Review

Gene variants in eating disorders. Focus on anorexia nervosa, bulimia nervosa, and binge-eating disorder

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Summary

Eating disorders such as anorexia nervosa, bulimia nervosa and binge-eating disorder, have a deep social impact, concluding with death in cases of severe disease. Eating disorders affect up to 5% of the population in the industrialized countries, but probably the phenomenon is under-detection and under-diagnosis. Eating disorders are multifactorial disorders, resulting from the interaction between environmental triggers, psychological factors, but there is also a strong genetic component. In fact, genetic factors predispose for approximately 33-84% to anorexia nervosa, 28-83% to bulimia nervosa, and 41-57% to binge eating disorder. Twins and family studies have provided an unassailable proof on the heritability of these disorders. Other types of genetic studies, including genome-wide association studies, whole genome sequencing and linkage analysis, allowed to identify the genes and their variants associated with eating disorders and moreover global collaborative efforts have led to delineate the etiology of these disorders. Next Generation Sequencing technologies can be considered as an ideal diagnostic approach to identify not only the common variants, such as single nucleotide polymorphism, but also rare variants. Here we summarize the present knowledge on the molecular etiology and genetic determinants of eating disorders including serotonergic genes, dopaminergic genes, opioid genes, appetite regulation genes, endocannabinoid genes and vitamin D3.

Introduction

Eating disorders (EDs) are disorders characterized by an alteration in eating habits and by excessive worry and distorted vision of one's own body weight, associated with a high rate of morbility and mortality [1]. The main EDs recognized by the Diagnostic and Statistical Manual of Mental Disorders are anorexia nervosa (AN), that is characterized by distorted body image and weight loss, bulimia nervosa (BN) and binge-eating disorder (BED) characterized by consume of large quantities of food in a short time with loss of control, which in the case of BN can be followed by compensatory behaviors such as abuse of diuretics and laxatives and self-induced vomiting [2]. About 70 million people across the world of every gender, age and ethnic group have been reported an eating disorder. The etiology of eating disorders is influenced by developmental, social, and biological processes [3].

By twin and family studies, it was extensively demonstrated that eating disorders are heritable [4]. These studies had also demonstrated a high level of shared genetics between AN and BN [5-6]. Subsequent genome-wide association studies (GWAS) were fundamental to understand the molecular mechanisms involved in eating disorders. In particular, genetic risk score from GWAS results can be very useful in clinical practice [7]. Currently, there are especially GWAS results on anorexia nervosa with multiple genetic loci identification, suggesting that several genetic variants are associated with AN disease risk [8].

The role of rare and structural variants in eating disorders it was explored by studies of whole-exome and whole-genome analyses. Instead, gene expression studies had offer insight into the genes and molecular mechanisms that influence phenotypes [4].

Several neuropeptides, neurotransmitters and hormones are involved in eating disorders. The complex brain homeostatic control of feeding involves neural circuits located in the hypothalamus (hunger signals, initiating feeding behavior) and the brainstem (satiation signals, limiting meal size) [9]. Hypothalamic NPY/AgRP neurons produce Neuropeptide Y and Agouti-related peptide responsible for an orexigenic signal increasing the ACTH, cortisol and prolactin release and involved in appetite regulation. These neuropeptides are associated to high food intake with up-regulation in AN [10]. Instead, orexins are orexigenic neuropeptides involved in endocrine system regulation, with an important function in insulin, glucagon, and leptin secretion in response to

glucose [11]. Another neuropeptide involved in eating disorders is Proopiomelanocortin (POMC) is an anorexigenic peptide at the hypothalamic ARC regulated by leptin [12]. Several research connect also the peptidic hormone oxytocin signaling and eating disorders. Specific oxytocin receptor genes polymorphisms have been found [13].

Neurobiological mechanisms underlying eating disorders might involve an overreaction of the immune system, generating, in turn, a dysfunction of neuropeptide signaling. Also, the brain- gut-microbiota axis allows a bidirectional communication between gut microbes and the brain through endocrine, neural, immune, and metabolic pathways [9].

Although determining the cause of eating disorders is complex because there are both genetic and environment factors that can contribute to their development, there is growing scientific interest to identifying causal genes of eating disorders.

Genetics research can improve knowledge about the heritability of eating disorders thanks to new molecular technologies such as *Next Generation Sequencing* [4].

Here, we focus on genetic knowledge summarized in order of the type of eating disorder considering all the most recent genetic results.

Anorexia nervosa

The genetic mechanisms underlying AN have been the most investigated and studies related to this disorder are those that have provided the most results. AN is a multifactorial disorder with a strong genetic component. The familial nature of AN has already been demonstrated for several decades, with a heritability range of 33-84% [14-15].

Several genetic studies have made it possible to identify many genetic loci involved in molecular pathways that might lead to anorexia [16].

- *Serotonergic genes*: the serotonin or 5-hydroxytryptamine (5-HT) system is involved in food intake, mood, and body weight regulation [17]. It has been hypothesized that 5-HT activity is altered in the acute illness state of AN. Most positron emission tomography studies of AN patients have targeted the 5HT1A and 5HT2A receptors and 5HTT [18]. In particular, important AN targets could be the 5-HT2A receptor gene and the 5HT-transporter-linked polymorphic region (5-HTTLPR) [19]. An increase in 5-HT reuptake occurs following the administration of estrogens which alter the mRNA and protein levels of some markers of serotonin [20]. Moreover, AN patients may have *HTR1D* gene variations [21]. Recently, it has been identified a positive relationship between the serotonin transporter gene *SLC6A4* methylation levels and resting-state functional connectivity between the dorsolateral prefrontal cortex and the salience network in AN patients [22]. Anyway, it is unlikely that this pathway is the only one involved in the onset of AN in a subject because it is associated with numerous psychiatric disorders and therefore cannot be considered a specific vulnerability factor for AN [16-19].
- *Dopaminergic genes*: The dopaminergic system modulates thinking processes, reward, emotional behavior, substance dependence, feeding and motor activity. Dopamine (DA) is a catecholamine that acts primly through of two G protein-coupled DA, D1 (D1R) and D2 (D2R) receptors. DA has been implicated in the pathophysiology of AN by preclinical and clinical evidence. A gene that plays an important role in the dopamine system is DAT1 that encodes a transmembrane protein that regulates dopamine reuptake from synapses and possesses variable number of tandem repeats in its 3'-untranslated region. Polymorphisms in the number of repeats influence *DAT1* expression (VNTR 10R/9R). The TaqIA restriction endonuclease site in *DRD2* (rs1800497) has been shown to reduce the density of D2 autoreceptors in the striatum. Moreover, the rs6280 variant in *DRD3* increases the affinity for endogenous dopamine. Recently, it has been demonstrated that AN patients carrying the homozygous variant Gly9Gly genotype in the dopamine D3 receptor have worse symptomatology [23].
- *Opioid genes*: Opioid receptors are involved in food intake, reward sensitivity, pain, and vulnerability to addictive disorders. Several *OPRD1* polymorphisms were associated with AN. In particular, *OPRD1* variants were associated with AN restricting type [21].
- *Appetite Regulation Genes:* The communication between gut and hypothalamus involves a huge numbers of appetite hormones. After stimulation, anorexigenic peptides are released while the levels of the orexigenic peptide ghrelin reduce. Ghrelin is an appetite stimulating hormone produced in the stomach and pancreatic cells that is inversely associated with body mass index (BMI) [24]. In response to prolonged starvation the level of ghrelin in the plasma increases [25]. Leptin is a hormone produced by adipocytes and involved in the food intake and regulation of energy balance [26]. In AN patients the level of plasma circulating leptin in cerebrospinal fluid is reduced (hypoleptinemia) [27]. The serum level of leptin is significantly decreased in AN patients but only moderately increased in obese patients [28]. An increased concentration of NPY, which mediates leptin receptors, is associated to body mass deficiency with high concentrations of leptin, suggesting defects in the regulatory axis [29].

