M55. PHARMACOGENETIC STUDY OF ANTIPSYCHOTIC RESPONSE TO TREATMENT IN MEXICAN PATIENTS WITH SCHIZOPHRENIA: ANALYSIS OF RESPONSE AND RESISTANCE

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Background The efficacy of antipsychotics treatment in schizophrenia patients has long been established; however, clinical response to these drugs is not the same in all patients. Genetic variability has been proposed as the main reason for the different outcomes.The dopaminergic pathways, the principal mechanism of action of the antipsychotics, have been the main focus of pharmacogenetic studies in schizophrenia. Some functional single nucleotide polymorphisms (SNPs) have been associated with dopamine disposition or dopamine receptor expression, modifying the response to treatment. The aim of the study was to analyze the association between two response phenotypes (patients with response and resistant) and COMT (Val58Met), DRD2 (A-241G, C/G exon 8, C939T, Taq1A) and DRD3 (Ser9Gly) gene polymorphisms.

Methods Treatment response was retrospectively/prospectively assessed. First, we gathered all reliable antipsychotics assays from medical files and through interviews with attending physicians. If these data were not conclusive, a mandatory follow-up period was added with regularly scheduled ratings (using the Positive and Negative Symptom Scale PANSS and the Functional Assessment Scale for Comprehensive Treatment of Schizophrenia FACT-Sz).Treatment response was defined on a $\geq$ 30% decrease on the total PANSS score (with an antipsychotic different from clozapine).

The sample was classified in two main phenotypes: 95 patients on response to treatment group and 81 on resistant-to-treatment group.

The genotyping of the COMT (Val58Met), DRD2 (A-241G, C/G exon 8, C939T, Taq1A), and DRD3 (Ser9Gly) gene polymorphisms was performed with allelic discrimination, using TaqMan assays.

Differences in genotypes and allele frequencies between the phenotypes of patients were calculated using the X2 test. Also, we performed a logistic regression analysis to predict the likelihood of the resistance-to-treatment phenotype.

Results Analysis of Val158Met/COMT showed differences between the response and the resistance groups. The GG genotype (Val/Val) was more frequent in the response group than the resistance group (47% vs. 33%, X2=6.26, 2 df , p=0.04) . We also found allele differences between groups (X2=6.65, 1 df, p<0.01). The Val allele was more frequent in the response group (65%) than the resistance. There were no significant associations of DRD2 (A-241G, C/G exon 8, C939T, Taq1A) or the DRD3 (Ser9Gly) SNPs with any of the phenotypes. The logistic regression model showed that the COMT/Val158Met (Met/Met) and DRD3 Ser9Gly (CT) genotypes were predictive for the resistant-to-treatment phenotype, classifying correctly 66% of them (β Exp=1.99, 1.086-3.66 CI 95%, p=0.02).

Discussion The COMT/Val158Met SNP (Val/Val) was associated with the response to treatment phenotype. This finding is consistent with the antipsychotics proposed mechanism of action. The antipsychotic efficay on lowering the hyperdopaminergic state would be greater in those patients with the high-activity COMT genotype.

The DRD2 SNPs analysis, the main target of several studies, did not show any significant association with the phenotypes. The COMT and DRD3 gene analyses

could be associated with the resistant-to-treatment patients, so they elicit the possibility as plausible mediators of the resistance to treatment for schizophrenia.One of the limitations of this study is the size of the sample.
Further analyses should be performed for the validation of these SNPs as mediators for the response or resistance to antipsychotics.
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