ABC genes, especially ABCB1 (ATP-binding cassette, sub-family B (MDR/TAP), member 1; Doxorubicin resistance; Multidrug resistance 1; Multidrug resistance protein 1; P-glycoprotein 1; P-glycoprotein 1/multiple drug resistance 1; P-gp) (7q21.12), ABCCI (9q31.1), ABCG2 (White1) (21q22.3), and other genes of this family encode proteins which are essential for drug metabolism and transport. The multidrug efflux transporters P-gp, multidrug-resistance associated protein 4 (MRP4) and breast cancer resistance protein (BCRP), located on endothelial cells lining brain vasculature, play important roles in limiting movement of substances into and enhancing their efflux from the brain. Transporters also cooperate with Phase I/Phase II metabolism enzymes by eliminating drug metabolites. Their major features are their capacity to recognize drugs belonging to unrelated pharmacological classes, and their redundacy, by which a single molecule can act as a substrate for different transporters. This ensures an efficient neuroprotection against xenobiotic invasions. The pharmacological induction of ABC gene expression is a mechanism of drug interaction, which may affect substrates of the up-regulated transporter, and over expression of MDR transporters confers resistance to anticancer agents and CNS drugs [1,2]. Mutations in ABC transporters influence pathogenesis and therapeutics of brain disorders [3].

ABCB1 is probably the most important drug transporter in the brain. The ABCB1 gene maps on 7q21.12 spanning 209.39 kb (29 Exons) with the structure of a P-glycoprotein and a Y-box sequence 5′-CTGATTGG-3′ in its cis-regulatory elements. Several transcripts/variants (ABCB1-001: 4645 bp, ABCB1-002: 3602 bp, ABCB1-003: 461 bp, ABCB1-004: 582 bp, ABCB1-005: 555 bp, ABCB1-006: 913 bp, ABCB1-007: 1864 bp, ABCB1-008: 642 bp, ABCB1-009: 787 bp, ABCB1-010: 539 bp, ABCB1-201: 345 bp) are highly expressed in adrenal gland, blood-brain barrier (BBB), brain, kidney, liver, placentα, small intestine, and uterus, and low expression is present in many other tissues. These gene maps on 7q21.12 spanning 209.39 kb (29 Exons) with the structure of a P-glycoprotein and a Y-box sequence 5′-CTGATTGG-3′ in its cis-regulatory elements. Several transcripts/variants (ABCB1-001: 4645 bp, ABCB1-002: 3602 bp, ABCB1-003: 461 bp, ABCB1-004: 582 bp, ABCB1-005: 555 bp, ABCB1-006: 913 bp, ABCB1-007: 1864 bp, ABCB1-008: 642 bp, ABCB1-009: 787 bp, ABCB1-010: 539 bp, ABCB1-201: 345 bp) are highly expressed in adrenal gland, blood-brain barrier (BBB), brain, kidney, liver, placentα, small intestine, and uterus, and low expression is present in many other tissues. These

About 1630 ABCB1 variants have been identified [4]. Of interest, ABCB1 has approximately 116 polymorphic sites in Caucasians and 127 in African-Americans with a minor allele frequency greater than 5%. Some of the most commonly studied variants are 1236C>T, 2677G>A/T and 3435C>T and the most commonly studied haplotype involves the 1236, 2677 and 3435 (TTT) SNPs and 3 intronic SNPs (intron 9, intron 13, intron 14) named ABCB1*13. There are many other ABCB1 variants such as 129C>T (5′-UTR), 61A>G (Asn21Asp) and 1199G>A (Ser400Asn) that have been studied in vivo and in vitro. To date, there is no clear consensus on the impact of any of these variants on drug disposition, response or toxicity [4].

Variants of the ABCB1 gene have been associated with a diverse number of diseases and with a great variety of drugs, natural products and endogenous agents [4]. Over 1270 drugs have been reported to be associated with the ABCB1 transporter protein (P-gp), of which 490 are substrates, 618 are inhibitors, 182 are inducers, and 269 additional compounds which belong to different pharmacological categories of products with potential ABCB1 interaction [4].

