

Review

Association of Genotypes and Haplotypes of Low-Functioning and Non-Functional Single Nucleotide Variants of the *ABCB1* Gene with the Risk of Antipsychotic-Induced Cognitive Disorders in Patients with Schizophrenia Spectrum Disorders

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Abstract: Cognitive disorders (CDs) are among the most disabling components of the clinical picture of schizophrenia spectrum disorders (SSDs) and lead to a pronounced decline in the quality of life, as well as in social and occupational functioning of patients. CDs in patients with SSDs may be primary or secondary, with the latter developing during antipsychotic (AP) therapy. Individual predisposition to AP-induced CDs may arise from genetically rooted features of AP pharmacokinetics — in particular, the functional state of the efflux transporter P-glycoprotein (P-gp), encoded by the *ABCB1* gene. This narrative review demonstrates that three single nucleotide variants of the *ABCB1* gene (3435C>T, 1236C>T, and 2677G>T/A) have a proven effect on P-gp expression and substrate specificity. Carriage of the non-functional TTT haplotype — the most common alongside the “wild-type” CGC haplotype — is associated with increased AP concentrations in the blood and brain tissue, leading to enhanced neurotoxic adverse drug reactions (ADRs). Analysis of clinical studies confirms an association between non-functional *ABCB1* genotypes and haplotypes and an increased risk of ADRs to AP therapy. However, direct evidence linking *ABCB1* haplotypes to neurocognitive outcomes in SSD has not yet been found. The association of certain *ABCB1* haplotypes with AP-induced CDs is theoretically justified but requires clinical confirmation in prospective studies. Preventive pharmacogenetic testing for the *ABCB1* gene appears to be a promising tool for personalizing AP therapy in patients with SSDs. It enables the identification of patients at risk for CDs prior to treatment initiation and allows adjustment of drug selection and dosing regimen.

Keywords: *ABCB1*, P-glycoprotein, single nucleotide variant, haplotype, antipsychotic, adverse drug reaction, cognitive disorders, schizophrenia, pharmacogenetics

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1. INTRODUCTION

Cognitive disorders (CDs) are among the most disabling components of the clinical picture of schizophrenia spectrum disorders (SSDs), leading to reduced quality of life, impaired social and occupational functioning, and profound patient maladjustment [1]. The level of cognitive functioning in psychotic disorders is heterogeneous and depends, among other factors, on the specific psychiatric disorder. Warren H. et al. (2025) [2] investigated the distribution patterns of CDs in patients with psychoses and demonstrated that CDs are arrayed along a single continuous quantitative axis. At the same time, patients with different diagnoses (schizophrenia, schizoaffective disorder, bipolar affective disorder with psychotic symptoms) overlap on this continuum. The model proposed by the authors — the Basic NeuroCognitive Continuum (BANCC) — reflects the shift from a categorical (ICD-10) to a dimensional approach in assessing cognitive dysfunction and can be used to stratify patients for personalized therapy [2].

Cognitive disorders in SSD may have different underlying mechanisms [3]. There is a concept according to which CDs can be divided into primary, that is, directly related to the disease itself, and secondary, caused by other modifiable and non-modifiable factors (**Figure 1**).

