Abstract

Obsessive-Compulsive Disorder (OCD) is a prevalent and severe clinical condition whose hallmarks are excessive, unwanted thoughts (obsessions) and repetitive behaviors (compulsions). The onset of symptoms generally occurs during pre-adult life and typically affects subjects in different aspects of their life's, compromising social and professional relationships.

Although robust evidence suggests a genetic component in the etiopathogenesis of OCD, the causes of the disorder are still not completely understood. It is thus of relevance to take into account how genes interact with environmental risk factors, thought to be mediated by epigenetic mechanisms. We here provide an overview of genetic and epigenetic mechanisms of OCD, focusing on the modulation of key central nervous system genes, in the attempt to suggest possible disease biomarkers.

Genetic and epigenetic architecture of Obsessive-Compulsive Disorder: in search of possible diagnostic and prognostic biomarkers

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1. Introduction

Obsessive-Compulsive Disorder (OCD) is a psychiatric condition characterized by intrusive, unwanted, and recurrent thoughts, urges, or images (obsessions) and/or repetitive behaviors or mental acts that are performed to reduce anxiety/distress or according to rigid rules (compulsions) (American Psychiatric Association, 2013). The last/upcoming editions of mental disorders classification systems, the ICD-11 (International Classification of Diseases, 11th edition (World Health Organization, 2018) and the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association, 2013) incorporated in the same diagnostic group (Obsessive-compulsive and/or related disorders, OCRDs) different psychiatric conditions characterized by urges to perform distressing and time-consuming compulsive acts. Specifically, in the DSM-5, OCD was separated from anxiety disorders and incorporated in the OCRDs cluster, in addition to body dysmorphic disorder (BDD), trichotillomania (hair-pulling disorder), excoriation (skin-picking) disorder, and hoarding disorder. In the ICD-11 classification, OCRDs group comprises also olfactory reference disorder and hypochondriasis. Overall, OCRDs are early-onset highly disabling conditions responsible for considerable morbidity and socioeconomic burden (Denys et al., 2006a). Available treatments are usually only partially successful and there is an urgent need to implement the understanding of etiological factors and neurobiological bases of these disorders, in order to develop new and more effective strategies for prevention, early detection, and effective treatments.

The objective of the present review is to provide an overview of OCD, describing first its clinical aspects, diagnosis, symptoms and currently available treatments, then considering the genetic and epigenetic of the disorder focusing the attention on the more relevant brain pathways known to play a major role in OCD development.

1.1 Epidemiological data

OCD shows a lifetime prevalence of 2-3% in the general population (Kessler et al., 2005; Ruscio et al., 2010) and within OCRDs, it is considered the archetypal condition, as well as the most investigated and, arguably, the most well understood. Considering the spectrum-oriented view of OCRDs, the cumulative prevalence of OCRDs is notably much higher than that of OCD alone. Summing up the prevalence of the various OCRDs and considering the comorbidity rates, the overall lifetime prevalence of OCRDs has been reported as high as 9.5% (Murphy et al., 2016). Interestingly, some degree of clinically-relevant OC symptomatology was found to be extremely common, affecting as many as 20% of the general population (Fineberg et al., 2013). However, OCD remains yet a poorly recognized disorder, as affected individuals tend to be ashamed and secretive about their symptoms (e.g., due to a sense of shame or guilt, or lack of knowledge that their problems constitute categorized mental disorders), with negative influence on epidemiologic investigation and, ultimately, to diagnosis and treatment.

1.2 Clinical presentation

OCRDs typically show an early age of onset, usually in late adolescent or in the early adulthood (Heyman et al., 2003). In the United States, the mean age of onset for OCD is 19.5 years, with 1 out of 4 patients showing the first symptoms by the age of 14 (Kessler et al., 2005; Ruscio et al., 2010). Onset after 35 years of age is not common, but it has been described (Grant et al., 2007). Typically, an earlier age of onset is associated with a worse course and a higher rate of comorbid tic-disorder. Sexual/religious and symmetry/ordering symptoms are also reported to be more frequently associated with early-onset OCD (Labad et al., 2008).

Some studies reported a slightly higher OCD prevalence in females, (Rasmussen and Eisen, 1990). Moreover, a gender-related expression of symptoms has been reported, with increased contamination/cleaning factors in females and increased sexual/religious and symmetry/ordering factors in males (Labad et al., 2008). OCRDs commonly co-occur and are often comorbid with other psychiatric conditions, in particular anxiety disorders, mood disorders (Dell'osso et al., 2020; Ruscio et al., 2010), obsessive-compulsive personality disorder (Starcevic et al., 2013), neurodevelopmental disorders (Gadelkarim et al., 2019), and tic disorders (de Alvarenga et al., 2012). Comorbidity with tic disorder has been emphasized in the DSM-5, through the addition of a tic specifier to OCD definition (American Psychiatric Association, 2013). Of relevance, comorbidity between OCD and anorexia with shared genetic risk has been also been reported (Brainstorm Consortium, 2018; Yilmaz et al., 2020).

The clinical course of OCD is typically chronic and, in the absence of an effective treatment, the disorder waxes and wanes throughout its course (Pinto et al., 2006; Ravizza et al., 1997). The chronic course of the disease, alongside with the high rate of comorbidities, determine OCD as an highly disabling condition associated with poor quality of life and high economic cost to the individual and to the society as a whole (Denys et al., 2006a). The public health burden associated with OCD is likely to be greater than its prevalence suggests, comprising the direct costs of treatments for the disorder and the associated comorbidities, together with the indirect costs associated with lost occupational income for patients and their caregivers (Fineberg et al., 2013). These features, as a whole, contribute to the dramatic burden of suicidal behaviors in OCD patients, as reported in an international sample where the lifetime prevalence of suicide attempt reached up to 15% of affected patients (Dell'Osso et al., 2018).

1.3 Etiopathogenesis

The etiopathogenesis of OCD foresees the interaction of genetic and environmental factors. Among genetic predisposition, twin and family studies confirmed the genetic contribution to OCD, with greater influences in pediatric-onset OCD compared with adult-onset OCD (Pauls et al., 2014). The risk of developing OCD symptoms is four-fold higher in first-degree relatives of OCD patients compared with family members of non-OCD subjects (Pauls, 2008).

Genetic investigations indicate that genes regulating the serotonergic, dopaminergic and glutamatergic systems, and the interaction between them, are relevant in the functioning of specific circuits in OCD (Pauls et al., 2014). In particular, different gene variants (polymorphisms) have been associated with structural and functional alterations in cortico-striato-thalamo-cortical (CSTC) circuit (Reghunandanan et al., 2015). The CSTC circuit is one of the most involved in the pathophysiology of the disorder, but other brain circuits (e.g., the fronto-limbic, the fronto-parietal, and the cerebellar networks) play a role as well (Milad and Rauch, 2012; van den Heuvel et al., 2016). Different interdisciplinary translational strategies have been proposed to investigate OCRDs complex pathogenesis through the use of potential genetic biomarkers related to their diagnosis and treatment-response. Among these: the early access to new candidate genes for OCRDs (e.g., glutamate-transporter SLC1A1, glutamate-receptor GRIK2, and tryptophan-hydroxylase 2); the collaboration in genome-wide association studies (GWAS); and the investigation of behavioral neurobiology (neurochemistry, brain morphology, and functional imaging) of new animal models, including neuropsychological models and genetically modified mouse lines (Fineberg et al., 2013).

