Genetic Variation and Effects on Human Eating Behavior

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Abstract

Feeding is a physiological process, influenced by genetic factors and the environment. In recent years, many studies have been performed to unravel the involvement of genetics in both eating behavior and its pathological forms: eating disorders and obesity. In this review, we provide a condensed introduction on the neurological aspects of eating and we describe the current status of research into the genetics of eating behavior, primarily focused on specific traits such as taste, satiation, and hunger. This is followed by an overview on the genetic studies done to unravel the heritable background of obesity and eating disorders. We examine the discussion currently taking place in the field of genetics of complex disorders and phenotypes on how to perform good and powerful studies, with the use of large-scale whole-genome association studies as one of the possible solutions. In the final part of this review, we give our view on the latest developments, including endophenotype approaches and animal studies. Studies of endophenotypes of eating behavior may help to identify core traits that are genetically influenced. Such studies would yield important knowledge on the underlying biological scaffold on which diagnostic criteria for eating disorders could be based and would provide information to influence eating behavior toward healthier living.

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INTRODUCTION

Feeding is a physiological process, influenced by genetic factors and the environment. When eating behavior gets disordered, resulting in unbalanced energy expenditure and intake, the consequence is a pathophysiological status of energy balance, which manifests itself in extreme forms as an eating disorder or obesity (**Table 1**). To understand the influence of genetic variation on normal and pathological human eating behavior, it is important to understand the physiological basis of energy balance and the different systems involved in eating behavior. The regulation of feeding is a complex interaction between periphery and the brain. It involves several peripheral hormones and (neuro)peptides (see reviews by 2, 57, 106, 124).

The interaction between the brain and periphery has been described using two paradigms: the glycostatic hypothesis by Mayer & Thomas (1967) (100) and the lipostatic model by Kennedy (1953) (87). The glycostatic hypothesis is based on the assumption that small changes in plasma glucose levels trigger meal initiation and termination; however, it does not take into account how the body signals energy stores and energy expenditure. The lipostatic model hypothesizes that specific signals in the periphery give information on the amount of fat present in the body and thereby the amount of food needed to be eaten to maintain a healthy energy balance (87).

The latter has been supported by the discovery of leptin (156), which is an adipokine released proportional to the amount of stored fat (the main body energy reserve; 135, 156). The brain is the main target organ of leptin, and the discovery of the presence of the leptin receptors in specific neural circuits in the brain led to the identification of several neuropeptides that transmit the leptin signal further into the brain (78, 104, 156). Many of these neural circuits had already been implicated in energy balance, since brain lesion studies had shown that deletion of specific parts of the hypothalamus resulted in a hyperphagic state [deletion of ventromedial hypothalamic nucleus (VMH), dorsomedial hypothalamic nucleus (DMH), or paraventricular hypothalamic nucleus (PVN)] (21, 22, 73, 74) or a hypophagic state [deletion of the lateral hypothalamus (LH)] (5). In these brain sites, novel neuropeptides, receptors, and other factors were discovered that mediate the signals of leptin in the hypothalamus, such as neuropeptides of the melanocortin system, a key neuronal system in the control of energy balance downstream of leptin signaling (11, 38, 52, 152). Although the hypothalamus is an important center for the regulation of energy balance, the input from other brain regions (e.g., brainstem, the cortical and striatal structures) is also essential for modulating eating behavior (for overview, see 2). For instance, neural circuits in the brainstem are shown to play an essential role in the autonomic regulation of eating by limiting meal size via the regulation of the satiety response, whereas hunger feelings

Table 1 DSM-IV[a] criteria for eating disorders and characteristics of obesity

Disorder and subtype	(Diagnostic) characteristics
Anorexia nervosa (AN)	1: Refusal to maintain body weight at or above a minimal normal weight for age and height
	2: Intense fear of gaining weight
	3: Misperception of one's body weight or shape
	4: In postmenarcheal women, occurrence of amenorrhea
Restricting type	The above, plus no engagement in binge eating or purging
Binge-eating/purging type	The above, plus regularly binge eating or purging behavior
Bulimia nervosa (BN)	1: Recurrent episodes of binge eating
	2: Recurrent behavior with the purpose to compensate binging to prevent weight gain
	3: Characteristics 1 and 2 occur at least twice a week for three months
	4: Misperception of one's body weight or shape
	5: Characteristic 4 does not exclusively occur during episodes of anorexia nervosa
Purging type	The above, plus during the bulimia episode the person has induced vomiting or misused laxatives, diuretics, or enemas
Nonpurging type	The above, plus during the bulimia episode the individual used means other than those of the purging type to prevent excessive weight gain (e.g., excessive exercise or fasting)
Eating disorder not otherwise specified (EDNOS)	1: All criteria for AN are met except characteristic 4
	2: All criteria for AN are met except the individual has a normal weight
	3: All criteria for BN are met except the frequency of binging and compensatory behavior occurs less than twice a week during three months
	4: Individual with normal weight who shows compensatory behavior after eating small amounts of food
	5: Spitting out (large amounts) of food after chewing, but not swallowing
	6: Binge eating disorder; recurrent episodes of binge eating without the compensatory behavior of BN
Obesity	1: BMI: 30.0–34.9 class I
	BMI: 35.0–39.9 class II
	BMI: >40 class III
	2: Waist circumference for women should be below 35 inches
	3: Waist circumference for men should be below 40 inches

[a]Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. 2000. Arlington, VA: American Psychiatr. Publ.

are regulated by more rostral circuits (18, 65, 66, 92, 126). The hypothalamus, on the other hand, is seen as the center for neuronal control of long-term energy balance, with the initiation of eating, hunger signaling, and integration of energy balance signals regulated by nuclei of the hypothalamus, the PVN, arcuate nucleus (Arc), and LH (reviews by 57, 58 and references therein). The motivation to eat, reward of food, and the anticipation of eating are regulated in yet another area of the brain. These aspects of eating behavior are regulated by the reward system of the brain, with important roles for the nucleus accumbens and the ventral tegmental area (VTA), in which dopamine, opioid, and cannabinoid signals are integrated (86, 109, 133, 145).