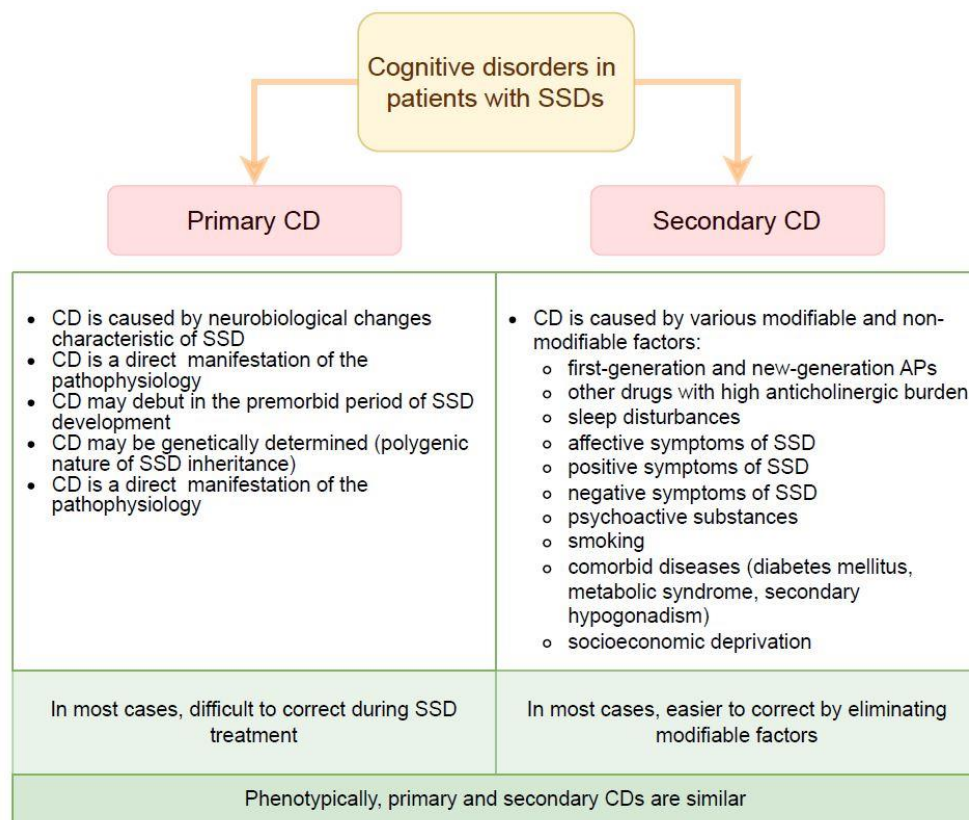


Figure 1. The concept of primary and secondary cognitive disorders in patients with schizophrenia spectrum disorders (prepared by the authors based on [3,4,5]).

Abbreviations: CD — cognitive disorder; SSDs — schizophrenia spectrum disorders; AP — antipsychotic.

Although primary CD is considered an important pathogenetic component of SSDs, pharmacotherapy, including antipsychotics (APs), can itself impair neurocognitive functioning [6, 7]. Cognitive decline associated with short-term and long-term AP use is secondary and is classified as AP-induced CDs [4, 6, 8, 9].

Studies over the past decade have shown that certain APs may impair cognitive functioning in patients with SSD. The most pronounced cognitive decline is observed in information processing speed, verbal learning, and memory [1, 10]. At the same time, different new-generation APs may have both less and more pronounced negative effects on cognitive processes than first-generation APs [11, 12, 13]. There is evidence of positive effects of certain APs on cognitive functions in SSD; however, this may be explained by a practice effect from repeated cognitive testing, specific study design features, or the aforementioned differences in the effects of first-generation versus new-generation APs. A meta-analysis by Feber L. et al. (2025) showed that APs do not improve the cognitive status of patients with SSD. In this regard, the authors recommend avoiding first-generation APs with a high anticholinergic burden (particularly haloperidol and fluphenazine) as well as clozapine [11]. In addition, APs with a high anticholinergic burden (high-risk group for secondary CDs) include chlorpromazine, levomepromazine, thioridazine, and chlorprothixene. Among new-generation APs, olanzapine, quetiapine, and asenapine have a moderate anticholinergic burden (moderate-risk group for secondary CDs) [12].

Possible mechanisms mediating the effects of APs on cognitive functions include modulation of glutamatergic, GABAergic, and anticholinergic systems; however, their relative contribution varies depending on the drug class, overall pharmacokinetic and pharmacodynamic characteristics of the drug, dosing regimen, and duration of therapy [6, 10, 14, 15]. Furthermore, according to brain positron emission tomography (PET) data, there is a hyperbolic relationship between AP dose and dopamine type 2 receptor (DRD2) occupancy: as the AP dose increases, the increment in DRD2

occupancy significantly decreases, whereas the severity of adverse drug reactions (ADRs), including AP-induced CDs, increases [16,17].

The severity of CDs may also be partly attributable to other AP-induced ADRs (e.g., somnolence, extrapyramidal motor disorders, blurred vision) [10]. The occurrence of ADRs during AP treatment often leads to reduced compliance and patient withdrawal from pharmacotherapy for SSD, which in turn contributes to disease progression and worsens both medical and social prognosis [1]. One of the key factors determining the variability in pharmacological response to APs and the risk of neurotoxic ADRs is genetically determined features of AP pharmacokinetics. Over the past two decades, the *ABCB1* gene (ATP-binding cassette subfamily B member 1, locus: 7q21.12), which encodes the transmembrane protein P-glycoprotein (P-gp), has attracted the attention of researchers. P-gp is an efflux transporter that facilitates the removal of xenobiotics across barrier tissues, including in particular the blood–brain barrier (BBB), hepatic bile ducts, and proximal renal tubules (Figures 2, 3) [18].

