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REVIEW

Eating disorders: the current status of molecular genetic research

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Abstract Anorexia nervosa (AN) and bulimia nervosa (BN) are complex disorders characterized by disordered eating behavior where the patient's attitude towards weight and shape, as well as their perception of body shape, are disturbed. Formal genetic studies on twins and families suggested a substantial genetic influence for AN and BN. Candidate gene studies have initially focused on the serotonergic and other central neurotransmitter systems and on genes involved in body weight regulation. Hardly any of the positive findings achieved in these studies were unequivocally confirmed or substantiated in meta-analyses. This might be due to too small sample sizes and thus low power and/or the genes underlying eating disorders have not yet been analyzed. However, some studies that also used subphenotypes (e.g., restricting type of AN) led to more specific results; however, confirmation is as yet mostly lacking. Systematic genome-wide linkage scans based on families with at least two individuals with an eating disorder (AN or BN) revealed initial linkage regions on chromosomes 1, 3 and 4 (AN) and 10p (BN). Analyses on candidate genes in the chromosome 1 linkage region led to the (as yet unconfirmed) identification of certain variants associated with AN. Genome-wide association studies are under way and will presumably help to identify genes and pathways involved in these eating disorders. The elucidation of the molecular mechanisms underlying eating disorders might improve therapeutic approaches.

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Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are complex eating disorders that are commonly defined by criteria either of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [1] or the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [2]. Formal genetic studies suggest a substantial genetic influence in these disorders [3–6]. Disturbances of neurotransmitter, neuropeptide, and neuroendocrine systems have been reported in acutely ill and patients who have been followed up for several years [7] so that an involvement of these systems in the etiology of eating disorders appears possible. As candidate gene approaches did not unequivocally identify susceptibility genes (alleles) for AN or BN, systematic model-free genome-wide linkage screens have been performed in order to identify unknown genes involved in the etiology of these eating disorders.

Twin and family studies

Twin studies can be powerful, but their methodology is complicated and their results are easily misjudged. Caveats regarding twin studies include ascertainment and power issues [8]. Use of a clinical sample for a twin study usually implies a greater severity of the illness; hence, the genetic loading might be different from that of patients from the general population. Additionally, factors like an equal environment assumption, as well as the generalizability of results need to be considered [9].

Evidence from family and twin studies suggests a substantial genetic contribution to the etiology of both AN and BN [4, 10–15]. Holland et al. [10] showed proband-wise concordance rates for AN of 0.71 for monozygotic twins and 0.1 for dizygotic twins. Heritability estimates based on these rates ranged from 0.86 to 0.98 for AN [11]. Higher concordance rates for monozygotic twins than for dizygotic twins have been shown in most twin studies. However, Walters and Kendler [16] could not detect a genetic component to AN. They analyzed an epidemiological female twin sample ($n = 2{,}163$); only a small number of twins were retrospectively diagnosed with AN. Surprisingly, concordance rates were higher for dizygotic than for monozygotic twins. Interestingly, co-twins of index cases with AN had significantly lower body mass index (BMI in kg/m^2) and higher depression rates than co-twins of unaffected twins. Overlapping of the genetic predisposition to both BN and depression was found in the Virginia twin study [16]. Interestingly, Klump et al. [17] found that genetic effects were significantly more important for disordered eating during mid to late adolescence than during prepubertal adolescence. Puberty may therefore be a critical period to activate some of the genetic factors which make certain individuals more susceptible for the development of eating disorders. Klump et al. [15] identified 26 AN patients by interviewing 672 female 17-year-old twins. Biometrical analyses indicated that genetic and non-shared environmental factors accounted for 74 and 26% of the variance in AN, respectively. Based on data of the Swedish Twin Registry, Bulik et al. [18] estimate the heritability of AN at 56%, with the remaining variance attributable to shared environment (5%) and non-shared environment (39%).

Two controlled family studies have found an average 3% lifetime risk of AN in first-degree relatives of patients, being equivalent to an approximate relative risk of at least 10 [7, 19, 20]. AN was found to be infrequent in 1,831 relatives of 504 patients with eating disorders, whereas full and partial syndromes of these eating disorders aggregated in female relatives of both anorexic and bulimic probands (Strober et al. [21]). Relative risks were 11.3 and 12.3 for the full syndrome of AN in first-degree female relatives of patients with AN or BN, respectively [21], suggesting that specific genes can predispose to both eating disorders. The relative risks for BN were 4.2 and 4.4 for first-degree female relatives of patients with AN or BN, respectively. Overlapping of the genetic predisposition to both BN and depression was found in the Virginia twin study [22]. Interestingly, Klump et al. [17] found that genetic effects were significantly more important for disordered eating during mid to late adolescence than during prepubertal adolescence, accounting for 46% of variance from 14 to 18 years of age versus only 6% of variance at 11 years of age. Puberty may therefore be a critical period to activate some of the genetic factors which make certain individuals more susceptible to the development of eating disorders.

