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Role of eating disorders-related polymorphisms in obesity pathophysiology

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Abstract

Human biological system provides innumerable neuroendocrine inputs for food intake control, with effects on appetite's modulation and the satiety signs. Its regulation is very complex, engaging several molecular interactions with many tissues, hormones, and neural circuits. Thus, signaling molecules that control food intake are critical for normal energy homeostasis and a deregulation of these pathways can lead to eating disorders and obesity. In line of this, genetic factors have a significantly influence of the regulation of neural circuits controlling the appetite and satiety pathways, as well as the regulation of brain reward systems. Single Nucleotide Polymorphisms (SNPs) in genes related to hypothalamic appetite and satiety mechanisms, further in multiple neurotransmitter systems may contribute to the development of major Eating Disorders (EDs) related to obesity, among them Binge Eating Disorder (BED) and Bulimia Nervosa (BN), which are discussed in this review.

Keywords Obesity · Food intake · Eating disorders · Binge eating disorder (BED) · Bulimia nervosa (BN) · Polymorphism

Abbreviations

SNP	Single Nucleotide Polymorphisms
ED	Eating Disorders
BED	Binge Eating Disorder
BN	Bulimia Nervosa
MC4R	Melanocortin 4 receptor
OPRD1	Opioid Receptor delta 1
BDNF	Brain derived neurotropic factor
FTO	Fat mass and obesity associated
VTA	ventral tegmental area VTA
NAc	nucleus accumbens
PYY	peptide tyrosine tyrosine
CCK	cholecystokinin
ARC	arcuate nucleus
PVN	paraventricular nucleus
DMN	dorsomedial nucleus
VMN	ventromedial nucleus
LHA	lateral hypothalamic area
NPY	neuropeptide Y
AgRP	agouti related peptide
POMC	pro-opiomelanocortin
CART	cocaine- and amphetamine-regulated transcript
α-MSH	α-melanocyte-stimulating hormone
MC-Rs	G protein coupled melanocortin receptors
CRH	corticotropin-releasing hormone
TRH	thyrotropin-releasing hormone
CSF	lumbar cerebrospinal fluid
DSR	dopamine 2 receptors
DAT	dopamine transporter genes
DRD2	dopamine receptor gene
5-HTTLPR	serotonin transporter gene
BDNF	brain derived neurotrophic factor
ESR1	estrogen receptor 1
ESR2	estrogen receptor 2
CB1	cannabinoid receptor 1
DAT	dopamine transporter
COMT	catechol-O-methyltransferase

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1 Introduction

Obesity is a complex and chronic medical condition with a lager negative impact on human health [1], which has been associated with increased morbidity and considered a risk factor for cardiovascular disease, type 2 diabetes mellitus, hypertension, dyslipidemia and multiple cancers [2]. Obesity is often labeled and stigmatized, however there is a wide literature based on evidence that this is a complex disease caused by the interaction of multiple genetic, environmental, metabolic, psychological and behavioral factors [1].

Among genetic factors, single nucleotide polymorphisms (SNPs) can influence obesity risk; as well both gain and weight maintenance. Studies with twins and relatives have shown that the heritability of obesity ranges from 25 to 90%, confirming that a portion of the risk for the disease may be due to hereditary factors [3]. Also, genetic polymorphism is associated with different weight loss outcomes in patients submitted to diverse strategies for weight loss (clinical /or surgical) [4].

Obesity is closely associated with eating disorders (ED) and it shares several psychological and genetic factors [5]. According to a gene-environment approach, psychopathological differences can be influenced by genetic variability, which would explain the variance of susceptibility to ED [6]. The literature has shown the existence of neurobiological mechanisms common to these diseases that involve the regulation of food intake and emotion control [7]. An imbalance between appetite and satiety control associated with the rewarding aspect of food is possibly linked to genetic predisposition [8]. Thus, several confirmed genetic loci for obesity are expressed in regions of the brain that regulate energy consumption and reward seeking behavior [9].

