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Review

Frequencies of *ABCB1* Gene Variant Alleles and Their Role in Response to Antipsychotic Therapy in Patients with Schizophrenia Spectrum Disorders: Narrative Review

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Abstract: The ABCB1 transporter protein (also known as P-glycoprotein, P-gp) plays a crucial role in the pharmacokinetics of antipsychotics (APs), determining their bioavailability and distribution in the body. The *ABCB1* genetic polymorphisms significantly contributes to interindividual differences in response to AP therapy in patients with schizophrenia spectrum disorders (SSDs). Increased P-gp functional activity is associated with the development of pseudoresistance to APs, while decreased activity is linked to the development of AP-induced adverse drug reactions. This review aims to systematize current data on the population frequencies of *ABCB1* gene allelic variants that influence the activity of P-gp and to establish a scientific foundation for the development of domestic, ethnically-oriented pharmacogenetic diagnostic test systems. A search was conducted in the databases PubMed, eLIBRARY.RU, Google Scholar, PharmGKB, DrugBank, the Geography of Genetic Variants Browser, ClinVar, dbSNP, SNPedia, Drugs@FDA, Russian State Register of Medicines, the Database of Population Frequencies of Genetic Variants in the Russian Population, the RUSeq Browser, The Rubricator of Clinical Recommendations. Available data on the population frequencies of the most extensively studied high-function (n = 5), low-function (n = 15), and loss-of-function (n = 5) allelic variants of the *ABCB1* gene were retrieved and analyzed. The frequency of variant alleles of the *ABCB1* gene is heterogeneous across different global populations, a critical factor to consider in the development of pharmacogenetic diagnostic test systems. The ethno-territorial heterogeneity of the Russian gene pool necessitates the development and subsequent validation of local (region-specific) pharmacogenetic diagnostic test systems, based on large-scale population studies conducted within specific administrative-territorial units.

Keywords: *antipsychotic, schizophrenia, pharmacogenetics, pharmacogenetic testing, genetic polymorphism, single nucleotide variant, P-glycoprotein, ABCB1, MDR1, pharmacoresistance, pseudoresistance*

1. INTRODUCTION

Antipsychotics (also referred to as "neuroleptics" or "dopamine blockers," APs) occupy a central role in the pharmacotherapy of schizophrenia spectrum disorders (SSDs). Despite this, clinical outcomes of APs use remain heterogeneous [1]. Interindividual variability in APs transport determines differences in their pharmacokinetics and, consequently, impacts the efficacy and safety of AP therapy. This variability is genetically determined and also depends on drug-drug interactions, constituting a primary cause of poor response to APs (pseudoresistance, treatment resistance, adverse drug reactions – ADRs) in the management of SSDs [2,3].

The transport of APs into the brain is regulated at the level of endothelial cells of the blood-brain barrier (BBB) via membrane transporter proteins [3]. Certain proteins of the ABC (ATP-binding cassette) transporter family are

responsible for the active efflux of various compounds of both endogenous and exogenous origin (xenobiotics), including APs. The intensity of efflux transport is a determining factor for achieving sufficient and excessive AP concentrations in the brain and, consequently, for the realization and nature of their pharmacodynamic effect (**Figure 1**). The most extensively studied and clinically relevant efflux transporter protein is ABCB1 (also known as P-glycoprotein, P-gp; multidrug resistance protein 1, MDR1) [4].

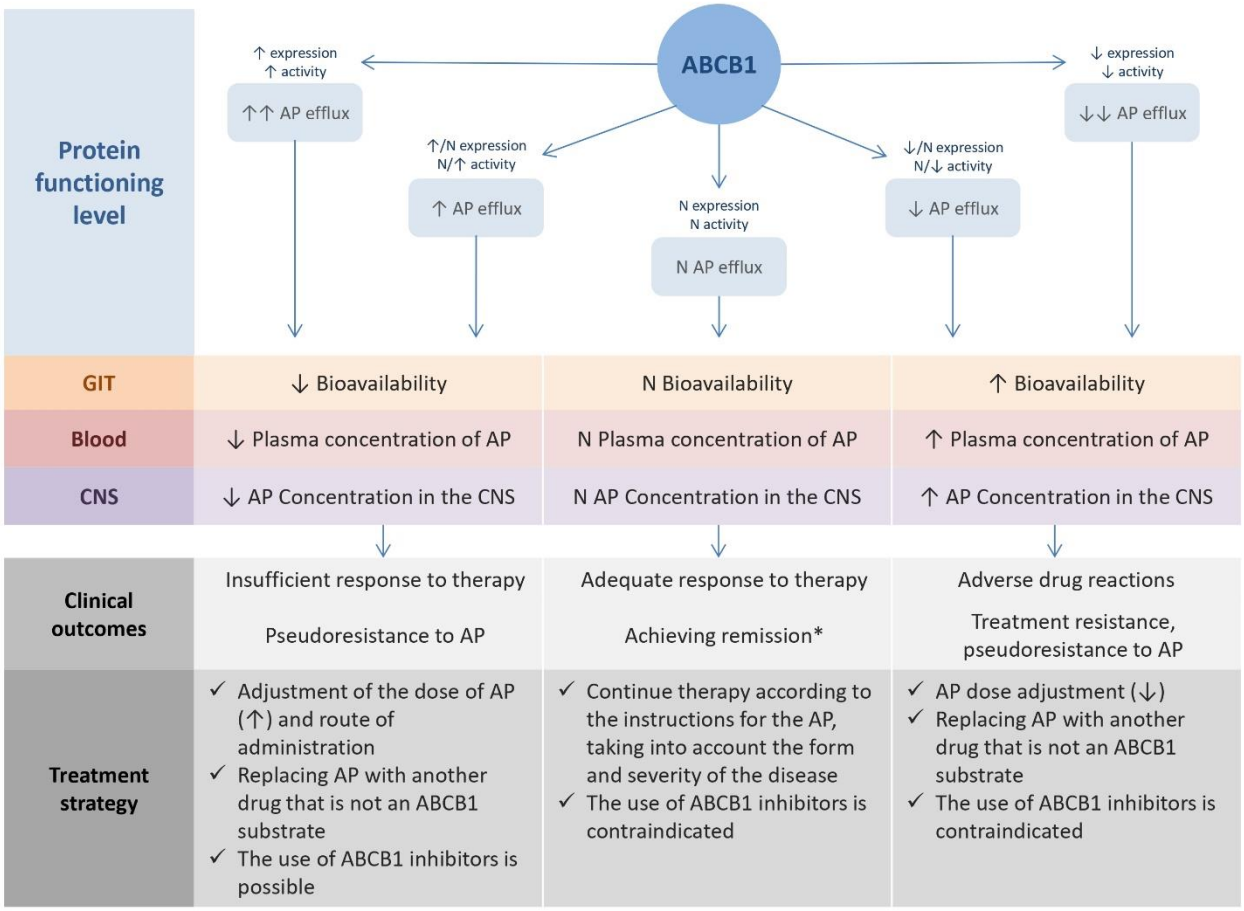

Figure 1. The effect of P-glycoprotein (ABCB1) on the pharmacokinetics of antipsychotics.
The figure was prepared by the authors.
Note: *ABCB1 – ATP binding cassette subfamily B member 1; AP – antipsychotic; N – normal; ↑/↓ – increased/decreased; GIT – gastrointestinal tract; CNS – central nervous system; * A decrease in the response to therapy is possible in the case of genetically determined changes in AP metabolism in the liver (β-oxidation, β-oxidation, glucuronidation) and modification of AP target proteins (receptors in the CNS (cited from [5]).*

P-gp possesses low substrate specificity and thus mediates the active efflux of a broad range of APs (**Table 1**). In addition, the *ABCB1* gene is expressed in the organs of the gastrointestinal tract (small and large intestine, liver, pancreas, gallbladder), kidneys and adrenal glands, and barrier tissues (e.g., the blood-testis and placental barriers). Elevated *ABCB1* expression is characteristic of neoplasms [6]. Overall, this transporter affects the bioavailability, blood concentration, and concentration of APs in target organs.

