

Review

Serotonin Transporter Polymorphism in Major Depressive Disorder (MDD), Psychiatric Disorders, and in MDD in Response to Stressful Life Events: Causes and Treatment with Antidepressant

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Abstract. A functional polymorphism in the promoter region of the 5-hydroxytryptamine transporter gene (5-HTTLPR), alters its transcription. Short allele (SS) variation decreases the transcriptional efficacy of serotonin, causing psychiatric disorders, major depressive disorder (MDD) and major depression in response to stressful life events. The aim of this study was to determine the current understanding of the role of 5-HTTLPR polymorphism in the development of depressive episodes and its response to treatment. Twenty-five articles were identified from PubMed, utilizing the following keyword, 5-HTT transporter gene, polymorphism, depression, stressful condition, psychiatric disorder. All articles were read and notes were made regarding study participant, measures, data analysis and results, and were used to write this review. The distribution of the SS allele in patients is associated with an increased risk of MDD following exposure to stressful events of life. Additionally, this genetic variant is closely associated with several psychiatric conditions such as suicidal behaviour, psychoses, personality disorders, and aggressive-impulsive traits.

The human serotonin transporter gene is located on the long arm of chromosome 17 (17q11.2) and encodes for the serotonin transporter that is involved in the communication

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between neurons. The 5-hydroxy – tryptamine (5-HTT) gene polymorphism is due to a 44 base pair deletion (SS)/insertion (LL) in the 5' regulatory region LPR (linked polymorphic region) that results in differential expression of 5-HTT binding sites in cell lines (Figure 1). In the human population, the frequency of the long allele (LL) of 5-HTT is approximately 57%, while that of the short allele is 43%. This polymorphism has been linked to the onset of neurotic disorders, major depression and suicidal behaviors. Such polymorphism have been regarded with particular interest because they introduce a different quantitative expression of the serotonin transporter molecules in the functionally active form. Subsequently, functional consequences arise that are reflected in the intracellular pool, and concentrations of synaptic and intercellular neurotransmitters (2). Several studies showed a significant correlation between the expression of the gene 5-HTT and environmental factors. It has been shown that serotonin transporter polymorphism in addition to stressful life events can determine the onset of depression. In the literature, 5-HTT gene polymorphism has been primarily associated with three following outcomes: i) MDD and MDD associated with stressful life events, such as cancer; ii) suicidal behaviour, and iii) response to antidepressant treatment. The etiology of MDD appear to be due to the lack of serotonergic transmission in the serotonin system. Alterations include a decrease in the level of L-tryptophan (a serotonin precursor) and alterations in the mechanism that regulates serotonin reuptake, which effects behavior such as mood, sleep, wakefulness, memory and learning. In people with depression, serotonin levels are lower than in healthy individuals, and this seems to cause depressive symptoms (3-5). The 5-HTTLPR polymorphism of the serotonin transporter (SERT) has been widely