Although the neural circuits involved in eating behavior are similar in all people, individuals respond differently to the same feeding opportunities, and under the same conditions, some individuals do and some don't develop an eating disorder or obesity phenotype. The explanation probably lies in a more thorough

dissection of the overall term of "eating behavior" into different aspects and characteristics of eating behavior, such as satiation, liking of sweet or bitter tastes, and meal size. Environmental influences in combination with the specific genetic make-up of an individual affect the relative contribution of each neural circuit on eating behavior and will determine how a person handles his physiological energy balance and whether this leads to a pathological status such as an eating disorder or obesity.

GENETICS OF SPECIFIC ASPECTS OF EATING BEHAVIOR

Normal eating behavior is the overall term for a characteristic that can be separated in a variety of different aspects, such as satiety, hunger, response to bitter and sweet taste, meal size, meal frequency, and macronutrient preference. Genes that play a role in these processes of eating behavior may provide important insight into why people act differently on various aspects of eating behavior.

A recent review describes the current knowledge about the genetics of food intake and eating behavior phenotypes in humans, with a focus on the genetics of macronutrient intake (113). Eating behavior is a heritable trait, as was shown in family and twin studies. A role of genetics has been reported for the amount of calories consumed, the preference for specific nutrients and food items, meal size, and meal frequency. However, the magnitude of these genetic heritability estimates, ranging from 20% to 40% of the age- and sex-adjusted variance, is heterogeneous among studies, as is the complex genetic background of food intake phenotypes. A comparable variability in the magnitude of the genetic effects has also been described for eating behavior traits such as restraint eating, disinhibition, and hunger (113).

In this review, we discuss what is known in humans about the following aspects of eating behavior: meal size and meal frequency, satiation and hunger, and taste preference in relation to genetic susceptibility. First, we focus on taste preference and taste perception, which are the first stimuli after food intake. These taste stimuli then start up the cascade of signals and stimuli by the brain that lead to feelings of satiation or hunger, the main eating behavior traits, which are described subsequently.

Taste

Food is ingested via the oral cavity, the first gatekeeper of the body in the control of eating behavior. The liking of foods, taste, is a powerful determinant in food selection. There are five established different types of tastes: sweet, salt, sour, bitter, and umami (also called savory, the taste of monosodium glutamate) (7, 136).

Individuals respond differently to these tastes due to, for instance, differences in density of the papillae on the tongue, the number of taste receptor cells, and the activity of the brain in response to different tastes. The fundamental underlying concepts of all of these aspects are genes and genetic susceptibility. For each type of taste, specialized taste receptors are present. A taste receptor functions as a chemoreceptor that interacts with taste stimuli to initiate an afferent signal to the brain, which results in taste perception (7). The taste receptors for sweet and umami involve different combinations of three proteins in taste receptor family 1. For sweet taste, these are proteins 2 and 3 (T1R2 and T1R3), and umami is composed of T1R1 and T1R3. Three genes encode for these receptors (*TAS1R1*, *TAS1R2* and *TAS1R3*). Bitter receptors are formed by proteins from the taste receptor family 2. Many different proteins in this family are encoded by different genes, the *TAS2R* genes (7, 115). Sour and salty taste receptors are ion channels. It is unclear which genes encode for these receptors (7).

Genes in the taste receptor pathway have been reviewed elsewhere (7, 115). Little is known about the genetic aspects of taste perception. There is some information about genetic variation in the sweet and umami taste receptors (115). However, there is a lack of knowledge regarding the taste receptor genes of sweet, umami, sour, and salt in relation to

normal eating behavior. Bitter taste has been studied the most because of the synthetic compounds phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP). These compounds are not found in foods, but chemically related compounds are found mostly in vegetables. Heritable components of the taste perception of PTC and PROP are easy to measure because of their large diversity in individuals. To some people, these compounds taste bitter, whereas others cannot taste them at all. Tasters to whom PTC and PROP are extremely bitter are so-called supertasters. Polymorphisms in a single gene, *TAS2R38* (a member of the bitter gene receptor family), have been determined to account for most (60%–85%) of the variation in PTC/PROP sensitivity among individuals (115, 136). Variation in bitter taste perception may also lead to differences in the selection of healthy, bitter foods such as citrus fruits and cruciferous vegetables and, because of the dislike of these healthy vegetables, eventually to diet-related obesity. Unfortunately, findings to date have been inconsistent, perhaps because the PTC/PROP taste components are synthetic and not present in real-life food (115, 136). Further research is necessary to study these hypotheses and to reveal the underlying mechanisms of the sweet, umami, salt, and sour perception.

Hunger, Satiation, Meal Size, and Meal Frequency

In several areas of the brain, including the brainstem, amygdala, and hypothalamus, the information of taste stimuli is integrated with the signals of hunger, satiation, and appetite (7, 18, 136). However, the precise underlying mechanisms are not yet fully understood. In animal studies, it has been shown that the integration of taste and gastrointestinal signals occurs in the brainstem to codetermine the size of meals in the short term (64), possibly mediated by the gut hormones cholecystokinine (CCK) and peptide YY (PYY) (18, 69).

