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Analyzing Hereditary 5-HT Abnormalities in Obsessive-Compulsive Disorder (OCD)

Phantira Suppathavevut[1], Preedaporn Pholphuet[2]

[1,2]Triamudomsuksa, Pathumwan, Bangkok, Thailand 10330

Corresponding Author: Phantira Suppathavevut

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ABSTRACT

Serotonin (5-HT) is one of the most essential and complicated neurotransmitters in humans, being an underlying cause of several neuropsychiatric disorders. Obsessive-Compulsive Disorder (OCD) is one of the disorders that is proved to be strongly correlated with 5-HT. This review focuses on how genetics of 5-HT influences the manifestation of OCD and suggests that further study needs to be done in order to find the genuine genetic cause of the disease and approach better treatments in the future. Smaller units, such as single nucleotide polymorphism (SNP), can bring an enormous change to the expression of gene and unveil the paradox of the findings from the past decades. Therefore, the unexplainable variety of findings might be answered if it is studied more thoroughly and utilizes new advanced technology.

Keywords: Behavioral and social sciences; Neuroscience; Obsessive-Compulsive Disorder; Serotonin; Polymorphism

INTRODUCTION

Obsessive-Compulsive Disorder or OCD is a chronic neuropsychiatric disorder that affects 2%-3% of the U.S. population(1). The real cause of the disorder is still unknown, but from replicated family and twin studies, it is statistically and scientifically proven to be strongly associated with genetics(2,3). However, it fails to follow Mendelian patterns of inheritance and therefore is considered a complex disease(4). Patients with OCD might develop obsessive and compulsive behaviors, recurrent, intrusive and unwanted thoughts and urge to do something repetitively, which oftentimes causes a functional impairment in social areas(5). OCD patients show abnormalities in neurotransmitters such as serotonin, dopamine and glutamate systems(6). As of nowadays' knowledge, serotonin reuptake inhibitors (SRIs) medication is one of a few effective treatments for OCD as some OCD patients show progress after being treated with SRIs, denoting a role of serotonin in OCD(7). Additionally, patients treated with 5-HT2C receptor, a subtype of serotonin receptor, agonist like meta-chlorophenyl piperazine (mCPP) show exacerbation in OC symptoms, emphasizing association between serotonin and OCD more(8). Therefore, understanding genes and polymorphisms of the serotonergic system is important for the future of OCD treatments.

The involvement of serotonin in neuropsychiatric disorders

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that was discovered more than 60 years ago, and is now targeted as one of the most influential neurotransmitters in neuropsychiatric disorders. From mood, expression, behaviors to regulations of other vital organs, they are all found to be related to serotonin and serotonin receptors(9,10). However, most of serotonin in the body instead of residing in the central nervous system (CNS), it is rather found in the guts, where it was first discovered(11). Despite

studies and interests from researchers from the past decades, its roles still remain to be elucidated. Nevertheless, supported by a series of replicated results and findings, people diagnosed with mental disorders (e.g. anxiety disorder, schizophrenia, bipolar disorder and including obsessive-compulsive disorder) are observed to have abnormalities in the serotonin system. Thus therapeutic agents of several neuropsychiatric disorders are based on modulation of the serotonergic system(12). Further evidence comes from replicated results reported anxiety-like, depression-like and neuropsychiatric symptoms in human and animal models that demonstrate serotonin dysfunction(13,14).

