

# Clinical Implications of Genetic Variation in the Serotonin Transporter Promoter Region: A Review

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**Objective:** To determine the state of the art in understanding the role of genetic variation in the serotonin transporter (5-HTT) promoter region (5-HTTLPR) in the development of a depressive episode and in its response to treatment.

**Data Sources:** PubMed and Ovid were used to search for articles published prior to December 2007 utilizing the key words *serotonin transporter*, *5-HTT*, *5-HTTLPR*, *serotonin transporter gene*, and *SLC6A4*.

**Study Selection:** All studies were reviewed, but case reports and small case series were excluded.

**Data Extraction:** All relevant articles were read by at least 2 of the coauthors and notes regarding study design, measures, data analysis, and findings were later used to construct the review.

**Data Synthesis:** A common genetic variant, the short allele, in which 44 base pairs are missing from the promoter of *SLC6A4*, is associated with a greater risk for developing a major depressive disorder in patients following exposure to adversity. This association appears to be most important in the early stages of the depressive disorder. Additionally, the likelihood of a positive response to antidepressant treatment may be reduced in these patients in terms of delayed response, greater adverse event load, or, in bipolar patients, mania induction and rapid cycling.

**Conclusions:** Selected genetic testing of patients with a recent history of significant adversity may be a reasonable tool that can enlighten treatment options and the course of illness. Ongoing work with the short allele of 5-HTT may also inform clinical guidelines of long-term treatment with antidepressants.

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The pathogenesis of major depressive disorder (MDD) remains unknown, but the illness is believed to result from an interaction of genetic and environmental factors. While environmental variables have been investigated for many decades, contributing genetic alterations have only recently been extensively studied. The serotonin (5-HT) transporter (5-HTT) gene *SLC6A4* has been the focus of several recent studies. The majority of published studies suggest that subjects with genotypes that lead to the expression of fewer 5-HTT proteins have an associated greater risk of developing a major depressive disorder following adversity. Additionally, when these patients are treated with a serotonergic antidepressant, they may have a delayed therapeutic response and a greater load of adverse effects than patients with genotypes that are associated with greater 5-HTT expression.

It is important to note that low 5-HTT expression genotypes may have many similarities to the pharmacologic blockade of these proteins with the use of 5-HT reuptake inhibitors (SRIs). Consequently, these gene/environment studies may also shed light on possible effects of long-term antidepressant treatments. Additionally, the documentation of modulation of the course and outcome of MDD by a genetic variant raises questions regarding the potential of genetic testing in clinical samples. Previous reviews have been written that have focused on the role of early life stress<sup>1</sup>; however, this review will provide an update of the current status of this fast-moving area of research and will begin discussions regarding questions of antidepressant treatment and genetic testing.

## METHOD

A widespread literature review was conducted using PubMed and Ovid databases to search for articles published prior to December 2007 using key words *serotonin transporter*, *5-HTT*, *5-HTTLPR*, *serotonin transporter gene*, and *SLC6A4*. All articles that discussed the long and short polymorphism in the promoter region and were relevant to the course and outcome of MDD (the risk of developing a depression and its response to treatment) were critically reviewed. Articles that dealt with polymorphisms of the promoter region of the serotonin transporter were included. Other polymorphisms of the reuptake pump exist and have been associated with clinical outcomes, but these were not included because they are less well understood. All relevant articles were read by at least 2 of the coauthors and notes regarding study design, measures, data analysis, and findings were later used to construct the review.

This is a fast-moving field, and it is expected that by the time this review is published, additional data will have been published.

## RESULTS AND DISCUSSION

### The Serotonin Transporter

The 5-HTT is a membrane protein with 12 transmembrane segments that is generally localized at the presynaptic terminals of serotonergic neurons, and, by virtue of binding and removing 5-HT from the synapse, is important in terminating the neurotransmitter effect after an action potential.<sup>2,3</sup> Most effective antidepressant agents inhibit the action of this protein, thereby extending the duration and potency of the 5-HT in the synapse with a reduction of 5-HT release in the long term.<sup>4,5</sup> The 5-HTT is coded for by its gene, which is categorized as the fourth member of the solute carrier family 6 genes (*SLC6A4*). It is a large gene (31 kilobases) that contains 14 exons (transcribed regions)<sup>6</sup> and has been mapped to 17q11.1.<sup>3</sup>

A common polymorphism in the nontranscribed promoter region (5-HTT-linked promoter region [5-HTTLPR]) has been identified in human populations.<sup>7</sup> This is a 44 base pair (bp) insertion/deletion that is respectively called the long (L) and short (S) forms of *SLC6A4*. The S allele is associated with nearly a 50% reduction in transcription of messenger ribonucleic acid and protein of 5-HTT compared to the L allele.<sup>8-10</sup> However, the actual function of the synthesized protein is not different between the S or L alleles.<sup>11,12</sup>

In addition to the S allele, a variant of the L allele in which an adenine has been replaced with a guanine (designated L<sub>G</sub>) is also associated with reduced 5-HTT expression to a level comparable to the S allele.<sup>13</sup> In examining effect of genotypes on the course and outcome of depression, the L<sub>G</sub> allele is frequently grouped with the S allele.