In this case, the literature highlights the genes *MC4R* (Melanocortin 4 receptor), *OPRD1* (Opioid Receptor delta 1), *BDNF* (Brain derived neurotropic factor), *FTO* (Fat mass and obesity associated) and others, which have also been associated with mechanisms related to ED [9–12]. Thus, individuals with ED may be prone to food-related hedonic responses through genetic, dopaminergic, and opioidergic influences in reward-related processes [9, 13].

In this context, this review shows the role of polymorphisms involved with different eating disorders and its association with the pathophysiology of obesity (Fig. 1).

2 Obesity and food intake control

In the context of obesogenic environment, it is important to understand the mechanisms that control human appetite and satiety, which leads to the balance or imbalance between energy intake and energy expenditure, and consequently to overweight and obesity [14, 15]. Satiety can be defined as the

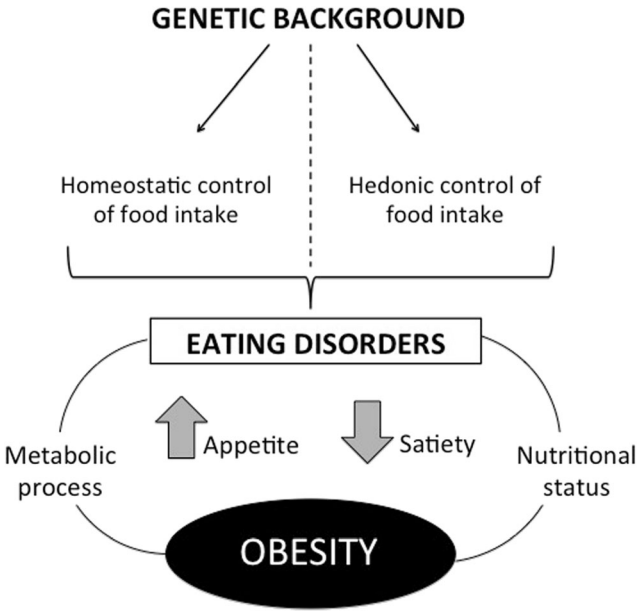

Fig. 1 Genetic polymorphism can affect appetite and satiety control, leading to eating disorders and consequently to obesity

feeling of fullness that persists after eating and, also is one important psycho-biological mechanism whose function is to inhibit intake following food ingestion, being able to suppress overconsumption [14]. In addition, satiety is modulated by macronutrient intake, as well as micronutrients, non-nutrients, bioactive food compounds and gut microbiota [15]. On the other hand, appetite is defined as the process that leads to the qualitative selection and quantitative ingestion of specific foods [16].

Briefly, gastric and intestinal signals interact with central nervous system pathways to terminate food intake [17]. The first phase of this control is the cephalic phase that denotes to the physiological preprandial responses due to olfaction and cognizance [18]. In post-prandial phase, food contact and digested food components in gastrointestinal track promotes a physical distension of stomach and hormones secretion that increase satiety levels. After absorption and digestion process, food metabolites promote secretion of hormones from adipose tissue (leptin) and pancreas (insulin), which suppress appetite through the hypothalamic circuits [19].

Thus, food intake is regulated by peripheral nutritional signals, through hormonal and neuronal pathways (Table 1) that are carried to specific brain areas, hypothalamic nuclei and the brainstem, both involved energy balance regulation (homeostatic regulation). However, the control of food intake is also performed by a hedonic behavior in which food ingestion occurs for pleasure regardless of the need for energy (non-homeostatic regulation). In this way, feeding is based on food reward properties and involves brain central areas such as the mesolimbic reward system, ventral tegmental area (VTA), nucleus accumbens (NAc), and the opioid, endocannabinoid and dopamine systems [20, 21].

