Genetics of eating behavior: established and emerging concepts

Eleanor R Grimm and Nanette I Steinle

Understanding why we eat and the motivational factors driving food choices is important for addressing the epidemics of obesity, diabetes, and cardiovascular disease. Eating behavior is a complex interplay of physiological, psychological, social, and genetic factors that influence meal timing, quantity of food intake, and food preference. Reviewed here is the current and emerging knowledge of the genetic influences on eating behavior and how these relate to obesity; particular emphasis is placed on the genetics of taste, meal size, and selection, and the emerging use of functional magnetic resonance imaging to study neural reactions in response to food stimuli in normal, overweight, and obese individuals.

INTRODUCTION

Understanding why we eat and the motivational factors driving food choices is important for addressing the epidemics of obesity, diabetes, and cardiovascular disease, as food intake is a significant factor impacting the development and treatment of these disorders. Eating behavior is a complex interplay of physiological, psychological, social, and genetic factors that influence meal timing, quantity of food intake, food preference, and food selection. Active research involving the genetics of taste, food preference, pathological eating behaviors, meal size, and meal selection is rapidly expanding our understanding of how and why we eat. More recently, neural imaging modalities, specifically functional magnetic resonance imaging (FMRI), has emerged as a modality to effectively study eating behavior and genetics in fascinating ways. Reviewed here is the current knowledge of the genetic influences of eating behavior, with particular emphasis on the genetics of taste, meal size and selection, and the emerging use of FMRI as it applies to imaging the neurophysiological response to food stimuli. The primary focus of this review is on obesity as a consequence of eating behavior, but other pathological disorders of eating behavior, including anorexia nervosa and bulimia nervosa, also have strong genetic, psychological, and environmental components.[1]

The rapid rise in obesity and associated comorbidities (metabolic syndrome, coronary artery disease, sleep apnea, skeletal disorders, hyperlipidemia, and hypertension) over the past 30 years has led to the present urgency of efforts to obtain a more complete understanding of the pathophysiology of obesity. The study of eating behavior attempts to define eating patterns and food preferences, to explain why there is gravitation toward specific behaviors and food choices, and aims to develop approaches to bring about effective changes in modifiable behaviors. Knowledge of the biological mechanisms guiding eating behavior can provide effective treatment targets for obesity and associated disorders.

Rare monogenic genetic disorders involving hyperphagia and obesity have been identified.[2] Resulting from a deletion of the11-13q region of chromosome 15, Prader Willi (PW) is characterized by hypotonia and poor feeding in early infancy, cognitive, motor, and behavioral impairment, followed by insatiable hunger and the development of morbid obesity and diabetes during childhood.[3] PW patients rarely survive beyond 25–30 years of age; the cause of death is often related to diabetes and cardiac failure. Monosomy 1p36 has also been associated

Affiliations: *ER Grimm* and *NI Steinle* are with the Department of Medicine and University of Maryland School of Medicine, Baltimore, Maryland, USA.

Correspondence: *N Steinle*, Department of Medicine and University of Maryland School of Medicine, 660 West Redwood Street Room 467, Baltimore, Maryland 21201, USA. E-mail: nsteinle@medicine.umaryland.edu, Phone: +41-07-061-512, Fax: +41-07-061-646.

Key words: eating behavior, genetics, obesity

doi:10.1111/j.1753-4887.2010.00361.x

with obesity and hyperphagia in a PW-negative cohort.[4] Individuals with loss-of-function mutations of the leptin (*LEP*) gene on chromosome 7q31.3, or its receptor (*LEPR*) also display abnormal eating behavior and develop early-onset morbid obesity.[5,6] Leptin replacement can improve satiety and promote weight loss in leptin-deficient individuals.[7] Leptin promotes α-melanocyte-stimulating hormone(α-MSH) synthesis, which promotes satiety.[8] α-MSH is bound by the melanocortin 4 receptor (MCR4) protein. *MC4R* mutations are associated with early-onset obesity.[9,10] Discoveries of the genes and their respective proteins involved in these rare forms of obesity help shed light on the pathways involved in regulating eating behavior and energy homeostasis. Although important, monogenic forms of obesity account for less than 10% of today's obesity epidemic.[11]