The regulation of P-gp activity occurs through two main mechanisms: 1) modulation of the *ABCB1* gene expression (locus: 7q21.12, OMIM: 171050) and, consequently, an increase or decrease in the quantity of the P-gp transporter protein; 2) alteration (increase/decrease) of the functional activity of the P-gp transporter protein. APs and other drugs that enhance the functional activity of P-gp are termed inducers, while those that reduce it are termed inhibitors. In turn, inhibitors can be classified as competitive (where a substance is structurally similar to the transporter protein's substrate and binds to its substrate-binding site, thereby blocking access for APs, which can lead to reduced oral bioavailability of APs) and noncompetitive (where a substance is not a P-gp substrate but can modulate its functional activity by interacting with an allosteric site on the protein) [11,12].

Table 1. Interactions between antipsychotics and the P-gp transporter protein [7,8,9,10].

INN	Substrate	Inhibitor	Inducer	FDA	RSRM
Acetophenazine	ND	ND	ND	Discontinued	×
Amisulpride	+	ND	ND	✓	✓
Aripiprazole	+	+	ND	✓	✓
Asenapine	ND	ND	ND	✓	Discontinued
Benperidol	ND	ND	ND	×	×
Blonanserin*	-	ND	ND	×	×
Brexpiprazole	-	*In vitro*, no significance *in vivo*	ND	✓	✓
Cariprazine	-	*in vitro*	ND	✓	✓
Chlorpromazine	+	+	ND	✓	✓
Chlorprothixene	-	+	ND	Discontinued	✓
Clopenthixol	ND	ND	ND	×	×
Clotiapine	ND	ND	ND	×	×
Clozapine	+	+	ND	✓	✓
Droperidol	ND	ND	ND	✓	✓
Flupentixol	-	+	ND	×	✓
Fluphenazine	+	+	ND	✓	✓
Fluspirilene	ND	ND	ND	×	×
Haloperidol	+	+	ND	✓	✓
Iloperidone	ND	+	ND	✓	×
Levomepromazine	+	ND	ND	Discontinued	✓
Loxapine	-	+	ND	✓	×
Lumateperone	ND	ND	ND	✓	×
Lurasidone	ND	+	ND	✓	✓
Melperone	-	ND	ND	×	×
Mesoridazine	ND	ND	ND	Discontinued	×
Molindone	ND	ND	ND	✓	×
Mosapramine**	ND	ND	ND	×	×
Olanzapine	+	+	ND	✓	✓
Paliperidone	+	+	ND	✓	✓
Penfluridol	ND	ND	ND	×	×
Perazine	ND	ND	ND	×	×
Periciazine	ND	ND	ND	×	✓
Perospirone**	ND	+	ND	×	×
Perphenazine	-	+	ND	✓	✓
Pimavanserin	+	ND	ND	✓	×
Pimozide	+	+	ND	✓	×
Pipamperone	ND	ND	ND	×	×
Prochlorperazine	ND	+	ND	✓	×
Promazine	-	ND	ND	×	✓
Quetiapine	+	+	ND	✓	✓
Remoxipride	ND	ND	ND	×	✓
Risperidone	+	ND	ND	✓	✓
Sertindole	ND	ND	ND	×	✓
Sulpiride	+	ND	ND	×	✓
Thioridazine	ND	+	ND	✓	✓
Tiapride	ND	ND	ND	×	✓
Trifluoperazine	ND	+	ND	✓	✓
Triflupromazine	ND	+	ND	Discontinued	×
Xanomeline	ND	+	ND	✓	×
Ziprasidone	+	+	ND	✓	✓
Zotepine	ND	ND	ND	✓	✓
Zuclopenthixol	ND	ND	ND	×	✓

Note: ** Approved in Japan, South Korea and China. ** Approved in Japan. Abbreviations: INN – international nonproprietary name, FDA – Food and Drug Administration (USA), ND – no data; RSRM – Russian State Register of Medicines.*

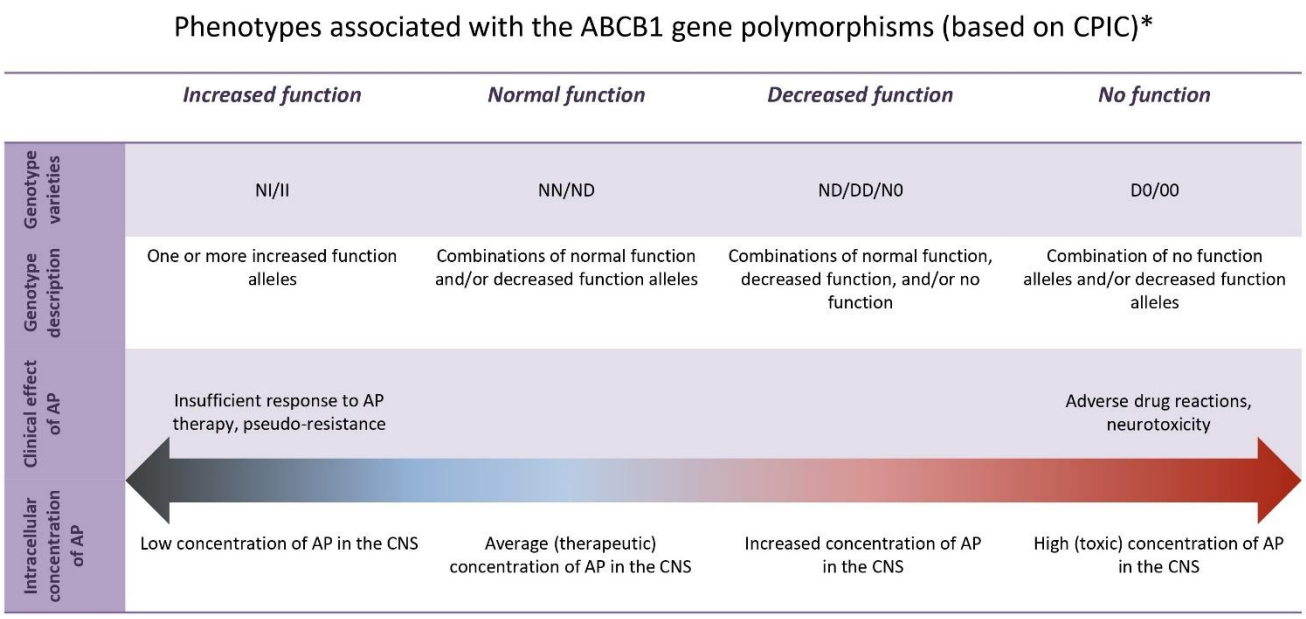

Figure 2. Phenotypes associated with the *ABCB1* gene polymorphisms (based on CPIC [13]).
The figure was prepared by the authors.
Note: *CPIC – Clinical Pharmacogenetics Implementation Consortium, N – normal function; I – increased function; D – decreased function; 0 – no function; AP – antipsychotic; CNS – central nervous system.*