Table 1 Summary of orexigenic and anorexigenic hormones/ peptides of hedonic food intake control

Tissue	Orexigenic factor	Anorexigenic factors
Gut	Ghrelin	CCK
		PYY
		PP
		Enterostatin
		GLP-1
		Glucagon
		OXM
Neurons	NPY	POMC
	AgRP	CART
	Orexin A	ACTH
	MCH	α-MSH
Adipose tissue		Leptin
		Insulin

CCK cholecystokinin, *PYY* peptide tyrosine tyrosine, *PP* pancreatic polypeptide, *GLP-1* glucagon-like peptide-1, *OXM* oxyntomodulin, *NPY* co-expressing neuropeptide Y, *AgRP* agouti related peptide, *MCH* melanin-concentrating hormone, *POMC* co-expressing pro-opiomelanocortin, *CART* cocaine- and amphetamine-regulated transcript, *ACTH* α-MSH: α-melanocyte-stimulating hormone

2.1 Homeostatic food intake control

2.1.1 Gut hormone and peptides

Gastrointestinal tract secretes hormones and peptides responsible for peripheral control of the food intake by controlling the initiation and termination of the meal. The biggest signal for the secretion of these peptides is gastric distension [22]. Among gut hormone and peptides, we highlight the peptide tyrosine tyrosine (PYY), cholecystokinin (CCK) and ghrelin.

CCK is secreted by I cells of the gastrointestinal tract, in response to the presence of lipids and protein, promotes prandial satiety and induces the secretion pancreatic, biliary secretion and vesicular contraction [23]. PYY peptide is expressed by the gut endocrine cells and acts as an inhibitor of food intake. On the other hand, ghrelin is secreted by gastric mucosal cells and is one of the most important factors in promote food intake, by increasing the appetite, and stimulates digestives secretions [23].

2.1.2 Peripheral adiposity signals

Leptin and insulin act as peripheral adiposity signals for informing the brain about the adipose tissue mass. Leptin, a hormone produced in white adipose tissue, promotes satiety and regulate energy balance for acting on its receptors expressed in the hypothalamus [24]. In arcuate nucleus (ARC), leptin exerts anorexigenic effect via inhibition of neuropeptide Y (NPY)/ agouti related peptide (AgRP) neurons and activation of co-expressing pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons [25]. Insulin is produced by the pancreatic β-cells and has an important function in the central nervous system to increase satiety, energy expenditure and regulate action of leptin [26].

2.1.3 Neuronal signals

The hypothalamus plays a major role in the control of the appetite by processing afferent signals from the gut and brainstem. Specific neuronal regions take part in the regulation of food intake such as ARC, the paraventricular nucleus (PVN), the dorsomedial nucleus (DMN), the ventromedial nucleus (VMN) and the lateral hypothalamic area (LHA) [27].

In the ARC nucleus, different neurons with opposing effects act in food intake control: 1. co-expressing NPY and 2. AgRP neurons, which stimulate appetite and 3. POMC and 4. CART neurons, that suppress the feeding (stimulate satiety) [25]. Also, in ARC, the cleavage of POMC results in the production of α-melanocyte-stimulating hormone (α-MSH) that exert their effects by binding to G protein coupled melanocortin receptors (MC-Rs). On the other hand, PVN nucleus contains neurons that secrete peptides responsible to reduce food consumption (i.e. corticotropin-releasing hormone (CRH), oxytocin, and thyrotropin-releasing hormone (TRH).

2.2 Brain reward systems and the hedonic food intake control

Brain reward systems involved in eating behavior have two mechanisms, one related with motivating the desire for food, referred to as 'wanting', and another mechanism related with the hedonic properties of the food, referred to as 'liking'. Since dopamine (DA) is predominantly involved in 'wanting', opioids and cannabinoids are predominantly involved in food 'liking' [28].

The dopaminergic system is a central component of the hedonic feeding. DA is a key neurotransmitter able to modulate reward, which does mainly through its projections from the VTA into the NAc [29]. DA receptors are expressed in specific hypothalamic nucleus and its effects depend on the specific region of its actions [30, 31]. The DA acts in two major regions, LHA and VMH that have opposed effects on dietary intake. In the LHA area, dopamine levels increased immediately with the meal, remain high during the meal consumption, and normalize when it ends [32, 33]. In contrast, in the VMH region, dopamine levels decrease after food ingestion and increase during fast [32].