  The pancreatic polypeptide (PP) peptide tyrosine-tyrosine (PYY) belongs to NPY family and is postprandially secreted in ileum and colon with an anorexigenic role [30]. Its peripheral administration decreases appetite along with weight loss through inhibition of the arcuate hypothalamic nucleus expression of NPY/AGRP [31]. Anyway, serum levels of PYY hormone are less diminished in AN as comparated to BN/BED [6].

  Cholecystokinin (CCK) is a peptidic hormone of the gastrointestinal system that promotes satiety but has

been also associated with anxiety [32]. CCK plasma levels in AN patients and control group are similar both prior to and after a fooding suggesting a hormonal adaptation. However, in older analysis, in AN patients CKK plasma showed a postprandial increase [33-34].

GLP-1 is a brain-gut peptide that exerts a hormone-neurotransmitter action increasing satiety and inhibiting food intake, energetic expenditure, and insulin levels [35]. GLP-1 level decreases in AN patients, while insulin and glucagon levels increase, indicating an alteration in glucose homeostasis [36]. Oxyntomodulin (OXM), which acts through GLP-1 receptor, inhibits food intake, and reduces plasma levels of ghrelin [24].

- *Endocannabinoid genes*: endocannabinoid system controls food intake through both central and peripheral mechanisms. CB1 and CB2, the cannabinoid receptors, are expressed in multiple brain regions that control food intake [37]. Genetic variants in *CNR1* and *CNR2* genes, influence food intake and body weight and they have been associated to AN [38]. Systemic and local administrations in animals of both exogenous cannabinoids (i.e. THC) and endocannabinoids (i.e. AEA, 2-AG) increase food intake [39]. CB1 receptor antagonists are hypophagic and reduce body weight [40]. Cannabidiol, quite the opposite, can prevent the hyperphagic effect induced by the CB1 receptor agonist [41-42]. Genetic variants in *CNR1*, which encodes the CB1 receptor, are related to the susceptibility to AN. The basis of the non-Mendelian inheritance of AN could be associated with *CNR1* (AAT)n trinucleotide repeats, but functional studies are needed to prove the differential effect [43].

  Anandamide, also known as arachidonoylethanolamine (AEA) plays a key role in feeding behaviour generating pleasure after food consumption [44]. Plasma levels of this lipid mediator are downregulated in AN patients [45].

  In fact, anandamide binds to CB1R and inhibits neuronal differentiation [46].

  Palmitoylethanolamide (PEA) binds the cannabinoid-like G-coupled receptors GPR55 and GPR119. The anorectic action of exogenous PEA is mediated by transcription factor PPARα in the small intestine [47]. After a high-fat feeding in mouse the concentration of PEA decreases [48]. Plasma PEA concentration increases in AN patients after exposure to a non-favorite meal [49].
- *Vitamin D3:* Vitamin D3 is a steroid hormone whose deficiency, that leads to defects in bone mineralization, has been associated to AN [50-51]. Vitamin D3 modulates peroxisome proliferator-activated receptor gamma (PPARγ), involved in inflammation related to the diet [52]. The role of vitamin D3 in AN might be associated to its ability to regulate neurotrophic factors, guaranteeing neuroprotection and neurotransmission control [53].

By linkage and association studies on AN, chromosomes 1, 2, 4, and 13 were identified as possible regions associated to AN. The analyzed genes were associated to neural signaling, either by neurotransmitters or by hormones affecting the satiety regulatory system in subcortical structures of the brain, such as the hypothalamus. However, the small sample size of these type of studies was a limit and meta-analyses gived disaccord evidence [5].

Several GWAS for the identification of genetic variations related to the disorder were conducted on AN. Until 2019 a single genome-wide locus on chromosome 12 (lead SNP: rs4622308) related to AN was identified in a region that regard also diabetes mellitus type 1 and autoimmune disorders. Interestingly, successively the Anorexia Nervosa Genetics Initiative (ANGI) the Genetic Consortium for Anorexia Nervosa (GCAN), and the Wellcome Trust Case Control Consortium-3 (WTCCC-3) along with UK Biobank have detected eight chromosomal regions, comprising 120 genes, significantly associated with AN. Analyses in silico and research by available large-scale in vitro data have revealed that four of the genes of these chromosome regions might be more likely to be associated to the AN etiology: *CADM*1, *MGMT*, *FOXP1*, and *PTBP2* [8, 16, 17]. Interestingly, Hinney et al. (2017) [53] described three significantly altered loci correlating AN risk with increased BMI. The genes associated to those loci are *CTBP2*, *CCNE1*, *CARF* and *NBEAL1* [54]. In a large screening of 152 candidate genes by GWAS rare variants associated to AN were identified in *EPHX2* that encodes a protein involved in cholesterol metabolism. Moreover, variants in *ESR2*, encoding the estrogen receptor 2, can be associated with AN in female [55].However, at the base of the limits of these studies there are several factors, such as the winner's curse, small sample size, moderator variables explaining and lack of heterogeneity of the cohorts [4, 8]. Anyway, the results of these GWAS showed that AN is highly polygenic.

By whole genome sequencing and linkage analysis to analyze two families with recurrence of eating disorders, were detected a missense variant cosegregating with the affected family members in *ESRRA*, and a potentially damaging variant in *HDAC4* (histone deacetylase 4) that play a significant role in the estrogen system. transcriptional studies revealed that expression of the *HDAC*4 deacetylase repressed the transcription of ESRRA- induced target genes, whereas *ESRRA* and *HDAC4* exhibited interaction in both in vivo and in vitro studies. For which variants in *ESRRA* and *HDAC4* cause a decrease in the activity of ESRRA and an increase in the likelihood of AN onset [56].