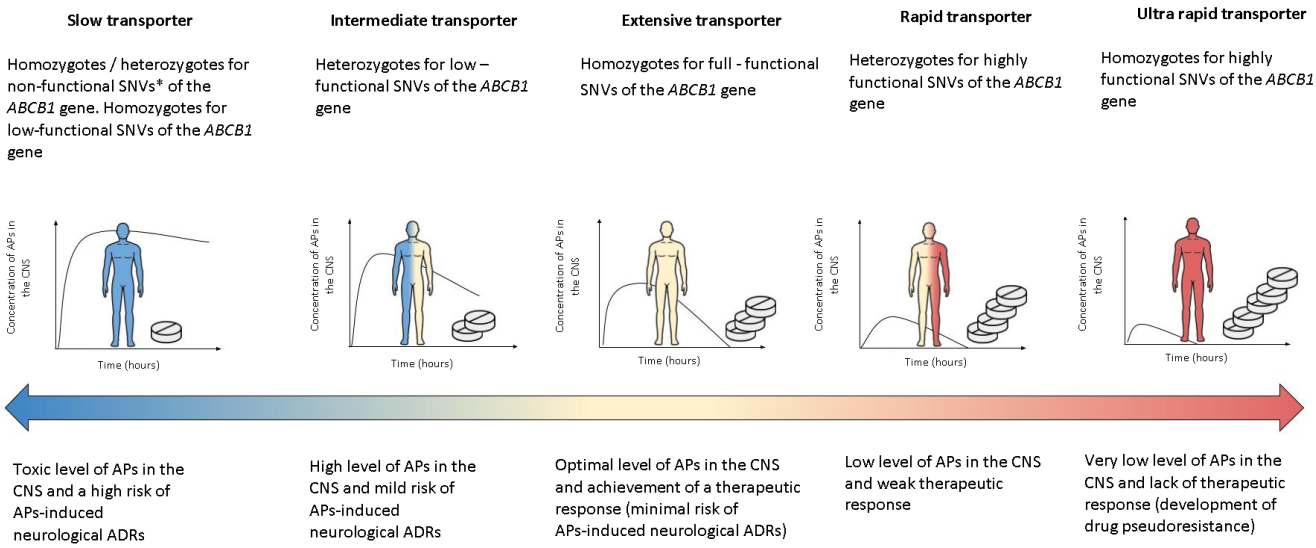

Figure 3. Phenotypes of transporters depending on the pharmacogenetic profile of patients with schizophrenia spectrum disorders depending on single nucleotide variants of the *ABCB1* gene.
The figure was prepared by the authors.
Note: *ABCB1 – ATP-binding cassette protein 1; ADRs – adverse drug reactions; APs – antipsychotics; CNS – central nervous system; SNVs – single nucleotide variants.*

Polymorphisms in the *ABCB1* gene (e.g., single nucleotide variants – SNVs), which determine the expression level and functional activity of its encoded transporter protein, largely account for interindividual differences in pharmacological response and are often the cause of pseudoresistance, therapeutic resistance to APs, or neurotoxic ADRs. Depending on their effect on P-gp function, SNV alleles of the *ABCB1* gene are categorized as high-function, full-function, low-function, or loss-of-function. The carriage of these alleles gives rise to four phenotypic profiles: a transporter protein with normal, increased, decreased, or low (near-zero) function [13].

As illustrated in **Figure 1** and **Figure 2**, increased P-gp function reduces the oral bioavailability of APs and limits their penetration into the brain, which, in turn, leads to an insufficient therapeutic response and the development of a clinical presentation of AP pseudoresistance. Conversely, decreased function of this transporter protein is associated with increased bioavailability and elevated drug concentration in the brain, reaching toxic levels due to impaired efflux across the BBB from the brain into the systemic circulation. This results in the development of neurological ADRs, also known as neurotoxicity, including extrapyramidal, neurocognitive, and neuroendocrine disorders (**Figure 3**) [4, 14].

However, the frequency of low-, high-, and loss-of-function SNV alleles can vary across different world regions and ethnic groups [16,17], a critical factor to consider when developing domestic pharmacogenetic diagnostic test systems. **The aim of this review** is to update the current knowledge on the frequency of variant alleles of the *ABCB1* gene that may affect the rate of AP-efflux across the BBB and increase the risk of neurotoxicity and pseudoresistance in patients with SSDs.

2. MATERIALS AND METHODS

A search and analysis of publications for the period 2020–2025 was conducted in the PubMed, eLIBRARY.RU, and Google Scholar databases. The Introduction and Discussion include references to publications issued prior to 2020 that are of historical interest. The supplementary materials (figures and tables), as well as the Results section, are based on data from open-access information resources, including: PharmGKB, DrugBank, Geography of Genetic Variants Browser, ClinVar, dbSNP, SNPedia, Drugs@FDA, the State Register of Medicines, the Database of Population Frequencies of Genetic Variants in the Russian Population, the RUSeq Browser, The Rubricator of Clinical Recommendations.

3. RESULTS

As a result of this study, available data on population minor (also known as variable or alternative) allele frequencies (MAF) have been retrieved and analyzed. This includes data for the most extensively studied high-function (n = 5, **Table 2**), low-function (n = 15, **Table 3**), and loss-of-function (n = 5, **Table 4**) SNV alleles of the *ABCB1* gene.

These variants may be associated with interindividual differences in response to therapy with both first- and subsequent-generation APs, including pseudoresistance, therapeutic resistance, and neurotoxicity, respectively [3,18]. In addition, 26 SNVs were identified for which the impact on P-gp functional activity has not been studied or for which data from genetic association studies are unavailable (**Table 5**). Notably, the MAF of *ABCB1* gene variants, which encodes the P-gp, varies widely across different countries, as well as among ethnic and racial groups within a single country.

3.1. Population Frequencies of High-Function Allelic Variants of the ABCB1 Gene

Data were obtained on 5 high-function allelic variants of the *ABCB1* gene (**Table 2**): rs2032582 (chr7:87160618 A>C, 2677G>T), rs1882478 (chr7:87137018 C>T), rs2235047 (chr7:87138532 A>C), rs2235048 (chr7:87509195 T>C), rs6949448 (chr7:87141814 C>T). All mentioned SNVs exhibit a high population frequency in East Asian countries (MAF ranging from 0.37 in Japan to 0.64 in China).

The highest population frequency in African countries is observed for rs1882478 (MAF ranging from 0.60 in Gambia to 0.67 in Nigeria); in South Asian countries – for rs2032582, rs2235048, and rs6949448 (MAF from 0.56 in Bangladesh to 0.62 in Sri Lanka); and in European and North American countries – for rs2032582, rs2235048, and rs6949448 (MAF from 0.40 in Italy and United Kingdom to 0.57 in Finland).

Table 2. Population frequencies of high-function genetic variants of the *ABCB1* gene [19-21].

rsID	MAF in regions of the world*	MAF in the Russia / Carrier Frequency in the Russia**
rs2032582	**South Asia** (Bangladesh – 0.61; Sri Lanka – 0.62; India – 0.61) **East Asia** (China – 0.44; Japan – 0.41) **Europe** (Finland – 0.44; UK – 0.41; Italy – 0.40) **North America** (USA – 0.42)	0.51 / 0.75 (heterozygote – 0.48; homozygote – 0.27) ****
rs1882478	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.60-0.67 **South Asia** (Bangladesh – 0.24; Pakistan – 0.33; India – 0.24) **East Asia** (China – 0.64; Japan – 0.49) **Europe** (Finland – 0.26; UK – 0.26; Italy – 0.31; Spain – 0.26) **North America** (USA – 0.20)	0.32 / 0.53 (heterozygote – 0.43; homozygote – 0.10)
rs2235047	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.16-0.20 **South Asia** (Bangladesh – 0.15; Pakistan – 0.14; India – 0.11) **East Asia** (China – 0.49; Japan – 0.37) **Europe** (Finland – 0.03; Italy – 0.03; Spain – 0.02) **North and South America** (USA – 0.01, Peru – 0.17) **Caribbean Basin** (Barbados – 0.18)	0.05 / 0.09 (heterozygote – 0.08; homozygote – 0.004)
rs2235048	**South Asia** (Bangladesh – 0.61; Sri Lanka – 0.60; India – 0.60) **East Asia** (China – 0.40; Japan – 0.48) **Europe** (Finland – 0.57; UK – 0.53; Italy – 0.47; Spain – 0.46) **North and South America** (USA – 0.56, Peru – 0.50) **Caribbean Basin** (Barbados – 0.57)	0.45 / 0.69 (heterozygote – 0.49; homozygote – 0.20)
rs6949448	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.13-0.21 **South Asia** (Bangladesh – 0.56; Sri Lanka – 0.60; India – 0.59) **East Asia** (China – 0.42; Japan – 0.42) **Europe** (Finland – 0.44; UK – 0.40; Italy – 0.42; Spain – 0.38) **North and South America** (USA – 0.42; Colombia – 0.45) **Caribbean Basin** (Puerto Rico – 0.40)	0.54 / 0.79 (heterozygote – 0.49; homozygote – 0.29)