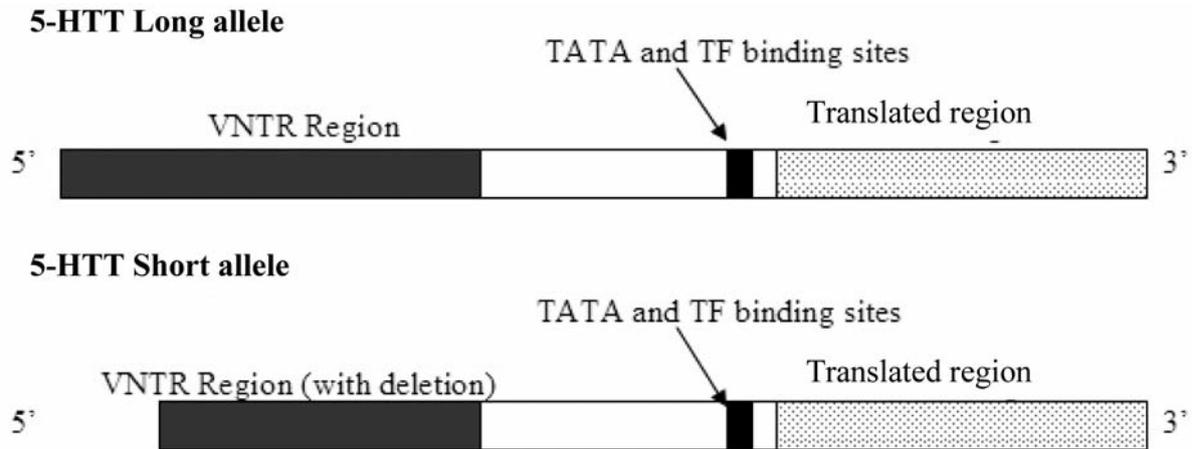


Figure 1. Diagram of 5-HTT gene-associated region of polymorphism. The diagram shows the two alleles of the 5-HTT gene region. The transcription factor binding sites and actual translated region of the gene are identical, but the alleles differ in the 5' repeat (VNTR) region. Image idea from Glatz *et al.* (51).

examined in relation to the difficulties of adaptation to stressful life events and to the possible consequence of an increased risk of developing depressive mood disorders (6-12). Depression is one of the most important psychiatric complications of cancer, affecting between 10 and 58% patients (13). The associated depression persists long after cancer therapy and causes remarkable negative consequences, such as impairment of quality of life, increased risk of suicide, increased pain, and reduction of survival (14).

In 2009, a report by the World Health Organisation (WHO) indicated that 30-50 millions people worldwide currently live with cancer, and that the incidence of cancer will increase by 50% by 2030, with approximately 16 millions new cases in that year. The exploration of possible risk factors for depression in cancer patients is thus very important. According to the WHO, suicide is the ninth leading cause of death worldwide and the third leading cause in the people that are the ages of 15 and 34. Suicide individual, especially those, who have chosen a violent death, as well as in those with high levels of aggression and impulsivity, has been found to have a deficit in serotonergic transmission in the prefrontal cortex, reducing its ability to inhibit action of impulsive-aggressive behaviours originated in the hypothalamus and limbic system (15).

Methods

A widespread literature review was carried out and a total of 25 articles published between 1996 and 2010 using the PUBMED-MEDLINE database were selected. The key words used were as follows: 5-HTT transporter gene, polymorphism, depression, stressful condition, psychiatric disorder. Articles that dealt with polymorphism of the promoter region of the serotonin transporter

were considered. Others polymorphism of 5-HTT gene were excluded from this analysis because it was not considered priority for the aim of this study. Data assessed in this review relate to the association between depression and/or psychiatric disorders and genotyping of participants, with the aim of analyzing the 5-HTTLPR gene polymorphism only in relation to its biological and genetic aspects. All articles included in this study were read carefully by at least two coauthors and notes were made regarding research design, data analysis, results and finding, and were used to write this review.

Results

Polymorphism of 5-HTTLPR, MDD, or MDD associated with stressful life events enclosed those due to cancer disease. The first association between 5-HTTLPR and major depression was reported by Lesch *et al.* (1), who examined 505 lymphoblastoid cell line, finding a significant relationship between subject with S allele (S/S or S/L) and neuroticism factor (anxiety and depressive symptoms and traits). Subsequently, Caspi *et al.* examined 867 individuals. The study focused on stressful life events which occurred between the ages of 21 and 26. The authors reported a more significant association ($p=0.02$) between homozygous S/S subjects ($n=435$; 51%) than heterozygous subjects ($n=147$; 17%) and depression, with respect to L/L subject ($n=265$; 31%). Homozygous S/S subjects experienced the majority depressive symptoms in the 5 years preceding their assessment at age 26 (16). The correlation between the potential relevance of the polymorphism in the promoter region of the 5-HTTLPR gene, and the risk of suffering MDD in 70 white European psychiatric outpatients with MDD and 142 healthy volunteers (HV) was studied by Dorado *et al.* in 2007 (17). They found that the frequency

Table I. State of the literature references used to analyze the relationship between 5-HTTLPR polymorphism and major depression disorder (MDD) or MDD caused by stressful life events.