Hunger and satiation are feelings that are driven by many different processes and molecules in which the brain, and especially the hypothalamus, plays a major role (for more detailed information, see 2). Hunger feelings should lead to an increased food intake, and food intake should lead to a feeling of satiation. The effect of hunger on food intake and the effect of food intake on hunger and on the size and frequency of meals are heritable (41–43).

The control of meal size is mainly determined by the onset of satiety. People who are quickly satiated will take smaller meal sizes. The control of meal frequency is mainly determined by the onset of hunger. People who feel hungry frequently will have a higher meal frequency than that of persons not often hungry (50). All these processes are controlled through hormones, peptides, and neurons and can also interact with each other. Therefore, it is possible to find genetic susceptibility for meal size and frequency in the genes that encode for hormones, peptides, and neurons involved in hunger and satiety feelings.

Peripheral hormones and peptides from the oral cavity and gastrointestinal tract are released in response to a meal and signal a change in energy status to the brain. Some gut peptides that are well studied and are known to give satiety signals to the brainstem and the hypothalamus, and thereby terminate the meal, are PYY, glucagon-like peptide 1 (GLP-1), and CCK. PYY inhibits neuropeptide Y (NPY) and Agouti-related protein (AGRP) neurons in the arcuate nucleus of the hypothalamus, which produce orexigenic signals to the PVN. GLP-1 inhibits food intake via the brainstem and the PVN of the hypothalamus and CCK via the nucleus of the solitary tract of the brainstem (10, 17, 18, 35, 50).

Ghrelin, produced by the stomach and duodenum, has the opposite effect and is known to be involved in hunger feelings and meal initiation. It stimulates the NPY/AGRP neurons in the hypothalamus to give orexigenic signals to the PVN (10, 17, 50).

In addition, insulin and leptin play an important role in hunger and satiety feelings. Leptin is secreted from adipose tissue and inhibits the NPY/ARC neurons and stimulates

Table 2 Gene polymorphisms affecting regulation of food intake and energy homeostasis[a]

Gene	SNPs (*n*)	Determinant	Overall finding	Reference
AGRP	1	Macronutrient intake	The rare allele of Ala67Thr was associated in whites with less energy derived from fat, specially saturated fat, and more from carbohydrates	(97)
			-38>T was associated in blacks with protein intake; TT homozygotes had lower protein intake than the C carriers	
NPY	1	Macronutrient intake	Leu7Pro polymorphism not associated with intakes of energy, macronutrients	(82)
TUB	1	Macronutrient intake	rs2272382 was associated with fat and carbohydrate intake	(144)
MC4R	1	Macronutrient intake	rs17782313 was associated with total energy, total fat, and protein	(112)
FTO	1	Satiety	The A allele of rs9939609 was associated with increased adiposity and satiety in children	(147)
CCK	4	Extreme meal size	Four SNPs showed associations with extreme meal size	(45)
Leptin and leptin receptor	3	Extreme snack behavior	One SNP in the leptin receptor and two SNPs of leptin were associated with extreme snack behavior	(45)

[a]Addition on table 1 of Loktionov (95).

Abbreviations: AGRP, Agouti-related protein; CCK, cholecystokinine; FTO, fat mass and obesity associated; MC4R, melanocortin-4-receptor; SNP, single-nucleotide polymorphism.

the pro-opiomelanocortin and cocaine- and amphetamine-related transcript neurons, which results in inhibition of food intake. Insulin is secreted by the pancreas and also has an anorexigenic influence on the hypothalamus (10, 17).

Knowledge of the genetics of the above-mentioned aspects of eating behavior, however, is limited. Most of the studies into genes involved in hunger and satiation have not examined these specific aspects, but rather have focused on end results of disturbed hunger or satiation, such as obesity, type 2 diabetes, and body fatness. However, some data on genetic influences are available [**Table 2** updates what is known about genetic polymorphisms affecting the regulation of food intake and energy homeostasis since the publication of A. Loktionov et al. (2003) (95)], and three genes are of particular interest. A gene related to the hypothalamic pathway, but not yet intensively studied in relation to eating behavior is the *TUB* gene, which has recently been associated with the selective intake of fats and carbohydrates in women (144). Carriers of the *TUB* variants consumed a diet high in carbohydrates and low in fats. The melanocortin-4-receptor (*MC4R*) gene is part of the melanocortin pathway controlling food intake and energy balance. A common obesity-associated variant in this gene, rs17782313, was associated with high intake of total energy and elevated intakes of dietary fat and protein, in line with experimental data indicating that MC4-R plays a role in controlling fat preference (112). Interestingly, the newly discovered fat mass and obesity-associated gene, *FTO*, shows a relation to satiety in children (147). Satiety responsiveness was statistically significantly lower in homozygotes for the A allele ($p < 0.01$).

Knowledge on genetic susceptibility of meal size and meal frequency in humans is also scarce. Leptin and CCK have been implicated in the control of meal size and meal frequency (18, 159). Recently, common single-nucleotide polymorphisms (SNPs) and haplotypes of the CCK gene and leptin genes have been studied in a population-based sample from Prospect-EPIC (European Prospective Study into Cancer and Nutrition) (45). CCK SNPs and haplotypes were associated with extreme meal size. Leptin SNPs and haplotypes were associated with extreme snack behavior. So, difference in satiety seems to be determined by the amount

of CCK that goes to the brain, and this amount seems to differ due to meal size (45, 105). Determinations of hunger feelings seem to be the result of different amounts of leptin according to difference in meal frequency (45, 159). However, no confirmation studies have been performed so far.