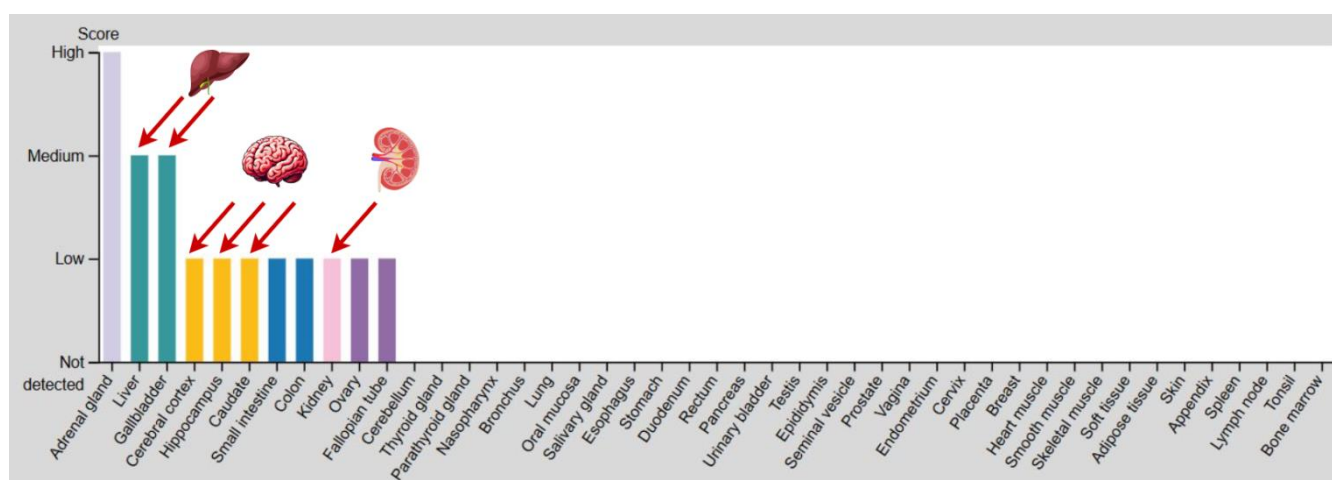


Figure 2. Levels of *ABCB1* expression in various tissues (modified by the authors from Human Protein Atlas, <https://www.proteinatlas.org/ENSG00000085563-ABCB1/tissue#cbox>)

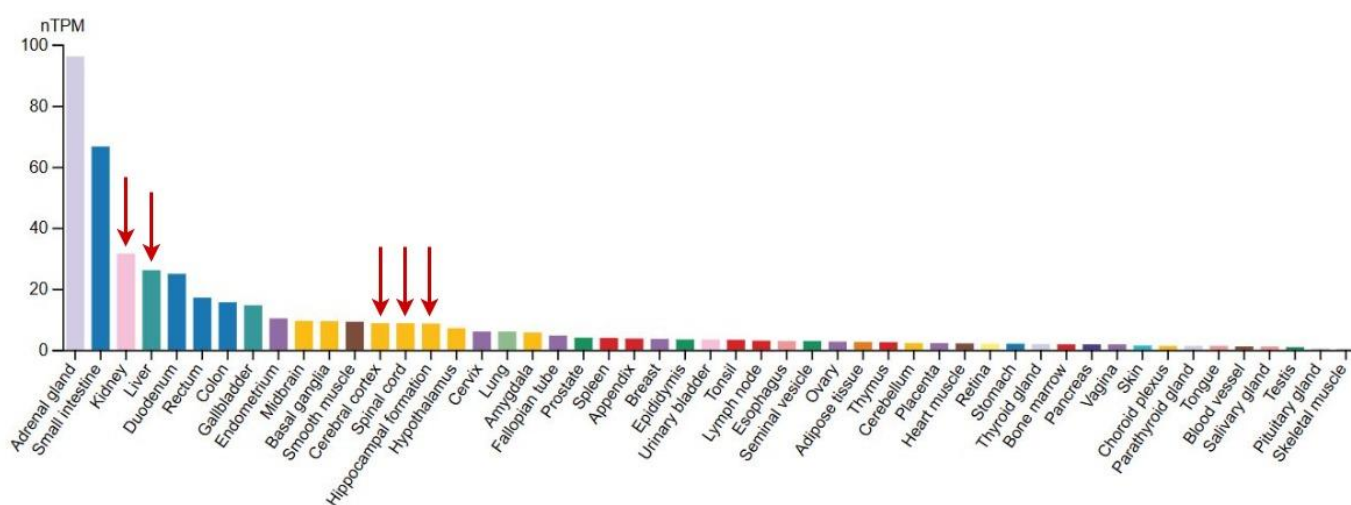


Figure 3. Tissue specificity of *ABCB1* gene RNA (modified by the authors from Human Protein Atlas, <https://www.proteinatlas.org/ENSG00000085563-ABCB1/tissue#cbox>)

It is important to note that the highest level of *ABCB1* expression in the brain is observed in vascular endothelial cells. In addition, P-gp is found on the membranes of astrocytes and pericytes, which form the neurovascular unit and

are involved in regulating the transport of xenobiotics across the BBB [19, 20]. As shown in **Figure 2**, the highest level of *ABCB1* expression is observed in the cortex, hippocampus, and caudate nucleus. These brain structures are critically important for cognitive functioning; therefore, disruption of *ABCB1* expression on neuronal membranes in these regions represents one of the possible mechanisms underlying the development of AP-induced CDs [21]. Furthermore, *ABCB1* is expressed in the bile ducts of the liver, the gallbladder, and the epithelial cells of the proximal renal tubules. Thus, P-gp can influence the plasma concentration of APs and their elimination from the body [18]. As shown by Taskar K. et al. (2022) [22], inhibition of renal and hepatic P-gp leads to an increase in the plasma concentration of P-gp substrates, but by no more than 2-fold.

