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A Preliminary Investigation of Genetic Variants Linked to Aripiprazole-Induced Adverse Effects

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ABSTRACT

The hepatic enzymes CYP2D6 and CYP3A4 are primarily accountable for the transformation of the atypical antipsychotic medication aripirazole. It is recommended that CYP2D6-poor metabolizers adjust their dosage. Most adult patients handle aripiprazole well; however, occasionally, some people may experience negative side effects that lead to the medication being stopped. According to recent research, the effectiveness and safety of pharmacological therapy may be correlated with additional genes implicated in drug metabolism, transport, and excretion. The goal of this research was to compare the genetic variations of patients who had good treatment tolerance and those who had side effects that caused them to stop taking the medication. 20 genes were genetically profiled using the MassARRAY technique. The ABCB1, COMT, CYP2D6, CYP3A4, and CYP3A5 polymorphisms did not differ between the two groups. Suddenly, we found that the group with negative effects had a higher frequency of CYP1A2 ultra-rapid metabolizers, as well as homozygous CYP1A21F/*1F (78% vs. 45%) and CYP2B6*1/*1 (80% vs. 45%). Furthermore, the only individuals experiencing negative effects have been found to have a mixed homozygous condition (CYP1A2*1F/*1F/CYP2B6*1/*1). The potential involvement of CYP1A2 and CYP2B6 enzymes in the aripiprazole metabolism has not yet been explored. Accordingly, our first findings suggest that the CYP1A2*F and/or CYP2B6*1 alleles could be involved in the negative effects of aripiprazole. Therefore, further studies with larger sample sizes are needed to validate our results.

Keywords: Aripiprazole, Adverse drug effect, Cytochrome P450, Pharmacogenetics, Phenotype, SNP polymorphisms

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Introduction

Many psychotic illnesses, such as schizophrenia, bipolar disorder, severe depression, and irritability linked to autism disorder, are treated with aripiprazole (ARI). A third-generation medication, ARI is an atypical antipsychotic [1]. Although it has a high affinity for D2, D3, 5-HT1A, and 5-HT2A receptors, it may bind to a variety of receptors. The feature of ARI that sets it apart from other antipsychotics is its partial agonism at serotonin receptors (5-HT1A and 5-HT2C) and dopamine receptors (D2 and D3) [2, 3]. The ACBC1 transporter and CYP3A5 enzyme play a minor role in the pharmacokinetics of ARI, whereas CYP2D6 and CYP3A4 enzymes play a major role [4, 5]. The active metabolite of the parent medication is dehydro-aripiprazole (D-ARI). To improve the drug's reaction, the Food and Drug Administration (FDA) advises adjusting the dosage based on the metabolic state of CYP2D6 as predicted by genetics [6]. For CYP2D6 PMs, half of the usual dosage is advised; for PMs who concurrently take powerful CYP3A4 inhibitors for longer than 14 days, the suggested dosage may

even be as low as 25%. There is no discernible impact of smoking, age, or gender on the pharmacokinetics of ARI (EMEA/H/C/002755/0000).

ARI is more efficient than other antipsychotics and is often well tolerated by individuals with autism spectrum, bipolar disorder, and schizophrenia. But in certain individuals, negative impacts from ARI medication might be observed, such as tardive dyskinesia, akathisia, attention issues, restlessness, somnolence, and sedative fatigue [7]. Weight gain is possible in certain people using aripiprazole, however, metabolic markers such as total glucose and lipids are not substantially changed [8].

Many investigations have proposed a link between ARI responsiveness and negative impacts during medication therapy and polymorphisms in various genes, including ABCB1, DRD2, and 5-HTRs [5, 9, 10]. Even though ARI is not a substrate for CYP1A2 or CYP2B6, the research conducted by Koller *et al.* [11] revealed that CYP1A2 gene polymorphism can affect the pharmacokinetics of ARI and D-ARI and that CYP1A2 phenotype can be linked to negative pharmacological effects. Surprisingly, the brain expresses the CYP2B6 enzyme, which is comparable to CYP1A2 and may play a role in the metabolism of CNS-acting medicines and neurological negative impacts of specific pharmaceuticals [12]. But as of yet, it is unknown how CYP1A2 and/or CYP2B6 enzymes function in the metabolism of ARI.

The current study sought to ascertain whether patients receiving aripiprazole monotherapy and patients experiencing negative medication impacts differed in the allocation of polymorphic variations of genes implicated in medication metabolism, transport, and mechanism of action.