Conversely, the role of DA in mesolimbic/mesocortical has been associated with reward processing in reaction to feeding stimuli [34]. Environmental stimulus induces burst-firing of

dopamine neurons with subsequent phasic DA release. This increase in DA signaling will motivate specific behaviors, such as 'wanting' food [28, 35]. On the other hand, the activation of the opioid and cannabinoid systems seems to stimulate in part by enhancing the 'liking' of the food. Although the brain reward systems involved in eating behavior are separate, they act together to regulating food intake [28].

Also, serotonin (5-HT) has been implicated in the control of food intake [36]. Brain 5-HT interacts within the hypothalamus and acts on central melanocortin neurons to promote satiety. Activation of 5-HT_{2c} receptor increases the activity of anorexigenic POMC neurons and the activation of 5-HT_{1b} receptor inhibits the orexigenic NPY/AgRP neurons [37]. In the nucleus of the solitary tract serotonin integrates peripheral satiety signals [36].

2.3 Cross-talk between homeostatic and hedonic systems

There is a crosstalk between the neurochemical substrates of the two systems [38] in which food deprivation or satiation affects attraction for food (Fig. 2). Interestingly, this cross-talk is mediated by the direct action of leptin, insulin, GLP-1 and ghrelin, on the mesocorticolimbic dopamine system [39]. In addition to acting through peripheral pathways by stimulating energy storage, insulin can also excite specific brain receptors (negative feedback), reducing activity in mesolimbic dopamine circuits and consequently food reward [40, 41]. In the same direction, GLP-1 signaling in the mesolimbic system can have a selective effect to reduce the rewarding value for tasty food [42]. In addition, ghrelin has an important role in increasing the neural response to food photos in reward-related circuits [43]. In line of this, the incresead of signalling by the stomach-derived orexigenic hormone, ghrelin, can activate the mesoaccumbal dopamine system and the reward from palatable food [44]. Besides these direct mechanisms described between the two systems, there are indirect effects mediated by heterogeneous projections from the LH to the VTA, including neurons expressing orexin [45], gamma-aminobutyric acid (GABA) and glutamate [46, 47].

In this context, human biological system provides innumerable neuroendocrine inputs for food intake control, exerting effects on modulation of appetite and the satiety signs. As above, its regulation is very complex, engaging several molecular interactions with many tissues, hormones, and neural circuits. Thus, signaling molecules that affect food intake are critical for normal energy homeostasis [26, 48]. In addition, the homeostatic and hedonic circuits act together to promote