Although rare genetic mutations cause dramatic hyperphagia, most of the common genetic variants have smaller effect sizes. The risk of obesity, metabolic syndrome, and other complications is increased by a variety of common genetic variants, and many of these are associated with specific eating behaviors. Research tools used to measure eating behavior include food logs, observation, food preference flash cards, labeled scaling, and, more recently, FMRI. A widely used research tool known as the three-factor questionnaire (TFQ) has been used to quantify eating behaviors in normal-weight and obese individuals as well as those with eating disorders.[12] This questionnaire uses a series of questions to measure three patterns of behavior: restraint, disinhibition, and hunger. High restraint and disinhibition scores are both positively correlated with BMI.[13,14] Restraint is characterized by the intentional avoidance of certain foods in order to control body weight, and is measured by response to questions on the TFQ such as "I avoid certain foods because they make me fat." Disinhibition is the tendency to overeat when surrounded by others who are overeating. Hunger measures the subjective sense of an individual's need to eat. Heritability and linkage analysis of eating behavior measured by the TFQ provides evidence that these behavior traits are heritable.[15,16] Although much remains to be understood about the genes regulating these behaviors, genetic influence of disinhibition has been linked to *neuromedin*, a factor mediating satiety, in a French Canadian cohort and to *TAS2R38*, a bitter taste receptor, in a cohort of Amish women.[16,17] *GAD* (glutamic acid decarboxylase) has also been linked to eating behavior. GAD decarboxylates glutamate into GABA (γ-aminobutyric acid), a major inhibitory neurotransmitter in the brain. Two specific *GAD* variants, rs7908975 and rs992990, have been reported to be associated with disinhibition and disordered food intake, specifically, increased carbohydrate intake in women.[18]

GENETICS OF TASTE

Taste affects food preference and food intake, thereby directly influencing eating behavior. However, not all humans perceive taste in exactly the same way. The density of taste papillae on the tongue, genetic differences in taste receptors or sensitivity of taste receptors, constituents of saliva, and other factors all contribute to an individual's taste perception and subsequent food preferences.[19] Differences in taste papillae density impacts taste sensitivity and are thought to be genetically determined[20]; however, the gene or genes responsible for this trait have yet to be identified. Differences in taste perception and preference influence food choices and have significant impact on nutrient and caloric intake.

Five tastes are recognized by humans: sweet, bitter, sour, salty, and umami (described as the taste of glutamate or the taste of amino acids and proteins). Food preference and intake is influenced by sweet and bitter taste. For example, individuals who possess enhanced perception of bitter taste tend to avoid certain foods, including specific fruit and vegetables.[21] Preference for sweet and high-fat food has been reported to decrease with increasing perception of bitter taste.[21–24] Evidence suggest bitter tasting ability may be related to body mass index (BMI), adiposity, and risk factors for CVD,[25,26] while the perceived sweetness of foods has been shown to be inversely correlated with BMI.[27] Bitter taste sensitivity has also been linked to height variations among children, suggesting this trait may influence food selection and impact growth rate.[28,29] Individuals who are particularly sensitive to bitter compounds tend to avoid the bitter taste of beer and alcohol and avoid cigarette smoking as well.[25,30] Bitter taste as well as preference for sweet and fat guide ingestive behaviors and have been linked to obesity; these food preference traits may, in part, be genetically determined.

Bitter, sweet, and umami tastes are mediated by G-protein-coupled receptors (GPCRs). Bitter taste receptors are encoded by 25–30 *TAS2R* genes, located on chromosomes 12p13, 7q34, and 5p15.31. The ligand specificity of TAS2Rs appears to be quite broad, consistent with their roles in detecting thousands of bitter-tasting compounds.[31] One of these, *TAS2R38* has been extensively characterized in vitro, in vivo, and in human populations, and is responsive to the bitter stimuli phenylthiocarbamide, propylthiouracil (PROP), and to thiocyanates – bitter compounds found in brassia vegetables such as brussels sprouts and broccoli. Two common haplotypes of *TAS2R38* have been shown to influence perception of bitter taste and are significantly related to differences in bitter taste sensitivity,[32] preference for sucrose and sweet-tasting foods and beverages, and to modestly lower the risk of type 2 diabetes among participants of the British

Table 1 **Common variants associated with variations in taste and ingestive behavior.**