Authors	Series of cases	Analysis	Genotype-associated
Lesch <i>et al.</i> (1)	505	Association with neuroticism factor	S/S and S/L
Caspi <i>et al.</i> (6)	867	Depressive symptoms associated with stressful events	SS>SL>LL
Dorado <i>et al.</i> (17)	272	Increased risk of suffering major depression	S/S
Kendler <i>et al.</i> (18)	549	Association between major depression and generalized anxiety syndrome	S/S
Kiyohara <i>et al.</i> (19)	-	Increased risk of MDD among Caucasian population	S/S
Wurtman <i>et al.</i> (20)	-	The effect of stressful life events on depressive symptoms in young adults	S/S
Chorbov <i>et al.</i> (21)	247	Increased risk of developing MDD following adverse life events	S/S
Schillani <i>et al.</i> (22)	126	Outset of MDD in patients with early breast cancer and terminally ill patients with different type of cancer	L/L
Grassi <i>et al.</i> (23)	145	Increased risk of MDD following diagnosis of breast cancer	None

Table II. List of literature references which analyze the relationship between 5-HTTLPR polymorphism and suicidal behaviour.

Authors	Series of cases	Analysis	Genotype-correlated
Anguelova <i>et al.</i> (35)	1599	Association with suicidal behaviour and impulsive trait	S/S
Lyn PY <i>et al.</i> (31)	379	Association with violent suicide and suicide attempt	S/S
Li D <i>et al.</i> (32)	-	Association with suicidal behaviour	S/S
Bah J <i>et al.</i> (34)	9	Association with the brain serotonin transporter in suicide attempt	S/S
Neves <i>et al.</i> (35)	351	Association with suicidal behaviour and BPD (bipolar disorder)	S/S (SB); None (BPD)
Helbecque (37)	134	Association with suicidal behaviour	None
Pungergic <i>et al.</i> (39)	268	Association with suicidal behaviour	None
Courtet <i>et al.</i> (40)	166	Association with non-violent suicidal behaviour	None

of subjects with the 5-HTTLPR-S allele was higher ($p<0.01$; odds ratio=2.03) in MDD patients than in HV. These authors suggested that there is a greater risk of MDD for individuals carrying the 5-HTTLPR-S allele (17). In an article by Kendler *et al.* 2005, whether stressful life events could lead to the onset of depression and whether this could be somewhat favored by the presence of short allele in the promoter region of the 5-HTT gene were examined. They enrolled 549 subjects, male and female, with established episode of major depression and generalized anxiety syndrome (GAS) such as anxiety, nervousness, feelings of being worried, and muscles felt tense, in the last year. The results of this work emphasized that individuals with 2 short alleles (homozygous SS) at the 5-HTT locus were more sensitive to the effects of depression associated with the effects of stressful life events (SLEs) than were those with heterozygous (SL) or 2 homozygous long alleles (homozygous LL), ($p<0.01$). This suggests that the variation at the 5-HTT locus moderates the sensitivity of individuals to the depressogenic effects of SLEs largely producing an increase sensitivity to the impact of mild stressors in SS individuals (18). A recent meta-analysis by Kiyohara *et al.* 2010, reported a summary frequencies of the SS allele of 5-