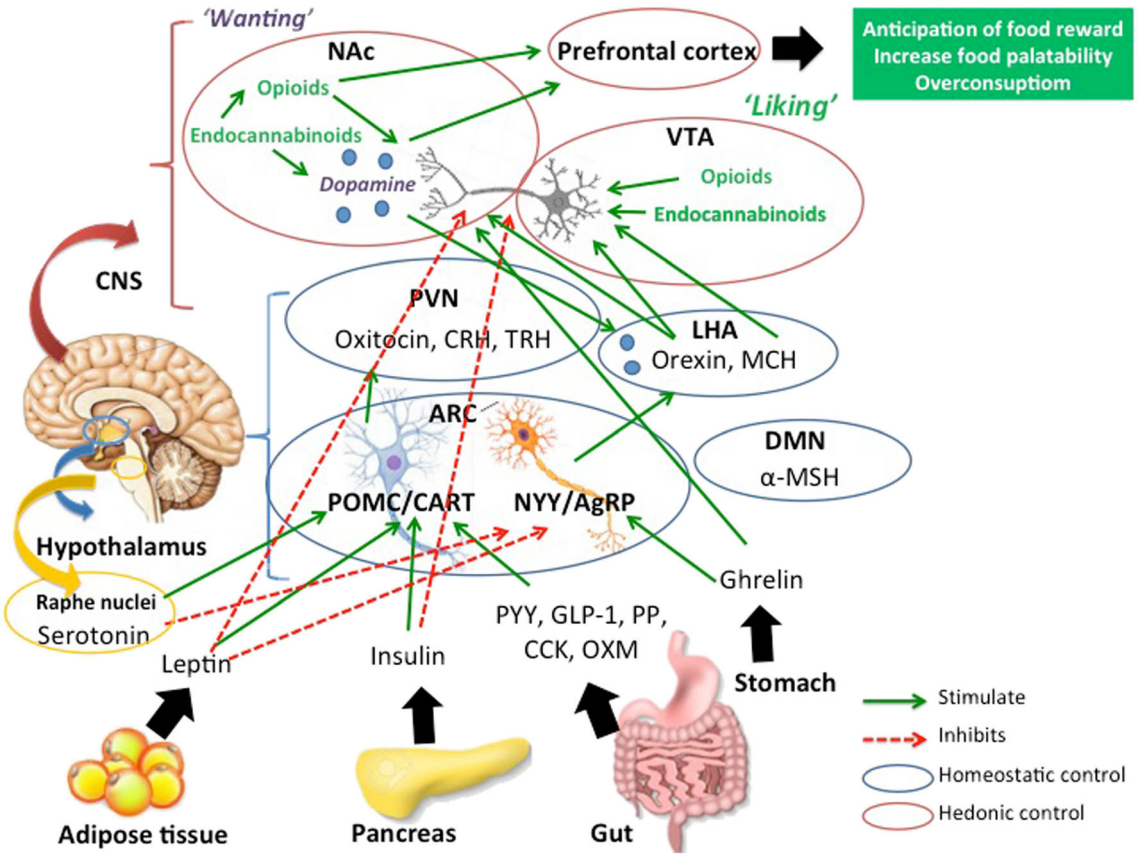

Fig. 2 Cross-talk between homeostatic and hedonic regulation of food intake. The action of gut hormones, neural and hormonal signals (peripheral signals), dopamine and serotonin in hypothalamus and central nervous system

food intake in times of deprivation and to inhibit food intake in satiety conditions. Interruption of the interaction between these circuits may promote the development of EDs such as Bulimia Nervosa (BN) and Binge Eating Disorder (BED) and contribute to the development and/or aggravation of obesity [28]. An increase in EDs and in atypical eating patterns such as binge eating and weight control behaviors associated with EDs and obesity have been reported globally [49], and the next chapter addresses EDs main characteristics.

3 Eating disorders associated with obesity: Binge eating disorder (BED) and bulimia nervosa (BN)

EDs are characterized by regular and persistent disturbances in eating or eating behavior, culminating in the consumption and altered absorption of food, significantly compromising physical health and psychosocial functioning, thus generating a reduction in quality of life [50]. The etiology of EDs is multifactorial, involving biological, psychological and sociocultural factors [51]. Among the biological aspects, the genetic factors have a significantly influence of the regulation of neural circuits controlling the appetite and satiety pathways, as well as the regulation of brain reward systems [52, 53].

Several studies have shown a significant association between EDs and obesity, and the most prevalent EDs in obese subjects are BED and BN [54]. In the adult population the prevalence is about 2–5% for BED and 1% for BN, being more frequent in females [55–57]. Recurrent episodes of binge eating are the main feature of both conditions and are characterized by the consumption of an excessive amount of food associated with the feeling of loss of control over food. This feeling of loss of control of the amount of food intake during a binge eating episode is one of the most important clinical features in this population and contributes to the feeling of guilt, disappointment, sadness and depression [54, 58, 59]. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies and establishes some criteria for the diagnosis of these eating disorders.

3.1 Binge eating disorder (BED)

BED is characterized by recurrent episodes of binge eating that occur at least once a week over a three-month period associated with lack of control and pronounced distress. Episodes of binge eating are usually associated with eating faster than normal, eating a quantity that exceeds gastric capacity, eating in large quantities in the absence of physical hunger, eating alone because of the amount of food consumed, and the feeling of guilt after episodes of compulsion. However, it is not associated with inappropriate compensatory strategies after compulsion. Therefore BED is often associated with obesity [50, 55, 60].