Implication of effectiveness of SRIs in OCD patients

Typically, SRIs are common medication for several neuropsychiatric disorders; however, for OCD, SRIs medication is one of a few alternative treatments since other antidepressants that are not associated with serotonergic neurotransmitters are ineffective in OCD, making SRIs stand out in this disorder and attract many researchers' attention(15). SRIs' main target is serotonin transporter (5-HTT, SERT), which modulates and maintains the level of serotonin. They block the reabsorption or reuptake of serotonin into presynaptic nerve terminals, which, as a result, increases serotonin and synapses in vivo(16). (Figure 1) At least half of SRIs treated OCD patients demonstrating a reduction in OC symptoms leads to a hypothesis that serotonin and serotonin transporter are involved in OCD. Accordingly, 5-HTT binding level is one of the factors that modulate neuropsychiatric symptoms and disorders including OCD. In addition, increased OCD severity has been observed in fluoxetine-treated patients after a dose of serotonin antagonist medication, which points out the importance of 5-HT receptors in OCD.

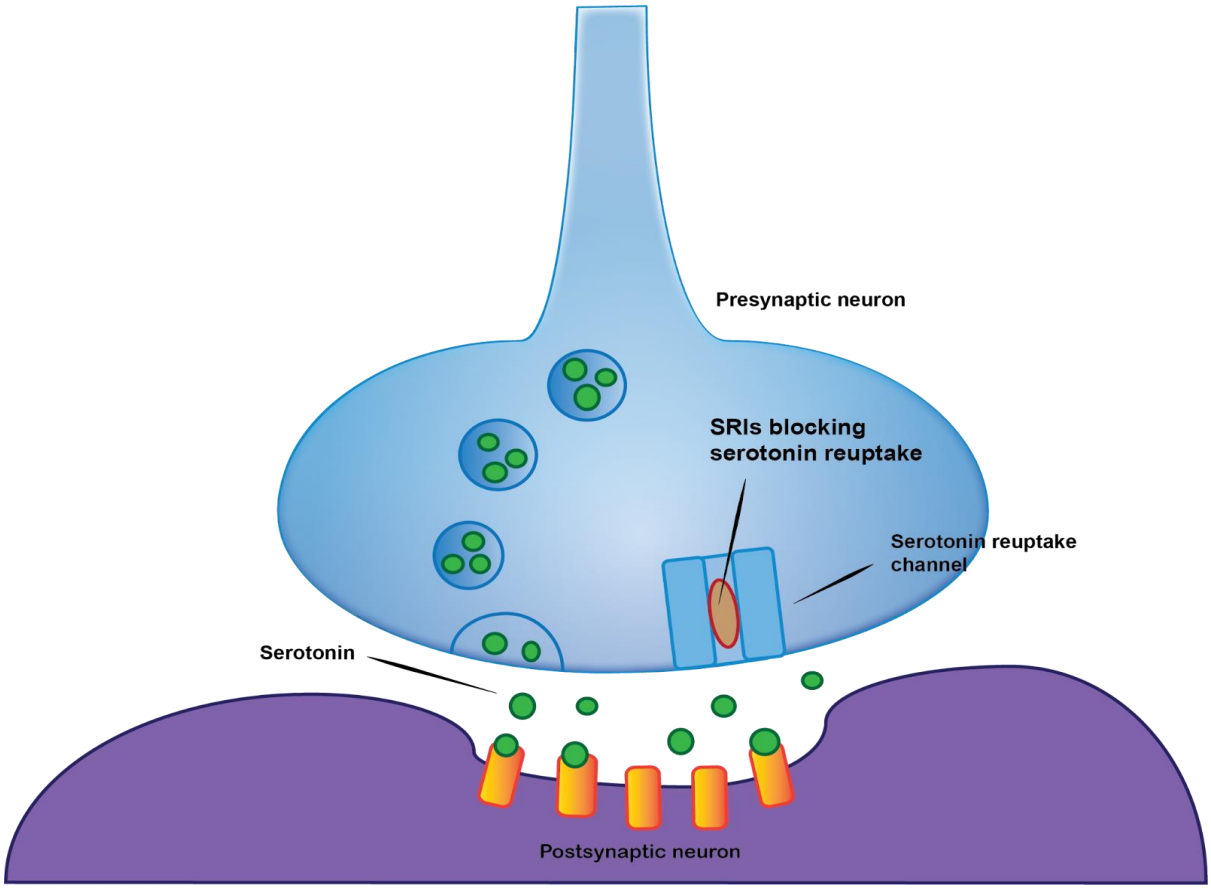

Figure 1: Diagram showing how SRIs work by inhibiting reuptake of 5-HT by 5-HTT into presynaptic cells and, as a result, increase levels of serotonin in synaptic clefts and synapses in vivo.