Materials and Methods

Patients

The research included 19 patients of Caucasian descent, 9 of whom were men and 10 of whom were women. The majority of the patients (77%) had a personality disorder (13%) and bipolar illness (10%), being less common. The Babinski University Hospital in Krakow, Poland, served as the source of all patients. Before their inclusion in the study, all individuals gave their informed consent. The following were the requirements for inclusion: (1) current or discontinued aripiprazole (ARI) treatment, and (2) age range of 18–60 years. The following were the criteria for exclusion: (1) polypharmacy including medications classified as CYP2D6 inhibitors or CYP3A4 inducers or inhibitors, (2) central nervous system organic lesions, and (3) mental retardation. Two subgroups of patients were created: the first group got simply ARI, while the second group, known as ARI-ADE, had previously had ARI treatment but had it discontinued owing to negative medication impacts.

Genotyping

DNA was taken out utilizing the QIAamp DNA Blood Mini Kit (Qiagen) from 200 µl of whole blood. Agarose gel electrophoresis was used to evaluate the quality, and spectrophotometry was used to determine the amount in a NanoDrop One (Thermo Scientific). Thermo Scientific's Qubit dsDNA BR test kit and Invitrogen QubitTM 3.0 Fluorometer were also used for DNA quantification, following the guidelines provided by the manufacturer. All patients were genotyped utilizing the MassArray® System (Agena Bioscience) for 68 SNPs/INDELs across 20 genes, in addition to five CYP2D6 CNV targets included in the Agena VeriDose Core panel and hybrid CYP2D6 alleles contained in the Agena VeriDose CYP2D6 CNV Panel.

Translation of Genotype into Phenotype

To make it easier to comprehend the CYP2D6 and CYP1A2 genotypes, an activity score (AS) depending on the functioning of the alleles was used. No-function alleles have a value of 0, fall-function alleles have a value of 0.25 or 0.5, and normal-function alleles have a value of 1. The AS of a genotype is calculated by adding its values. The following characteristics are identified by the Clinical Pharmacogenetics Implementation Consortium (CPIC): 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.

Based on their functioning, CYP1A2 alleles were given the following values: 0.5 to *1C, 1 to *1, 1.25 to *1B, and 1.5 to *1F [13]. The total of the functioning values was used to predict the CYP1A2 phenotypes: NM 1.75-2.5; UM 2.75-3; PM 1-1.5 [14]

The CYP3A phenotype is a combination of the CYP3A4 and CYP3A5 genotypes. The star alleles were identified as CYP3A4*1 and CYP3A5*1 normal alleles, CYP3A4*22 decreased activity one allele, and CYP3A5*3 no

activity one allele. Based on genetic clusters, the traits listed below were identified: IM for CYP3A4*1/*1 and CYP3A5*3/*3; IM for CYP3A4*22/*22 or CYP3A4*1/*22 and CYP3A5*1/*1 or CYP3A5*1/*3; NM for CYP3A4*1/*1 and CYP3A5*1/*1 or CYP3A5*1/*3; PM for CYP3A4*22/*22 or CYP3A4*1/*22 and CYP3A5*1/*1 or CYP3A5.

Statistical Analysis

Utilizing GraphPad Prism 9.4.1 (GraphPad Software, Inc.), statistical analyses were conducted. P-values < 0.05 were considered statistically significant. The study utilized a T-test to compare demographic variables. The Chi-square test was used to analyze the Hardy-Weinberg equilibrium. With the use of an odds ratio (OR) and a 95% CI for the odds ratio, the association between genotypes, polymorphic alleles, and pharmaceutical response was assessed.

Results and Discussion

Males and females in the group under study had similar mean ages (37.4 ± 8.6 years and 33.4 ± 12.8 years), with no substantial variance (P = 0.435). Table 1 displays the demographic information.

Table 1. Demographic and clinical parameters of the studied patient groups.

Group		N (%)	Age (y)	Weight (kg)	Height (m)	BMI (kg/m$^{2)}$	ARI dose [mg]	Duration of ARI therapy (N/y)	Adverse drug effects
ARI	All	9 (100)	36.56 (± 11.66)	70.71 (± 27.23)	1.66 (± 0.11)	24.84 (± 6.54)	2.5 - 30	5/ > 1 4/ < 1	Not observed
	Males	3 (33)							
	Females	6 (67)							
ARI-ADE	All	10 (100)	34.20 (± 10.67)	72.29 (± 19.64)	1.67 (± 0.10)	25.5 (± 4.58)	3.75 - 30	4/ > 1 6/ < 1	Agitation, anxiety, somnolence, hypertension, akathisia, increased sleep latency, weight gain, reduced motor activity, and concentration difficulties.
	Males	6 (60)							
	Females	4 (40)							
			P = 0.652	**P = 0.904**	**P = 0.838**	**P = 0.831**			

