Mallen et al., 2005b); in platelets, MAO-B activity has been observed to be higher in G-allele carriers compared to A-allele carriers (Garpenstrand et al., 2000). In human brain however, the A-allele has been associated with higher messenger Ribonucleic Acid (mRNA) levels of MAO-B (Balciuniene et al., 2002). These differences could be caused by separate and tissue-specific control mechanisms of MAOB activity.

The MAOB A644G SNP has been investigated in several case–control studies, mainly in patients suffering from Parkinson's disease (PD) (for an overview of studies, see Parsian et al., 2004 and references inside). Most recently, genotype A/AA has been shown to be associated with a 2-fold increased risk for early-onset PD compared to healthy controls (Bialecka et al., 2007). Moreover, patients with sporadic PD and carrying the genotype A may benefit from more efficient and safer levodopa therapy (Bialecka et al., 2004). Sex-specific effects of this MAOB gene variant on different phenotypes have also repeatedly been reported, *e.g.* Kelada et al. (2002) showed strong gender differences with respect to the modifying effect of the MAOB A644G SNP on the smoking association with PD. Recently, Kang et al. (2006) found in their large family-based case–control study an association between the MAOB A644G SNP with PD in females, but not in males.

The above mentioned existing evidences for the close relation between MAO-B and major depression make the MAOB gene to a candidate for pharmacogenetic studies on the antidepressive effect of paroxetine and mirtazapine. To our knowledge, there is no other published study addressing the influence of variations in the MAOB gene on antidepressant treatment response. The aim of the present study was to investigate the possible association between the MAOB A644G intron 13 gene variant (rs1799836) and the outcome of paroxetine and mirtazapine treatment in patients with major depression.

2. Subjects and methods

2.1. Subjects

A detailed description of the recruitment procedure, clinical assessments and treatment schedule has been reported previously (Benkert et al., 2000). In brief, 272 outpatients were enrolled in a randomized, double-blind comparison of mirtazapine and