Obsessive-Compulsive Disorder and DNA Damage

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Abstract

Obsessive-compulsive disorder (OCD) is a multifaceted neuropsychiatric condition influenced by genetic, neurobiological, and environmental factors. Genetic studies emphasize the heritability of OCD, especially in early-onset cases, yet specific genes remain elusive. Neurobiological research implicates alterations in cortico-striato-thalamo-cortical (CSTC) circuits and dysregulation of neurotransmitter systems, shedding light on OCD symptomatology. Environmental factors like infectious diseases, hormonal fluctuations, and traumatic experiences contribute to symptom development. Additionally, dysregulation of DNA repair mechanisms, particularly in response to oxidative stress, has been linked to OCD pathogenesis. Genetic polymorphisms in DNA repair genes such as XPD, XRCC1, and XRCC3 suggest susceptibility to OCD. Elevated levels of oxidative DNA damage, like 8-hydroxy-2′-deoxyguanosine (8-OHdG), are observed in OCD, influencing neurobiological alterations. Understanding the interplay between DNA damage and OCD symptoms offers insights into potential therapeutic targets, including antioxidant strategies and neurotransmitter-targeting medications, necessitating further research for personalized treatment approaches.

Keywords

Obsessive-compulsive disorder (OCD) · DNA repair mechanisms · Genetic susceptibility · Oxidative stress · Neurobiological pathways · DNA damage · Genetic polymorphisms · Oxidative DNA damage · Neurological dysfunction · Antioxidant strategies · Neurotransmitter systems · Personalized treatment approaches · Genetic foundations · Environmental factors · Therapeutic targets

Abbreviations

8-OHdG	8-Hydroxy-2′-deoxyguanosine
AP	Apurinic/Apyrimidinic
APE1	Apurinic/Apyrimidinic Endonuclease-1
APEX-1	Apurinic/Apyrimidinic Endonuclease-1
BER	Base Excision Repair
CoQ	Coenzyme Q
DNA	Deoxyribonucleic Acid
DSBR	Double Strand Break Repair
GPx	Glutathione Peroxidase
HOGG1	Human Oxoguanine Glycosylase 1
HR	Homologous Recombination
MMR	Mismatch Repair
NER	Nucleotide Excision Repair
NHEJ	Non-Homologous End Joining

OCD	Obsessive-Compulsive Disorder
PolD	Delta Polymerase
PolE	Epsilon Polymerase
PolG	Gamma Polymerase
SSB	Single-Strand Break
SSBR	Single-Strand Break Repair
XPD	Xeroderma Pigmentosum Group D
XPG	Xeroderma Pigmentosum Group G
XRCC1	X-ray Repair Cross-Complementing 1
XRCC3	X-ray Repair Cross-Complementing 3

Introduction

General Description of Obsessive-Compulsive Disorder

The general description of obsessive-compulsive disorder (OCD) is defined as a psychiatric disorder included in the obsessive-compulsive spectrum disorders category in the DSM-5. Its core symptoms involve uncontrollable thoughts (obsessions) and ritualistic behaviors performed to suppress or neutralize these thoughts (compulsions) (American Psychiatric Association 2013). OCD, affecting more than 1% of the global population, is a prevalent disorder with a lifetime prevalence ranging between 2% and 3% in the general population, exhibiting an equal distribution between genders (Stein et al. 2019). These statistics not only suggest a significant global impact of OCD but also indicate a complex etiological structure across various segments of society. The prevalence of OCD may be considered as a condition that can arise based on the interaction of genetic, neurobiological, and environmental factors. Furthermore, the equal distribution between genders suggests that OCD can affect a broad spectrum of the population.

Early-onset OCD often carries a familial trait and is more frequently observed in males compared to females, suggesting a potential genetic basis for OCD (Grassi et al. 2021). The onset age of OCD peaks in two distinct periods; the first peak typically occurs in childhood or early adolescence (Grassi et al. 2021), while the second peak occurs in early adulthood, around the age of 30 (Sharma et al. 2015). The symptoms and interactions during these periods provide significant clues about how OCD may change with age. Although childhood-onset and adult-onset forms of OCD may have a similar clinical appearance, they can differ in terms of associated comorbidities. Understanding the similarities and differences between OCD symptoms in children and adults is crucial for comprehending the evolutionary aspects of the disorder. In this context, understanding how OCD is influenced by age, gender, and genetic factors is essential for shaping treatment and intervention strategies. The course of OCD is generally chronic and exhibits a fluctuating pattern (Stein et al. 2019). Additionally, stressful life events can play a significant role in the clinical course of OCD; stress associated with these events can contribute to the worsening of clinical symptoms.

Biological Foundations of Obsessive-Compulsive Disorder

To comprehend the etiopathogenesis of OCD, the investigation has been focused on genetic, neurobiological, psychological, infectious, hormonal, and traumatic factors. Twin and family studies from a genetic perspective have indicated a higher genetic impact on pediatric-onset OCD compared to adult-onset OCD, with heritability ranging approximately between 30% and 40% (Hettema et al. 2001). However, specific genes unique to OCD have not yet been fully identified, and research in this regard is ongoing. From a neurobiological perspective, alterations and/or neurochemical abnormalities in the cortico-striato-thalamo-cortical (CSTC) circuits, which play a role in the pathogenesis of OCD, are a significant focus. Structural and functional imaging studies have demonstrated changes in CSTC circuits and abnormalities in brain regions such as the orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex, striatum, hippocampus, and pallidum, which are most commonly reported in OCD patients (Bourne et al. 2012; Jalal et al. 2023). Additionally, neurochemical abnormalities involving serotonin, dopamine, and/or glutamate are believed to impact the pathophysiology of OCD (Pauls et al. 2014).

Furthermore, it is known that infectious diseases, hormonal factors, and traumatic elements contribute to the development of OCD. Specifically in children, a relationship has been observed between recently experienced infectious infections and OCD symptoms (Westwell-Roper et al. 2019). Hormonal fluctuations have been observed to play a role in the onset or exacerbation of OCD, with distinct occurrences during premenstrual and perinatal periods (Guglielmi et al. 2017). Additionally, it has been suggested that stress and trauma can accelerate OCD, with traumatic events in adults potentially leading to the onset of acute OCD following exposure to such events (Adams et al. 2018).