By familial whole-exome analysis, were been identified variants of *NNAT* in two male AN probands: one nonsense variant (p.Trp33*) and one rare variant in the 5′UTR. Moreover, by a large screening were identified 11 *NNAT* variants in AN patients (40% male and 6% female) [57].

In an another whole-exome sequencing study were identified genes carrying damaging variants belonged to

three pathways: (a) neuropeptide hormone signaling, (b) inflammatory pathway, and (c) cholinergic neurotransmission [58].

Recently, have been sequenced the whole exome of one family and found three ultra-rare deleterious variants of *DRD4*, *NMS*, and *CCKAR*, linked with the reward pathway, in three affected members. In the other study, the authors identified de novo variants in *CSMD1*, *CREB3*, *PTPRD* and *GAB1* involved in the dopamine pathway and neuron differentiation [59, 60].

Epigenetic mechanism may help initiate and maintain AN. Frieling et al. described higher levels of methylation in the promotors of DAT1 (dopamine active transporter 1) and DRD2 (dopamine receptor D2) in AN patients. Other study linked AN weight loss to hypermethylation and reduced expression of *POMC* [61].

Bulimia nervosa

Twin studies have yielded heritability estimates for BN ranging from 28% to 83% [14, 15]. As for AN, specific biological systems are involved in BN.

- *Serotonergic genes*: As with AN, BN patients develop an egosyntonic personality and is associated with other psychiatric diseases, moreover medications acting over 5-HT pathways are efficacy over BN patients, so it is conceivable role of serotonergic system dysfunction in eating disorders onset and progression [62]. Abnormalities in peripheral 5-HT uptake have been observed in BN patients [63]. As with AN, most genetic studies of the 5-HT system in BN have focused on the *5-HTTLPR* transporter gene and the *5-HT2A* receptor gene [64]. However, there are conflicting results on the involvement of this route on the BN [19].
- *Dopaminergic genes:* The dopaminergic system has also been of interest in the pathophysiology of BN, in fact abnormalities in DA system have been observed through neuroimaging investigations [65]. Mesocorticolimbic dopaminergic alterations correlate with an high physical activity in BN patients and can trigger a dopamine-dependent stress response. The dopaminergic system modulates thinking processes, reward, emotional behavior, substance dependence, feeding and motor activity. Dopamine (DA) is a catecholamine that acts primly through of two G protein-coupled DA, D1 (D1R) and D2 (D2R) receptors. DA has been implicated in the pathophysiology of AN by preclinical and clinical evidence. A gene that plays an important role in the dopamine system is *DAT1* that encodes a transmembrane protein that regulates dopamine reuptake from synapses and possesses variable number of tandem repeats (VNTRs) in its 3'-untranslated region (3'-UTR). Polymorphisms in the number of repeats influence *DAT*1 expression (VNTR 10R/9R). The TaqIA restriction endonuclease site in *DRD2* (rs1800497) has been shown to reduce the density of D2 autoreceptors in the striatum. Moreover, the rs6280 variant in *DRD3* increases the affinity for endogenous dopamine. Recently, it has been demonstrated that AN patients carrying the homozygous variant Gly9Gly genotype in the dopamine D3 receptor have worse symptomatology [66].
- *Opioid genes:* opioid peptides play a key role in feeding behaviour generating motivation and pleasure in food consumption, so it is likely to believe that opioid genes also play a decisive role in BN [43]. In fact, some reward-related brain dysfunctions have been described also on rodent animal models of BN by affecting also opioid levels [67]. The bulimia treatment with naloxone that is an opioid receptor blocker is very effective [68].
- *Appetite Regulation Genes*: Although appetite regulation genes are genetic candidates to BN, studies thus far have been limited as compared to AN studies. Polymorphisms in ghrelin and its receptor *GHS-R1a* are not associated with bulimia [69].

Although leptin modulate reward-related behavior that has a relationship with BN, currently conflicting results were obtained on the association of reward learning and plasma leptin levels in BN. However, a positive correlation of plasma leptin levels and BMI in subjects with BN has been described. The plasma leptin levels are restored in remitted BN patients and are a relevant factor for remission [70]. Finally, serum levels of PYY hormone are decreased in BN patients compared with AN patients [71]. Anyway, basal plasma PYY levels increase in the phases of abstinence from binge eating and vomiting to return to control levels after recovery in BN. However, fasting plasma PYY levels during symptomatic phase of BN were unchanged. BN patients have impaired secretion of CKK that is a satiety factor and PYY secretion inductor. Hence, depressed PYY levels may result from reduced CCK secretion. Moreover, there is a negative correlation between PYY increase and ghrelin decrease. For which a pathway involving peripheral hormonal signals, such as ghrelin and PYY, may be related to BN [72]. GLP-1 secretory decrease was detected in BN patients being this concurrence limited to binge-eating and vomiting episodes [73].

- *Endocannabinoid genes*: the endocannabinoid system plays an important role in the control
- of BN by acting via central and peripheral mechanisms. *FAAH* and *CNR1* polymorphisms have been associated to BN, but not found a synergistic effect of the two polymorphisms in BN. An association of a *CNR2* polymorphism with BN has also been identified [74].
- *Vitamin D3*: BN patients can show severe hypovitaminosis D3 responsible for lack of inflammatory response and reduction in mood in patients with long-term eating disorders.

Many linkage and candidate gene studies of BN have been conducted but have provided few definitive conclusions. Interestingly, in a linkage study of 308 families with BN a suggestive peak of linkage on chromosome 10p13-12 already associated to obesity was been identified. This linkage value increased in families with BN and self-induced vomiting [75].

By a GWAS three polymorphism for *HTR2A* have been associated with poor treatment response in BN patients [76].

Binge-eating disorder

Twins' studies have showed that the heritability of BED is 41-57% [15]. BED, obesity, and weight-related co-morbidities are genetically correlated [77].
Specific biological systems are involved also in BED.

- *Serotonergic Genes*: Polymorphisms of three serotonergic genes, *5-HTT, 5-HT2C* and *5-HT2A* have been investigated in BED [78]. In particular, important results were found by Monteleone et al., who analyzed the *5-HTTLPR* polymorphism of the *5-HTT* gene more frequent in obese people with BED [69, 78].
- *Dopaminergic genes*: Several studies have been examined the role of polymorphisms of 6 dopaminergic genes in BED: *DRD2, ANKK1, OPRM1, COMT, DAT1*, and *DRD3* [76]. In particular, the polymorphism Taq1A of *DRD2* in BED patients is associated to higher reward sensitivity and obesity [78-80].
- *Opioid genes*: The opioid antagonists treatment decrease intake of fat and sucrose diets and suppress palatable food intake [81]. Interestingly, in rat BED model, memantine treatment blocks the compulsivity associated with the intake of the highly palatable food [82].
- *Appetite Regulation Genes*: Serum levels of PYY hormone are decreased in BED compared with AN [71].
- *Other Genes*: Several polymorphisms of 8 other genes in BED have been investigated: *GR, MC4R, BDNF, prepro-NPY, prepro-GHRL, FAAH, FTO* and *CLOCK*. A significant association was found between the polymorphism rs6198 within exon 9 beta of *NR3C1*and BED [78].