Single nucleotide variants (SNVs) of the *ABCB1* gene influence individual variability in the bioavailability, distribution, and elimination of P-gp substrates in tissues and organs. Synonymous and non-synonymous substitutions in the coding region of the gene can alter the rate of P-gp synthesis, its conformation, and substrate specificity [23,23]. These SNVs differ in their impact on the primary structure of the protein. A synonymous nucleotide substitution preserves the encoded amino acid due to the degeneracy of the genetic code, whereas a non-synonymous substitution leads to a change in the amino acid sequence [25]. The consequence of these changes may be the accumulation of APs in brain tissue, disruption of neurochemical homeostasis, and enhancement of neurotoxic ADRs — up to the development of persistent and pronounced CDs (dementia) (**Figure 4**) [9].

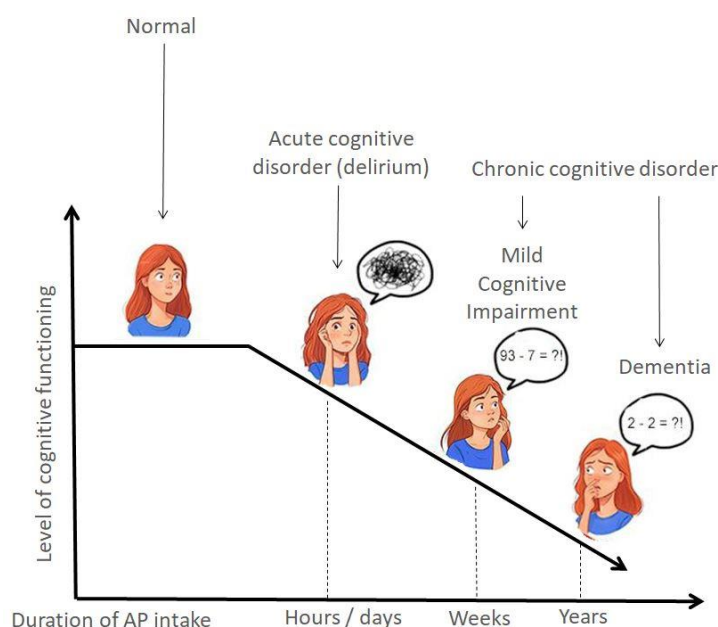


Figure 4. Dynamics of the development of antipsychotic-induced cognitive disorders (modified by the authors from [9]).

The aim of this narrative review is to summarize the results of Russian and international studies on the role of the allelic variants of the *ABCB1* gene 3435C>T (rs1045642), 1236C>T (rs1128503), and 2677G>T (rs2032582), as well as the haplotypes they form, in the development of AP-induced CDs in patients with SSDs.

The search of publications was conducted in the eLIBRARY, PubMed/MEDLINE, Cochrane Library, Semantic Scholar, and Google Scholar databases in Russian and English for the period 2016–2026. Due to the limited number of contemporary studies devoted to this topic, earlier works of historical interest were also included in this review. Information on genes, allelic variants, and proteins was obtained from the dbSNP database (<https://www.ncbi.nlm.nih.gov/snp/>) и «Human Protein Atlas» (<https://www.proteinatlas.org/>).

2. KEY SINGLE NUCLEOTIDE VARIANTS OF THE *ABCB1* GENE AND THEIR IMPACT ON P-GLYCOPROTEIN FUNCTION

The most studied SNVs of the *ABCB1* gene are 3435C>T (rs1045642), 1236C>T (rs1128503), and 2677G>T (rs2032582) [23]. These SNVs form the majority of the studied haplotypes associated with AP-induced neurotoxicity. A brief description of the SNVs is presented in **Table 1** [23, 23, 26, 27, 28, 29, 30].

Table 1. Characteristics of key single nucleotide variants of the *ABCB1* gene (locus: 7q21.12, OMIM ID: 171050) [23,23].

SNV of the <i>ABCB1</i> gene	rsID	Locus	Substitution type	Observed effects	Effect on P-gp function	MAF in the Russia*
1236C>T	rs1128503	Exon 12	Synonymous	↓ mRNA translation rate, ↓ P-gp expression ↓↓ Transport activity	Low-functioning	0.53
2677G>T	rs2032582	Exon 21	Non-synonymous	↓ Substrate specificity ↓↓↓ Transport activity	Non-functional	0.51
3435C>T	rs1045642	Exon 26	Synonymous	↓ P-gp expression ↓↓ Transport activity	Non-functional	0.45

Abbreviations: C – cytosine; G – guanine; T – thymine; MAF – Minor allele frequency; mRNA – messenger ribonucleic acid; P-gp – P-glycoprotein; SNV – single nucleotide variant.

