High-risk genetic profiles for Pharmacoresistant Schizophrenia: Insights from Belarusian Patients

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RELEVANCE OF THE STUDY

Modern therapy for schizophrenia, based on the use of antipsychotic drugs, is an effective treatment method for many patients.

However, **20–30% do not respond** adequately to treatment.

Currently, researchers emphasize the need to identify population-specific pharmacogenes whose polymorphic loci can serve as **reliable biomarkers to predict treatment response to antipsychotic therapy** accurately.

The aim of the study was to investigate the association of a number of polymorphic gene loci with pharmacoresistance (PR) in schizophrenia patients among residents of Belarus.

PARTICIPANTS AND GENOTYPED LOCI

161 participants

(ICD10: F20.0, age18-60, no acute somatic and infectious diseases

Treatments included clozapine (42.1%) or combined atypical and typical antipsychotics (39.5%))

Responders (N=57)

(respond correctly on antipsychotic treatment in 6-8 weeks)

Pharmacoresistant (N=104)

(no response on antipsychotic treatment in 6-8 weeks)

Genotyped polymorphic loci

CYP450	Serotonergic system	Dopaminergic system	Others
CYP2D6*3	HTR1A (rs6295)	ANKK1 (rs1800497)	MDR1 (rs1045642,
CYP2D6*4	HTR2A (rs6311)	DRD2 (rs6277)	C3435T)
CYP2D6*10	HTR2C(rs1414334)	COMT (rs4680)	UGT1A(*28) (rs3064744)
CYP2C9*2	MAOA (30bp-VNTR)		BDNF(rs6265)
CYP2C9*3			
CYP2C19*2			
CYP2C19*17			
CYP1A2*F			

RESULTS & DISCUSSION

Alleles and genotypes, associated with PR risk

A-allele and AG genotype of CYP2D6*4 (rs3892097),
(OR=2.159; CI=1.018-4.578 and OR=2.975; CI=1.269-6.977, respectively);
G-allele of COMT (rs4680, V158),
(OR=2.786; CI=1.414-5.489);
CC genotype of HTR1A (rs6295),
(OR=2.703; CI=1.151-6.348)

Combined genotypes showed even greater PR risk

A-/A- (CYP2D6/CYP1A2),
(OR = 2.926; 95% CI = 1.206–7.102);
A-/A-/T- (CYP2D6/CYP1A2/MDR1),
(OR = 4.833; 95% CI = 1.753–13.328)
G-/LL (COMT/SLC6A4),
(OR = 6.923; 95% CI = 1.900–25.227);
CC/T- (HTR1A/MDR1),
(OR = 2.564; 95% CI = 1.120–5.873)

Protective alleles and genotypes

GG genotype of CYP2D6 (rs3892097),
(OR=0.463; CI=0.218-0.928);
G allele of HTR1A (rs6295),
(OR=0.367; CI=0.156-0.864);
AA genotype (Met/Met) of COMT (rs4680),
(OR=0.359; CI=0.182-0.707)

In conclusion, variants in CYP2D6, HTR1A, and COMT, especially when combined with CYP1A2, MDR1, and SLC6A4, significantly contribute to PR schizophrenia risk in Belarus.

These findings support the use of pharmacogenetic testing for personalized antipsychotic treatment, already implemented in the Republican Research and Practice Center for Mental Health (Minsk, Belarus).

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