The current review will specifically outline data in which the L<sub>G</sub> allele has been examined. There is also a 17 bp variable number tandem repeat sequence in the second intron (nontranscribed portion) (VNTR-2), which also has a low expressing allele.<sup>14</sup> However, this sequence will not be considered in this review.

While some reports suggest that the S allele acts as a dominant gene in terms of 5-HT protein expression,<sup>14</sup> expression of 5-HTT in S/L heterozygote individuals is actually midway between L/L and S/S subjects.<sup>15</sup>

Allele frequencies of the L and S forms vary among different populations. The S form is relatively uncommon among sub-Saharan African populations (11%) and increase in frequency in European Caucasians (50%) and Asians (70%).<sup>16</sup> Aboriginal Australians (29%) and Native Americans (35%–61%) are intermediate (Gelernter et al.<sup>16</sup>). These frequencies suggest differing susceptibilities to the effects of the S allele in different ethnic groups.

### Polymorphism of 5-HTTLPR and MDD

Early studies in the biology of depression have reported reductions in platelet 5-HT transport and blood cell and brain imipramine or paroxetine binding in subjects with MDD.<sup>12,17</sup> And these changes now appear to be, in part, related to the polymorphism of 5-HTTLPR.<sup>11,12</sup>

The first association between the 5-HTTLPR and depression was reported by Lesch and colleagues<sup>8</sup> (Table 1). They examined 505 lymphoblastoid cell lines previously collected for other protocols for which data regarding personality testing were available (the Neuroticism Extraversion Openness personality inventory). A significant relationship between subjects with an S allele (either S/S or S/L) and the neuroticism factor (which is reflective of both anxiety and depressive symptoms and traits) was found.<sup>8</sup> More recently, Must et al.<sup>18</sup> found that subjects who are homozygous for the S allele appear to have reduced persistence in a psychological test that tests reward sensitivity (the ABCD version of the Iowa Gambling Test) and are more influenced by a high immediate reward.

Subsequently, Caspi and colleagues<sup>19</sup> examined 867 individuals who had been assessed at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and 26 years. The study focused on stressful life events between ages 21 and 26 years. Seventeen percent reported experiencing a major depression the previous year (58% female, 42% male). For those experiencing a depression, the association between stressful life events and having an S allele (homozygous N = 147, 17% of the population, or heterozygous N = 435, 51% of the population) was significantly greater ( $p = .02$ ) than for the L allele homozygotes (N = 265, 31% of the population).<sup>19</sup> Homozygous S/S subjects experienced the most depressive symptoms in the 5 years preceding their age 26 year assessment ( $\beta = 1.55$ ,  $t = 2.35$ ,  $p = .02$ ).<sup>19</sup> Heterozygous subjects (S/L) also experienced a significant amount of depression ( $\beta = 1.25$ ,  $t = 3.66$ ,  $p < .0001$ ).<sup>19</sup> However,

**Table 1. Summary of Studies Examining the Relationship Between Depression, Depressive Symptoms, and Adversity and the 5-HTTLPR Polymorphism<sup>a</sup>**

Study	N	Findings	Implicated Alleles
Lesch et al <sup>8</sup>	505	Association with neuroticism factor (reflective of anxiety and depression)	S/S and S/L
Caspi et al <sup>19</sup>	867	Depressive symptoms associated with experience of adverse life events within last 5 years	S/S > S/L
Wilhelm et al <sup>20</sup>	127	Risk of developing MDD within 5 years of an adverse life event	S/S > S/L
Kendler et al <sup>21</sup>	549	Increased risk for depression following adverse life events	S
Cervilla et al <sup>22</sup>	737	Increased risk for depression following adverse life events	S
Kaufman et al <sup>24</sup>	101	Increased risk for depression following childhood maltreatment	S
Steiger et al <sup>25</sup>	92	Increased risk for depression following childhood maltreatment	S
Eley et al <sup>26</sup>	377	Increased risk for depression associated with a poor family environment	S
Grabe et al <sup>27</sup>	1005	Increased risk for depression associated with chronic disease	S
Otte et al <sup>28</sup>	557	Increased risk for depression associated with coronary artery disease	S
Jarrett et al <sup>29</sup>	138	Increased risk for depression associated with irritable bowel syndrome	S
Sojoberg et al <sup>30</sup>	180	Increased risk for depression associated with a variety of stressors	S
Dorado et al <sup>31</sup>	212	More common in depressed subjects than nondepressed	S
Taylor et al <sup>32</sup>	118	More depressive symptoms with a history or adversity in nonclinical sample of college students	S
Gonda et al <sup>33</sup>	128	More depressive symptoms in nonclinical sample of women	S
Gonda et al <sup>34</sup>	110	No Axis I disorder but more symptoms of depression, anxiety, and irritability	S
Gillespie et al <sup>35</sup> and Surtees et al <sup>36</sup>	5265	No association with stressful life events or social adversity	None