From this overview, it is clear that still many questions remain to be solved concerning the genes and genetics involved in normal eating behavior. What is known about the pathological side of eating behavior—eating disorders and obesity? This topic is discussed in the following part of this review.

GENETICS OF EATING DISORDERS AND OBESITY

Obesity and eating disorders are complex traits with various underlying etiological pathways, which include behavioral risk factors as well as those regulating food intake and the environment (cheap, energy-dense food, culture, pressure to be thin, stress, and adverse experiences) (19). Body composition, obesity, and eating disorders have all been shown to be heritable traits (4, 28, 130). Both human twin studies and animal models clearly indicate the involvement of genetics.

Strong support for the influence of genetic variation on feeding behavior and body composition in humans comes from family, twin, and adoption studies (70). Heritabilities reported from family studies are in the range of 25% to 40%, and for twin studies in the range of 50% to 80% (8); i.e., twin studies typically show higher heritability than do family or adoption studies. The reasons for this are not clear but probably relate to the nature of environmental influence and the equal environment assumption in twins. Although twin studies show that genetics are a major factor influencing body composition, it is important to note that environmental factors significantly contribute to variance; this may be higher than expected if gene-environment interaction has a major role, as seems likely. One of the most robust environmental associations with obesity is low socioeconomic status (117). However, it is likely that this is a distal risk factor that indexes other causes such as unhealthy dietary habits, psychological disturbance, or lack of exercise, which may all contribute to a positive energy balance. Besides twin studies, animal studies have given clear indications that genes and genetic load play an important role in (the deregulation of) eating behavior.

Most research in the area of animal models of obesity has focused on mice, but the livestock industry has also examined body composition, including adiposity, extensively. Allelic effects are detected in rodents via a number of different methods including spontaneous mutations arising in stock, deliberate (chemical- or radiation-induced) mutagenesis, targeted transgenic animals (e.g., gene knockouts), quantitative trait loci screening for natural strain variation, or other methods such as RNAi knockdown of transcripts. The Mouse Genome Informatics Web site (**http://www.informatics.jax.org/**) currently lists 1087 alleles associated with an "obese" search term; likewise, the obesity gene map menu describes ten spontaneous and about 250 engineered transgenic mice that have an obesity or related phenotype. In addition, a similar number of QTL loci also show an obesity phenotype (**http://obesitygene.pbrc.edu/**), although most of the genes underlying these have not been mapped. The most famous mouse is the recessive *ob/ob* (156), with a spontaneous nonsense mutation that occurred in the leptin (*ob*) gene, which eventually led to the discovery of the mechanisms of central appetite regulation in the hypothalamus (30, 40). Although the understanding of the basic biological mechanisms of feeding and single-gene forms of obesity have benefited greatly from mouse models, the role of individual genes and normal genetic variation is largely untapped.

Anorexia (AN) is a behavioral disorder and thus is more difficult to model in animals. However, one model of activity-based anorexia (34, 121) found that food-restricted rodents given unlimited access to a running wheel became excessively active and lost body weight. This finding is very interesting, particularly because

young female rodents are more vulnerable (3). For bulimia nervosa (BN), animal models tend to focus on environmental determinants of binge eating behavior, such as sham-feeding, restriction/refeeding cycle, stress, and limited access to optional foods (39). Thin sow syndrome (TSS) (99) is a stress-related syndrome observed in pigs that has parallels with AN (142). Young, female pigs are the most vulnerable to TSS, which is often found in lean hybrid strains and has some evidence of a genetic basis (99). Affected pigs display hyperactive behavior and develop a prominent dorsal spine and long, coarse hair, the latter analogous to lanugo (growth of body hair) seen in women with AN. TSS is frequently treated with amperozide, implicating the serotonin system, a neurotransmitter system also thought to be involved in human AN (83).

The twin and animal studies have led to studies investigating in more detail the genetics behind eating disorders and obesity by linkage and association studies and are briefly summarized below. Obesity and body mass index have received much more attention than eating disorders, with many hundreds of genetic association studies published.

Linkage Analysis

There have been more than 40 genomewide scans for linkage of body mass index (BMI)-defined obesity or BMI (122; **http://obesitygene.pbrc.edu**). These studies have had limited success in defining loci for obesity; recently, a genome scan meta-analysis was performed of these studies, and no locus reached genomewide significance for linkage, although several loci approached significance (122). Linkage studies of other phenotypes, such as fat mass, fat-free mass, and associated traits such as metabolic syndrome, have also been performed, but their validity is not yet clear, as there is less opportunity to replicate these more detailed phenotypes than a simple one such as BMI.

For eating disorders such as AN, there have been a few genomewide scans focusing on the illness itself or quantitative phenotypes derived from illness trait measures such as the Eating Disorders Inventory (27). This includes studies of anorexia itself, of a subtype, restricting AN, where the symptoms are principally food restriction, and BN, as well as trait measures such as drive for thinness, obsessionality traits, and self-induced vomiting. These findings, discussed in more detail below, are as yet unreplicated because of the difficulty in ascertaining sufficient multiply affected families.

Linkage Studies of Obesity

Although individual studies typically identify regions of suggestive linkage, there has been limited consistency between studies. These inconsistencies could be due to many different factors related to methodological and etiological factors: Different studies use different sample sizes with variations in statistical power, potentially leading to false negative (or false positive) results. There is likely to be substantial genetic heterogeneity, along with a substantial role for environmental factors, and these two factors are likely to interact. Thus, distinct populations may have a different emphasis on the various genetic risks, and this emphasis is likely to be further modified by the well-documented geographic variation in environmental factors. It is thought that the very many genetic loci that contribute to adiposity will each be of very small effect size. These may be influenced by a further variety of genetic loci in different populations, each subject to different environmental exposure.