Among these three variants, 1236C>T (rs1128503) is a low-functioning SNV in the *ABCB1* gene, while 2677G>T (rs2032582) and 3435C>T (rs1045642) are non-functioning SNVs. According to the standardized terminology developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC), a low-functioning allele is defined as an allele whose gene product exhibits lower function than the product of the reference ("wild-type") allele [31]. According to the definition of the U.S. National Cancer Institute (NCI), a non-functioning SNV ("null allele") results in a complete absence of expression or activity of the gene product [32]. A combination of normal-functioning, low-functioning, and/or non-functioning alleles results in a genotype with reduced P-gp function. At the same time, carrying more than one non-functioning SNV results in a non-functioning genotype [31].

Two of the SNVs considered in this narrative review – 1236C>T (rs1128503) and 3435C>T (rs1045642) – are synonymous. The single nucleotide substitution in the *ABCB1* gene involves the replacement of cytosine (C) with thymine (T). This reduces the expression of the efflux transporter P-gp on the membrane of neurons, BBB endothelial cells, and renal tubular epithelial cells.

One of the SNVs under consideration, 2677G>T (rs2032582) is a non-synonymous substitution, in which the nucleotide guanine (G) is replaced by thymine (T). This leads to a decrease in the substrate specificity of the efflux transporter P-gp at the aforementioned cellular and tissue barriers.

The frequency of the minor low-functioning 1236T allele (rs1128503) is higher in the Russian population compared with the frequencies of 2677T (rs2032582) and 3435T (rs1045642), amounting to 0.53 versus 0.51 and 0.45, respectively [23]. This is an important consideration for the development of Russian panels for pharmacogenetic testing (PGx). The importance of accounting for the ethnic component in pharmacogenetics has also been emphasized in the work of D.A. Sychev, D.V. Ivashchenko, N.A. Shnayder, and other Russian scientists [33, 34, 35, 36, 37].

The *ABCB1* gene contains 28 exons, and the SNVs 1236C>T (rs1128503), 2677G>T/A (rs2032582), and 3435C>T (rs1045642) are located in exons 12, 21, and 26, respectively. The role of low-functioning SNVs has been demonstrated in carriers of homozygous genotypes and/or haplotypes, i.e., in combination with the carriage of low- or non-functioning SNVs in this gene. The clinical role of non-functioning SNVs has been confirmed in both heterozygous and homozygous carriers of the 2677GT/2677TT (rs2032582) and 3435CT/3435TT (rs1045642) genotypes, as well as in haplotype carriers [23]. If a patient with SSD receiving AP substrates of the efflux transporter P-gp (e.g., risperidone, paliperidone, amisulpride, fluphenazine [38, 39]) is found by DNA typing to carry two or three low-functioning/non-functioning SNVs simultaneously (compound heterozygote) in the *ABCB1* gene on chromosome 7 (**Figure 5**), then the transport of APs across cellular and tissue barriers is clinically significantly delayed. This explains the growing scientific and clinical interest in studying haplotypes from the perspective of modern personalized psychiatry.

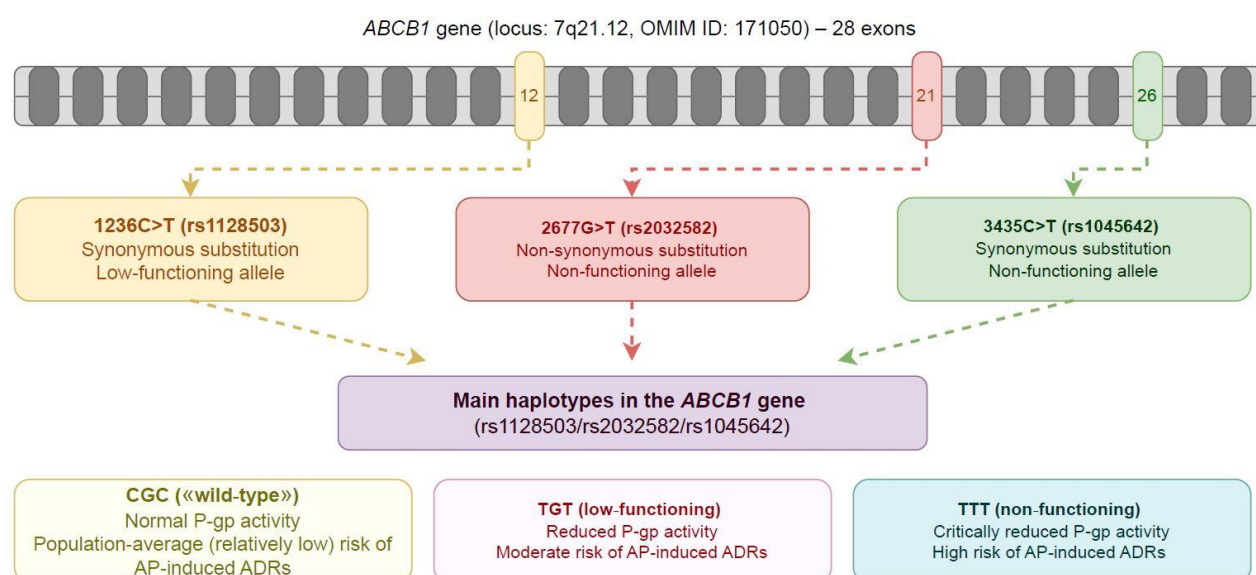


Figure 5. Structural and functional organization of the *ABCB1* gene: single nucleotide variants, selected haplotypes, and the risk of developing antipsychotic-induced cognitive disorders.

