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Potential association of *CYPs, COMT, DRD2, 5HTR2A* polymorphisms with susceptibility to the adverse effect of aripiprazole: preliminary observations

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ABSTRACT

Introduction: Aripiprazole is a third-generation antipsychotic drug generally well tolerated, but some patients experience adverse effects. Variability in a patient's response to aripiprazole can be associated with genetic variants in genes involved in drug pharmacokinetics and pharmacodynamics. The purpose of this study was to perform genetic profiling on patients with schizophrenia, bipolar disorder, and personality disorder to find an association between SNPs and adverse events.

Materials and methods: The gDNA of 74 patients was used to assess 71 polymorphisms in 21 genes by mass spectrometric analysis and PCR-RFLP method.

Results: Patients were divided into well- and badly-reacting groups. The CYP2D6 UM/NM phenotypes and the combined homozygous genotype *CYP1A2*1F*/*CYP2B6*1* were observed more frequently in the badly-reacting group. Moreover, the frequency of the combined homozygous status of *5HTR2A* (*AA*/*TT* rs6311/rs6313) differed significantly between groups. For the polymorphism of the *COMT* rs4680 variant, the frequency of the *A* allele was significantly higher in the well-reacting group.

Conclusions: The present preliminary findings showed that polymorphisms of the *DRD2* and *5HTR2A* genes may be related to adverse drug effects. Alleles determining the higher density of receptors were observed more frequently in the badly reacting group. Moreover, the *G* allele of *COMT* was observed significantly more frequently in patients who experienced adverse effects. Surprisingly, it was noticed that patients in the badly reacting group most often had the CYP2D6 UM/NM phenotype, which does not require standard dose adjustments.

Keywords: aripiprazole, genetic polymorphism, neurotransmitter receptors, pharmacogenetics, schizophrenia

Introduction

Aripiprazole is an atypical antipsychotic drug and due to its unique pharmacological profile is defined as a third-generation antipsychotic drug [1]. The FDA-approved aripiprazole as medication used to treat schizophrenia, mania associated with bipolar disorder type I, irritability associated with an autism spectrum disorder, disjunctive therapy in major depressive disorder, and Tourette syndrome [2]. Aripiprazole is mostly metabolized by hepatic enzymes, CYP2D6 and CYP3A4, and its active metabolite, dehydro-aripiprazole, representing about 40% of the parent drug levels in plasma [3]. A dose reduction is recommended when using strong CYP3A4 or CYP2D6 inhibitors concomitantly, and an increase of the dose is recommended when using strong CYP3A4 inducers [3]. Aripiprazole can modulate the properties of different neurotransmitter systems. It has high affinities for dopamine and serotonin receptors as well as exhibits a moderate affinity for adrenergic, and histamine receptors [4]. Partial agonism of the dopamine D2, D3, and serotonin 5HT1A receptors as well as antagonism of the serotonin 5HT2A receptor is considered to be the functional basis of its clinical effect [5]. Although, aripiprazole is well tolerated both in short- and long-term treatment, adverse drug reactions are observed including extrapyramidal effects, headache, agitation, insomnia, anxiety, nausea, vomiting, akathisia, light-headedness, and constipation [2, 6]. To avoid side effects, the FDA and Clinical Pharmacogenetics Implementation Consortium recommended half of the usual dose of aripiprazole administration only for CYP2D6 PMs [7, 8]. However, it was demonstrated that both IM and PM CYP2D6 phenotypes increase the risk of extrapyramidal reactions, nausea, or vomiting [8, 9]. Possibly, the polymorphisms in other CYP genes can be involved in aripiprazole metabolism. A recent study has revealed that the CYP1A2 enzyme can influence the metabolism of aripiprazole and dehydro-aripiprazole in healthy volunteers treated with aripiprazole 10 mg daily [10]. An analysis of previous studies conducted on commonly used

antipsychotic drugs showed that higher activity of CYP1A2 was associated with lower adverse effects [11]. In addition, several studies demonstrated that genetic variants in the *ABCB1*, *COMT*, *DRD2*, and *5-HTRs* genes can be related to aripiprazole response and adverse effects [8, 12–14].

Because there are no studies examining the wide single-nucleotide polymorphism analysis of patients treated with aripiprazole regarding adverse effects the authors investigated 71 polymorphisms in 21 genes in patients with schizophrenia, bipolar disorder, and personality disorder.

The purpose of this study was to perform genetic profiling on patients with schizophrenia, bipolar disorder, and personality disorder to find an association between SNPs and adverse events.

