IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Molecular Mechanism of Obsessive-Compulsive Disorder

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Abstract: A serious psychiatric condition called obsessive-compulsive disorder (OCD) affects about 2% of both children and adults in society. OCD has been linked to families in studies of family aggregation, and findings from twin studies show that this relationship is partially influenced by genetic factors. Only three genome-wide linkage studies have been finished so far, and the findings are merely suggestive. More than 80 candidate gene studies have also been released. These studies have mainly concentrated on genes in the dopaminergic and serotonergic pathways. Unfortunately, none have been replicated and, with the exception of the glutamate transporter gene, none have reached genome-wide significance. In order to obtain sufficiently large samples of people with OCD, use cutting-edge laboratory techniques, and carry out the bioinformatic analyses necessary to identify risk loci, multidisciplinary teams of investigators will need to collaborate in future studies. Steroids may be influencing how the disorder develops, according to some theories. However, only a few studies have examined hormone levels and obsessive-compulsive (OC) symptoms simultaneously to date; as a result, there is little direct proof of this association. As a result, more thorough research into neurotransmission in OC patients has linked OCD pathology to the serotonergic, dopaminergic, and glutamatergic neurotransmitter systems. The molecular and cellular mechanisms underlying the pathogenesis of "obsessive-compulsive disorder-like" behaviors have started to come into focus in recent studies of novel mouse genetic models with excessive grooming behaviors Hoxb8, Sapap3, and Slitrk5 are three genes that are genetically deleted in mice, resulting in pathological behaviors such as adult-onset excessive grooming with mild to severe hair loss and self-injury. The abnormal grooming behaviors are linked to increased anxiety in two of the models, the Sapap3-deficient and the Slitrk5-deficient mice, and these pathological behaviors can be reduced with subchronic administration of a selective serotonin reuptake inhibitor, indicating the predictive validity of such models. These models' molecular, pathophysiological, and genetic analyses offer several new insights into the causes of these mice's abnormal behaviors. In this review, we are going to focus on understanding these genetic and hormonal influences in triggering OCD.

Index Terms **- Obsessive-Compulsive Disorder, Molecular Mechanism, Genetic Factors, Hormonal Factors**

I. INTRODUCTION

Obsessive-compulsive disorder is one of the leading heterogeneous neuropsychiatric disorders involving obsession and then that obsession results in compulsive behavior over many different aspects of peoples' personal and social life. Patients suffering from OCD have a constant urge to double-check everything, be it just as simple as washing their hands multiple times or turning the stove off or double-checking the door knob before leaving the house because a voice in their head is always telling them something's wrong and their negligence may lead to dreadful situations. People living with this disease have an obsessive thought running around in their head all the time and that thought urges them to behave compulsively over and over again to make sure their obsessive thought is relieved [1]. Though some OCD patients sometimes realize that their obsessive thoughts are illogical, still they cannot stop their obsession and behave compulsively. Some patients believe that their thoughts are legit and they should act on them as soon as possible. No matter how the patients behave with their compulsive thoughts it takes a good amount of time out of their daily life and makes them mentally exhausted.

Many genetic and environmental factors do have a great influence on the occurrence of this increased anxiety and ritualistic behavior that comes with OCD [2]. This complex nature of the disorder cannot exactly predict the genetic influence it has on patients, as the genetic inheritance pattern is complex yet known up to some extinct [3]. Complex behavior of OCD may lead the symptoms to overlap with chronic hair pulling, anxiety, Tourette syndrome, etc. The effect of these genes in the elevation of OCD can be better understood with the help of protein-protein network analysis [4]. As we know that there's a genetic influence in the regulation of OCD but there's inconsistency in that study due to differences in gene size, subtype, and single nucleotide polymorphism [5]. Mapping the protein-protein network analysis and recognizing the central gene in the network system may be evaluated further to obtain more data on the occurrence of this neuropsychiatric disorder.

Not just genetic or environmental factors but hormonal regulation throughout the body also influences OCD. Studies proved that the symptom of OCD was mostly influenced by the Serotonin hormone as OCD is triggered by miscommunication between the front part of the brain and deeper brain parts. Brain regions affected by OCD include the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPC), basal ganglia, orbito-frontal cortex (OFC), striatum, amygdala, thalamus, and brainstem [6]. Though the complete information about hormonal regulation and OCD is not known yet, some links between neurohormones, gonadal hormones and how

can these trigger OCD have been found and further evolution is still continuing.