HTTLPR among Caucasian and Asians, based on the random effects model, as 42% and 40.5% respectively. Besides the distribution of the S allele, there was a significant difference between Asians and Caucasian ($p<0.001$), and the SS genotype of was significantly associated with an increased risk of MDD among the Caucasian population (19). The effect of stressful life events on depressive symptoms in young adults was found to be significantly stronger among SS or SL subjects than among LL subjects, as reported by Wurtman. Neuroimaging studies showed that those with the SS or SL alleles exhibited a greater activation of the amygdala in response to fearful stimuli than those with LL. It has been reported recently that mutations in the gene that controls serotonin synthesis in the human brain (tryptophan hydroxylase) also predispose these individuals to mood disturbances. It may be asked whether people who lack a psychiatric history should be advised to avoid stressful environments if they are found to carry the SS or SL alleles (20). In contrast with this is a study by Chorbov *et al.* in which 247 young adult female twins from Missouri were examined with the aim of determining whether the 5-HTT polymorphism interacts with the effect of adverse life events to increase the risk for developing

depression; They found that L allele was associated with a statistically significant ($p > 0.0001$) increase in MDD (21). Some authors, however have focused their attention on another aspect of the onset of depressive syndrome, that which occurs following a diagnosis of cancer. Cancer patients who survive this serious disease may develop major depression when they become aware of having cancer. Schillani *et al.* observed a series of 53 consecutive early breast cancer patients and 73 consecutive terminally ill patients who were affected by different types of advanced cancer. The authors analyzed the correlations between SERT polymorphism and mental adjustment to cancer, by assessing Mini-Mac Hopelessness-Helplessness (HH) scores in relation to 5-HTTLPR polymorphism in two groups of cancer patients. Their results showed a significant correlation between HH scores in depression and early breast cancer patients carrying the L/L variant only (22). The results concerning this aspect, are in contrast with what has been described by others authors, because in this work L allele to be associated with a depressive illness after cancer. On the others hand, Grassi *et al.* 2010 did not find a possible association between 5-HTTLPR polymorphism in conjunction with life events and depression in diagnosed breast cancer (23).

Polymorphism of 5-HTTLPR in suicidal behaviour and borderline personality disorder. Several lines of evidence suggest that suicidal behaviour such as others psychopathologies have a genetic component. Evidence of genetic involvement comes from studies of family history of suicide (24), and more definitively from twin and adoption studies (25). Aggressive and impulsive traits, alcoholism and substance abuse are also associated with serotonergic abnormalities, all of which carry an elevated risk of suicide. (26). It is therefore noteworthy that the 5-HTTLPR genotype is associated, in some but not all studies, with harm avoidance temperament, alcoholism, anxiety or impulsive traits (27).

However the literature concerning the association between the 5-HTTLPR polymorphism and suicidal behaviour is conflicting, and has reported both negative and positive findings. A meta-analyses carried out by Anguelova *et al.*, examined 12 studies comprising a total of 1599 subjects and found that there was a significant association between the 5-HTTLPR polymorphism with low expressing S allele and suicidal behaviour (28-30). These findings have been confirmed in two meta-analyses of Lin *et al.* and by Li *et al.* In the first, a series of 379 patients, it was found that the genotypes carrying the S allele were significantly more frequent in these attempting suicide than in those not ($p = .004$). Additionally, the S allele was associated with violent suicide ($p = 0.0001$) but not with nonviolent suicide ($p = 1.00$; 31). In the second study, the authors examined 39

studies and suggested that there was a significant association between the 5-HTTLPR polymorphism and suicidal behaviour with a value of 0.0068 (overall odds ratio=0.88 (45% CI 0.8, 0.97), thus supporting the involvement of 5-HTT in the pathogenesis of suicidal behavior (32). One potential pathways by which the 5-HTTLPR genes are related to impulsivity, aggression and suicide is through observed alterations in amygdala function as the amygdalae, along with the prefrontal cortex and orbital cortex, play an important role in the emergence of violent behaviour via faulty regulation of negative emotions (33). Others studies of these attempting suicide found association between the 5-HTTLPR polymorphism and suicide attempts (34-36). Neves *et al.* examined 351 patients and found that those who carried the S allele made violent suicide attempts more frequently ($\chi^2 = 20.2$; $p = 0.0001$) and made more suicide attempts ($t = 2.6$; $P = 0.01$) than those with L/L genotype. However, although they were not able to show an association between the S allele bipolar disorder (BPD). On the other hand, in people with committed suicide in whom the diagnosis was made post-mortem, there does not appear to be an association between suicide and 5-HTTLPR (37-39). Among patients ($n = 166$) who had previously attempted suicide the frequency of S/S genotype in those who attempted non-violent suicide were not statistically different to those in the controls ($n = 139$) (40).