Saunders and colleagues recently attempted to combine information from 37 of these studies involving more than 10,000 families in a genome scan meta-analysis (GSMA) in order to form a global picture and eliminate some of these problems (122). Using this method it should be possible to identify consistent small effects that are not significant in individual studies but are significant in the general population. The increased statistical power of the meta-analysis grants the ability to rule out spurious false positives that appear in multiple studies as

well as the ability to identify small consistent effects that are not identified in individual studies.

In the Saunders et al. study, GSMA results were presented for studies pertaining to BMI as the phenotype and obesity as the phenotype, as well as separate studies in diabetic and hypertensive populations; in addition, a meta-analysis of studies involving participants of European ancestry was presented (122). Although no genomewide level of significance was reached, there was suggestive evidence for linkage in a few regions of the genome. A meta-analysis of BMI linkage studies showed the strongest evidence for linkage at chromosome 13q13.2-13q33.1. Other evidence for linkage was found at 12q23.2-q24.31 in BMI and obesity studies and at 16q12.2-q23.1 in families reporting obesity. The evidence on chromosome 16 is particularly interesting as it spans the FTO locus at 16q12.2. FTO has shown the strongest evidence so far reported in studies reporting association with BMI and/or type 2 diabetes (48, 56, 79, 90). There was some evidence for linkage on chromosome 18 but in an adjacent bin to the MC4R locus, which has also been associated with BMI at two loci in candidate-gene and genome-scan studies (59, 96, 131).

Although Saunders and colleagues identified a number of regions, there is no conclusive evidence of linkage despite the large number of studies and high statistical power contained in the meta-analysis (122). The failure to find a conclusive resounding linkage signal associated with obesity or BMI is likely a result of the genetic heterogeneity of BMI and obesity as quantitative traits. Thus, although there have been contributions toward identifying genetic loci of interest linked with BMI, there has not yet been any irrefutable evidence.

Linkage Analysis of Eating Disorders

Current research findings suggest a substantial influence of genetic factors in the liability to develop AN and BN, leading molecular geneticists to attempt to identify these genetic vulnerability factors. Findings from genetic studies of eating disorders are quite typical of those found in most psychiatric disorders: initial intriguing findings belittled by the absence of clear-cut replication or definitive identification of causal DNA sequence variation between cases and controls (27). Additionally, relative to other psychiatric problems, eating disorders have been somewhat neglected by geneticists, mainly because they were thought to be psychosocial in origin until a decade or so ago.

The Price Foundation of Geneva funded a series of genetic linkage studies that have delivered interesting results for both AN and BN. Kaye et al. (85) describe the methods and sample used in their search for susceptibility loci for AN, which was the first linkage study of AN. Although the study found no evidence of linkage, two additional modified investigations did. The only significant linkage found thus far for AN is for the restrictive subtype of the disorder (RAN). Grice et al. (63) used families with at least two people diagnosed with RAN (using criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*). Significant linkage was found to chromosome 1p. The importance of strict and accurate phenotyping to reduce genotypic heterogeneity was highlighted by this study because when a symptomatically heterogeneous sample of AN cases was used, only modest evidence of linkage was found. Similarly, incorporating behavioral covariates into linkage analyses (47), namely "drive for thinness" and "obsessionality" (known traits in AN), revealed several regions of interest on chromosomes 1, 2, and 13. Although these findings are exciting, they do not suggest strong candidate genes for the etiology of AN. Bulik et al. (27) detail how the three linkage studies for anorexia nervosa have highlighted 27 areas of "suggestive linkage," just two of which are significant. These significant findings have yet to be replicated.

Bulik et al. (26) report the only published study of significant linkage in BN, which reported significant linkage to chromosome 10, particularly when the sample was restricted to families with elevated reports of self-induced vomiting. Areas on chromosomes

10p13, 1q31.3, 4q35.2, and 8q13.1 have shown linkage to obsessionality, age at menarche, anxiety, concern over mistakes, food-related obsessions, and minimum lifetime body mass index, which are known eating disorders traits (6). Again, probably because of the difficulty in ascertaining sufficient multiply affected families, these findings have yet to be replicated.

As pointed out by Bulik et al. (27), present findings from linkage studies constitute tentative knowledge: They may contain genes that are etiologically relevant to eating disorders, or they may represent false signals. A promising, large replication study using an independent sample is underway, which should be a valuable step in advancing the field of eating disorder genetics.

Association Studies

There have been several hundred positive associations between obesity and candidate genes (**http://obesitygene.pbrc.edu/static/association_table.htm**); of these, only the association with the melanocortin 4 receptor (MC4R) appears to have been replicated, although other associations may yet turn out to be true but of very small effect. This will not become evident until definitive samples sizes are brought together to maximize statistical power. The paradigm changed recently with the advent of GWAS, and in an analysis of more than 30,000 individuals, the FTO gene was identified as a risk factor for both obesity and type 2 diabetes (48, 56, 79, 90). More recently, the melanocortin 4 receptor locus, a gene that has been the subject of more than one dozen association studies, was also identified by GWAS as an obesity susceptibility gene (96). Intense follow-up of GWAS data is expected to identify further genetic risk factors in the near future. Until now, eating disorders association studies have focused more on candidate genes from specific systems, such as dopamine and serotonin, with some success, including genes from linkage loci such as 1p. The discussion of this topic below is based upon the latest views and studies published in literature.