With respect to environmental factors implicated in OCRDs etiology, the perinatal and adolescent periods are particularly critical, with early life adverse events representing a significant risk factor for the development of OCRDs. In particular, infections, physical abuse, negative emotionality, perinatal insults, poor motor-development and personality or

conduct problems have been related to an increased risk (Grisham et al., 2011). For instance, a group A streptococcal infection has been associated with the onset or exacerbation of OCD in some children, defining a syndrome known as pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS), which is triggered by an autoimmune reaction that damages the basal ganglia of the central nervous system (Snider and Swedo, 2004).

Alongside the direct effect of environmental factors on OCD etiopathogenesis, an additional mechanism is constituted by the epigenetic modulation. In particular, environmental signals are integrated by epigenetic processes in order to activate or repress gene expression, regulating DNA accessibility for transcription factors. Indeed, the role of epigenetic modulation has been recently considered in OCD patients (Cappi et al., 2016; D'Addario et al., 2019; Grünblatt et al., 2018).

Despite numerous investigations and promising results, OCD etiopathogenesis remains largely unknown. Therefore, a strong effort in research is needed to clarify OCRDs pathogenesis through the implementation of new genetic biomarkers that might be useful to better understand OCD etiology and potentially discover new altered pathogenetic mechanisms to target with specific therapies.

1.4 Diagnosis

As for many other mental health disorders, OCD is diagnosed on a clinical basis. If compulsions are among the core-features of OCD and OCRDs, compulsive behaviors are observed in many other psychiatric disorders, particularly those characterized by altered impulse control. For example, urge-driven, repetitive behaviors are associated with eating disorders, substance use disorders, and "behavioral addiction", such as problematic usage of the Internet (PUI) and pathological gambling (Everitt and Robbins, 2005; Ioannidis et al., 2016; Robbins et al., 2012), increasing the difficulty in distinguishing between comorbid

conditions and primary disorders. OCD diagnosis is complex and biomarkers with a high level of specificity and sensitivity are needed in order to provide an innovative platform of diagnostic tools as a basis for early illness-detection.

As mentioned above, due to reticence and shame associated with OC symptoms, these conditions are poorly recognized and only a minority of cases receives timely treatment. As a result, there is usually a considerable time interval between first symptoms and OCD diagnosis and appropriate treatment prescription. In the case of OCD, the estimated mean time interval can exceed 10 years (Dell'Osso et al., 2013). The duration of untreated illness represents one important clinical factor in OCD, being overall a negative predictor of long-term outcome (Dell'Osso et al., 2013). In this respect, biomarkers might help clinicians in the early detection of OCD, particularly in groups of patients with a late first clinical assessment. Moreover, targeting biomarkers research to young subjects at high risk of developing OCRDs (i.e. unaffected offspring of OCRDs parents), or in a prodromal phase, may advance early interventions that might alter the course of the disorder toward a better long term outcome.

1.5 Evidence-Based Treatment of OCD and Related Disorders

Serotonin reuptake inhibitors (SRIs) – particularly clomipramine and selective SRIs (SSRIs) - are the first-line pharmacological treatments for OCD, typically characterized by a dose-response relationship (i.e. high doses are needed to obtain clinical response). SRIs combined with antipsychotic agents at low dosages can be prescribed to patients with an unsatisfactory response to SRIs alone and in cases with comorbid tics (Bloch et al., 2006; Fineberg et al., 2015). Among psychological therapies, cognitive behavioral therapy (CBT), in particular involving exposure and response prevention, showed to be effective in different trials (Fineberg et al., 2015).

Among OCRDs, Body Dysmorphic Disorder (BDD) shows a similar pattern of treatment response (Phillips et al., 2016; Rashid et al., 2015), though more data are needed to assess whether higher SRI dosages and adjunctive antipsychotics are as effective as in OCD (Reghunandanan et al., 2015).

Some data showed SSRIs and venlafaxine to be effective for the treatment of hoarding behaviors in the context of comorbid OCD (Saxena and Sumner, 2014), but no specific pharmacological treatment has been defined for primary hoarding disorder. There are limited reports of improvement with CBT intervention in hoarding behavior (Uhm et al., 2016). As concerns, the treatment of hair-pulling disorder, some data supported the use of SSRIs and clomipramine (Rothbart et al., 2013), olanzapine (Van Ameringen et al., 2010), n-acetyl cysteine (Grant et al., 2009), and naltrexone (De Sousa, 2008). Among psychological therapies, habit reversal therapy has shown some efficacy (McGuire et al., 2014). Skin picking disorder showed some degree of response to SSRIs and n-acetyl cysteine (Reghunandanan et al., 2015).

Despite the existence of numerous treatment strategies, these are far from providing optimal results for most subjects. Approximately 40% of OCD patients fail to respond to first-line standard therapy and higher doses or adjunctive treatments are associated with higher rates of side effects (Fineberg et al., 2015). Of great interest, a wide range of pharmacological compounds has been tested in treatment-resistant OCD and some have been found effective in small-sized trials, implicating a multiplicity of potential treatment targets and mechanisms. Therefore, a better understanding of treatment resistance mechanisms and potential biomarkers linked to treatment response is highly needed in OCRDs. This will empower the creation of prediction models to implement ‘personalized’ treatment to tackle treatment-resistant cases and to allow limited resources (e.g. CBT) to be targeted to those patients who are most likely to benefit (Fineberg et al., 2013).

2. Genetic complexity of OCD

Whole-genome studies, including linkage studies and GWAS, of OCD or OC symptoms have been published, showing multiple regions of interest (Den Braber et al., 2016; Hanna et al., 2002, 2007; Mathews et al., 2012; Mattheisen et al., 2015; Qin et al., 2016; Ross et al., 2011; Samuels et al., 2007; Shugart et al., 2006; Stewart et al., 2013; Y. Wang et al., 2009). However, available data are inconclusive with mixed, and sometimes conflicting, results and their implications for clinical practice remain unclear.