In a GWAS 15 polymorphisms in *HTR2A*, a gene implicated in appetite process and satiety, have been analyzed in BED and the polymorphism rs2296972 in *HTR2A* has been associated with trend level of less likelihood of BED [76].
In conclusion, several genetic factors contribute to the etiology of eating disorders. The genetic studies show that while there are great genetic similarities between AN, BN and BED, there are also notable differences. Anyway, it is important a correct diagnosis also genetic because eating-disorders have a deep social impact and an enormous cost to public healthcare systems [83]. An important goal for clinical care of eating disorders is obtaining individual-level genetic information for improving management of the patients. Indeed, a precise genetic diagnosis of eating disorders is complicated by the fact that a complex and dynamic interplay between environmental factors, epigenetic marks, and genetic predisposition is involved in the development of these disorders. Gene variants identification in known genes and novel candidate genes identification are necessary. The limited success of genetic studies so far may also result from a focus on symptoms of the disorders, rather than the causes of them. Currently, it's possible integrating basic scientific understanding of the role of genetic risk in eating disorders into clinical practice and the ability to identify genetic markers of risk could allow for early screening in those at high risk. By genetic analysis can be obtained results to pursue to examine treatment response. Findings can also be included in multifactorial risk estimation algorithms that account for other genetic factors, such as rare variants, and environmental risk factors to improve prediction. Moreover, the use of animal models to determine genetic influences on feeding can improve understanding of genes that might represent novel pharmacotherapeutic targets for eating disorders. It is clear that there is a need for a specific and comprehensive molecular diagnostic test with optimal performance for the diagnosis of eating disorders. In this scenario, the usefulness of next-generation sequencing technology arises. It would be useful to use a molecular test that may include genes that have been found to carry polymorphisms conferring a higher susceptibility to the onset of eating disorders, genes that have been found to carry rare variants in eating disorders patients for whom segregation analysis has been performed, genes associated with syndromes presenting eating disorders among their main features and genes that have been found to carry polymorphisms conferring a higher susceptibility to the onset of disorders of food intake [16]. The UK Biobank (ukbiobank.ac.uk) is a unique epidemiological resource to improve prevention, diagnosis, and treatment of psychiatric and somatic illnesses [84]. Recently, it has been processed the Eating Disorders Genetic Initiative (EDGI) designed to expand genomic discovery across the three major eating disorders, AN, BN and BED, that represents the largest genetic study of eating disorders ever to be conducted and it builds on the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED and ANGI) studies. The data that EDGI regard the genetic factors influencing stability versus fluctuation of eating disorder clinical presentation and precision-medicine questions regarding identification of optimal interventions informed by genotype [85]. Therefore, ever new scientific efforts are underway to identify the genetic basis of eating disorders and to develop better eating disorders patient management.

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

Matteo B: study conception, editing and critical revision of the manuscript; Kevin D, MRC, Kristjana D, GB, MCM, GM, VP, SX, Marsida B, DB, TB: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

References

[1] Fichter MM, Quadflieg N. Mortality in eating disorders - results of a large prospective clinical longitudinal study. Int J Eat Disord 2016;49:391-401. https://doi.org/10.1002/eat.22501

[2] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Washington DC: American Psychiatric Publishing 2013

[3] Ceccarini MR, Precone V, Manara E, Paolacci S, Maltese PE, Benfatti V, Dhuli K, Donato K, Guerri G, Marceddu G, Chiurazzi P, Dalla Ragione L, Beccari T, Bertelli M. A next generation sequencing gene panel for use in the diagnosis of anorexia nervosa. Eat Weight Disord 2022;27:1869-80. https://doi.org/10.1007/s40519-021-01331-0

[4] Watson HJ, Palmos AB, Hunjan A, Baker JH, Yilmaz Z, Davies HL. Genetics of eating disorders in the genome-wide era. Psychol Med 2021;51:2287-97. https://doi.org/10.1017/S0033291720005474

[5] Himmerich H, Bentley J, Kan C, Treasure J. Genetic risk factors for eating disorders: an update and insights into pathophysiology. Ther Adv Psychopharmacol 2019;9:2045125318814734. https://doi.org/10.1177/2045125318814734

[6] Yao S, Larsson H, Norring C, Birgegård A, Lichtenstein P, D'Onofrio BM, Almqvist C, Thornton LM, Bulik CM, Kuja-Halkola R. Genetic and environmental contributions to diagnostic fluctuation in anorexia nervosa and bulimia nervosa. Psychol Med 2021;51:62-9. https://doi.org/10.1017/S0033291719002976

[7] Wray NR, Lin T, Austin J, McGrath JJ, Hickie IB, Murray GK, Visscher PM. From Basic Science to Clinical Application of Polygenic Risk Scores: A Primer. JAMA Psychiatry 2021;78:101-9. https://doi.org/10.1001/jamapsychiatry.2020.3049

