Dopamine-related gene polymorphisms in schizophrenia and in therapeutic response

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INTRODUCTION

Genetic epidemiological studies have demonstrated that schizophrenia (SCZ) has a high heritability, indicating a significant genetic component to its aetiology. In light of the dopamine hypothesis of SCZ, genes encoding dopaminergic receptors and enzymes related to the metabolism of dopamine might be regarded as candidate genes [1].

The aim of our study was to evaluate the possible role of the dopamine transporter gene (SLC6A3) 40 bp VNTR, the dopamine receptor 2 gene (DRD2) TaqIA and the dopamine beta-hydroxylase gene (DBH) C-1021T polymorphisms in SCZ and in therapeutic response either alone or in genetic interaction.

SUBJECTS AND METHODS

A total of 303 Hungarian Caucasian subjects were enrolled in the study: 120 SCZ patients and 183 healthy control (HC) probands (Table 1.) The SCZ patients received atypical antipsychotics (amisulpride, olanzapine, risperidone) for 12 weeks before the evaluations. Seventy-three percent of the SCZ patients were responder (R) and 27 percent of them were non-responder (NR) subjects. A patient was considered to be responder if there was an improvement of at least 20 points in the Global Assessment of Functioning scale during the treatment period.

DNA was extracted from peripheral blood leukocytes, the genetic analyses were performed by PCR amplifications. Fisher's exact and Pearson's $\chi 2$ tests were used to compare allele and genotype frequencies between the investigated groups. A logistic regression model was used to test for the interaction between the investigated polymorphisms and to calculate odds ratios (ORs) with 95% confidence intervals (CI).

Table 1. Characteristics of the probands

	Schizophrenic patients n=120		Healthy controls n=183
	Responder n=88	Non-responder n=32	
Male	40	19	89
Female	48	13	94
Mean age (years)	36.8±10.4	35.3±11.2	38.2±10.8

Figure 1. SLC6A3 genotype distribution

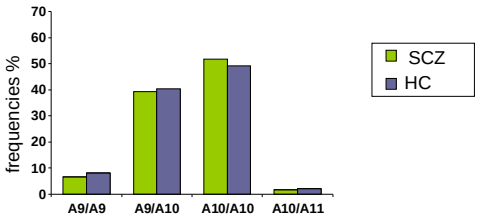


Figure 2. DRD2 genotype distribution

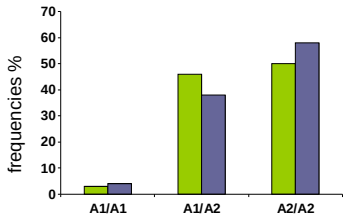


Figure 3. DBH genotype distribution

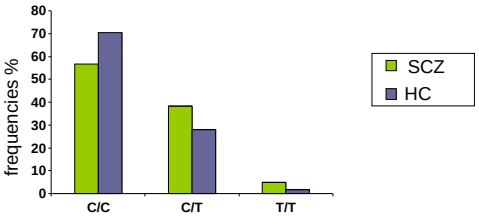


Figure 4. Odds ratios with 95% CI for SCZ conferred by DBH genotypes

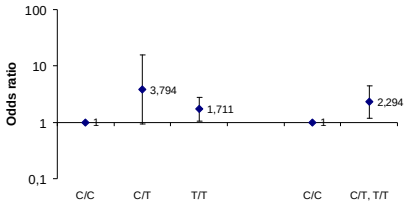


Figure 5. SLC6A3 genotype distribution

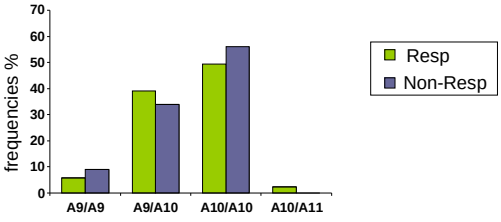


Figure 6. DRD2 genotype distribution

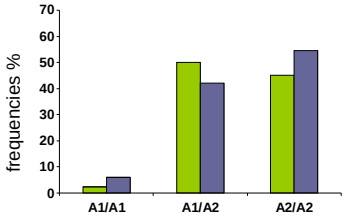
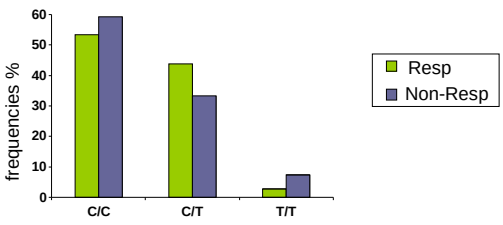


Figure 7. DBH genotype distribution



RESULTS

Comparison of SLC6A3 and DRD2 genotype frequencies between SCZ and HC groups did not reach statistically significant difference (SLC6A3: p=0.742; DRD2: p=0.069). (Figure 1., 2.)

The frequencies of the **DBH C/T and T/T genotypes were significantly higher in SCZ** as compared to HC group (C/T: SCZ: 38.3%, HC: 27.9%; T/T: SCZ: 5.0%, HC: 1.6%; p=0.025). (Figure 3.)

Given the relatively low occurrence of the T/T genotype both in SCZ cases and in controls, the analysis was also conducted by presence or absence of the T allele in the genotypes. The **T+ genotypes had a significantly increased risk for SCZ (OR=2.29, 95%CI: 1.18-4.45; p=0.014)** considering C/C genotype as reference category (OR=1). (Figure 4.)

The distributions of the SLC6A3, DRD2 and DBH genotypes did not differ significantly between the R and NR groups (SLC6A3: p=0.751; DRD2: p=0.218; DBH: p=0.422). (Figure 5., 6., 7.)

Logistic regression analysis revealed no interaction between the investigated polymorphisms affecting the therapeutic response in SCZ.

CONCLUSION

According to our results, there is no association between the SLC6A3 40 bp VNTR or the DRD2 TaqIA polymorphisms and SCZ. We also failed to detect a significant correlation of these polymorphisms and the therapeutic response in SCZ.

The results suggest however that the DBH T allele carriers may have an increased risk for developing SCZ, but the DBH C-1021T polymorphism does not have any influence on therapeutic response, although further investigations are required.

[1] Di Forti, M., Lappin, J.M., Murray R.M., 2007 Risk factors for schizophrenia - All roads lead to dopamine. European Neuropsychopharmacology 17, S101–S107.

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