Materials and methods

Patients

Caucasian subjects taken into consideration were those diagnosed with schizophrenia (n = 58), bipolar disorder (n = 10), and personality disorder (n = 6). A total of 74 patients (47 males, and 27 females) aged between 19 to 60 years (mean ± standard deviation 35.9 ± 10.4 years) were recruited in Babinski University Hospital (Krakow, Poland). Written informed consent was obtained from all subjects. Inclusion criteria were as follows: (1) aripiprazole therapy (ongoing or withdrawn), and (2) age 18 to 60 years. Exclusion criteria were as follows: (1) polypharmacy with drugs listed as CYP2D6 inhibitors or CYP3A4 inducers or inhibitors, (2) organic lesions of the central nervous system, and (3) mental retardation. Patients were divided into two main groups: well-reacting (WR) and badly-reacting (BR) which included patients previously treated with aripiprazole, but the drug was withdrawn due to side effects. The WR group was composed of two subgroups: patients treated with

aripiprazole alone (ARI) and patients treated with aripiprazole and one or more second-generation antipsychotics (ARI + SGA).

DNA extraction and genotyping

DNA from blood samples were genotyped using MassArray® System and VeriDose Core and VeriDose CYP2D6 CNV Panel (Agena Bioscience). In addition, the PCR-RFLP method was used to analyze three polymorphisms in the *5-HTR2A* gene. The description of genotyping, analyzed genes, and consequences of polymorphism are presented in Supplementary Material: Table S1 and S2.

Translation of genotype into phenotype

To classify patients into a specific phenotypic group the calculation of activity score (AS), based on the functionality of the alleles, was applied. Each *CYP2D6* allele is assigned an activity value: wild type (normal function) allele — 1; decreased-function allele — 0.5 or 0.25; no-function allele — 0. The sum of the values assigned to each allele allows the translation of genotype into phenotype. According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, the following phenotypes are distinguished: poor metabolizer (PM) when AS = 0, intermediate metabolizer (IM) when AS > 0 and ≤ 1.25, normal metabolizer (NM) when AS > 1.25 and ≤ 2.25, and ultra-rapid metabolizer (UM) when AS > 2.25.

CYP3A4 and *CYP3A5* genotypes are merged into a CYP3A phenotype. The star allele **1* for the *CYP3A4* and *CYP3A5* was defined as a normal allele, allele **22* for the *CYP3A4* as a reduced activity allele, and allele **3* for the *CYP3A5* as an inactive allele. The following phenotypes were determined based on genotype clusters: PM for *CYP3A4*1/*22* and *CYP3A5*3/*3* cluster; IM for *CYP3A4*1/*1* and *CYP3A5*3/*3*; and NM for *CYP3A4*1/*1* and *CYP3A5*1A/*3*.

Also, the calculation of AS was used to determine CYP1A2 phenotypes. The activity values assigned to the **1C*, **1*, **1B*, and **1F* alleles were 0.5, 1, 1.25, and 1.5, respectively. CYP1A2 phenotypes were predicted based on the sum of functionality values: PM 1–1.5, NM 1.75–2.5, and UM 2.75–3.

Statistical analysis

Statistical analyses were performed using the GraphPad Prism 9.4.1 software (GraphPad Software, Inc). A T-test was used to compare demographic variables. The Chi-squared test was selected to evaluate the Hardy-Weinberg equilibrium. An odds ratio (OR) with their corresponding 95% confidence intervals (95% CI) was calculated to assess the association of genotypes and polymorphic alleles with adverse drug effects susceptibility. The p-value ≤ 0.05 was considered statistically significant.

Results

This study included 74 patients, 47 males, and 27 females, divided into two main groups based on the presence or absence of adverse effects: (1) BR – badly-reacting (n = 10) and (2) WR - well-reacting (n = 64) to ARI. Average age, weight, and BMI did not differ significantly between the three groups. Detailed information on demographics and clinical characteristics in groups and subgroups are shown in Table 1 and Supplementary Material Table S3.

The distribution of genotypes in the study population was in the Hardy-Weinberg equilibrium (p≥0.05), except for *COMT* and *5HTR2A* (rs6314) polymorphisms (Table 2). The present results showed that the frequencies of functional alleles (**1* and **2*) of the *CYP2D6* gene were 75% in the BR group and 68% in the WR group (data not shown). Based on the allele activity score the patients were classified into two phenotype groups: (1) UM+NM and (2) IM+PM. The UM/NM phenotypes were observed more frequently in the BR group (88%) than in the WR group (55%) (Fig. 1A). Surprisingly, an almost 4 times lower

frequency of the IM/PM phenotype was observed in the BR group (12%) compared to the WR group (45%) (Fig. 1A).