Genetic Factors

With the help of a previously published paper on the Genetics influence of obsessive-compulsive disorder and software named Cytoscape (an open software networking tool to help load molecular and genetic data sets) has been used to obtain these below-mentioned OCD-related genes. All these genes may not have a direct correlation with triggering OCD but their functions in the neuropsychiatric system can lead to consequences that have some effect on the influence of this disease. Studies on linkage, Family, twins, candidate gene studies, and Mouse models have helped in finding those genes related to OCD. In this review, we are going to talk about all these methods proven helpful in OCD gene determination.

Linkage Studies

Genome-wide linkage studies have been used to find if there exist any specific alleles or any specific chromosomal region with genes related to OCD that get passed on from generation to generation in a family. To narrow down if the specific region has any linkage with OCD, fine mapping scans in families have been performed by adding additional markers. Such kind of linkage study performed in 219 families with multiple OCD patients (mostly affected were siblings), has shown that on chromosome 3, in the 3q27-28 region, the linkage was strongest, and associated linkage was found on the 1,6,7, and 15 chromosomal regions [7]. Another study with 56 members in a total of 7 families has shown a strong linkage at the 9p24 region on chromosome 9. This region contains the SLC1A1 gene, which is a high-affinity glutamate transporter gene that works as a neurotransmitter and has been proven to be highly associated with OCD [8]. The family linkage may not have been directly yet proven to be responsible for the occurrence of OCD but the influence is surely there.

Family Studies

Family studies have proved that 4%–8% of relatives of patients have OCD, and 20%–40% of first-degree relatives have somewhat obsessive traits in them [9]. First-degree relatives of patients have stronger OCD traits than distant members and to support this statement a study was done on first-degree relatives of 100 OCD patients which proved that the linkage between first-degree relatives' OCD and patient's OCD had a greater connection than distant ones (10% vs. 2%) [10]. Multiple studies have proved this statement over and over [11, 12]. Early onset symptoms of OCD Childhood separation, anxiety, and trauma have also been shown in the relatives of the case than control probands.

Twin Studies

Studies have shown that dizygotic twins (sharing 50% of their genes) had less OCD occurrence than monozygotic twins. In 1981 a study was done on 15 twin pairs where it was observed that OCD symptoms were observed in 87% of monozygotic twins and 47% of dizygotic twins. Twin studies have also shown some evidence regarding the genetic overlapping of anxiety disorder, and attention-deficit hyperactive disorder with OCD. A review has come up with some data regarding OCD patterns 27%–47% in adult-onset OCD cases and 45%–65% of the heritability in child-onset cases [13].

Candidate Gene Studies

OCD genes are related to multiple neurotransmission systems. Though the greater links were found with the serotonergic system pathways due to the proven treatment for OCD is SSRIs (selective serotonin reuptake inhibitors). Other pathways have also come up with genetic linkage influencing OCD triggers.

Serotonergic System

SLC6A4, HTR3A, HTR3B, HTR3D, HTR2A, and HTR1B are the discovered gene has been found to have a connection with OCD incidence, and all these genes are from the serotonin family. The most important enzyme in this family is SLC6A4, a serotonin transporter protein, involved in the regulation of serotonergic signaling via the transport of serotonin molecules from the synaptic cleft back into the pre-synaptic terminal in CNS, for re-utilization, mediates regulation of serotonin for serotonergic systems and terminates serotonin action. There's a promoter region in this gene named 5 HTTLPR, which exists as either short or long allelic forms and recent studies have proved that the long allelic form is directly linked with OCD [14]. Single nucleotide polymorphism Allele A of rs6311 and allele T of rs6313 from the promoter and coding region of HTR2A is under analysis for OCD influence and a recent study didn't find much association between them but it proved the relation between the STin2.12 allele of SLC6A4 gene and OCD [15].

Dopaminergic System

DRD2, DRD3, DRD4, and SLC6A3 are the dopaminergic family genes influencing OCD. DRD4 among them have shown the most positive results as the 7R and 2R allele of the gene is related to OCD symptom and other genes DRD3 and SLC6A4 are associated with white matter changes related to young-onset OCD [16].