The Genetic Foundations of Obsessive-Compulsive Disorder

Research on the genetic foundations of OCD emphasizes the significant role of genetic factors in the development of the disorder. These studies employ methods such as family and twin studies, revealing a link between the risk of developing OCD and genetic predisposition. In some sources, the lifetime recurrence risk of OCD among first-degree relatives is reported to range from 6% to 55%, indicating a substantial increase compared to the general population prevalence of 1–3% (Bienvenu et al. 2012; Grabe et al. 2006). This suggests strong evidence that OCD tends to cluster within specific families.

Prevalence of OCD in relatives of probands with early-onset ($\leq$18 years) OCD is notably higher than in those with late-onset OCD (Arumugham et al. 2014). When focusing on the familial clustering of OCD, a higher familial recurrence risk among relatives of probands is observed, particularly in terms of obsessive-compulsive symptom dimensions (Grabe et al. 2006). This indicates a more pronounced familial transmission, especially in cases of OCD onset at a young age.

Symptoms related to hoarding and contamination/cleaning exhibit the highest familial risk, while symptoms associated with symmetry are more commonly observed in familial OCD than sporadic cases (Brakoulias et al. 2016). Analyses of relatives of individuals with OCD and obsessive-compulsive symptoms support a strong genetic contribution to the manifestation of OCD and subthreshold OCD symptoms, suggesting a complex etiology involving both genetic factors and shared risk factors.

Family and twin studies investigating the genetic foundations of OCD contribute significantly to understanding the genetic predisposition to the disorder. Family studies, by observing a higher occurrence of the disorder among relatives of individuals with OCD, propose the influence of genetic factors in the development of OCD. These studies indicate that genetic predisposition is not merely a general tendency but is also associated with specific genetic variants, deepening our understanding of the genetic origins of OCD. Twin studies, evaluating genetic similarity between monozygotic (identical) and dizygotic (fraternal) twins, have consistently shown higher concordance rates for OCD in monozygotic twins, providing strong evidence for the genetic contribution to OCD pathogenesis (Mataix-Cols et al. 2013; Monzani et al. 2014).

Despite various study types and assessment methods, family and twin studies collectively highlight the heritability of OCD and obsessive-compulsive symptoms, emphasizing the importance of genetic foundations in this disorder (Arnold et al. 2018; Burton et al. 2021; Khramtsova et al. 2019; Yilmaz et al. 2020). However, these studies also underscore the complexity of OCD by revealing genetic correlations with other psychiatric disorders, emphasizing the need for further research and detailed analysis.

Genetic studies aimed at understanding the genetic foundations of OCD have identified some genes and genetic loci associated with OCD. These genetic variants indicate changes in molecular mechanisms regulating neurotransmitter systems, neural development, and connections. A more comprehensive understanding of the genetic basis of OCD could provide crucial insights for the development of future treatment strategies. Understanding the specific effects of genetic variants on certain neural networks may shed light on the pathophysiology of the disease, playing a critical role in shaping specific and effective treatment approaches.

Common variables: Molecular genetic studies of OCD, especially those focusing on candidate genes, have shown associations with genes deeply linked to neurotransmitter systems. However, results from these studies are limited in terms of complexity and replicable findings. Genome-wide studies have not yet identified significant variants associated with OCD. Nevertheless, loci in various genes have been associated with previously identified genes that affect neurotransmitter systems. In this context, advanced molecular analyses and a more detailed examination of genetic variations may be critical steps in revealing the full extent of the complex genetic mechanisms underlying OCD.

Recent genome-wide analyses have made significant strides in identifying shared genetic risk regions associated with OCD. Genes such as *PTPRD*, *CASC8*/*CASC11*, *GRID2*, *KIT*, *ASB13*, *GRIK2*, *CHD20*, *DLGAP1*, *FAIM2*, and *RSPO4* have strong

connections to OCD and underlying neurotransmitter systems (Burton et al. 2021; Stewart et al. 2013; Mattheisen et al. 2015). However, more extensive sample sizes are needed to ensure the reliability of results obtained from these comprehensive analyses. Future research may focus on these shared genetic risk regions to gain a deeper understanding of the genetic foundations of OCD and identify potential therapeutic targets.

Studies on the genetic basis of obsessive symptoms have identified a strong relationship, particularly with the *BORCS8* or *MEF2BNB* gene (Burton et al. 2021). These findings underscore the heterogeneity of the genetic basis of symptomatic dimensions of OCD and highlight the vital importance of gene-based analyses for better understanding symptoms. Therefore, future research delving into the genetic origins of OCD may provide crucial information for developing personalized treatment strategies by illuminating the specific genetic foundations of symptoms.

Genetic research on OCD has shown that specific rare genetic variants are associated with genetic susceptibility when investigating the correlation of genetic predisposition with specific rare genetic variants. Variations in genes associated with neurotransmitter systems such as serotonin, dopamine, and glutamate are particularly common in individuals with OCD. These genetic variants are thought to be linked to disorders in neural transmission, playing a significant role in explaining neural dysfunctions at the core of OCD. Investigating the specific effects of genetic variants in detail may be crucial for a more comprehensive understanding of genetic susceptibility to uncovering complex genetic mechanisms underlying OCD.

Single nucleotide polymorphism (SNP)-based heritability estimates from genome-wide association studies (GWAS) provide valuable information about the genetic architecture of OCD. However, these estimates may vary depending on measurement and detection methods. The heritability of OCD from common SNPs, depending on the onset age ranging from 1% to 5% minor allele frequency, varies between 0.25 and 0.43 (Arnold et al. 2018). Interestingly, heritability based on common SNPs for obsessive-compulsive symptoms is reported to be lower compared to clinical OCD (Burton et al. 2021). The reasons for this difference are yet unclear, and similar observations have been made in other psychiatric disorders. This emphasizes the need for advanced genetic analyses to better understand the genetic complexity underlying OCD and resolve the specific effects of genetic variations on clinical symptoms.

Observations indicate that heritability and genetic correlations with OCD are more pronounced for compulsive symptoms than for obsessive symptoms (Smit et al. 2020). The heritability of SNPs with minor allele frequencies ranging from 0.1% to 5% for OCD is reported to be 0% for obsessive symptoms (Davis et al. 2013). These results suggest that common genetic variants explain a significant portion of the variance in OCD, but the complexity in this field still requires further research. Additionally, DNA damage associated with neuropsychiatric disorders involves epigenetic changes regulating gene expression. Among these mechanisms are DNA methylation, histone modifications, and microRNA regulations, which modulate interactions between genetic susceptibility and environmental factors,

playing a crucial role in the emergence of neuropsychiatric disorders. Therefore, future research may need to focus more extensively on these areas to better understand the genetic and epigenetic foundations of OCD.

