The serotonin transporter gene (*5-HTT*) variant and psychiatric disorders

Hana Kuželová [1,2], Radek Ptáček [2], Milan Macek Jr. [1]

1 Institute of Biology and Medical Genetics, 2nd Faculty of Medicine, Charles University Prague
2 Department of Psychiatry, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Correspondence to: Mgr. Hana Kuželová
Ústav biologie a lékařské genetiky, FN Motol
V Úvalu 84, 150 06 Praha, Czech Republic.
TEL: +420 224433535, +420 728711606; E-MAIL: hana.kuzelova@lfmotol.cuni.cz

Submitted: 2009-12-14 Accepted: 2010-01-01 Published online: 2010-02-16

Key words: **serotonin transporter; *5-HTTLPR*; length variant; genetics; psychiatric disorders; *SLC6A4***

Neuroendocrinol Lett 2010; **31**(1):4–10 **PMID:** 20150867 NEL310110A05

Abstract

Both serotonin and the serotonin transporter, which transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons, play an important role in the pathophysiology of several psychiatric disorders. Mutations associated with the serotonin transporter gene may result in changes in serotonin transporter function. The serotonin transporter gene promoter variant, consisting of a long (L) and a short (S) variant, is one of the major factors which contribute to the etiology of many psychiatric disorders. In this regard, many studies have been published on association of this variant with various psychiatric disorders. This repeat length variant in the promoter region of this gene has been shown to affect the rate of serotonin uptake and may play a role in post-traumatic stress disorder and depression-susceptibility in people experiencing emotional trauma. Associations between a functional variant in the serotonin transporter anxiety-related personality traits were found, as well as the risk of developing depression, alcoholism or suicidal behavior. Understanding of possible associations of these variants and psychiatric disorders would bring progress in principles and treatment of many disorders.

R E V I E W

INTRODUCTION

Genetic factors are closely associated with psychiatric disorders but specific genes have not been definitely identified yet (Arango *et al.* 2003). Genes for neurotransmitters are the major candidate genes. Serotonin (5-HT) is an important neurotransmitter with wide-ranging functions throughout the central nervous system (Sugden *et al.* 2009). It mediates cellular effects through several proteins that are involved with its neurotransmission, synthesis, metabolism and membrane re-uptake. Serotonin is associated with several physiological mechanisms, e.g. it plays an important role in the amplification of platelet aggregation and has been implicated in the pathophysiology of migraine, pulmonary and systemic hypertension (Mohammad-Zadeh 2008). The neurotransmitter serotonin has been mainly implicated in mood regulation and the pathophysiology and treatment of depression (David *et al.* 2005) however other associations are still being under investigation.

Serotonin transporter (5-HTT) plays a main role in the serotonin transmission; since it transports the neurotransmitter serotonin from syn-

aptic spaces into presynaptic neurons. According to many studies, changes in the serotonin transporter is associated with several disorders, as affective disorders, emotional instability, agressivity and others (Caspi *et al.* 2003; Lesch *et al.* 2004; Lesch, 2002).

The serotonin transporter has received particular attention because it is involved in the reuptake of serotonin at the brain synapse (Lesch *et al.* 2002). The gene that encodes the serotonin transporter is called solute carrier family 6 neurotransmitter transporter, serotonin, member 4 (SLC6A4) and is found on chromosome 17 on location 17q11.1–q12. There are two main genetic variations in the promoter region, length variants (5-HTTLPR) – long (L) allele, comprised of 16 copies of 22 base pair (bp) repeat unit, and a short (S) allele, consisting of 14 copies (Hariri, Holmes, 2006; Hariri *et al.* 2002).

The short (S) allele of the 5-HTT gene-linked polymorphic region is associated with a lower level of transcriptional efficiency of the 5-HTT promoter. The S allele is associated with decreased transcriptional efficiency of the promoter which leads to reduced serotonin re-uptake in comparison to the long allele, which is associated with greater gene expression, and a 25% reduction in volume of the anterior cingulate cortex and amygdala (Lesch *et al.* 1996). The activity of the S/S and S/L variants appears to be similar and similarly different from the L/L variant (Lesch *et al.* 1996; Hu *et al.* 2006).