The first hypothesis of OCD pathogenesis has been linked to a dysfunction of the serotonergic system, since SSRIs are effective treatments for OCD symptoms (Fineberg et al., 2015; Koran and Simpson, 2013; Pittenger and Bloch, 2014). However, considering the lack of efficacy in a considerable amount of patients (Katzman et al., 2014; Soomro et al., 2008) and the delayed clinical response to these molecules, it is reasonable to assume that their therapeutic efficacy is due to the action of downstream targets. For instance, chronic antidepressants use is associated with reduced glutamatergic transmission (Bonanno et al., 2005), increased expression of brain-derived neurotrophic factor (BDNF) (Duman and Monteggia, 2006), and alterations in the dopaminergic pathway (Zhou et al., 2005), suggesting that more than one neurochemical system mediates OCD symptoms (McDougle et al., 1999). Furthermore, considering oxytocin (Oxt) anxiolytic properties and its effects on prosocial behaviors (Viero et al., 2010), an involvement of this molecule in the development of OCD has been hypothesized.

In the following paragraphs, we will thus analyze in details studies reporting an association between OCD and the above-mentioned relevant signaling pathways.

Though not specifically discussed in the present review, the analysis of genetic (Noh et al., 2017) and environmental (Yue et al., 2016) factors sheds light on genes related to regulation of actin cytoskeleton, cell adhesion molecules, endocytosis, gap junction, MAPK signaling pathway, and actin binding, which could play a role in the susceptibility to OCD. Additionally,

several studies with mixed results showed genetic variants association of OCD with *SAPAP3/DLGAP3* (Discs Large Homolog Associated Protein 3) (Bienvenu et al., 2009; Boardman et al., 2011; Crane et al., 2011; Mas et al., 2016; Züchner et al., 2009), a post-synaptic density component that forms a scaffolding complex with other proteins in the glutamatergic synapses (Scannevin and Huganir, 2000), and *SLITRK1* (SLIT And NTRK Like Family Member 1) (Melo-Felippe et al., 2019; Ozomaro et al., 2013; Wendland et al., 2006), which plays a role in the growth and development of nerve cells (Beaubien et al., 2016). Moreover, the involvement of endogenous opioid (Urraca et al., 2004), endocannabinoid (Kayser et al., 2020), and NPY-system (Franke et al., 2019) was investigated in relation to OCD development, even though their role still remains poorly understood.

2.1 Serotonergic system

A clear role in OCD development is played by serotonin (5-HT) and its transporter (5-HTT) (Billett et al., 1997). The human 5-HTT is encoded by the *SLC6A4* gene, located in chromosome 17q11.1-17q12, containing, in the promoter region, the 5HTT-linked degenerate repeated polymorphic region (5-HTTLPR). This consists of a 44 bp insertion/deletion and thus involves a short (S) and a long (L) allelic variant (Heils et al., 2002), linked respectively to low and high 5-HTTmRNA levels (Hu et al., 2006; Murphy and Moya, 2011). A positive association between the S allele and major depressive disorder (Bellivier et al., 1998; Cervilla et al., 2006; Gutiérrez et al., 1998; Talati et al., 2015), anxiety disorders (Gonda et al., 2007; Ohara et al., 1998), or alcoholism (Gorwood et al., 2000; Hallikainen et al., 1999; Hammoumi et al., 1999) has been reported and the hypothesis that 5-HTTLPR could be associated with OCD development has been considered by many retrospective studies. McDougle et al. (McDougle et al., 1998) reported the association and linkage disequilibrium between the L allele and OCD. The presence of the long allelic variant

in OCD patients was subsequently observed by other studies (Bengel et al., 1999; Bloch et al., 2008; Da Rocha et al., 2009; Honda et al., 2017; Hu et al., 2006; Kenezloi et al., 2018; Mak et al., 2015; Mattina and Steiner, 2016; Taylor, 2013; Tükel et al., 2016; Walitza et al., 2014), and associated with a gender-related mechanism, namely a selective over-transmission of the L allele in female but not in male subjects (Baca-García et al., 2005; Dickel et al., 2007). Moreover, a study considering only females (Denys et al., 2006b) and a meta-analysis of the published data (Lin, 2007) have indicated an association of the S allele with the disorder. However, these results must be interpreted with caution, as other studies failed to replicate this association (Camarena et al., 2001b; Chabane et al., 2004; Di Nocera et al., 2014; Frisch et al., 2000; Kim et al., 2005; Kinnear et al., 2000; Meira-Lima et al., 2004; Plana et al., 2019; Rashidi et al., 2018; Saiz et al., 2008; Tibrewal et al., 2010; Walitza et al., 2004). Other polymorphisms of the gene, in particular the single nucleotide polymorphisms (SNPs) rs25531, rs25532, and rs16965628, and the variable number of tandem repeat (VNTR) STin2, were studied in OCD with mixed results (Ahmadipour et al., 2018; Baca-Garcia et al., 2007; Gomes et al., 2018; Grünblatt et al., 2018; Ohara et al., 1999; Plana et al., 2019; Rashidi et al., 2018; Saiz et al., 2008; Sinopoli et al., 2019, 2020; Voyiaziakis et al., 2011; Wendland et al., 2007; Zhang et al., 2004) (see Table 1 for details). Though less extensively studied, *SLC6A4* gene variants within other 5HT system were investigated for a possible role in OCD, namely: *HTR1B* (5-Hydrozytryptamine Receptor 1B), *HTR2A* (5-Hydrozytryptamine Receptor 2A) and *HTR2C* (5-Hydrozytryptamine Receptor 2C) genes. The *HTR2A* polymorphism rs6311, also known as 1438G/A, was associated with OCD (Enoch et al., 1998; Taylor, 2013; Walitza et al., 2002, 2012); some studies highlighted, in particular, the presence of the minor allele after data stratification based on gender (W. Liu et al., 2011; Walitza et al., 2002, 2012), age at onset (W. Liu et al., 2011; Walitza et al., 2012), drug response (Zhang et al., 2004), symptoms severity (Tot et al., 2003), comorbid tic disorder (Dickel et al., 2007), whereas the presence of the major

allele with age at onset in patients with a positive family history (Denys et al., 2006b). However, other studies failed to observe these associations (Frisch et al., 2000; Gomes et al., 2018; Nicolini et al., 1996; Plana et al., 2019; Sina et al., 2018). OCD associations with rs6313 (Taylor, 2013), rs6305, and rs6308 polymorphisms (Noh et al., 2017), also considering early-onset (Mas et al., 2014), or symptoms severity (Tot et al., 2003), were reported. However, different studies did not report any association with these variants (Di Nocera et al., 2014; Gomes et al., 2018; Hemmings et al., 2003; Lochner et al., 2004; Miguita et al., 2011; Nicolini et al., 1996; Sina et al., 2018). The majority of studies conducted on *HTR2C* and *HTR1B* genes failed to demonstrate a direct link with the disorder (Camarena et al., 2004; Cristina Cavallini et al., 1998; Di Bella et al., 2002; Dickel et al., 2007; Frisch et al., 2000; Hemmings et al., 2003; Plana et al., 2019; Taylor, 2013; Walitza et al., 2004). Some studies showed no significant differences in genotype frequency of the tryptophan hydroxylases *TPH1* and *TPH2* genes variants, encoding for the enzymes involved in serotonin synthesis (Delorme et al., 2006; Frisch et al., 2000; Han et al., 1999; Walitza et al., 2004). Conversely, other investigations reported haplotype association between *TPH2* SNPs and the disorder (da Rocha et al., 2011; Mössner et al., 2006) or between rs4570625 and patients scrupulousness (Di Nocera et al., 2014).