[8] Watson HJ, Yilmaz Z, Thornton LM, Hübel C, Coleman JRI, Gaspar HA, Bryois J, Hinney A, Leppä VM, Mattheisen M, Medland SE, Ripke S, Yao S, Giusti-Rodríguez P; Anorexia Nervosa Genetics Initiative, Hanscombe KB, Purves KL; Eating Disorders Working Group of the Psychiatric Genomics Consortium, Adan RAH, Alfredsson L, Ando T, Andreassen OA, Baker JH, Berrettini WH, Boehm I, Boni C, Perica VB, Buehren K, Burghardt R, Cassina M, Cichon S, Clementi M, Cone RD, Courtet P, Crow S, Crowley JJ, Danner UN, Davis OSP, de Zwaan M, Dedoussis G, Degortes D, DeSocio JE, Dick DM, Dikeos D, Dina C, Dmitrzak-Weglarz M, Docampo E, Duncan LE, Egberts K, Ehrlich S, Escaramís G, Esko T, Estivill X, Farmer A, Favaro A, Fernández-Aranda F, Fichter MM, Fischer K, Föcker M, Foretova L, Forstner AJ, Forzan M, Franklin CS, Gallinger S, Giegling I, Giuranna J, Gonidakis F, Gorwood P, Mayora MG, Guillaume S, Guo Y, Hakonarson H, Hatzikotoulas K, Hauser J, Hebebrand J, Helder SG, Herms S, Herpertz-Dahlmann B, Herzog W, Huckins LM, Hudson JI, Imgart H, Inoko H, Janout V, Jiménez-Murcia S, Julià A, Kalsi G, Kaminská D, Kaprio J, Karhunen L, Karwautz A, Kas MJH, Kennedy JL, Keski-Rahkonen A, Kiezebrink K, Kim YR, Klareskog L, Klump KL, Knudsen GPS, La Via MC, Le Hellard S, Levitan RD, Li D, Lilenfeld L, Lin BD, Lissowska J, Luykx J, Magistretti PJ, Maj M, Mannik K, Marsal S, Marshall CR, Mattingsdal M, McDevitt S, McGuffin P, Metspalu A, Meulenbelt I, Micali N, Mitchell K, Monteleone AM, Monteleone P, Munn-Chernoff MA, Nacmias B, Navratilova M, Ntalla I, O'Toole JK, Ophoff RA, Padyukov L, Palotie A, Pantel J, Papezova H, Pinto D, Rabionet R, Raevuori A, Ramoz N, Reichborn-Kjennerud T, Ricca V, Ripatti S, Ritschel F, Roberts M, Rotondo A, Rujescu D, Rybakowski F, Santonastaso P, Scherag A, Scherer SW, Schmidt U, Schork NJ, Schosser A, Seitz J, Slachtova L, Slagboom PE, Slof-Op 't Landt MCT, Slopien A, Sorbi S, Świątkowska B, Szatkiewicz JP, Tachmazidou I, Tenconi E, Tortorella A, Tozzi F, Treasure J, Tsitsika A, Tyszkiewicz-Nwafor M, Tziouvas K, van Elburg AA, van Furth EF, Wagner G, Walton E, Widen E, Zeggini E, Zerwas S, Zipfel S, Bergen AW, Boden JM, Brandt H, Crawford S, Halmi KA, Horwood LJ, Johnson C, Kaplan AS, Kaye WH, Mitchell JE, Olsen CM, Pearson JF, Pedersen NL, Strober M, Werge T, Whiteman DC, Woodside DB, Stuber GD, Gordon S, Grove J, Henders AK, Juréus A, Kirk KM, Larsen JT, Parker R, Petersen L, Jordan J, Kennedy M, Montgomery GW, Wade TD, Birgegård A, Lichtenstein P, Norring C, Landén M, Martin NG, Mortensen PB, Sullivan PF, Breen G, Bulik CM. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet 2019;51:1207-14. https://doi.org/10.1038/s41588-019-0439-2

[9] Cuesto G, Everaerts C, León LG, Acebes A. Molecular bases of anorexia nervosa, bulimia nervosa and binge eating disorder: shedding light on the darkness. J Neurogenet 2017;31:266-87. https://doi.org/10.1080/01677063.2017.1353092

[10] Galusca B, Prévost G, Germain N, Dubuc I, Ling Y, Anouar Y, Estour B, Chartrel N. Neuropeptide Y and a-MSH circadian levels in two populations with low body weight: Anorexia nervosa and constitutional thinness. PLoS One 2015;10:e0122040. https://doi.org/10.1371/journal.pone.0122040

[11] Park JH, Shim HM, Na AY, Bae JH, Im SS, Song DK. Orexin A regulates plasma insulin and leptin levels in a time-dependent manner following a glucose load in mice. Diabetol 2015;58:1542-50. https://doi.org/10.1007/s00125-015-3573-0

[12] Zhou Y, Kreek MJ. Persistent increases in rat hypothalamic POMC gene expression following chronic withdrawal from chronic "binge" pattern escalating-dose, but not steady-dose, cocaine. Neuroscience 2015;289:63-70. https://doi.org/10.1038/npp.2011.97

[13] Burmester V, Nicholls D, Buckle A, Stanojevic B, Crous-Bou M. Review of eating disorders and oxytocin receptor polymorphisms. J Eat Disord 2021;9:85. https://doi.org/10.1186/s40337-021-00438-0

[14] Strober M, Freeman R, Lampert C, Diamond J, Kaye W. Controlled family study of anorexia nervosa and bulimia nervosa: evidence of shared liability and transmission of partial syndromes. Am J Psychiatry 2000;157:393-401. https://doi.org/10.1176/appi.ajp.157.3.393

[15] Munn-Chernoff MA, Baker JH. A primer on the genetics of comorbid eating disorders and substance use disorders. Eur Eat Disord Rev 2016;24:91-100. https://doi.org/10.1002/erv.2424

[16] Paolacci S, Kiani AK, Manara E, Beccari T, Ceccarini MR, Stuppia L, Chiurazzi P, Dalla Ragione L, Bertelli M. Genetic contributions to the etiology of anorexia nervosa: New perspectives in molecular diagnosis and treatment. Mol Genet Genomic Med 2020;8:e1244. https://doi.org/10.1002/mgg3.1244

[17] Yokokura M, Terada T, Bunai T, Nakaizumi K, Kato Y, Yoshikawa E, Futatsubashi M, Suzuki K, Yamasue H, Ouchi Y. Alterations in serotonin transporter and body image-related cognition in anorexia nervosa. Neuroimage Clin 2019;23:101928. https://doi.org/10.1002/mgg3.1244

[18] Boehm I, Walton E, Alexander N, Batury VL, Seidel M, Geisler D, King JA, Weidner K, Roessner V, Ehrlich S. Peripheral serotonin transporter DNA methylation is linked to increased salience network connectivity in females with anorexia nervosa. J Psychiatry Neurosci 2020;45:206-13. https://doi.org/10.1503/jpn.190016

[19] Trace SE, Baker JH, Peñas-Lledó E, Bulik CM. The genetics of eating disorders. Annu Rev Clin Psychol 2013;9:589-620. https://doi.org/10.1146/annurev-clinpsy-050212-185546

[20] Compan V. Serotonin 4 Receptors: A Cornerstone in anorexia nervosa? Autism Open Access 2017;7:207. https://doi.org/10.4172/2165-7890.1000207

[21] Brown KM, Bujac SR, Mann ET, Campbell DA, Stubbins MJ, Blundell JE. Further evidence of association of OPRD1 &

HTR1D polymorphisms with susceptibility to anorexia nervosa. Biol Psychiatry 2007;61:367-73. https://doi.org/10.1016/j.biopsych.2006.04.007

[22] Boraska V, Franklin CS, Floyd JA. A genome-wide association study of anorexia nervosa. Mol Psychiatry 2014;19:1085-94. https://doi.org/10.1038/mp.2013.187

[23] Duncan L, Yilmaz Z, Gaspar H, Walters R, Goldstein J, Anttila V, Bulik-Sullivan B, Ripke S; Eating Disorders Working Group of the Psychiatric Genomics Consortium, Thornton L, Hinney A, Daly M, Sullivan PF, Zeggini E, Breen G, Bulik CM. Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. Am J Psychiatry 2017;174:850-8. https://doi.org/10.1176/appi.ajp.2017.16121402