A common single nucleotide variant (SNP) occurs in the L allele at the sixth nucleotide (adenine to guanine) within the first of two extra 20 to 23 bp repeats. The variant with adenin is L_A, variant with guanin is called L_G. Some evidence indicates that, of the L alleles, only the L_A allele increases promoter activity, whereas the L_G allele may have the same transcriptional activity as the S allele (Hu *et al.* 2006). This variant has not been considered in many studies and therefore it is impossible to compare distribution and association of this variant well for the present. However the fact that this single nucleotide variant plays an important role in gene expression but has not been considered in many studies can distort the conclusions.

According to Gerretsen and Pollock (2008) S allele has 40%, L_A 50% and L_G 10% in Whites, S 25%, L_A 51% and L_G 24% in African–Americans, and S 65%, L_A 34% and L_G 1% in Native Americans. The S allele occurs in 72–79% of Asians depending on their ethnicity (Gerretsen and Pollock 2008).

Since the length variant of the promoter region in serotonin transporter gene had been identified it has received much attention in the literature. The length variant is considered to be important mediator of emotional temperament and predisposition to mental illness, high trait anxiety, predispositions to fear-related behaviors, negative emotionality (Lesch *et al.* 1996), mood and anxiety disorders but only in those individuals that had suffered multiple stressful life events (Caspi *et al.* 2003), both unipolar and bipolar forms of depression and neuroticism (Hariri, Holmes, 2003). Serotonin transporter variant has been also associated with suicidal behavior, alcohol dependence, eating disorders and others (e.g. Anguelova *et al.* 2003a; 2003b).

5-HTT GENE AND AFFECTIVE DISORDERS

Serotonin transporter gene is main candidate gene for affective disorders. In spite of the large number of studies investigating genes of the serotonergic system in affective disorders, it is difficult to make any consistent conclusion (Anguelova *et al.* 2003a).

Bipolar disorder is highly heritable but susceptibility genes for bipolar disorder have led to largely inconclusive results. Number of studies failed to find a role for variant in 5-HTT in bipolar disorder (Zhang *et al.* 2009). According to Rotondo *et al.* (2002) bipolar disorders can be associated with short allele S which was detected in the group with bipolar disorder and panic disorder in higher frequency (49%) than in control group (Rotondo *et al.* 2002).

Extensive studies have been done on the relationship between 5-HTTLPR variants and depression, and found that the S-allele is linked to the development of depression. The short version of the *5-HTT* gene reacts more sharply at brain level to stimuli of fear than those with the L allele (Hariri *et al.* 2002). A prospective study of geriatric patients also found that the S allele significantly predicted the time to a major depressive episode following hip fracture (Lenze *et al.* 2005). Another study revealed that subjects (with mean age 60 years) bearing the S allele were at a significantly greater risk of stroke-related major depression and the L/L genotype may have a protective effect (Ramassubu *et al.* 2006).

Lesch and colleagues (Lech *et al.* 1996; 2002) reported that individuals carrying the S allele displayed higher levels of trait anxiety, particularly neuroticism, and "harm avoidance" than L/L homozygotes. In patients with an anxiety disorder higher frequency of individuals with the homozygous S genotype were found compared to normal controls (Lee *et al.* 2005). According to several studies subjects with one or two copies of the S alleles may be more susceptible to anxiety (e.g. fear and anxiety-related behavioral features) or personality traits such as increased neuroticism, "harm avoidance", including post-traumatic disorders (Hariri *et al.* 2002; Lesch *et al.* 1996; Ptacek *et al.* 2008; Glaslova *et al.* 2004). Caspi *et al.* (2003) found an interaction between early adversity and the S/S allele in predicting subsequent depression.

Lau et al (2009) noticed that S/L_G alleles in healthy adolescents, as in healthy adults, predict enhanced amygdala activation to fearful faces. Contrary findings of increased activation in patients with L_A/L_A relative to the S or L_G alleles require further exploration. Lau and colleagues found that S/L_G alleles can increase risks

for psychopathology in healthy individuals, possibly through stress reactivity.

Interaction between physical neglect and the S/S genotype of the 5-HTT gene significantly predicted dissociation in patients with obsessive compulsive disorders. However, an association between 5-HTTLPR variant and obsessive compulsive disorder (OCD) has not been confirmed (Altemus *et al.* 1996; Di Bella, 2002), likely given the heterogeneity of this condition. Presence of one or two S alleles generally was a stronger correlation between trauma and dissociation and questionnaire DES, for L/S heterozygotes the correlations were weaker and for L/L homozygotes, no significant correlation was observed between trauma variables and DES. In this study, the role of gene and environment influences in dissociative experiences in obsessive compulsive disorder was investigated (Lochner *et al.* 2007).