Candidate gene studies

Basically, two approaches are involved in the molecular genetic analysis of a complex phenotype: (1) association studies (case–control studies; Table 1), including genome-wide association studies (GWAS) and (2) family-based linkage studies. Both approaches have in general been used for molecular genetic studies of eating disorders, although GWAS are still lacking. The candidate gene approach relies on genetic, physiological, biochemical or pharmacological evidence to determine the involvement of a specific gene in the analyzed phenotype.

Candidate gene studies in eating disorders need to consider the following clinical observations: (a) the prevalence of AN and BN is considerably higher in females (ratio 9:1). (b) The manifestation periods for both AN and BN are predominantly in puberty and late adolescence, respectively. (c) Approximately 30% of patients with AN later on develop BN; the opposite sequence is less frequent. (d) There is a high rate of comorbidity with obsessive compulsive disorder, major depression and generalized anxiety disorder [7, 23, 24].

In general terms, the lower the numbers of regulatory pathways involved in a complex phenotype, the fewer genes are likely to be involved. An example of such a putative narrow pathway into AN is weight loss-induced dysregulation of the maintenance of a normal body weight, for whatever reason, during the critical age period. If, however, subtle perturbations in several different pathways lead to an eating disorder, greater the heterogeneity and smaller the effect of a predisposing allele is likely to be. Molecular genetic analyses of other complex disorders suggest that the genetic basis underlying eating disorders is polygenic; effect sizes of predisposing alleles are likely to be small [Hebebrand et al., this issue].

Neurobiological disturbances that persist after recovery might be trait-related and thus implicated in the etiology of the disorder. Studies pertaining to long-term follow-up of patients with AN suggest that disturbances of monoaminergic pathways and weight regulation continue after recovery [25–28]. These studies implicate that genes involved in the serotonergic and dopaminergic systems and in weight regulation can be perceived as candidates [29].

Table 1 Summary of candidate genes selected from association studies for AN and BN

Gene	Variant	Test type	Evidence for association to		Study
			AN	BN	
Catechol-*O*-methyltransferase (*COMT*)	Val-158-Met	TDT	Yes	ND	Frisch et al. [66]
	Val-158-Met	TDT	Yes	ND	Michaelovsky et al. [68]
	Val-158-Met	CC	Yes	Yes	Frieling et al. [150]
	Val-158-Met	CC	Yes	No	Mikolajczyk et al. [69]
	Val-158-Met	TDT	No	ND	Gabrovsek et al. [70]
Dopamine D2 receptor (*DRD2*)	TaqA1	CC	Yes	Yes	Nisoli et al. [65]
	−141 Indel	TDT/CC	Yes	ND	Bergen et al. [64]
Dopamine D3 receptor (*DRD3*)	*Bal* I polymorphism in exon 1	CC	No	ND	Bruins-Slot et al. [151]
Dopamine D4 receptor (*DRD4*)	13 bp deletion	TDT	No	ND	Hinney et al. [60]
	48 bp deletion				
	Haplotype exon III VNTR, 120 bp repeat, 521C>T, 809A>G	TDT	Yes	ND	Bachner-Melman et al. [59]
	Exon III VNTR	CC		Yes	Kaplan et al. [63]
	Exon III VNTR	CC	No		Karwautz et al. [61]
Serotonin transporter (*SERT, 5-HTT, SCL6A4*)	5-HTTLPR	CC	No	ND	Sundaramurthy et al. [50]
	5-HTTLPR	CC	Yes	ND	Matsushita et al. [49]
	5-HTTLPR intron 2 VNTR	CC	ND	No	Lauzurica et al. [51]
	5-HTTLPR	Meta-analysis	Yes	ND	Gorwood et al. [52]
	5-HTTLPR	TDT	No	ND	Urwin et al. [55]
	5-HTTLPR	CC	No	ND	Rybakowski et al. [40]
	5-HTTLPR	CC	No	Yes	Di Bella et al. [152]
	5-HTTLPR	CC	Yes	ND	Fumeron et al. [153]
	5-HTTLPR	CC	No	ND	Hinney et al. [48]
5-HT$_{1B/1D\beta}$ receptor	821G>C	CC	Yes	ND	Levitan et al. [154]
	Phe-124-Cys	CC	No	ND	Hinney et al. [155]
5-HT$_{2A}$ receptor	−1438 G/A	CC	Yes	ND	Rybakowski et al. [40]
	−1438 G/A	CC	No	ND	Ando et al. [42]
	−1438 G/A	CC	No	Yes	Nishiguchi et al. [46]
	−1438 G/A	TDT	No	ND	Gorwood et al. [45]
	−1438 G/A	Meta-analysis	Yes	ND	Gorwood et al. [52]
	−1438 G/A	CC	Yes	No	Nacmias et al. [39]
	−1438 G/A	CC	Yes	ND	Collier et al. [37]
	−1438 G/A	CC	No	ND	Hinney et al. [156]
	−1438 G/A	CC	No	ND	Campbell et al. [44]
	−1438 G/A	CC	Yes	ND	Sorbi et al. [41]
5-HT$_{2A}$ receptor	−1438 G/A	CC	Yes	No	Enoch et al. [38]
	−1438 G/A	CC	No	No	Ziegler et al. [47]
	−1438 G/A	CC	Yes	Yes	Ricca et al. [157]
	−1438 G/A	CC	No	ND	Kipman et al. [96]
	Thr-25-Asn 102T>C, 516C>T, His-452-Tyr	CC	No	ND	Hinney et al. [48]
	Thr-25-Asn 102T>C, His-452-Tyr	CC	No	No	Nacmias et al. [39]
5-HTR$_{3B}$ receptor	Tyr129Ser	CC	Yes	No	Hammer et al. [158]
Norepinephrine transporter gene (*NET, SLC6A2*)	4-bp ins/del in AAGG4 repeat island	TDT	Yes	ND	Urwin et al. [53]
	Epistasis between 4-bp ins/del in AAGG4 repeat island and 5-HTTLPR	TDT	No	ND	Urwin et al. [55]