2.2 Dopaminergic system

Many studies failed to correlate Dopamine receptors D2 and D3 (*DRD2, DRD3*) genes polymorphisms with OCD (Billett et al., 1998; Di Nocera et al., 2014; Hemmings et al., 2003; Taylor, 2013; Viswanath et al., 2013; Vulink et al., 2012; Zhang et al., 2004). However, after data stratification, some reports showed an association with perseverance features and emotional control for *DRD2* rs1800497 and *DRD3* rs6280 (Di Nocera et al., 2014), or with early- onset for *DRD3* rs2134655 (Mas et al., 2014). Moreover, the allelic distribution of *DRD4* (Dopamine receptor D4) 48 bp VNTR was associated with OCD (Billett et al., 1998;

Frisch et al., 2000; Millet et al., 2003), considering both the 4R (4 repeats) (Camarena et al., 2007; Walitza et al., 2008) and the 7R (7 repeats) allele (Taj. M. J et al., 2013).

Within the 3' non-coding region of the dopamine transporter gene, *SLC6A3* (Solute Carrier Family 6 Member 3), there is a VNTR, with alleles ranging from 3 to 11 repeats, associated with various disease phenotypes and gene regulation (Vandenbergh et al., 1992). A recent study found that the presence of at least one 10 repeats (10R) allele in the genotype of the *SLC6A3* VNTR has a protective role against OCD in males (Cotrin et al., 2019). Several studies failed to replicate the association between the same polymorphism and the disorder (Billett et al., 1998; Frisch et al., 2000; Hemmings et al., 2003; Miguita et al., 2007, 2011; Taylor, 2013; Walitza et al., 2008; S. Zhang et al., 2015). Rs27072, a SNP in *SLC6A3* gene, was positively correlated with OCD severity (Mas et al., 2016).

Additional dopamine system genes that have been examined included enzymes responsible for its degradation. rs4680 (Val158Met) *COMT* (Catechol-O-Methyltransferase) polymorphism was associated with OCD (S. Liu et al., 2011), gender-specifically (Alsobrook et al., 2002; Denys et al., 2006a; Karayiorgou et al., 1997, 1999; Melo-Felippe et al., 2016; Pooley et al., 2007; Poyurovsky et al., 2005; Taylor, 2013), depending on the age at onset (Tükel et al., 2013) or Y-BOCS (Yale-Brown Obsessive-Compulsive Scale – the most frequently used interview to rate the severity of symptoms (Goodman et al., 1989)) scores (Erdal et al., 2003), or in patients with alexithymia tracts (Koh et al., 2016). However, other reports did not find an association between rs4680 and OCD (Bellivier et al., 1998; Camarena et al., 2004; Cristina Cavallini et al., 1998; da Rocha et al., 2011; Delorme et al., 2006; Di Bella et al., 2002; Han et al., 1999; Mak et al., 2015; Mössner et al., 2006; Walitza et al., 2002).

Several studies did not support the role of Monoamine Oxidase-A (*MAOA)* in the risk of OCD (Hemmings et al., 2003; Liu et al., 2013; McGregor et al., 2016; Sampaio et al., 2015; Zhang et al., 2004), besides rs6323 polymorphism that was associated in a gender-related modality

to OCD (Camarena et al., 1998, 2001a; Karayiorgou et al., 1999; Lochner et al., 2004; Taylor, 2013).

2.3 Glutamatergic system

Since alterations of excitatory synaptic function mediated by glutamate were observed in mood (Beneyto et al., 2007; Choudary et al., 2005; Grace, 2016; Hashimoto et al., 2007; Sanacora et al., 2008; Scarr et al., 2003) and anxiety disorders (Arnold et al., 2006; Miladinovic et al., 2015; Strawn et al., 2013), novel OCD treatments targeting the glutamatergic system in combination with SSRIs have been proposed (Kariuki-Nyuthe et al., 2014; Pittenger, 2015). Hanna et al. (Hanna et al., 2002) showed a strong link between human *SLC1A1* gene (Solute Carrier Family 1 Member 1), encoding for the glutamate transporter EAAT3 (Excitatory Amino Acid Transporter 3) in families with OCD. Allelic distribution of several *SLC1A1* polymorphisms was associated with OCD diagnosis in family-based association (Arnold et al., 2006; Dickel et al., 2006; Samuels et al., 2011; Shugart et al., 2009; Stewart et al., 2007) and case-control studies (de Salles Andrade et al., 2019; Shukla et al., 2020; Wang et al., 2010; Wendland et al., 2009). In a pharmacogenetic study (Abdolhosseinzadeh et al., 2019b), a significant association between the G allele of both rs2228622 and rs3780413 and fluvoxamine treatment response was observed. Additionally, Zhang et al. showed lower Y-BOCS scores in subjects with homozygosity (CC) for rs301430 treated with fluvoxamine (K. Zhang et al., 2015). No significative difference in genotype distribution for rs301430 and other *SLC1A1* SNPs was reported in OCD patients (Arnold et al., 2006; Grace, 2016; Melo-Felippe et al., 2019; Miguita et al., 2011; Miladinovic et al., 2015; Pittenger, 2015; Strawn et al., 2013), apart from haplotype associations with early-onset (Wu et al., 2013).

The T allele of rs890 at Glutamate Ionotropic N-Methyl D-Aspartate Receptor subunit 2B (*GRIN2B*) gene has been associated with OCD in a family-based association study (Arnold

et al., 2004). Additionally, the same research group observed an association between the rs1019385 and decreased anterior cingulate cortex glutamatergic concentration in 16 pediatric OCD patients, showing a relationship between the genetic variant and a neurochemical phenotype in OCD (Arnold et al., 2009). Further case-control studies observed the association of *GRIN2B* SNPs allelic distribution with specific OCD phenotypes such as symmetry/ordering (Kohlrausch et al., 2016), or washing and cleaning (Alonso et al., 2012), whereas others studies failed to replicate those findings (Liu et al., 2012; Mas et al., 2014; Viswanath et al., 2018).

Lastly, glutamate receptor ionotropic kainate (GRIK) SNPs were not associated with OCD (Delorme et al., 2004; Mas et al., 2014, 2016; Mattheisen et al., 2015) (Mas et al., 2016), except for *GRIK2* rs1556996 and rs2205748 (Mattheisen et al., 2015; Sampaio et al., 2011).

