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REVIEW

Epigenetic modifications and obsessive–compulsive disorder: what do we know?

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Abstract

Obsessive–Compulsive Disorder (OCD) is a chronic, severe disabling neuropsychiatric disorder whose pathophysiology is not yet well defined. Generally, the symptom onset occurs during pre-adult life and affects subjects in different life aspects, including professional and social relationships. Although robust evidence indicates the presence of genetic factors in the etiopathology of OCD, the entirely mechanisms are not totally clarified. Thus, the possible interactions between genes and environmental risk factors mediated by epigenetic mechanisms should be sought. Therefore, we provide a review of genetic and epigenetic mechanisms related to OCD with a deep focus on the regulation of critical genes of the central nervous system seeking possible potential biomarkers.

Keywords Obsessive-compulsive disorder · Epigenetic · Non-coding RNAs · Histone Modification · DNA Methylation

Abbreviations

5hmC	5-Hydroxymethylcytosine
5mC	5-Methylcytosine
ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
CREB	Camp-response element-binding protein
ESR1	Estrogen receptor 1
E-WAS	Epigenome-wide association studies
GABA	Gamma-aminobutyric acid
G-WAS	Genome-wide association study
HAMA	Hamilton anxiety rating scale
HAMD	Hamilton depression rating scale
LEPR	Leptin receptor gene
Limk1	Lim domain kinase 1
LTP	Long-term potentiation
MAOA	Monoamine oxidase A
miRNAs	MicroRNAs
MOG	Oligodendrocyte glycoprotein
NMDA	*N*-Methyl-D-aspartate
NTRK3	Neurotrophin-3 receptor gene
OCD	Obsessive–compulsive disorder
OXTR	Oxytocin receptor gene
RT-qPCR	Reverse transcription quantitative real-time polymerase chain reaction
SIRT1	Sirtuin
Y-BOCS	Yale-Brown obsessive–compulsive scale
YY1	Yin Yang 1
MDD	Major depressive disorder

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Introduction

Obsessive–compulsive disorder (OCD) is defined by the possession of obsessions and, or compulsions. Obsessions are persistent, recurrent, and distressing thoughts, impulses, or mental images experienced as unwanted and intrusive. OCD cases try to neutralize discomfort and anxiety induced by obsessions with compulsions (Edition 2013; Balandeh et al. 2021; Mohammadi et al. 2021a, 2021b; Beheshti et al. 2022, 2023). OCD has annual and lifetime prevalence of 1.1–1.8% and 2–3%, respectively (Ruscio et al. 2010). It shows a bimodal age of onset peaking at late childhood or

early adolescence and early adulthood (Anholt et al. 2014). It is known as a potentially disabling psychiatric disorder interfering with all life aspects, including school, work, and personal relationships. Besides, lower quality of life scores is observed in OCD cases, especially among females cases, even by controlling symptoms of anxiety and depression (Jahangard et al. 2018).

The critical role of both genetic and environmental factors is speculated in the development of OCD (Mataix-Cols et al. 2013). Environmental factors such as stress, model learning, and trauma are considered significant risk factors for the development of OCD (Grünblatt et al. 2018) that could alter gene transcription and expression. Indeed, there was a significantly higher rate of basal and perceived stress levels of plasma cortisol in OCD patients compared to control cases (Morgado et al. 2013). Thus, epigenetics is a chief interface between environmental changes resulting in alteration in gene expression. Histone modifications, DNA methylation, and microRNAs (miRNAs) are three primary epigenetic mechanisms (Bellia et al. 2021). Such epigenetic alterations influence gene expression and modulate accessibility for transcription factors (Jaenisch and Bird 2003). Epigenetic mechanisms involved in the regulation of some genes such as BTB domain containing 3, Disks large-associated protein two genes, gamma-aminobutyric acid (GABA) B receptor 1, myelin oligodendrocyte glycoprotein (MOG), BDNF (Brain-Derived Neurotrophic Factor) and leptin receptor gene (LEPR) (Bellia et al. 2021) could exert a role in the pathogenesis of OCD (Grünblatt et al. 2018). Herein, we will focus on investigations that have analyzed epigenetic players associated with OCD. Besides, we will briefly summarize the recent progressions in performed genetic and epigenetic investigations on OCD and discuss the possible interactions between genetics, environmental factors, and epigenetics in the pathogenesis of OCD.