Two phenotypes in each group, UM and NM, for CYP1A2, were determined using the allele activity score (Fig. 1B). Three *CYP2B6* genotypes (**1/*1*, **1/*6*, and *6/*6) were identified in the study population. The authors analyzed the combined homozygous condition (**1F/*1F*/**1/*1*) of the *CYP1A2* and *CYP2B6* genes, respectively. Interestingly, the combined homozygous genotype (**1F*/**1*) was observed more frequently in the BR group (56%) compared to the WR group (26%) (Fig. 1C). Probably the combined homozygous state may increase the chance of developing adverse drug effects, however, the OR was not statistically significant (p = 0.088, Table 3).

For the polymorphism of the *5HTR2A* rs6311, the frequency of *AA* homozygote was higher in the BR group compared to the WR group (45% vs. 15%) (Fig. 2A). Due to complete linkage disequilibrium between *HTR2A* rs6311 and rs6313 polymorphisms, the same frequency of *AA* and *TT* homozygote was found in the studied groups (Fig. 2A and 2B). The combined homozygote *AA/TT* (rs6311/rs6313) was 3-fold higher in the BR group than in the WR group (45% vs. 15%, respectively), and the OR was statistically significant (OR: 4.71; 95%CI: 1.06–20.96; p = 0.042) (Table 2 and 3). Such results suggest that *AA/TT* genotype may predispose to adverse effects. In turn, the frequency of *5HTR2A* (rs6314) *TT* genotypes did not differ significantly between groups (OR: 1.19; p = 0.912) (Fig. 2C, Tab. 3). The authors also analyzed rs1800497 polymorphism in the *DRD2* gene. The frequency of *WT/WT* homozygote was higher in the BR group compared to the WR group (78% vs. 61%) (Fig. 3A). Interestingly the frequency of the *Taq1A* allele was almost 2 times higher in the WR group than in the BR group (20% vs. 11%, respectively) (Fig. 3B). Probably this allele improves drug response, however, the OR was not statistically significant (p = 0.362) (Tab. 3)Polymorphisms in the *ABCB1* and *COMT* genes were also examined in this study.

Interestingly, only carriers of the major allele (*CC/CT*) of *ABCB1* rs1045642 were identified in the BR group. Therefore, it seems that the *C* allele may predispose to a worse response but the OR was not statistically significant (p = 0.136) (Tab. 3).

For the polymorphism of the *COMT* rs4680 variant, no *AA* homozygous was observed in the BR group (Fig. 4A). Interestingly, a nearly 2 times higher frequency of the *A* allele was observed in the WR group compared to the BR group (Fig. 4B). The OR for the *A* allele was statistically significant (p = 0.039), this allele probably reducing the risk of adverse effects (Tab. 3).

Discussion

The present study performed genetic profiling in patients treated with aripiprazole. Regarding the response to aripiprazole, two groups were distinguished: BR — badly-reacting (patients who experienced adverse effects) and WR — well-reacting. The pharmacogenetic analysis focused on genetic variations in drug-metabolizing and dopamine-degrading enzymes, drug transporter as well as dopamine and serotonin receptors. Polymorphic variants in the *CYP2D6*, *CYP3A4*, and *CYP3A5* genes that encode the most important enzymes involved in the metabolism of ARI were assessed. Interestingly, it was found that UM/NM CYP2D6 phenotypes were observed more frequently in the BR group (88%) than in the WR group (55%). Surprisingly, the frequency of IM/PM phenotypes was 4 times higher in the WR group (45%) compared to the BR group (12%). Furthermore, the frequency of IM combined CYP3A (CYP3A4 and CYP3A5) phenotype did not differ between those two groups (BR — 78%, vs. WR — 85%). Several studies suggested that CYP2D6 genotype/phenotype significantly influences aripiprazole pharmacokinetics [15–17]. It was found that IM and PM CYP2D6 phenotypes increase the risk of extrapyramidal reactions, nausea, or vomiting [8, 9]. Surprisingly, adverse drug effects were not observed in the WR group despite the high frequency of IMs, especially high in patients treated with aripiprazole alone (IM — 70%).