<sup>a</sup>All studies are retrospective in design with the exception of Caspi et al<sup>19</sup> and Wilhelm et al,<sup>20</sup> both of which collected data prospectively. Abbreviations: L = long, MDD = major depressive disorder, S = short.

homozygous L/L subjects experienced little depression ( $\beta = 0.17$ ,  $t = 0.41$ ,  $p = .68$ ).<sup>19</sup> Additionally, a history of childhood maltreatment was associated with adult depression only if the S allele was present, with the risk highest for the S/S homozygotes ( $\beta = 0.60$ ,  $z = 2.31$ ,  $p = .02$ ), high for S/L heterozygotes ( $\beta = 0.45$ ,  $z = 2.83$ ,  $p = .01$ ), but very low for L/L homozygotes ( $\beta = 0.01$ ,  $z = 0.01$ ,  $p = .99$ ).<sup>19</sup>

Wilhelm and colleagues<sup>20</sup> replicated these results in 127 subjects (85 women, 42 men) who were originally interviewed in 1978 and assessed every 5 years for 25 years. Fifty-three (42%) experienced a major depression at some point (mean  $\pm$  SD age at onset =  $30.6 \pm 8.4$  years; range, 15–50).<sup>20</sup> The likelihood of adverse life events was the same in patients who experienced depression (68%) as in those who did not (68%). However, the risk for developing an MDD within 5 years of an adverse life event was significantly greater for subjects with the S allele ( $p = .036$ ). The risk was greatest for S/S homozygous subjects and increased with the number of adverse life events. In another study,<sup>18</sup> however, a similar, but less striking pattern, existed for the S/L subjects. Homozygous L/L subjects appeared to be relatively protected with a lower likelihood of depression with increasing adverse life events.<sup>20</sup>

Several other studies have reported similar association of increased risk of depression in patients with the S allele who have experienced stressful life events (N = 549<sup>21</sup> and N = 737<sup>22</sup>), including hurricane exposure (N = 589)<sup>23</sup>; childhood maltreatment (N = 101<sup>24</sup> and N = 92<sup>25</sup>); poor family environment (N = 377)<sup>26</sup>; chronic disease (N = 1005),<sup>27</sup> including coronary disease (N = 557)<sup>28</sup> and irritable bowel syndrome (N = 138)<sup>29</sup>; or various stressors (N = 180).<sup>30</sup> In addition to the association with adversity,

the S allele appears to be more common in subjects with MDD compared to nondepressed subjects (N = 70 MDD and N = 142 non-MDD).<sup>31</sup>

The association between a history of adversity and depressive symptoms has also been described in a nonclinical population. Among 118 college students or employees (mean age, 20.6 years) without current depression or post-traumatic stress disorder, the presence and severity of depressive symptoms were significantly related to both a history of early or recent adversity and the S/S genotype.<sup>32</sup> Similarly, in 128 adult women without a history of depression, depressive symptoms were associated with S/S genotype.<sup>33</sup> In 110 adult women without an Axis I disorder, the S allele was associated with personality temperaments of depression, anxiety, and irritability.<sup>34</sup>

Two large studies comprising 5265 subjects and investigating stressful life events and social adversity did not find an association.<sup>35,36</sup> This has led some investigators to suggest that the positive association represents a publication bias.<sup>37</sup> However, in some of the positive studies,<sup>19,20</sup> the study subjects were followed prospectively for over 20 years. Occurrences of childhood maltreatment or other stressful life events were recorded as they happened, not retrospectively as in the larger studies.<sup>35,36</sup> Additionally, positive studies have tended to have younger patients (generally an average age < 30 years) while negative studies tended to have older patients (average age > 33 years). Similarly, in a study of patients with Alzheimer's disease, there is no association with 5-HTTLPR and depression.<sup>38</sup> An exception of this pattern is a study by Chorbov et al.<sup>39</sup> in which they examined young women and found that the L<sub>A</sub> allele is associated with an increase in MDD. Nonetheless, the greater weight of the data suggests that the short allele of 5-HTTLPR may be important early in the

course of the depressive illness, and that, as the disease progresses, other factors (e.g., kindling) may be of relatively greater importance. An additional issue is the L<sub>G</sub> variant, which has not been investigated in most of the above-referenced studies and which may reduce the apparent association between the lower expressing S and L<sub>G</sub> alleles and the higher expressing L<sub>A</sub> allele.