3.2 Bulimia nervosa (BN)

BN is characterized by self-assessment and excessive preoccupation with body image, recurrent eating compulsion and inappropriate compensatory behaviors to avoid weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, fasting and excessive physical exercise. According to DSM-5, binge eating episodes and compensatory behaviors should occur at least once a week for three months for the diagnosis of bulimia [50, 60].

3.3 Physiopathology of EDs

The homeostatic control of body energy balance is exerted by specific populations of neurons located, for the most part, in the hypothalamic nuclei, which through a neuroendocrine pathway respond to fluctuations in the energetic state, altering the expression of neuropeptides, resulting in changes in ingestion and energy expenditure [61, 62].

In addition to homeostatic regulation, hedonic controls of appetite exert a great influence on food intake, being related to feelings of pleasure and reward. Thus, there is a complex interaction between hedonic controls and homeostatic controls for regulating food intake as well as regulating body weight [38].

Brain reward systems mechanisms are closely involved in the pathophysiology of binge eating behavior, which is a symptom present in EDs (BN and BED) [63]. Multiple neurotransmitter systems (dopaminergic, serotonergic, opiodergic, GABAergic and glutamatergic) contribute to binge eating episodes, but dopaminergic, serotonergic and opiodergic neurotransmission are essential for the consumption of reward-related foods [64, 65].

DA is a key neurotransmitter involved in the reward and induction aspects of feeding. Some studies have shown that subjects who presented BN have lower levels of dopamine metabolites in lumbar cerebrospinal fluid (CSF) when compared to healthy individuals. Some studies have provided evidence that the decrease in DA signaling in striatal regions, either by reduction in the action or number of dopamine 2 receptors (D2R) or in DA release, is related to a reduction in sensitivity to natural rewards, in which obese individuals with EDs can compensate by eating more, especially high-fat foods [66–68]. Based on this, some studies have observed that individuals with polymorphisms in dopamine transporter genes (*DAT*), as well as in the dopamine receptor gene (*DRD2*) showed a change in the turnover of DA. These findings support the fact that there is a change in DA metabolism in BN, affecting the hedonic processes associated with food induction and reward mechanisms [52, 69].

5-HT also plays an important role, related to satiety. In animals and in humans, manipulations that increase 5-HT neurotransmission lead to reduced food intake, whereas those that reduce 5-HT activity lead to binge eating [70]. These tendencies lead to the expectation that EDs characterized by binge eating (such as BED and BN) should be related to reduced 5-HT activity [71] and it is evident that the deregulation of 5-HT system, like polymorphisms related to the serotonin transporter gene (*5-HTTLPR*), is associated with EDs, such as BED and BN [65].

4 Genetic polymorphisms and eating disorders associated with obesity

Genetic factors also contribute to changes in eating behavior and to the development of EDs [72]. Despite the mechanisms mentioned above in the appetite and satiety control, individual genetic variability (characterized by SNP) in the predisposition for obesity development and in the biological response to weight loss makes this regulation so complex [48]. In line of this, there are evidences among interactions of common genetic variants, altered circulating gut hormone levels and obesity-risk effects [73, 74]. These SNPs, or other variants located in hypothalamus appetite and satiety related genes, may are involved in the develop unusual food intake behavior/patterns that favor the establishment of EDs. In addition to SNPs in genes related to hypothalamic appetite and satiety mechanisms, some SNPs in genes involved in multiple neurotransmitter systems (dopaminergic, serotonergic, opioidergic, GABAergic and glutamatergic) contribute to the development of major EDs related to obesity, which will be discussed in the next subtopics [75].

4.1 Genetic polymorphisms and BED

With the advancement of studies in genomic medicine, estimates of heritability have been demonstrated for BED with variation from 41 to 57% [76–78], in addition to the association of BED with some SNPs [79–86].