Thus, the present findings are contradictory to the existing research. It should be emphasized that CYP2D6 is expressed not only in the liver but also in the brain where it is involved in local serotonin and dopamine syntheses [18]. It is postulated that pharmacogenetic variability of the CYP2D6 enzyme may influence the central nervous system's vulnerability to ADEs [19]. Notably, individuals with the UM phenotypes showed higher concentrations of platelet serotonin than those with NM and PM [20]. It is plausible that *CYP2D6* polymorphism influences the crosstalk of the DA and 5-HT endogenous systems, thus drugs interacting with the serotonergic and dopaminergic systems can provoke ADE symptoms [21]. The present study found more than a 2-fold higher frequency of UMs in the BR group compared to the WR group (Supplementary Material Table S4). An *in vivo* study suggested that PMs might have a higher DA tone in the pituitary with concomitant lower serotonin tone, serotonin systems exerting a tonic inhibitory control on the dopaminergic circuits [22, 23]. Given the above, it is currently difficult to explain why patients with UM phenotypes experienced adverse events. The role of *CYP2D6* polymorphisms appears to be more complex and requires further studies to elucidate the relationship between adverse effects and patient phenotypes. In addition, polymorphisms in other genes important for drug metabolism and response should be considered.

Also, polymorphisms in other cytochrome P450 families were assessed, including *CYP1A2* and *CYP2B6* genes. The combined homozygous *CYP1A2*1F/CYP2B6*1/* status was more frequently observed in the BR group (56%) than in the WR group (27%). The CYP1A2 is considered to be one of five of the most important CYPs (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A), which are responsible for approximately 90% of the oxidative metabolism of drugs [24], while the CYP2B6 enzyme is involved in the metabolic hydroxylation of nearly 8% of clinically used drugs [25]. The *CYP1A2*1A* allele has normal activity and is considered the reference allele [26], but the *CYP1A2*1F* allele contains a

single variation (−163C > A), which is located in intron 1 that increases the inducibility of caffeine metabolism by smoking [27]. Generally, this variant is associated with higher enzyme activity due to increased induction of expression [26]. *CYP1A2*1F/*1F* carriers may have 30-70% higher CYP1A2 activity than *CYP1A2*1A/*1F* and *CYP1A2*1A/*1A* carriers [28]. For example, the *CYP1A2∗1F* allele enhanced clozapine clearance and increased plasma concentrations leading to adverse effects, particularly in smokers [29]. It is worth noticing that the present study observed a high frequency of combined homozygous (*CYP1A2*1F/CYP2B6*1*) status in patients with adverse drug effects. The role of CYP1A2 and CYP2B6 enzymes is unknown in aripiprazole metabolism, however, a recent study has shown that the metabolism of aripiprazole and dehydro-aripiprazole may be affected by the CYP1A2 enzyme [10]. Unlike the present study, Cendrós et al. suggested that psychic adverse effects were less frequent in patients with higher CYP1A2 activity [11]. Currently, it is very difficult to find a clear explanation for the role of the *CYP1A2*1F* and *CYP2B6*1* alleles in the metabolism of aripiprazole, therefore further studies on the involvement of these enzymes are needed.

According to previous studies, the CYP2B6 enzyme is expressed in different brain structures and similar to CYP1A2 may also contribute to the metabolism of CNS-acting drugs and neurological side effects of certain medications [24, 30].

In addition to enzymes involved in drug metabolism, other proteins, such as enzymes involved in catecholamine metabolism and their receptors, are important for drug response. To assess the relationship between polymorphisms in genes engaged in catecholamine action and drug response, variants in the *COMT*, *DRD2*, and *5HTR2A* genes were studied. *COMT* encodes an important enzyme that degrades catecholamines and regulates dopamine availability in the prefrontal cortex (PFC), where the expression of dopamine transporters is low [31]. The *COMT* rs4680 (472G > A, Val158Met) polymorphism significantly affects

enzyme activity and therefore prefrontal dopamine levels and function [32]. A missense *G* to *A* transition results in the valine (Val) to methionine (Met) substitution at codon 158. The Met variant is associated with lower thermostability, a 3- to 4-fold reduction in enzyme activity [33] as well as lower protein expression [34]. It was/has been observed that this polymorphism can affect the response to antipsychotics and the metabolism of neurotransmitters during the treatment of schizophrenia [14]. A greater improvement in PANSS score was observed in the *AA* homozygous (Met/Met) after the treatment with aripiprazole. The present results seem to be in line with these observations, the frequency of the *G* allele in the BR group was higher than in the WR group (72% vs. 45%). Moreover, in patients from the BR group, the *AA* genotype was not identified at all, while in the WR group, the frequency was 37%. Indeed, the allelic odds ratio calculation revealed that the *G* allele increased susceptibility to adverse effects 3 times ($p = 0.039$). It is plausible that the Met/Met genotype leads to hyperdopaminergic neurotransmission due to less efficient dopamine metabolism. In turn aripiprazole, a partial agonist at D2 receptors, can restore appropriate dopamine neurotransmission and may also stabilize dopamine function in the prefrontal cortex.