Pathogenesis of obsessive–compulsive disorder

Data derived from different investigations implicate the involvement of basal ganglia, prefrontal cortex (orbitofrontal and anterior cingulate cortices), and thalamus in OCD etiopathogenesis. The most important neurotransmitters associated with OCD pathogenesis are glutamate, serotonin, GABA, and dopamine (Huey et al. 2008; Pittenger 2017). Glutamatergic neurons are extensively distributed at different brain locations such as brainstem circuits, cerebellum, basal ganglia, and numerous intracortical and cortico-subcortical connections. Classically, Glutamate receptors are divided into two subgroups metabotropic and ionotropic. The former contains mGLU1-8. The principal ionotropic receptors are α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, N-methyl-D-aspartate (NMDA), and kainate receptors. Investigations demonstrated the role of dysregulated glutamate transmission in cortico-striato-thalamo-cortical circuits in the pathogenesis of OCD (Sheshachala and Narayanaswamy 2019). Selective serotonin reuptake inhibitors (SSRIs) exert their anti-obsessional impact through blockage of the 5-HT connection to the serotonin transporter, which surprises serotonin reuptake (Baumgarten and Grozdanovic 1998; Lissemore et al. 2014). Indeed, the volume of specific brain parts responsible for dopaminergic activities is observed in OCD cases. No appropriate response to SRI monotherapy has been reported in 40 to 60% of OCD cases, which indicates the consideration of dopaminergic and SRIs antagonists in the treatment of OCD cases (Hemmings et al. 2003; Koo et al. 2010).

Epigenetic and psychiatric disorders

A large body of evidence implicates the interaction between genes and environment in developing numerous complex disorders, such as mental disorders (Pittenger 2017). As shown in Fig. 1, epigenetic mechanisms regulating gene expression could mediate these interactions. DNA methylation, histone modifications, and microRNAs are three central epigenetic mechanisms (D'Addario et al. 2013). Histone modifications imply the chemical modifications of histones at amino acid residues on their N-terminal tails, including phosphorylation, acetylation, methylation, and ubiquitination that enhance or diminish gene expression (Strahl and Allis 2000). DNA methylation occurs through the addition of a methyl group to the C5 position of cytosine (C) in a CpG dinucleotide, forming the 5-methylcytosine (5-mC) (Bellia et al. 2021). DNA methylation occurs at gene regulatory regions that could lead to the repression of gene transcription. 5-HydroxyMethylcytosine (5hmC) resulted from oxidation of 5 mC by the Ten–Eleven Translocation enzymes. Since 5-mC is associated with enhanced gene expression, it could be considered a novel epigenetic modification (Pucci et al. 2019). The post-translational regulatory mechanisms are mediated by miRNAs which are short single-strand RNA sequences with about 20 nucleotides capable of silencing gene expression. This process develops by inhibition or degradation of target mRNA through a process mediated by RNA-induced silencing complex (RISC) (Ouellet et al. 2006; Bellia et al. 2020). Numerous investigations demonstrated an important role of epigenetics players in the development of psychiatric disorders (Martins-Ferreira et al. 2020; Masini et al. 2020; Gürel et al. 2020).