[24] Perry B, Wang Y. Appetite regulation and weight control: The role of gut hormones. Nutr Diabetes 2012;2:e26. https://doi.org/10.1038/nutd.2011.21

[25] Blauwhoff-Buskermolen S, Langius JA, Heijboer AC, Becker A, de van der Schueren MA, Verheul HM. Plasma ghrelin levels are associated with anorexia but not cachexia in patients with NSCLC. Front Physiol 2017;8:119. https://doi.org/10.3389/fphys.2017.00119

[26] Steiner AA, Romanovsky AA. Leptin: At the cross- roads of energy balance and systemic inflammation. Prog Lipid Res 2007;46:89-107. https://doi.org/10.1016/j.plipres.2006.11.001

[27] Föcker M, Timmesfeld N, Scherag S, Bühren K, Langkamp M, Dempfle A, Sheridan EM, de Zwaan M, Fleischhaker C, Herzog W, Egberts K, Zipfel S, Herpertz-Dahlmann B, Hebebrand J. Screening for anorexia nervosa via measurement of serum leptin levels. J Neural Transm (Vienna) 2011;118:571-8. https://doi.org/10.1007/s00702-010-0551-z

[28] Monteleone P, Matias I, Martiadis V, De Petrocellis L, Maj M, Di Marzo V. Blood levels of the endocannabinoid anandamide are increased in anorexia nervosa and in binge-eating disorder, but not in bulimia nervosa. Neuropsychopharmacology 2005;30:1216-21. https://doi.org/10.1038/sj.npp.1300695

[29] Monteleone P, Fabrazzo M, Tortorella A, Fuschino A, Maj M. Opposite modifications in circulating leptin and soluble lep- tin receptor across the eating disorder spectrum. Mol Psychiatry 2002;7:641-6. https://doi.org/10.1038/sj.mp.4001043

[30] Karra E, Chandarana K, Batterham RL. The role of peptide YY in appetite regulation and obesity. J Physiol 2009;587:19-25. https://doi.org/10.1113/jphysiol.2008.164269

[31] De Silva A, Bloom SR. Gut hormones and appetite control: A focus on PYY and GLP-1 as therapeutic targets in obesity. Gut Liver 2012;6:10-20. https://doi.org/10.5009/gnl.2012.6.1.10

[32] Lenka A, Arumugham SS, Christopher R, Pal PK. Genetic substrates of psychosis in patients with Parkinson's disease: A critical review. J Neurol Sci 2016;364:33-41. https://doi.org/10.1016/j.jns.2016.03.005

[33] Cuntz U, Enck P, Frühauf E, Lehnert P, Riepl RL, Fichter MM, Otto B. Cholecystokinin revisited: CCK and the hunger trap in anorexia nervosa. PloS One 2013;8:e54457. https://doi.org/10.1371/journal.pone.0054457

[34] Richard JE, Farkas I, Anesten F. GLP-1 receptor stimulation of the lateral parabrachial nucleus reduces food intake: Neuroanatomical, electrophysiological, and behavioral evidence. Endocrinology 2014;155:4356-67. https://doi.org/10.1210/en.2014-1248

[35] Tomasik PJ, Sztefko K, Starzyk J, Rogatko I, Szafran Z. Entero-insular axis in children with anorexia nervosa. Psychoneuroendocrinology 2005;30:364-72. https://doi.org/10.1016/j.psyneuen.2004.10.003

[36] González LM, García-Herráiz A, Mota-Zamorano S, Flores I, Albuquerque D, Gervasini G. Variability in cannabinoid receptor genes is associated with psychiatric comorbidities in anorexia nervosa. Eat Weight Disord 2021;26:2597-606. https://doi.org/10.1007/s40519-021-01106-7

[37] González LM, Mota-Zamorano S, García-Herráiz A, López-Nevado E, Gervasini G. Genetic variants in dopamine pathways affect personality dimensions displayed by patients with eating disorders. Eating and Weight Disorders. Eat Weight Disord 2021;26:93-101. https://doi.org/10.1007/s40519-019-00820-7

[38] Soria-Gómez E, Matias I, Rueda-Orozco PE, Cisneros M, Petrosino S, Navarro L, Di Marzo V, Prospéro-García O. Pharmacological enhancement of the endocannabinoid system in the nucleus ac- cumbens shell stimulates food intake and increases c-Fos expression in the hypothalamus. Br J Pharmacol 2007;151:1109-16. https://doi.org/10.1038/sj.bjp.0707313

[39] Scopinho AA, Guimarães FS, Corrêa FM, Resstel LB. Cannabidiol inhibits the hyperphagia induced by cannabinoid-1 or serotonin-1A receptor agonists. Pharmacol Biochem Behav 2011;98:268-72. https://doi.org/10.1016/j.pbb.2011.01.007

[40] Riedel G, Fadda P, McKillop-Smith S, Pertwee RG, Platt B, Robinson L. Synthetic and plant-derived cannabinoid receptor antagonists show hypophagic properties in fasted and non-fasted mice. Br J Pharmacol 2009;156:1154-66. https://doi.org/10.1111/j.1476-5381.2008.00107.x

[41] McLaughlin PJ, Winston K, Swezey L, Wisniecki A, Aberman J, Tardif DJ, Betz AJ, Ishiwari K, Makriyannis A, Salamone JD. The cannabinoid CB1 antagonists SR 141716A and AM 251 suppress food intake and food-reinforced behavior in a variety of tasks in rats. Behav Pharmacol 2003;14:583-8. https://doi.org/10.1097/00008877-200312000-00002

[42] Siegfried Z, Kanyas K, Latzer Y, Karni O, Bloch M, Lerer B, Berry EM. Association study of cannabinoid receptor gene (CNR1) alleles and anorexia nervosa: dif- ferences between restricting and binging/purging subtypes. Am J Med Genet B Neuropsychiatr Genet 2004;125:126-30. https://doi.org/10.1002/ajmg.b.20089

[43] Fuss J, Steinle J, Bindila L, Auer MK, Kirchherr H, Lutz B, Gass P. A runner's high depends on cannabinoid receptors in mice. Proc Natl Acad Sci USA 2015;112:13105-8. https://doi.org/10.1073/pnas.1514996112

[44] Rueda D, Navarro B, Martinez-Serrano A, Guzman M, Galve-Roperh I. The endocannabinoid anandamide inhibits neuro- nal progenitor cell differentiation through attenuation of the Rap1/B. J Biol Chem 2002;277:46645-50. https://doi.org/10.1074/jbc.M206590200

[45] Hansen HS, Kleberg K,Hassing HA. Non- endocannabinoid N-acylethanolamines and monoacylglycerols: old molecules new targets. In: Di Marzo V, Wang J, eds. The Endocannabinoidome. Amsterdam: Academic Press 2015, pp. 1-13. https://doi.org/10.1016/B978-0-12-420126-2.00001-8

[46] Gaetani S, Kaye WH, Cuomo V, Piomelli D. Role of endocannabinoids and their analogues in obesity and eating disorders. Eat Weight Disord 2008;13:e42–e48.

