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Commentary

Influence of ABCB1 Gene Variants on Antidepressant Response in Major Depressive Disorder

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DESCRIPTION

The treatment of Major Depressive Disorder (MDD) remains a significant challenge due to the complex interplay of genetic, biochemical and environmental factors that determine therapeutic response. Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs) are commonly prescribed pharmacological agents; however, response rates vary widely among patients. One of the critical determinants of interindividual variability in antidepressant efficacy and toxicity is the expression and function of drug transporters, particularly P-glycoprotein encoded by the *ABCB1* gene.

ABCB1, also known as MDR1, is a member of the ATP-binding cassette transporter family and plays a key role in the efflux of various xenobiotics across the blood-brain barrier. It limits the penetration of several antidepressants into the central nervous system, thereby affecting their therapeutic concentrations in target tissues. Polymorphisms in the *ABCB1* gene have been implicated in modulating the pharmacokinetics and pharmacodynamics of multiple psychotropic agents, influencing both efficacy and adverse event profiles.

Among the several Single Nucleotide Polymorphisms (SNPs) identified in the *ABCB1 gene, C3435T (rs1045642), G2677T/A (rs2032582)* and *C1236T (rs1128503)* have been most extensively studied. These SNPs are often in linkage disequilibrium and may form haplotypes that affect the expression levels or function of P-glycoprotein. Patients carrying the TT genotype at position 3435 have been reported to exhibit lower P-glycoprotein expression, resulting in higher central nervous system concentrations of P-glycoprotein substrates such as paroxetine, venlafaxine and amitriptyline.

In a large European cohort study involving over 800 patients with MDD, those with the TT genotype at rs1045642 were found to have a significantly higher remission rate to SSRIs after 8 weeks of treatment compared to those with CC or CT genotypes. Interestingly, these patients also reported fewer central nervous system-related adverse effects, suggesting that genetic modulation of P-glycoprotein expression has dual relevance for both efficacy and tolerability. This aligns with the hypothesis that enhanced drug delivery to the brain improves clinical response without substantially increasing toxicity.

On the other hand, poor responders to antidepressant therapy often carry alleles associated with increased P-glycoprotein function, which leads to sub therapeutic central concentrations despite normal plasma levels. This pharmacoresistance contributes to the observed lag in treatment response and the frequent need for dose escalation or drug switching. Incorporating *ABCB1* genotyping into routine psychiatric practice could therefore allow for early identification of likely responders and non-responders, streamlining therapeutic decisions and reducing trial-and-error prescribing.

Despite encouraging results, the utility of *ABCB1* pharmacogenetic testing in routine clinical practice is not yet universally accepted. Some studies have reported inconsistent associations between *ABCB1* polymorphisms and antidepressant outcomes, possibly due to differences in study design, population genetics and drug-specific substrate characteristics. Moreover, the presence of compensatory transport mechanisms and metabolic enzyme polymorphisms such as those in *CYP2D6* and *CYP2C19* further complicate the interpretation of *ABCB1's* role in antidepressant pharmacokinetics.

Nevertheless, clinical guidelines are slowly evolving. The Dutch Pharmacogenetics Working Group and other international consortia have begun to acknowledge the contribution of transporter polymorphisms in psychopharmacology. Pilot programs in Spain and Italy have introduced *ABCB1* genotyping into precision psychiatry protocols, integrating it with broader pharmacogenomics panels to guide treatment in refractory MDD cases. The cost-effectiveness of such approaches is currently under evaluation, with preliminary results indicating a reduction in hospitalization rates and improved medication adherence.

From a Pharmacoproteomic perspective, ongoing research is also focused on identifying protein expression profiles associated with *ABCB1* polymorphisms. Quantitative proteomic assays using mass spectrometry have demonstrated altered P-

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glycoprotein abundance in patients with the *3435TT* genotype, further validating the functional consequences of this variant. Proteomic biomarkers could eventually complement genetic data to provide a more comprehensive assessment of transporter function and drug disposition in the brain.