It is well known that *DRD2 Taq1A* polymorphism (rs1800497), is related to a reduced number of dopamine receptors in the brain [35]. A study by Kwon et al. demonstrated that patients carrying the *Taq1A/Taq1A* genotype had a better therapeutic response to aripiprazole [12]. In the present population, the frequency of the *Taq1A/Taq1A* genotype was extremely low (BR group – 0% WR group – 2%), but the frequency of the *Taq1A* allele was almost 2 times higher in well-reacting than badly reacting patients.

Aripiprazole acts as an antagonist at the 5HT2A receptor, which is extensively expressed in the prefrontal cortex [36]. Thus, analyzed were also three SNPs *5HTR2A*, rs6311, rs6313, and rs6314 that potentially could influence drug response. The SNP rs6311 and

rs6313 are in complete linkage disequilibrium in the Caucasian population (the *A* and *T* alleles always appear together). It was found that the frequency of the *AA*/*TT* genotype group of 5*HTR2A* rs6311/rs6313 was almost 3-fold higher in the BR group (45%) compared to the WR group (15%). An odds ratio showed a statistically significant ($p = 0.042$) relationship between genotype and ADE susceptibility. Therefore, the present results suggest that *AA*/*TT* genotype may be associated with aripiprazole adverse events. However, a meta-analysis by Lin et al. demonstrated that the *T* allele of rs6313 correlated with a better response to antidepressants [37]. Other studies uncovered that the *GG* genotype of rs6311 had reduced mRNA levels compared with *AA* and *GA* genotype subjects [38], and higher receptor density was observed in a healthy control group with the *AA* genotype [39]. In addition, unlike the *T* allele, the *C* allele of rs6313 reduced the mRNA level and decreased protein expression [38]. It is postulated that epigenetic regulation can also influence the *5HTR2A* expression. The *CC* genotype (rs6313) was related to reduced post-synaptic serotonin receptor expression, probably due to the cytosine methylation at the polymorphic site [40]. Considering the above, it was postulated that the *AA/TT* genotype observed in the study patients may result in higher receptor density and possibly affect drug response. However, further studies are needed to confirm the association between *HTR2A* combined homozygous status and susceptibility to ADEs after aripiprazole treatment.

Conclusions

In conclusion, the present results indicate that the *G* allele of the *COMT* gene might increase susceptibility to side effects. The authors speculated that alleles of the *5HTR2A* gene may be related to adverse drug effects. However, this supposition should be additionally confirmed by large-scale studies. The main limitation of the present study is the low number of individuals in the BR group. In addition, the authors did not measure the concentration of aripiprazole and its main metabolite, and brain imaging studies to show neurotransmitter

receptor densities were not performed. Therefore, these preliminary findings should be interpreted with caution.

Article information

Data availability statement: *The data are available at the Department of Genetics CM UAFM.*

Ethics statement: *The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Bioethics Committee of the Andrzej Frycz Modrzewski Krakow University No KBKA/33/O/2021.*

Author contributions: *AS-C: conceptualization, methodology, sample preparation, investigation, analysis, writing, review; BA: sample preparation, investigation, analysis, writing, review; GK, SA, and RA: sample preparation, analysis, writing, review.*

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Conflict of interest: *The authors declare no competing interests.*

Supplementary material: *The supporting information contains the description of DNA genotyping and Tables S1, S2, S3, and S4.*

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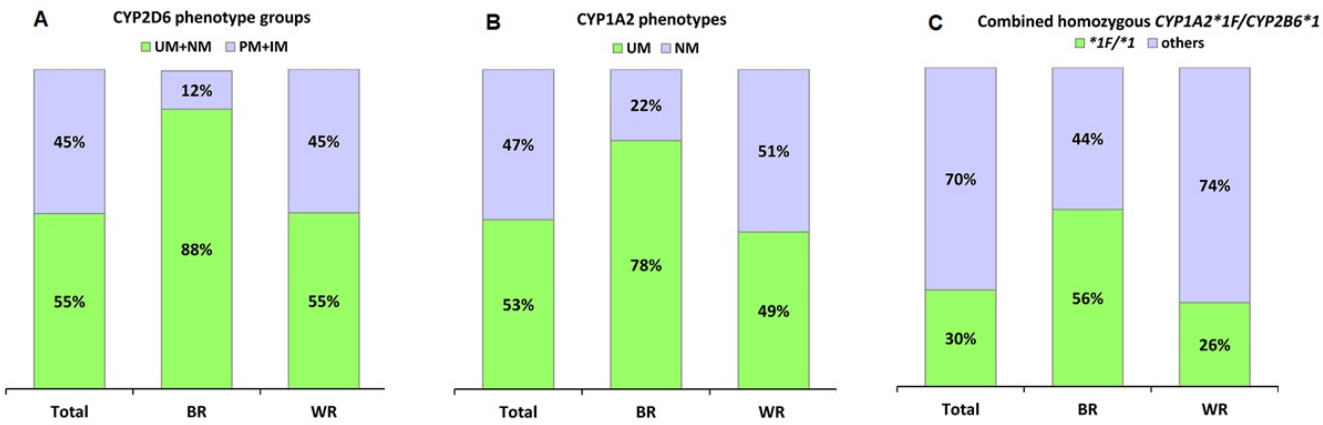