Polymorphism of 5-HTTLPR and non-psychiatric disorders. Recurrent aphthous stomatitis (RAS) is the most common oral mucosal disease, characterized by periodic painful, single or multiple ulcers that heal spontaneously.

Netto Victoria *et al.* investigated 5-HTTLPR polymorphism in patients with RAS compared with control subjects. They examined 69 patients affected by minor or major form of RAS, and 70 healthy subjects, finding a significant increase in the genotype of SS ($p = 0.05$) in the group patients with respect to healthy individuals. They suggest that patients with RAS have a tendency to exhibit polymorphism associated with anxiety-related traits (41).

Polymorphism of 5-HTTLPR and antidepressant response. 5-HTT is the site of primary action for selective serotonin reuptake inhibitors (SSRIs). Several reports have demonstrated that the L/L allele polymorphism in 5-HTTLPR is associated with better selective SSRIs. The citalopram, fluvoxamine, paroxetine and setraline have revolutionized the treatment of major depressive disorder because of their favourable side-effects profiles (42). The primary mode of action for SSRIs is by binding to serotonin transporter, inhibiting its capacity to transport serotonin and thus modulating serotonergic activity. It has been determined that in terms of transcriptional activity, the L variant in the 5-HTTLPR has more than twice that of the S allele, with

important difference in 5-HTT RNA synthesis. (43). YU *et al.* tested the hypothesis that the 5-HTTLPR polymorphism is associated with SSRI antidepressant response by evaluating total and cluster depressive symptoms in 121 Chinese patients diagnosed with major depression. These authors reported that patients with the L/L genotype had a significantly better response to fluoxetine (20-60 mg/day) for 4 weeks when compared with S/S carriers ($p=0.002$). (44)

A study by Zanardi *et al.* of 58 depressed Italian patients receiving paroxetine showed that patients with L/L and L/S genotype, improved to a greater degree than those with S/S between 2 and 4 weeks of treatment (45). A blinded placebo-controlled study by Smeraldi *et al.* concerning pindolol augmentation in 102 patients not responding to fluvoxamine found that the L allele carriers (S/L and L/L) had a better response to fluvoxamine plus placebo than those with S/S (46).

Pharmacogenetic data concerning SSRIs are available, indicating that their effects are more pronounced in patients with depressive mood disorders carrying the L/L 5-HTTLPR polymorphism in comparison with those carrying at least one S allele (47, 48). Response to fluvoxamine plus pindolol did not vary by genotype. An opposing conclusion was provided by the work of Kraft *et al.*, in a study which included 1914 subjects treated with citalopram (20-60 mg/day) for 12 weeks. This study did not find an association between any of the 5-HTTLPR polymorphism and response to citalopram (49). This data is also supported by the work of the Hu *et al.* (50).