Association Studies of Obesity

There have been many association studies of BMI and obesity. Initially, these were typically candidate gene studies in relatively small populations. All of these studies are listed in the Human Obesity Gene Map. Probably the most successful finding from these early studies was a replicable association found at SNPrs2229616 in the MC4R gene, in which a rare nonsynonymous change protects against obesity (59). The MC4R, part of the central melanocortinergic pathway, plays a pivotal role in the control of energy homeostasis, as shown by studies in rodents and humans (51). It is expressed in the hypothalamus of the brain, where it is thought to be involved in appetite and satiety control (80, 107). Since this initial study, human studies have shown that the prevalence of functionally relevant MC4R mutations ranges from 0.5% to 5.8% in obese children and adolescents ascertained for molecular genetic studies, and more than 90 mutations have been described (75, 134), producing a large quantitative effect on BMI (46). Other associations found in functional candidate gene studies were generally not well replicated; either associations are false positives or studies thus far have been underpowered to reliably detect their true effect.

Following the advance of new genotyping technology and the ability to genotype hundreds of thousands of SNPs quickly and relatively cheaply, a number of GWAS have searched for polymorphisms associated with BMI, obesity, and other related phenotypes. The most robust association with BMI and obesity (and also type 2 diabetes) was found in the FTO gene with the SNP rs9939609 (56, 79, 90) as part of a multidisease scan performed by the Wellcome Trust Case-Control Consortium. This association has been well replicated in further studies by different groups (e.g., 48, 79) and subsequently has been associated with a number of related phenotypes involving dietary intake and satiety (90, 138, 147).

Genome scans have also pointed to association in other genes, including a common SNP variant close to the MC4R gene (96), which differs from the rare obesity-associated variants

from within the gene in that it is much more common and has a smaller effect on risk. This variant is associated with higher intakes of total energy and dietary fat, weight change, and diabetes risk in women (112), whereas uncommon variants affecting receptor function have been associated with failure to maintain weight loss (116), indicating poorer dietary control.

Other genes recently identified by well-powered studies include the central cannabinoid receptor CNR1 (12), CTNNBL1 (94), NYD-SP18 (150), and PCSK1 (13) although as yet these have not been independently replicated.

Genome scans of conditions such as obesity present a number of statistical obstacles. With very large numbers (typically hundreds of thousands) of SNPs being tested, there is a multiple testing burden, with a large number of expected false positives. A significance value of around $p < 5 \times 10\text{-}8$ is now required for publication in many leading journals. Coupled with the fact that genetic effect sizes are expected to be very small (the FTO SNP accounts for about 0.1% of the variance in BMI), very large numbers of participants (>30,000) are now required in performing well-powered genome scans. Of course, these problems are not exclusive to the search for genetic associations with obesity or BMI, but are common to many complex disorders such as schizophrenia or depression. As such, many of the most recent genome scans in well-powered samples are performed as a result of collaboration between different groups. Although high-powered studies of this nature are undoubtedly the next step in GWAS, and combining participant samples for initial statistical power is favored, there is still a desire for positive results to be replicated.

Follow-up investigations of GWAS are expected to reveal more consistent associations that thus far have not obtained the most significant p values in individual scans but are present steadily throughout. One of the more high-profile initial reports of association with BMI and obesity was found in the INSIG2 gene (72), but despite optimism, this association failed to replicate in subsequent studies (e.g., 68). It is now common for positive associations to be replicated in several population samples prior to initial publication.

Association Studies of Eating Disorders

Many genetic studies of eating disorders have focused on the serotonergic, dopaminergic, and opioid neurotransmitter systems because they are involved in central energy-balance pathways (128). For example, serotonergic signaling suppresses food intake, whereas dopamine signaling has been associated with obesity and obesity vulnerability. Disturbances in the serotonergic and neurotransmitter systems occur in individuals with AN and BN and appear to persist after recovery, which suggests that serotonergic dysfunction might be a premorbid trait that contributes to the susceptibility of eating disorders (84). The most frequently examined gene is the serotonin 5-HT2A receptor. Inconsistent findings have been reported for a variant (-1438 G/A) of this gene and AN; four studies in different population groups reported an increase in the A-allele of the 5-HT2a variant in AN women compared with controls (36, 53, 108, 127), but three studies could not replicate this positive association (29, 76, 157). A meta-analysis of all the results detected no association between AN and the A-allele of this 5-HT2a gene variant (157). Different diagnostic criteria and the use of heterogeneous populations or small sample sizes may, in part, account for the inconsistent results from these studies (75). No association has been reported between this 5-HT2a gene variant and BN (53, 108, 157).

In a study of candidate genes for AN in the 1p33–36 linkage region described above, serotonin 1D and delta opioid receptor loci exhibited significant association to AN (14). These genes were subsequently examined by Brown et al. (23), who also found evidence for their association with AN. The finding of an association with opioid receptors is interesting because neural opioid systems have been implicated in appetite control in animal studies and human studies based on the use of pharmacological

agonists and antagonists (16, 89). Opioids may mediate the hedonic aspects of eating within the brain's reward pathways (49, 143), and opioids are implicated in food craving and BN (155).