Glutamatergic System

SLC1A1, GRIN2B, GAD2, GRIK2, and DLGAP3/SAPAP3 are glutamatergic system OCD genes. Studies have proved the reduced glutamate transport into the postsynaptic neuron may influence OCD. SLC1A1 is a mediator in the uptaking of L-glutamate and also L-aspartate and D-aspartate, Plays a key role in the reabsorption of L-glutamate, and L-aspartate transports L-cysteine and is highly associated with basal ganglia-dependent repetitive behaviors in mice models of OCD [17]. DLGAP3/SAPAP3 helps in the molecular organization of neuronal cell signaling and synapses. In the mice model Gene knockout mice for SAPAP3 display compulsive and anxious behaviors which respond to treatment with SRI.

Mouse Model Studies

As of now the direct correlation between genes and their influence in triggering OCD has not been completely established. But with

recent reports, the designed Novel mouse models with excessive grooming-like behaviors may have a connection to OCD symptoms. To find the actual cause of the cellular and molecular mechanism of OCD in these mouse models we have to look much further. The deletion of three genes namely Hoxb8, Sapap3, and Slitrk5 in the mouse models has shown increased grooming behaviors like enhanced anxiety, hair pooling, and self-injury. Two of these models with Sapap3 and Slitrk5 deficient mice have a good response to SSRI treatment. Now to shed light on each of these gene-deficient mouse behaviors and responses to given treatment we have gone through past studies on them and described available information below ---

Hoxb8 Deficient Mouse

Hoxb8 was not previously suspected to play a part in the regulation of OCD as it is a Hox transcription factor family member which plays a role in patterning the anterior-posterior axis. Greer and Capecchi created Hoxb8 null mutant mouse with a small loxP site in exon 2 of the gene that caused a stop codon, resulting in a frameshift mutation and non-sense mediated RNA decay [18]. A surprising finding was made in this experiment it was found that Hoxb8 null mutant mouse with small loxP site insertions in exon 2 doesn't interfere with skeletal deficits. So it may be the case that larger exogenous sequences were interfering with Hox gene expression, important for skeletal development, and were causing this kind of obsessive grooming behavior in mice. Also, further findings have shown that most of the Hoxb8 gene expressing cell in the brain is Microgila originating from bone marrow during development. So if that is the case then the bone marrow transplantation of wild-type mice to the Hoxb8 null mutant type mouse will be the solution to resolve excessive grooming behaviors in them but the result turned out to still cause abnormal excessive grooming behaviors in a few subsets of recipient mice. So Hoxb8 deficient microglia may be enough to bring out the obsessive grooming phenotype. Another study [by Chen et al.] with deletion of the gene not in the microglia but in the spinal cord or hematopoietic lineage proved that it gives rise to reduced spinal cord sensory neurons (no heat sensitivity) which proved to be responsible for obsessive grooming. Further studies need to be done in order to find out the link between Human type OCD and the Hoxb8 gene influence on it.

SAPAP3 Deficient Mouse

OCD has been said to be linked with the cortico-striatal-thalamo-cortical loop (Brain circuit connecting orbitofrontal and anterior cortex, striatum, thalamus, and back of cortex).In recent studies, it has been definitely established that SAPAP3 knockout mice exhibit OCD-like behaviors. SAPAP3 null mouse features excessive self-grooming, hair loss, and lesions from a very young age, though the phenotype isn't related to this behavior. Surprisingly mutant mice exhibit similar behavior but these can be resolved by using SSRIs. Though the correlation between SSRIs and relieving symptoms of OCD caused by SAPAP3 gene knockout is yet to be established. As SAPAP3 is a protein present in the postsynaptic density of excitatory synapses, the mutant mice have deficits in excitatory synapses of MSNs resulting in an increase of NMDA-dependent neurotransmission and structural changes in the synapse. To look into further relations Welch and Colleagues injected lentivirus expressing SAPAP3 with a green fluorescent protein in the striatum of SAPAP3 null mouse, which resulted in expressing only those mice who were expressing fluorescence to have shown rescue OCD phenotypes. These findings show that SAPAP3 has the importance of cortico-striatal circuitry in OCD.