In addition to an association between adversity, the S allele of the 5-HTT, and the occurrence of MDD, there appears to be an association with the severity of depression.<sup>40</sup> Lower expressing alleles (S and L<sub>G</sub>) may be responsible for as much as 31% of the variance of the severity of the depression.<sup>41</sup>

It is not clear how the S allele may affect the biology of stress response to increase the risk for depression. A recent meta-analysis of both published and unpublished imaging studies finds that some 10% of phenotypic variance of activation of the amygdala may be explained by the allele.<sup>42</sup>

Surprisingly, positron emission tomography imaging of the 5-HTT with [<sup>11</sup>C]-3-amino-4-(2 dimethylaminomethylphenylsulfanyl)-benzonitrile ([<sup>11</sup>C]DASB) finds that subjects with MDD without comorbidity have a normal or elevated binding potential of the 5-HTT compared to normal controls.<sup>43</sup> However, when MDD is associated with another comorbid Axis I condition, the binding potential of the 5-HTT is reduced compared to normal controls,<sup>43</sup> suggesting that if the short form predisposes subjects to depression, one would expect other Axis I disorders to also be present. In this regard, it is important to note that the *SLC6A4* gene is not the only gene associated with adversity and depression. Both catechol-O-methyltransferase<sup>44</sup> and the cytochrome P450 allele *CYP2C9\*3*<sup>31</sup> have been significantly associated with depression, adversity, and *SLC6A4*.

It should be noted that most of the studies utilized the standardized diagnostic criteria found in the Diagnostic and Statistical Manual of Mental Disorders. However, there are no standardized definitions of adversity, abuse, or stress. Nonetheless, most studies that have investigated the association of adversity and subsequent risk for depression find that the long form of the 5-HTT increases that risk, with the greatest liability found in homozygous S/S subjects. Homozygous L/L individuals appear to be *relatively* protected.

### The 5-HTTLPR Polymorphism and Suicide

There appears to be a relationship between 5-HTTLPR polymorphism and some personality traits. For example, anxiety,<sup>34</sup> irritability,<sup>34</sup> suspicion, negativism,<sup>45</sup> and impulsivity are more common in S carriers.<sup>18</sup> Subjects who are homozygous for the S allele are less able to delay rewards.<sup>18</sup> This may partially underlie a propensity towards alcohol dependence (odds ratio [OR] = 1.18, 95% CI = 1.03 to 1.33).<sup>46</sup> These personality traits would appear

to suggest an increased risk for suicidal behaviors. However, the literature regarding suicidality is clearly mixed. Many studies of suicide attempters find no association between 5-HTTLPR and suicide attempts.<sup>45,47-51</sup> Likewise, among people with completed suicides in whom the diagnosis is made post mortem, there does not appear to be an association with suicide and 5-HTTLPR.<sup>52-54</sup>

Nonetheless, a sufficient number of studies do find a relationship between suicidal ideation<sup>55,56</sup> and suicide attempts.<sup>57-59</sup> There have been alternating reports of increased association of the S alleles with violent<sup>60</sup> and non-violent<sup>58</sup> suicide attempts. Meta-analyses of the literature find that there is an association between 5-HTTLPR polymorphism and suicidality.<sup>61,62</sup> Among patients who had previously attempted suicide (N = 103), the S allele predicted a suicide attempt within a 1-year follow-up so that S/S individuals were 6.5 times more likely to attempt again compared to L/L subjects (95% CI = 1.18 to 35.84).<sup>63</sup> However, nearly all of these studies excluded examination of patients' histories. When histories of abuse or neglect are incorporated into the analyses, it appears that the risk for suicide attempts is more closely related to childhood trauma<sup>64,65</sup> but may be moderated by the S allele.<sup>65</sup>

### The 5-HTTLPR Polymorphism and Antidepressant Response

Given that 5-HTT inhibition is believed to be important for the action of most antidepressants, it is reasonable to examine the efficacy of SRI antidepressant treatments in subjects with low- and high-expressing alleles (Table 2).

Several studies find that patients carrying the S allele respond equally to those carrying the L but require a longer time period. Murphy et al.<sup>66</sup> reported a double-blind, randomized 8-week trial of paroxetine (20–40 mg/day) versus mirtazapine (15–45 mg/day) in a sample of 246 geriatric, depressed outpatients. Geriatric patients with the S/S and S/L genotypes receiving paroxetine were slower to respond, with greater depression scores at days 7 and 28 on the Geriatric Depression Scale (GDS) and with little effect seen with mirtazapine or if depression was measured with the Hamilton Rating Scale for Depression (HAM-D).