The dopamine system has also been implicated in anorexia nervosa. Dopaminergic neuronal function modulates feeding behavior, motor activity, and reward-motivated and drug-seeking behavior. Kaye et al. (84) showed that AN-recovered individuals have lower cerebrospinal fluid homovanillic acid concentrations than do individuals with a history of BN diagnosis or control individuals. Evidence from animal studies suggests that dopamine neurons in the nucleus accumbens/limbic regions, which are involved in reward alterations and novelty seeking (37, 151), are most likely to be involved. Food intake leads to an increase in the release of dopamine in the circuits that mediate the pleasurable aspects of eating, and chronic food deprivation resulting in decreased body weight leads to lower dopamine levels. Therefore, overeating or binge eating may represent a compensatory attempt to restore baseline dopamine levels, whereas in AN, anhedonia may mean that the dopamine system is ineffective in the drive to eat; there is evidence from neuroimaging of dopamine disturbance in AN (55). In a study by Bergen et al. (14), multiple dopamine D2 receptor gene polymorphisms were associated with AN. However, this finding has not yet been replicated.

The neurotrophins have also been implicated in eating disorders. These signaling proteins are important for proliferation, differentiation, and survival of neurons in both the central and peripheral nervous system (123). In adults, they control neural plasticity and regulate synaptic activity and neurotransmitter synthesis. The family consists of nerve growth factor, brain-derived neurotrophic factor, and neurotrophins 3 and 4/5, whose effects of neurotrophins are mediated by specific tyrosine kinase receptors. Since brain-derived neurotrophic factor and its receptor NTRK2 have been shown to be involved in the regulation of eating behavior and energy balance (88, 154), several groups have investigated these genes and have found that both genes play a role in the disease susceptibility (62, 75, 101, 118–120). More recently, the NTRK3 gene was associated with eating disorders (102), which indicates that the neurotrophin system as a whole may encode vulnerability to this disorder.

EATING BEHAVIOR, GENETICS, AND FUTURE PROSPECTS

The above discussion has given an overview on the current status of genetic research and understanding of (pathological) eating behavior. In the final part of this review, we address new opportunities and research angles to further unravel the genetics of eating behavior.

Endophenotyping the New Approach into Genetic Studies

Success in unraveling the genetic background of Mendelian disorders led to the belief that soon the genetic basis of complex disorders and behaviors, e.g., psychiatric disorders and eating behavior, also would be unraveled. However, the optimism soon turned into pessimism because genetic findings were not replicated. The effects of the genetic findings were very small, and it was hard to get enough power for the studies to find a significant effect size (149, 153, and the references in reviews by 9, 32). This showed that the straightforward genetic approaches such as linkage and association analyses were suited for disorders caused by single gene mutations but were much less effective in studying the genetic background of complex behaviors and disorders in which many genes have an effect combined with environmental influences.

The most probable cause for this failure of the standard genetic studies, and thus the finding of genes contributing to complex disorders and behaviors, is the inherent imprecision in description and heterogeneity of psychiatric phenotyping of complex behaviors (9). This imprecision and heterogeneity is caused by the lack of a biological basis in the descriptions. Furthermore, the joint influence of multiple genes

and environmental factors on the complex phenotype should also be taken into account, as described above.

The combination of genes and the downstream and upstream effects of mutations in genes involved in a certain complex behavior make it difficult to determine whether a certain gene/variation in a gene is indeed playing an important role. Furthermore, since multiple genes are involved, the effect size of a single gene is probably small and can even be masked by other genes of the pathway of the gene that is studied. To understand the genetic background of a complex behavior in total, it is necessary to study the combinations of minor and subtle effects in genes in a total gene system/pathway and/or increase the power of the genetic studies by enlarging study populations, as has recently been done for obesity.

This can, however, still be difficult. An alternative approach therefore might be to take into account the complexity of the phenotype and to break down the complex phenotype into smaller bricks of specific phenotypes for which a biological or environmental explanation can be given to unravel the genetics. This may facilitate the identification of susceptibility genes for complex (inherited) behaviors (32).

This concept of working with phenotypes within phenotypes was already posted in 1973 by Gottesman & Shields and has been resurrected to unravel the genetic background of complex behaviors and disorders. Gottesman & Shields posted the concept of endophenotypes with the following definition: "Endophenotype: an internal phenotype (i.e., not obvious to the unaided eye) that lies intermediate between the gene and the disease itself." An endophenotype can be anything in nature, e.g., endocrinological, biochemical, cognitive, or neurobiological, as long as it complies with a number of set rules. An endophenotype is heritable, is present in combination with the studied complex behavior, is independent of state of the individual, and is more often observed in family members then in the general population. For a clear overview of the criteria to which an endophenotype should comply and how an endophenotype can be found and defined, we refer to the review of Bearden & Freimer (9) and the references therein, and the articles of Gottesman & Could (61) and de Geus & Boomsma (44).

The definition of an endophenotype and the criteria set for this kind of phenotype suggests that (*a*) fewer genes are involved, making it easier to unravel a genetic background; and (*b*) better ideas concerning biological backgrounds exist, which in theory should simplify the detection of contributing genetic loci. Taken together, the genetic background and the description of a complex behavior based on biology will result in better understanding of the genetics of obesity (15, 20).

Although the above could be a major step forward in unraveling the genetic background of complex behaviors, there is still skepticism on the usefulness of the endophenotype approach. A recent meta-analysis of association studies done using the endophenotype approach showed that for the loci studied, the effect sizes are no larger than are those found in genetic studies of the total complex phenotype (54), which suggests that the approach is not (yet) delivering what it promises. However, a closer look into studies on psychiatric disorders shows that the endophenotype approach certainly can be successful. It has been shown to result in new insights in the biological processes and pathways involved in complex behaviors and disorders, and it has thereby facilitated a more successful genetic approach (31, 33, 60, 71, 111).