Slitrk5 Deficient Mouse

Deletion of the Slitrk5 gene in mice models causes excessive OCD-like symptoms like skin lesions and hair loss. The transmembrane protein known as Slitrk5 has an extracellular domain that is homologous to the Slit/Robo family of axon guidance molecules and an intercellular domain that is similar to the trkB receptor. It is enriched at cortico-striatal synapses. Despite a prior link between Slitrk1 and Tourette's syndrome based on genetic studies, knockout of the Slitrk1 gene did not result in abnormal repetitive behaviors instead, it resulted in increased anxiety. With a relatively unknown role and no prior association with psychiatric illnesses, Slitrk5 was specifically inactivated, which resulted in perseverative grooming, lesions, and elevated anxiety. Treatment with chronic fluoxetine, but not acute fluoxetine, restored both of these behaviors, which is consistent with the pharmacologic response profile reported in OCD patients. By measuring baseline expression of the immediate early gene, FosB, Slitrk5 KOs also demonstrated selective overactivation of OFC, drawing another analogy to human fMRI and PET studies indicating baseline OFC hyperactivation. Additionally, they exhibit diminished striatal glutamate receptor expression, including diminished GluR1, GluR2, NR2A, and NR2B levels. This indicates a paradigm whereby disruption of striatal post-synaptic density proteins results in incorrect glutamate receptor trafficking and insertion in striatal synapses, as well as inappropriate cortico-striatal communication when combined with the results from SAPAP3 KO mice stated above. It is unknown if these alterations in synaptic function are unique to certain projections or neuronal subtypes. Preliminary research suggests that OCD patients have rare Slitrk5 genetic variations, however, these results need to be confirmed before being able to be applied to humans.

Hormonal Factor Serotonin in OCD

Pharmacological study findings first suggested that the serotonergic system was involved in the etiology of OCD symptoms. Early research indicated that the tricyclic antidepressant clomipramine, a strong serotonin reuptake inhibitor (SRI), reduced the symptoms of OCD. Other research has demonstrated that the serotonin reuptake agonist meta chlorophenyl-piperazine made some patients' OCD symptoms worse. This implies that those who have OCD or are exhibiting signs of OCD may have a dysregulation that prevents prolonged serotonin release and/or signaling. Later research with selective SRIs (SSRIs) such as fluoxetine, paroxetine, sertraline, citalopram, and escitalopram demonstrated similar outcomes to clomipramine therapy. Other studies have measured the availability of serotonin reuptake transporter (SERT) in small samples of OCD patients using single-photon emission computed tomography. The availability of SERT in OCD patients has decreased, increased, or remained unchanged, according to this study's conflicting findings. Later research confirmed the function of serotonin in OCD using more precise physiological markers.

Although these findings are not always reliable, it was discovered that patients with OCD symptoms had significantly higher levels of the serotonin metabolite 5-hydroxy indole acetic acid in their cerebrospinal fluid (CSF) than healthy volunteers did. This finding suggests that the brain's serotonin turnover is increased.

Hormonal Factor Dopamin in OCD

Dopamine is a neurotransmitter that has also been linked to the pathophysiology of OCD. Dopamine blockers have been successfully utilized to treat several OCD spectrum illnesses, including Tourette's syndrome, whereas studies have shown that the administration of dopamine agonists causes a worsening of OC symptoms. In rat models of OCD, quinpirole, a dopamine D2/D3 receptor agonist, has been shown to promote compulsive checking. Fluvoxamine, an SSRI, was used to treat patients, which improved symptoms and boosted D2 receptor binding. It was hypothesized that fluvoxamine's modulation of the serotonergic system is what caused this alteration in the availability of D2 receptors. Dopamine is the major neurotransmitter in the cortico-striato-thalamo-cortical (CSTC) loop, which is related to OCD, and serotonergic neurons projecting from the raphe nuclei are hypothesized to control this loop. Serotonin may bind to 5-HT2A receptors on the somatodendritic surface of dopamine neurons when it is released from a presynaptic cell. As a result of this interaction's inhibitory effect on the dopamine neuron, less dopamine will be released into the synaptic cleft, which will stop more downstream dopamine signaling. An SSRI will cause sustained serotonin signaling, which will have a long-lasting inhibitory effect on the dopaminergic system. In contrast, the dopamine neuron may release its neurotransmitter to trigger a dopamine signaling cascade in the absence of serotonin or in the presence of a 5-HT2A antagonist or 5-HT1A autoreceptor agonist]. As was previously mentioned, since serotonin signaling is likely to be reduced in OCD patients, it is probable that this lack is causing the dopaminergic hyperactivity that is a hallmark of OCD.