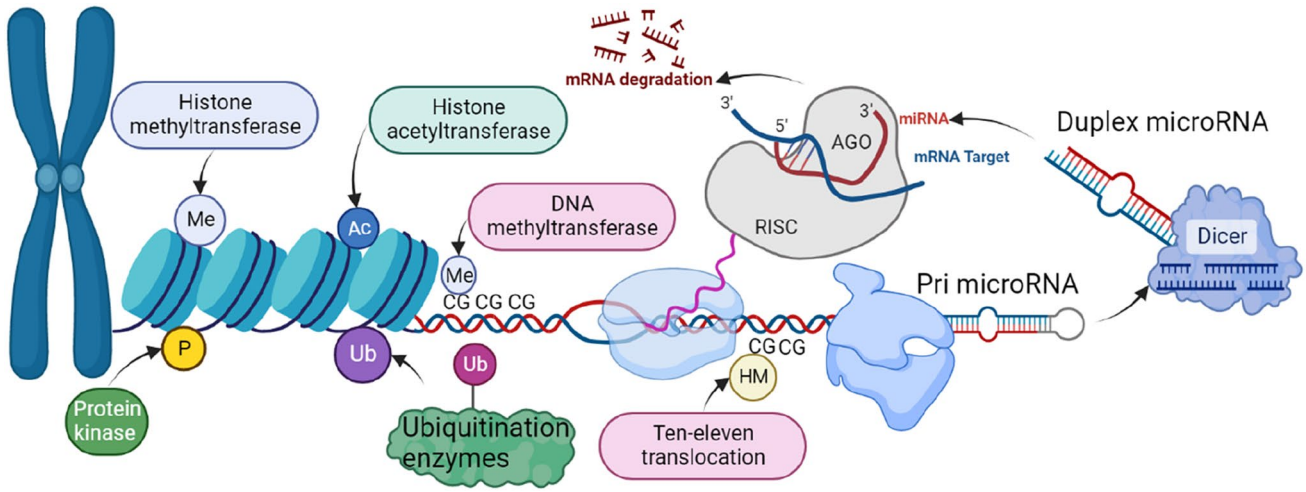

Fig. 1 Schematic representation of the primary epigenetic mechanisms. *Me*Methyl, *Ub* Ubiquitin, *P*: Phosphoril, *Ac* Acetyl, *HM* Hydroxymethyl, *AGO* Argonaute protein. This figure is adapted from Bellia et al. (2020, 2021)

In a study, the role of possible epigenetic mechanisms in psychiatric disorders such as major depressive disorder (MDD), addiction, and schizophrenia was discussed (Mahgoub and Monteggia 2013). Nestler (2009) has stated that the study of epigenetics can push the transcriptional mechanisms involved in psychiatric disorders to the next required level of analysis. As such, epigenetics provides a uniquely powerful tool for studying transcriptional mechanisms in psychiatric disease and its treatment. However, the potential importance of epigenetics is much greater. Epigenetics represents a third type of general mechanism that likely contributes to each individual's unique vulnerability or resistance to a mental disorder. For example, epigenetic changes, including those that occur randomly during the highly complex process of brain development, can explain the high rates of discordance between identical twins for many psychiatric syndromes, the chronic relapsing nature of these syndromes, and the striking differences in Outbreaks are observed, help. Also, epigenetic changes provide a mechanism by which environmental experiences can alter gene function in the absence of DNA sequence changes and may help explain the largely inconsistent genetic association studies of mental illness, for example, with attenuation of the transcriptional effect of DNA sequence polymorphisms due to epigenetic changes on those gene promoters (Nestler 2009).

Search strategy

Following PRISMA protocol (Moher et al. 2009), an online databases search including Web of Science, Google Scholar, PubMed, and Scopus was employed for published literatures in the area of Epigenetic and OCD until September 2021 (Fig. 2).

Epigenetic and obsessive–compulsive disorder

Besides genetics, OCD could be mediated by epigenetic factors. Epigenetics indicates the heritable alterations of chromatin state independent of alterations in DNA sequence, including those accompanying cellular reprogramming (Bird 2007; Greally 2018). The crucial implication of epigenetic mechanisms, including histone modification, non-coding RNAs, and DNA methylation, have been demonstrated at the junction between genetic issues and environmental factors by the critical influence of gene regulation and adaptation to environmental factors (Schiele and Domschke 2018; Schiele et al. 2020a; Gottschalk et al. 2020). Meanwhile, epigenetic changes associated with OCD have been demonstrated previously (Grünblatt et al. 2018; Stewart et al. 2013; Schiele et al. 2020b; Nissen et al. 2016a; Yue et al. 2016a; Cappi et al. 2016a).