Conclusion

The studies of the functionally relevant biological effects of serotonin transporter gene promoter region (5-HTTLPR) polymorphism is especially important given the current controversy about the clinical relevance of these polymorphism. A functional polymorphism in the promoter region of the 5-HTT gene, denoted 5-HTTLPR, alters transcription of the 5-HTT gene. Much work suggests that the short allele variation (SS) results in reduced transcriptional efficacy of serotonin, a variation which can lead to psychiatric disorders, MDD and major depression dependent on stressful events of life, such as cancer. However, homozygous LL individuals appear to be relatively protected. Pertaining to post-cancer MDD, there are few literature references to date that confirm a predisposition to major depression after diagnosis of cancer. There is even less data regarding depression in long-term survival or after successfully treated cancer. Caspi *et al.* in a much larger study, established involvement of the SERT polymorphism in the onset of major depression in cancer patients and lung cancer survivors. This work has made an important contribution to the

knowledge base of the administration of drugs and the effectiveness of chemo, hormone, and radiotherapy. Although larger studies do not agree with these observations, the difference appears to be that positive studies are predominantly prospective and examine patients in the course of the depressive disease while the negative studies are retrospective and examine the illness later in life. Additionally the relationship between the short and the long form of the 5-HTT and antidepressant response has been extensively examined; in general. In general a delay in response to SSRI treatment appears to be associated with the S genotype although the administration of the SSRI antidepressant fluvoxamine in addition with placebo effects of pindolol induced a significant reduction of the genetic effects, indicating a treatment to be applied for those who are carriers of the genotype S/S. However, the largest studies did not find an association between 5-HTTLPR polymorphism and antidepressant treatment. This could be at least in part explained by the fact that most of these studies included a large fraction of chronically or recurrently depressed individuals, which may confounded the results.

References

- 1 Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD and Petri S: Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 274: 1527-1531, 1996.
- 2 Mann JJ, Huang Y, Underwood MD, Kasasir SA, Oppenheim S, Kelly TM, Dwork AJ and Arango V: A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch Gen Psych* 57: 729-738, 2000.
- 3 Zelman FP and Garver DL: Depression and antidepressant therapy: receptor dynamics. *Prog Neuropsychopharmacol Biol Psychiatry* 14: 503-523, 1990.
- 4 Cowen PJ: A role for 5-HT in the action of antidepressant drugs. *Pharmacol Ther* 46: 43-51, 1990.
- 5 Risch SC and Nemeroff CB: Neurochemical alterations of serotonergic neuronal systems in depression. *J Clin Psychiatry* 53: 3-7, 1992.
- 6 Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A and Poulton R: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301: 386-389, 2003.
- 7 Lotrich FE and Pollock BG: Meta-analysis of serotonin transporter polymorphisms and affective disorders. *Psychiatr Genet* 14: 121-129, 2004.
- 8 Kendler KS, Kuhn JW, Vittum J, Prescott CA and Riley B: The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression. *Arch Gen Psychiatry* 62: 529-535, 2005.
- 9 Stein MB, Schork NJ and Gelenter J: Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. *Neuropsychopharmacology* 33: 312-319, 2008.