In another randomized, double-blind study of 96 depressed geriatric subjects, Pollock et al.<sup>67</sup> randomly assigned patients to nortriptyline (target plasma concentration, 50–150 ng/mL) or paroxetine (20–30 mg/day) for 12 weeks. Subjects with the S allele took longer to improve than the L/L homozygotes. Additionally, none of the S carriers (S/S or S/L) versus 52% of the homozygous L/L patients experienced a greater than 50% reduction in symptoms by the end of the second week in the paroxetine-treated patients (p < .0001), but response was comparable by the end of the study.<sup>67</sup> There was no

Table 2. Summary of Studies Examining the Relationship Between SRI Antidepressant Treatment and the 5-HTTLPR Polymorphism

Study	N	Design	Major Findings	Association
Murphy et al <sup>66</sup>	246	Double-blind, randomized 8-week trial of paroxetine (20–40 mg/d) vs mirtazapine (15–45 mg/d)	Slower response rates to SRIs in depressed geriatric patients	S/S and S/L
Pollock et al <sup>67</sup>	96	Double-blind, randomized 12-week trial of nortriptyline (target plasma concentration, 50–150 ng/mL) vs paroxetine (20–30 mg/d)	Slower response rates to SRIs or tricyclics in depressed geriatric patients	S/S and S/L
Durham et al <sup>68</sup>	117	Double-blind, placebo-controlled, 8-week study of sertraline (50–100 mg/d)	Slower response rates to SRIs in depressed geriatric patients	S/S and S/L
Zanardi et al <sup>69</sup>	58	Open administration of paroxetine	Reduced improvement with SRI	S/S
Zanardi et al <sup>70</sup>	155	Subanalysis of 52 patients with depression with psychosis receiving fluvoxamine (both bipolar and unipolar patients)	Poorer response to fluvoxamine among the 52 delusional patients	S/S and S/L
Yu et al <sup>71</sup>	121	Open administration of fluoxetine to depressed patients (all Chinese)	Overall no difference in remission rates, but statistically more depressive symptoms	S/S and S/L
Kronenberg et al <sup>56</sup>	74	Open administration of citalopram in subjects aged 7–18 y	Poorer response and greater suicidal ideation	S/S
Rausch et al <sup>72</sup>	51	Placebo-controlled study of fluoxetine	Greater response and greater placebo response	L/L
Smeraldi et al <sup>73</sup>	102	Placebo-controlled add-on study of pindolol or placebo added to fluvoxamine in nonresponders to fluvoxamine	Greater response to placebo plus fluvoxamine, no difference in response to pindolol plus fluvoxamine	S/L and L/L
Kim et al <sup>74</sup>	120	Open administration of fluoxetine or paroxetine (all Korean patients)	Smaller fraction of responders	S/L and L/L
Kang et al <sup>75</sup>	101	Open mirtazapine for 4 weeks	Lesser improvement of depressive symptoms compared to those without LL genotype	L/L
Kato et al <sup>76</sup>	81	Open administration of fluvoxamine or paroxetine (all Japanese patients)	Lesser improvement of depressive symptoms compared to those without LL genotype	S/L and L/L
Kraft et al <sup>77</sup>	1914	Open citalopram for 12 weeks	No difference	None

Abbreviations: L = long, S = short, SRI = serotonin reuptake inhibitor.

genotype-related difference in response to nortriptyline at any time in the study.

A double-blind, placebo-controlled, 8-week study of sertraline (50–100 mg/day) in depressed elders (> 60 years) found that significantly more L/L patients responded by weeks 1 and 2 compared to S carriers, but there was no difference at study end point.<sup>68</sup>

A similar pattern is evident in younger patients. Among 58 Italian depressed patients receiving paroxetine, L/L and L/S patients improved to a greater degree than S/S patients by weeks 2 and 4.<sup>69</sup>

Another study of 155 Italian depressed patients (47 with bipolar disorder, 108 with unipolar disorder) found that among delusional patients (N = 52), subjects with any S allele (homozygous or heterozygous) did more poorly with fluvoxamine compared with those homozygous for the L allele.<sup>70</sup>

A study of depressed Chinese adults (N = 121) receiving fluoxetine (20–60 mg/day) for 4 weeks found that L/L genotype predicted response (i.e., more responders had this genotype), but there was no difference in the percentage of remitters by the end of the study period.<sup>71</sup> Nonetheless, S allele carriers generally had statistically signifi-

cantly more depressive symptoms than those who were L/L homozygous.<sup>71</sup>

A placebo-controlled study of fluoxetine in 51 depressed adults found that L/L homozygous subjects both responded better to active drug and had a higher placebo-response rate than S allele carriers.<sup>72</sup>

A blinded, placebo-controlled study of pindolol augmentation in 102 patients not responding to fluvoxamine (up to 200 mg/day) found that the L allele carriers (L/L and S/L) had a better response to fluvoxamine plus placebo than did S/S patients. Response to fluvoxamine plus pindolol did not vary by genotype.<sup>73</sup> These studies suggest that differences seen between the genotypes may be due to a greater placebo response in patients with the L 5-HTTLPR allele.

