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PHARMACOGENETICS OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN IN SCHIZOPHRENIC PATIENTS

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Background:

Antipsychotic-induced weight gain (AIWG) is a major drawback in the treatment of schizophrenic patients with second-generation antipsychotics (SGAs). Pharmacogenetic studies have established several polymorphisms in genes of different pathways contributing to the development of weight gain in schizophrenic patients. However interactions of genetic polymorphisms and clinical predictors have not been studied extensively enough to reliable predict weight gain before initiating antipsychotic treatment.

Methods:

We analyzed several single-nucleotide polymorphisms (SNPs) of candidate genes (e.g. APOA, GHRL, SNAP-25, LDLR, LPL, INSIG2, Resistin, 5HTR2C, MC4R) and clinical predictors (e.g. age gender, BMI at baseline, number of episodes, pretreatment, PANSS-scores) in a sample of 259 (n=138 for regression analyses) schizophrenic patients participating in different monotherapeutic trials of atypical antipsychotics (risperidone, olanzapine, quetiapine, amisulpride, aripiprazole) with up to six weeks of treatment. We used Univariate tests, regression analysis and Classification and Regression-Tree (CART)-analysis to determine relevant clinical and genetic predictors and their interactions.

Results:

We found younger age, male gender and weight at baseline as strongest clinical predictors. APOA variants and the Resistin -420 C/G rs1862513 polymorphism were associated with weight gain in the overall patient sample. Heterocygotic GC-allele carriers (n=53) gained less weight (1 kg) compared to 2,2 kg in homocygotic G-allele carriers (n=76) (p<0.0075). We found several interactions of the clinical predictors and genetic variants or type of used SGAs in linear regression models. Use of quetiapine and olanzapine and PANSS total scores showed significant interactions over the time. APOA polymorphisms showed a tendency towards significance in linear regression models (p=0.09). The Resistin -420 C/G rs1862513 polymorphism showed significant interaction in patients treated with risperidone (p<0.0001) and amisulpride (p=0.0006) in a model adjusted for all clinical predictors. CART-analyses support to some extend the relevance of the Resistin polymorphism.

Discussion:

In this sample we found a polymorphism in the Resistin gene (-420 C/G rs1862513) to potentially contribute to AIWG. CART-analysis shows interactions of several clinical predictors and this polymorphism. Our approach of combining clinical and genetic predictors may help to identify subgroups of patients a priori of SGA treatment in order to reduce development of severe weight gain. Further investigations on larger samples are necessary to confirm our results.

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