MiRNAs on–off switch gene expression patterns and exert a fundamental role in the synaptic plasticity of the central nervous system (CNS) (Muiños-Gimeno et al. 2009a). For instance, MiR-132 is closely associated with neurite outgrowth, whereas miR-134 exerts a fundamental role in postsynaptic regulation suggesting the crucial role of brain-specific miRNA families in synaptic plasticity. cAMP- CREB and BDNF are two genes with a close relationship and substantial involvement in synaptic plasticity and modulation of synapse formation (Flavell and Greenberg 2008). It has been suggested that CREB and BDNF in mediating OCD occurrence (Arora et al. 2013; Hall et al. 2003). BDNF is both a downstream target and an upstream regulator of CREB. BDNF regulates miR-132 partially and acts upstream of the CREB-dependent miR-132/212 transcription via a cascade

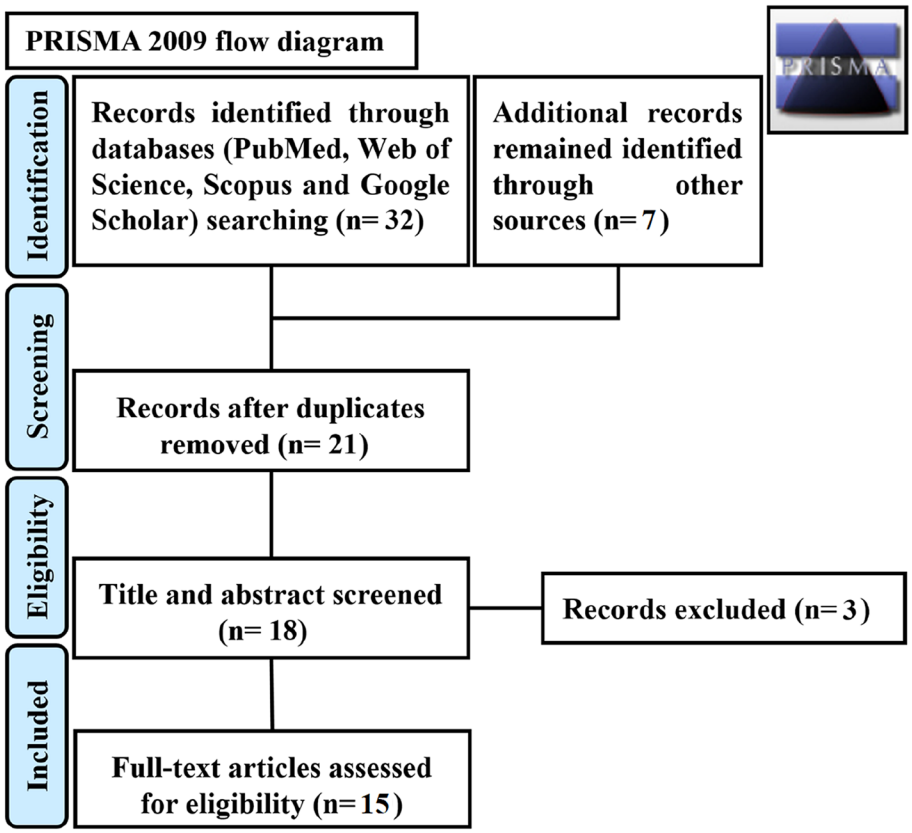

Fig. 2 PRISMA flow diagram

involving ERK1/2 and mitogen- and stress-activated protein kinase (MSK)1/2 activation (Salta and Strooper 2017).