Table 1 continued

Gene	Variant	Test type	Evidence for association to		Study
			AN	BN	
Leptin	−1387G>A (promoter)	CC	No	No	Hinney et al. [81]
Agouti related protein	526G>A (silent) in linkage disequilibrium with Ala-67-Thr	CC	Yes	ND	Vink et al. [83]
	605C>T (silent)	CC	No		
Pro-opiomelanocortin (*POMC*)	Insertion of 9 bp between codon 73 and 74	CC	No	ND	Hinney et al. [159]
Brain-derived neurotrophic factor (*BDNF*)	−270C>T, Val-66-Met	CC	Yes	ND	Ribasés et al. [105]
	−270C>T, Val-66-Met	CC	Yes	Yes	Ribasés et al. [106]
	−270C>T, Val-66-Met	FBAT	Yes	ND	Ribasés et al. [114]
	−270C>T, Val-66-Met	CC	No	No	Friedel et al. [108]
	−270C>T, Val-66-Met	CC	Yes	ND	Rybakowski et al. [109]
	Val-66-Met	TDT	No	ND	Dardennes et al. [23]
	−270C>T, Val-66-Met	nd		Yes	Kaplan et al. [84]
Neurotrophic tyrosine kinase receptor type 3 (*NTRK3*)	rs7180942	FBAT	Yes	Yes	Mercader et al. [110]
Cannabinoid receptor gene (*CNR1*)	rs1049353 rs2180619 rs806379 rs1535255 rs2023239	TDT/CC	No	ND	Müller et al. [113]
	AAT trinucleotide repeat	ETDT	Yes	ND	Siegfried et al. [43]
Fatty acid amide hydrolase (*FAAH*)	rs932816	TDT	No	ND	Müller et al. [113]
	rs324420 rs324419				
	rs873978 rs2295632				
N-acylethanolamine-hydrolyzing acid amidase (*NAAA*)	rs2292534 rs4859567 rs10518142 rs6819442	TDT	No	ND	Müller et al. [113]
Monoglyceride lipase (*MGLL*)	rs893294	TDT	No	ND	Müller et al. [113]

TDT Transmission disequilibrium test, *CC* case–control study, *ND* no data

Neurotransmitter systems implicated in eating disorders

Serotonergic system

Serotonin (5-hydroxytryptamine; 5-HT) is involved in a broad range of biological, physiological and behavioral functions [30, 31]. The neurotransmitter system includes tryptophan hydroxylase, the 5-HT transporter (SLC6A4 or 5-HTT) and 5-HT receptors. Several lines of evidence implicate the serotonergic system in body weight regulation and more specifically in eating behavior [30–32] and eating disorders [33, 34]. In cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) levels were elevated in long-term weight-restored patients with AN or BN in comparison with controls, suggesting that hyperserotonergic function is a trait marker in eating disorders [35]. The increased serotonergic neurotransmission could also account for characteristic psychopathological features such as perfectionism, rigidity and obsessiveness frequently associated with AN [7, 23]. However, results of most of the molecular genetic studies pertaining to the serotonergic system were negative or equivocal see [36]. Two exceptions should be mentioned:

1. The A-allele of the promoter polymorphism −1438G>A of the *5-HT2A receptor* gene was initially reported to be associated with AN [37]. Some of the subsequent studies confirmed this result [38–41], others did not [42–46]. Additionally, an early meta-

analysis showed lack of association [47]. A later meta-analysis, comprising more studies, showed that a large heterogeneity between samples exists, but the association of the −1438A allele persisted for AN [6]. Hence, the 5-HT2A receptor gene might tentatively be considered as a candidate gene for AN.

