Get to know a gene: SLC6A4

Summary: The serotonin transporter gene, SLC6A4, has demonstrated the ability to predict efficacy and adverse events with SSRI treatment, particularly for patients of Caucasian ancestry. The SLC6A4 promoter has two main variants: long and short. The short allele results in lower transcription rates, leading to less active sites for SSRIs. This may result in a reduced response to these medications. Therefore, individuals carrying the short allele may benefit from medications outside of the SSRI class. However, more data is needed before another variant, the rs25531 SNP, can be recommended for use in treatment selection.

What is SLC6A4?

The serotonin transporter, encoded by the SLC6A4 gene, is responsible for serotonin reuptake into the presynaptic neuron. While many antidepressants have some serotonin reuptake blocking activity, it is thought to be the major mechanism of action of the selective serotonin reuptake inhibitors (SSRIs).

Several polymorphisms have been identified in this gene. The best studied is an insertion/deletion in the promoter region of the gene, called the 5-HTTLPR. Individuals who carry the deletion (called the "short" or "S" allele) have lower transcription rates than those who carry the insertion (called the "long" or "L" allele), resulting in lower transporter density on the presynaptic neuron (Figure 1). Since this would result in less active sites for SSRIs, individuals carrying the S allele may have a reduced response to these medications.

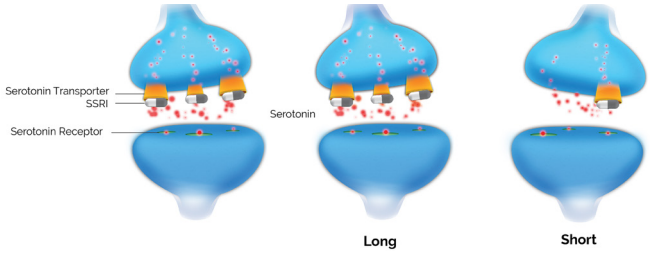

Figure 1: The SLC6A4 5-HTTLPR

Another variant, rs25531, is a single A>G substitution near the promoter region of SLC6A4. An initial study found that this allele stratified the long form of the gene into two groups: high transcriptional activity (L_A) and transcriptional activity comparable to the short allele (L_G).[1] However, subsequent attempts to replicate this finding have failed.[2,3] Nevertheless, many studies have genotyped the rs25531 SNP in conjunction with the 5-HTTLPR to measure their impact on SSRI efficacy and adverse events, producing mixed results.

Is there a connection between SLC6A4 genotype and antidepressant efficacy?

Multiple meta-analyses have reviewed the impact of the 5-HTTLPR on antidepressant efficacy. Most recently, Karlovic et al. reviewed results from 35 studies and 3 meta-analyses (n=8,424).[4] The results were divided by medication class and ethnicity. Among Caucasians taking SSRIs, 14 of 17 studies showed an impact of the 5-HTTLPR on treatment outcome. Seven of those 14 studies found that carriers of the S allele (L/S or S/S) had a poorer outcome when taking SSRIs, while the other 7 found the S/S genotype to have a poorer outcome. In contrast, analyses for patients of other ancestries taking SSRI antidepressants showed mixed results, suggesting a weaker effect within non-Caucasian populations. These results mirror that of Porcelli et al., who found that when analyzing 9 studies of Caucasians taking SSRIs, individuals with the S/S genotype were significantly less likely to respond to SSRI treatment than individuals with the L/L genotype (OR=1.71, p=0.003).[5] These findings are similar to the results of a previous meta-analysis, where individuals carrying the S allele were significantly less likely to respond to SSRI treatment.[6]

The rs25531 SNP has been evaluated in 12 publications to determine its impact on antidepressant efficacy, as described in Table 1.[7–18] Four of the 12 studies[7,8,12,13], including two independent analyses of STAR*D data[8,13], analyzed the rs25531 SNP alone and found no impact of the rs25531 SNP on SSRI efficacy. Eight of the 12 studies assessed the rs25531 SNP in combination with the 5-HTTLPR (i.e. L_A vs. L_G + S).[9–11,14–18] Four of these studies showed that the L_A allele was able to predict treatment outcome.[9,16–18] However, one of these studies was only significant for anxious depression.[9] Additionally, 2 of these 4 studies also analyzed the effect of the 5-HTTLPR alone. They found that analyzing 5-HTTLPR in combination with rs25531 did not add additional specificity to 5-HTTLPR testing alone.[9,18] Furthermore, the remaining 4 of 8 studies found no association between the 5-HTTLPR/rs25531 combination and treatment outcome.[10,11,14,15]

Table 1: Studies Evaluating the Effect of the rs25531 SNP on Antidepressant Efficacy

Polymorphisms Analyzed	No Association	LA allele able to predict outcome
rs25531	4 studies (n=3,734)[7,8,12,13]	0 studies
5-HTTLPR/rs25531	4 studies (n=350)[10,11,14,15]	4 studies (n=378)[9,16–18]

Is there a connection between SLC6A4 genotype and antidepressant-induced adverse events?