MicroRNA-134 (miR-134) exerts a fundamental role in the modulation of synapse formation and synaptic plasticity. MiR-134, located in the synaptodendritic part of rat hippocampal neurons, exerts a negative regulation on dendritic spine size as a postsynaptic location of excitatory synaptic transmission (Schratt et al. 2006). Furthermore, miR-134-5p prohibits translation of synaptic LIM domain kinase 1 (Limk1) until synaptic activation with inactivated miR-134-5p, an expressed Limk1 protein at this point leads to the growth of the dendritic spine (Liu et al. 2009). Furthermore, BDNF can relieve the repressive impacts of miR-134 on the translation of Limk1 mRNA. Modulation of translation by microRNAs through a BDNF-sensitive manner might highlight a mechanism that postsynaptic proteome is regulated in dendrites by neurotrophin during the late phases of long-term potentiation (LTP). Neuronal plasticity and memory were demonstrated to be regulated by miR-134 (Gao et al. 2010). Besides, Sirtuin 1 (SIRT1) usually functions to restrict miR-134 expression through a repressor complex with transcription factor Yin Yang 1 (YY1). Down-regulated expression of BDNF and CREB occurs following unchecked miR-134 expression due to SIRT1 deficiency which impairs synaptic plasticity. Several lines of evidence have demonstrated the pivotal role of synaptic plasticity in the development of mental disorders (Frank and Greenberg 1994; Kang and Schuman 1995; Jeffery and Reid 1997), such as OCD (Muiños-Gimeno et al. 2009a; Taylor 2011).miR155 plays a fundamental role in the maintenance of homeostasis and immune system functioning. A wide range of miR155-regulated genes include transcription factors, cytokines, and chemokines (Rodriguez et al. 2007). miR155 is induced in lipopolysaccharide-stimulated human monocytes (Liu et al. 2009). Immune mechanisms are speculated to be directly involved in the pathogenesis of some OCD subtypes, including autoimmune neuropsychiatric disorders accompanied by streptococcal infections. Clinical observation of increased frequency of obsessive–compulsive symptoms in cases with rheumatic fever considered a post-streptococcal autoimmune disease, led to the launching of studies on immune parameters in OCD (Teixeira et al. 2014). Therefore, miR155 might be involved in developing OCD (Kandemir et al. 2015a).

Some studies have been conducted on the effect of microRNAs regulation on OCD and have provided interesting results (Table 1). For example, Yue et al. (2020) measured the plasma levels of miRNA-132 and miRNA-134 in OCD disease. Their results showed that the level of these two types of microRNA in the plasma of people with OCD is abnormal and, therefore, it may affect the dendrites number in the cerebral cortex and the synapses formation (Yue

Table 1 Epigenetic modifications association studies in obsessive–compulsive disorder

Epigenetic players	Results	Methods	Country	Model	Sample size	Ref
*Non-coding RNA*s						
miRNA-132 and miRNA-134	In OCD groups, the plasma level of miRNA-132 and miRNA 134 were significantly higher compared with the control group	Quantitative reverse transcription polymerase chain reaction	China	Human	30 patients with OCD *vs.* 32 normal controls	Yue et al. (2020)
miR18a-5p, miR22-3p, miR24-3p, miR106b-5p, miR107, miR125b-5p, and miR155a-5p	The whole plasma level of miR24-3p, miR22-3p, miR106b-5p, miR155a-5p, and miR125b-5p were significantly enhanced in OCD cases	RT-PCR	Turkey	Human	23 child and adolescent OCD cases *vs*. 40 healthy volunteer control	Kandemir et al. (2015a)
	The rs28521337 and ss102661458 variants significantly change the miRNA-mediated regulation of NTRK3, resulting in recovery of gene expression	PCR	Spain	Human	153 patients with OCD, *vs.* 324 control subjects	Muiños-Gimeno et al. (2009a)
Histone modification	A probable relationship between the process of histone H3Ser10 phosphorylation and the responsibility of obsessive–compulsive disorders in humans was discussed	Immunohistochemical	Russian	Male rats		Pavlova et al. (2013b)
DNA methylation						
OXTR	Hypermethylation of OXTR might constitute a predictive marker of impaired treatment response in OCD and so carries great potential for future personalized treatment efforts in OCD	Direct sequencing	Germany	Human	113 OCD inpatient cases (57 females) *vs.* 113 age and Sex-matched healthy controls	Schiele et al. (2021)
SLC6A4	No significant difference was observed between GTS + OCD, GTS only, and the control group regarding mean DNA methylation levels	PCR	Denmark	Human	50 GTS-only *vs.* 21 GTS + OCD and 87 controls. All participants were adolescent males	Hildonen et al. (2021)
MAOA	Hypomethylation of MAOA is a potential risk marker for obsessive–compulsive disorder	Direct sequencing and Electropherogram	Germany	Human	14 unmedicated female cases with primary OCD and 14 age and gender-matched healthy controls	Schiele et al. (2020b)