Considering the limited number of comprehensive epigenetic studies on OCD, most existing research has often focused solely on DNA methylation. Studies examining DNA methylation extensively from blood samples have identified some genes that are differentially methylated in patients with OCD (Yue et al. 2016). On the other hand, small-scale studies using newborn blood and saliva samples have suggested that DNA methylation may not show significant differences but could vary according to OCD severity and symptoms (Goodman et al. 2020). Furthermore, candidate gene studies on OXTR and the serotonin transporter gene (SLC6A4) have shown that the age of symptom onset and tissue type may play a role (Park et al. 2020). These findings highlight the need for future comprehensive research to better understand the epigenetic complexity of OCD and unravel different aspects of the disease.

One of the limited studies examining genome-wide gene expression in OCD has identified 51 mRNAs that exhibit significant differences in patients with OCD (Song et al. 2018). This study particularly emphasized a gene expression pathway where mRNAs associated with ribosomes are most intensely expressed. A GWAS focusing on obsessive-compulsive symptoms reported an enrichment of gene expression, especially in genes expressed in the brain, anterior cingulate cortex (ACC), nucleus accumbens, and amygdala (Smit et al. 2020). Studies conducted on larger sample groups suggest that our understanding of gene expression in OCD will further develop. These findings represent a significant path for future research, aiming to understand the complexity of gene expression in OCD and develop potential treatment strategies (Table 1).

How Does Stress Cause ROS Imbalance?

The question is why OCD patients tend to have oxidative stress-induced damages. Studies have shown that stress changes cellular metabolism disrupting cell homeostasis to cope with and recover from stress (Ulrich-Lai and Herman 2009; de Kloet et al. 2005; McEwen 2007). This organization results in releasing corticosteroids, which can cross blood blood-brain barrier and affect brain energetics (McKay and Cidlowski 2003). Glucocorticoids stimulate mitochondrial respiration and oxidative phosphorylation, which resulted in the elevated production of ROS, mitochondrial membrane potential, and inhibition of calcium releasing in the mitochondria (Du et al. 2009). In a study, applying in vitro glucocorticoids to cortical and hippocampal neuron cells was found that ROS levels increased after administration (McIntosh and Sapolsky 1996). Furthermore, in vivo administration of corticosterone to rats showed increased lipid peroxidation and protein carbonylation in the hippocampus and downregulation of the antioxidant system in which the enzymes acting as antioxidants (Sato et al. 2010). The link between stress and oxidative stress and DNA damage was also shown in breast cancer cell cultures (Flaherty et al.

Table 1 Summary of genetic factors associated with obsessive-compulsive disorder (OCD)

Genetic factor	Description
Heritability	Observed higher heritability rates for compulsive symptoms compared to obsessive symptoms
	SNPs with minor allele frequencies ranging from 0.1% to 5% show heritability of 0% for obsessive symptoms
	Heritability based on common SNPs varies between 0.25 and 0.43 for clinical OCD
	Heritability based on common SNPs for obsessive-compulsive symptoms is lower than for clinical OCD
Shared genetic risk regions	Significant genetic risk regions identified through genome-wide analyses: PTPRD, CASC8/CASC11, GRID2, KIT, ASB13, GRIK2, CHD20, DLGAP1, FAIM2, and RSPO4
	Genes associated with neurotransmitter systems, impacting neural development and connections
Specific genetic variants	Variations in genes associated with serotonin, dopamine, and glutamate neurotransmitter systems
	Rare genetic variants associated with genetic susceptibility to OCD
	Strong relationship with BORCS8 or MEF2BNB gene regarding obsessive symptoms
Gene expression	Significant differences in mRNA expression observed in OCD patients, particularly related to ribosomal pathways
	Enrichment of gene expression in brain regions such as the anterior cingulate cortex, nucleus accumbens, and amygdala

This table provides a concise summary of genetic factors associated with obsessive-compulsive disorder (OCD), including heritability rates, shared genetic risk regions, specific genetic variants, and gene expression patterns observed in OCD patients. These genetic factors contribute to our understanding of the complex etiology of OCD and may inform future research directions and treatment strategies

2017). In the study, increasing ROS and reactive nitrogen species (RNS) increased by corticosteroid administration caused DNA damage. Furthermore, chronic stress that increased mitochondrial activation was also shown in the in vivo experiment, in which chronic stress caused upregulation of the mitochondrial ND6 gene (Hunter et al. 2016).

ROS and DNA Damage

DNA is highly susceptible to chemical modifications since it is a reactive molecule. DNA can be affected from the hydrolytic reactions with water and oxidative reactions with ROS, which is present naturally in the cell, and this gives rise to the majority of the endogenous DNA damage. DNA facing with free radicals tends to be chemically modified such as DNA base damage, deoxyribose damage, abasic sites, single- and double-stranded breaks, and/or DNA-protein cross-linking (Dizdaroglu et al. 1991).

ROS are mainly produced as byproduct during aerobic metabolism in the electron transport chain in the mitochondria. In addition to that, it is also generated from the anabolic process, catabolic oxidases, and peroxisomal metabolism (Henle and Linn 1997). Apart from their dangerous effects, ROS are required for important cellular functions including messengers in redox signaling reactions and important immunological defense at low levels (Segal 2005). Unfortunately, ROS can give rise to 2-deoxyribose modifications and several oxidative base lesions at unbalanced levels (Cadet and Wagner 2014). Cells try to control ROS danger using several mechanisms including restricting respiration, packaging of DNA by histone proteins, and activating cellular antioxidant defense mechanism, catalase, superoxide dismutase, and peroxiredoxin (Matés and Sánchez-Jiménez 1999). The most dangerous ROS species are hydroxyl radicals (•OH), superoxide radical ($\bullet O^{-2}$), and the hydrogen peroxide (H_2O_2). The hydroxyl radicals are the most reactive one, and it is generated by a byproduct of a Fenton's reaction. The hydroxyl radicals react with protein, lipids, and DNA damaging them by several ways (Dizdaroglu et al. 1991). The DNA is the most important molecule since its damage can cause mutations. The electrophilic hydroxyl radicals react with DNA bases, resulting in double bond disruption, separating hydrogen atoms from methyl groups, and attracting the sugar residue (Winterbourn 2008). This reaction results in DNA damage in several ways. The major oxidative lesion occurs at the C-8 residue of guanine. Hydroxylation of guanine leads to a saturated imidazole ring on the 7,8 dihydro-8-oxoguanine (which is well known as 8-OH-dG). The significance of the hydroxylation of the guanine base lies in its potential to cause mutation. During replication, 8-OH-dG can pair incorrectly with adenine incorrectly, leading to mutations. 8-OH-dG can be further oxidized resulting in secondary DNA lesions (Cadet et al. 2010). Also, thymine base can also be damaged by ROS, as hydroxyl radicals attack the fifth and sixth carbon bonds of thymine, leading to the formation of thymine glycol residues. Furthermore, the •OH radical attacks the imidazole ring in guanine and adenine, leading to ring opening and the formation of the fragmented purine structure known as formamidopyrimidine (Chetsanga et al. 1981). Apart from the base modification, DNA backbone is injured by ROS radicals, where single-strand breaks (SSB) are generated (Henner et al. 1982). On the other hand, it was reported that lipid peroxidation byproducts such as malondialdehyde and 4-hydroxynonenal can react with bases to form mutagenic adducts (Plastaras et al. 2000).