Taste	Chromosome	Gene	Influence on ingestive behavior	Reference
Sweet	1p36	TAS1R2, TAS1R3	Unknown	Nie et al. (2005),[41] Nie et al. (2006),[40] Scott et al. (2005)[31]
Umami	1p36	TAS1R1, TAS1R3	Unknown	Scott et al. (2005)[31]
Bitter	12p13, 7q34, 5p15.31	TAS2Rs: TAS2R38, TAS2R5, TAS2R16	Vegetable avoidance, increased fat and sweet intake, disinhibited eating behavior among women Alcohol dependence	Kim et al. (2003)[32] Drewnowski et al. (1997)[21] Mennella et al. (2005)[33] Timpson et al. (2005)[34] Dotson et al. (2008)[46] Lin (2005),[38] Hinrichs (2006)[39]

Women's Heart and Health Study.[33,34] While studies are not all in complete agreement, individuals most sensitive to the taste of PROP more often dislike bitter fruits and vegetables, such as grapefruit and kale. These low-energy foods may be replaced by more energy-dense foods among individuals more sensitive to bitter taste.[35] *TAS2R38* haplotype has been suggested to be predictive of obesity[36]; however, to date, studies involving large cohorts have failed to demonstrate convincing evidence for a direct relationship between *TAS2R38* and BMI in spite of evidence that polymorphisms in this gene influence ingestive behavior.[37] The majority of *TAS2R38* studies have been conducted in Caucasian populations; therefore, further research is necessary to determine how well current findings can be generalized to other ethnic populations.

TAS2R5, another bitter receptor, may be an important regulator of ingestive behavior. This gene resides in a region of chromosome 7 that is significantly associated with a quantitative phenotypic marker of alcohol dependence called ttth 1. Furthermore, a single nucleotide polymorphism (SNP) located within a linkage disequilibrium block that includes *TAS2R5* accounts for this association.[38] A SNP in another chromosome 7 gene, *TAS2R16*, has been linked to alcohol dependence as well.[39] These findings suggest that genetic variation in TAS2R genes may be involved in regulating ingestive behaviors.

The receptors for sweet and umami taste are encoded by three *TAS1R* genes located on chromosome 1p36. Heteromeric TAS1R2:TAS1R3 taste receptors respond to sweet-tasting compounds such as sugars, high-potency sweeteners, and some D-amino acids, while TAS1R1:TAS1R3 heteromers comprise an umami taste receptor sensitive to L-amino acids.[31] Both subunits of the sweet taste receptor bind sugar ligands, though they do so with distinct affinities and ligand-dependent conformational changes.[40,41] Although variability in both sweet and umami taste have been described, these traits are not as well defined as those of PROP tasting, and specific genetic variants responsible for variation in sweet and umami taste remain to be identified.

TAS1Rs and *TAS2Rs* are expressed in diverse tissue, including brain, adrenal gland, pancreas, small intestine, retina, skeletal muscle, salivary gland, and tongue.[42–44] Of particular interest is the observation that TAS1R and TAS2R receptors, as well as other proteins involved in taste transduction, are expressed in the gastrointestinal mucosa, where they modulate responses to ingested nutrients via glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and gastric inhibitory polypeptide (GIP).[44,45] GIP, GLP-1, and CCK regulate gut motility and appetite. Therefore, TAS1Rs and TAS2Rs may be integral to modulating both taste and ingestive behavior via mediating enteroendocrine secretion. Dotson et al.[46] demonstrated *TAS2R9* to be involved in GLP-1 secretion, with a loss-of-function mutation in the gene resulting in attenuated GLP-1 response to agonist. In another study performed by Dotson et al.,[17] genetic variation in *TAS2R38* was shown to be associated with eating behavior in a cohort of Amish women. Genetic variation in TAS1Rs and TAS2Rs may impact eating behavior via altered taste perception as well as via alteration in neuroendocrine signals impacting satiety. The observation that these receptors are involved in both taste and secretion of the hormones involved in satiety tell us that these processes may be biologically entwined. Table 1 summarizes gene variants linked to eating behavior and taste.

