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# 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 biomarkerdriven 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 ɛ4 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

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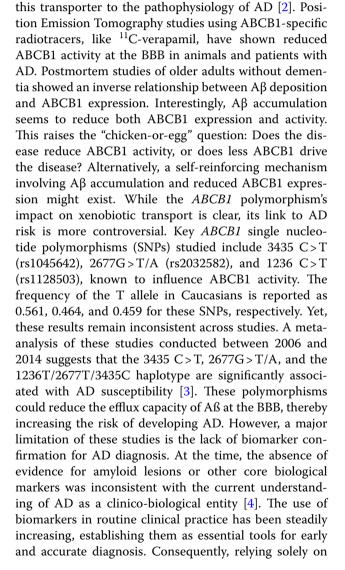
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outdated clinical approaches—with diagnostic error rates as high as 20-30%—hampers the accurate assessment of the impact of ABCB1 polymorphisms on Aß pathology in AD. In other words, since ABCB1 clears AB, the lack of evidence for amyloid pathology 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 A $\beta$  clearance dynamics to guide personalized interventions.

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#### **Competing interests**

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