ROSs in OCD Pathogenesis

ROS-induced oxidative cellular damage is the well-known or most accepted hypothesis in OCD pathogenesis. As described above, in OCD patients, oxidative balance is disrupted, and hemostasis is lost. Several studies have highlighted the oxidative stress-induced damages in OCD. Alici et al. (2016) evaluated oxidative DNA damage in patients with OCD to determine oxidative stress levels. Their results showed that 8-OHdG levels were significantly higher in OCD patients. Furthermore, treatment in OCD patients has been shown to decrease 8-OHdG levels. Şimşek et al.

(2016) evaluated DNA damage and antioxidants levels in children with OCD. 8-OHdG levels were found to be highest in pediatric patients. Furthermore, Kurhan et al. (2022a) investigated oxidative DNA damage and thiol/disulfide levels in OCD patients. They found that oxidative DNA damage levels (8-OH-dG) were higher in OCD patient. Other oxidative damage marker is the malondialdehyde (MDA), which is generated by oxidation of PUFAs and shows cell destruction (Bennett 2010). Furthermore, malondialdehyde is mutagenic itself (Plastaras et al. 2000). Malondialdehyde levels were higher in OCD patients (Kurhan et al. 2022b). These results strongly indicate that oxidative DNA damage is a common and important topic in OCD pathogenesis, and it should be considered for treatment and prognosis of OCD.

DNA Repair Mechanism and Its Importance in OCD

To maintain genomic stability, DNA is protected against mutation agents by various repair and damage-bypass mechanisms. The balance between repair mechanism and damage leads to cellular metabolic homeostasis. Once the balance is disrupted, DNA damage-related mutagenesis occurs. Even though this promotes evolution and genomic diversity, disease and aging are inevitable. Therefore, the balance should be controlled carefully. The cell repairs its injured DNA through DNA repair mechanisms. Several DNA repair mechanisms were reported such as base excision repair (BER), nucleotide excision repair (NER), double-strand break repair (DSBR), mismatch repair (MMR), homologous recombination (HR), and nonhomologous end joining (NHEJ) (Chatterjee and Walker 2017). While oxidative stress-triggered DNA damage can be repaired by the BER pathway, strand breaks in the DNA are repaired by the SSB repair (SSBR) pathways or the double-strand break repair (DSBR) pathways (Demple and Harrison 1994).

In the BER, several enzyme complexes take a role in the removal of oxidized bases from DNA. Base removal is the first step, involving monofunctional glycosylases such as Nei like DNA glycosylases (NEIL1, NEIL2, and NEIL3) or bifunctional glycosylase like 8-oxoguanine glycosylase (OGG1) and endonuclease III-like protein 1 (NTH). The glycosylase OGG1 specifically acts on 8-hydroxydeoxyguanosine (8-OHdG) lesions to remove the injured bases from DNA. NTH glycosylase removes the damaged 5-hydroxycytosine (5-OHC) and thymine glycol from the DNA chain. On the other hand, OGG1, NEIL1, and NEIL3 glycosylases remove damaged purines from the DNA chain. After the base is removed by the glycosylases, apurinic/apyrimidinic (AP) sites are formed in the base location. APEX-1 (apurinic/apyrimidinic endonuclease-1) enzyme creates a strand break at the AP sites. Gamma (PolG), delta (PolD), and epsilon (PolE) classes of polymerase enzymes add the new base, and DNA ligase 1 (LIG1) and DNA ligase 3 (LIG3) ligate strands to form intact DNA (Chatterjee and Walker 2017). Therefore, the damaged DNA repair mechanisms are also important in the pathogenesis of OCD. The first evidence came from Celik et al. (2017). In the study, several gene coding base excision repair enzymes such as *HOGG1* (human oxoguanine

glycosylase 1), *XRCC1* (X-ray repair cross-complementing 1), XPD (Xeroderma pigmentosum group D), *XRCC3*, *XPG,* and *APE1* gene were evaluated in the OCD patients. The study highlighted that *XPD* gene was found to be associated with the development of OCD (Celik et al. 2017).

DNA Methylation

DNA methylation is another damage type in DNA, and their effects can be mutagenic or regulatory affecting gene expression. S-adenosylmethionine (SAM) is the main methylating agent in cells, and it is used methyl donor for methyl transferases during normal methylation reactions (De Bont and van Larebeke 2004). Choline, nitrosated bile salts, and betaine are other endogenous methylation agents, while tobacco smoke, pollution, and derivatives of N-nitroso compounds serve as environmental methylating agents (Zhao et al. 1999). It is reported that guanine and thymine bases can be methylated, and highly mutagenic O6-ethylguanine, O4-methylthymine, and O4-ethylthymine can be generated (Singer et al. 1989). Also, DNA can be methylated by DNA methyltransferases (DNMTs). DNMTs use SAM as a cofactor to add methyl to C5 of cytosine to form 5-methylcytosine (5mC) (Sriraman et al. 2020). This methylation pattern is frequently observed in C bases in the CpG dinucleotide region. CpG nucleotides are found in the promoter region of the genes, frequently, and methylation of cytosine in this promoter region resulted in transcriptional gene silencing (Jones 2012). The 5mC can undergo several reactions such as alkylating, oxidizing, and hydrolytic deamination. While hydrolytic deamination of cytosine, which results in uracil formation, can be repaired by the uracil DNA glycosylase-directed BER pathway, the deamination of 5mC leads to the formation of thymine, which is particularly difficult to repair through base excision repair and often results in a transition mutation (C → T) during DNA replication (Sassa et al. 2016).

