White Paper Series

Get to know a gene: *HTR2A*

What is *HTR2A?*

The 5-HT_{2A} receptor, encoded by the *HTR2A* gene, is responsible for post-synaptic serotonin signaling and is a target for many antipsychotics and antidepressants.[1] Two single nucleotide polymorphisms (SNPs) in *HTR2A,* rs6311 (-1438G>A) and rs6313 (102C>T), have been studied for associations with response and side effects associated with various psychotropic medications. These two polymorphisms, which do not change the encoded protein, are in high linkage disequilibrium.[1–4] Data for a third polymorphism, rs7997012, is also summarized here.[5]

What are the functional effects of *HTR2A* variants?

Six studies have investigated the effects of the -1438G>A and 102C>T polymorphisms on *HTR2A* RNA levels, with inconsistent results. Three *ex vivo* studies failed to find a consistent association between the SNPs and *HTR2A* RNA expression.[6–8] A fourth *ex vivo* study found that healthy controls (n=35) with the -1438GG genotype had reduced mRNA levels compared with AA genotype subjects, with heterozygotes displaying intermediate levels.[9]

These results are contradicted by two recent studies that showed no differences in total *HTR2A* mRNA across genotypes, but did find that GG tissue samples had greater expression of an extended 5'UTR.[1,10] This extended 5'UTR was shown to increase translational efficiency, implying increased protein production.[1] However, receptor density studies have not supported this hypothesis; five studies failed to find association,[3,6,11-13] while two studies found an opposite association wherein the -1438G allele was associated with lower receptor densities[9,14]. One study did find the AA genotype to be associated with higher receptor density in a healthy control group, but found no association in patients with mood disorders.[15] Three additional studies that investigated the impact of -1438G>A on promoter activity failed to find a consistent association, providing no clarification of the functional effect of this polymorphism.[2,8,16] The rs7997012 SNP is located in an intronic region; its function is unknown.[17]

What is the clinical significance of the *HTR2A* polymorphisms?

The -1438G>A and 102C>T variants have been extensively studied for associations with medication response, particularly with paroxetine. Three studies investigated the association between the -1438G>A and 102C>T polymorphisms and adverse events in paroxetine-treated patients. All three studies (total n = 237) found significantly increased incidence of adverse events in patients with the -1438GG (102CC) genotype.[18–20] The effect size was large; a weighted average of these studies showed side effect rates increasing from 15% among -1438A (102T) carriers to 42% among -1438G (102C) homozygotes. Similar results have been found for other selective serotonin reuptake inhibitors (SSRIs), such as citalopram and fluvoxamine, but these results await replication in larger cohorts.[21,22]

Conversely, the effect of the *HTR2A* polymorphisms of efficacy is not well defined. No association was found between *HTR2A* genotype and paroxetine efficacy in two articles (total n = 115).[23,24] Inconsistent results have been found for other antidepressants and antipsychotics.[5,20,25]

The rs7997012 was originally identified as a marker of citalopram response in the STAR*D study, but has so far failed to replicate. Three studies showed no impact of the polymorphism on antidepressant efficacy response,[17,25,26] while two studies showed an association in the opposite direction.[27,28] A meta-analysis by Niitsu et al. that included the aforementioned studies (including the STAR*D data) found no overall effect of the polymorphism.[29] Limited evidence exists for the relationship between rs7997012 and side effects. Two studies (total n = 135) in subjects receiving SSRIs found that patients with the AA genotype suffered from significantly more side effects compared to G allele carriers.[30,31] However, these results must be replicated in larger cohorts before a reliable association can be drawn.

Conclusions

The functional effects of *HTR2A* -1438A>G and 102T>C polymorphisms remain unclear and research on the impact of these polymorphisms (and rs7997012) on antidepressant efficacy is inconclusive. However, the 1438A>G and 102T>C polymorphisms appear to be reliable predictors of SSRI-induced adverse events (particularly with paroxetine), with side effect rates increasing from 15% among wild type carriers to 42% among homozygous variant individuals. HTR2A may be viewed as a clinically validated predictor of SSRI-induced side effects.

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