2. The promoter region of the serotonin transporter (5-HTTLPR) harbors a functional insertion/deletion polymorphism with two frequent alleles that were designated as short (*S) and long (*L) alleles. The frequency of the 5-HTTLPR *S allele has been assessed in AN [48–50] and BN [51], with conflicting results. A meta-analysis for AN indicates that the *S allele could represent a risk factor for AN [52].

Norepinephrine

In long-term weight-restored patients with AN, lower serum norepinephrine levels than in controls were measured [53]. A repeat polymorphism within the norepinephrine transporter (*SLC6A2* or *NET*) promoter region alters a potential transcription factor binding site therefore presumably entailing altered norepinephrine reuptake. Preferential transmission of the L4 allele was detected in 87 Australian trios each comprising a patient with AN of the restricting type and both biological parents. These results suggested that L4 or a DNA variant in linkage disequilibrium with it doubles the risk to develop this type of AN [53]. Following up on previous studies [48, 53, 54] on single genes, Urwin et al. [55] investigated epistasis between the *5-HTT* and *NET* in AN. However, epistasis between the *5-HTTLPR* and the polymorphism within the *NET* promoter polymorphic region (*NETpPR*) was not observed.

Dopaminergic system

The dopaminergic system has been implicated in the pathophysiology of AN and BN [23, 56, 57]. For example, major symptoms related to AN like repulsion to food, weight loss, hyperactivity, distortion of body image, and obsessive–compulsive behavior have all been related to dopamine activity [58].

Association studies on the role of polymorphisms in the dopamine D4 receptor gene (*DRD4*), mainly the 7-repeat allele of the *DRD4* exon 3 repeat, in AN have yielded positive [59] as well as negative results [60, 61]. The 7-repeat allele is seemingly relevant for binge eating disorder (BED) and BN: Levitan et al. [62] identified an elevated rate of binge eaters in a group of carriers of the 7-repeat allele. A similar finding was reported by Kaplan et al. [63] who showed that the 7-repeat allele of *DRD4* contributes to weight gain in woman with BN. Bergen et al. [64] analyzed seven polymorphisms within the dopamine D2 receptor gene *(DRD2)* and reported nominal association for two of them and AN. However, Nisoli et al. [65] did confirm the association with AN or BN.

The *catechol-O-methyltransferase* gene (*COMT*) catabolizes brain catecholamine neurotransmitters such as dopamine and norepinephrine. An initial study suggested an influence of the Val158Met polymorphism on susceptibility to AN [66]. Data were confirmed in some [67–69] but not all studies [64, 70].

As most of the reported studies on the genetic influence of the dopaminergic system on the etiology of AN and BN did not have sufficient statistical power, these findings require replication in large independent samples or at least in a meta-analytical approach.

Body weight regulation: leptinergic–melanocortinergic system

There has been a tremendous increase in the number of molecular genetic studies pertaining to body weight regulation in the last 15 years see also [Hinney et al.]. Since its discovery in 1994, research has focused on leptin-mediated signaling pathways. Leptin is not only a key hormone implicated in the regulation of energy balance, but it is also a pleiotropic hormone involved in various neuroendocrine and behavioral alterations associated with profound changes in energy storage, including the adaptation of the organism to semi-starvation [71, 72].

Hypoleptinemia is a cardinal feature of acute AN, and in most studies the low leptin levels are typically below those of healthy gender- and age-matched controls and reflect the low fat mass, thus signaling energy depletion to the brain. In most studies, circulating levels of leptin were highly correlated with percent body fat [50, 73–78] and, to a lesser extent, with BMI on referral [26, 39, 50, 73, 76, 78]. In further studies patients who had recovered from eating disorders also had reduced serum leptin levels after adjustment for BMI and/or fat mass [79], suggesting that relative hypoleptinemia might be a trait marker in eating disorders. According to Frey et al. [25] females with a past history of AN (followed up 10-years after in-patient treatment) seemingly have a lower percent body fat and a trend to lower serum leptin levels than BMI-matched controls. However, other studies did not confirm such findings [80].

A mutation analysis of the coding region and part of the promoter region of the leptin gene in patients with AN, followed by case–control studies of the detected polymorphisms, yielded negative results [81]. Leptin receptor gene SNPs also do not appear to be associated with regulation of body weight or with AN [82].

Agouti related peptide (AGRP) is an important orexigenic peptide that regulates energy balance downstream of leptin. AGRP is an endogenous inverse agonist at melanocortinergic receptors and therefore involved in body weight regulation. Loss-of-function mutations in *AGRP* could result in an inadequate starvation signaling in the brain. In patients with AN three polymorphisms were detected in *AGRP*. The Ala67 allele was significantly enriched in patients with AN compared to controls [83]. In contrast, another study [84] observed over-transmission of the other allele (67Thr) to patients with AN (114 AN-trios). Hence, an influence of variations within *AGRP* on the development of AN is currently not shown unequivocally.

