Get to know a gene: UGT1A4

What is UGT1A4?

The UGT1A4 gene encodes an enzyme of the glucuronidation pathway, a phase II metabolism process that transforms small lipophilic molecules into water-soluble excretable metabolites. The UGT1A4 enzyme mediates the metabolism of important psychotropic medications, including some tricyclic antidepressants, antipsychotics, and mood stabilizers[1–20]. Therefore, genetic polymorphisms in this gene may have pharmacological importance.

More than 100 UGT1A4 polymorphisms have been identified. Two of the best studied polymorphisms are UGT1A4*2, which results in a proline to threonine amino acid change at codon 24 (P24T) caused by a single C>A substitution, and UGT1A4*3, which results in a leucine to valine amino acid change at codon 48 (L48V) caused by a single T>G substitution[21]. Both of these variants are located in the first exon of the UGT1A4 gene and may result in altered enzyme activity, with UGT1A4*3 increasing glucuronidation and UGT1A4*2 decreasing glucuronidation.

Is there a connection between UGT1A4*3 rapid metabolism and the efficacy of psychotropic medications?

The UGT1A4*3 variant has been shown to have an effect on the metabolism of lamotrigine. Three in vivo studies (n=413) investigated the effect of UGT1A4*3 on lamotrigine metabolism and demonstrated that carriers of the G allele (TG + GG) had significantly reduced lamotrigine concentrations compared to wild-type (TT)[3,22,23]. One of these studies specifically examined the effect of genotype on lamotrigine efficacy by comparing seizure frequency before and after lamotrigine therapy. This study found that wild-type (TT) subjects exhibited significantly better therapeutic efficacy compared to carriers of the G allele[22]. While a fourth in vivo study (n=75) failed to find an association between UGT1A4*3 and lamotrigine clearance, the authors acknowledge several limitations to the study, which may cause this finding to be a false null association[24]. Contrary to the in vivo results, one in vitro study reported a decrease in the rate of lamotrigine glucuronidation in cells expressing the UGT1A4*3 variant. However, the authors give potential explanations for these contradictory findings, such as differences in experimental design and stability of enzyme preparations[25].

The UGT1A4*3 variant has also been shown to affect the metabolism of olanzapine. Two in vitro studies investigated the effect of UGT1A4*3 on olanzapine metabolism and found that UGT1A4*3 causes increased enzyme activity[9,26]. Multivariate analyses indicated that Caucasian subjects (n=129) who were either heterozygous or homozygous for the UGT1A4*3 allelic variant exhibited a significant increase in olanzapine glucuronidation over patients with homozygous wild type genotypes (38% and 246% higher in *1/*3 and *3/*3 patients, respectively). Although serum concentrations of the parent drug were not affected by UGT1A4 genotype in this study, an increase in the glucuronidation rate supports the ultrarapid phenotype of this polymorphism[26]. Additionally, three in vivo studies (n=247) showed clear trends towards lower olanzapine concentrations in *3 allele carriers[27–29]. While another in vivo study (n=47) found a trend towards higher olanzapine concentrations in UGT1A4*3 carriers[30], it has been shown that this contradictory finding may be attributed to erroneous genotyping methods [29].

Is there a connection between UGT1A4*2 reduced metabolism and the efficacy of psychotropic medications?

The overall literature on UGT1A4*2 is quite limited. Olanzapine, clozapine, and lamotrigine have been individually evaluated in three separate in vitro studies, each examining the effect of UGT1A4*2 on metabolism. All three studies found that UGT1A4*2 may cause lower enzyme activity[9,20,25]. However, three in vivo studies (n=415) examined the effect of UGT1A4*2 on lamotrigine metabolism, and found that the variant allele frequency was either too low to determine the effect of this polymorphism or the results were not significant[3,22,23].

Conclusions

Multiple clinical studies have found UGT1A4*3 to be associated with higher enzyme activity[3,22,23,26–29]. This could result in clinically relevant reductions in exposure of drugs for which UGT1A4 is the major elimination route. Furthermore, it has also been shown that carriers of the UGT1A4*3 variant exhibited reduced therapeutic efficacy[22]. Thus, higher than average doses of UGT1A4 substrates may be required for patients carrying the UGT1A4*3 variant.

Due to the lack of in vivo evidence, more data is needed before UGT1A4*2 can be recommended for use in treatment selection.

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