Figure 1. The frequency of CYP phenotypes or genotypes. BR — badly-reacting group, WR — well-reacting group

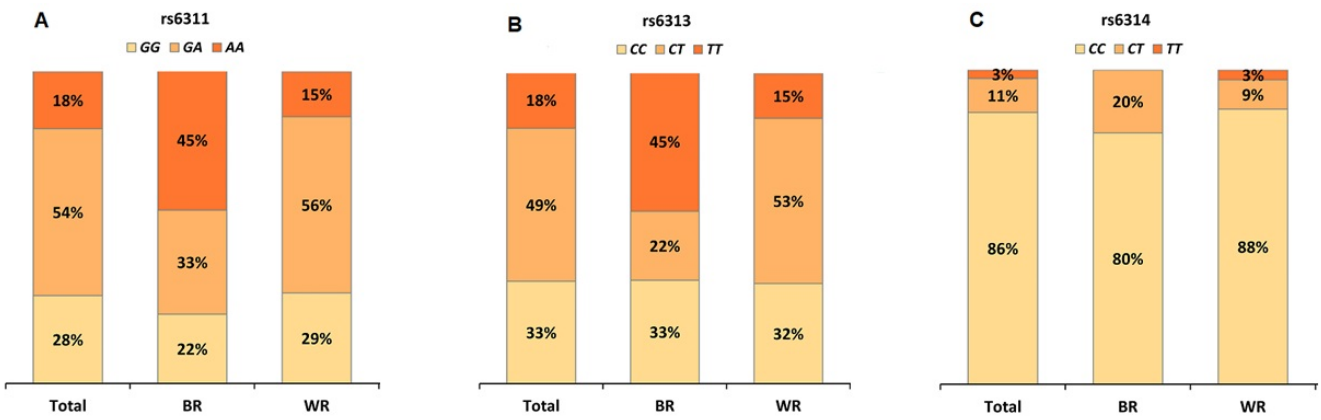

Figure 2. The frequency of *5HTR2A* genotypes. BR — badly-reacting group, WR — well-reacting group

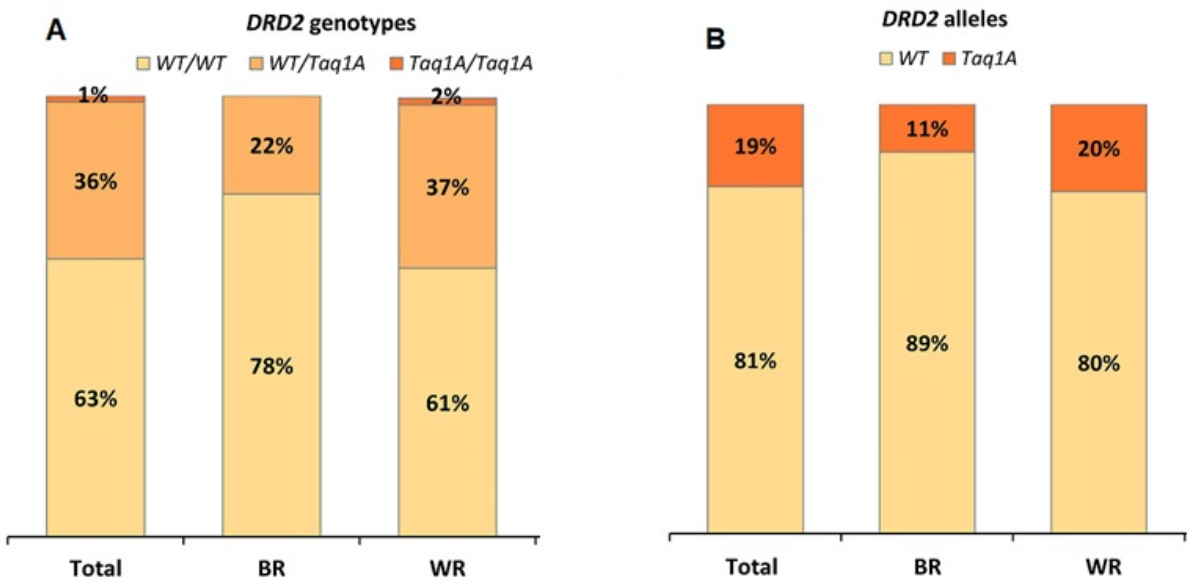

Figure 3. The frequency of *DRD2* genotypes and alleles. BR — badly-reacting group, WR — well-reacting group

