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LETTER TO THE EDITOR Open Access

# Revisiting *ABCB1* polymorphism: a missing piece in Alzheimer's risk and treatment?

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**To the editor**

Alzheimer's disease (AD) research is entering a transformative era, with new treatments and biomarker-driven diagnosis reshaping the field. These advancements call for a renewed focus on understanding disease mechanisms to refine prevention and personalize care. A solid body of evidence highlights a complex interaction between environmental and genetic factors, with amyloid-beta (Aß) protein accumulation initiating AD pathogenesis [1]. The APOE ε4 allele is the strongest genetic risk factor identified for sporadic AD. Beyond APOE, other genetic risk factors include genes encoding ABC transporters, such as ABCB1, ABCC1, ABCC4, ABCG2, and ABCA7, which have different levels of impact on the disease [2]. Among these, ABCB1 is the most studied; however, the role of its polymorphisms in AD remains unclear and requires further investigation. ABCB1 belongs to ATP-Binding Cassette (ABC) transporters, which facilitate the movement of diverse molecules across cellular membranes, including those within the central nervous system. ABCB1 limits the passage of xenobiotics and transports endogenous compounds, such as Aß, across the blood-brain barrier (BBB). A defect in ABCB1-mediated Aß clearance directly links this transporter to the pathophysiology of AD [2]. Position Emission Tomography studies using ABCB1-specific radiotracers, like $^{11}$C-verapamil, have shown reduced ABCB1 activity at the BBB in animals and patients with AD. Postmortem studies of older adults without dementia showed an inverse relationship between Aβ deposition and ABCB1 expression. Interestingly, Aβ accumulation seems to reduce both ABCB1 expression and activity. This raises the "chicken-or-egg" question: Does the disease reduce ABCB1 activity, or does less ABCB1 drive the disease? Alternatively, a self-reinforcing mechanism involving Aβ accumulation and reduced ABCB1 expression might exist. While the *ABCB1* polymorphism's impact on xenobiotic transport is clear, its link to AD risk is more controversial. Key *ABCB1* single nucleotide polymorphisms (SNPs) studied include 3435 C > T (rs1045642), 2677G > T/A (rs2032582), and 1236 C > T (rs1128503), known to influence ABCB1 activity. The frequency of the T allele in Caucasians is reported as 0.561, 0.464, and 0.459 for these SNPs, respectively. Yet, these results remain inconsistent across studies. A meta-analysis of these studies conducted between 2006 and 2014 suggests that the 3435 C > T, 2677G > T/A, and the 1236T/2677T/3435C haplotype are significantly associated with AD susceptibility [3]. These polymorphisms could reduce the efflux capacity of Aß at the BBB, thereby increasing the risk of developing AD. However, a major limitation of these studies is the lack of biomarker confirmation for AD diagnosis. At the time, the absence of evidence for amyloid lesions or other core biological markers was inconsistent with the current understanding of AD as a clinico-biological entity [4]. The use of biomarkers in routine clinical practice has been steadily increasing, establishing them as essential tools for early and accurate diagnosis. Consequently, relying solely on

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outdated clinical approaches—with diagnostic error rates as high as 20–30%—hampers the accurate assessment of the impact of *ABCB1* polymorphisms on Aß pathology in AD. In other words, since ABCB1 clears Aβ, the lack of evidence for amyloid pathology in these studies is problematic. These studies also lacked data on potential confounders, such as cardiovascular risk factors and *APOE* genotyping. Refining these analyses with crucial data could unlock deeper insights into AD risk, offering clarity where uncertainty persists. Anti-amyloid immunotherapies, which have emerged in the USA and Asia and will soon be available in Europe, represent a breakthrough in the therapeutic landscape of AD. The issue of treatment tolerance is critical, with experts highlighting the risk of complications associated with amyloid clearance, known as Amyloid-Related Imaging Abnormalities (ARIA) [5]. These complications are closely linked to the *APOE* genotype, which influences Aß clearance. Furthermore, the *ABCB1* polymorphism may act as a modulator of this effect, further influencing Aß clearance dynamics and consequently the risk of ARIA. Recent advances in AD research and the therapeutic landscape underscore the need to re-examine the role of ABCB1 polymorphisms. By leveraging modern biomarkers and exploring their potential as modulators of treatment response, particularly in the context of anti-amyloid immunotherapies, we can unlock critical insights into AD pathophysiology and improve patient outcomes. Future clinical trials should prioritize biomarker-integrated approaches and investigate the interplay between *ABCB1* polymorphisms, *APOE* genotype, and Aβ clearance dynamics to guide personalized interventions.

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