In relation to SNPs in genes involved with the mechanisms of appetite and satiety, one is related to the hunger hormone, ghrelin, which stimulates the release of orexigenic neuropeptides NPY and AgRP, increasing food intake, was identified that carriers of the Leu72Met variant of the ghrelin gene (*GHRL*), that is possibly involved with some physiological effects by biding to ghrelin receptors, was associated with BED in preliminary results in a pilot study [87]. A recent systematic review and meta-analysis that evaluated a possible association between coding variants in the melanocortin 4 receptor gene (*MC4R*), which is the α-MSH receptor and is involved in inhibiting food intake and increasing the energy expenditure, with BED in obese individuals, showed a positive association between variants of gain-of-function (GOF) in MC4R and risk of BED [88].

Dopamine is an important neurotransmitter that is involved in a wide variety of brain functions, including eating behavior and reward mechanisms. Based on this, dopaminergic SNPs have been studied and some have been associated with BED, such as dopamine D2 receptor (*DRD2*) and neighboring ankyrin repeat and kinase domain containing 1 (*ANKK1*) [13, 89, 90]. The most prevalent variations in individuals with BED are *Taq1A*$^{+}$ allele (A1/A1 and A1/A2 genotypes), which are associated with a reduced DA function, due to a 30–40% reduction in DRD2 density in the striated and diminished glucose metabolism in brains of these individuals [13, 91, 92]. The *VNTR* polymorphisms of the human dopamine transporter (*DAT1*) are also related to BED [93].

5-HT is another neurotransmitter that is involved in eating behavior, and serotonergic genes and their relation in EDs have been studied extensively [94]. In relation to the SNPs involved with the serotonergic system and BED, one study observed a significantly higher frequency of LL genotype and L allele for polymorphism in the *5-HTTLPR* of the serotonin transporter gene (*5HTT*) in individuals with BED (n = 77), compared to individuals without BED (n = 61) [95].

The endogenous opioid system in reward processes presents a major role in μ-opioid receptors, which activation enhances positive hedonic aspects to eat more sweet and fatty foods [96] and one study revealed that individuals with obesity and BED (n = 66) had a higher "Gain of function" G allele prevalence of rs1799971 polymorphism for the *OPRM1* gene (μ 1 opioid receptor gene), compared to individuals with obesity without BED (n = 70) [13].

The brain derived neurotrophic factor (BDNF) and its tyrosine kinase receptor are expressed in various hypothalamic nuclei and when active decrease food ingestion and increase energy expenditure [97]. One cohort study in women with obesity identified a greater association between the 66met allele of the *BDNF* rs6265 and BED [82], and a higher frequency and more severe episodes of binge eating in those carrying the 196G/A polymorphism (val66met) for the *BDNF* gene [95] thus suggesting a relationship of these SNPs with the BED. These polymorphisms related to BED are presented in Table 2.

4.2 Genetic polymorphisms and BN

BN is also familial and individuals who have a relative with BN are at elevated risk for developing this ED [98, 99]. Although few studies show a direct association between SNPs and BN [100–102], others associate some SNPs with the aggravation of psychological symptoms of this disorder [102, 103] and we will mention those of greater relevance in the current literature.