N - Number
y – year

Nineteen blood samples taken from patients were subjected to genetic profiles. All genotypes in the research population, except the CYP2D6 polymorphism, were in the Hardy-Weinberg equilibrium (P ≥ 0.05). We concentrated our investigation primarily on genes that were or likely were engaged in aripiprazole metabolism, absorption, and excretion. **Table 2** displays allele and genotype frequencies for the ARI and ARI-ADE groups.

Table 2. Genotype frequencies of selected polymorphisms.

Gene/variants	Genotypes/ haplotype/ alleles	Frequency		OR	95% CI
		ARI	ARI-ADE		
ABCB1 rs1045642	*C*	0.500	0.650	2.00	0.52-7.69
	T	0.500	0.350	0.50	0.13-1.92
	C/C	22%	30%		
	C/T	56%	70%		
	T/T	22%	0 %		
COMT rs4680	*G*	0.500	0.688	2.20	0.54-8.96

	A	0.500	0.312	0.45	0.11-1.85
	G/G	22%	37%		
	G/A	56%	62%		
	A/A	22%	0%		
CYP1A2	**1A*	0.333	0.111	0.25	0.04-1.46
	**1F*	0.667	0.889	**4.00**	0.68-23.41
	**1A/*1A*	11%	0%		
	**1A/*1F*	45%	22%		
	**1F/*1F*	45%	78%		
CYP2B6	**1*	0.667	0.900	**4.50**	0.77-26.13
	**6*	0.333	0.100	0.22	0.04-1.29
	**1/*1*	45%	80%		
	**1/*6*	45%	20%		
	**6/*6*	11%	0%		
DRD2 rs1800497	*WT*	0.778	0.850	1.62	0.31-8.48
	Taq1A	0.222	0.150	0.62	0.11-3.23
	WT/WT	56%	70%		
	WT/Taq1A	44%	30%		
	Taq1A/Taq1A	0%	0%		

ARI: patients with aripiprazole monotherapy
ARI-ADE: patients experiencing adverse drug effects and aripiprazole withdrawal

There were no homozygous SNP genotypes for the ABCB1 and COMT gene polymorphisms in the ARI-ADE group (TT and AA, respectively) (**Table 2**). Concerning the CYP1A2 polymorphism, it is noteworthy that the frequency of the *1F allele, which is linked to elevated activity, was greater than that of the ARI group (0.889 vs. 0.667). In the ARI-ADE group, the wild-type *1A/*1A genotype was absent; 78% of patients in this group were found to be homozygous (*1F/*1F). Both normal and ultra-rapid metabolizers were the phenotypic groupings assigned to the patient based on their CYP1A2 genotype. The NM group only included 22% of patients with negative medication effects. Additionally, compared to the ARI group, we discovered that patients in the ARI-ADE group had a higher prevalence of the UM phenotype (78% vs. 45%, respectively) (**Figure 1a**). Adverse medication's impact may be more likely to emerge if the CYP1A2*1F allele is present (OR = 4.00, 95% CI: 0.68-23.41). According to a comparison of CYP2B6 genotype frequency, 80% of patients in the ARI-ADE group were wild-type homozygous (*1/*1), whereas 45% of patients in the ARI group shared the same genotype. According to the odds ratio, the CYP2B6*1 allele may raise the likelihood of experiencing negative medication side effects (OR = 4.50, 95% CI: 0.77-26.13). The ARI and ARI-ADE groups had comparable distributions of functional alleles (*1 and *2) of the CYP2D6 gene (64% and 63%, respectively) (**Figure 1b**). We divided individuals into two phenotypic subgroups—normal and intermediate metabolizers—based on their genetics. The ARI-ADE group had a higher frequency of the NM phenotype than the ARI group (75% vs. 43%, respectively) (**Figure 1c**). About the combined CYP3A phenotype, 75% of patients in the ARI-ADE group and all patients in the ARI group had the IM phenotype (**Figure 1d**).

In all research groups, we only detected two genotypes for DRD2 rs1800497: wild-type homozygotes (WT/WT) and heterozygotes (WT/Taq1A). The DRD2 WT/WT genotype was found in up to 70% of patients in the ARI-ADE group and 56% of patients in the ARI group.

