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Perspective

Biomarkers for Taxonomy of Neuropsychiatric Diseases

Andreas Menke*
Department of Psychiatry, University of Wuerzburg, Germany

***Corresponding author:** Andreas Menke, Department of Psychiatry, Psychosomatics and Psychotherapy, University of Wuerzburg, Fuechsleinstr. 15, 97080 Wuerzburg, Germany, Tel: 0931-20176590; Fax: 0931-20176519; Email: Menke_A@ukw.de

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Perspective

Unlike other disciplines of medicine the diagnostic process in psychiatry is based solely on clinical judgment, without incorporating lab-derived objective measures. Even with the advent of DMS-V, no biomarkers gathered from genomics, peripheral blood or brain imaging has been established for the diagnostic process in psychiatric disorders [1]. The neuropsychiatric fields lag behind others such as oncology, where biomarkers are established for diagnosis, treatment options and prognosis [2]. Biomarkers for risk or to determine the stage of a neuropsychiatric disorder are still in their infancy. Potential staging biomarkers include amyloid-β-1-42; tau and phosphor-tau 181 proteins sampled from cerebrospinal fluid of patients with mild cognitive impairment and may predict a progression to Alzheimer's disease [3]. These markers are already well-studied and are partly used in clinical settings. A new and very interesting cross-species translational approach investigated DNA methylation profiles from peripheral blood of euthymic pregnant women [4]. These methylation profiles were cross-referenced with 17β-estradiol-induced hippocampal DNA methylation changes in mice. Two genes were identified, HP1BP3 andTTC9B, which could predict post-partum depression with an area under the Receiver Operator Characteristic (ROC) curve of 0.87. Pathway analysis implicated the genes with hippocampal synaptic plasticity. Since only women with a history of mood disorders were investigated, these results await further replication in a general population [4].

Next, biomarkers predicting response to therapy with antidepressants or antipsychotics could facilitate the therapy choice and shorten the time to remission and thus provide personalized medicine in psychiatry [5]. However, in spite of numerous studies performed, robust markers which withstand replication are still lacking. Considering antidepressants, some candidate genes were identified, as solute carrier family 6, member 4; serotonin receptor 1A and 2A; Brain-Derived Neurotrophic Factor (BDNF); or catechol-O-methyltransferase [6]. Unfortunately, a meta-analysis of three genome-wide pharmacogenetic studies including 2,256 depressed patients did not detect polymorphisms significantly associated with treatment response after correction for multiple testing [7]. Lately, a genome-wide association study in bipolar I disorder patients of Han Chinese descent observed two polymorphisms located in the gene encoding glutamate decarboxylase-like protein 1 (GADL1), which could predict a response to lithium with a sensitivity of 93% [8]. But still, a confirmation in larger case series is warranted. A similar pattern has been observed for treatment with antipsychotics. At least, there are some identified genetic polymorphisms of the cytochrome P450 system, the dopamine and the serotonin transmitter systems [9]. But still these markers await replication and validation, before they can be integrated in clinical algorithms. Aside from genetic markers, in the Genome-Based Therapeutic Drugs for Depression (GENDEP) study, a multicenter open-label randomized clinical trial, CRP plasma levels were analyzed in depressed patients treated either with escitalopram or nortriptyline [10]. Interestingly, patients with CRP levels below 1 mg/l responded better to escitalopram, patients with higher CRP levels displayed a better response after treatment with nortriptyline [10]. These results, if successfully replicated, could help to personalize treatment choice.

Studies investigating biomarkers for treatment response are significantly hampered by an adequate phenotype definition within a large spectrum of affected patients, and often a combination of several treatment strategies. In contrast, testing side effects due to antidepressants or antipsychotics facilitates phenotype definition. Thus, the US Food and Drug Administration (FDA) recommends screening for the HLA-B*1502 allele before initiation of carbamazepine therapy in patients of Asien ancestry to avoid the development of Stevens-Johnson Syndrome (SJS), a potentially fatal skin reaction, and toxic epidermal necrolysis [11]. Another well-studied relation is the activity of CYP2D6 and the metabolism of codeine. Individuals who lack CYP2D6 activity can't process codeine and don't get pain relief from the medication. Those carrying three or more active versions of CYP2D6 metabolize codeine rapidly, which could be toxic [12]. Another possible fatal side effect is suicidality. In 2004, the FDA issued a black-box warning on antidepressants indicating that they were associated with Treatment-Emergent Suicidal Ideation (TESI). A series of meta-analyses of 372 randomized clinical trials of antidepressants involving nearly 100,000 participants showed that 4% of patients taking antidepressants reported suicidal thinking or behavior, as compared with 2% among those assigned to receive placebo, although none of the documented suicide attempts were fatal [13]. A subsequent analysis observed that children and adolescents under the age of 18 years exhibited the greatest risk to develop TESI. Therefore, several attempts were made to find genetic markers predicting the development of TESI, finding markers within glutamate receptors [14,15], BDNF [16], FKBP5 and ABCB1 [17,18]. Up to now there is only one study which could successfully replicate a set of genetic markers to predict the onset of TESI [18].

The use of clozapine, which is a common and very effective antipsychotic, is somewhat restricted due to agranulocytosis, a distinct, rare, but life-threatening side effect. Meanwhile, there is accumulating evidence implicating variants of the HLA-DQB1 locus with the occurrence of agranulocytosis [19]. However, efforts to identify key mechanisms that would be useful to predict clozapine side effects in the clinical setting have not been fully successful,

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therefore further studies with larger sample sizes are needed. Sexual dysfunction and weight gain represent side effects which are not fatal, but nevertheless may jeopardize the success of the therapy by treatment discontinuation and no adherence. Using a set-based test for association in data derived from the STAR*D study, a multicenter, prospective, effectiveness trail in depressed outpatients, polymorphisms within glutamatergic genes were associated with decreased libido (GRIA3; GRIK2), difficulty of achieving orgasm (GRIA1) and difficulty achieving erection (GRIN3A) [20].Weight gain is an extremely common side effect due to medication with antipsychotic, and many studies investigated genetic markers identifying patients at risk. The most consistently replicated genes are located in the melanocortin 4 receptor (MC4R), the serotonin 2C receptor (HTR2C), the leptin, the neuropeptide Y (NPY) and the cannabinoid receptor 1 (CNR1) genes [21]. However, a clinical application of these genetic markers is still not foreseeable.

For most of the reported genetic variants or biomarkers validation in larger case series is required. Also, an in-depth analysis of pathophysiological underpinnings related to disease, treatment response or side effects in small, but well-characterized samples and the cross-reference with animal models may further boost the search for biomarkers.

Disclosures

Inventor of: Means and methods for diagnosing predisposition for treatment emergent suicidal ideation (TESI). *European patent number: 2166112. International application number: PCT/EP2009/061575.*

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