2.5 Brain-derived neurotrophic factor

BDNF plays a key role in the development and survival of dopaminergic, GABAergic, cholinergic, and serotonergic neurons (Autry and Monteggia, 2012; Pillai, 2008). BDNF expression is modulated by many regulatory mechanisms and a well-studied SNP, the Val66Met, also known as rs6265, has been associated with different neuropsychiatric disorders (González-Castro et al., 2015; Gyekis et al., 2013; Kanazawa et al., 2007; Naoe et al., 2007; Verhagen et al., 2010; Y. Wang et al., 2015; Zhao et al., 2015). In a case-control study, Liu et al. analyzed the genotype distribution of Val66Met in Chinese subjects with OCD and Tourette's syndrome, observing significative differences in allele frequencies in OCD patients compared with controls and Tourette patients (Liu et al., 2015), showing also a gender-related association in female OCD subjects when compared to controls. This result is consistent with other association studies (Hall et al., 2003; Márquez et al., 2013; Taj M J et al., 2018) also considering age at onset (Hemmings et al., 2008; Katerberg et al., 2009) or symptoms severity (Abdolhosseinzadeh et al., 2019a), whereas several other studies did

not report any association (D'Addario et al., 2019; Dickel et al., 2007; Umehara et al., 2016; J. Wang et al., 2015; Wendland et al., 2007). Additionally, rs1519480 and rs2883187 have been associated with OCD diagnosis (Abdolhosseinzadeh et al., 2019a; Márquez et al., 2013) and disease severity (Tükel et al., 2014), while rs7124442 only in male patients (Márquez et al., 2013), and finally rs988748 and rs2049046 were related to age at onset (Hall et al., 2003).

2.5 Oxytocin system

Oxt, one of the brain's most abundant neuropeptide, is involved in several physiological responses and has been reported to be associated with anxiety and depression (Gottschalk and Domschke, 2017; Gouin et al., 2017; Maud et al., 2018; Simons et al., 2017; Ziegler et al., 2015). To elicit its effect, Oxt must be able to bind its receptor (OxtR) which is located in different brain regions responsible for mood regulation, social behaviors, and addiction mechanisms (Burri et al., 2008; Sarnyai, 2011). Few genetic studies have analyzed the role of *OxtR* in OCD. Kang et al. did not observe differences in allelic distribution between OCD patients and controls in 10 *OxtR* SNPs analyzed, however rs2268493 and rs13316193 polymorphisms were significantly associated with the age at onset, showing that people carrying the minor allele of the two polymorphisms tend to develop OCD in adulthood rather than in childhood (Kang et al., 2017). Koh et al. investigated the possible correlation between OCD patients' alexithymic traits and the presence of several *OxtR* SNPs, without reporting any positive findings (Koh et al., 2015).

3. Epigenetic mechanisms in OCD

Increasing evidence suggests that for many complex disorders, including mental disorders, the interactions between gene and environment (GxE) should be considered (Liu et al.,

2008). These GxE interactions are mediated by epigenetic mechanisms that regulate gene expression independently of DNA sequence.

Histone modifications, DNA methylation and microRNAs (miRNAs), are the three major epigenetic mechanisms (D'Addario et al., 2013) (see Fig. 1). Histone modifications refer to chemical modification of histones at amino acid residues on their N-terminal tails, such as acetylation, phosphorylation, ubiquitination and methylation, leading to an increase or decrease in gene expression (Strahl and Allis, 2000).

DNA methylation takes place through the addition of a methyl group to the C5 position of cytosine (C) in a CG dinucleotide, forming a 5-methylcytosine (5mC) (Robertson, 2005). DNA methylation, occurring at gene regulatory regions, might exert a repressive effect on gene transcription. From the oxidation of 5mC by the Ten-Eleven Translocation (TET) enzymes, the 5-HydroxyMethylcytosine (5hmC) is formed. Given the associations of 5hmC with gene expression increase, it is now considered a novel epigenetic modification (Pucci et al., 2019).

The post-translational regulation mechanisms are represented by miRNAs, short single-strand RNA sequences (about 20 nucleotides) able to silence gene expression. This process takes place through the degradation of target mRNA, through a process mediated by the RISC complex (RNA-induced silencing complex), or inhibiting translation through blocking target mRNA (Ouellet et al., 2006).

In the next paragraphs, we will consider the most relevant studies investigating epigenetic modifications in OCD for genes belonging to the previously discussed systems. Apart from these systems, different studies analyzed the epigenetic regulation of other mechanisms involved in OCD. Indeed, a genome-wide DNA methylation study examining over 485,000 CpG sites reported a different methylation of 2,190 genes between OCD patients and healthy controls (Yue et al., 2016), including some methylations previously associated with OCD by GWAS studies, such as *BTBD3* (BTB Domain Containing 3) and *DLGAP2* (Disks

large-associated protein 2) (Stewart et al., 2013), suggesting their possible relevant role in the pathogenesis of OCD.

Moreover, DNA methylation profile in OCD females was investigated by Nissen et al. (Nissen et al., 2016), showing altered blood DNA methylation at specific CpG sites for gamma-aminobutyric acid (*GABA*) B receptor 1 at birth and, for myelin oligodendrocyte glycoprotein and *BDNF,* at the time of diagnosis. Additionally, a lower DNA methylation at cg21655790, located near the transcription start site of leptin receptor, was observed in infants of mothers with prenatal psychiatric disorders, including OCD (Ciesielski et al., 2015). Lastly, studies on miRNAs role in OCD have been carried out (Kandemir et al., 2015; Mattheisen et al., 2015; Privitera et al., 2015) suggesting that these molecules may serve as potential treatment targets (Issler and Chen, 2015).

3.1 Serotonergic system

Unlike the high number of genetic-based studies, only few investigations evaluated serotonin-related genes epigenetic regulation in OCD (Table 2). DNA methylation levels in the promoter region of *SLC6A4* gene were analyzed in patients with a diagnosis of anxiety or depressive disorder as a possible marker of the pathology, but no differences were observed in patients when compared to healthy controls (Chagnon et al., 2015). In a case-control study, Grunblatt et al. (Grünblatt et al., 2018) analyzed *SLC6A4* DNA methylation levels in pediatric, adolescent and adult OCD patients, analyzing peripheral blood and saliva. As a result, early-onset subjects showed increased methylation levels compared to the control group, and adult OCD patients reported decreased levels compared to both controls and early-onset patients in saliva samples. Moreover, in saliva samples, a positive correlation between DNA methylation levels and morning salivary cortisol levels and a negative correlation between DNA methylation levels and symptoms severity in pediatric subjects emerged. In blood samples, no differences were observed in peripheral gene

expression, neither considering OCD subjects compared to controls nor considering the two sub-groups of patients. This lack of difference is consistent with results reported by Wang et al. (Wang et al., 2017) in the Chinese population, suggesting that *SLC6A4* peripheral gene expression may not be a useful biomarker for this disorder.

3.2 Dopaminergic system

Literature evidence about dopaminergic epigenetic mechanisms in OCD is limited. Considering the overlap between OC features and some craving aspects of alcohol dependence (Anton, 2000), Hillemaker et al. (Hillemacher et al., 2009) analyzed *SLC6A3* DNA methylation in alcoholics. A negative association between DNA methylation levels and OCDS (Obsessive Compulsive Drinking Scale) scores emerged, suggesting that this mechanism could be a biomarker for the severity of the disorder.