Gene encoding the serotonin transporter: Intensively studied genetic area of OCD

Serotonin transporter integral membrane protein that transports serotonin into presynaptic neurons is encoded by solute carrier family 6 member 4 gene (SLC6A4), which is known to influence serotonin reuptake ability(17). A genetic variation at the serotonin transporter-linked promoter region (5-HTTLPR), promoter region of SLC6A4, results in a deletion (short allele, S) and an insertion (long allele, L). Thus, the L allele appears to consist of two primary variants determined by single nucleotide polymorphism (SNP) rs25531: LA and LG. Therefore, 5-HTTLPR is often functionally considered triallelic polymorphism consisting of S, LA and LG(18). Despite that being mentioned, a nucleotide base substitution (A—>G) at the sixth nucleotide affects AP2 functionality, which has an impact on transcription, thereby influencing transcription and level of expression, with LG allele demonstrating the strongest AP2 binding sites. As for S allele, a reduction in transcriptional efficacy is detected resulting in lower expression of 5-HTT. Consequently, LG and S alleles are observed to have slight differences in expression of 5-HTT whereas LA shows higher expression(19).

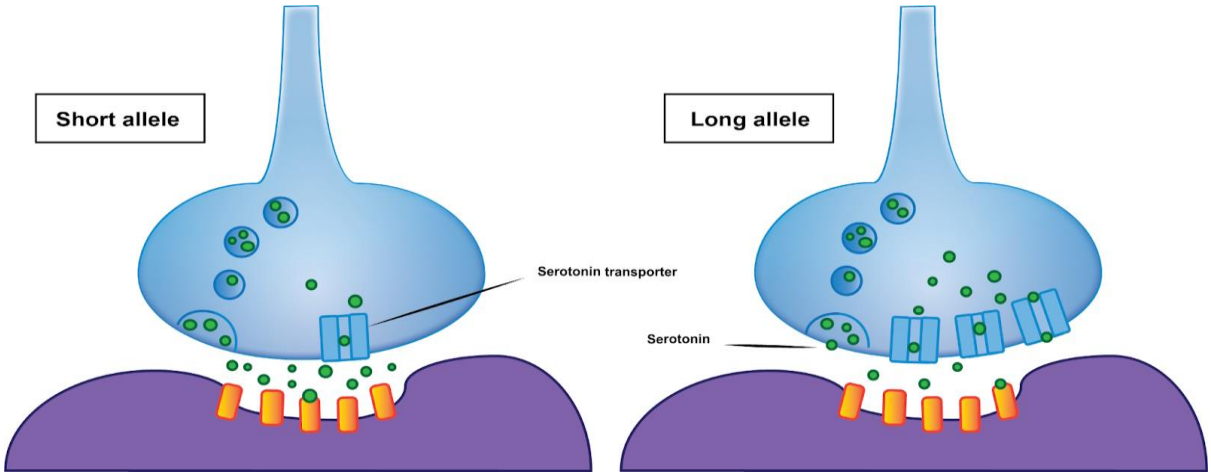

Figure 2: Differences in serotonin transporter (5-HTT) between S allele and L allele carriers. S allele leads to lower 5-HTT expression compared to L allele, and thus it results in higher serotonin level in synaptic clefts.

DISCUSSION

5-HTTLPR is the focus of OCD's genetic studies comprising several allelic variants but three main variants: S, LG, LA. According to conducted studies, AP2 binding in LG allele suppresses SLC6A4 transcription driving functional expression of LG to nearly equivalent to that of S allele(19).