MEAL SELECTION AND SIZE

Research into meal size and selection is especially complex as an individual's socioeconomic environment, learned eating behaviors, physiological conditions such as depression, and even medical treatments can all influence appetite and food selection, independent of genetics; however, meal quantity, frequency, and timing are thought to be, at least in part, under genetic control. The study of genetic variants in digestive neuroendocrine hormones, such as CCK, leptin, and ghrelin, are providing new insights into how these hormones and their genetic variants may be involved in pathways regulating appetite and eating behavior.

Ghrelin, a 28-amino acid peptide, is primarily produced by the stomach and pancreas and is involved in promoting meal intake and hunger through receptors in the hypothalamus.[47] Plasma ghrelin levels rise pre-meal and are suppressed by food intake.[48] *GHRL* is located on chromosome 3. The gene product is involved in growth hormone release, and post-translational modifications yield the hormones ghrelin and obstatin. Obstatin opposes the effects of ghrelin and is responsible for satiety and decreasing food intake.[49] Many studies have been devoted to investigating *GHRL* variants with respect to obesity. A common variant, Leu72Met, has been associated with obesity,[50,51] metabolic syndrome,[52] and binge eating.[53]

Leptin and CCK work in opposition to ghrelin to promote satiety. CCK is released in response to lipids and promotes rapid post-prandial satiety in contrast to the long-term action of leptin.[54] In a large case-control study of 17,000 obese and normal-weight women, three common leptin variants (rs4577902, rs2060736, and rs4731413), were associated with increased risk of extreme snacking behavior (top fifth percentile based on 11-question questionnaire), but not increased meal size.[55] CCK variants (rs6809785, rs7611677, rs6801844, and rs6791019) were found to be more associated with extreme meal size (top fifth percentile based on estimated portion sizes using 28 picture cards) but not increased snacking behavior in the same study. The results of this study suggest that genetic variation in genes encoding CCK and leptin may contribute to obesity risk by influencing satiety and may have independent effects. Additional studies are needed to further clarify the role of genetic variation in these genes to provide a better understanding of how they may modulate eating behavior.

FTO, fat mass and obesity-associated gene, has been highly associated with increased risk of obesity.[56] *FTO* is localized to chromosome 16 and is expressed in adipocytes, the pancreas, and the hypothalamus, particularly in regions known to regulate appetite. *FTO* may contribute to obesity by downregulating adipocyte production of leptin.[57] A common variant (rs9939609) is associated with adiposity, and possibly satiety responsiveness. den Hoed et al.[56] demonstrated the A allele of rs9939609 is associated with reduced post-prandial satiety and may also contribute to excess caloric intake in a study of men and women of Western European descent with BMIs ranging from 19 to 31 (5 of 62 subjects had a BMI >30). This study also analyzed post-prandial response to hunger and the interaction among variants in leptin, the leptin receptor, and methyltransferase genes. The authors concluded that the effect of the rs9939609 A allele on the postprandial response in hunger appears to be mediated by an epistatic interaction involving variants in a methyltransferase gene and the leptin receptor. In another study, Scottish children who were homozygous or heterozygous for the rs9939609 A allele also demonstrated increased energy intake without associated energy expenditure. Of interest, all the children ate approximately the same weight of food, but those children with the rs9939609 A allele consumed more energy-dense foods.[58] The authors of this study concluded that this *FTO* variant confers a predisposition to obesity and may play a role in the control of food intake and food choice, perhaps involving a hyperphagic phenotype or a preference for energy-dense foods. Tanofsky-Kraff[59] replicated these findings in a cohort of 289 children and adolescents, suggesting that *FTO* may indeed contribute to preference for higher fat intake and large meal size. Although provoking, these findings should be interpreted with some caution, as at least one study has shown rs9939609 not to be correlated with increased risk of obesity[60]; however, the current accumulated evidence clearly implicates *FTO* as having a significant impact on food intake and obesity.

Genetic variations in *FTO*, leptin, the leptin receptor, and ghrelin, genes involved in the neuroregulation of food intake, appear to contribute to obesity risk by influencing satiety and hunger, and they may contribute to increased caloric intake. Larger and more genetically diverse cohorts need to confirm these observations. Functional studies of the impact of these variants on gene expression or action are also needed. Improving our understanding of the mechanisms whereby these genes interact and their potential molecular crosstalk may provide novel targets for developing treatments for individuals with reduced satiety in response to meals. Table 2 summarizes the current knowledge with respect to genetic variants linked to meal selection and size. Figure 1 depicts genes whose common variants have been implicated with eating behavior and obesity.