Studies have shown that methylation changes in DNA are important genetic regulation alterations of pathogenesis or susceptibility of OCD. Cappi et al. (2016) investigated DNA methylation levels of the oxytocin receptor gene (*OXTR*) to determine its epigenetic alteration in OCD. They found that higher methylation in the OCD patients as well as the methylation pattern was correlated with the severity of OCD. Park et al. (2020) also reported that patients with OCD had lower methylation levels at CpG1 and CpG2 sites on the UTR of *OXTR* exon 2, significantly. D'Addario et al. (2019) investigated the role of transcriptional regulation of brain-derived neurotrophic factor (*BDNF*) in blood mononuclear cells in OCD patients. They showed that *BDNF* gene expression increased significantly and also determined that the two methylation sites at promoter exon I were associated with this regulation. In addition to these single-gene level studies, genome-wide (high-throughput) studies have also shed light on detailed understanding the OCD pathogenesis. Yue et al. (2016) evaluated genome-wide DNA methylation in OCD patients and healthy control. This study not only highlighted the previously found genes, *BCYRN1*, *BCOR*, *FGF13*, *HLA-DRB1*, and *ARX*, but also indicated new

cellular functional pathways. The pathways are actin binding, actin cytoskeleton, transcription regulator activity, and cell adhesion molecules (CAMs), and the pathways are important for the development of OCD. Their results strongly indicated that differential DNA methylation patterns of DNA play an important role in the pathogenesis of OCD. Furthermore, Goodman et al. (2020) investigated epigenome from the saliva samples of the patient with attention-deficit/hyperactivity disorder (ADHD) and OCD. Their study showed that individuals with the most endorsed symptoms of ADHD or OCD have a more distinct DNA methylation pattern, indicating that altered DNA methylation reflects the phenotypic heterogeneity of these disorders. In addition, de Oliveira et al. (2021) evaluated DNA methylation changes and gene expression in postmortem brain tissues of the cortical and ventral striatum areas in OCD patients. They reported that genetic and environmental factors associated with OCD are related to genes involved in the synaptic plasticity and the immune system. A recent study evaluated the epigenome of OCD patients and determined 305 differentially methylated CpG positions. The epigenome findings in the study showed that the sweet-compulsive brain hypothesis is important for pathogenesis of OCD (Campos-Martin et al. 2023).

Telomere

Nowel finding-related DNA damage in OCD is related to telomeric DNA alterations and accelerated aging. There are evidences that serious mental disorders show accelerated biological aging (Wolkowitz 2018). However, the telomeric alteration was not known in OCD. The first study and evidence related to this topic came from Kang et al. (2021). They investigated telomere shortening as well as mtDNA copy numbers in OCD patients. Their result indicated a significant overall effect on cellular aging markers in men and women patients with OCD. This finding supports the hypothesis that aging-associated molecular mechanisms may be important in the pathophysiology of OCD. However, which mechanism plays a role shortening of telomere is not known exactly in the pathogenesis of OCD. Epel et al. (2004) highlighted that psychological stress is significantly associated with lower telomerase activity, higher oxidative stress, and shorter telomere length. Therefore, stress triggered-oxidative stress could play role major role in this dysregulation (Epel et al. 2004; Blackburn et al. 2015) (Table 2).

The Connection Between Mental Disorders and DNA Damage

Extensive research has been dedicated to uncovering the biological foundations of OCD. Epidemiological studies reveal an elevated mortality rate associated with somatic conditions in psychiatric disorders. In countries with robust healthcare accessibility, conditions like schizophrenia and bipolar disorders lead to a decrease in life expectancy by approximately 8–20 years (Lomholt et al. 2019). Severe depression contributes to a reduction in life expectancy by around 10–14 years

Table 2 Summary of DNA damage and repair mechanisms in obsessive-compulsive disorder (OCD)

Mechanism	Description
Oxidative stress	Stress-induced corticosteroid release leads to mitochondrial dysfunction and elevated ROS production
	Elevated ROS levels cause oxidative damage to DNA, resulting in base modifications, strand breaks, and adduct formation
	Increased lipid peroxidation and protein carbonylation observed in brain regions such as the hippocampus
	ROS-induced oxidative damage is implicated in the pathogenesis of OCD, evidenced by higher levels of oxidative DNA damage markers
	ROS generation can cause mutations in DNA bases, particularly guanine, leading to potential mutagenesis and DNA strand breaks
	ROS-induced DNA damage contributes to cellular aging and may play a role in telomere shortening observed in OCD patients
DNA repair mechanisms	Base excision repair (BER) pathway involved in removing oxidized DNA bases and repairing oxidative DNA damage
	Glycosylases such as OGG1 and NTH remove damaged bases, followed by endonuclease cleavage and DNA polymerase-mediated repair
	Single-strand break repair (SSBR) pathways repair oxidative DNA strand breaks to maintain genomic stability
	BER and SSBR mechanisms are crucial for repairing ROS-induced DNA damage and preventing mutations in OCD patients
DNA methylation	DNA methylation alterations observed in OCD patients, affecting gene expression and regulatory mechanisms
	Higher methylation levels in certain gene regions correlated with OCD severity
	Dysregulated DNA methylation patterns implicated in the pathogenesis and susceptibility of OCD
	Genome-wide studies revealed differential DNA methylation patterns associated with OCD and identified key cellular pathways involved
	DNA methylation changes observed in genes related to synaptic plasticity and immune system function in OCD patients
Telomere dynamics	Telomere shortening observed in OCD patients, indicating accelerated cellular aging
	Stress-induced oxidative stress may contribute to telomere shortening and accelerated aging in OCD
	Dysregulation of telomere maintenance mechanisms may play a role in the pathophysiology of OCD
	Telomere alterations suggest potential links between psychological stress, oxidative stress, and OCD pathology

This table provides a comprehensive summary of DNA damage and repair mechanisms observed in obsessive-compulsive disorder (OCD), including oxidative stress-induced damage, DNA repair pathways, DNA methylation alterations, and telomere dynamics. These mechanisms shed light on the molecular pathways underlying OCD pathology and offer potential targets for therapeutic interventions

(Laursen et al. 2016). Additionally, personality disorders, substance use disorders, anxiety disorders, and post-traumatic stress disorder are linked to increased mortality rates (Hapke et al. 2006; Toftdahl et al. 2016). The impact of psychiatric morbidity on physical health encompasses various factors, including unhealthy lifestyles, inadequate physical care, metabolic side effects of psychotropic medications, and chronic neurohormonal stress associated with psychiatric disorders.