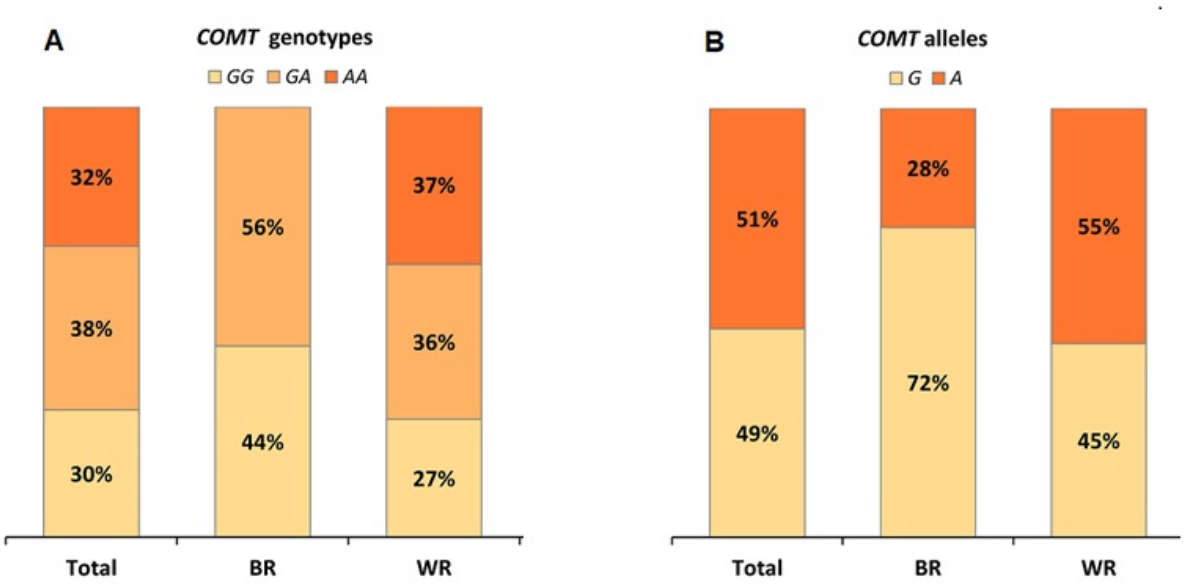

Figure 4. The frequency of *COMT* genotypes and alleles. BR — badly-reacting group, WR — well-reacting group

Table 1. Demographic and clinical parameters of studied patient groups

Group		n (%)	Age (y)	Weight (kg)	Height (m)	BMI (kg/m^2)	ARI dose [mg]	Duration of ARI therapy (n / y)
WR	All	64 (100)	35.98 (± 10.09)	82.68 (±17.54)	1.74 (± 0.10)	26.74 (± 96.42)	Oral / 2.5–30 / day Oral / 7.5–30 / day LAI / Once–monthly / 400	9 / > 1 19 / > 1 36 / < 1
	Males	41 (67)						
	Females	23 (33)						
BR	All	10 (100)	35.30 (± 12.54)	74.85 (± 20.01)	1.69 (± 0.10)	25.95 (± 4.71)	Oral / 3.75–30 / day LAI / Once-monthly / 400	5 / > 1 5 / < 1
	Males	6 (60)						
	Females	4 (40)						
			p = 0.270	**p = 0.437**	**p = 0.387**	**p = 0.347**		

N — number, y — year, BMI — body mass index, LAI — long-acting injection
BR — badly reacting group (aripiprazole has been replaced by another drug due to adverse effects)
WR — well-reacting group (the sum of ARI and ARI+SGA subgroups)

Table 2. Alleles/haplotypes/genotypes/phenotypes frequencies of the selected polymorphisms and associated p values for Chi-Square tests for deviation from Hardy–Weinberg equilibrium