Melanocortin-4 receptor

A dominant form of obesity is conferred by mutations in *MC4R* that lead to a reduced receptor function e.g., [85–91]. Obesity has been identified as a risk factor for the development of BN [92]. Accordingly, genotypes predisposing to obesity might be detected more commonly in patients with BN than in controls not selected for body weight. A mutation screen in the *MC4R* of 81 BN patients revealed that a single extremely obese patient had a haploinsufficiency mutation in the *MC4R*. This was the first report on the detection of a validated genotype predisposing to obesity in a patient with BN [93]. Two further studies described that all identified obese carriers of *MC4R* variants were shown to have BED [94–96]. However, Branson et al. [94] included the Ile103 variant of the Val103Ile polymorphism as one of the risk alleles; this allele was however subsequently found to be negatively associated with obesity [95–97]. Furthermore, another study did not detect any *MC4R* mutation among extremely obese adults with BED [98]. Finally, in our own families with a total of 43 *MC4R* mutation carriers we found no evidence for elevated rates of binge eating behavior in carriers of *MC4R* mutations [99]. In conclusion, it is unlikely that BED is strongly associated with *MC4R* mutations.

Brain-derived neurotrophic factor (BDNF)

BDNF acts downstream of the MC4R [100]. It regulates synaptic efficiency through the modulation of key neurotransmitter systems previously shown to be involved in ED. BDNF is expressed in the hypothalamic nuclei associated with weight regulation and feeding control. $Bdnf^{+/-}$ mice show altered eating behavior, increased body weight and hypertrophic adipocytes. Humans with low serum BDNF levels display an aberrant eating behavior [101, 102]. BDNF levels might be involved in the severity of eating disorders (EDs) through the modulation of psychopathological traits that are associated with the ED phenotype [103]. Very recently, Ehrlich et al. [104] measured in acute patients with AN, in addition to hypoleptinemia, reduced peripheral BDNF concentrations. Short-term recovered patients had elevated BDNF levels compared with acutely underweight patients. This might be part of a regenerative process after biochemical and molecular neuronal injury and may also be related to the regulation of appetite and eating behavior [104]. Several studies investigated the role of the *BDNF* non-synonymous polymorphism Val66Met in the etiology of EDs. The 66Met variant was found to be associated with AN restricting type in a Spanish sample [105]. A confirmatory study revealed association with investigated eating disorder subtypes (restricting AN, binge eating/purging AN) in a case–control study of 1,142 Caucasian patients with EDs consecutively recruited in six different centers from five European countries (France, Germany, Italy, Spain and UK) [106]. This finding was replicated by some [39, 107], but not all studies [84, 108, 109]. Beside *BDNF*, association studies of its receptors neurotrophic tyrosine kinase receptor types 2 and 3 (*NTRK2* and *NTRK3*) revealed an association to eating disorders [110, 111]. These data point to the neurotrophin family as key regulators of eating behavior and as potential susceptibility factors for EDs.

Endocannabinoid system

One of the endogenous systems that, due to its therapeutic potential in the treatment of obesity [112], recently reached scientific interest for ED is the endocannabinoid system. Both exogenous and endogenous cannabinoids stimulate food intake through activation of the cannabinoid receptor 1 (CNR1). The central CNR1 as well as the major endocannabinoid degrading enzymes fatty acid amide hydrolase (FAAH), *N*-acylethanolamine-hydrolyzing acid amidase (NAAA) and monoglyceride lipase (MGLL) are implicated in mediating the orexigenic effects of cannabinoids. Initially, Siegfried et al. [43] investigated an (AAT)*n* repeat in the downstream flanking region of *CNR1* and found that the 14-repeat allele was preferentially transmitted in the binge eating/purging AN group but not in the restricting AN group. The 13-repeat allele was slightly more often transmitted in the restricting AN group. As the sample comprised only 52 families, this finding should be viewed with caution in light of the small sample size. A second study on the endocannabinoid system in patients with AN pertained to the previously described (AAT)*n* repeat as well as a total of 15 SNPs in *CNR1*, *FAAH*, *NAAA* or *MGLL* in up to 91 German AN trios. Evidence for association (measured by transmission disequilibrium test) of any of the SNPs or the (AAT)*n* repeat in AN was not detected [113].