Although there is much evidence suggesting that OCD is related to serotonergic abnormalities, no association was detected between the 5-HTTLPR variant and OCD (Chabane *et al.* 2004; Devor *et al.* 1999). Moreover, current studies have not confirmed the role of 5-HTTLPR in susceptibility to panic disorders (Manor *et al.* 2001). Finally, there are other disorders which are considered to be influenced by the serotonergic system, but most of them are multifactorial (Ptacek and Bob 2009; Hariri *et al.* 2002; Bob and Ptacek 2001).

5-HTTLPR variant probably influences also response to treatment. Selective serotonin reuptake inhibitors (SSRIs) are usually prescribed in psychiatric disorders. The prevalence of non-responders, and the presence of a functional genetic variant in the promotor region of 5-HTT gene, emphasizes the potential utility of psychopharmacogenetics in prescribing SSRIs in the treatment of patients (Racine *et al.* 2009). Side effects of the treatment by SSRIs as disturbances in sleep, included gastrointestinal complaints, fatigue, agitation, sweating and dizziness, diarrhea are found more in homozygotes for the S allele (Perlis *et al.* 2003).

5-HTT GENE AND EATING DISORDERS

The investigation of serotonin transmission in eating disorders has received much attention. Serotonin is known to influence food intake, body weight regulation, and mood and its functioning is disrupted in patients with eating disorders (Kaye *et al.* 2005). Serotonin genes are thought to be involved in the etiology of bulimia nervosa, binge eating and anorexia nervosa (Racine *et al.* 2009; Steiger *et al.* 2006; Sulek *et al.* 2007). Also pharmacological studies demonstrate decreased 5-HTT in people with bulimia nervosa (Steiger *et al.* 2006). Blundell (1986) reported that increased serotonin neurotransmission led to reduced appetite and decreased serotonin activity precipitate compulsive or binge eating. Thus, altered serotonin neurotransmission may have an important role in eating disorders (Gorwood *et al.* 2004). However, results are still rather heterogenous in that several studies reported no 5-HTTLPR association with bulimia nervosa and binge eating (Lauzurica *et al.* 2003; Racine *et al.* 2009), including no association between 5-HTTLPR genotype and susceptibility to anorexia (Sundaramurthy *et al.* 2000). Nevertheless, recent studies reported an increased frequency of the L, rather than the S allele, in females with bulimia nervosa and binge eating disorder (Monteleone 2006a,b). Furthermore, Monteleone (2006a) mentions that the distribution of the genotypes does not significantly differ between patients and control subjects, although the L allele is significantly more frequent in the former. In the study, bulimic individuals carrying at least one copy of the S allele had significantly lower mean body mass index and body fat mass values and significantly higher mean harm avoidance score than patients with the L/L genotype (Monteleone 2006a).

On the other hand, another study demonstrated that the S/S genotype was significantly overrepresented in patients with anorexia nervosa than in other groups, with the frequency of the S allele being higher in the group with anorexia (51.5%) and lower in the overweight subjects (39.8%), compared to controls with normal weight (44.6%) (Fumeron *et al.* 2001). However, Fumeron (2001) claims that results might be false positive because the sample was small. Nevertheless, in the more recent studies an excess of S allele was found in anorectic patients although this was not statistically significant. In accordance with these results the S allele could represent a moderate risk factor that increases the chance of anorexia nervosa development (Gorwood *et al.* 2004). An additional line of support for the notion that the S allele may increase impulsivity (Lesch *et al.* 1996), stems from its association with eating disorders. As a note of caution, one should bear in mind that eating disorders are multifactorial and thus many other factors play role in their development (Papezova, 2001).

5-HTT GENE AND ALCOHOL ABUSE/ DEPENDANCE

Many studies suggested that genetic factors account for 40–60% of the variance in alcohol dependence (Dick, Beirut, 2006). Deficits in the serotonergic neurotransmission have been associated with higher alcohol intake, while the short allele of the 5-HTTLPR variant leads to reduced serotonin re-uptake in comparison to the long allele. Bliech *et al.* (2007) suggest an association of compulsive alcohol craving with serotonergic neurotransmission.

Several animal and human studies suggested that L/L homozygotes display a low response to the acute effects of alcohol (Hu *et al.* 2005; Barr *et al.* 2003). In this regard, a higher frequency of the S allele is associated with better ethanol tolerance in young adults and thus self-regulation of alcohol intake may be influenced by the presence of this allele (Turecki 2001). Other study confirmed that HTT genotype correlated with

the level of response to alcohol and predicted alcohol intake among adolescents (Hinckers *et al.* 2008). On the other hand low level of response to alcohol is associated with the L/L genotype and predicts the amount of alcohol intake in adolescents.