Table 1 (continued)

Epigenetic players	Results	Methods	Country	Model	Sample size	Ref
OXTR	Epigenetic alterations of OXTR might influence the pathophysiology of OCD	PCR and Pyrosequencing	Korea	Human	151 cases with OCD (45 drug-naïve cases) *vs.* 108 healthy controls	Park et al. (2020a)
Epigenome-wide association studies (E-WAS)	Principal component analysis following linear regression demonstrated more distinct patterns of DNA methylation in cases with most endorsed OCD or ADHA symptoms compared to controls	Illumina Human Methylation450K	Canada and USA	Human	59 OCD, 22 ADHD, and 54 controls	Goodman et al. (2020)
BDNF	Regulation of BDNF in transcriptional level in OCD engages epigenetic mechanisms, and could propose that this is likely evoked by the long-term pharmacotherapy	PCR	Italy	Human	35 OCD outpatients *vs.* 32 Controls	D'Addario et al. (2019)
SLC6A4	The preliminary data demonstrated a significantly higher plasma level of *SLC6A4* DNA methylation in an amplicon at the beginning of the first intron in pediatric OCD cases compared to controls and adult OCD cases	PCR	Switzerland	Human	164 trios 186 OCD and 152 controls	Grünblatt et al. (2018)
OXTR	It was observed a greater methylation level of cytosine-phosphate-guanine sites in two analyzed target sequences in OCD cases compared to controls. Higher methylation level was in parallel with OCD severity. DNA methylation level was measured in peripheral blood, which prohibited us from drawing any conclusions regarding processes in the central nervous system	PCR	Brazil	Human	43 OCD outpatients *vs.* 34 healthy controls	Cappi et al. (2016a)
SLC1A1, SLC25A12, GABBR1, GAD1, DLGAP1, MOG, BDNF, OLIG2, NTRK2 and 3, ESR1, SL6A4, TPH2, and *COMT*	This study suggested possible differences in methylation profiles in some studied genes and correlation with OCD severity	Illumina Infinium Human Methylation450 BeadChip probes	Denmark	Human	21 female children/adolescents with a definite diagnosis of OCD *vs.* 12 female controls	Nissen et al. (2016a)
Genome-wide DNA methylation	These study strongly suggested that differential methylation of DNA may have a main role in etiology of OCD	Illumina Infinium Human Methylation450 BeadChip	China	Human	65 OCD cases *vs.* 96 healthy controls	Yue et al. (2016a)

Table 1 (continued)

Epigenetic players	Results	Methods	Country	Model	Sample size	Ref
Genome-wide Association Study (G-WAS)	Although no SNPs were identified to be associated with OCD at a genome-wide significant level in the combined trio-case–control sample, a significant enrichment of methylation QTLs and frontal lobe expression quantitative trait loci (eQTLs) was observed within the top-ranked SNPs from the trio-case–control analysis			Human	1817 cases, 6158 ancestry-matched controls and 663 complete trios remained	Stewart et al. (2013)

et al. 2020). In another study, there was a close relationship between levels of some circulating microRNAs and OCD (Kandemir et al. 2015b). Moreover, Muiños-Gimeno et al. investigated the genetic variants in two different NTRK3 isoforms as candidate susceptibility factors for anxiety by resequencing their 3'UTRs in patients with OCD. They found a significant association between the C allele of rs28521337, which is located at a functional target site for miR-485-3p in the truncated isoform of NTRK3, and the hoarding phenotype of OCD. Besides, the ss102661458 variant, located in a functional target site for miR-765, and the ss102661460 in functional target sites for two miRNAs, miR-509 and miR-128, the latter being a brain-enriched miRNA involved in synaptic processing and neuronal differentiation. Surprisingly, the miRNA-mediated NTRK3 regulation was significantly altered by these two variants leading to the recovery of gene expression (Muiños-Gimeno et al. 2009b).