- 10 Kim JM, Stewart R, Kim SJ, Shin IS, Kim YH, and Yoon JS: Interactions between life stressors and susceptibility genes (*5-HTTLPR* and *BDNF*) on depression in Korean Elders. *Biol Psychiatry* 62: 423-428, 2007.
- 11 Zalsman G, Huang Y, Oquendo MA, Burke AK, Hu X, Brent DA, Ellis SP, Goldmann D and Mann JJ: Association of triallelic serotonin transporter gene promoter region (*5-HTTLPR*) polymorphism with stressful life events and severity of depression. *Am J Psychiatry* 163: 1588-1593, 2006.
- 12 Hoefgen B, Schulze TG, Ohlraun S, von Widdern O, Höfels S, Gross M, Heidmann V, Kovalenko s, Eckermann A, Kölsch H, Mettern M, Zobel A, Becker T, Nöthen MM, Propping P, Heun R, Maier W and Rietschel M: The power of sample size and homogenous sampling: association between the *5-HTTLPR* serotonin transporter polymorphism and major depressive disorder. *Biol Psychiatry* 57: 247-251, 2005.
- 13 Massie MJ: Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr* 32: 57-71, 2004.
- 14 Chochinov H: Depression in cancer patients. *Lancet Oncol* 2: 499-505, 2001.
- 15 Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A and Poulton R: Influence of life stress on depression: moderation by a polymorphism in the *5-HTT* gene. *Science* 301: 386-389, 2003.
- 16 Mann JJ: Neurobiology of suicidal behaviour. *Nat Rev Neuroscience* 4: 819-828, 2003.
- 17 Dorado P, Peñas-Lledò EM, Gonzales AP, Càceres MC, Cobaleda J and Llerena A: Increased risk for major depression associated with the short allele of the serotonin transporter promoter region (*5-HTTLPR*) and the *CYP2C9*3* allele. *Fund Clin Pharmacol* 21: 451-453, 2007.
- 18 Kendler KS, Kuhn JW, Wittum J, Prescott CA and Riley B: The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episode of major depression. *Arch Gen Psychiatry* 62: 529-535, 2005.
- 19 Kiyohara C and Yoshimasu K: Association between major depressive disorder and a functional polymorphism of the 5-hydroxytryptamine (serotonin) transporter gene: a meta-analysis. *Psychiatry Genet* 20(2): 49-58, 2010.
- 20 Wurtmann RG: Gene stress and depression. *Metabolism Suppl* 1: 16-19, 2005.
- 21 Chorbov VM, Lobos EA and Todorov AA: relationship of *5-HTTLPR* genotypes and depression risk in the presence of trauma in a female twin sample. *Am J Med Genet B Neuropsychiatry Genet* 144: 830-833, 2007.
- 22 Schillani G, Martinis E, Capozzo MA, Era D, Cristante T, Mustacchi G, Conte MA, De Vanna M, Grassi L and Giraldi T: Psychological response to cancer: role of *5-HTTLPR* genetic polymorphism of serotonin transporter. *Anticancer Res* 30: 3823-3826, 2010.
- 23 Grassi L, Rossi E, Cobianchi M, Aguiari L, Capozzo M, Martinis E, Nanni MG, Lelli G, Schillani G, Biancosino B and Giraldi T: depression and serotonin transporter (*5-HTTLPR*) polymorphism in breast cancer patients. *J Affective Disord* 124: 346-350, 2010.
- 24 Garfinkelò BD, Froese A and Hood J: Suicide attempts in children and adolescent. *Am J Psychiatry* 139: 1257-1261, 1982.
- 25 Roy A, Rytander G and Sarchiapone M: Genetics of suicide. Family studies and molecular genetics. *Ann NY Acad* 836: 135-157, 1997.
- 26 Withaker-Azmitia PM and Peroutka SJ (eds): *The Neuropharmacology of Serotonin Vol 600*: 1990.
- 27 Mann JJ, Brent DA and Arago V: The neurobiology and genetics of suicide and attempts suicide: a focus on the serotonergic system. *Neuropsychopharmacology* 24: 467-477, 2001.
- 28 Angelova M, Benkelfat C and Turecki G: A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. *Mol Psychiatry* 8: 646-653, 2003.
- 29 Arango V, Huang Y-Yu, Underwood MD and Mann JJ: Genetics of the serotonergic system in suicidal behaviour. *J Psychiatry Res* 37: 375-386, 2003.
- 30 Currier D and Mann JJ: Stress, Genes and the biology of suicidal behaviour. *Psychiatry Clin North Am* 31(2): 247-269, 2008.
- 31 Lin PY and Tsai G: Association between serotonin transporter gene promoter polymorphism and suicide: results of meta-analysis. *Biol Psychiatry* 55: 1023-1030, 2004.
- 32 Li D and He I: Meta-analysis supports association between serotonin transporter (*5-HTT*) and suicidal behaviour. *Mol Psychiatry* 12: 47-54, 2007.
- 33 Davidson RJ and Putnam KM, Larson CI: Dysfunction in the neural circuitry of emotion regulation- a possible prelude to violence. *Science* 289: 591-594, 2000.
- 34 Bah J, Lindström M, Wesberg L: Serotonin transporter gene polymorphism: effect on serotonin transporter availability in the brain of suicide attempters. *Psychiatry Res* 162: 221-229, 2008.
- 35 Neves FS, Silveira G and Romano-Silva MA: Is the *5-HTTLPR* polymorphism associated with bipolar disorder or with suicidal behaviour of bipolar disorder patients? *Am J Med Genet B Neuropsychiatry Genet* 147B: 114-116, 2008.
- 36 Limosin F, Loze JY and Bonu C: Male-specific association between the *5-HTTLPR* S allele and suicide attempts in alcohol-dependent subjects. *J Psychiatry Res* 39: 179-182, 2005.
- 37 Helbecque N, Sparks DL and Hunsaker JC 3rd: The serotonin transporter promoter polymorphism and suicide. *Neuroscience Lett* 400: 13-15, 2006.
- 38 Lopez de Lara C, Dumais A and Rouleau G: *STIN2* variant and family history of suicide as significant predictor of suicide completion in major depression. *Biol Psychiatry* 59: 114-120, 2006.
- 39 Pungergic G, Videtic A and Pestomik A: Serotonin transporter gene promoter (*5-HTTLPR*) and intron 2 (*VNTR*) polymorphisms: a study on Slovenian population of suicide victims. *Psychiatry Genet* 16: 187-191, 2006.
- 40 Courtet P, Buresi C and Abbar M: No association between non-violent suicidal behavior and the serotonin transporter promoter polymorphism. *Am J Med Genet B Neuropsychiatry Genet* 116B: 72-76, 2003.
- 41 Netto Victoria JM, Correia-Silva JdF, Pimenta FJ, Kalapothakis E and Gomez RS: Serotonin transporter gene polymorphism (*5-HTTLPR*) in patients with recurrent aphthous stomatitis. *J Oral Pathol* 34: 494-497, 2005.
- 42 Fava M: Management of nonresponse and intolerance: switching strategies. *J Clin Psychiatry* 61(Suppl 2): 10-12, 2000.
- 43 Heils A, Teufel A, Petri S, Stober G, Riederer P and Bengel D: Allelic variation of human serotonin transporter gene expression. *J Neurochem* 66: 2621-2624, 1996.
- 44 Yu YW, Tsai SJ, Chen TJ, Lin CH and Hong CJ: Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. *Molecular Psychiatry* 7: 1115-1119, 2002.