Table 2 Overview of SNPs findings in eating disorders

Gene	Description	Polymorphism	ED	References
GHRL	Ghrelin	rs696217	BED	Monteleone et al. [87]
MC4R	Melanocortin 4 receptor	rs2229616 (Val103Ile)	BED	Qasin et al. [115]
		rs52820871 (Ile251Leu)		Potoczna et al. [116]
DRD2	Dopamine receptor D2	rs6277 (957 C/T)	BED	Davis et al. [13, 89, 90]
ANKK1	Ankyrin repeat and kinase domain containing I	rs1800497 (Taq1A)	BED	Davis et al. [13, 89, 90]
DAT1	Dopamine transporter 1	rs2270912 rs28363130	BED	Hirata et al. [117]
SLC6A4	Serotonin transporter	5-HTTLPR	BED	Monteleone et al. [95]
OPRM1	Mu I opioid receptor	rs1799971 (118A/G)	BED	Davis et al. [13]
BDNF	Brain derived neurotrophic factor	rs6265 (Val66Met)	BED	Beckers et al. [82]
ESR1	Estrogen receptor 1	rs928554	BN	Nilsson et al. [118]
CNR1	Cannabinoid receptor 1	rs1049353	BN	Monteleone et al. [100]
SLC6A4	Serotonin transporter	5-HTTLPR	BN	Steiger et al. [103, 107]; Thaler et al. [119]
DRD2	Dopamine receptor D2	rs1800497 (Taq1A)	BN	Thaler et al. [102]
COMT	Catechol-O-methyltransferase	rs4680 (Val158Met)	BN	Thaler et al. [102]
FTO	Fat mass and obesity associated	rs9939609	BN	Müller et al. [101]

The role of sex hormones in the development or aggravation of EDs has recently gained research attention [104] and as estrogen has also been implicated in feeding behavior, the focus has been on the estrogen receptor 1 (ESR1) and estrogen receptor 2 (ESR2 or ERβ). One study showed a positive association between *ERβ* rs928554 SNP and BN in 76 women, which may be related to a reduction in the *ERβ* function [105].

The endocannabinoid system, with activation of cannabinoid receptor 1 (CB1), is involved in the modulation of energy balance by controlling food intake, possibly with the mesolimbic pathway involved in reward mechanisms and by the hypothalamus, interacting with other orexigenic and anorexigenic mediators to modulate appetite and satiety [105, 106]. One study identified that the *CNR1* (gene coding the CB1 receptor) rs1049353 SNP is significantly associated with BN patients ($n = 149$), which may have functional effects by altering mRNA stability or translation of CB1 [100].

5-HT has an important role in food intake and is involved in BN [94]. Based on this, genetic factors associated with reduced 5-HT neurotransmission, like low-function alleles of the serotonin transporter polymorphism (*5-HTTLPR*) have been linked to BN in some studies [102, 103, 107].

The dopaminergic system is a system of interest in BN, due to demonstrated associations between dopamine (DA) activity and food intake [108], and the fact that people with BN display decrease DA metabolites [109] and decreased DA transporter (DAT) availability [110]. Some associations between polymorphisms acting upon postsynaptic receptors like dopamine D2 receptor (*DRD2*) TaqA1 rs1800497 and dopamine D4 receptor (DRD4) 7R and dopamine regulators catechol-O-methyltransferase (*COMT*) rs4680 and DA transporter 1 (*DAT1*) are related to increased psychopathology and body mass in women with BN [102]. One study shows that the hypofunctional 7R allele of DRD4 contributes to weight gain in Caucasian women with BN and that the Met66 allele of *BDNF* gene acts with DRD4 to influence weight regulation in these women [111].

Several studies have demonstrated a strong association between SNPs in the fat mass and obesity associated gene (*FTO*) and obesity in different age groups [112–114]. The FTO SNP rs9939609 which is strongly associated with obesity, also was associated with BN in 477 patients in a German study [100]. These polymorphisms related to BN are presented in Table 2.

5 Conclusion

This review manuscript highlights that genetic and psychological factors are closely associated with eating disorders, including BED and BN, and to obesity development. Neurobiological mechanisms in common to these diseases are involved in food intake and emotion control, and to an imbalance between appetite and satiety associated with the rewarding aspect of food, which is possibly linked to genetic predisposition. Given the evidence found in current literature, it is safe to say that there is a clear link between these diseases that needs to be explored in the field of molecular biology. Therefore, it is important to highlight the relevance in the identification of genetic risk factors for a possible personalized treatment and consequently more effective for these

patients. However, it is also important to point out that obesity treatment success remains a challenge, partly since obesity pathophysiology is orchestrated by complex interactions among environment, genetic background and behaviors. Thus, the analysis of polymorphisms can be a useful tool in obesity treatment, mainly in the early diagnosis of eating disorders, therefore it should be used by trained professionals with caution.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest.

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