Abbreviations: *ABCB1* – ATP-binding cassette (ABC) transporter type 1 (P-glycoprotein); C – cytosine; G – guanine; T – thymine; P-gp – P-glycoprotein; AP – antipsychotic; ADRs – adverse drug reactions; OMIM – Online Mendelian Inheritance in Man (data base); ID – identification number.

3. KEY HAPLOTYPES IN THE *ABCB1* GENE AND THEIR SIGNIFICANCE IN ANTIPSYCHOTIC PHARMACOGENETICS

Haplotype analysis of the *ABCB1* gene takes into account the linked inheritance of minor alleles within a single chromosome and allows assessment of their combined effect on P-gp expression levels and transport activity [23, 40]. The three SNVs described above – rs1128503 (1236C>T), rs2032582 (2677G>T) and rs1045642 (3435C>T) – form several stable haplotypes, the most common of which are CGC (the so-called "wild-type" or normal, fully functional haplotype) and TTT (the minor, non-functional haplotype) [40, 41] (**Figure 5**). The TTT haplotype (minor low-functioning and non-functioning alleles at positions 1236, 2677, and 3435) in the *ABCB1* gene is associated with the most significant reduction in *ABCB1* expression and P-gp activity. Skogh E. et al. (2011) [42] showed that carriers of the TTT haplotype had significantly higher concentrations of olanzapine both in plasma and in cerebrospinal fluid. Carriage of two copies of this haplotype (TTT/TTT homozygotes) is accompanied by a marked reduction in the efflux of AP substrates of P-gp across the membrane of neurons, the BBB, and renal tubules [18, 40]. A brief description of the most studied *ABCB1* haplotypes and their combinations is presented in **Tables 2** and **3**, respectively.

Table 2. Characteristics of key haplotypes of the *ABCB1* gene [27, 40, 41, 43].

Haplotype (rs1128503/ rs2032582/ rs1045642)	Functional status of P-glycoprotein	Frequency of the haplotype in different populations (%)
CGC	Normal or fully functional ("wild-type haplotype")	23.60-46.90
CGT	Low-functioning	6.02 – 14.40
TGC	Low-functioning	1.00 – 11.00
TGT	Low-functioning	0.00 – 7.10
TT	Non-functional (critically reduced)	23.60 – 47.80
CTT	Low-functioning	1.00 – 22.80
CTC	ND	0.20 – 6.0
TTC	ND	1.0 – 6.67

Abbreviations: ND – not data; C – cytosine; G – guanine; T – thymine.

Table 3. Frequencies of *ABCB1* haplotype combinations in a population of middle European descent [40].

Haplotype combination (rs1128503-rs2032582-rs1045642)	Frequency of the haplotype combination, %
CGC/TTT	34.2 – 38.1
CGC/CGC	21.1 – 22.4
TTT/TTT	14.3 – 16.2
CGC/CGT	6.7 – 9.2
TTT/CGT	7.6 – 7.9

Abbreviations: C – cytosine; G – guanine; T – thymine.

As shown in **Tables 2** and **3**, the frequencies of *ABCB1* haplotypes vary widely across different populations worldwide; however, the most common haplotypes in the *ABCB1* gene are the fully functional CGC and the non-functional TTT [40,41,44]. According to Zimprich F. et al. (2004), only three haplotypes – CGC, TTT, and CGT – had a frequency >3%. In the study by Sipeky C. et al. (2011), the frequencies of the TAT, CAC, CAT, and TAC haplotypes ranged from 0.29% to 2.5%, and their association with P-gp functional activity continues to be investigated [40, 41].

4. ASSOCIATION OF *ABCB1* GENOTYPES AND HAPLOTYPES WITH THE RISK OF ANTIPSYCHOTIC-INDUCED ADVERSE DRUG REACTIONS IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

The Japanese study by Hattori S. et al. (2018) [45], which included 233 patients with schizophrenia receiving four new-generation APs as monotherapy, demonstrated an AP-specific pattern of associations between ADRs and certain haplotypes in the *ABCB1* gene. Specifically, the TCTA haplotype (rs1045642-rs2235048-rs1128503-rs2032582) was associated with reduced overall and sympathetic autonomic nervous system activity in the patient group treated with aripiprazole. In contrast, no significant associations of this haplotype with autonomic nervous system activity were found during monotherapy with risperidone, olanzapine, or quetiapine. The authors suggested that aripiprazole is a substrate of the P-gp transporter with higher affinity than the other APs they studied. They recommended that clinicians exercise caution in patients carrying haplotypes that include the 3435T (rs1045642) and C (G>C, intron 27, rs2235048) allelic variants due to the risk of developing AP-induced autonomic ADRs (bradycardia, decreased blood pressure, orthostatic hypotension, lethargy, somnolence) [45]. However, the association of the studied haplotypes with the risk of AP-induced CDs was not analyzed.