[47] Clayton P, Hill M, Bogoda N, Subah S, Venkatesh R. Palmitoylethanolamide: A Natural Compound for Health Management. Int J Mol Sci 2021;22:5305. https://doi.org/10.3390/ijms22105305

[48] Monteleone AM, Di Marzo V, Aveta T, Piscitelli F, Dalle Grave R, Scognamiglio P, El Ghoch M, Calugi S, Monteleone P, Maj M. Deranged endocannabinoid responses to hedonic eating in underweight and recently weight-restored patients with anorexia nervosa. Am J Clin Nutr 2015;101:262-9. https://doi.org/10.3945/ajcn.114.096164

[49] Giollo A, Idolazzi L, Caimmi C, Fassio A, Bertoldo F, Dalle Grave R, El Ghoch M, Calugi S, Bazzani PV, Viapiana O, Rossini M, Gatti D. Vitamin D levels strongly influence bone mineral density and bone turnover markers during weight gain in female patients with anorexia nervosa. Int J Eat Disord 2017;50:1041-9. https://doi.org/10.1002/eat.22731

[50] Bella VL, Gizzi G, Albi E, Codini M, Marucci S, Ragione L, Beccari T, Ceccarini MR. Vitamin D3 as possible diagnostic marker of Eating Disorders. EuroBiotech J 2021;5:24-33. https://doi.org/10.2478/ebtj-2021-0005

[51] Tasegian A, Curcio F, Dalla Ragione L, Rossetti F, Cataldi S, Codini M, Ambesi-Impiombato FS, Beccari T, Albi E. Hypovitaminosis D3, leukopenia, and human serotonin transporter polymorphism

in anorexia nervosa and bulimia nervosa. Mediators Inflamm 2016;8046479. https://doi.org/10.1155/2016/8046479

[52] Groves NJ, McGrath JJ, Burne THJ. Vitamin D as a neurosteroid affecting the developing and adult brain. Annu Rev Nutr 2014;34:117-41. https://doi.org/10.1146/annurev-nutr-071813-105557

[53] Hinney A, Kesselmeier M, Jall S, Volckmar AL, Föcker M, Antel J; GCAN; WTCCC3, Heid IM, Winkler TW; GIANT, Grant SF; EGG, Guo Y, Bergen AW, Kaye W, Berrettini W, Hakonarson H; Price Foundation Collaborative Group; Children's Hospital of Philadelphia/Price Foundation, Herpertz-Dahlmann B, de Zwaan M, Herzog W, Ehrlich S, Zipfel S, Egberts KM, Adan R, Brandys M, van Elburg A, Boraska Perica V, Franklin CS, Tschöp MH, Zeggini E, Bulik CM, Collier D, Scherag A, Müller TD, Hebebrand J. Evidence for three genetic loci involved in both anorexia nervosa risk and variation of body mass index. Mol Psychiatry 2015;22:192-201. https://doi.org/10.1038/mp.2016.71

[54] Scott-Van Zeeland AA, Bloss CS, Tewhey R, Bansal V, Torkamani A, Libiger O, Duvvuri V, Wineinger N, Galvez L, Darst BF, Smith EN, Carson A, Pham P, Phillips T, Villarasa N, Tisch R, Zhang G, Levy S, Murray S, Chen W, Srinivasan S, Berenson G, Brandt H, Crawford S, Crow S, Fichter MM, Halmi KA, Johnson C, Kaplan AS, La Via M, Mitchell JE, Strober M, Rotondo A, Treasure J, Woodside DB, Bulik CM, Keel P, Klump KL, Lilenfeld L, Plotnicov K, Topol EJ, Shih PB, Magistretti P, Bergen AW, Berrettini W, Kaye W, Schork NJ. Evidence for the role of EPHX2 gene variants in anorexia nervosa. Mol Psychiatry 2014;19:724-32. https://doi.org/10.1038/mp.2013.91

[55] Cui H, Moore J, Ashimi SS, Mason BL, Drawbridge JN, Han S, Hing B, Matthews A, McAdams CJ, Darbro BW, Pieper AA, Waller DA, Xing C, Lutter M. Eating disorder predisposition is associated with ESRRA and HDAC4 mutations. J Clin Invest 2013;123:4706-13. https://doi.org/10.1172/JCI71400

[56] Sild M, Booij L. Histone deacetylase 4 (HDAC4): A new player in anorexia nervosa? Mol Psychiatry 2019;24:1425-34. https://doi.org/10.1038/s41380-019-0366-8

[57] Lombardi L, Blanchet C, Poirier K, Lebrun N, Ramoz N, Rose Moro M, Gorwood P, Bienvenu T. Anorexia nervosa is associated with Neuronatin variants. Psychiatr Genet 2019;29:103-10. https://doi.org/10.1097/YPG.0000000000000224

[58] Lutter M, Bahl E, Hannah C, Hofammann D, Acevedo S, Cui H, McAdams CJ, Michaelson JJ. Novel and ultra-rare damaging variants in neuropeptide signaling are associated with disordered eating behaviors. PLoS One 2017;12:e0181556. https://doi.org/10.1371/journal.pone.0181556

[59] Bienvenu T, Lebrun N, Clarke J, Duriez P, Gorwood P, Ramoz N. De novo deleterious variants that may alter the dopami- nergic reward pathway are associated with anorexia nervosa. Eat Weight Disord 2019;1:1-8. https://doi.org/10.1007/s40519-019-00802-9

[60] Bienvenu T, Lebrun N, Clarke J, Duriez P, Gorwood P, Ramoz N. Exome sequencing in a familial form of anorexia ner- vosa supports multigenic etiology. J Neural Transm (Vienna) 2019;126:1505-11. https://doi.org/10.1007/s00702-019-02056-2

[61] Steiger H, Thaler L. Eating disorders, gene-environment interactions and the epigenome: Roles of stress exposures and nutritional status. Physiol Behav 2016;162:181-5. https://doi.org/10.1016/j.physbeh.2016.01.041

[62] Kaye WH, Bailer UF, Frank GK, Wagner A, Henry SE. Brain imaging of serotonin after recovery from anorexia and bulimia nervosa. Physiol Behav 2005;86:15-7. https://doi.org/10.1016/j.physbeh.2005.06.019