Apart from revealing the identical basal activity of LG and S alleles, Hu et al. suggested that the gain-of-function LA allele underlies the causes of OCD(19). A number of prior and subsequent studies replicated the same result; however, several studies did not yield the same finding nor positive association between 5-HTTLPR polymorphism and OCD. A hierarchical linear model is used to investigate the association between 5-HTTLPR and anxiety-like symptoms in Chinese adolescents. They found that there is a higher tendency to develop anxiety-like symptoms under stressful situations under the presence of L allele(20). Conducted on Caucasian population, it is found that OCD patients are more likely to carry L alleles compared to ethnically matched control groups(19,21). According to several studies, the linkage between 5-HTTLPR and OCD is still in conflict whether there is a linkage and which allele is the underlying cause(22-25). A study aiming to examine 5-HTTLPR polymorphisms and neuroticism-related traits concluded that S allele is significantly associated with neuropsychiatric

symptoms(26). Correspondingly, the S allele also results in alteration in physiology of the brain, which leads to difference in neurotransmitter functionality, yet will be further discussed down below(27,28).

Figure 3 indicated the results from the studies reviewed by the author which range from 1990 to 2020(19-26, 29-37). LG will be converted into S, so there will be S, L(which refers to LA allele), and no association. From the histogram, it can be concluded that LA allele carriers are more susceptible to OCD; however, some studies argued S allele carriers are more prone to OCD or there is no association. The inconsistency in results may be caused from other factors such as environment and other alleles. Different ethnics and sample sizes can also contribute to this result as every study conducted in different populations.

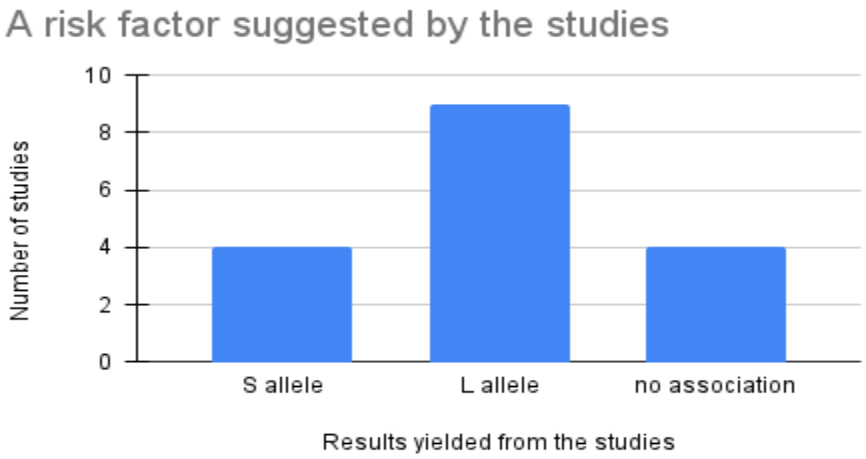

Figure 3: The statistics of genetic risk factors identified from 17 studies. More than 50% of them suggested that L(LA) allele is associated with the manifestation of OCD while lower prevalence of S allele was observed according to the histogram. However, some studies found no significant differences between S and L allele.

More interestingly, as the the influence of rs25531 is recognized just after 2006, the studies conducted before this finding may unintentionally integrate LG and LA together, causing an inaccuracy in result. The almost same number of research supporting each hypothesis can be explained by the point above. Comparing figure 3 to figure 4, the difference in distribution of the results is significant; while a higher prevalence of L allele can be seen in figure 3, figure 4 showed a marginal difference. Moreover, the percentage of no association found in figure 4 is higher than that in figure 3, implying that there might be a factor distorting the results which, in this case, assumes that it is rs25531.