In the Turkish study by Çevik F. et al. (2025) [46], differences in *ABCB1* expression levels in patients with schizophrenia before and after AP administration were examined. The results were compared with those in a healthy control population. The authors showed that during the acute phase of the disease, *ABCB1* gene expression was significantly reduced compared with the control group, and partially normalized after the initiation of AP therapy. The authors also note that reduced functional activity of the P-gp transporter may lead to decreased efflux of inflammatory mediators, neurotoxic metabolites, and xenobiotics from brain tissue, which in turn may influence the risk of developing and progressing AP-induced CDs [46].

5. ASSOCIATION *ABCB1* GENOTYPES AND HAPLOTYPES WITH COGNITIVE FUNCTION IN SCHIZOPHRENIC PATIENTS: LIMITED DIRECT EVIDENCE

At the time of completing this narrative review, we found no available publications directly confirming an association between homozygous/heterozygous genotypes of low-functioning and non-functioning SNVs or haplotypes in the *ABCB1* gene and the risk of AP-induced CDs in patients with SSDs. Most researchers assessed either indirect markers (plasma AP concentrations, treatment response based on psychopathological scales, including the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS)) or other neurological ADRs (extrapyramidal symptoms, autonomic nervous system symptoms). **Table 4** presents selected studies that investigated the effect of various *ABCB1* SNVs on AP efficacy and safety. Despite the relevance of CDs and their high prevalence in SSDs (more than 80% of patients with schizophrenia), the etiology and predictability of AP-induced CDs in patients with SSD remain largely unclear [3]. Primary and secondary CDs, similar in their phenotypic manifestations, also occur in other psychiatric disorders; however, their severity is generally less than that in SSD. The question of whether the pathophysiological mechanisms underlying the development of CD in these conditions are similar remains open. Furthermore, it

is unclear whether the differences in cognitive status among patients with SSD are a consequence of the disease itself or reflect premorbid characteristics and patient age [1].

Table 4. Characteristics of select associative genetic studies of the *ABCB1* gene.

Authors, year, country	Sample size	SSD / antipsychotic	rsID of SNVs studied	Main findings
Jovanović et al., 2010 Croatia [47]	83	First-episode psychosis / Risperidone	rs2032582 rs1045642	TT genotypes at rs2032582 and rs1045642 are associated with reduced plasma levels of the active fraction of risperidone and a lower frequency of extrapyramidal symptoms.
Hattori et al., 2018 Japan [45]	233	Schizophrenia / Risperidone, olanzapine, aripiprazole, quetiapine	rs1045642 rs1128503 rs2032582 rs2235048	The TCTA haplotype (rs1045642-rs2235048-rs1128503-rs2032582) is associated with reduced autonomic nervous system activity during aripiprazole treatment. No associations were found with the other APs studied in the research.
Saiz-Rodríguez et al., 2018 Spain [29]	473	Healthy volunteers (single dose) / Olanzapine, quetiapine, risperidone, aripiprazole	rs1045642	The TT genotype is associated with reduced olanzapine clearance, increased risperidone clearance, and no effect on quetiapine clearance.
Vijayan et al., 2012 South India [48]	192	Schizophrenia / First-generation and new-generation APs	rs1045642 rs2032582	Carriers of the minor TT homozygous genotypes demonstrated refractoriness to AP dose escalation. Significant allelic, genotypic, and haplotypic associations with response to APs were identified.

Abbreviations: A – adenine; T – thymine; C – cytosine; AP – antipsychotic; ID – identification number; SNV – single nucleotide variant; SSD – schizophrenic spectrum disorder.

From a clinical perspective, it is important to distinguish between primary and secondary CDs in patients with SSD (**Figure 1**). Secondary CDs, developing in particular during AP therapy, are more frequently observed in carriers of low-functioning and non-functioning *ABCB1* genotypes and haplotypes. It is important to bear in mind that these CDs have a clinically significant and prognostically favorable profile: through proactive or reactive PGx, it is possible to reduce the risk or minimize the severity of AP-induced secondary CDs (e.g., by optimizing the dosing regimen or switching antipsychotics) [9,23,49].

It should also be borne in mind that many psychotropic drugs, including agents used to correct AP-induced extrapyramidal disorders, may possess anticholinergic properties [9,13,50,51]. In this regard, dose adjustment of anticholinergic drugs prescribed to alleviate AP-induced extrapyramidal ADRs may potentially improve cognitive functioning in patients with SSD [53].