The epigenetic regulation of the *SLC6A3* gene was also studied in children with ADHD (attention-deficit/hyperactivity disorder) and emerged to be associated with decreased DNA methylation levels in patients compared to controls (Adriani et al., 2018). It was also investigated in patients with schizophrenia, without showing differences compared to the controls group, neither in methylation levels nor in peripheral gene expression (Kordi-Tamandani et al., 2012).

Wang et al. investigated the peripheral gene expression of *COMT* in 35 OCD patients (Z. Wang et al., 2009), observing a downregulation in patients compared to healthy controls, with lower levels in female vs male subjects. Despite there was no correlation between gene expression levels and OCD severity, it was suggested that *COMT* down-regulation in OCD patients could induce an increase in dopaminergic signaling due to a reduced COMT activity (Denys et al., 2004; Westenberg et al., 2007). In another case-control study, conducted in children and adolescents with OCD, an overexpression of miR22-3p in OCD patients compared to controls was observed (Kandemir et al., 2015). Of relevance, miR22-3p seems

to regulate *MAOA* and *BDNF* gene expression (Muiños-Gimeno et al., 2011). Moreover, other four miRNAs involved in processes such as DNA damage, lipid peroxidation, and inflammation, were found to be altered in OCD patients (Z. Wang et al., 2009). A recent study by Schiele et al (Schiele et al., 2020) analyzed *MAOA* DNA methylation in 14 unmedicated OCD female patients, observing significant decreased levels when compared to healthy controls. They also observed that after 8-10 weeks of Cognitive Behavior Therapy, DNA methylation levels increased as a function of treatment response (Schiele et al., 2020), as previously reported in panic disorder (Ziegler et al., 2016) and acrophobia (Schiele et al., 2018), underlining the importance of environmental factors on gene regulation.

Although only limited studies on the regulation of these genes were carried in OCD patients, the reduction of *COMT* and *MAOA* genes expression could affect directly the dopamine metabolism and lead to variations compared to the physiological levels in specific brain areas, supporting the dopamine hypothesis within OCD pathophysiology (Westenberg et al., 2007).

3.3 Glutamatergic system

Despite several studies supporting the effectiveness of drugs acting on the glutamatergic system in drug-resistant OCD (Kariuki-Nyuthe et al., 2014; Pittenger, 2015), only few focused on the transcriptional regulation of glutamate pathway-related genes. A study by Porton et al. investigated the different regulation of *SLC1A1* analyzing the expression of three transcripts of the gene. Authors observed a significant lower level of two *SLC1A1* isoforms in OCD subjects compared to the control group (Porton et al., 2013). Considering that these isoforms may act as negative modulators of the SLC1A1 function, it is possible that the lower levels found in OCD could be a mechanism to compensate for the increase in local concentrations of extracellular glutamate (Porton et al., 2013).

To the best of our knowledge, the only study that analyzed *GRIN2B* regulation in psychiatric disorders was carried out by Gray et al., who analyzed the expression of glutamatergic system-related genes in postmortem brain tissues of patients with major depressive disorder (MDD). As a result, an increased expression of *GRIN2B, GRIK3,* and *GRM2* genes in MDD patients who died by suicide, compared to MDD patients who passed away for other causes, emerged, with a greater difference considering female patients (Gray et al., 2015). Assuming that this outcome is due to the suicide in combination with the disorder, this type of analysis could also be repeated in OCD patients, considering that, as discussed in the first paragraph, there is a certain rate of suicidal attempts in OCD patients (Dell'Osso et al., 2018).

3.4 Brain-derived neurotrophic factor

Different studies evaluated serum levels of BDNF as a possible biomarker of OCD. In a case-control study by Maina et al. (Maina et al., 2010), serum BDNF levels were significantly decreased in 24 drug-naïve OCD patients compared to controls. The same result was subsequently observed by Wang et al. (Wang et al., 2011) in both drug-naïve and drug-treated patients respect to healthy controls, with higher BDNF levels associated with longer mean treatment period, as a result of the long-term treatment with antidepressants, as observed by different reports (Björkholm and Monteggia, 2016). This latter association has been observed by Dos Santos et al. (dos Santos et al., 2011) who found reduced levels of BDNF in patients compared to controls, with patients under SSRIs treatment displaying higher levels than drug-naïve ones. Moreover, authors observed that BDNF levels directly correlated with the severity of compulsion scores (Y-BOCS). Sivri et al. (Çolak Sivri et al., 2018) did not observe altered levels in BDNF in unmedicated OCD children, whereas a study investigating 29 OCD children before treatment found higher BDNF levels in patients

respect to controls, assuming that this increase was due to an adaptive response occurring during the early stages of OCD development (Şimşek et al., 2016).

Nissen et al. (Nissen et al., 2016) examined DNA methylation profiles of several genes in blood samples of newborns and in the same subjects at the time of OCD diagnosis, compared with controls. Authors did not observe a significant difference in *BDNF* methylation levels, neither considering patients compared to controls nor considering the two time points, even if the small sample size has to be considered. A case-control study investigated *BDNF* DNA methylation in 35 OCD subjects under stable pharmacological treatment, observing significantly a lower methylation, along with higher hydroxymethylation levels, in patients compared to healthy controls (D'Addario et al., 2019). In the same study, an up-regulation of *BDNF* gene expression in OCD patients compared to controls was observed, negatively correlated with DNA methylation and positively with DNA hydroxymethylation.

3.5 Oxytocin system

DNA methylation of the OxtR gene has been related to human social and emotional functioning (Maud et al., 2018). Ziegler et al. analyzed DNA methylation levels in the promoter region located in the third exon of the *OxtR* gene in blood samples of subjects with social anxiety, observing reduced DNA methylation levels in patients with respect to healthy controls (Ziegler et al., 2015). An interesting study by Unternaehrer et al. evaluated the long-term consequences of early adversities in subjects exposed to war adversities early in life. In this group, authors observed an increase in *OxtR* methylation in both pre- and post-stress phases and a decrease in post-stress during follow-up (Unternaehrer et al., 2012), underlying the importance of this gene in stress-related behaviors. Another study analyzed *OxtR* gene regulation in subjects with anxiety and/or depression, observing a greater DNA methylation levels in those carrying AA genotype for rs53576 compared to controls

(Chagnon et al., 2015), suggesting that the crosstalk between the genetic background and the epigenetic mechanisms has to be considered in phenotypes' manifestation.

So far, only a case-control study analyzed the regulation of this gene in OCD. Cappi et al. (Cappi et al., 2016) analyzed DNA methylation levels in 9 CpG sites located in the third exon of the gene, observing significantly higher levels in OCD patients compared to controls. Considering the relatively low number of subjects, it was not possible to compare sub-groups, even though authors reported a negative correlation between the severity of depressive symptoms and the levels of DNA methylation, suggesting these mechanisms as possible biomarkers of the disorder.