Functional magnetic resonance imaging

A variety of cognitive pathways are involved in motivation and control of eating behavior. The new use of neuroimaging techniques, specifically FMRI, to demonstrate specific neural reactions in response to food stimulus is revolutionizing the study of eating behavior. Other imaging techniques, such as positron emission tomography, have been previously used to investigate neural responses to taste and to identify neural pathways involved in eating behavior.[61] FMRI has previously been a well-established tool to identify pathology in studies of schizophrenia,[62] Alzheimer's disease,[63] and many other areas of neuroscience research. Nearly all FMRI studies utilize blood oxygen level dependence (BOLD) to identify areas in the brain that demonstrate increased glucose uptake and therefore increased activity in response to specific stimuli. Eating behavior research utilizing FMRI

Table 2 **Common variants associated with meal selection and size.**

Hormone	Gene variants	Physiologic effect of gene product	Contribution to eating behavior	References
CCK	rs6809785, rs7611677, rs6801844	Rapid post-prandial satiety	Extreme meal size	de Krom et al. (2007)[55]
Leptin	rs4577902, rs2060736, rs4731413	Promotes satiety	Extreme snacking behavior	de Krom et al. (2007)[55]
Ghrelin	Leu72Met, 51GLN	Promotes meal intake and hunger Metabolic syndrome Obesity	Binge eating	Monteleone et al. (2007)[53] Hinney et al. (2002)[51] Korbonits et al. (2002)[50] Steinle et al. (2005)[52]
FTO	rs9939609	Downregulates leptin, suppresses satiety	Reduced post-prandial satiety, increased caloric intake	den Hoed et al. (2009)[56] Cecil et al. (2008)[58] Tanofsky-Kraff et al. (2009)[59]
GAD	rs7908975, rs992990	Promotes GABA, regulates food intake	Increased carbohydrate intake	Choquette et al. (1998)[18]

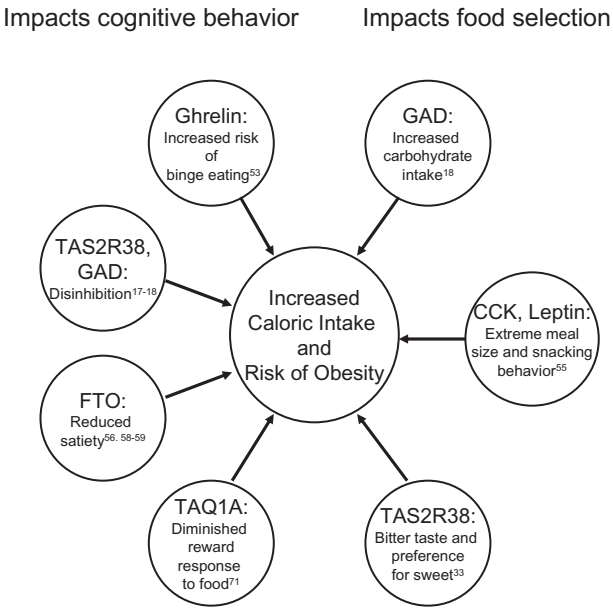

Figure 1 **Genes identified with common variants influencing eating behavior with potential impact on obesity.**

has focused on BOLD changes in specific brain regions in obese compared to normal-weight individuals.

Eating behavior studies utilizing FMRI have shown that a fasting state increases cortical activation among lean individuals,[64] increases preference for high-calorie foods in obese individuals,[64–66] and that obese men have attenuated post-prandial brain reactions to satiety that may explain excess caloric intake.[67] Ghrelin infusion in normal-weight volunteers produced increased BOLD response to food pictures in the amygdala, orbitofrontal cortex, anterior insula, and striatum, areas of the brain involved in activating ingestive behavior, and elicited increased self-reports of hunger.[68] Likewise, patients with lower leptin levels secondary to weight loss or secondary to genetic leptin deficiency have increased BOLD activity in brain areas involved in emotional, cognitive, and sensory control of food intake in response to food stimuli, which subsequently normalize with leptin infusion.[7,69]