Note: ** based on data from Geography of Genetic Variants Browser [19]; ** based on data from the Database of population frequencies of genetic variants in the population of the Russian Federation [20]; *** based on data from RUSeq [21]; **** for chr7:87160618, A>C. Abbreviations: MAF – minor (variant, alternative) allele frequency; UK – United Kingdom of Great Britain and Northern Ireland; USA – United States of America*

In Russian population, the most frequently occurring SNVs are rs2032582, rs1882478, rs2235048, and rs6949448 (MAF ranging from 0.32 to 0.54), while the frequencies of heterozygous and homozygous carriage of these variant alleles vary widely. Thus, for rs6949448, the variant allele carrier frequency is 0.78 (heterozygote – 0.49, homozygote – 0.29); for rs2032582 – 0.75 (heterozygote – 0.48, homozygote – 0.27); for rs2235048 – 0.69 (heterozygote – 0.49, homozygote – 0.20); and for rs1882478 – 0.53 (heterozygote – 0.43, homozygote – 0.10) [20]. The lowest population frequency in Russia is observed for rs2235047 (MAF = 0.05), which is comparable to that in European countries (MAF ranging from 0.02 in Spain to 0.03 in Finland). The carrier frequency of rs2235047 in Russian population is also minimal, amounting to 0.09 (heterozygote – 0.08, homozygote – 0.004).

Table 3. Population frequencies of low-function variants of the *ABCB1* gene [19-21]

rsID	MAF in regions of the world*	MAF in the Russia / Carrier Frequency in the Russia**
rs1128503	**South Asia** (Bangladesh; Sri Lanka – 0.62; India – 0.59) **East Asia** (China – 0.69; Japan – 0.60) **Europe** (Finland, UK, Italy – 0.42) **North America** (USA – 0.42)	0.53 (European Russia – 0.54; Caucasus – 0.51; Eastern Russia – 0.46***) / 0.78 (heterozygote – 0.49; homozygote – 0.29)
rs2032583	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.13-0.25 **South Asia** (Bangladesh – 0.13; Sri Lanka – 0.19; India – 0.21) **East Asia** (China – 0.07; Japan – 0.09) **Europe** (UK – 0.15; Italy, Spain – 0.16) **North America** (USA – 0.13) **Caribbean Basin** (Barbados – 0.21)	0.09 (European Russia – 0.08; Caucasus – 0.13; Eastern Russia – 0.08***) / 0.16 (heterozygote – 0.16; homozygote – 0.01)
rs2235040	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.12-0.21 **South Asia** (Bangladesh – 0.61; Sri Lanka – 0.19; India – 0.21) **East Asia** (China – 0.07; Japan – 0.09) **Europe** (UK – 0.15; Italy – 0.16; Spain – 0.15) **North America** (USA – 0.13)	0.09 (European Russia – 0.08; Caucasus – 0.13; Eastern Russia – 0.08***) / 0.16 (heterozygote – 0.16; homozygote – 0.01)
rs1202186	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.28-0.35 **South Asia** (Bangladesh – 0.13; Sri Lanka – 0.16; India – 0.21) **East Asia** (China – 0.01; Japan – 0.06) **Europe** (Finland – 0.35; UK – 0.36; Italy – 0.32; Spain – 0.35) **North America** (USA – 0.40) **Caribbean Basin** (Barbados – 0.37)	0.72 / 0.92 (heterozygote – 0.40; homozygote – 0.52)
rs2091766	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.42-0.53 **South Asia** (Bangladesh – 0.19; Sri Lanka – 0.16; India – 0.20) **East Asia** (China – 0.30; Japan – 0.30) **Europe** (Finland – 0.44; UK – 0.36; Italy – 0.38; Spain – 0.44) **North and South America** (USA – 0.39; Peru – 0.56)	0.41 / 0.65 (heterozygote – 0.48; homozygote – 0.17)
rs2235035	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.18-0.22 **South Asia** (Bangladesh – 0.21; Pakistan – 0.30; India – 0.19) **East Asia** (China – 0.30; Japan – 0.30) **Europe** (Finland – 0.33; UK – 0.30; Italy – 0.31; Spain – 0.36) **North and South America** (USA – 0.27; Peru – 0.55)	0.37 / 0.60 (heterozygote – 0.46; homozygote – 0.14)
rs2235046	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.15-0.27 **South Asia** (Bangladesh – 0.66; Sri Lanka – 0.63; India – 0.61) **East Asia** (China – 0.68; Japan – 0.60) **Europe** (Finland – 0.48; UK – 0.43; Italy – 0.43; Spain – 0.37) **North and South America** (USA – 0.44; Colombia – 0.43)	0.51 / 0.76 (heterozygote – 0.50; homozygote – 0.26)
rs2235067	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.13-0.22 **South Asia** (Bangladesh – 0.13; Sri Lanka – 0.18; India – 0.17) **East Asia** (China – 0.07; Japan – 0.09) **Europe** (Finland – 0.05; UK, Italy, Spain – 0.15) **North America** (USA – 0.13) **Caribbean Basin** (Barbados – 0.19)	0.09 / 0.17 (heterozygote – 0.16; homozygote – 0.01)
rs3789243	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.46-0.59 **South Asia** (Bangladesh – 0.31; Sri Lanka – 0.26; India – 0.36) **East Asia** (China – 0.45; Japan – 0.41) **Europe** (Finland – 0.52; UK – 0.53; Italy – 0.50; Spain – 0.54) **North and South America** (USA – 0.53; Peru – 0.58)	0.53 / 0.78 (heterozygote – 0.50; homozygote – 0.28)
rs4148739	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.13-0.25 **South Asia** (Bangladesh – 0.13; Sri Lanka – 0.19; India – 0.21) **East Asia** (China – 0.07; Japan – 0.09) **Europe** (Finland – 0.04; UK – 0.15; Italy; Spain – 0.16) **North America** (USA – 0.13) **Caribbean Basin** (Barbados – 0.21)	0.09 / 0.17 (heterozygote – 0.16; homozygote – 0.01)

rsID	MAF in regions of the world*	MAF in the Russia / Carrier Frequency in the Russia**
rs4148740	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.13-0.24 **South Asia** (Bangladesh – 0.13; Sri Lanka – 0.19; India – 0.21) **East Asia** (China – 0.07; Japan – 0.09) **Europe** (Finland – 0.04; UK – 0.15; Italy, Spain – 0.16) **North America** (USA – 0.13) **Caribbean Basin** (Barbados – 0.21)	0.09 / 0.17 (heterozygote – 0.16; homozygote – 0.01)
rs7787082	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.57-0.69 **South Asia** (Bangladesh – 0.23; Pakistan – 0.23; India – 0.26) **East Asia** (China – 0.49; Japan – 0.42) **Europe** (Finland – 0.10; UK – 0.17; Italy, Spain – 0.21) **North America** (USA – 0.16) **Caribbean Basin** (Barbados – 0.61)	0.16 / 0.29 (heterozygote – 0.26; homozygote – 0.03)
rs9282564	**Europe** (Finland – 0.12; UK – 0.09; Italy – 0.06; Spain – 0.04) **North America** (USA – 0.10)	0.12 (European Russia – 0.13; Caucasus – 0.03; Eastern Russia – 0.03***) / 0.23 (heterozygote – 0.21; homozygote –0.02)
rs10280101	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.13-0.24 **South Asia** (Bangladesh – 0.13; Sri Lanka – 0.19; India – 0.21) **East Asia** (China – 0.07; Japan – 0.09) **Europe** (Finland – 0.04; UK, Italy, Spain – 0.16) **North America** (USA – 0.13) **Caribbean Basin** (Barbados – 0.21)	0.09 / 0.164563 (heterozygote – 0.1568; homozygote – 0.007764)
rs12720067	**South Asia** (Bangladesh – 0.13; Sri Lanka – 0.19; India – 0.19) **East Asia** (China – 0.06; Japan – 0.09) **Europe** (Finland – 0.04; UK, Italy, Spain – 0.15) **North America** (USA – 0.13)	0.09 / 0.17 (heterozygote – 0.16; homozygote – 0.008)