Three studies with Asian populations found that patients with the S allele do better with antidepressants. A study of a Korean patient sample found that, among 120 depressed adults receiving fluoxetine (20–50 mg/day) or paroxetine (20–60 mg/day), subjects with the S/S genotype had the greatest number of responders (64.4% vs. 36.4% for other groups) and the greatest reduction in HAM-D scores.<sup>74</sup> Another study with a Korean population

found that when 101 depressed patients were given mirtazapine for 4 weeks, those with the S/S genotype improved to a significantly greater degree than did those with either the S/L or L/L genotypes.<sup>75</sup> A small study with 81 depressed Japanese patients receiving open-label paroxetine (20–40 mg/day) or fluvoxamine (50–150 mg/day) over 6 weeks found that S/S homozygotes had statistically significantly greater reductions in HAM-D scores at weeks 4 and 6 in the paroxetine arm.<sup>76</sup>

The largest study thus far was reported by Kraft et al.<sup>77</sup> and included 1914 subjects from the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study. Subjects were treated for 12 weeks with 20 to 60 mg/day of citalopram. Using the Quick Inventory of Depressive Symptomatology–Self-Report version (QIDS-SR) to assess response, the authors found no association between any of the 5-HTTLPR polymorphisms and response to citalopram. Many of these individual patients were reported on in the 1775 subjects studied by Hu et al.<sup>78</sup> These researchers also found no relationship between 5-HTTLPR polymorphisms and citalopram response.

A meta-analysis<sup>79</sup> and a mega-analysis<sup>80</sup> that did not include the STAR\*D data both found significantly poorer antidepressant response in S/S homozygotes. Nonetheless, the lack of reproducibility raises doubt as to the true association between the 5-HTTLPR polymorphism and response to SRIs. Some of the differences may be explained by high rates of S allele in Asian populations,<sup>74,76</sup> which may have confounded the outcome. Additionally, the chronicity of antidepressant treatment prior to study entry might create an important variable. Specifically, SRI antidepressant treatment may mimic the low 5-HTT expression of the S/S genotype. Thus, while the STAR\*D study examined nearly 2000 patients, 80% had chronic or recurrent depression and a history of prestudy antidepressant treatment,<sup>81</sup> which may have overshadowed any genotype-specific difference (see Theoretical Implications below). This issue may best be addressed with studies in children. In this regard, a study of 74 depressed children and adolescents between 7 and 18 years of age found that S/S homozygous subjects had a poorer response to the SRI citalopram and more severe suicidal ideation than either S/L or L/L subjects.<sup>56</sup>

The relationship between the short and long forms of the 5-HTT and antidepressant response is not clear. A delay in response to SRI treatment appears to be associated with the S genotype. The largest study<sup>77</sup> to date did not find an association, but it included a very large fraction of chronically or recurrently depressed subjects, which may confound the results.

### The 5-HTTLPR Polymorphism and Adverse Effects

The presence of reduced levels of 5-HTT in subjects with the S allele may increase sensitivity to specific

SRI-related adverse effects. Investigators have studied antidepressant-induced mania (AIM) and general SRI-related adverse effects.

Mundo et al.<sup>82</sup> examined 27 bipolar disorder type I or bipolar disorder type II patients with 1 or more prior episodes of mania or hypomania induced by treatment with a proserotonergic antidepressant (fluoxetine, fluvoxamine, paroxetine, nefazodone, moclobemide, venlafaxine, imipramine, and sertraline) and 29 bipolar (type I or II) patients who had never experienced AIM. All patients had received antidepressants during previous depressive episodes. Patients who had experienced AIM had a greater frequency of the S allele (63%) compared to the L allele (37%). Conversely, the S allele was rare in patients who had never experienced AIM despite antidepressant treatment (29%) while the L allele was common (71%,  $p < .001$ ).<sup>82</sup> Similarly, 37% of those with AIM were S/S homozygous, while only 11% were L/L homozygous ( $p = .002$ ).<sup>82</sup>

Rousseva et al.<sup>83</sup> performed a case control study of 309 bipolar subjects. While the S allele was more common in subjects with AIM, the difference was not significant. However, there were associations with both allele ( $p = .002$ ) and genotype ( $p = .0009$ ) with rapid cycling. Specifically, individuals with a history of rapid cycling were more likely to be S/S homozygous (58.8%) compared to the L/L genotype (17.6%).