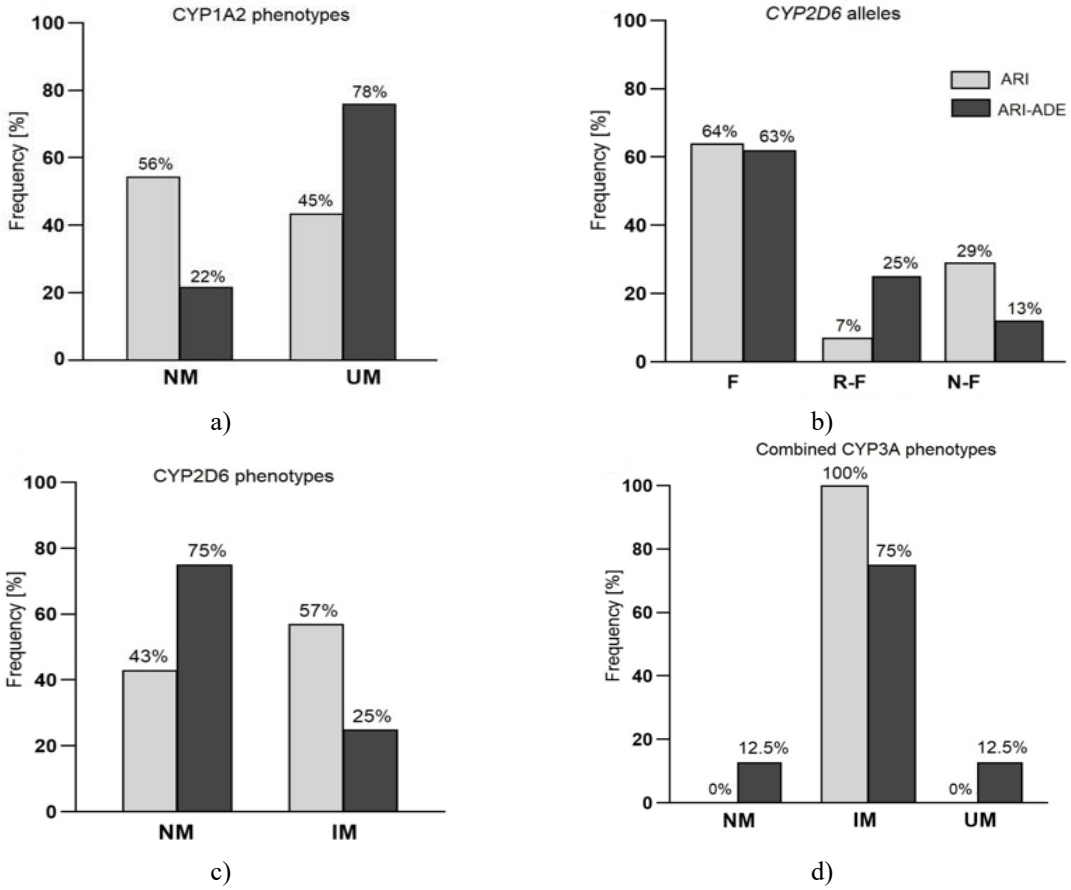

Figure 1. Allele and phenotypic frequencies of certain CYPs; ARI-ADE: patients who are suffering negative medication effects and aripiprazole withdrawal; ARI: patients receiving aripiprazole monotherapy; normal metabolizers (NM), intermediate metabolizers (IM), and ultra-rapid metabolizers (UM); F: functional alleles (sum of *1 and *2), R: reduced-function alleles (sum of *9, *10, and *41), and N: non-function alleles (sum of *4 and *5).

In this investigation, we conducted genetic profiling on two patient groups: the ARI-ADE group, which consisted of individuals experiencing negative medication effects following aripiprazole treatment, and the ARI group, which consisted of patients who received aripiprazole monotherapy. We primarily looked at genetic differences in dopamine-degrading and drug-metabolizing enzymes and transporters. A member of the ABC protein transporter superfamily is encoded by the ABCB1 gene. Drug distribution, absorption, and excretion are all significantly impacted by this transporter [15, 16]. Protein expression is influenced by the ABCB1 rs1045642 (3435C > T) polymorphism. TT homozygous individuals showed greater Tmax of ARI and D-ARI, and carriers of the T allele are expected to have poor transporter expression [13]. The COMT gene-encoded enzyme, in turn, plays a role in the removal of dopamine from the human brain's prefrontal cortex. Protein quantity and enzyme activity were impacted by the substitution of valine to methionine (Val158Met) caused by the SNP polymorphism rs4680 (472G > A) [17]. The AA genotype is linked to decreased enzymatic activity, which raises dopamine levels.