Note: ** based on data from Geography of Genetic Variants Browser [19]; ** based on data from the Database of population frequencies of genetic variants in the population of the Russian Federation [20]; *** based on data from RUSeq [21]. Abbreviations: MAF – minor allele frequency; UK – United Kingdom of Great Britain and Northern Ireland; USA – United States of America.*

3.2. Population Frequencies of Low-Function Allelic variants of the ABCB1 Gene

Data were obtained on 15 low-function allelic variants of the *ABCB1* gene (**Table 3**): rs1128503 (1236C>T), rs2032583 (chr7:87160561 A>G), rs2235040 (chr7:87165750 C>T), rs1202186 (chr7:87213258 T>C AG), rs2091766 (chr7:87174504 C>T), rs2235035 (chr7:87179086 G>A), rs2235046 (chr7:87174066 C>T), rs2235067 (chr7:87149922 C>T), rs3789243 (chr7:87220886 G>A), rs4148739 (chr7:87161049 T>C), rs4148740 (chr7:87152103 A>G), rs7787082 (chr7:87157051 G>A), rs9282564 (chr7:87229440 T>C), rs10280101 (chr7:87153585 A>C), rs12720067 (chr7:87169356 C>T).

The highest population frequency in the countries of Europe, North America (MAF ranging from 0.30 in United Kingdom to 0.54 in Spain), and East Asia (MAF ranging from 0.30 in China and Japan to 0.69 in China) is observed for rs1128503, rs2091766, rs2235035, rs2235046, rs3789243. The variants rs2235040, rs2235067, rs4148739, rs4148740, rs10280101 are characterized by relatively high population frequencies in African countries (MAF ranging from 0.12 in Sierra Leone to 0.25 in Kenya) and low frequencies in European countries (MAF ranging from 0.04 in Finland to 0.16 in Italy and Spain), East Asian countries (MAF ranging from 0.07 in China to 0.09 in Japan) [19], and Russia (MAF = 0.09). The carrier frequency of these SNVs in Russian population is minimal, with an MAF of 0.17 (heterozygote – 0.16; homozygote – 0.01).

The most clinically significant low-function SNVs of the *ABCB1* gene in Russia are rs1202186 (MAF = 0.72), rs1128503 (MAF = 0.53), rs3789243 (MAF = 0.53), rs2235046 (MAF = 0.51), rs2091766 (MAF = 0.41), rs2235035 (MAF = 0.37), rs7787082 (MAF = 0.16). The carrier frequency of these variant alleles ranges from 0.29 to 0.92, specifically: 0.92 for rs1202186 (heterozygote – 0.40, homozygote – 0.52); 0.78 for rs1128503 (heterozygote – 0.49, homozygote – 0.29); 0.78 for rs3789243 (heterozygote – 0.50, homozygote – 0.28); 0.76 for rs2235046 (heterozygote – 0.50, homozygote – 0.26); 0.65 for rs2091766 (heterozygote – 0.48, homozygote – 0.17); 0.60 for rs2235035 (heterozygote – 0.46, homozygote – 0.14); and 0.29 for rs7787082 (heterozygote – 0.26, homozygote – 0.03) [20].

Table 4. Population frequencies of loss-of-function variants of the *ABCB1* gene [19-21]

rsID	MAF in regions of the world*	MAF in Russia / Carrier Frequency in Russia**
rs1045642	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.11-0.19 **South Asia** (Bangladesh – 0.61; Sri Lanka; India – 0.59) **East Asia** (China – 0.40; Japan – 0.48) **Europe** (Finland – 0.57; UK – 0.53) **North America** (USA – 0.56)	0.45 (European Russia – 0.45; Caucasus – 0.48; Eastern Russia – 0.53***) / 0.70 (heterozygote – 0.49; homozygote – 0.20)
rs2032582	**South Asia** (Bangladesh – 0.61; Sri Lanka – 0.62; India – 0.61) **East Asia** (China – 0.44; Japan – 0.41) **Europe** (Finland – 0.44; UK – 0.41; Italy – 0.40) **North America** (USA – 0.42)	0.03 / 0.05 (heterozygote – 0.05; homozygote – 0.001)****
rs2235015	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.12-0.21 **South Asia** (Bangladesh – 0.13; Sri Lanka – 0.19; India – 0.21) **East Asia** (China – 0.03; Japan – 0.09) **Europe** (UK, Italy, Spain) – 0.16 **North America** (USA – 0.13) **Caribbean Basin** (Barbados – 0.40)	0.15 (European Russia – 0.15; Caucasus – 0.15; Eastern Russia – 0.10***) / 0.27 (heterozygote – 0.25; homozygote – 0.02)
rs10248420	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.44-0.61 **South Asia** (Bangladesh – 0.23; Sri Lanka – 0.22; India – 0.25) **East Asia** (China – 0.49; Japan – 0.42) **Europe** (Finland – 0.10; UK – 0.17; Italy, Spain – 0.21) **North America** (USA – 0.16) **Caribbean Basin** (Barbados – 0.53)	0.16 / 0.29 (heterozygote – 0.26; homozygote – 0.03)
rs11983225	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.13-0.24 **South Asia** (Bangladesh – 0.13; Sri Lanka – 0.19; India – 0.21) **East Asia** (China – 0.07; Japan – 0.09) **Europe** (Finland – 0.04; UK, Italy, Spain – 0.16) **North America** (USA – 0.13) **Caribbean Basin** (Barbados – 0.21)	0.09 / 0.17 (heterozygote – 0.16; homozygote – 0.01)

Note: ** based on data from Geography of Genetic Variants Browser [19]; ** based on data from the Database of population frequencies of genetic variants in the population of the Russian Federation [20]; *** based on data from RUSeq [21]; **** for chr7:87160618, A>C. Abbreviations: MAF - minor allele frequency; UK – United Kingdom of Great Britain and Northern Ireland; USA – United States of America.*

3.3. Population Frequencies of Loss-of-Function Allelic Variants of the ABCB1 Gene

Data were obtained on 5 loss-of-function allelic variants of the *ABCB1* gene (**Table 4**): rs1045642 (chr7:87138645 G>A, 3435C>T), rs2032582 (chr7:87160618 A>T, 2677G>T), rs2235015 (chr7:87199564 C>A), rs10248420 (chr7:87164986 A>G), rs11983225 (chr7:87161520 T>C). The highest population frequency in African countries is observed for the variant alleles rs10248420 (MAF ranging from 0.44 in Sierra Leone to 0.61 in Nigeria); in South Asian, European, and North American countries – for rs1045642 and rs2032582 (MAF from 0.59 in India to 0.62 in Sri Lanka; from 0.40 in Italy to 0.57 in Finland); and in East Asian countries – for rs1045642, rs2032582, and rs10248420 (MAF from 0.40 in China to 0.48 in Japan). Thus, the highest frequency across all global populations (except African population) is observed for rs1045642 (MAF ranging from 0.40 in China to 0.61 in Bangladesh) [19].