Hormonal Factor Glutamate in OCD

Glutamate levels in the CSF of OCD patients who are not receiving treatment have been measured in two studies. Both studies discovered that OCD patients' CSF had glutamate levels that were noticeably greater than those of controls. MRI studies that measured the brain concentrations of glutamate in OCD patients revealed higher levels in the caudate nucleus and decreased levels in the ACC. However, a more recent study that measured neurometabolic concentrations in the ACC using 3T proton-magnetic resonance spectroscopy reported no change in the concentration of glutamate plus glutamine in OCD patients compared to healthy controls. Some interest in the use of glutamate-modulating drugs in the treatment of OCD has also been sparked by the potential involvement of the glutamatergic system in OCD pathogenesis. In addition to increasing glial uptake of extrasynaptic glutamate, riluzole, which blocks certain voltage-gated sodium channels, decreases glutamate release. In patients with refractory OCD, riluzole has produced some encouraging clinical results. But the outcomes of more rigorous investigations have only revealed minor advantages. As previously mentioned, several investigations have revealed elevated levels of glutamate in the central nervous system in OCD patients; as a result, NMDA receptor antagonism has been recommended to reduce excessive glutamate signaling. NMDA receptor blockers memantine and ketamine have shown some promise in small clinical trials. Overall, investigations of glutamate involvement in OCD pathology have yielded interesting results that appear to be promising avenues for future research. However, to date, many of the findings have been far from conclusive; thus, the glutamatergic system is only suspected to be involved in OCD.

Results and Discussion

Table 4.1: Genes Found In Human System May Be Linked With OCD Influence

UA Code	Gene Name	Function
P14416	DRD2 *(Nicolini et al., 1996)*	Dopamine receptor, G protein-mediated activity inhibits adenylyl cyclase, and regulates postnatal regression of retinal hyaloid vessels via suppression of VEGFR2/KDR activity, downstream of OPN5 [19].
P35462	DRD3 *(Nicolini et al., 1996)*	Dopamine receptor, G protein-mediated activity inhibits adenylyl cyclase, and increase the proliferation of cell [20], some evidence was found for association with schizophrenia, in Caucasians but no discovered evidence for association of sequence variants, bipolar disorder, or attention-deficit hyperactivity disorder.
P28221	HTR1D *(Mundo et al., 2000)*	EE Enables G protein-coupled serotonin receptor activity. Acts in the regulation of the other neurotransmitters' release. Regulates the release of 5-hydroxytryptamine in the brain, and affects neural activity. This receptor is located primarily in the basal ganglia, cortex, spinal cord, hippocampus, and vascular smooth muscle cells. Receptors influence neuropsychiatric disorders like depression. [21,22]
P21917	DRD4 *(Millet et al., 2003)*	Dopamine receptor protein-mediated activity inhibits adenylyl cyclase, Controls neuronal signaling at the mesolimbic system, a part of the brain that regulates complex behavior and emotions. Activated by dopamine, epinephrine, and norepinephrine, synthetic agonists, and drugs. [23,24,25,26,27,28,29,30]
Q16653	MOG *(Zai et al., 2004)*	Myelin-oligodendrocyte glycoprotein, a myelin sheath component, is involved in the completion and maintenance of the myelin sheath and in cell-cell communication. Works as a mediator in homophilic cell-cell adhesion.[31]
Q13224	GRIN2B *(Arnold et al., 2004)*	Glutamate receptor, ionotropic, N-methyl D-aspartate 2B, Sensitive to glutamate, and channel kinetics depend on the subunit composition. The component of NMDA receptor complexes works as heterotetrameric, ligand-gated ion channels with high calcium permeability and voltage-dependent sensitivity to magnesium. Acts as a central mediator for