Neurophysiologic processing in response to food is largely accomplished in the left hemisphere, specifically in the dorsal and ventral striatum, fusiform gyri, and insula, with the latter two known as the "primary gustatory complex."[64] Feeding is associated with dopamine release,[70] and the amount of dopamine release positively correlates with perceived food pleasure.[71] Obese individuals have lower striatal concentrations of the D2 dopamine receptor,[71] which is a finding that suggests the lower concentrations of this G protein-coupled receptor may evoke overeating in obese individuals in order to produce a reward response. An alternative interpretation is that dopamine receptors may be downregulated in response to excessive food stimuli. Martin et al.[72] demonstrated that brain regions involved in pathways of food reward in obese individuals exhibited increased BOLD activation, specifically the limbic region and the prefrontal region, both of which have high concentrations of dopamine receptors. Obese individuals also had greater memory for foods in the fasted state. Fasted obese individuals have also been shown to exhibit higher pre-meal activation of the anterior cingulated cortex and medial prefrontal cortex, areas of the brain implicated in motivational processing.[72] These findings have been supported by Haase et al.[73] who also noted increased BOLD activation in the prefrontal and limbic regions in response to taste stimuli among fasting obese individuals. Although these studies are promising, they remain limited by small numbers of

participants and many of these studies have focused largely on obese women. Because magnetic resonance imaging equipment can withstand limited study subject body weight, studies using this tool are restricted to the inclusion of subjects whose body weights can be accommodated by the equipment. Despite these limitations, FMRI has been used successfully to shed light on the pathways involved in eating behavior and to demonstrate important functional differences in brain imaging among obese individuals.

Of particular interest are innovative studies combining genetic studies with FMRI to investigate eating behavior. Combining these modalities may help uncover interrelationships among genetics and the neurophysiologic pathways involved in food response and eating behavior. Felsted et al.[74] hypothesized that polymorphisms in genes involved in the neurophysiology of feeding and reward processing would demonstrate differential responses in brain regions known to be involved in food reward. They chose to investigate a particular variant, TAQ1A,[75] a restriction fragment length polymorphism located on *ANKK1* (ankyrin repeat and protein kinase domain-containing protein 1), a regulatory gene downstream of the dopamine D2 receptor, and to perform functional magnetic resonance imaging to measure neural response to the ingestion of palatable and caloric milkshakes in 26 healthy subjects (24 women and 2 men). The TAQ1A variant has previously been implicated as having a role in obesity and eating behavior, particularly with respect to the relationship between neural response to food and prospective weight gain.[71] Individuals with the A1/A1 or A1/A2 allele of TAQ1A are more likely to be obese and have 30–40% fewer dopamine receptors.[71] In the Felsted study, either a milkshake or a tasteless, odorless liquid was randomly dripped into the mouths of the subjects while the subjects rested within the MRI device. The investigators attempted to control for confounding variables that may influence food response. Participants were all matched for BMI, hunger rating, and for psychological factors such as impulsivity, addiction, and eating style assessed through a variety of psychological and food intake surveys. No subject reported taking prescriptions or over-the-counter medications. This study elegantly demonstrated that individuals possessing the A1 TAQ1A allele had decreased BOLD response to a milkshake in midbrain, thalamus, and orbital frontal cortex regions of the brain, all of which are involved in regulating eating behavior, even though all participants rated similarly the perceived pleasantness and familiarity of the milkshake.[74] These findings suggest that individuals possessing the A1 allele might be predisposed to overeating as they experience attenuated neural reward response to food. Whether this variation in response to food stimulus is due to a diminished number of dopamine receptors is yet to be determined. This study is, to our knowledge, the first to directly demonstrate that individuals with a specific genetic variant have measurable neural changes directly correlated with eating behavior in response to a food stimulus. These findings provide hope for the future development of treatment aimed at modulating food-induced sensitivity to pleasure and satiety centers in genetically susceptible individuals.