4. Discussion and Conclusions

OCD is highly heritable, involving multiple loci of small to moderate effect with meta-analytic studies indicating a clear role for polymorphisms related to catecholamine modulation (Taylor, 2013). However, so far there have been few consistent findings (Pauls, 2008) due to OCD etiologic heterogeneity with differences in relation to gender and evidence of different subtypes underlying that several genes might have a role in predisposing to, but not in triggering, the disorder. It should be taken in higher consideration the role of environmental factors as possible triggers and their interaction with genetic factors during the development of the disorder. Indeed, alterations in DNA methylation occur during critical periods of development between pregnancy and birth (Numata et al., 2012). For instance, diet, physical exercise, drugs and socio-economic status may be related to altered transcriptional regulation of several endogenous pathways and thus play an important role in the development of complex disorders, including OCD. Moreover, Türksoy and colleagues reported in OCD subjects a deficiency in vitamin B12 as well as higher homocysteine levels, important intermediate in the one-carbon metabolism and thus relevant in DNA methylation (Türksoy et al., 2014).

Additionally, it should be considered how different therapies assumed over the years might regulate genes transcription via epigenetic mechanisms, in order to identify useful diagnostic and prognostic biomarkers.

Therefore, an enzyme mediating DNA methylation/demethylation might be a potential target for intervention. This approach has been already investigated in animal models of OCD. Two knock-out mice models that generated a phenotype replicating the features observed in patients showed a phenotype very similar to the OCD features observed in patients: the *SAPAP3*-/- (Welch et al., 2007) and the *SLITRK1*-/- mice (Katayama et al., 2010), exhibiting increased anxiety and compulsive grooming behaviors. Todorov et al. (Todorov et al., 2019) observed that inhibition of DNA methyltransferase in these mice induced marked symptom improvement lasting for at least one week, as well as reversed altered methylation of protein phosphatase 1 gene, which inhibits memory formation and learning (Genoux et al., 2002). Histone acetylation could also be proposed as a valuable therapeutic target. Some studies underlined the essential role of striatal histone deacetylase 1, histone deacetylase 2, and methyl-CpG binding protein 2, known as “readers” of DNA methylation and involved in the pathophysiology of Rett syndrome, in the regulation of *SAPAP3* for suppression of repetitive behaviors (Mahgoub et al., 2016).

Overall, further investigation in epigenetics in OCD is needed for the understanding of GxE interactions that would be of great value in order to identify new potential biomarkers to depict disease trajectories and, thus, design new effective therapeutic strategies to modify its course (Dell’Osso et al., 2013).

Figure legend:

Figure 1. Schematic representation of the major epigenetic mechanisms.

Figure 2. Schematic representation of the course of OCD. A good biomarker could help to diagnose the disorder before its chronic evolution, thus being able to better manage the course of the disorder.

Table 1 - Published population and family-based genetic association studies in OCD considering the pathways discussed above. Number and ethnicity of subjects included in each study are reported in Supplementary Table 1.

Table 2 - Published population and family-based epigenetic association studies in OCD considering the pathways discussed above. Number and ethnicity of subjects included in each study are reported in Supplementary Table 1.

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Supplementary materials:

Study	Ethnicity	Healthy subjects	OCD patients
Cappi et al., 2016	Latin American	31	42
Grünblatt et al., 2018	European	152	352
D'Addario et al., 2019	European	32	35
Van Ameringen et al., 2010	American		25
Mattheisen et al., 2015	American	1984	1406
Noh et al., 2017	European	560	592
Mas et al., 2016	European	56	87
Hu et al., 2006	American	253	169
McDougle et al.,1998	European-American		35
Bengel et al., 1999	American	397	75
Bloch et al., 2008	European-Asian	3786	1797
Kenezloi et al., 2018	European	222	102
Honda et al., 2017	Asian	40	40
Mak et al., 2015	Asian-European-Latin American	2722	1696
Da Rocha et al., 2009	Latin American	115	92
Taylor 2013	Latin American - Asian-European	-	113
Tukel et al., 2016	Asian	80	98
Mattina, Steiner 2016	American	253	102
Dickel et al., 2007	American	-	47
Baca-Garcia et al., 2005	European	112	24
Frisch et al., 2000	European	172	75
Kinnear et al., 2000	African	82	54
Saiz et al., 2008	European	420	99
Di Nocera et al., 2014	European	-	72
Plana et al., 2019	European	-	74
Meira-Lima et al., 2004	Latin American	202	79
Kim et al., 2005	Asian	171	124
Denys et al., 2006b	European	134	156
Chabane et al., 2004	European	171	106
Camarena et al., 2001	Latin American	136	115
Tibrewal et al.,2010	Asian	92	93
Rashidi et al., 2018	Asian	192	184
Walitza et al., 2004	European	-	63
Lin 2007	Asian-European-Amercan-Latin American	2203	1242
Wendland et al., 2007	American	749	347
Ahmadipour et al., 2018	Asian	224	279
Ohara et al., 1999	Asian	103	103
Baca-Garcia et al., 2007	European	406	97
Voyiaziakis et al., 2011	American	-	1241

Gomes et al., 2018	Latin American	205	203
Sinopoli et al., 2019	American	857	1161
Sinopoli et al., 2020	American	857	1161
Walitza et al., 2012	European	106	136
Walitza et al., 2002	European	223	55
Enoch et al.,1998	American	144	62
Liu et al., 2011	Asian	-	103
Tot et al., 2003	Asian	83	58
Sina et al., 2018	Asian	245	293
Nicolini et al., 1996	Latin American	54	67
Mas et al., 2014	European	-	75
Lochner et al., 2004	African	99	79
Hemmings 2003	African	129	71
Miguita et al., 2011	Latin American	-	41
Cavallini et al., 1998	European	107	109
Camarena et al., 2004	Latin American	-	72
Di Bella et al., 2002	European	-	79
Mundo et al., 2000	American	-	67
Mundo et al., 2002	American	-	157
Kim et al., 2009	Asian	107	167
Delorme et al., 2006	African-Asian-European	246	201
Da Rocha et al., 2011a	Latin American	224	107
Mössner et al., 2006	European	-	71
Viswanath et al., 2013	Asian	-	146
Billet et al., 1998	American	103	103
Vulink et al., 2012	European	-	64
Millet et al., 2003	European	-	55
Walitza et al., 2008	European	-	69
Camarena et al., 2007	Latin American	202	210
Taj et al., 2013	Asian	201	176
Cotrin et al., 2019	Latin American	201	199
Miguita et al., 2007	Latin American	865	208
Zhang et al., 2015	Asian	435	305
Liu et al., 2011	Asian	403	200
Denys et al., 2006a	European	150	150
Karayiorgou et al., 1999	American	-	103
Pooley et al., 2007	European	327	87
Poyurovsky et al., 2005	Asian	171	79
Melo-Felippe et al., 2016	Latin American	200	199
Alsobrook et al., 2002	Asian-European-American	-	56
Tukel et al., 2013	Asian	100	101
Erdal et al., 2003	Asian	114	59
Koh et al., 2016	Asian	-	244
Sampaio et al., 2015	America-Latin American	-	783
Azzam et al., 2003	African-Asian-European	528	169
McGregor et al., 2016	African	195	52