In peripheral blood of cases with Attention-deficit/hyperactivity disorder (ADHD), major depression, and children with childhood physical aggression, increased methylation of the SLC6A4 promoter has been observed compared to controls (Ji et al. 2016; Wang et al. 2012; Park et al. 2015) and in the saliva of pediatric OCD (Grünblatt et al. 2018). Indeed, a correlation was observed between the hypermethylation of two CpG sites and enhanced mRNA expression of SLC6A4 in affected cases (Ji et al. 2016). Besides, human brain serotonin synthesis was correlated with SLC6A4 methylation in peripheral blood (Wang et al. 2012). Epigenetic changes in the OXTR gene sound an attractive candidate gene for OCD and a candidate marker to mediate genetic susceptibility to OCD. OXTRs are observed in specific brain areas, including the cortex, limbic system, cortex, basal ganglia, hypothalamus, and hypothalamus and whole areas involved in the etiology of OCD due to the functions of transduced oxytocin using OXTR (Rasmussen et al. 2013). Indeed, various genetic works in the OXTR gene are related to the identification of its role in various social psychopathologies and the sociality of humans (Feldman et al. 2016). Numerous OXTR gene variants are consistent with autism spectrum disorder (ASD) (LoParo and Waldman 2015). Furthermore, clinical trials on ASD have demonstrated the relationship between variants of the OXTR gene and differential treatment responses after oxytocin performance in autism cases (Kosaka et al. 2017; Watanabe et al. 2017). Nevertheless, there are few genetic works performed on OXTR's impacts on OCD. An epigenetic work reported an association between the OXTR gene and OCD (Cappi et al. 2016b). Considering the role of OXTR in the pathogenesis of OCD pathogenesis, studies on epigenetic alterations of OXTR could facilitate understanding underlying molecular mechanisms in the development of OCD and the identification of novel biomarkers for the development and progression of OCD (Park et al. 2020a).

The BDNF gene is located on chromosome 11p13-14 and participates in hippocampal function and human episodic memory. It can adjust the secretion of BDNF. The human BDNF gene is located on chromosome 11p13-14 and contains 11 exons (I-IX, Vh, and VIIIh). Changes in DNA methylation of BDNF promoter exon I and IV are observed in cases with diverse psychiatric situations, including depressive disorders, Schizophrenia, bipolar disorder, suicidal deaths (D'Addario et al. 2019), and female adolescent OCD cases (Nissen et al. 2016a). Selective regulation of DNA methylation of BDNF gene promoter exon I might occur in different pathological conditions that require different therapies, such as pharmacological therapies for the treatment of OCD and somatic ones (e.g., electroconvulsive in MDD) (D'Addario et al. 2019).