In a recent study by Masoliver et al.,<sup>84</sup> 37 of 103 bipolar subjects had AIM. Subjects with AIM more commonly had the S allele (55.4%) than the L allele (44.6%,  $p = .058$ ).<sup>84</sup>

There are no known polymorphisms of the 5-HTT, including 5-HTTLPR, that are overrepresented in bipolar illness.<sup>85</sup> Thus, the overrepresentation of the S allele among subjects with rapid cycling or AIM is more likely to be real. However, given the bias against publication of negative studies, ongoing investigation is required to confirm the association of the short form or 5-HTTLPR and AIM.

Among unipolar patients, Perlis et al.<sup>86</sup> studied 36 patients with major depression treated in an outpatient setting with fluoxetine (20–60 mg/day). Genotyping revealed 9 individuals to be S/S, 16 to be L/L, and 11 were S/L. The frequency of insomnia and agitation after treatment initiation was statistically higher in S/S patients. Seventy-eight percent of S/S patients developed insomnia compared to only 22% of L/L and S/L individuals ( $p = .005$ ). Likewise, 67% of S/S patients reported agitation compared to only 7% of L/L and S/L subjects ( $p = .001$ ).<sup>86</sup>

Popp et al.<sup>87</sup> studied 65 patients receiving agents with a predominant serotonergic mechanism. Half of patients with S/S suffered significant adverse effects, 40.0% of S/L patients had side effects, but none of the L/L patients reported side effects ( $p = .002$ ).<sup>87</sup>

Smits et al.<sup>88</sup> studied 214 patients receiving an SRI for major depression for at least 6 weeks. Patients with the S/S genotype had increased adverse effect load, with an odds ratio of 1.77 (95% CI = 0.80 to 3.92), as did patients with the S/L genotype, with an odds ratio of 2.37 (95% CI = 1.13 to 4.96). The adverse effects that have been generally reported with SRIs are weight change, fatigue, and skin reactions.

In the previously discussed geriatric study comparing paroxetine and mirtazapine, Murphy et al.<sup>66</sup> also reported on adverse effects. Adverse effects among paroxetine-treated patients with the S/S genotype included gastrointestinal complaints, fatigue, agitation, sweating, and dizziness. As a whole, S/S genotype patients experienced more intense side effects with paroxetine than did their L/L counterparts. Consequently, S/S patients received lower final doses of paroxetine and had decreased compliance than L/L homozygotes.<sup>66</sup>

Similarly, the previously discussed Hu et al.<sup>78</sup> STAR\*D study, which grouped the S allele with the low expressing L<sub>G</sub> allele in 1775 patients receiving citalopram for depression, it was found that the high expressing L<sub>A</sub> allele is associated with a lower adverse effect burden ( $p = .007$ ), with gastrointestinal adverse effects being the most common.

The L genotype may predispose unipolar subjects to more adverse effects and bipolar subjects to antidepressant-associated cycling, mania, or hypomania.

### Alternative Treatment Strategies

If treatment with SRI agents is less than ideal for patients with the S allele, what alternatives exist? To date, no studies examining this question have been published, but there are unpublished studies that begin to address this issue.<sup>89,90</sup> One study involved 146 major depression patients (from a sample of 276) who did not respond to 8 weeks of sertraline treatment and were randomly assigned to blindly receive either sertraline plus atomoxetine (a relatively pure norepinephrine reuptake inhibitor) or sertraline plus placebo for an additional 8 weeks.<sup>91</sup> Overall, at the final analysis there were no differences between the 2 groups (e.g., remission rate for sertraline + atomoxetine patients was 29/72 [40.3%] and for sertraline + placebo patients was 28/74 [37.8%],  $p = .87$ ).<sup>91</sup> However, the S/S genotype subjects who were given sertraline + atomoxetine had a greater rate of remission (9/11 [81.8%]) than those who received sertraline + placebo (5/14 [35.7%]),  $p = .042$ .<sup>89,90</sup> Other genotypes (L/L or S/L) did not show this change.

Other studies have focused on treatment-resistant depression. Most such patients have failed treatment with serotonergic agents. Among 50 patients with treatment-resistant depression, augmentation of antidepressant treatment (SRI or serotonin-norepinephrine reuptake inhibitor [SNRI]) with lithium was effective only in patients

homozygous for the S allele compared to heterozygous S/L individuals (hazard ratio [HR] = 6.9,  $p = .005$ ) and homozygous L/L subjects (HR = 4.5,  $p = .003$ ).<sup>92</sup> Similarly, in a study of 155 severely depressed patients, augmentation with the  $\beta$ -blocker pindolol resulted in faster improvement, with the effect greater in subjects with the S allele.<sup>70</sup>

These early studies suggest that S/S patients may preferentially benefit from approaches that involve interventions other than use of a pure SRI.