Students homozygous for the short allele of the 5-HTTLPR engaged in a higher frequency of "binge drinking", drank more often in order to get drunk, and consumed an increased number of alcoholic drinks during drinking sessions compared to L homozygotes or heterozygotes (Harman *et al.* 2003). However, the explanation for this observation might be that S/S homozygous exhibit higher levels of anxiety and can use alcohol as a readily available anxiolytic, since the S/S genotype is associated with increased anxiety and affective instability (Lesch *et al.* 1996; Melke *et al.* 2001). Heavy drinking as a tension reducing strategy was also described in a college population (Rutledge and Sher 2001). Covault *et al.* (2007) suggest that 5-HTTLPR S allele is associated with increased drinking and drug use among college students who have experienced multiple adverse life events. The S allele carriers may be at risk for a variety of adverse behavioral outcomes in response to increased levels of stress.

Johnson *et al.* (2008) found that S/S homozygotes were younger with respect to their chronological age and generally tended to drink more heavily than L-carriers. These authors found that the 5-HTTLPR variant was functional in the platelets of alcoholics in comparison to S/S homozygotes. S/S homozygous subjects tended to drink more and to be of a younger chronological age, than those with the L/L genotype.

Saiz *et al.* (2009) did not support the role of serotonergic variants in alcohol dependence, but the authors suggest a differential genetic background to alcohol and heroin dependence. The ethnicity might play a role in determining the genetic heterogeneity among studies. In Lin´s (2007) study on Han Chinese population in Taiwan frequency of S allele in non-alcoholic controls was 78.3%, similar frequency to the Japanese and Korean populations. In Caucasians populations, the frequency of S allele was 33–42% in the controls.

Hu *et al.* (2006) described a novel allele of 5-HTTLPR, L_G in differentiating the L allele into two functionally distinct alleles where only the L_A allele is high expressing.

The relationship between the multiple loci or haplotype of candidate genes and personality traits in alcoholism as well as other mental illnesses should be examined in future studies with a larger sample size a taking into account ethnicity of the study cohort.

5-HTT GENE AND GROUP OF DEVELOPMENTAL DISORDERS

Serotonergic activity is involved in multiple physiological functions (e.g. aggression, impulsivity, sleep, appetite, pain) and has been implicated with several diseases (such as anxiety, depression, schizophrenia). Interesting, an association was found also in the attention deficit hyperactivity disorder (ADHD) (Zoroglu *et al.* 2002). It was also suggested that low serotonine metabolite concentrations are associated with impulsiveness (Lesch *et al.* 1996). The S/S genotype was represented significantly less in ADHD group and homozygous and heterozygous L genotype predominated in this group compared with the controls (Zoroglu *et al.* 2002). Furthermore, Seeger (2001) confirmed this finding, that there is an overrepresentation of the L/L genotype in ADHD children (Seeger *et al.* 2001) and Manor (2001) agrees that the S/S genotype was represented less in the ADHD combined type (Manor *et al.* 2001). According to mentioned results variant of 5-HTTLPR or its L or S allele are associated with a risk of ADHD. However, the variant of 5-HTTLPR is merely one of the contributing factors, since many other candidate genes have been putatively implicated in the development of ADHD, which belongs to the multifactorial disease category (Ptacek *et al.* 2009a, 2009b).

Tab. 1. Publications related to the association of 5-HTTLPR and various psychiatric disorders.

Disorder	Allele	Reference
Anxiety disorder	S	Hariri *et al.* 2002; Lesch *et al.* 1996, Lee *et al.* 2005; Stein *et al.* 2008; Jorm *et al.* 2000
Bipolar disorder	S	Rotondo *et al.* 2002;
Depression	S	Lenze *et al.* 2005; Ramassubu *et al.* 2006; Caspi *et al.* 2003; Barr *et al.* 2003;
Dissociation	S	Lochner *et al.* 2006
Anorexia nervosa	S	Fumeron *et al.* 2001; Gorwood 2004
Bulimia nervosa	L	Monteleone 2006a,b
Attention deficit hyperactivity disorder	L	Seeger 2001; Manor 2001; Melke *et al.* 2001
Alcohol dependence	S	Gerra *et al.* 2005; Rutlege *et al.* 2001
Suicidal behavior	not definite results	Segal *et al.* 2006; Gorwood *et al.* 2000; Anguelova *et al.* 2003