[63] Steiger H, Bruce KR, Groleau P. Neural circuits, neurotransmitters, and behavior: serotonin and temperament in bulimic syndromes. Curr Top Behav Neurosci 2011;6:125-38. https://doi.org/10.1007/7854_2010_88

[64] Polsinelli GN, Levitan RN, De Luca V. 5-HTTLPR polymorphism in bulimia nervosa: a multiple-model meta-analysis. Psychiatr Genet 2012;22:219-25. https://doi.org/10.1097/YPG.0b013e32835669b3

[65] Berner LA, Winter SR, Matheson BE, Benson L, Lowe MR. Behind binge eating: A review of food-specific adaptations of neurocognitive and neuroimaging tasks. Physiol Behav 2017;176:59-70. https://doi.org/10.1016/j.physbeh.2017.03.037

[66] Kalyanasundar B, Perez CI, Luna A. D1 and D2 antagonists reverse the effects of appetite suppressants on weight loss, food intake, locomotion, and rebalance spiking inhibition in the rat NAc shell. J Neurophysiol 2015;114:585-607. https://doi.org/10.1152/jn.00012.2015

[67] Avena NM, Rada P, Hoebel BG. Underweight rats have enhanced dopamine release and blunted acetylcholine response in the nucleus accumbens while bingeing on sucrose. Neuroscience 2008;156:865-71. https://doi.org/10.1016/j.neuroscience.2008.08.017

[68] Valbrun LP, Zvonarev V. The opioid system and food intake: use of opiate antagonists in treatment of binge eating disorder and abnormal eating behavior. J Clin Med Res 2020;12:41-63. https://doi.org/10.14740/jocmr4066

[69] Monteleone P, Tortorella A, Castaldo E. No association of the Arg51Gln and Leu72Met polymorphisms of the ghrelin gene with anorexia nervosa or bulimia nervosa. Neurosci Lett. 2006;398:325-7. https://doi.org/10.1016/j.neulet.2006.01.023

[70] Homan P, Grob S, Milos G, Schnyder U, Eckert A, Lang U, Hasler G. The role of BDNF, leptin, and catecholamines in reward learning in bulimia nervosa. Int J Neuropsychopharmacol 2014;18:pyu092. https://doi.org/10.1093/ijnp/pyu092

[71] Eddy KT, Lawson EA, Meade C, Meenaghan E, Horton SE, Misra M, Klibanski A, Miller KK. Appetite regulatory hormones in women with anorexia nervosa: Binge-eating/purging versus restricting type. J Clin Psychiatry 2015;76:19-24. https://doi.org/10.4088/JCP.13m08753

[72] Smitka K, Papezova H, Vondra K, Hill M, Hainer V, Nedvidkova J. The role of "mixed" orexigenic and anorexigenic signals and autoantibodies reacting with appetite-regulating neuropeptides and peptides of the adipose tissue-gut-brain axis: relevance to food intake and nutritional status in patients with anorexia nervosa and bulimia nervosa. Int J Endocrinol 2013;2013:483145. https://doi.org/10.1155/2013/483145

[73] Dossat AM, Bodell LP, Williams DL, Eckel LA, Keel PK. Preliminary examination of glucagon-like peptide-1 levels in women with purging disorder and bulimia nervosa. Int J Eat Disord 2015;48:199-205. https://doi.org/10.1002/eat.22264

[74] Scherma M, Fattore L, Castelli MP, Fratta W, Fadda P. The role of the endocannabinoid system in eating disorders: neurochemical and behavioural preclinical evidence. Curr Pharm Des 2014;20:2089-99. https://doi.org/10.2174/13816128113199990429

[75] Mayhew AJ, Pigeyre M, Couturier J, Meyre D. An evolutionary genetic perspective of eating disorders. Neuroendocrinology 2018;106:292-306. https://doi.org/10.1159/000484525

[76] Koren R, Duncan AE, Munn-Chernoff MA, Bucholz KK, Lynskey MT, Heath AC, Agrawal A. Preliminary evidence for the role of HTR2A variants in binge eating in young women. Psychiatr Genet 2014;24:28-33. https://doi.org/10.1097/YPG.0000000000000014

[77] McCuen-Wurst C, Ruggieri M, Allison KC. Disordered eating and obesity: associations between binge-eating disorder, night-eating syndrome, and weight-related comorbidities. Ann N Y Acad Sci 2018;1411:96-105. https://doi.org/10.1111/nyas.13467

[78] Manfredi L, Accoto A, Couyoumdjian A, Conversi D. A systematic review of genetic polymorphisms associated with binge eating disorder. Nutrients 2021;13:848. https://doi.org/10.3390/nu13030848

[79] Davis C, Levitan RD, Kaplan AS, Carter J, Reid C, Curtis C, Patte K, Hwang R, Kennedy JL. Reward sensitivity and the D2 dopamine receptor gene: a case-control study of binge eating disorder. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:620-8. https://doi.org/10.1016/j.pnpbp.2007.09.024

[80] Palacios A, Canto P, Tejeda ME, Stephano S, Luján H, García-García E, Rojano-Mejía D, Méndez JP. Complete sequence of the ANKK1 gene in Mexican-Mestizo individuals with obesity, with or without binge eating disorder. Eur Psychiatry 2018;54:59-64. https://doi.org/10.1016/j.eurpsy.2018.07.010

[81] Naleid AM, Grace MK, Chimukangara M, Billington CJ, Levine AS. Paraventricular opioids alter intake of high-fat but not high-sucrose diet depending on diet preference in a binge model of feeding. Am J Physiol Regul Integr Comp Physiol 2007;293:99.105. https://doi.org/10.1152/ajpregu.00675.2006

[82] Popik P, Kos T, Zhang Y, Bisaga A. Memantine reduces consumption of highly palatable food in a rat model of binge eating. Amino Acids 2011;40:477-85. https://doi.org/10.1007/s00726-010-0659-3

[83] Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: Prevalence, incidence, comorbidity, course, consequences, and risk factors. Curr Opin Psychiatry 2016;29:340-5. https://doi.org/10.1097/YCO.0000000000000278

[84] Hübel C, Abdulkadir M, Herle M, Loos RJF, Breen G, Bulik CM, Micali N. One size does not fit all. Genomics differentiates among anorexia nervosa, bulimia nervosa, and binge-eating disorder. Int J Eat Disord 2021;54:785-793. https://doi.org/10.1002/eat.23481

[85] Bulik CM, Thornton LM, Parker R, Kennedy H, Baker JH, MacDermod C, Guintivano J, Cleland L, Miller AL, Harper L, Larsen JT, Yilmaz Z, Grove J, Sullivan PF, Petersen LV, Jordan J, Kennedy MA, Martin NG. The Eating Disorders Genetics Initiative (EDGI): study protocol. BMC Psychiatry 2021;21:234. https://doi.org/10.1186/s12888-021-03212-3

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