In Russian population, the most frequently occurring variant alleles are rs1045642 (MAF = 0.45). Moderate population frequencies are characteristic of rs2235015, rs10248420, and rs11983225 (MAF = 0.09–0.16), while the lowest frequency is observed for rs2032582 (MAF = 0.03). A notable and seemingly paradoxical distribution pattern is observed for the population frequencies of rs2032582. The variant allele of this SNV is among the most common worldwide (MAF ranging from 0.40 in Italy to 0.62 in Sri Lanka), yet it is rare in Russian population (MAF = 0.03). The carrier frequencies of these SNVs range from 0.05 to 0.70, specifically: 0.70 for rs1045642 (heterozygote - 0.50, homozygote - 0.20); 0.05 for rs2032582 (heterozygote - 0.05, homozygote - 0.001); 0.27 for rs2235015 (heterozygote: 0.25, homozygote: 0.02); 0.29 for rs10248420 (heterozygote - 0.26, homozygote - 0.03); and 0.17 for rs11983225 (heterozygote - 0.16, homozygote - 0.01) [20].

Table 5. Population frequencies of genetic variants of the *ABCB1* gene with unknown or uncharacterized functional impact [19-21].

rsID	MAF in regions of the world*	MAF in the Russia / Carrier frequency in the Russia**
rs956825	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.16-0.22 **South Asia** (Bangladesh – 0.21; Pakistan – 0.29; India – 0.16) **East Asia** (China – 0.32; Japan – 0.30) **Europe** (Finland – 0.32; UK – 0.30; Italy – 0.31; Spain – 0.35) **North and South America** (USA – 0.27; Peru – 0.55)	0.35 / 0.58 (heterozygote – 0.45; homozygote – 0.13)
rs2229109	**Europe** (UK – 0.04; Italy – 0.06; Spain – 0.02)	0.03 (European Russia – 0.03; Caucasus – 0.02; Eastern Russia – 0.01***) / 0.06 (heterozygote – 0.05851; homozygote – 0.000944)
rs4148738	**South Asia** (Bangladesh – 0.61; Sri Lanka – 0.62; India – 0.61) **East Asia** (China – 0.44; Japan – 0.41) **Europe** (Finland – 0.47; UK – 0.44; Italy – 0.42; Spain – 0.38) **North and South America** (USA – 0.45; Colombia – 0.43)	0.54 / 0.80 (heterozygote – 0.50; homozygote – 0.30)
rs1002205	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.28-0.31 **South Asia** (Bangladesh – 0.20; Sri Lanka – 0.14; India – 0.15) **East Asia** (China – 0.47; Japan – 0.35) **Europe** (Finland – 0.08; UK – 0.05; Italy – 0.07; Spain – 0.06) **North America** (USA – 0.02) **Caribbean Basin** (Barbados – 0.28)	0.08 / 0.16 (heterozygote – 0.14697; homozygote – 0.009245)
rs10276036	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.15-0.24 **South Asia** (Bangladesh – 0.62; Sri Lanka – 0.62; India – 0.59) **East Asia** (China – 0.69; Japan – 0.60) **Europe** (Finland, UK, Italy – 0.42; Spain – 0.37) **North and South America** (USA – 0.42; Colombia – 0.43)	0.000008 (European Russia – 0.54; Caucasus – 0.51; Eastern Russia – 0.45***) / 0.000017 (heterozygote – 0.000017)
rs4728702	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.10-0.16 **South Asia** (Bangladesh – 0.62; Sri Lanka – 0.62; India – 0.59) **East Asia** (China – 0.69; Japan – 0.60) **Europe** (Finland – 0.42; UK; Italy – 0.42; Spain – 0.37) **North and South America** (USA – 0.42; Colombia – 0.43)	0.53 / 0.78 (heterozygote – 0.50; homozygote – 0.28)
rs35810889	ND	0.000037 / 0.000075 (heterozygote – 0.000075)
rs1202184	**South Asia** (Bangladesh – 0.66; Sri Lanka – 0.70; India – 0.66) **East Asia** (China – 0.75; Japan – 0.62) **Europe** (Finland – 0.50; UK – 0.51; Italy – 0.47; Spain – 0.42) **North and South America** (USA – 0.48; Colombia – 0.47)	0.53 / 0.78 (heterozygote – 0.50; homozygote – 0.28)
rs4148737	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.42-0.53 **South Asia** (Bangladesh – 0.19; Pakistan – 0.32; India – 0.20) **East Asia** (China, Japan – 0.30) **Europe** (Finland – 0.47; UK – 0.40; Italy – 0.41; Spain – 0.46) **North and South America** (USA – 0.41; Peru – 0.56)	0.43 / 0.67 (heterozygote – 0.48; homozygote – 0.19)
rs17327442	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.22-0.30 **South Asia** (Bangladesh – 0.12; Sri Lanka – 0.09; India – 0.21) **East Asia** (China – 0.16; Japan – 0.12) **Europe** (Finland – 0.12; UK – 0.11; Italy – 0.17; Spain – 0.16) **North and South America** (USA – 0.09; Peru – 0.41)	0.16 / 0.30 (heterozygote – 0.27; homozygote – 0.03)
rs2157926	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.35-0.45 **South Asia** (Bangladesh, Sri Lanka, India – 0.05) **East Asia** (China, Japan – 0.13) **Europe** (Finland – 0.06; UK – 0.04; Italy – 0.07; Spain – 0.06) **North America** (USA – 0.05) **Caribbean Basin** (Barbados – 0.38)	0.06 / 0.11 (heterozygote – 0.107453; homozygote – 0.003636)

rs2188524	**East Asia** (China, Japan – 0.11)	(European Russia – 0.01; Caucasus – 0.00; Eastern Russia – 0.07***) / 0.03 (heterozygote – 0.024917; homozygote – 0.000663)
rs2214102	**South Asia** (India – 0.02) **Europe** (Finland – 0.12; UK – 0.11; Italy – 0.05; Spain – 0.07) **North America** (USA – 0.10)	0.93 (European Russia – 0.92; Caucasus – 0.97; Eastern Russia – 0.97***) / 0.99 (heterozygote – 0.12; homozygote – 0.87)
rs2229107	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.05-0.10 **Caribbean Basin** (Barbados – 0.06)	0.000012/0.000025 (heterozygote – 0.000025)
rs28364274	**South America** (Colombia – 0.06; Peru – 0.10)	0.001 (European Russia – 0.00; Caucasus – 0.00; Eastern Russia – 0.01***) / 0.002 (heterozygote – 0.002004; homozygote – 0.000017)
rs28373093	**South Asia** (Bangladesh – 0.64; Sri Lanka – 0.70; India – 0.68) **East Asia** (China – 0.53; Japan – 0.45) **Europe** (Finland – 0.43; UK – 0.47; Italy – 0.45; Spain – 0.50) **North and South America** (USA – 0.45; Colombia – 0.43)	0.50 / 0.75 (heterozygote – 0.50; homozygote – 0.25)
rs28401781	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.15-0.27 **South Asia** (Bangladesh – 0.13; Sri Lanka – 0.18; India – 0.18) **East Asia** (China – 0.07; Japan – 0.09) **Europe** (Finland – 0.05; UK, Italy, Spain – 0.16) **North America** (USA – 0.13) **Caribbean Basin** (Barbados – 0.22)	0.09 / 0.17 (heterozygote – 0.16; homozygote – 0.01)
rs28746504	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.05-0.14 **South Asia** (Bangladesh – 0.02; Sri Lanka; India – 0.03) **East Asia** (China – 0.06; Japan – 0.05) **Europe** (Finland – 0.03; UK – 0.04; Italy; Spain – 0.03) **North America** (USA – 0.03) **Caribbean Basin** (Barbados – 0.08)	0.03 / 0.06 (heterozygote – 0.06; homozygote – 0.000986)
rs3213619	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.05-0.14 **South Asia** (Bangladesh – 0.02; Sri Lanka; India – 0.04) **East Asia** (China – 0.06; Japan – 0.05) **Europe** (Finland – 0.03; UK – 0;04; Italy, Spain – 0.03) **North America** (USA – 0.03) **Caribbean Basin** (Barbados– 0.07)	0.03 (European Russia – 0.02; Caucasus – 0.03; Eastern Russia – 0.04***) / 0.06 (heterozygote – 0.0565; homozygote – 0.000969)
rs34976462	**East Asia** (China – 0.0046; Japan – 0.0096)	0.000224 / 0.000447 (heterozygote – 0.000447)
rs35023033 (chr7:87544882 G>A)	**East Asia** (China – 0.0046; Japan – 0.0096)	0.000224 / 0.000447 (heterozygote – 0.000447)
rs35023033 (chr7:87544882 G>T)	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.01 **Barbados** – 0.02	0.000004 / 0.000008 (heterozygote – 0.000008)
rs35730308	ND	0.000025 / 0.00005 (heterozygote – 0.00005)
rs3842	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.01	ND / ND
rs7779562 (chr7:87515500 G>A)	**Africa** (Gambia, Sierra Leone, Nigeria, Kenya) – 0.11-0.24 **South Asia** (Bangladesh – 0.19; Pakistan – 0.21; India – 0.18) **East Asia** (China – 0.32; Japan – 0.30) **Europe** (Finland – 0.16; UK – 0.10; Italy – 0.12; Spain – 0.16) **North and South America** (USA – 0.12; Peru – 0.15)	0.14 / 0.26 (heterozygote – 0.24; homozygote – 0.02)
rs7779562 (chr7:87515500 G>C)	**Europe** (Italy – 0.0046) **North America** (Mexico – 0.0074)	0.001388 / 0.002775 (heterozygots – 0.002775)
rs1128501	**Europe** (Italy – 0.0046) **North America** (Mexico – 0.0074)	0.07 / 0.14 (heterozygote – 0.13; homozygote – 0.01)