Gene/variants	Genotypes / Haplotype / Alleles	Frequency			χ^2	p-value
		Total	BR	WR		
ABCB1 rs1045642	*C*	0.493	0,650	0.468	0,52	0,471
	T	0.507	0,350	0.532		
	C/C	26%	30%	26%		
	C/T	46%	70%	42%		
	T/T	28%	0%	32%		
COMT rs4680	*G*	0.486	0.722	0.452	4,05	**0.042**
	A	0.514	0.278	0.548		
	G / G	30%	44%	27%		
	G / A	38%	56%	35%		
	A / A	32%	0%	37%		
DRD2 rs1800497	*WT*	0.808	0.889	0.797	1,72	0,190
	Taq1A	0.192	0.111	0.203		
	WT / WT	63%	78%	61%		
	WT / Taq1A	36%	22%	38%		
	Taq1A / Taq1A	1%	0%	2%		
5HTR2A rs6311	*G*	0,549	0.389	0,573	0,47	0,493
	A	0,451	0.611	0,427		
	G / G	28%	22%	29%		
	G / A	54%	33%	56%		
	A / A	18%	44%	15%		
5HTR2A rs6313	*C*	0.,570	0,444	0,589	0,02	0.791
	T	0,420	0,556	0,411		
	C / C	31%	33%	31%		
	C / T	50%	22%	54%		
	T / T	19%	44%	15%		
5HTR2A rs6314	*C*	0,919	0,900	0,922	5,94	**0,015**
	T	0,081	0,100	0,078		
	C / C	86%	80%	88%		
	C / T	11%	20%	9%		
	T / T	3%	0%	3%		
CYP2D6	UM + NM	56%	88%	51%	N/A	N/A
	IM + PM	44%	13%	49%		
CYP3A	NM	9%	11%	8%	N/A	N/A
	IM	84%	78%	85%		
	PM	7%	11%	7%		
*CYP1A2/CYP2B6 *1F/*1F/*1/*1*	**1F / *1*	28%	67%	23%	N/A	N/A
	others	72%	30%	77%		

BR — badly reacting group (aripiprazole has been replaced by another drug due to adverse effects); WR — well-reacting group (the sum of ARI and ARI+SGA subgroups).
Phenotypes: UM — ultrarapid metabolizer; NM — normal metabolizer; IM — intermediate metabolizer; PM — poor metabolizer; N/A — not applicable

Table 3. The odds ratio for the selected polymorphisms

Gene/variants	**Alleles / Haplotypes / Genotypes / Phenotypes**	**OR BR vs. WR**	**95% CI**	**p-value**
ABCB1 rs1045642	*C*	2.11	0.79−5.65	0.136
	T	0.47	0.18−1.27	0.136
	CC vs. *CT* + *TT*	1.23	0.28−5.34	0.780
COMT rs4680	*G*	**3.16**	1.06−9.39	**0.039**
	A	**0.32**	0.11−0.94	**0.039**
	GG vs. *GA* + *AA*	2.12	0.51−8.83	0.303
*CYP1A2/CYP2B6 *1F/*1F/*1/*1*	**1F / *1* vs. others	3.50	0.82−14.79	0.088
CYP2D6	UM + NM vs. IM + PM	7.00	0.81−60.93	0.078
DRD2 rs1800497	*WT*	2.04	0.44−9.43	0.302
	Taq1	0.49	0.11−2.27	0.362
	WT / WT vs. *WT / Taq1*	2.24	0.43−11.68	0.337
	WT / Taq1 vs. *WT / WT*	0.45	0.09−2.32	0.337
5HTR2A rs6311	*G*	0.48	0.17−1.31	0.150
	A	2.11	0.77−5.79	0.150
	GG vs. *GA* + *AA*	0.70	0.13−3.69	0.673
	AA vs. *GG* + *GA*	**4.71**	1.06−20.96	**0.042**
5HTR2A rs6313	*C*	0.57	0.21−1.53	0.261
	T	1.77	0.65−4.78	0.261
	CC vs. *CT* + *TT*	1.05	0.24−4.63	0.949
	TT vs. *CC* + *CT*	**4.71**	1.06−20.96	**0.042**
5HTR2A rs6314	*C*	0.763	0.12−3.77	0.740
	T	1.311	0.27−6.48	0.740
	CC vs. *CT* + *TT*	0.571	0.11−3.18	0.523
	TT vs. *CC* + *CT*	1.19	0.05−26.58	0.912
5HTR2A rs6311/rs6313	*AA / TT* vs. others	**4.71**	1.06−20.96	**0.042**

BR — badly reacting group (aripiprazole has been replaced by another drug due to adverse effects); WR — well-reacting group (the sum of ARI and ARI + SGA subgroups)

Supplementary Tables

Table S1. Primers and conditions of PCR-RFLP analysis

Table S2. List of all analyzed genes and polymorphisms

Table S3. Demographic and clinical parameters of studied groups and subgroups

Table S4. Genotype/haplotype/phenotype frequencies of all analyzed polymorphisms