In the study by Tani H. et al. (2020) [52], dose reduction of APs increased the risk of relapse of SSD but improved neurocognitive functions. At the same time, a moderate reduction in AP dose (to no less than 200 mg/day in chlorpromazine equivalents) was associated with a decrease in the severity of AP-induced extrapyramidal ADRs and negative symptoms of SSD during maintenance therapy of the psychiatric disorder. Thus, when reducing the AP dose, the long-term risk of relapse should be considered in young patients with a relatively short duration of illness, and the AP dose should not be reduced below 200 mg/day in chlorpromazine equivalents [52]. The study by Allot K. et al. (2024) [10] partially confirms these findings: controlled reduction of AP dose may lead to improved cognitive functioning in patients with SSD.

Dose-dependent AP-induced ADRs also include extrapyramidal disorders [49]. It is well known that there is a close relationship between extrapyramidal disorders, neurocognitive deficits, and negative symptoms of SSD [52, 54, 55], and that genetic factors play a significant role in the development of these ADRs. In this regard, it can be hypothesized that personalized selection of APs based on PGx and identification of carriers of minor *ABCB1* genotypes/haplotypes, together with controlled dose reduction under psychiatric supervision, may prevent or significantly reduce the severity of extrapyramidal disorders and, consequently, the associated secondary CDs.

It is well known that sleep and cognitive functions are interrelated [56]. In the population of patients with schizophrenia, this relationship takes on particular clinical significance. Sleep disturbances are highly prevalent in these patients. Correction of sleep disturbances may potentially improve the cognitive status of patients with SSD [57, 58]. Sleep disorders secondary to extrapyramidal disorders may also be corrected by switching APs or adjusting the dosing regimen. Thus, direct interventions (sleep hygiene normalization, pharmacotherapy of insomnia) are complemented by indirect strategies that take into account genetic factors (carriage of minor homozygous/heterozygous genotypes and haplotypes of low-functioning and non-functioning SNVs in the *ABCB1* gene)

6. METHODOLOGICAL LIMITATIONS OF ASSOCIATIVE GENETIC STUDIES IN PSYCHIATRY

The main methodological problems and limitations of associative genetic studies are presented in **Table 5**: usually small sample size of associative genetic studies of the *ABCB1* gene in psychiatry; heterogeneity of the sample with respect to AP therapy of SSDs; inconsistency of data on previously studied *ABCB1* SNVs; ethnic heterogeneity of the sample; lack of standardization of neurocognitive testing methods in patients with SSDs.

Table 5. Main methodological problems in studying the association between *ABCB1* genotypes and haplotypes and the development of antipsychotic-induced cognitive disorders.

Methodological problem	Examples	Potential solutions
Small sample size	In most clinical and associative genetic studies of the <i>ABCB1</i> gene in SSDs, the sample size is fewer than 250 subjects (for examples: Vijayan N. et al., 2012 — n = 192; Jovanović N. et al., 2010 — n = 83) [47, 48]	Large prospective cohort studies; meta-analyses on pooled samples
Heterogeneity of the sample with respect to AP therapy	Mixing of monotherapy and polytherapy within the same sample [30]	Studies of monotherapy with a specific AP
Inconsistency of data on previously studied <i>ABCB1</i> SNVs	Effect of the homozygous TT phenotype at rs1045642 of the <i>ABCB1</i> gene on risperidone pharmacokinetics (for examples: Jovanović N. et al., 2010 — increased plasma concentration; Saiz-Rodríguez M. et al., 2018 — enhanced elimination (decreased plasma concentration) [29, 47]	Haplotype analysis (1236C>T + 2677G>T + 3435>T) instead of analysis of isolated SNVs
Ethnic heterogeneity	Frequencies of minor alleles in the <i>ABCB1</i> gene vary significantly across different populations [23, 45, 48]	Ethno-specific studies. Adjustment for ethnicity of patients with SSD
Lack of standardization of neurocognitive testing methods	The use of different psychometric instruments (BACS, PANSS, BPRS) complicates the comparison of results [30, 46]	Adoption of the MATRICS Consensus Cognitive Battery as a standard

Abbreviations: BPRS – the brief psychiatric rating scale; PANSS – the positive and negative syndrome scale; BACS – the brief assessment of cognition in schizophrenia; SSDs – schizophrenia spectrum disorders.

Notes: The MATRICS Consensus Cognitive Battery is a standardized tool for assessing cognitive disorders in patients with schizophrenia, developed within the framework of the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative of the U.S. National Institute of Mental Health (NIMH).

7. CONCLUSIONS

Thus, three SNVs in the *ABCB1* gene – rs1128503 (C1236T), rs2032582 (G2677T/A) and rs1045642 (C3435T) – have proven pharmacokinetic significance in AP therapy of SSD. At the same time, direct, methodologically rigorous evidence for an association of genotypes and/or haplotypes of these SNVs with neurocognitive outcomes during AP therapy of SSDs has not yet been found. Although the association remains theoretically justified, it has not yet been confirmed by clinical studies. To address this problem, prospective associative studies with haplotype analysis of the three key SNVs in the *ABCB1* gene, AP monotherapy, and ethnically homogeneous samples of patients with SSDs are needed.

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