Table 2 Linkage studies for eating disorders

Chr	Grice et al. [121] AN sample			Devlin et al. [122] AN sample		Bulik et al. [126] BN sample		Bacanu et al. [125] AN and BN samples			
	Position in cM	Mulitipoint NPL (AN sample)	Mulitipoint NPL (subsample with ANR)	Position in cM	LOD score (covariate obsessionality in AN)	Position in cM	MLS (BN sample)	Position in cM	LOD (AN sample)	Position in cM	LOD (BN sample)
1	NR	NR	NR	202	**1.06**	NR	NR	206	**1.549**	208	**0.773**
2	186	**0.12**	**1.70**	184	**1.12**	NR	NR	134	**0.73**	NR	NR
4	25	**1.42**	**1.82**	22	**1.10**	NR	NR	NR	NR	NR	NR
6	NR	NR	NR	NR	NR	NR	NR	153	**1.052**	179	**0.944**
10	NR	NR	NR	NR	NR	24	**2.70**	NR	NR	NR	NR
10	NR	NR	NR	NR	NR	44	**2.92**	NR	NR	NR	NR
11	NR	NR	NR	NR	NR	NR	NR	136	**0.406**	100	**1.039**
13	NR	NR	NR	29	**1.18**	NR	NR	15	**0.525**	NR	NR
16	22	**0.78**	**1.70**	NR	NR	NR		NR	NR	15	**0.88**

Results were included if at least one signal with a LOD >2 was detected or an initial signal was confirmed or narrowed down in the subanalyses for the same phenotype. Please note that the results of Grice et al. [121], Devlin et al. [122], and Bacanu et al. [125] are based on the same data set of families ascertained via a patient with AN or BN

AN anorexia nervosa, *ANR* anorexia nervosa restricting type, *BN* bulimia nervosa, *cM* centi Morgan, *NPL* nonparametric linkage score, *MLS* multipoint maximum LOD scores, *NR* not reported

Genes with effect on BMI from genome-wide association studies

The neuroendocrine and molecular genetic pathways involved in body weight regulation might also be of major importance for eating disorders as suggested by identified common molecular mechanisms for, e.g., BN and obesity [29, 114, 115]. The first GWAS for BMI and obesity marked the beginning of a new hypothesis-free era to unravel the neurobiological mechanisms involved in body weight regulation e.g., [116–118]. Consequently, a recent report focussed on GWAS-based candidate gene variants [119] to test for association with AN and to investigate a combined effect of BMI-increasing alleles (as derived from the original GWA studies) on the risk of developing AN. However, association between individual SNPs and AN was not detected; combined effects of BMI-increasing alleles were also not found.

Genome-wide linkage studies

Despite considerable efforts hardly any of the candidate gene analyses (exceptions: 5HT2A receptor; BDNF; see Table 2) has yielded unequivocal and clearly confirmed evidence for the involvement of specific alleles in the etiology of eating disorders. The candidate gene approach in eating disorders is hampered by the fact that there is no clear-cut evidence implicating a specific regulatory system. In this situation a systematic genome-wide approach that does not rely on any a priori hypotheses as to the underlying genes offers a useful alternative to detect genes involved in the etiology of eating disorders.

Anorexia nervosa

For AN, an international, multi-site collaborative group (The Price Foundation Collaborative Group) [120] collected a large study group of 196 AN patients and 237 affected relatives [AN, BN or eating disorders not otherwise specified (EDNOS)]. The genome-wide linkage study [121] using 386 microsatellite markers, revealed a single non-significant multipoint nonparametric linkage score (NPL) above 1.5 on chromosome 4. NPL >1 were observed at additional markers on chromosome 4, 11, 13 and 15 [121]. Linkage analysis in a subset ($n = 37$) of families of individuals with restricting AN, the highest multipoint NPL score observed was 3.03, at marker D1S3721 on chromosome 1p. Using the same data set, an additional multipoint affected sibling pair (ASP) linkage analysis was performed specifically devised to incorporate covariates. By exploring seven attributes thought to typify individuals with eating disorders, two variables (drive-for-thinness and obsessionality) were identified, which delimit populations among the ASPs. For both of these traits, or covariates, there were clusters of ASPs who were highly concordant for these

traits. When these covariates were incorporated into the ASP linkage analysis, both jointly and separately, several regions of suggestive linkage were found: one close to genome-wide significance on chromosome 1, chromosome 2 and on chromosome 13. By comparing these results with those implemented using more standard linkage methods, covariates that convey substantial information for the linkage analysis were found [122].

Initial candidate gene analyses pertaining to the linkage region on chromosome 1p36.3–34.3 described above have been published [123, 124]. Linkage analysis of polymorphisms in the serotonin 1D receptor *gene* (*5-HT1DR*) and the opioid delta receptor gene (*OPRD1*) together with 33 microsatellite markers in families including relative pairs concordantly affected with restricting AN ($N = 37$) substantially increased the evidence for linkage of this region to restricting AN. Statistically significant genotypic, allelic, and haplotypic association to AN was observed at *5-HT1DR* and *OPRD1* [123]. Brown et al. [124] conducted an independent association study to replicate this finding. One of 4 genotyped SNPs in *5-HTR1D* supported the hypothesis that the *5-HTR1D* gene is involved in susceptibility to AN, whereas in *OPRD1* 3 out of 6 investigated SNPs were found to be nominally associated to AN [124]. However, further analyses are required to validate these findings. Currently, there is no evidence to suggest that any of the polymorphisms examined has a functional consequence on the biological activity of 5-HT1DR and OPRD1 [124].