Despite diverse underlying causes, the somatic consequences of psychiatric illnesses can be conceptualized as an accelerated aging process on multiple fronts. Across diagnostic categories of psychiatric disorders, conditions arise that exhibit anatomical and biochemical changes resembling the aging process, including progressively atrophic alterations in the brain over time. Telomeres, which cap chromosomal ends and shorten with cell division, undergo rapid attrition in various psychiatric disorders such as schizophrenia, bipolar disorder, depression, and OCD. In light of these conditions, medical issues that manifest at higher rates and earlier ages in individuals with psychiatric disorders (e.g., circulatory, pulmonary, nervous, and endocrine system disorders) become more prevalent as the general population ages. Consequently, the question arises: Have the general cellular mechanisms of aging increased among individuals in the spectrum of psychiatric disorders?

Nucleic acids (DNA and RNA), continuously undergoing chemical modifications due to reactive oxygen species, are associated with oxidative DNA damage, serving as a molecular mediator of aging (Gladyshev et al. 2021). Oxidative DNA damage leads to downstream consequences such as mutations, telomere shortening, cellular aging, and apoptosis (Zhang and Ju 2010). It is considered a pathogenic event in a range of age-related disorders, including type 2 diabetes, dementia, and cancer (Liguori et al. 2018). Furthermore, a bidirectional relationship exists between oxidative stress on mitochondrial DNA (mtDNA) and mitochondrial dysfunction, another significant event in aging (Liguori et al. 2018).

The Relationship Between Obsessive-Compulsive Disorder and DNA Damage

The etiology of OCD is linked to oxidative damage, a phenomenon also observed in other psychiatric disorders. The human body, in its generation of free radicals, regulates this process to maintain stability by employing various elimination methods. Excessive free oxygen radicals, however, pose a risk, leading to cell membrane damage, DNA degradation, protein carboxylation, lipid peroxidation, and cell death (Kurhan et al. 2022b). Central nervous system tissues are particularly vulnerable to oxidative damage, prompting the development of antioxidant mechanisms within metabolism. Key enzymes involved in these mechanisms include superoxide dismutase, glutathione peroxidase, catalase, and thiols (Kurhan et al. 2022a).

When oxidative-antioxidant imbalances persist, DNA undergoes changes affecting both intracellular and extracellular structures as free oxygen radicals accumulate, disrupting genetic codes. The biomarker 8-hydroxy-2′-deoxyguanosine (8-OHdG),

indicative of post-oxidation mitochondrial damage, serves as a marker in this process (Di Minno et al. 2015). Ordinarily, cellular mechanisms repair damaged DNA after oxidation reactions, and the indicator of mitochondrial damage, 8-OHdG, is expelled from the body (Di Minno et al. 2015). Consequently, endogenous 8-OHdG, detectable in both blood and urine, increases as a marker of DNA damage in neuropsychiatric disorders and is employed as a biomarker in various diseases.

Studies have indicated elevated levels of oxidative stress markers in individuals with OCD, accompanied by disrupted oxidative balance (Kurhan et al. 2022a). The basal ganglia, rich in catecholamines and implicated in OCD's etiopathogenesis, is reported to be significantly affected by free oxygen radicals (Kurhan et al. 2022b). Moreover, the rise in catecholamine levels in the brain is associated with damage caused by free oxygen radicals due to catecholamine metabolism, the primary source of free oxygen radicals in the brain (Spencer et al. 2011). This insight contributes to comprehending the intricate interplay between OCD and DNA damage, guiding further exploration in this domain.

Free radicals are integral to maintaining physiological conditions in the body; however, their overproduction can be detrimental, leading to oxidative stress, an imbalance between reactive oxygen species (ROS), and antioxidant defense mechanisms. The brain's heightened sensitivity to oxidative stress, owing to its high oxygen demand, can disrupt normal functions like neurogenesis, modify neuronal transmission, and induce mitochondrial dysfunction.

The antioxidant defense system comprises enzymatic and nonenzymatic components. Enzymatic antioxidants, including superoxide dismutase (SOD) and glutathione peroxidase (GPx), play pivotal roles. Nonenzymatic antioxidants like coenzyme Q (CoQ) are also present, a lipid-soluble compound found in high concentrations in the brain and heart, serving as a mitochondrial electron transport complex cofactor. Conversely, 8-hydroxy-2′-deoxyguanosine (8-OHdG) acts as a biochemical marker for DNA damage resulting from ROS.

In the last decade's adult OCD studies, oxidative stress has emerged as a potential contributor to the disease's pathogenesis. Specifically, the basal ganglia, rich in catecholamines, is deemed to play a significant role in OCD's etiopathology. Given its susceptibility to oxidative damage and the association between increased catecholamine levels and damage caused by free oxygen radicals, the basal ganglia is a focal point in understanding OCD's genetic and molecular underpinnings.

High levels of 8-OHdG signify oxidative DNA damage, serving as an indicator of oxidative stress. Antioxidant enzymes like GPx and CoQ play crucial roles in the antioxidant defense system, and their heightened levels may be regarded as an adaptive mechanism against oxidative stress.

The Relationship Between Obsessive-Compulsive Disorder and DNA Repair Genes

Extensive investigations into OCD have employed various research approaches, including family studies, segregation analyses, twin studies, and linkage studies,

aiming to unravel the genetic and molecular mechanisms underlying the disorder. These efforts have significantly contributed to our comprehension of OCD's development in the context of both genetic and environmental factors. It is established that genetic factors play a role in approximately 50% of OCD symptoms, with specific gene polymorphisms being associated with the disorder. Notably, the identification of polymorphisms in the XPD gene, which may have either a facilitating or protective role in OCD development, represents a significant breakthrough in this field (Balmus et al. 2016). Furthermore, investigations have assessed the distribution of polymorphisms in DNA repair genes such as *XRCC1*, *XRCC3*, *XPD*, *XPG*, *APE1*, and *HOGG1* among OCD patients (Celik et al. 2017). Particularly, polymorphisms in the XPD gene have been shown to exert an influence on OCD development (Celik et al. 2017), reinforcing the hypothesis that DNA repair mechanisms might impact neural pathways, contributing to behavior regulation and supporting the biological underpinnings of OCD.