Note: ** based on data from Geography of Genetic Variants Browser [19]; ** based on data from the Database of population frequencies of genetic variants in the population of the Russian Federation [20]; *** based on data from RUSeq [21]. Abbreviations: MAF –minor allele frequency; UK – United Kingdom of Great Britain and Northern Ireland; USA – United States of America.*

3.4. Population Frequencies of ABCB1 Gene Allelic Variants with Uncharacterized or Poorly Characterized Impact on P-glycoprotein Functional Activity

Data were obtained on 26 allelic variants of the *ABCB1* gene (**Table 5**). In African countries, the highest population frequencies are observed for the variant alleles of the following SNVs: rs1002205 (chr7:87141174 C>G), rs4148737 (chr7:87171152 T>C), rs17327442 (chr7:87212990 T>A), rs2157926 (chr7:87270500 T>A). For these SNVs, MAF in Gambia ranges from 0.22 to 0.53. In South Asian countries, the highest population frequencies are observed for: rs4148738 (chr7:87163049 T>C), rs10276036 (chr7:87180198 T>C), rs4728702 (chr7:87180678 T>A), rs1202184 (chr7:87213901 C>T), rs28373093 (chr7:87344023 G>C).

The MAF range for these SNVs varies from 0.59 in India to 0.70 in Sri Lanka. In European and North American countries, the variant alleles of the following SNVs are more frequently observed: rs956825 (chr7:87192275 C>T), rs4148738, rs10276036, rs4728702, rs1202184, rs4148737, rs28373093. The MAF range for these SNVs is from 0.27 in the USA to 0.51 in the United Kingdom. A high frequency in the populations of East Asian countries is observed for: rs956825, rs4148738, rs1002204 (chr7:87141497 C>A), rs10276036, rs4728702, rs1202184, rs28373093, rs3842 (chr7:87133366 T>C their MAF ranges from 0.30 in Japan to 0.75 in China [19].

In Russia, the most frequently occurring variants are: rs2214102 (chr7:87600185 T>C), rs956825 (chr7:87562959 C>T), rs4148738 (chr7:87533733 C>T), rs4728702 (chr7:87551362 A>T), rs1202184 (chr7:87584585 C>T), rs4148737 (chr7:87541836 T>C), rs17327442 (chr7:87583674 T>A), rs28373093 (chr7:87714707 G>C), rs3842 (chr7:87504050 T>C). The variant alleles of these SNVs exhibit the highest MAF (ranging from 0.14 to 0.93) and carrier frequency (ranging from 0.26 to 0.99) [20].

4. DISCUSSION

4.1. The Role of P-glycoprotein in the Development of Pseudoresistance, Therapeutic Resistance, and Neurotoxic Adverse Drug Reactions

Individual pharmacogenetic features that influence AP pharmacokinetics make a substantial contribution to the development of therapeutic resistance, pseudoresistance to APs, and neurotoxicity [22]. However, pseudoresistance is a multifactorial phenomenon (**Figure 4**). Potential contributing factors also include diagnostic, therapeutic, organizational, pharmacokinetic, and pharmacodynamic factors, low adherence to AP-therapy among patients with SSDs, and the presence of comorbid conditions in patients with SSDs. A diagnosis of true therapeutic resistance to APs in a patient with SSD can only be considered after all possible causes of pseudoresistance have been ruled out [23]. According to the current Russian clinical guidelines [24], the criteria for pharmacoresistance in schizophrenia include a lack of efficacy after two consecutive treatment trials with APs from different classes (excluding clozapine), one of which must be a second-generation (atypical) APs (SGAPs), each administered for 4–6 weeks, provided there is good tolerability of the AP prescribed at an optimal therapeutic dose. Most international guidelines contain similar definitions of pharmacoresistance in SSDs. However, some of them lack the criterion requiring APs to belong to different pharmacological classes or to be SGAP [25-28] with the required treatment duration varying from 2 to 8 weeks across different guidelines [23,25,29,30].

Knowledge of the specific genotype and phenotype of a patient with SSD, along with the pharmacokinetic characteristics of an AP based on its genetically determined alterations in P-gp functional activity, enables the prediction of the treatment response profile even before therapy initiation. This allows for the selection of the optimal AP, dosing regimen, and route of administration. Such a personalized approach may help reduce the risk of neurotoxic ADRs and pseudoresistance, achieve an optimal balance between efficacy and safety of APs in both monotherapy and polytherapy regimens, and lower state expenditures associated with providing comprehensive care to patients with SSDs (**Figure 4**) [31,32].