		stroke damage, with DAPK1 at extrasynaptic sites. Involved in neural pattern formation in the developing brain, long-term depression (LTD) of hippocampus membrane currents, and synaptic plasticity. [32,33]
Q01959	SLC6A3(*the journal of the European College of Neuropsychopharmacology 2005)*	Amine transporter and with the help of high-affinity sodium-dependent reuptake in presynaptic terminals terminate Dopamine action.
Q16288	NTRK3 *(Alonso et al., 2008)*	Ne Neurotrophic tyrosine kinase, receptor, type 3, involved in heart development and nervous system, after binding of its ligand NTF3/neurotrophin-3, NTRK3 auto-phosphorylate and activates phosphatidylinositol 3-kinase/AKT and the MAPK signaling pathways, control cell survival and differentiation. [34]
O75751	EMT (SLC22A3) *(Lazar et al., 2008)*	SS Solute carrier family 22 member 3, plays a key role in the disposition of cationic neurotoxins and neurotransmitters in the brain.[35]
O95886	DLGAP3 (SAPAP3) *(Boardman et al., 2011)*	Disks large-associated protein 3, which helps in the molecular organization of neuronal cell signaling and synapses. Can increase amount of PSD-95/SAP90 at the plasma membrane. By linking ion channel to sub-synaptic cytoskeleton works as an adapter protein.
P03372	ESR1 *(Alonso et al., 2011)*	Estrogen receptor 1, steroid hormone, involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Studies have shown relation between ESR1 polymorphism and risk developing dementia. The link between *ESR1* and cognitive impairment tend to driven by women and develop risk for Alzheimer's disease rather than other dementia causes. Also It is linked with childhood onset mood disorder. [36]
Q16620	NTRK2 *(Taylor, 2013)*	BDNF/NT-3 growth factors receptor, has an important contribution in development and maturation of the central and peripheral part of nervous system by survival of neuron, proliferation, migration, differentiation, and synapse formation. Helps in learning and memorizing by regulating long-term potentiation and short term synaptic function. Mediates communication between neuron and glia. Mutations in this gene have been associated with obesity and mood disorders.[37]
Q13002	GRIK2 *(Taylor, 2013)*	Glutamate receptor ionotropic, as L-glutamate is an excitatory neurotransmitter at many synapses in the CNS, binding of the excitatory neurotransmitter induces change and open ion channel that converts chemical signal to electrical signal, then the receptor desensitize fast and enters transient (inactive) state. [38]
P28223	HTR2A *(Taylor, 2013)*	G-coupled 5-hydroxytryptamine (serotonin) receptor 2A, Affects neural activity, mood, perception and cognition [39]. Plays a key role in responses to anxiogenic situations & psychoactive substances.
P21397	MAOA *(Taylor, 2013)*	Monoamine oxidase A protein, oxidizes serotonin [39], catalyzes oxidative determination of neurotransmitter, plays key role in metabolism of neuroactive and vasoactive amines in CNS and PNS [40,41,42,43].
Q13516	OLIG2 *(Taylor, 2013)*	Oligodendrocyte transcription factor 2 protein, helps in differentiation of oligodendrocyte and motor neuron, it is required for somatic mototr neuron development in hindbrain. This gene is associated with down syndrome [44], its association with Alzheimer's & schizophrenia is still under research.
P43005	SLC1A1 *(Stewart et al., 2013)*	Solute carrier family 1 (neuronal/epithelial high-affinity glutamate transporter, system Xag), member 1 protein, which is a mediator in uptaking of L-glutamate and also L-aspartate and D-aspartate [45, 46, 47, 48]. Plays key role in reabsorption of L-glutamate and L-aspartate [49], transports L-cysteine [50]
P01375	TNFA *(Taylor, 2013)*	Tumor necrosis factor protein, secreted by macrophages and can induce cell death of tumor. Helps in angiogenesis by inducing VEGF production synergistically with IL1B and IL6 [51].