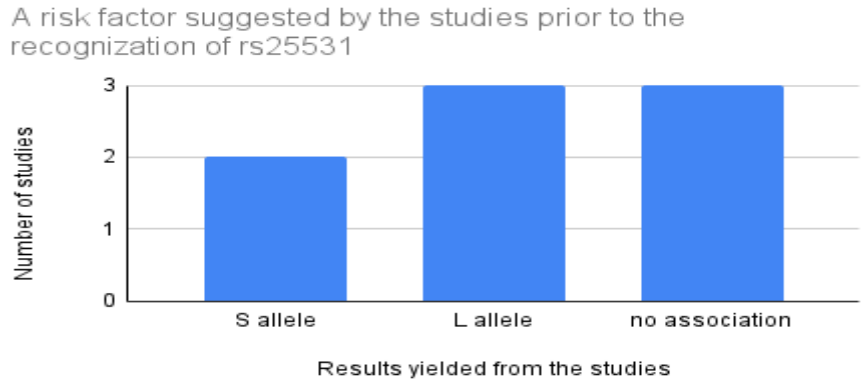

Figure 4: No significant result observed according to the findings from the studies of genetic risk factors of OCD prior to the recognition of SNP rs25531 that causes the basal activity of LG allele equivalent to S allele's.

Although most studies reviewed found that more L allele carriers have OCD or vice versa, some studies found that S/LA carriers are more likely to have OCD compared to those with homozygous genotypes(34,36). Additionally, among the studies that yielded this result, there are both studies that suggested that L allele is a risk factor and S allele is a risk factor.

Moreover, according to Kilic et al., an uncommon gain-of-function variant, Val425, is found to contribute to the vulnerability to OCD, indicating that gain-of-function variants may lead to OCD(38).

SLC6A4 polymorphisms and physiology of OCD

Based on recent studies, limbic regions and hippocampus including hippocampal alteration may play roles in OCD(39). Anterior cingulate cortex (ACC) hyperactivity during rest and provocation has been found in OCD patients, suggesting its importance in OCD(40). From a positron emission tomography (PET) study, OCD patients show reduction in 5-HTT binding in limbic regions, and that supports a hypothesis that OCD is attributable to dysfunction in limbic area and serotonergic system, which may be under influence of SLC6A4 polymorphisms(41). Pezawas et al. revealed S allele carriers show reduced gray matter volume in limbic regions, which regulates emotion and memory and modulates behaviors, and increased amygdala reactivity(42). As for LA allele carriers, there is a tendency to have a reduction in gray matter volume in the right frontal pole, higher volume in left thalamus and again decreased 5-HTT binding observed(43). All findings considered, SLC6A4, which encodes 5-HTT, is associated with physiology of OCD and serotonergic system and the linkage needs to be elucidated and further studied.

Other serotonin-related factors other than SLC6A4 Serotonin receptor (5-HT receptor) gene:

Apart from serotonin transporter(5-HTT), 5-HT receptor has also been the most investigated area and is found to be associated with several neurological disorders such as OCD. Comprising many subtypes, 5-HT receptors that will be discussed here are 5-HT2A, 5-HT2C, 5-HT1B and 5-HT1Dβ receptors respectively.

5-HT2A receptor is the most extensively studied among all and has shown significant association with OCD. Supported by findings from studies, the hypothesis is partly derived from the baseline abnormalities in 5-HT2A receptors detected in pre-treated OCD patients(44). Furthermore, differences and changes in 5-HT2A receptor availability observed in patients treated with SRIs and other medications such as mCPP, as well as replicated results from genetic studies and Genome-Wide Association Studies (GWAS), which are going to be further elaborated, contribute to association between 5-HT2A and OCD(45). The gene that is responsible for 5-HT2A receptor is located on chromosome 13q4-q21 with two primary SNPs: rs6311 and rs6313(46). According to Tot et al., tendency for severe OCD patients to carry homozygous T genotype for rs6313 and homozygous A genotype is higher than that for moderate OCD patients(47).