5-HTTLPR variant is probably associated with other psychiatric diagnosis. The potential role of the serotonergic system in the etiology of autism is still under investigation since the first report in late nineties (Klauck *et al.* 1997). Increase blood serotonin level in autism is supposed to be in connection with serotonin transporter gene. Thus, serotonin transporter gene is possible candidate gene for autism. In the Indian autistic population S allele was preferentially transmitted as compared to the L allele (Guhathakurta *et al.* 2006). Other studies indicated a greater S allele transmission in severely affected probands and an increased L allele transmission in moderately affected subjects (Tordjman *et al.* 2001). However, more studies are necessary given the heterogeneous nature of autism.

5-HTT GENE AND SUICIDAL BEHAVIOR

There is also consistent evidence suggesting that the predisposition to suicidal behavior has a genetic component. The candidate genes most investigated include tryptophan hydroxylase, the 5-HT receptors, and serotonin transporter (5-HTT). According to Anguelova *et al.* (2003b) there is a positive association between suicidal behavior and the short allele of the 5-HTTLPR, association between the S allele with suicide victims or its attempters. It was also found that S/L variant was significantly associated with a completed suicide.

The frequency of the L/L genotype in depressed suicide victims was almost double of that found in control group (48.6% vs. 26.2%). The association between variant in serotonergic genes and suicidality supports the hypothesis that genetic factors can modulate suicide risk by influencing serotonergic activity (Du *et al.* 2001). Segal *et al.* (2006) found a higher risk for suicide behavior among depressed patients with S/S or L/S genotypes.

However these results are very heterogeneous and sometimes contradictory. Arango *et al.* (2003) found no association between the promoter genotype and suicidal behavior. This is supported also by Bah *et al.* (2008).

5-HTT GENE AND OTHER MENTAL DISORDERS

Serotonin transporter gene variant is supposed to be associated with many other diagnoses. For instance there is an association between quality of life scores (QOL) and low serotonin tone level has been reported in patient populations (Tsai *et al.* 2009). On the other hand the S allele is associated with a vulnerable cognitive style related to the appraisal of negative emotion (Szily *et al.* 2008). Many other associations are still under scientific scrutiny.

CONCLUSIONS

Identification of biological mechanisms via which various genes lead to individual differences in behavior and personality is important for our understanding of how such differences confer differential risk of neuropsychiatric illness (Hariri and Holmes 2006).

The serotonin transporter gene belongs to the most examined gene, thus far. The serotonin transporter plays a main role in the serotonin transmission and influences several physiological mechanisms (e.g. platelet activation, muscle contraction) and its gene, and mainly promotor length variant, is supposed to be a candidate gene for many psychiatric disorders. The S variant of serotonin transporter gene promoter variant is associated with a reduced transcriptional activity of the gene promoter and consequently associated with depression, anxiety, emotional instability, agressivity and others. Conversely, the L variant is associated with greater gene expression and according to studies it could have protecting effect from depression. However, the L variant is considered to increase risk of tromboembolic complications.

There is a high number of areas in which 5-HTT variant likely plays an important role. In spite of the high number of published studies and reviews, no systematic review describing all possible disorders connecting with 5-HTT gene has been published according to our knowledge, thus far. Moreover, a high number of studies investigating serotonin transporter gene variant had rather heterogenous results, which were often contradictory. Before the discovery of trialelic status of the 5-HTT gene locus, data were grouped only into S/S, S/L and L/L genotypes. However, the L_G allele closely resembles the S allele functionally, while L_G drives expression equivalently as S. Therefore, studies that included only S/L and L/L genotypes may underestimate the effect of 5-HTTLPR. Also the distribution of the alleles is different among the different ethnic groups which could explain such heterogeneity.

Intensive research efforts have not clarified the role of the 5-HTTLPR variant. Moreover, since psychiatric disorders are multifactorial, this gene variant needs to be assessed amongst all other other, factors (Zukov *et al.* 2009; Ptacek and Bob 2009; Hariri and Holmes 2006). This general notion is substantiated by conflicting results in literature. Therefore, the serotonin transporter gene variant could rather be considered factor which modulates human behavior.

In summary, identification of other genes, which the serotonine transporter gene variant modulates, would aid our understanding of many psychiatric disorders and could help assure more targeted treatment modalities.

ACKNOWLEDGMENT

Supported by VZFNM00064203.

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