Studies have been conducted on histone modification and DNA methylation in OCD, some of which are summarized in Table 1. In an in vivo study, rats with a high threshold of excitability showed higher basal H3Ser10 histone phosphorylation in neurons of midbrain reticular formation compared with those with a low excitability threshold. Neurons of sensorimotor cortical regions of the two strains showed no difference regarding this parameter. Stress resulted in a significant enhancement in the nuclei counts of immune-positive neurons in rats with a low threshold of excitability. Meanwhile, this parameter showed a significant increase in the sensorimotor cortex following 24 h of exposure and then normalized in 2 weeks following neurotization. Strain stress stimulated phosphorylation of H3Ser10 histone in midbrain reticular formation of this rat following 24 h. This parameter normalized after neurotization within 2 months. Then, genetically determined the nervous system excitability was essential for basal phosphorylation of neurons and for the time course of this process following long-term exposure to pain and mental stress based on the brain structure. Data indicate the association between high levels of neuronal excitability with active phosphorylation of H3Ser10 histone as a risk factor for the development of OCD. The development of measures for drug correction of OCD through the prohibition of enzymes involved in this process, such as kinases and phosphatase, sounds to be promising (Pavlova et al. 2013a). Schiele et al. (2021) reported that in OCD cases, OXTR methylation was demonstrated to be significantly higher than in controls. Indeed, baseline *OXTR* methylation was higher in OCD cases predicting impaired therapeutic responses at both dimensional (relative Y-BOCS reduction) and categorical levels (responders *vs.* non-responders). In comparison, symptom improvement and treatment response were associated with lower baseline methylation. Analysis of Y-BOCS sub-dimensions revealed the association between impaired treatment response, specifically for obsession, not compulsion, and *OXTR* hypermethylation (Schiele et al. 2021). In study by Schiele et al. (2020), in OCD cases, significantly lower methylation of *MAOA* promoter was observed in OCD cases compared to healthy subjects. Data were derived from 12 OCD cases and 14 control subjects. Besides, clinical improvements such as diminished OCD symptoms manifested by lower Y-BOCS score were observed after cognitive behavioral therapy, which was significantly correlated with enhanced methylation level of *MAOA* in patients (Schiele et al. 2020c). In a study by Park et al. (2020), OCD cases were observed to have a significantly lower methylation rate at CpG1 and CpG2 sites on the UTR of *OXTR* exon two compared to healthy subjects for both genders. In 45 drug-naïve OCD cases, a significantly lower DNA methylation was observed than control subjects. Indeed, there was a negative association between CpG1 methylation level and ordering symptom dimension (Park et al. 2020b). In another study, transcriptional regulation of *BDNF* in OCD engages epigenetic mechanisms and can suggest that this is likely evoked by long-term pharmacotherapy. It is noteworthy to highlight that numerous diverse risk factors must be considered, including gender, age, treatment, and duration of illness), and further studies are required to evaluate their role in the epigenetic modulation of the *BDNF* gene (D'Addario et al. 2019). The study observed no significant differential methylation. Indeed, there was preliminary support regarding a difference for estrogen receptor 1 (*ESR1*) (cg10939667), the myelin oligodendrocyte glycoprotein (*MOG*) (cg16650906), and the *BDNF* (cg14080521) in blood samples on diagnosis and the *GABA* B receptor 1 (cg17099072, cg10234998) in blood samples at birth. Preliminary support for an association was demonstrated between the methylation patterns of *MOG* and *GABBR1* and baseline severity, responder status, and treatment effect, and between the methylation pattern of *ESR1* and baseline severity (Nissen et al. 2016b). In a study by Yue et al. (2016), they found 8417 probes corresponding to 2,190 unique genes to be differentially methylated between OCD *vs.* healthy controls. Among these genes, 4013 and 2478 loci were located in CpG islands and promoters, respectively. These included *BCOR*, *BCYRN1*, *ARX*, *HLA-DRB1*, *FGF13*, etc. which have been previously reported to be linked with OCD. Pathway analyses suggested modulation of cell adhesion molecules (CAMs), actin cytoskeleton, transcription regulator activity, actin binding, and other pathways that could be associated with OCD risk. Unsupervised clustering analysis of the top 3,000 most variable probes demonstrated two distinct groups with significantly more people with OCD in cluster *vs.* controls (67.74% of cases *vs.* 27.13% of controls). These data highly indicate the possible role of differential DNA methylation in the pathogenesis of OCD (Yue et al. 2016b).

Conclusion

OCD is the final consequence of complicated impacts related to genetic, epigenetic, and environmental factors. Presently, no epigenetic risk factors showed a convincible association with OCD. Besides, direct causal links and interconnected mechanisms involved in OCD symptomatology, pathogenesis, histone modifications, non-coding RNA silencing, and DNA methylation, are remained to be fully clarified. Further investigation on the role of epigenetic mechanisms in the development and progression of OCD should be performed to provide novel uncovering of OCD mechanisms and potential therapeutic targets.

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Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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