Although different fields of psychiatry have embraced research on endophenotypes, only four references were found in the eating disorder field (77, 125, 129, 146). However, the concept of endophenotypes is getting more and more attention, since it is clear that traditional genetic studies are not getting us any closer to understanding the mechanisms behind eating behavior and its disorders. This lag in understanding is probably due to the small effect size of the many genes involved and to poorly powered studies that result from very heterogeneous study populations (27, 141). By starting

to use an endophenotype approach, chances increase that researchers will be able to dissect (all) different genetic factors that play a role in specific parts of eating behavior. This will lead to understanding which genes are altered in eating disorders and obesity. Moreover, the study into endophenotypes of eating behavior may help to identify core traits that are genetically influenced (27), and this would give information on the underlying biological scaffold on which diagnostic criteria for eating disorders could be based. This could lead to the definition of a homogenous classification system for the description and diagnosis of eating disorders and obesity based on biological endophenotypes of eating behavior (for examples and suggestions on endophenotypes within eating disorders, we refer the reader to 27, 141).

An example that the endophenotype approach could indeed be effective is our own study (45) in which we demonstrate the influence of genetic changes in the CCK gene and the leptin gene on specific traits within eating behavior.

The Future with Animal Models

Although single-gene knock-out mouse models have revealed several important players in the regulation of energy balance, the general assumption is that obesity results from small changes in activity and function of various genes in combination with an obesogenic environment. In an obesogenic environment, a term used for the "risky" environment that contributes to obesity, diets that are palatable, highly nutritious, and energy dense are easily accessible, and physical activity is not stimulated. Thus, when using animal models to understand the genetics of eating behavior in obesity, it is important to include the aspect of eating such as described above (taste, hunger, satiety, meal size, and frequency) within such an obesogenic environment. A variety of commercially available diets are used to induce obesity in rodents. Recently, these diets have been reviewed extensively with respect to the obesity and related pathologies induced (25, 103). Here, we focus on specific aspects of eating behavior, such as palatability, choice, meal size, and frequency of meals, that are comparable to the endophenotypes examined in human genetic studies of eating disorders.

When studying eating behavior in diet-induced obesity, it is important to consider the role of palatability and choice that is characteristic in human obesity and probably underlies the development of obesity. The diets used in the majority of studies on diet-induced obesity are commercially produced pellet diets that are fed as the sole source of food. These diets initially increase food intake; however, several compensatory mechanisms (for example, centrally) occur that reduce the meal size (110) and lower total caloric intake after a period of time (158). We recently started subjecting rats to a diet with saturated fat and a 30% sucrose solution in addition to their normal pellet diet and observed persistent increased caloric intake with stable amount of calories from each source (91). Furthermore, rats consumed enough proteins to ensure growth. This diet nicely mimics the composition and the palatability of the Western-style diet and provides a design in which different aspects of eating behavior can be studied. Within this paradigm, we offer foods that are different in nature. Recently, it has been shown that the nature of optional foods (nutrient composition and physical form) is important for overconsumption (1). However, it has also been postulated that presenting more of the same highly palatable food (such as five bottles of 32% sucrose) results in more overconsumption (139). This is, however, under debate, because others could not reproduce these findings (1).

The mechanisms underlying overconsumption are not fully understood. As described above, several neuropeptides in the brain are involved in the regulation of feeding behavior, yet most of these neuropeptides are unchanged when rodents are fed a high-fat diet (103). However, for the choice or preference of different nutrients, genetic background may play an

important role (114, 140). Marked strain differences in fat and sugar intake have been reported (93). Furthermore, specific genes have been described to play a role in the choice for palatable food items, such as melanocortins that alter fat intake specifically (24, 67) and NPY that stimulates the intake of a high-carbohydrate diet specifically (81).

In humans, overconsumption is characterized by increased meal size and/or increased number of meals. It has been shown that meal size is increased when rodents are switched to a high-fat diet (98, 132) and that the higher the fat content in the diet, the bigger the size of the meal (148). In addition, the effects of high-energy-dense diets on frequency have not been described. It could well be that providing rats or mice with multiple choices of a variety of foods will affect the number of meals. We recently showed that a diet with saturated fat and sugar solution in addition to chow increases the motivation to work for a sucrose reward (91), which could point toward an increase in meal initiations and thus an effect on meal frequency. It remains to be determined whether meal patterns are affected by including choice in an energy-dense diet.

There are several reports of specific gene effects on meal size or meal frequency. As described above, it has been shown in human genetics studies that the CCK gene and the leptin gene were differentially changed with meal number and portion size. For rats, several neuropeptides have been described to affect meal size, such as ghrelin, leptin, and CCK. Recently, we showed that one neuropeptide can affect both meal frequency and size, depending on the site of action (137). We showed that NPY overexpressed in either the LHA or the PVN resulted in obesity; however, NPY overexpression in the PVN resulted in more meals, whereas NPY in the LHA resulted in larger meals (137). Thus, although some neuropeptides have been implicated in playing a role only in meal size, depending on the site of action, a gene could be involved in both elements of food intake.

Overall, several genes have been identified to play a role in energy balance and feeding regulation. However, limited information is available on the role of specific genes in preferences for certain foods and in effects on meal patterns. In addition, the identification of strains with diverging preferences for fat and sugar or alterations in meal patterns may lead to the successful identification of genes related to different traits of eating behavior.

SUMMARY

In recent years, many studies have been conducted to unravel the genetic background of human eating behavior. In this review, we have attempted to describe the current status of research on genetic background in both normal and pathological eating behavior. It is clear that we are getting closer to an understanding of the different aspects of eating behavior, but that much still needs to be done. The combination of animal studies and large genetic studies in combination with the dissection of complex phenotypes into smaller bricks of specific traits will be important.

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Errata

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