The same genome scan for AN was subsequently used to increase the likelihood of finding genetic variation conferring liability to eating disorders. Bacanu et al. [125] measured over 100 attributes thought to be related to liability to eating disorders in affected individuals from multiplex families of two cohorts: one recruited through a proband with AN (AN cohort); the other recruited through a proband with BN (BN cohort, see below). By a multilayer decision process based on expert evaluation and statistical analysis, six traits were selected for linkage analysis: obsessionality (OBS), age at menarche (MENAR) and anxiety (ANX) for quantitative trait locus (QTL) linkage analysis, and lifetime minimum BMI, concern over mistakes (CM) and food-related obsessions (OBF) for covariate-based linkage analysis. Results from the AN cohort were less compelling than those for BN (see below): The investigators detected two suggestive signals (OBS, ANX) for QTL linkage analysis and five suggestive signals (BMI, CM, OBF) for covariate-based linkage analysis. Despite multiple analyses, correction for multiple testing was not performed. Hence, it remains elusive if these peak regions indeed harbor gene variants underlying the genetic susceptibility to AN. Fine mapping or a confirmed positional candidate gene study have not been published yet.

Bulimia nervosa

A linkage analysis on 308 multiplex families with eating disorders that were identified through a proband with BN yielded a double peak, with the highest nonparametric multipoint maximum LOD score (MLS) on chromosome 10 [126]. Linkage analysis was performed in a subset of 133 families in which at least two affected relatives reported a symptom pattern that included self-induced vomiting. The highest linkage peak provided evidence for the presence of a susceptibility locus for BN on chromosome 10p [126]. Interestingly, this region already showed up in full and partial genome scans for obesity [54, 88, 127, 128]; attempts to identify the underlying gene variant(s) have however not led to clear-cut results [129, 130]. Nevertheless, a gene on chromosome 10p might well be involved in both obesity and BN. Another region on 14q met the criterion for genome-wide suggestive linkage for BN at 62 cM from p-ter [126]. The underlying genes for BN have not been described yet.

As described above, Bacanu et al. [125] determined over 100 attributes thought to be related to liability to eating disorders. The BN cohort produced the largest linkage signals, a QTL linkage analysis revealed four suggestive signals for MENAR and ANX; covariate-based linkage analyses revealed both significant and suggestive linkages for BMI, CM and OBF. Overlap between the two cohorts was minimal for substantial linkage signals. To our knowledge, candidate gene analyses for the chromosomal regions identified for BN have not been published yet.

Genome-wide association studies (GWAS)

Within the last 3 years the number of genetic association studies using large numbers of genetic markers (up to 1,000,000) to search for genetic variation underlying common diseases like obesity, diabetes, cardiovascular disease and cancer has increased dramatically. GWAS rely on the assumption that linkage disequilibrium (LD) enables one SNP to act as a surrogate marker for association to other sequence variants in the same region [131]. By genotyping a large number of SNPs, there is a good chance that at least one SNP will be in LD with common functional variant(s) relevant for the investigated phenotype. Genome-wide association studies represent a major step forward in the study of common genetic variation in complex diseases like eating disorders. Until today, several GWAS revealed previously unknown gene-disease associations, e.g., *FTO* and obesity [116, 117]. There are currently no published GWAS for eating disorders. To our knowledge, the first GWAS for AN will be conducted in the nearest future. One study is for instance funded by the

Wellcome Trust and will soon be conducted by the International Wellcome Trust Case Control Consortium (WTCCC3) on 4,000 patients with AN and population-based controls.

Epigenetics

Epigenetic factors are thought to mediate, at least in part, the relationship between the genome and the environment. Research on epigenetic factors underlying eating disorders is at the very beginning. A first study revealed global DNA hypomethylation, but at the same time DNA hypermethylation of the alpha synuclein gene promoter in females with AN [132]. Two further studies investigated whether the mRNA expression of dopaminergic genes or of genes for the peptide hormones vasopressin and atrial natriuretic peptide (*ANP*) are altered in blood of patients suffering from eating disorders. It was also analyzed if these alterations can be explained by changes in the promoter specific DNA methylation of these genes [67, 133]. The primary results in a very small sample ($n = 46$) pointed to a disturbed expression of the dopaminergic genes and *ANP*. Further studies in independent samples are necessary to provide more insight into the epigenetic dysregulation of, e.g., dopaminergic neurotransmission in the pathophysiology of eating disorders.

Eating disorders sub(pheno)types and endophenotypes

The definition of ED sub(pheno)types and endophenotypes and their use for genetic association studies to reduce the heterogeneity in samples based on a clinical diagnostic category has been widely discussed, e.g., [9, 134]. Regarding sub(pheno)types we refer to the findings of Ribases et al. [104, 105, 114] already mentioned above. First studies showed that the 66Met variant of the BDNF Val66Met polymorphism was associated only with the restricting type of AN, whereas it was not associated with AN in general. Hence, a mere analysis of the gene in AN cases versus controls, at the given sample size, would have led to the wrong assumption that the gene is not involved in AN.