Exposure to specific chemicals, notably substances like hydrocarbons, arylamines, and nitrosamines known to induce reactive oxygen species, has the potential to affect DNA functions (Kawanishi et al. 2002). Within this context, the heightened production of reactive oxygen species resulting from compromised DNA repair mechanisms may render the dopaminergic mesocortical pathway more susceptible to environmental factors. The prospect of XPD genes having an undiscovered function in dopamine and/or serotonin metabolism underscores an area that warrants further exploration. In summary, this study provides a novel perspective for a comprehensive understanding of the genetic foundations of OCD and the assessment of the impact of DNA repair genes.

The Clinical and Therapeutic Potential Effects of DNA Damage on OCD Symptoms

OCD is a neuropsychiatric disorder that arises from the complex interaction of genetic predisposition, neurotransmitter imbalances, and environmental factors. In this context, understanding the potential effects of DNA damage at the cellular level on OCD symptoms is crucial for comprehending the biological foundations of the disorder.

DNA damage is a process that compromises the integrity of genetic material, and this damage can have significant effects on neuropsychiatric disorders, particularly OCD. This process, forming the basis of obsessions and compulsive behaviors, can lead to stress and anxiety when combined with genetic predisposition and environmental factors. These emotional states can trigger and accumulate DNA damage at the cellular level.

Considering the potential effects on nerve cells, DNA damage can contribute to OCD symptoms by influencing neurotransmitter systems. DNA damage resulting from stress and anxiety may impact the release of neurotransmitters that regulate the communication of nerve cells, potentially increasing the severity of obsessions or affecting the continuity of compulsive behaviors.

Furthermore, genetic changes resulting from DNA damage can influence the connections and brain structure of nerve cells. This situation can create long-term effects on OCD symptoms, necessitating the consideration of these genetic changes in the development of treatment strategies.

At this point, research continues to shed light on the genetic and cellular mechanisms to better understand the potential effects on OCD symptoms and illuminate the biological foundations of neuropsychiatric disorders.

Genetic studies aim to identify specific genetic risk factors and biological foundations of OCD. Despite our incomplete understanding of the genetics/genomics of OCD, it is hoped that studies with larger samples can make progress in identifying genetic risk factors for OCD and personalizing treatment strategies.

Pharmacogenetic studies have focused on the role of genetic factors in variable treatment responses. However, because there is no solid consensus on the pharmacogenetics of OCD, it is essential to evaluate the results critically. Future studies in this field could guide the clinical decision-making process toward more personalized therapeutic interventions.

Based on findings from genetic studies, medications proposed for OCD include glutamate-modulating drugs and ketamine, an N-methyl-D-aspartate receptor antagonist (Bandeira et al. 2022). However, these recommendations need further support from randomized, placebo-controlled studies. In conclusion, ongoing research on the genetic foundations and treatment strategies for OCD may contribute to the understanding of this complex neuropsychiatric disorder and the development of effective interventions (Table 3).

DNA Damage and Advanced Research on Obsessive-Compulsive Disorder

In light of general findings, an important avenue for deepening the understanding of the genetic foundations of OCD is to investigate in more detail the relationship between DNA damage and OCD symptoms. In this context, meta-analyses with large samples and comprehensive molecular studies are necessary to better understand the contributions of both common and rare genetic variants, along with environmental risk factors, in shaping the hereditary and polygenic elements related to OCD. Additionally, future research in this field will be guided by a detailed examination of factors shaping the genetic architecture of OCD, including interactions between genetic variations and DNA damage.

Potential Developments in Molecular-Level Treatment Strategies

Future research should aim to develop new molecular-level treatment strategies for OCD based on its genetic foundations. In this context, clinical studies evaluating the effectiveness of therapeutic interventions targeting genetic factors in individuals at risk or those with specific symptomatic features will play a crucial role. Investigating

Table 3 Summary of the relationship between obsessive-compulsive disorder (OCD) and DNA damage

Aspect	Description
Biological consequences of psychiatric disorders	Psychiatric disorders like OCD are associated with an elevated mortality rate and somatic conditions, leading to accelerated aging processes
	Telomere shortening and rapid attrition observed in psychiatric disorders resemble aging-related changes at the cellular level
	Anatomical and biochemical changes resembling aging occur in brain regions affected by psychiatric disorders over time
	DNA damage, including oxidative DNA damage and telomere attrition, contributes to cellular aging in psychiatric disorders
Oxidative stress in OCD	OCD is linked to oxidative damage, with the brain being particularly vulnerable due to high oxygen demand
	Elevated levels of oxidative stress markers, disrupted oxidative balance, and increased catecholamine levels observed in OCD
	Free radicals, primarily generated by catecholamine metabolism, contribute to DNA damage and cellular dysfunction in OCD
DNA repair genes in OCD	Polymorphisms in DNA repair genes such as *XPD* have been associated with OCD development, suggesting a role in behavior regulation
	Compromised DNA repair mechanisms may render neural pathways susceptible to environmental factors in OCD pathogenesis
Potential effects of DNA damage on OCD symptoms	DNA damage can influence neurotransmitter systems and neuronal connections, contributing to OCD symptom severity
	Stress and anxiety-induced DNA damage may exacerbate obsessions and compulsions in individuals with genetic predisposition to OCD
	Genetic changes resulting from DNA damage can have long-term effects on OCD symptoms, necessitating consideration in treatment strategies
Molecular-level treatment strategies	Future treatment strategies targeting genetic factors and DNA damage may offer personalized interventions for OCD patients
	Clinical studies evaluating therapeutic interventions based on genetic variations and DNA damage are warranted for effective OCD management
Forward-looking recommendations for genetic research	Increasing sample size from diverse populations and prioritizing environmental factors will enhance understanding of genetic risk factors in OCD

(continued)

Table 3 (continued)

Aspect	Description
	Investigating genetic variations in relation to age of onset, symptomatic features, and treatment outcomes can improve nosology and personalized treatment for OCD

This table summarizes key aspects of the relationship between obsessive-compulsive disorder (OCD) and DNA damage, including biological consequences of psychiatric disorders, oxidative stress in OCD, DNA repair genes, potential effects of DNA damage on OCD symptoms, molecular-level treatment strategies, and recommendations for future genetic research. These insights contribute to a better understanding of the biological foundations of OCD and guide future research and treatment approaches

treatment methods specific to DNA damage and genetic variations has the potential to enhance the provision of more personalized and effective treatments for OCD patients.

