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The *ABCB1* transporter gene and antidepressant response

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Abstract

P-glycoprotein, encoded by the *ABCB1* gene, may modulate the brain concentration of several antidepressants. Functional genetic variation is thought to exist in this gene, and here we review several studies that have attempted to associate this variation with clinical response to antidepressant treatment.

Introduction and context

Major depression is one of the most common and debilitating psychiatric disorders [1]. The most common first line pharmacotherapy for depression is selective serotonin uptake inhibitors (SSRIs). Unfortunately, only approximately one-third of patients achieve remission (absence of depressive symptoms) after an adequate trial of a single SSRI [2]. Among other possible causes, genetic variation in relevant pharmacokinetic genes may be one factor that leads to variable patient response to SSRIs.

P-glycoprotein, which is encoded by the *ABCB1* gene (also known as *MDR1*), is an ABC-transporter that is expressed in many tissues, including the liver, intestines and endothelial cells of the blood-brain barrier [3]. The function of P-glycoprotein is to facilitate the transport of a broad range of endogenous and xenobiotic molecules across cellular membranes. Of particular relevance is the protein's role in the blood-brain barrier, where *in vivo* studies of mice deficient for the *ABCB1* gene have shown that P-glycoprotein may play a part in modulating the concentration of certain antidepressants in the brain. Studies using *ABCB1* knockout mice by Uhr and colleagues [4–7] have shown that amitriptyline, trimipramine, venlafaxine, doxepin and the SSRIs, citalopram and paroxetine, appear to be substrates of P-glycoprotein, while melperone, mirtazapine, and the SSRI fluoxetine do not. However, contradictory evidence suggesting that citalopram is not a substrate for P-glycoprotein was observed by other groups utilizing different *in vitro* model systems. Using monolayers of bovine brain microvessel endothelial cells, Rochat *et al.* [8] showed no change in citalopram efflux with the potent P-glycoprotein inhibitor, cyclosporin A, indicating that citalopram is not actively transported by P-glycoprotein. In a large-scale study investigating the active transport of many drugs, Mahar Doan and colleagues [9] found citalopram was not strongly transported across monolayers of a Madin-Darby canine kidney (MDCK type II) cell line stably transfected with *ABCB1*. In addition, utilizing both a porcine kidney epithelial cell line (LLC-PK1) stably transfected with *ABCB1* and primary porcine brain capillary endothelial cells as model systems, Weiss *et al.* [10] showed that citalopram and venlafaxine were not strong inhibitors of P-glycoprotein.

Naturally occurring DNA variation in the human *ABCB1* gene has been shown to affect the function of P-glycoprotein [11]. Thus, it is reasonable to hypothesize that a portion of the variation in response to antidepressants may be due to inter-patient variability in P-glycoprotein function. Three common variants in linkage disequilibrium in the *ABCB1* gene have been repeatedly investigated in association studies; the synonymous C1236T single nucleotide polymorphism (SNP; rs1128502) in exon 12, the non-synonymous SNP G2677T/A (rs2032582) in exon 2, and the synonymous

SNP C3435T (rs1045642) in exon 26. Studies by Hoffmeyer *et al*. [11] showed that the C3435T SNP leads to variable expression of P-glycoprotein in the intestines, although this effect has not been observed in all studies [12].

One of the earliest association studies of *ABCB1* genetic variants and response to antidepressants involved 55 subjects with bipolar disorder treated with a variety of antidepressants [13]. The C3435T SNP genotype status of 26 subjects with a history of antidepressant-induced mania were compared to 29 age, ethnicity and gender matched subjects without a history of antidepressant-induced mania. This study observed no association between antidepressant-induced mania and the C3435T SNP in the *ABCB1* gene in this clinical population.

Major recent advances

A study by Laika and colleagues [14] investigated the association between the G2677T/A SNP and response to treatment with amitriptyline, a tricyclic antidepressant. This study involved 50 Caucasian inpatients with major depressive disorder that received a fixed dose of 75 mg amitriptyline for 3 weeks. The authors utilized the Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impression Scale to gauge therapeutic response and the Dosage Record and Treatment Emergent Symptoms Scale (DOTES) to gauge subjects' side-effect profiles. No association between the G2677T/A SNP and therapeutic response, side-effects or mean serum concentration of amitriptyline after 3 weeks of treatment was observed. Interestingly, the authors previously reported an association between functional polymorphisms in CYP2C19 and CYP2D6 and response to amitriptyline in the same clinical population [15].

In a recent study by Fukui *et al*. [16], the C3435T SNP was investigated and shown to affect mean fluvoxamine plasma concentration. This study involved 62 Japanese outpatients, of which 55 were diagnosed with major depressive disorder. Subjects were given fluvoxamine in 50 mg/day increments up to a 200 mg/day dosage. Serum levels were obtained after 2 weeks on the same dosage in order to obtain steady state levels. Association between plasma concentration and C3435T genotype was observed at the 200 mg/day dosage, but not at the 150 mg/day, 100 mg/day, or 50 mg/day dosages.