Liu et al., 2013	Asian	414	240
Camarena et al., 2001	Latin American	124	122
Camarena et al., 1998	Latin American	41	41
Arnold et al., 2006	American	270	206
Dickel et al., 2006	American	-	66
Stewart et al., 2007	American-European	-	66
Shugart et al., 2009	American	-	1006
Samuels et al., 2011	American	-	1576
Wendland et al., 2009	American	662	325
De Salles Andrade et al., 2019	Latin American	200	199
Shukla et al., 2020	Asian	333	377
Wang et al., 2010	American	281	378
Abdolhosseinzadeh et al., 2019	Asian	221	239
Zhang et al., 2015	Asian	350	340
Wu et al., 2013	Asian	244	488
Arnold et al., 2004	American	211	178
Arnold et al., 2009	American	-	16
Kohlrausch et al., 2016	Latin American	200	199
Alonso et al., 2012	European	279	225
Liu et al., 2012	Asian	413	206
Viswanath et al., 2018	Asian	333	372
Delorme et al., 2004	European	141	156
Sampaio et al., 2011	European-American	-	47
Wang et al., 2015	Asian	99	148
Liu et al., 2015	Asian	426	321
Hall et al., 2003	American	-	169
Marquez et al., 2013	Latin American	283	343
Taj et al., 2018	Asian	449	377
Hemmings et al., 2008	African	140	112
Katerberg et al., 2009	African	650	419
Abdolhosseinzadeh et al., 2020	Asian	224	219
Umehara et al., 2016	Asian	2027	175
Tukel et al., 2014	Asian	110	100
Kang et al., 2017	Asian	581	615
Koh et al., 2015	Asian	-	355
Nissen et al., 2016	European	12	21
Kandemir et al., 2015	Asian	40	23
Wang et al., 2017	Asian	60	50
Wang et al., 2009	Asian	31	35
Schiele et al., 2020	European	14	12
Porton et al., 2013	American	9	14
Maina et al., 2010	European	24	24
Wang et al., 2011	Asian	63	74
Dos Santos et al., 2011	Latin American	25	25
Sivri et al., 2018	Asian	40	44

Şimşek et al., 2016	Asian	-	34
Enoch et al., 2001	American	138	101
Karayiorgou et al., 1997	American	148	68
Schindler et al., 2000	American	144	72
Kim et al., 2018	Asian	508	615
Kwon et al., 2009	Asian	-	40
Cai et al., 2013	Asian	-	144
Da Rocha et al., 2011b	Latin American	-	122
Alonso et al., 2008	European	342	215

Supplementary Table 1 - Number and ethnicity of subjects considered in each study reported in Table 1 and Table 2.

Figure 1

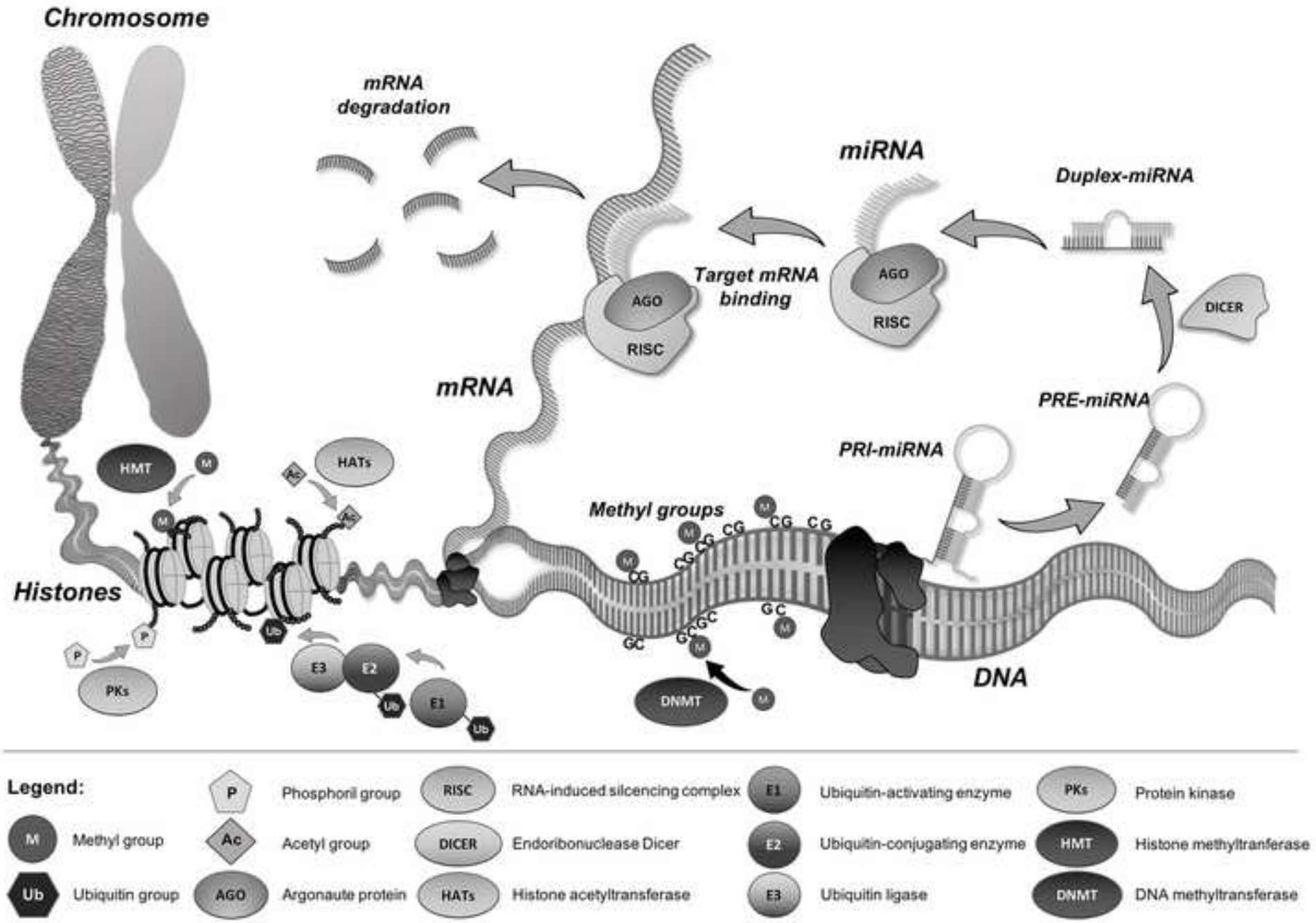

Figure 2