ATP-binding cassette (ABC) transporters, which are localized on the surface of brain endothelial cells of the BBB and brain parenchyma, affect Aβ transport (flux) across the BBB contributing to the pathogenesis of Alzheimer’s disease (AD) [5-12]. One of the clearance pathways of amyloid-β is transport across the BBB via efflux transporters. Several BBB transporters have been implicated in Aβ exchange between brain parenchyma and the circulation [5-12]. Deficiency of either of the two major efflux pumps, ABCB1 and ABCG2, involved in Aβ trafficking across the BBB, results in increased accumulation of peripherally-injected Aβ42 in the brain [13]. Decreased clearance of amyloid-β from the brain may lead to elevated amyloid-β levels. There is an age-related decrease in P-gp expression, Aβ42 itself downregulates the expression of P-gp and other Aβ transporters, which could exacerbate the intracerebral accumulation of Aβ and thereby accelerate neurodegeneration in AD and cerebral β-amyloid angiopathy [11]. Amyloid efflux transporter expression at the BBB declines with aging in normal conditions [14], and expression of P-gp protein is significantly lower in hippocampal vessels of patients with AD compared to normal individuals [12].

ATP binding cassette subfamily G member 2 (ABCG2) is involved in amyloid-β transport and was found to be up-regulated in AD brains. A functional polymorphism of the ABCG2 gene (C421A; rs2231142) (ABCG2 C/C genotype) was associated with AD in the Hungarian population. The ABCG2 C/C genotype and the APOE E4 allele may also exert an interactive effect on AD risk [15]. Genome-wide significance in fully adjusted models was observed for a single-nucleotide polymorphism (SNP) in ABCA7 (rs11556088, allele = G; frequency, 0.09 cases and 0.06 controls), which is in linkage disequilibrium with SNPs associated with AD in Europeans. The effect size for the SNP in
ABCA7 was comparable with that of the APOE e4-determining SNP rs429358 (allele = C; frequency, 0.30 cases and 0.18 controls) [5].

Single-nucleotide polymorphisms in the ABCB1 gene have been associated with altered P-glycoprotein expression and function. Van Assema et al. [10] assessed the effects of C1236T, G2677T/A and C3435T single-nucleotide polymorphisms in ABCB1 on BBB P-gp function in healthy subjects and patients with AD. In healthy controls, binding potential did not differ between subjects without and with one or more T present in C1236T, G2677T and C3435T. In contrast, patients with AD with one or more T in C1236T, G2677T and C3435T had significantly higher binding potential values than patients without a T. There was a relationship between binding potential and T dose in C1236T and G2677T. In AD patients, C1236T, G2677T/A and C3435T SNPs may be related to changes in P-gp function at the BBB, and genetic variations in ABCB1 might contribute to the progression of amyloid-β deposition in the brain. Kohen et al. [16] investigated a possible association between 2 common ABCB1 polymorphisms, G2677T/A (Ala893Ser/Thr) and C3435T, AD, and CSF levels of Aβ in patients with mild cognitive impairment (MCI), AD, as well as normal controls only the ABCB1 gene exhibited significantly positive correlation.

The drug transporter ABCB1 directly transports Aβ from the brain into the blood circulation, whereas the cholesterol transporter ABCA1 neutralizes Aβ aggregation capacity in an Apolipoprotein E (ApoE)-dependent manner, facilitating Aβ subsequent elimination from the biomarker of AD [18].

It is also important that drugs for AD treatment optimize CNS penetration by minimizing hydrogen bond donors and reducing P-gp-mediated efflux [28-30]. The increase of P-gp expression and activity at the BBB may represent a novel approach to restoring diminished BBB function. LXR activation may affect the transport of Aβ peptides across the BBB. LXR agonists (24S-hydroxycholesterol, 27-hydroxycholesterol and T0901317) modulate the expression of target genes involved in cholesterol homeostasis (ABCA1) and promote cellular cholesterol efflux to apolipoprotein A-I and high density lipoproteins. LXR stimulation increases the expression of the ABCB1 transporter, which restricts Aβ peptide influx [27].

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