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The impact of COMT gene polymorphisms on suicidality in treatment resistant major depressive disorder — A European Multicenter Study

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Abstract

Many association studies have reported associations between the catechol-O-methyltransferase (COMT) gene and psychiatric disorders including major depression (MDD). The COMT gene has further been associated with suicidal behaviour, as well as with treatment response, although with conflicting results. In the present study, we further elucidate the impact of COMT in treatment response in MDD patients with suicide risk and/or a personal history of suicide attempts. Two hundred fifty MDD patients were collected in the context of a European multicentre resistant depression study and treated with antidepressants at adequate doses for at least 4 weeks. Suicidality was assessed using Mini International Neuropsychiatric Interview (MINI) and the Hamilton Rating Scale for Depression (HAM-D). Treatment response was defined as HAM-D $\leq$ 17 and remission as HAM-D $\leq$ 7 after 4 weeks of treatment with antidepressants at adequate dose. Genotyping was performed for seven SNPs (rs4680, rs2075507, rs737865, rs6269, rs4633, rs4818 and rs165599) within the COMT gene. With regard to suicide risk and personal history of suicide attempts, neither single marker nor

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haplotypic association was found with any SNP after multiple testing correction. In non-responders, we found significant single marker and haplotypic association with suicide risk, but not in responders. The same holds true for both remitters and non-remitters, and when testing for association with a personal history of suicide attempts and treatment response phenotypes. In conclusion, we found significant association of COMT SNPs with suicide risk in MDD patients not responding to antidepressant treatment. Larger well-defined cohorts will be required to dissect this further.

1. Background

Major depressive disorder (MDD) is a major clinical problem with a mean lifetime prevalence of 16% (Wittchen, 2000). Many clinical studies have shown that 30–40% of the MDD patients fail to respond to the first-line treatment (Mulder et al., 2006), and even after several treatment trials, one in every three patients does not fully recover from MDD (Ising et al., 2009). Treatment resistant depression (TRD) is usually seen as the failure to reach response after an adequate treatment, and different definitions that need to be validated before they are used in clinical practice have been proposed (Souery et al., 2007; Ruhé et al., 2011).

According to the WHO, suicide accounts for 1.5% of the deaths throughout the world (WHO, 2000), thus being a significant public health issue and major cause of death. The lifetime prevalence of attempted suicide has been estimated to be around 3.5%, and approximately 10% of suicide attempters will commit suicide within 10 years (Suominen et al., 2004). Mental disorders, in particular mood disorders and substance problems, are present in more than 90% of suicides (Arsenault-Lapierre et al., 2004). Besides, among other variables, suicidal risk has been associated to TRD (Souery et al., 2007).

Suicidal behaviour runs in families and the existence of genetic vulnerability to suicidality is well established. Pooled twin studies of completed suicide showed a higher concordance in monozygotic than dizygotic twins (11% vs. 2%) and the heritability of completed suicide has been estimated to be 43%, with no contribution of shared family environment (Roy et al., 1991; McGuffin et al., 2001; Fu et al., 2002). Depending on the definition of suicidal ideation and sample characteristics, the incidence of treatment emergent suicidal ideation in MDD varies from 4% to 20% (Laje et al., 2007; Nelson et al., 2007; Perlis et al., 2007a, 2007b; Szanto et al., 2007).

The catechol-O-methyltransferase (COMT) is one of the major catabolic pathways of the catecholamine neurotransmitters and thus has been a promising candidate for neuropsychiatric genetic studies, including MDD, and in studying the mechanism of action of antidepressants (e.g. Shifman et al., 2002; Hosak, 2007; Michaelovsky et al., 2007; Halleland et al., 2009; Mier et al., 2009).

Among a number of investigated COMT SNPs, a functional Val158Met polymorphism (rs4680) has been identified, causing a valine (Val) to methionine (Met) substitution in codon 158 of the membrane-bound form of the enzyme (codon 108 of the soluble form) that generates alleles encoding high and low activity forms of the enzymes. The Met108/158 allele has been associated with decreased enzyme activity, protein level and thermal stability (Lachman et al., 1996; Shield et al., 2004; Mier et al., 2009). The COMT val158met polymorphism as well as other polymorphisms within this gene have repeatedly been investigated for association with MDD (Kunugi et al., 1997; Ohara et al., 1998; Frisch et al., 1999; Cusin et al., 2002; Serretti et al., 2003; Funke et al., 2005; Massat et al., 2005) and antidepressant treatment response (Szegedi et al., 2005; Arias et al., 2006; Baune et al., 2008; Ji et al., 2010; Kocabas et al., 2010; Massat et al., 2011), both with contradictory results.

We carried out an association study investigating seven COMT SNPs in a sample of 250 MDD patients collected in the context of a European multicentre treatment resistant depression study. The functional Val158Met (rs4680) polymorphism as well as six other SNPs (rs2075507, rs737865, rs6269, rs4633, rs4818 and rs165599) covering the COMT genomic region were selected for genotyping. This is the first study investigating suicidality in predefined treatment resistant MDD.

2. Methods

2.1. Subjects and diagnostic interviews

A total of 250 (68 males, 182 females) unrelated MDD patients (97.2% Caucasian, 0.8% Asian, 1.6% African, 0.4% North-American) were recruited in the context of the European multicentre project "Patterns of treatment resistance and switching strategies in unipolar affective disorder". Seven centres took part in the project: 1) Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria; 2) Department of Psychiatry, Chaim Sheba Medical Center Tel-Hashomer, Israel; 3) Department of Psychiatry, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; 4) Department of Psychiatry, University Hospital Gasthuisberg, Leuven, Belgium; 6) Hôpital la Salpetriere, INSERM U302, Paris, France; 7) Sint-Truiden, Psychiatric center, Sint-Truiden, Belgium. MDD was diagnosed by experienced psychiatrists using the Mini-International Neuropsychiatric Interview version 5.0.0 (MINI), modified for the Group for the Study of the Resistant Depression (Souery et al., 2007). The Hamilton Rating Scale for Depression (HAM-D) 17-item version was administered to all patients at the end of the last antidepressant treatment for the current episode. Each patient was also evaluated for demographic and psychosocial characteristics of the current episode, including personal and family history of psychiatric disorders and data on the last antidepressant treatment received for the current or most recent depressive episode. Inclusion criteria were: male or female inpatients or outpatients ≥ 18 years of age, patients with primary diagnosed MDD (i.e. mood disorder pre-existing to any other psychiatric disorder) and receiving at least one adequate antidepressant treatment during the current or last episode of depression. Treatment adequacy was defined as at least 4 weeks of