In a larger study by Uhr and colleagues [7], the authors investigated the association of *ABCB1* variants with antidepressant remission. The study included 443 inpatients with major depression that were treated with a variety of antidepressants and evaluated with the HAM-D rating scale. The authors genotyped these subjects for G2677T/A and C3435T SNPs, as well as 93 other variants in the *ABCB1* gene and tested them for association with remission (HAM-D < 10) at treatment weeks 4, 5, and 6. The G2677T/A and C3435T SNPs were not associated with remission; however, two haplotype blocks were associated with remission at week 4 ($P = 0.0003$), week 5 ($P = 0.008$) and week 6 ($P = 0.007$) in subjects taking putative P-glycoprotein substrates (amitriptyline, citalopram, paroxetine, or venlafaxine). Interestingly, the association was not observed in subjects taking the putative non-P-glycoprotein substrate mirtazapine. The associated SNPs were contained in intronic regions of the gene and were captured by two haplotype blocks, one containing SNPs rs2235067, rs4148740, rs2032583, rs4148739, rs11983225, rs2235040, and rs12720067, and the other containing SNPs rs7787082 and rs10248420. Within each block, the reported SNPs were highly correlated with one another. The authors note that the associated variants exhibit strong ethnic differences in allele frequencies and speculate that these variants could contribute to the ethnic differences seen in clinical response to antidepressants.

In a study utilizing the much larger Sequenced Treatment Alternatives to Relieve Depression (STAR*D) clinical trial population, Peters and colleagues [17] investigated the association of *ABCB1* variants and response to the SSRI citalopram. In an effort to limit type I error, the authors utilized a two-stage approach for analysis. Within each ethnic group, clinical response and gender, the subjects were randomly split into a discovery (n = 831) and validation sample (n = 1,046) set. Variants that were associated at $P < 0.05$ in the discovery set were investigated in the validation set. Clinical response was assessed using the Quick Inventory of Depressive Symptomatology (QIDS) scale. The authors observed no association between the *ABCB1* variants investigated (C1236T, G2677T/A, and C3435T) and citalopram response, response specificity, remission, or intolerance after at least 6 weeks of treatment. While not the original focus of their study, the authors also report data regarding the *ABCB1* SNPs associated with remission from Uhr *et al*. [7]. As part of a genome-wide association study, two of the variants in the first haplotype block reported by Uhr *et al*. were genotyped in the discovery sample set and were not associated with citalopram remission in the STAR*D population. Unfortunately, the authors did not have genotype data on the second haplotype block reported by Uhr *et al*. [7], and thus could not test whether this region was associated with antidepressant response.

In a study of 68 Japanese subjects with major depression, Kato *et al*. [18] investigated the association between the C1236T, G2677T/A, and C3435T SNPs and response to the SSRI paroxetine. Subjects were scored for depression severity using the HAM-D rating scale, and the authors used linear regression to test for association between the variants and percent decrease of HAM-D score from baseline. A significant association was observed between the G2677T/A SNP and paroxetine response at week 6 (P = 0.01), though no associations were observed with the other two SNPs. Interestingly, the authors noted that the variants were not in linkage disequilibrium as strong as previously reported, which they attributed to the small sample size used in this study.

Future directions

Some studies have suggested that P-glycoprotein may modulate brain concentrations of certain antidepressant drugs [4–7], while other studies indicate weak or no interaction between antidepressants and P-glycoprotein [8–10]. Despite this conflicting evidence, several studies to date have further investigated the effect of *ABCB1* variation and clinical response to antidepressants. Results have been equivocal, with many studies failing to report a strong association. There are several possible reasons for these conflicting results, including limited sample sizes, differing statistical methods, phenotypic heterogeneity, or population stratification. These factors are also thought to confound genetic association studies with other complex phenotypes [19]. A careful meta-analysis of the data may give insight into any true genetic effects. Furthermore, standardization of clinical response phenotype definitions would help mitigate risks of missing true effects. Given that the functional effects of the three most commonly studied *ABCB1* variants are not completely understood and may in fact be in linkage disequilibrium with the true causative variants, more work is needed to understand the genetic architecture of this gene and the functional and clinical impact of both common and rare variants. The study by Uhr *et al*. shows that comprehensive genotyping of the entire *ABCB1* locus may be preferable to simple assessment of a small set of putatively functional variants. Finally, in order to fully dissect the role of *ABCB1* variants in response to antidepressants, well-powered, prospective clinical trials need to be initiated.

Abbreviations

HAM-D, Hamilton Depression Rating Scale; SNP, single nucleotide polymorphism; SSRI, selective serotonin uptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

Competing interests

The authors declare that they have no competing interests.

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