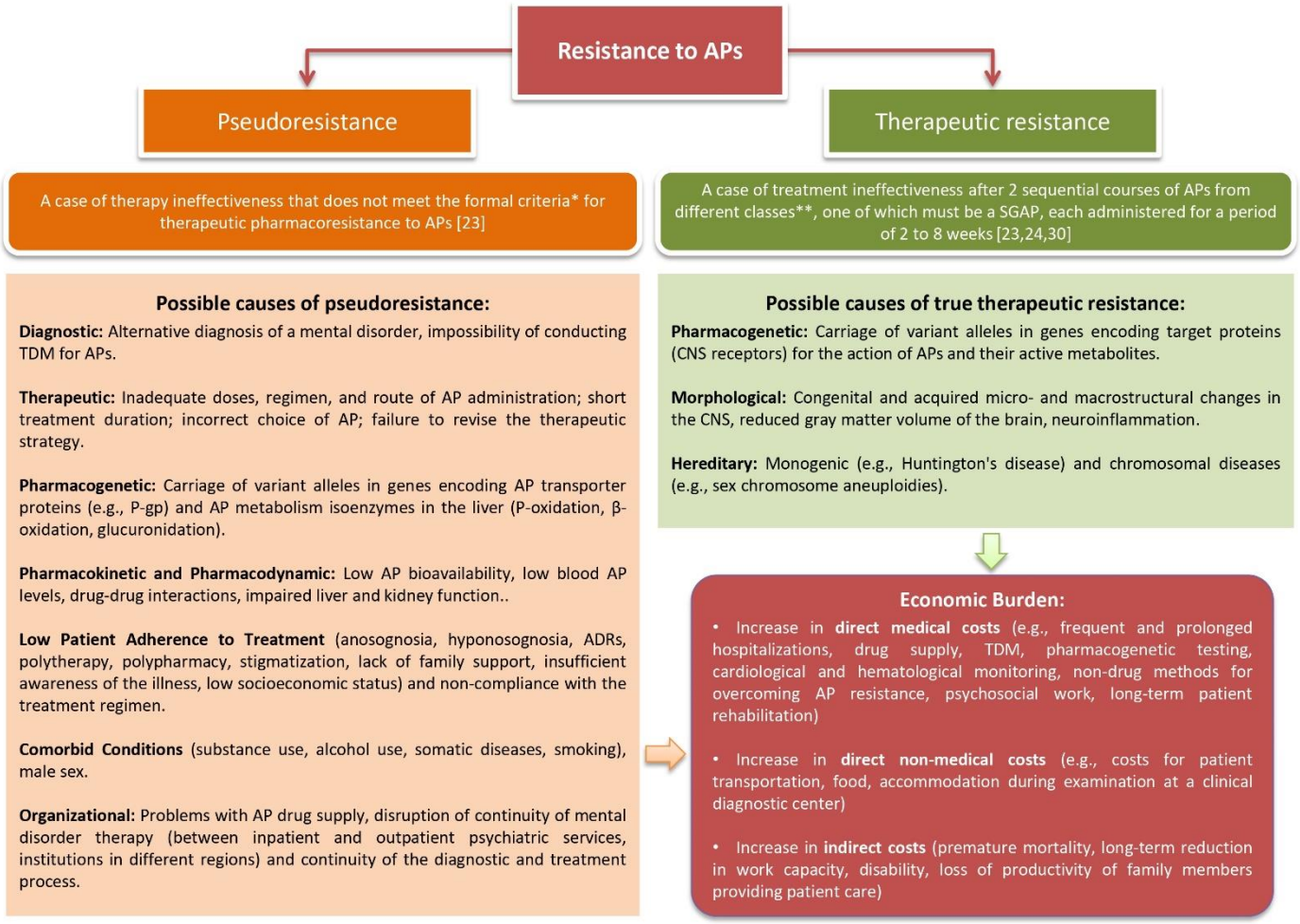

Figure 4. Antipsychotic treatment resistance: etiology and implications.
The figure was prepared by the authors.
Note: *AP – antipsychotic; SGAP – second-generation antipsychotic; CNS – central nervous system; TDM – therapeutic drug monitoring; ADRs – adverse drug reactions. * Lack of efficacy after two consecutive treatment trials (2–8 weeks each) with APs from different classes, one of which is SGAP (except clozapine). ** except clozapine.*

5.2. Challenges of Limited and Inconsistent Data on Antipsychotic-P-glycoprotein Interactions

Despite the persistent interest among researchers in the role of transporter proteins in the development of pseudoresistance and neurotoxic ADRs, experimental and clinical data on the interactions between APs and P-gp remain limited. Results from preclinical (*in vitro*) studies do not always correlate with the findings of clinical (*in vivo*) studies. For instance, a study by Sasabe H. et al. (2021) demonstrated that brexpiprazole exhibits P-gp inhibitory properties in cellular models, yet it fails to reduce P-gp function *in vivo*. Most previously studied APs have been identified as P-gp inhibitors (**Table 1**).

Some APs (e.g., phenothiazines, thioxanthenes, brexpiprazole) are not substrates for P-gp or other transporter proteins, such as BCRP (breast cancer resistance protein). Consequently, the intestinal absorption of these APs is not limited by their efflux. Moreover, some of these APs act as allosteric modulators of transporter proteins, thereby affecting the bioavailability of other drugs. For example, brexpiprazole is not a substrate for P-gp or BCRP, its oral bioavailability approaches 100%, and *in vitro* it can slightly reduce the transport function of these proteins. However, clinical studies have not confirmed any significant impact of brexpiprazole on the pharmacokinetics of typical P-gp and BCRP substrates [33].

5.3. Specific Features of the Genetic Landscape in Russia in the Context of Antipsychotic Pharmacogenetics

Modern clinical guidelines and national treatment protocols are based on data obtained from studies conducted in European and North American populations and are designed for the "average patient" with normal (extensive) pharmacogenetic phenotype [32]. Consequently, pharmacogenetic diagnostic test systems and therapeutic algorithms derived from such guidelines will most likely have limited applicability in other racial and ethnic groups [31,34,35].

Evaluating the frequency of *ABCB1* SNV alleles linked to AP efflux and treatment response variability in Russian SSD patients requires consideration of key demographic factors. It is essential to account for the country's vast geographical expanse, as well as the racial and ethnic heterogeneity of its population [3,34]. Thus, in certain regions of the Far Eastern and Siberian Federal Districts, an increase in the frequencies of homozygous and heterozygous carriage of some variant SNV alleles common in East Asian countries is possible. This is due to specific population migration patterns and a rising proportion of migrants from China, Korea, and Japan, as well as an increase in mixed marriages [36]. This underscores the necessity for conducting additional large-scale population studies within these specific administrative-territorial units to develop and subsequently validate Russian pharmacogenetic diagnostic test systems [34,37]. The currently available data on the population frequencies of variant alleles of the *ABCB1* gene and their homozygous and heterozygous carrier frequencies primarily reflect the patterns of genetic drift among the european-descent populations residing in the central and western regions of Russia [34], and enable the development of pharmacogenetic diagnostic test systems that are valid for the European part of our country. However, such test systems may have insufficient predictive power for the populations of Western and Eastern Siberia, the Republic of Tuva, the Republic of Sakha (Yakutia), and the Far East.

5.4. Research Prospects for Single Nucleotide Variants in Russia

The present review demonstrates that, among the previously unstudied SNVs of the *ABCB1* gene, the following hold the greatest interest for researchers and developers of pharmacogenetic diagnostic test systems in Russia: rs2214102, rs956825, rs4148738, rs4728702, rs1202184, rs4148737, rs17327442, rs28373093, rs3842, as the variant alleles of these SNVs exhibit the highest MAF (ranging from 0.14 to 0.93) and carrier frequency (from 0.26 to 0.99). Notably, rs2214102 is the most prevalent SNV in Russian population (MAF = 0.93, carrier frequency = 0.99), while its MAF does not exceed 0.12 in other countries worldwide [19,20].

5. CONCLUSIONS

The *ABCB1* genetic polymorphism may play a clinically significant role in interindividual differences in response to AP-therapy among patients with SSDs. The allelic variants of this gene form four phenotypic profiles: with normal (extensive transporter), increased (rapid transporter), decreased (intermediate transporter), or near-zero (poor transporter) transporter protein function. Increased P-gp functional activity is associated with the development of pseudoresistance due to reduced AP bioavailability and restricted penetration across the BBB into the brain. Decreased function of this transporter protein can lead to elevated AP concentrations in the brain as a result of impaired AP efflux across the BBB, thereby inducing neurotoxic ADRs. The frequency of variant alleles of the *ABCB1* gene is heterogeneous across global populations, a critical factor to consider when developing pharmacogenetic diagnostic test systems. In Russia, the highest population frequencies are observed for SNVs, encompassing high-function (rs2032582, rs1882478, rs2235048, rs6949448), low-function (rs1202186, rs1128503, rs3789243, rs2235046, rs2091766, rs2235035, rs7787082), and loss-of-function (rs1045642, rs2235015, rs10248420, rs11983225) alleles.

Current data on the population frequencies of *ABCB1* gene allelic variants have been derived from studies primarily involving populations of European ancestry residing in the central and western regions of our country. Given the pronounced ethnic and racial heterogeneity of Russian population, there is a clear necessity for conducting additional large-scale population studies. The aim is to clarify regional peculiarities of the gene pool and to subsequently develop and validate pharmacogenetic diagnostic test systems with high predictive value for different territorial and geographical zones of the country. The creation of a validated diagnostic tool will enable the prediction of the response to AP-therapy even before its initiation, aid in achieving an optimal balance between its efficacy and safety, and reduce the state burden associated with providing comprehensive care to patients with SSDs.

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