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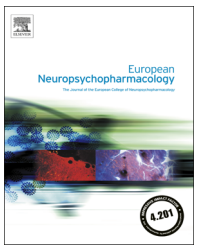

Genetics of emergent suicidality during antidepressive treatment—Data from a naturalistic study on a large sample of inpatients with a major depressive episode ☆

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Abstract
Factors contributing to treatment-emergent suicidal ideation (TESI) using antidepressants have been in the focus of recent research strategies. We investigated previously established clinical predictors of TESI and combined these with several polymorphisms of candidate genes in patients with major depressive disorder. Common polymorphisms involved in the tryptophan hydroxylase 1 (TPH1) and 2 (TPH2), serotonin transporter, monoamine oxidase A (MAOA) and brain-derived neurotrophic factor (BDNF) were investigated in a naturalistic inpatient study of the German research network on depression. We compared patients showing TESI with non-TESI suicidal patients and with non-suicidal patients using univariate tests to detect relevant factors, which were further tested in logistic regression and CART (Classification and Regression Trees) analyses. Of the 269 patients, TESI occurred in 22 patients (17 female), 117 patients were defined as non-TESI suicidal patients, and 130 patients were classified as non-suicidal. When comparing cases with both control groups we found the TPH2 rs1386494 (C/T) polymorphism to be moderately associated with TESI (Univariate tests: TESI vs. non-suicidality: p=0.005; adjusted: p=0.09; TESI vs. non-TESI suicidal patients: p=0.0024; adjusted: p=0.086). This polymorphism remained the only significant genetic factor in addition to clinical predictors in logistic regression and CART analyses. CART analyses suggested interactions with several clinical predictors. Haplotype analyses further supported a contribution of this polymorphism in TESI. The TPH2 rs1386494 (C/T) polymorphism might contribute to the genetic background of TESI. This polymorphism has been previously associated with committed suicide and major depressive disorder. The small number of cases warrants replication in larger patient samples. Lack of a placebo control group hampers definite conclusions on an association with antidepressive treatment.

1. Introduction

Suicidality is the most devastating symptom in patients suffering from major depressive disorder (MDD). Given the potential risk of pharmacologically induced suicidal behavior, regulatory authorities released warnings concerning antidepressant-induced suicidality, especially during initiation of treatment in patients aged 18–24 yr (FDA US Food & Drug Administration, 2007; Seemuller et al., 2010a). Being able to identify patients bearing a risk of becoming suicidal within the course of antidepressant treatment would be helpful and even crucial in clinical decision-making (Brent et al., 2010b). Treatment-emergent suicidal ideation (TESI) can be assessed by an increase in certain items of clinical depression rating scales during antidepressant treatment. In a previous analysis five out of 22 potential risk factors for emergent suicidality were found in a large sample of hospitalized depressed inpatients. These risk factors established by two independent statistical methods were age, treatment resistance, number of prior hospitalizations, presence of akathisia and any comorbid personality disorder (Seemuller et al., 2009a).

Apart from clinical risk factors researchers have attempted to elucidate genetic risk factors of TESI using candidate gene approaches or genome-wide association studies (GWAS). Genes that were previously associated with TESI include genes of the glutamatergic pathway (ionotropic glutamate receptors GRIA3 and GRIK2 (Menke et al., 2008; Laje et al., 2007)), noradrenergic system (alpha$_{2A}$-adrenergic receptor gene (Perroud et al., 2009)), neurotrophic system (cyclic adenosine monophosphate response element binding (CREB1) (Perlis et al., 2007), brain-derived neurotrophic factor (BDNF) and its receptor neurotrophic tyrosine kinase receptor type 2 (NTRK2) (Perroud et al., 2012, 2009)), hypothalamic–pituitary-axis system (FK506-binding protein 5 (FKBP5) (Brent et al., 2010a)), inflammatory pathways (IL28 α-receptor (Laje et al., 2009)) and genes suggesting new pathways such as e.g. papilin (PAPLN) gene (Perroud et al., 2012; Laje et al., 2009), RHEB, TMEM138, CYBASC3 or PIK3C3 (Menke et al., 2012).

Some studies found epistasis of genes (Perroud et al., 2009), gene $\times$ gender and gene $\times$ drug interactions (Perroud et al., 2009). Most analyses concentrated on the large patient samples of STAR*D (Laje et al., 2009, 2007; Perlis et al., 2007) and GENDEP studies (Perroud et al., 2012, 2009). These trials have the advantage of using monotherapeutic treatment strategies in patients with unipolar depression. However, results lack broader generalizability. Recently, Menke et al. reported on GWAS data of TESI in a naturalistic sample (Menke et al., 2012, 2008).

So far, most genes derived from pharmacogenetic trials and GWAS have not been replicated, apart from NTRK2, GRIA3 and GRIK2 and some evidence for the involvement of FKBP5 and ATP-binding cassette, subfamily B (MDR/TAP), member 1 (ABCB1) (Menke et al., 2012). We therefore relied on known candidate genes for suicidal behavior in general to approach the data set of a patient sample representative of ''real-world'' patients with major depressive disorder (MDD) (Seemuller et al., 2010b). We investigated several single nucleotide polymorphisms (SNPs) in candidate genes of suicidal behavior of the serotonergic system (tryptophan hydroxylase 1 (TPH1) and 2 (TPH2), serotonin transporter), monoamine metabolism (monoamine oxidase A (MAOA)) and neurotrophic functions (brain derived neurotrophic factor (BDNF)), controlling for the known clinical risk factors for emergent suicidality in this patient sample.

Using a three-staged procedure, we applied in a first step univariate tests and screened for simple associations of