Bulik et al. [9] defined endophenotypes as measurable neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological components see also [135]. Additionally, they are heritable, cosegregate with a psychiatric clinical phenotype in the general population, are state independent, and are found in non-affected family members at a higher rate than in the general population [135–137]. Examples of candidate endophenotypes are impaired set-shifting [138], excessive exercise [139], weak coherence [140] or endophenotypes related to temperament like thin-ideal internalization, ineffectiveness, body dissatisfaction and sensitivity to punishment [141]. Specific susceptibility gene variants may underly endophenotypes, which in turn may predispose individuals to develop eating disorders and related conditions. To date standardized definitions for endophenotypes of eating disorders are still missing. As a consequence, results of studies investigating endophenotypes and genetic variants are hard to compare. Thus, their impact may become clearer once studies circumventing methodological flaws like small sample sizes, biases in sample ascertainment (e.g., population stratification) or the testing of multiple subsamples and subphenotypes without addressing the multiple testing issues are performed [142].

Gene × environment interactions

Both genetic and environmental factors contribute to the development of complex diseases like eating disorders. If a genetic factor requires the presence of an environmental factor (or vice versa) to result in increased risk, a situation of gene × environment (G × E) interactions is given. Interacting genetic and environmental factors are distinguished by small to moderate effects. A number of genetic variants might affect several genes influencing vulnerability to eating disorders. As an example, an individual with genetic vulnerability to AN might become ill by exposure to high-risk environments like figure skating or fashion shows. While both the current knowledge on genetic risk factors and on environmental risk factors has been excellently reviewed previously [143] the knowledge on G × E is limited. To our knowledge, no studies have yet reported distinct findings on G × E interactions in eating disorders. In part this may be due to design challenges of G × E studies reviewed in [144, 145]. Following Dempfle et al. [144], the investigation of G × E interactions may be more rewarding for the detailed characterization of identified disease genes (i.e., at advanced stages of genetic research) as strong G × E interactions may have also contributed to the detection of the gene itself. To date, variations in the *5-HT2A* receptor gene as well as in the *BDNF* gene represent the most consistently supported genetic findings for eating disorders. As their genetic impact on the etiology of ED was solidly shown, they are presumably the best candidates to investigate interactions with environmental factors. In the future, this list will likely expand once the first large scale GWAS for eating disorders are conducted. Ideally, genetic research will help to improve the understanding of environmental risk factors for eating disorders [15, 143].

Conclusions and research directions

Similar to other complex disorders, genome-wide linkage studies for eating disorder have not led to unequivocally confirmed genes involved in these disorders. The same holds true for the candidate gene studies summarized above, which were often based on samples of small to moderate size. Variations in the *5-HT2A* receptor gene as well as the Val66Met variant in BDNF might represent the first exceptions from this rule. Inadequate power to detect associations with small effect sizes and multiple post hoc comparisons are the most common and obvious reasons for contradictory findings. One has to bear in mind that eating disorders likely have a polygenic etiology, each gene having a relatively small effect. To address this issue, large-scaled meta-analyses or studies of sufficient sample size and more stringent significance levels [146] are needed. Recent success of genetic research into other psychiatric disorders [147] has demonstrated that large sample sizes encompassing several thousands of cases and controls are required to identify and validate molecular genetic findings.

Studies which focus on subphenotypes (e.g., restricting type of AN) may lead to more specific results see [104, 105, 114]. These findings will also require additional independent confirmations, but still they also show the value of carefully selected study groups and equally carefully derived candidate genes. The analyses of GWAS data will benefit from the candidate genes analyses performed so far. Although these analyses were mainly equivocal the list of analyzed genes for eating disorders can and will be used for the GWAS. These genes will be specifically and thoroughly analyzed in a complementary hypothesis-driven approach. Regarding body weight regulation, we might soon gain a deeper insight into the molecular mechanisms due to the success of large-scaled GWAS, e.g., [(Hinney et al., this issue), 118, 148]. Furthermore, it can also be expected that some of the gene variants predisposing to obesity will play a role in the genetic susceptibility to eating disorders [29, 119].

In sum, GWAS have been a very successful tool for the identification of genes involved in various complex disorders and phenotypes, e.g., reviewed in [149]. The first GWAS for eating disorders are in progress and the results are eagerly awaited. Meanwhile, it is of crucial importance to recruit further patients with eating disorders in order to be in a solid position to confirm potential GWAS signals. In particular genes identified by epigenetic studies as well as studies focusing on well-defined endophenotypes will become more important to elucidate the etiology of eating disorders and to ultimately develop new treatment strategies.

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