Our findings demonstrated that, except for mutant homozygous (TT and AA, respectively), which were exclusively seen in the ARI group, there were no variations in the distribution of the ABCB1 rs1045642 and COMT rs4680 genotypes between the two patient groups. Consequently, it appears that these two examined polymorphisms had nothing to do with negative pharmacological effects.

We also examined genetic differences in the genes encoding the ARI metabolism-related enzymes CYP2D6, CYP3A4, and CYP3A5. IM and PM patients treated with ARI are more likely to experience extrapyramidal responses, nausea, or vomiting, and non-functional alleles are thought to be linked to these side effects [5, 18, 19]. We discovered that in the ARI group, the prevalence of CYP2D6-deficient alleles was more than doubled as in the ARI-ADE group (29% vs. 13%, respectively), although the proportion of operational alleles (*1 plus *2) was

comparable and represented over sixty percent in both of our groups. Furthermore, the majority of patients with ADEs were NM, and we only projected two phenotypes (NM and IM) in both groups according to the patient's genotypes. Similarly, we demonstrated that IM was the predominant trait in both groups by combining the CYP3A4 and CYP3A5 genotypes. Accordingly, our findings indicated that negative medication effects were unlikely to be linked to normal or intermediate metabolizer status concerning the CYP2D6 and CYP3A genes.
The prevalence of CYP1A2 and CYP2B6 polymorphisms in patients receiving aripiprazole monotherapy and those who encountered negative medication impacts was also assessed. It's interesting to note that we discovered variations in the ARI and ARI-ADE groups' CYP1A2 and CYP2B6 genotype frequencies. A greater frequency of the UM phenotype was also associated with the CYP1A2*1F/*1F genotype, which was more common in the ARI-ADE group (78% vs. 45% in the ARI group). In terms of the CYP2B6 genotype, 80% of patients in the ARI-ADE group were homozygous for CYP2B6*1 (wildtype), which meant that they were considered typical metabolizers. It is important to note that 70% of patients in the ARI-ADE group had both CYP1A2*1F/*1F and CYP2B6*1/*1; however, this combination genotype was not observed in the ARI group. It is presently very complicated to provide a definitive description for the genotype of the patient and sensitivity to the side effects of the medicine because aripiprazole is never a substrate for the enzymes CYP1A2 and CYP2B6 (EMEA/H/C/002755/0000). Despite this, Koller *et al.* [13] recently discovered that ARI and D-ARI metabolism can be impacted by the CYP1A2 enzyme. Interestingly, as compared to normal metabolizers, the CYP1A2 ultra-rapid metabolizer exhibited considerably greater D-ARI T1/2, ARI AUC, and Cmax [13]. Additionally, it was shown that NM patients had a greater prevalence of sleeplessness after ARI therapy compared to UM individuals [11]. Patients with increased CYP1A2 activities may be less likely to suffer from mental side effects, according to recent research [20]. The disparity between our results and those of other research may be caused by variations in the experiment groups and the length of aripiprazole medication. This study used mental patients rather than healthy volunteers for genotyping, and our patients received aripiprazole for at least a year rather than only five days. The formation of ADEs might arise from prolonged contact with ARI. Psychiatric patients' brain anatomy and genetic makeup may differ from those of healthy people.
Our study's primary drawback was the small patient population. Furthermore, the serum/plasma concentrations of ARI and D-ARI, and variations in serotonin receptors, have not been assessed. Additionally, other aspects, including food and smoking, were not considered. Consequently, care should be used when interpreting these early findings. Additional research with additional participants is required to improve the statistical reliability of the findings.

Conclusion

In this investigation, we examined genetic variations in individuals with ADEs associated with ARI medication as well as psychiatric patients receiving ARI monotherapy. Our results indicate that although the distribution of CYP2D6, ABCB1, COMT, DRD2, and CYP3A polymorphisms was comparable in both groups, it appears that these polymorphisms cannot be utilized as ADE predictors. Individuals with ADEs were more likely to have homozygous status for CYP1A2*1F and CYP2B6*1 than individuals receiving ARI monotherapy. Furthermore, only ADE patients have the compound genotype CYP1A2*1F/*1F/CYP2B6*1/*1. We suggest that the progression of ADEs to ARI may be influenced by polymorphisms in CYP1A2 and CYP2B6. Nevertheless, more research with a larger patient population is required to validate this correlation.

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Conflict of Interest: None

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