Forward-Looking Recommendations for Genetic Research

Future efforts in genetic research should particularly focus on increasing the sample size from populations of non-European origin, especially from Asian and other continents. This not only will contribute to a broader understanding of the genetic structure of OCD but will also reduce genetic disparities, providing more generalizability. Additional studies with a focus on environmental factors are crucial to comprehend the role of genetic and environmental interactions. Furthermore, understanding how the genetic risk for OCD varies with age of onset and symptomatic features can contribute significantly to the nosology and risk prediction of the disorder. Future research should also prioritize topics such as gender differences, unraveling the complexity between pharmacogenetics and genetic-psychological treatment outcomes.

Applications to Other Mental Disorders

This section explores the potential extension of insights gained from the study of OCD to other psychiatric conditions or disorders.

This chapter elucidates the intricate interplay of genetic, neurobiological, and environmental factors underlying OCD, shedding light on its complex etiological structure. However, these factors are not exclusive to OCD; they may be applicable to a spectrum of psychiatric disorders, including but not limited to schizophrenia, bipolar disorder, depression, and anxiety disorders. By extrapolating findings related to genetic variants, neurochemical abnormalities, and neural network alterations from OCD research, novel avenues for investigating and understanding other mental disorders may emerge. Furthermore, the integration of advanced molecular analyses and detailed examination of genetic variations, as discussed in the context of OCD, could potentially unravel the full extent of the complex genetic mechanisms underlying various psychiatric conditions. Thus, the insights gleaned from OCD research may

serve as a springboard for exploring shared neurobiological pathways and developing tailored treatment approaches for a diverse array of mental health disorders.

Applications to Other Scenarios

In addition to its relevance to psychiatric disorders, the understanding of oxidative stress and DNA damage mechanisms in OCD pathogenesis may hold implications for broader health contexts.

This chapter underscores the role of oxidative stress-induced damages in OCD, highlighting elevated levels of oxidative DNA damage markers such as 8-OHdG and malondialdehyde in OCD patients. Such insights into the cellular mechanisms underlying OCD pathophysiology may not only inform treatment and prognosis within the realm of psychiatric disorders but also extend to other scenarios characterized by oxidative stress-related pathologies. For instance, the link between oxidative stress and DNA damage has been implicated in various somatic conditions, including cancer, cardiovascular diseases, and neurodegenerative disorders. Therefore, understanding the connection between mental disorders like OCD and DNA damage could provide valuable insights into shared pathophysiological mechanisms across different health conditions. By elucidating these common mechanisms, novel therapeutic strategies targeting oxidative stress and DNA damage pathways may emerge, offering potential benefits for a wide range of health scenarios beyond psychiatric disorders.

Mini-dictionary of Terms

- **Obsessive-compulsive disorder**. A mental disorder including uncontrollable thoughts (obsessions) and ritualistic behaviors performed to suppress or neutralize these thoughts (compulsions).
- **Single nucleotide polymorphism (SNP)**. A type of mutation occurring a single-base position on DNA sequence or single nucleotide base alterations on DNA sequence.
- **Genome-wide association studies (GWAS)**. A type of study comparing the genomes from many different people to identify genetic alterations associated with a particular phenotype.
- **Reactive oxygen species**. A type of oxygen molecule(s) containing one or more unpaired electrons.
- **Corticosteroid**. Stress-induced hormone or a type of steroid hormones released form the adrenal cortex of mammalians.
- **Homeostasis**. A balance state of a cell or biological systems to maintain stability.
- **Pathogenesis**. A process of development or progression of a disease or disorder.
- **Sweet-compulsive brain hypothesis**. A state that abnormal dopaminergic transmission in the striatum may impair insulin signaling sensitivity in OCD patients.
- **Telomere**. A type of repetitive DNA sequences at the end of a chromosome and having role for chromosome stability.

Key Facts of Obsessive-Compulsive Disorder and DNA Damage

- Obsessive-compulsive disorder (OCD) is a psychiatric condition characterized by uncontrollable thoughts (obsessions) and ritualistic behaviors (compulsions) aimed at neutralizing these thoughts.
- OCD affects over 1% of the global population, with a lifetime prevalence ranging between 2% and 3% in the general population, and it equally affects both genders.
- Genetic studies suggest a heritability of approximately 30–40% for pediatric-onset OCD, indicating a significant genetic influence on the disorder.
- Neurobiological research highlights alterations in the cortico-striato-thalamo-cortical (CSTC) circuits and abnormalities in brain regions such as the orbitofrontal cortex, medial prefrontal cortex, and striatum in OCD patients.
- Neurochemical abnormalities involving serotonin, dopamine, and glutamate are believed to contribute to the pathophysiology of OCD.
- Stress-induced oxidative cellular damage is a prominent hypothesis in OCD pathogenesis, with studies showing disruptions in oxidative balance and increased levels of oxidative DNA damage markers like 8-OHdG and malondialdehyde in OCD patients.
- Psychiatric disorders, including OCD, are associated with elevated mortality rates and somatic conditions, resembling an accelerated aging process, with implications for various bodily systems and cellular mechanisms.
- Stress alters cellular metabolism, leading to disruptions in cellular homeostasis and the release of corticosteroids, which can impact brain energetics and mitochondrial function.
- Glucocorticoids, such as corticosterone, stimulate mitochondrial respiration and oxidative phosphorylation, resulting in elevated production of reactive oxygen species (ROS) and mitochondrial dysfunction.
- Increased levels of ROS can cause oxidative damage to DNA, including DNA base damage, deoxyribose damage, and DNA-protein cross-linking, contributing to the pathophysiology of OCD.
- Oxidative stress-induced damages in OCD patients are observed through elevated levels of oxidative DNA damage markers like 8-OHdG and malondialdehyde, suggesting a potential therapeutic target for the disorder.

Summary Points

- Stress-induced glucocorticoids stimulate mitochondrial respiration and oxidative phosphorylation, changing cellular metabolism and disrupting oxidative homeostasis
- Stress-induced dysregulation oxidative metabolism causes elevated production of ROS
- ROS gives rise to the majority of the endogenous DNA damage.
- ROS can damage protein and lipids, but the major oxidative lesion occurs at guanine base in DNA

- Hydroxylation of guanine leads to a saturated imidazole ring on the 7,8dihydro-8-oxoguanine (8-OH-dG)
- DNA damages due to oxidative imbalance, chancing methylation pattern, and telomere shortening are the major molecular alterations in OCD and have an important role pathogenesis of OCD.

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