In 2010, Kato et al. performed a meta-analysis of 8 studies (n=2,323) on the 5-HTTLPR and SSRI-induced side effects.[19] They found that subjects carrying the S allele (L/S or S/S) had an increased risk of side effects (OR=1.39, p=0.02). However, the impact of the rs25531 SNP on antidepressant-induced side effects is less well studied. In the STAR*D sample (n=1,655), Hu et al.[20] found a significant effect of SLC6A4 when using the undifferentiated L/S allele, as well as when differentiating the L allele by the rs25531 SNP (i.e. LA vs. LG + S). Smaller studies examining the impact of the rs25531 SNP have produced mixed results.[17,21,22]

What is the clinical significance of SLC6A4 genotyping?

The SLC6A4 5-HTTLPR has demonstrated the ability to predict efficacy and adverse events with SSRI treatment in multiple meta-analyses, particularly for patients of Caucasian ancestry. The effect size of the polymorphism (OR=1.71 for efficacy) exceeds the standard set for cost-effectiveness by Perlis et al. (OR=1.5) in a simulation of data from the STAR*D study.[23] The 5-HTTLPR polymorphism has also demonstrated cost-effectiveness in two independent cost-effectiveness modeling scenarios.[24,25] However, the rs25531 SNP has not demonstrated an impact on antidepressant efficacy, and there is not yet enough data to fully determine its impact on antidepressant-induced adverse events. More data is needed before the rs25531 SNP can be recommended for use in treatment selection.

What treatment options exist for individuals with genetic variation in SLC6A4?

Individuals with genetic variation in SLC6A4 may benefit from medications outside of the SSRI class. As shown in Figure 2, studies on mirtazapine, nortriptyline, venlafaxine, desvenlafaxine, milnacipran, and duloxetine mostly showed no impact of SLC6A4 genotype on efficacy (and in some cases, improved efficacy among S/S individuals).

For example, some studies have focused on mirtazapine, owing to its unique mechanism of action with little affinity for the serotonin transporter. One study found that individuals carrying an S allele had reduced side effects to mirtazapine[26], and another study found that those with the S/S genotype responded better to mirtazapine[27]. Two other studies found no impact of SLC6A4 genotype on mirtazapine response.[17,28] For nortriptyline, one study showed that S/S individuals had a favorable response[29], while another study failed to find an association[30]. Studies on venlafaxine have produced mixed results. One study found no impact of SLC6A4 genotype on venlafaxine response[31], a second study found poorer response among individuals with the S/S genotype[32], and a third study found poorer response among individuals with the LA/LA genotype[33].

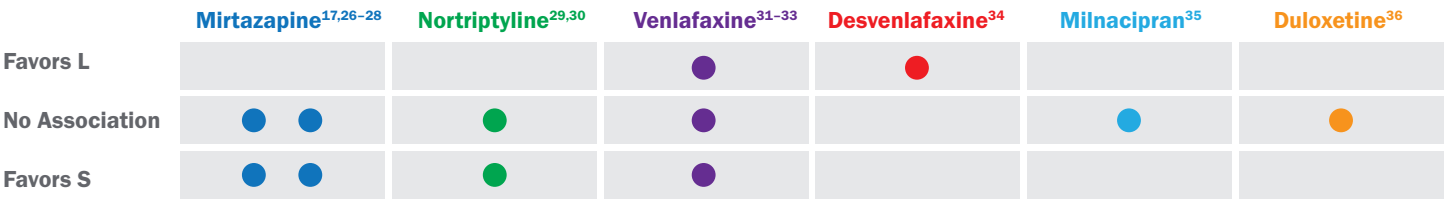

Figure 2: Outcome of Studies Evaluating the Effect of SLC6A4 on Non-SSRI Antidepressants. Each dot is a single study.

While these medications are potentially preferential over SSRIs among patients with SLC6A4 variation, they may be influenced by variation in other pharmacokinetic or pharmacodynamic genes. Weighted multi-gene pharmacogenomic testing through GeneSight® Psychotropic analyzes variation at 14 genetic loci (including SLC6A4) and has demonstrated clinical validity, clinical utility, and economic utility in multiple published clinical studies[37–42] and three meta-analyses[43-45].

For more information, contact the GeneSight Medical Information Department at:

PHONE: 855.891.9415
EMAIL: medinfo@genesight.com

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