- 45 Zanardi R, Benedetti F and Di Bella D: Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *J Clin Psychopharmacol* 20: 105-107, 2000.
- 46 Smeraldi F, Zanardi R and Benedetti F: Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Mol Psychiatry* 3(6): 508-511, 1998.
- 47 Luddington NS, Mandadapu A, Husk M and El-Mallakh RS: Clinical implications of genetic variation in the serotonin transporter promoter region: a review. *J Clin Psychiatry* 11(3): 93-102, 2009.
- 48 Serretti A, Mandelli L, and Lorenzi C: Serotonin transporter gene influences the time course of improvement of core depressive and somatic anxiety symptoms during treatment with SSRIs for recurrent mood disorders. *Psychiatry Res* 149: 185-193, 2007.
- 49 Krah JB, Peters JB and Slager SL: Analysis of association between the serotonin transporter and antidepressant response in a large clinical sample: *Biol Psychiatry* 61: 734-742, 2007.
- 50 Hu XZ, Rush AJ and Charney D: Association between a functional serotonin transporter promoter polymorphism and citalopram treatment in adult outpatients with major depression. *Arch Gen Psychiatry* 64(7): 783-792, 2007.
- 51 Glatz K, Mössner R, Heils A and Lesch KP: Glucocorticoid-regulated human serotonin transporter (5-HTT) expression is modulated by the 5-TT gene promoter-linked polymorphic region. *J Neurochem* 86: 1072-1078, 2003.

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