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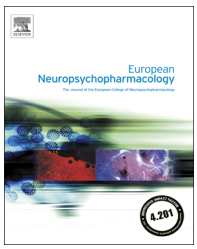

# The combined effect of genetic polymorphisms and clinical parameters on treatment outcome in treatment-resistant depression

Alexander Kautzky[a], Pia Baldinger[a], Daniel Souery[b,c], Stuart Montgomery[d], Julien Mendlewicz[e], Joseph Zohar[f], Alessandro Serretti[g], Rupert Lanzenberger[a], Siegfried Kasper[a,*]

[a]*Department of Psychiatry and Psychotherapy, Medical University of Vienna, Währinger Gürtel 18-20A-1090 Vienna, Austria*
[b]*Université Libre de Bruxelles, Belgium*
[c]*Psy Pluriel Centre Européen de Psychologie Medicale, Belgium*
[d]*Imperial College, University of London, United Kingdom*
[e]*School of Medicine, Free University of Brussels, Belgium*
[f]*Psychiatric Division, Chaim Sheba Medical Center, Israel*
[g]*Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy*

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**Abstract**
For over a decade, the European Group for the Study of Resistant Depression (GSRD) has examined single nucleotide polymorphisms (SNP) and clinical parameters in regard to treatment outcome. However, an interaction based model combining these factors has not been established yet. Regarding the low effect of individual SNPs, a model investigating the interactive role of SNPs and clinical variables in treatment-resistant depression (TRD) seems auspicious. Thus 225 patients featured in previous work of the GSRD were enrolled in this investigation. According to data availability and previous positive results, 12 SNPs in *HTR2A*, *COMT*, *ST8SIA2*, *PPP3CC* and *BDNF* as well as 8 clinical variables featured in other GSRD studies were chosen for this investigation. Random forests algorithm were used for variable shrinkage and k-means clustering for surfacing variable characteristics determining treatment outcome. Using these machine learning and clustering algorithms, we detected a set of 3 SNPs and a clinical variable that was significantly associated with treatment response. About 62% of patients exhibiting the allelic combination of GG-GG-TT for rs6265, rs7430 and rs6313 of the *BDNF*, *PPP3CC* and *HTR2A*

*Corresponding author. Tel.: +43 1 40400 35680; fax: +43 1 40400 30990.
*E-mail address:* sci-biolpsy@meduniwien.ac.at (S. Kasper).

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genes, respectively, and without melancholia showed a HAM-D decline under 17 compared to about 34% of the whole study sample. Our random forests prediction model for treatment outcome showed that combining clinical and genetic variables gradually increased the prediction performance recognizing correctly 25% of responders using all 4 factors. Thus, we could confirm our previous findings and furthermore show the strength of an interaction-based model combining statistical algorithms in identifying and operating treatment predictors.


## 1. Introduction

Major depressive disorder is the most striking neuropsychiatric disease, showing a lifetime prevalence up to 20% and causing 74.36 million disability adjusted life years in 2010 (Whiteford et al., 2013a). Although the importance of neuropsychiatric diseases cannot be dismissed, over the last decade little progress was made in developing new strategies of treatment. Despite a broad arsenal of well-established antidepressant agents, which can cure or alleviate the disease burden of most of the patients, about a third of those individuals treated adequately for major depressive disorder (MDD) do not respond sufficiently (Bauer et al., 2013). Even worse, 20% of patients remain significantly sick two years after disease onset and up to 15% are commonly regarded as treatment-resistant (Nierenberg et al., 2007). These patients demonstrate little or no symptom relief even after multiple treatment approaches.

Treatment-resistant depression (TRD) has first been described by Heimann in 1974 and many definitions of treatment resistance have been provided since (Berlim and Turecki, 2007; Heimann, 1974). While most studies on TRD consider different criteria concerning number, dosage and duration of antidepressive trials necessary for treatment resistance, a score of the Hamilton Rating Scale for Depression (HAM-D) above 17 after application of at least one treatment algorithm of adequate dosage and duration can be regarded as the concordant criteria for first level TRD (Souery et al., 1999; Thase, and Rush, 1997).

Researchers put a great effort into determining contributors to and predictors of treatment resistance. There are consistent findings pointing towards strong genetic effects on depression. Single nucleotide polymorphisms (SNP) have been suggested as decisive contributors to antidepressant response and many genetic polymorphisms, especially those related to the serotonergic system, have been studied as possible risk factors for MDD and TRD (Fabbri et al., 2013a; Fabbri et al., 2013b; Tansey et al., 2013). Our research consortium, “the European Group for the Study of Resistant Depression” (GSRD), investigating TRD in a pan-european sample for over a decade, demonstrated the importance of genes as *COMT*, *CREB*, *PPP3CC*, *ST8SIA2* and *BDNF*, involved in transcription, catecholamine inactivation and neuroplasticity (Fabbri et al., 2014; Kocabas et al., 2010; Kocabas et al., 2011; Schosser et al., 2012b).

On the other hand, clinical variables as comorbid anxiety disorders and suicidality impact the course and disease burden of MDD. An analysis of clinical variables in a large sample of TRD patients, undertaken by the GSRD, identified a selection of parameters as melancholia, suicide risk or comorbid anxiety disorder as independently associated with TRD (Souery et al., 2007).

Even though many risk factors have been identified, their individual prognostic values are not sufficient to detect patients at high risk of resistance early on. Regarding the multicausal etiology of a complex disease such as MDD, it seems plausible that most features do not determine treatment outcome phenotypes, taken individually, but rather interact with each other. Accordingly, common polymorphisms are believed to explain only about 0.05% of heritability when considered separately, most of them showing odds ratios (OR) around 1.5 (Gratten et al., 2014). Thus only a combination of several factors may lead to treatment resistance or response, respectively.

Regarding the substantial amount of data gathered over the last decade triggered by better cost effectiveness in genotyping and rapidly enhancing capabilities of data processing, the habitual analytical approach of studying main effects of single genes and SNPs using generalized linear regression and univariate approaches seems increasingly deficient (Chen et al., 2011).

While it is promising to study risk factors applying an interaction based model, up to now such approaches were hindered by limited patient numbers. However, the work of the GSRD and many others has made it possible to study a selection of interesting SNPs and clinical parameters previously analyzed and identified as auspicious targets of research in a combined model, using new algorithms such as machine learning and clustering. To our knowledge, this is the first study of this design in MDD. New statistical approaches to genetics in MDD have been repeatedly asked for. Thereby large datasets and accurate selection of variables based on previous research are required. This is specifically necessary with regard to combining genetic and clinical variables, which might explain the lack of interaction based machine learning and clustering algorithms on this topic so far.

We selected polymorphisms comprised in five genes that were previously studied in regard to MDD and treatment outcome by the GSRD and showed promising results, as described in Table 1. Some SNPs rendering inconclusive results in these studies were also included based on findings by other groups. These genes are coding for a serotonin-receptor, three enzymes and a neurotropic factor, all of which are related to the serotonergic system.

The 5-$HT_{2A}$-receptor, encoded by the *HTR2A* gene, is believed to be directly involved in the antidepressant potential of many drugs currently in use (Hamon and Blier, 2013). Accordingly it has been associated with depression as well as response to neuropsychiatric medication (Porcelli et al., 2011).

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