5-HT2C receptor knockout mice demonstrating compulsive behavior, exacerbation of OC symptoms after mCPP medication and roles of 5-HT2C in the serotonergic system substantiate the association between 5-HT2C receptor and OCD(8,48). However, it is self-conflicting that compulsive behaviors in 5-HT2C receptor knockout mice decreased after treatment with benzodiazepines, which are ineffective in OCD(48). Despite proofs that 5-HT2C receptor is related to OCD, Cavallini et al. investigated 5-HT2C receptor polymorphisms and OCD, but they did not find any genotypic linkages between

them(49). On the contrary, higher frequency of major affective disorders being HT2C ser23 carriers is reported supporting the genetic role of 5-HT2C receptor in major affective disorder(50).

Shanahan et al. reported induced OC behaviors in mice after 5-HT1B receptor agonist medication and suggested that 5-HT1B receptor has a role in OCD-like behaviors(51). To the best of the author's knowledge, 5-HT1B receptor polymorphisms appear to have no genetic association with OCD despite its roles in OCD; however, HTR1B C allele carriers are reported to be associated with substance abuse but not other neuropsychiatric disorders such as schizophrenia(52).

From an exacerbation or a reduction in OC symptoms after administration of sumatriptan, which is 5-HTDβ agonist, reported by Gross-Isseroff et al. and Stern et al., it suggests that 5-HTDβ has a role OCD though the results are conflicting(53,54). According to Mundo et al., there is overtransmission of the G861 allele in the 5-HT1Dβ receptor gene in OCD patients, albeit without replicated results from other studies(55). However, a family-based association study suggested that a preferential transmission of G861 is associated with severity of OCD(56).

Monoamine Oxidase A (MAOA)

Monoamine oxidase A (MAOA) is an essential enzyme that is related to metabolism of neurotransmitters including 5-HT. A MAOA hypomethylation is detected in OCD patients while a healthy control group shows higher MAOA methylation. In addition, an increase in MAOA methylation is also found to be associated with a better response to treatments(57). Brunner et al. identified prominent aggressive and violent behaviors in male with retarded MAOA gene(58). From the findings, it can be concluded that MAOA plays a role in behaviors, and the MAOA gene may link to the X chromosome. A family-based association study aiming to investigate COMT and MAOA polymorphisms and OCD found no significant association while another family-based and population-based study reported that T allele is associated with OCD in female patients(59,60). Kim et al. performed a study among the Korean population and found higher frequency of 3-repeats of MAOA-uVNTR, polymorphisms of the MAOA, in male patients but not in female patients(61).

Limitations of the serotonin and OCD study

Serotonin abnormalities are not the only cause of OCD despite being observed to have an important role. Neurotransmitters do not work alone as well as serotonin and, moreover, they significantly or partially influence each other. To illustrate, Aghajanian et al. proposed a model of 5-HT2A receptors inducing release of glutamate, which is also proven to be involved in OCD, indicating the cooperation and association of neurotransmitters(62). To determine and fully understand the basis of OCD, several factors need to be taken into account, not only genetic factors but also physiological factors and environmental factors.

CONCLUSION

Derived from several studies and findings, serotonin system and its genetic factors are involved with OCD and OCD severity; however, some studies did not replicate the same results and reported no association due to differences in approaching methods, populations and other factors. Be it serotonin transport, serotonin receptor or other neurotransmitters has evidence supporting its roles in OCD and human behaviors. GWAS and genetic studies have proved that 5-HT gene variants, for example LA in SL6A4, predispose the manifestation of OCD. Additionally, SNP rs25531 is important to the study of OCD as it is shown that there is a significant difference in results when comparing studies before recognition of rs25531 and after. Although genetic serotonin abnormalities are not the

only cause of OCD, serotonin and its genetics should not be excluded from OCD study as they are potential and novel areas for the future of OCD treatment and need to be elucidated further.

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