P31645	SLC6A4 *(Taylor, 2013)*	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 protein, it is involved in regulation of serotonergic signaling via transport of serotonin molecules from the synaptic cleft back into the pre-synaptic terminal in CNS, for re-utilization, mediates regulation of serotonin for serotonergic systems and terminates serotonin action.[52,53]
P21964	COMT *(Taylor, 2013)*	Catechol-O-methyltransferase a protein catalyzing O-methylation and then inactivate catechol hormones and catecholamine neurotransmitters also reduce half lives of few neuroactive drugs.[54,55]
Q96PX8	SLITRK1 *(Ozomaro et al., 2013)*	SLIT and NTRK-like family, member 1 protein, Increase neuronal dendrite outgrowth and promotes excitatory synapse differentitation and involved in synaptogenesis.[56,57,58,59]
P28222	HTR1B *(Mas et al., 2014)*	5-hydroxytryptamine (serotonin) receptor 1B, G protein-coupled, receptor for antidepressant and anxiolytic drugs. Plays important role in vasoconstriction of cerebral arteries. Also is involved in regulation of dopamine, 5-hydroxytryptamine and acetylcholine release in brain which influence various neural activity, mood, pain perception etc.[60,61,62]
Q05329	GAD2 *(Mas et al., 2014)*	Glutamate decarboxylase 2 protein, catalyzes GABA (Gamma-aminobutyric acid) production. [63]
P46098	HTR3A *(Lennertz et al., 2014)*	5-hydroxytryptamine serotonin receptor 3A protein is a hormone, neurotransmitter and mitogen, which is cation specific ligand-gated ion channel and after activation causes fast, depolarizing responses in neurons. [64,65]
O95264	HTR3B *(Lennertz et al., 2014)*	5-hydroxytryptamine (serotonin) receptor 3B protein works same as HTR3A.
Q8WXA8	HTR3C *(Lennertz et al., 2014)*	5-hydroxytryptamine receptor 3 subunit C protein works same as HTR3A.
Q70Z44	HTR3D *(Lennertz et al., 2014)*	5-hydroxytryptamine (serotonin) receptor 3 family member D protein, works same as HTR3A.
A5X5Y0	HTR3E *(Lennertz et al., 2014)*	5-hydroxytryptamine receptor 3E protein, works same as HTR3A.
P23560	BDNF *(Zai et al., 2015)*	Brain-derived neurotrophic factor and activates signaling cascades downstream of NTRK2, it has association with the long-term potentiation (LTP), long-term depression (LTD), homeostatic regulation of intrinsic neuronal excitability, as well as certain forms of short-term synaptic plasticity. Also influence axonal growth, dendritic growth modulation and promotes survival and differentiation of few neuronal populations in CNS & PNS. [66,67]
O14490	DLGAP1 *(Li et al., 2015)*	Discs, large homolog-associated protein 1, is a part of the post-synaptic scaffold of the neuronal cells.
P19022	CDH2 *(McGregor et al., 2016)*	Neuronal cadherin gene, cell adhesion protein, regulates neural stem cells quiescence, forks cell to cell junction between pancreatic beta cells and neural crest stem cells. Involves in neuronal recognition mechanism. [68]

Conclusion

The results of epidemiological and molecular genetic investigations strongly support the notion that OCD has a complicated hereditary origin. No documented genetic variant for OCD has been discovered to yet, with the exception of a few potential genetic variants such SLC1A1, DLGAP1, and PTPRD. For several of the above-mentioned empirical methods, larger samples are needed. Additional strategies, such as gene expression studies in brain tissues and the use of induced pluripotent stem cell technology, are in the pipeline or should be used in addition to the identification of associated genetic variants in order to better understand the functional basis for the relationship between the protein and the phenotype. Studies on epigenetics may help by clarifying how altered gene expression affects the risk of OCD. A program that will make a significant contribution in the future is the US National Institutes of Health's

Encyclopedia of DNA Elements program. These research are expected to change the phenotype of OCD and associated disorders. We anticipate the emergence of new clinical subtypes and the emergence of enlarged boundaries of features involving new psychiatric diseases. The discovery of logical OCD treatments and prevention strategies is our greatest hope as a result of these research efforts. Current lines of evidence show a role for gonadal hormones in OCD pathogenesis. Estrogen and progesterone have been demonstrated to influence serotonergic, dopaminergic, and glutamatergic neurotransmission, and these neurotransmitter systems have been proven to be dysregulated in OCD patients. From this evidence, it can be inferred that hormones play an important role in influencing the course of OCD. It is necessary to look into this connection further. Future research should prospectively evaluate OC symptom intensity along the course of female reproductive events, including contemporaneous measurements of hormone levels.

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