The ABCB1 Transporter in Alzheimer’s Disease

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ABSTRACT

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The ABCB1 gene encodes a subfamily B (MDR/TAP), member 1; Doxorubicin resistance; Multidrug resistance 1; Multidrug resistance protein 1; P-glycoprotein; P glycoprotein 1/ multiple drug resistance 1; P-gp; (7q21.12), ABCG2 (21q22.3), of the ATP binding cassette super-family, sub-family B 002: 5.89 kDa; 51 aa. ABCB1-003: 5.68 kDa; 48 aa. ABCB1-010: 539 bp. ABCB1-201: 141.48 kDa; 1280 aa. ABCB1-2010: 59 bp. ABCB1-201: 345 bp) are highly expressed in adrenal gland, brain, kidney, liver, placenta, small intestine, and uterus, and low expression is present in many other tissues. These transcripts encode a protein (ABCB1-001: 141.48 kDa; 1280 aa. ABCB1-002: 5.89 kDa; 51 aa. ABCB1-003: 5.68 kDa; 48 aa. ABCB1-201: 2.52 kDa; 22 aa) of the ATP binding cassette super-family, subfamily B (MDR/TAP) with two ATP binding and two transmembrane (2TM) domains (2 × 6 segments), acting as a transport carrier and a lipid translocase of broad specificity. This is a large transmembrane protein which is an integral part of the BBB and functions as a drug-transport pump transporting a variety of drugs from the brain back into the blood. Functions of this protein include the following: ABC transporter, traffic ATPase, energy-dependent efflux pump responsible for decreased drug accumulation in multidrug-resistant cells; potentially implicated in cholesterol transport; may maintain neural stem/progenitor cells in an undifferentiated state and could be a neural stem/progenitor marker [4].

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 intrinsic 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 pharmaceutical 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 Aβ1-40 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, Aβ1-40 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 ε4 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 (rs11556680, 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

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Received February 04, 2014; Accepted February 05, 2014; Published February 12, 2014


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ABCA7 was comparable with that of the APOE ε4-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. Kohren et al. [16] investigated a possible association between 2 common ABCB1 polymorphisms, G2677T/A (A1A893Ser/Thr) and C3435T; AD, and CSF levels of Aβ and no strong evidence for association was found. Frankfort et al. [17] studied ABCB1 SNPs (C1236T in exon 12, G2677T/A in exon 21 and C3435T in exon 26) and inferred haplotypes in patients with dementia and age-matched controls. They found no differences between both groups; however, in a transcriptome analysis of leukocytes from patients with mild cognitive impairment (MCI), AD, as well as normal controls only the ABCB1 gene exhibited significantly positive correlation with Mini-mental state examination (MMSE) scores, representing a novel biomarker of AD [18].

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 brain and tracers that are inhibitors of P-gp function [21,22]. The increase of P-gp expression and activity in AD has been associated with altered P-gp substrate binding sites [26]. Activation of the Liver X receptors (LXRs) by natural or synthetic agonists decreases the amyloid burden and enhances cognitive function in transgenic murine models of AD. LXR activation may affect the transport of Aβ peptides across the BBB. LXRs 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]. 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 by a P-gp inducer could be an effective pharmacological strategy in slowing or halting the progression of AD [31].

References