### Genotype Testing

The current weight of evidence suggests that the short form of the 5-HTT is associated with an increased risk for the development of a depressive syndrome following adversity. Additionally, these same subjects may be less likely to respond favorably to an antidepressant. These effects appear to be most important in young patients or in the early stages of a depressive illness. It follows that identification of these individuals early in the course of treatment might alter antidepressant choice and improve outcome. In a theoretical modeling study, 64.6% of genotype-tested patients would be expected to be in remission at 6 weeks compared with 60.0% who were not gene tested.<sup>93</sup> After 12 weeks, the difference is slightly larger, with 79.5% of those receiving dual-mechanism agents and 83.2% of those receiving tricyclic antidepressants in the genotyped groups being in remission compared to 76.7% of the nongenotyped group.<sup>93</sup> This study did not examine the cost of testing. However, additional social, legal, and ethical issues are involved in widespread gene testing.<sup>94</sup> However, targeted testing may be reasonable. This may be particularly true early in the course of the illness if there is a history of significant recent adversity, presence of childhood abuse, or a history of inadequate treatment response. Testing is more likely to disclose an S allele in Caucasians of European descent or Asians than in subjects of sub-Saharan African origins. A documentation of an S allele may provide greater understanding of the illness to both the patient and the clinician and may enlighten antidepressant choice.

### Theoretical Implications

There is obvious similarity between the S/S 5-HTTLPR genotype, in which subjects express half as many 5-HTT proteins, and administration of an SRI antidepressant, which must inhibit 60% to 80% of 5-HTT sites to be effective.<sup>95,96</sup> Stated differently, antidepressant treatment, particularly long-term treatment, mimics the S/S genotype. Consequently, understanding what may occur to S/S homozygous patients may enlighten the understanding of long-term antidepressant treatment.

In this light, it is reasonable to expect that the characteristics of the S allele—the propensity toward depression following adversity, the possibility of poorer response to

**Table 3. Characteristics of the S Allele and Long-Term Antidepressant Treatment**

Study	S Allele	Long-Term Antidepressant
Souery et al <sup>97</sup>	Propensity toward depression following adversity	High rates of treatment-resistant depression among chronically treated patients
Solomon et al <sup>98</sup>	Reduced therapeutic response to SRI	Antidepressant tachyphylaxis
Kukopulos et al <sup>99</sup> and Altshuler et al <sup>100</sup>	Propensity toward cycling or manic induction in bipolar patients	The appearance of cycling or illness destabilization following prolonged antidepressant treatment of bipolar patients

Abbreviations: S = short, SRI = serotonin reuptake inhibitor.

antidepressant treatment, the propensity toward cycling or manic induction, and the increased adverse consequences—are seen in patients treated with antidepressants over long periods of time. The possible relationship between the S allele characteristics and long-term antidepressant treatment are outlined in Table 3. For each identified characteristic (with the exception of increased adverse effects), there is an equivalent observation in patients receiving SRI antidepressants. It is important that the relationship of these potential adverse consequences of long-term antidepressant treatment with the 5-HTTLPR polymorphism be investigated. Additionally, it is important to determine if phenomena such as tachyphylaxis or antidepressant-related cycling might be related to chronic suppression of the 5-HTT that simulates underexpressing genotypes.

### Summary

A 44 bp deletion/insertion in the promoter region of the 5-HTT gene has been identified. A deletion of this region (the short form, or S) is most common among Asians and Caucasians of European descent and least frequent in sub-Saharan Africans. Many published reports suggest that the S allele may predispose subjects to developing major depression following significant life adversity. While larger studies do not replicate this observation, the difference appears to be that positive studies are predominantly prospective and examine patients early in the course of the depressive illness, and negative studies are retrospective and examine the illness later in life. One might conclude that the interaction of the S form of the 5-HTT and adversity may be important early in the course of major depression. Additionally, the S allele has been associated with a reduced likelihood of beneficial outcome with antidepressant treatment. This is seen both in delayed or reduced response rates, increased likelihood of developing antidepressant side effects, and, in bipolar patients, mania and rapid cycling. The inability to replicate studies finding reduced response to antidepressants in larger studies may be due to the fact that the larger studies were composed mainly of patients with long histories of antidepressant treatment. Additionally, several studies of eastern Asian subjects do not find reduced likelihood for response to antidepressants by S carriers. Long-term use of antide-

pressants may create the physiologic equivalent of the S allele (blockade of the 5-HTT mimics the reduced expression of the protein). There is early evidence that patients with the S/S genotype do better with SRI alternative treatments, but this still needs to be better defined. Genetic testing is available and may be of selected benefit, but the value of more widespread genetic testing has not been established.

**Drug names:** atomoxetine (Strattera), citalopram (Celexa and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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