CONCLUSION

Eating behavior is a complex trait with both genetic and environmental influences. While sequencing an individual's entire genome is expensive, this process will become less costly and more rapid in the future. Personalized medicine, tailoring pharmacologic and behavioral therapy to an individual's genetic code, is an emerging practice. Applications of research regarding the genetics of eating behavior may lead to the individualization of therapies targeting specific genetic mutations and behavioral interventions addressing eating behaviors. For example, once the role of specific gene variants in pathways involved in specific behaviors or food responses are well established, treatment could be individualized toward modifying these behaviors (e.g., carbohydrate craving, unrestrained or binge eating, comfort eating, food addiction) and toward pharmacologic modalities developed to modify the molecular pathways involved. Individuals with a TAS2R38 variant associated with enhanced bitter taste might be counseled to select healthy foods that might be more palatable or instructed regarding methods of food preparation to make bitter vegetables more palatable. While current research is limited, preliminary studies hold promise toward these ends. Authors of a nutra-genomic study involving customized treatment with a nutraceutical based on the study subjects' genetic profile report improvement in weight loss, sugar craving reduction, appetite suppression, snack reduction, and reduction of late-night eating among study participants who received therapy tailored toward their genetic profile.[76]

The risk of obesity, metabolic syndrome, and related complications is increased by a variety of common genetic variants, and many of these are associated with specific eating behaviors. Although rare genetic mutations cause dramatic hyperphagia, common genetic variants usually are responsible for smaller effect sizes. It is likely, however, that genetic susceptibility toward aberrant eating behavior and obesity may be overcome by practicing healthy behaviors. This principle was demonstrated among individuals harboring the common TCF7L2 variant, which is associated with increased risk of developing type 2 diabetes mellitus (T2DM). In the Diabetes Prevention Study, individuals with the at-risk

variant who were randomized to intense lifestyle interventions including prudent diet, weight loss, and physical activity, demonstrated reduced progression to T2DM in spite of their genetic predisposition.[77] Studies involving *FTO* variants also demonstrate that genetic predispositions to obesity can be overcome by prudent diet and exercise.[78,79] With additional research, individuals and physicians will have more tools to help identify susceptible individuals and to guide therapy and treatment. The study of the genetics of eating behavior and its interplay with obesity is progressing rapidly, and new techniques, including FMRI, are changing how behavioral research is performed and providing new insights into the mechanisms of eating behavior. While it is currently premature to know if developing pharmacologic therapies targeting the A1 allele of TAQ1A or other alleles discussed in this review will contribute to substantial changes in eating behavior or weight loss treatment, it may be helpful, nevertheless, for individuals to become aware of their genetic susceptibilities and to practice prudent nutritional behaviors before they become overweight or obese.

Acknowledgments

Funding. Nanette Steinle is supported by NIH R01HL076768 and NIH P30DK072488.

Declaration of interest. The authors have no relevant interests to declare.

REFERENCES

1. Magni P, Dozio E, Ruscica M, et al. Feeding behavior in mammals including humans. Ann NY Acad Sci. 2009;1163: 221–232.
2. Holsen LM, Zarcone JR, Brooks WM, et al. Neural mechanisms underlying hyperphagia in Prader-Willi syndrome. Obesity. 2006;14:1028–1037.
3. Greenswag LR. Adults with Prader-Willi syndrome: a survey of 232 cases. Dev Med Child Neurol. 1987;29:145–152.
4. D'Angelo CS, Kohl I, Varela MC, et al. Extending the phenotype of monosomy 1p36 syndrome and mapping of a critical region for obesity and hyperphagia. Am J Med Genet A. 2010;152A:102–110.
5. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997;387:903–908.
6. Clément K, Vaisse C, Lahlou N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature. 1998;392:398–401.
7. Baicy K, London ED, Monterosso J, et al. Leptin replacement alters brain response to food cues in genetically leptin-deficient adults. Proc Natl Acad Sci USA. 2007;104:18276–18279.
8. Shimizu H, Inoue K, Mori M. The leptin-dependent and -independent melanocortin signaling system: regulation of feeding and energy expenditure. J Endocrinol. 2007;193:1–9.
9. Hinney A, Schmidt A, Nottebom K, et al. Several mutations in the melanocortin-4 receptor gene including a nonsense and a frameshift mutation associated with dominantly inherited obesity in humans. J Clin Endocrinol Metab. 1999;84:1483–1486.
10. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med. 2003;348:1085–1095.
11. Farooqi S, O'Rahilly S. Genetics of obesity in humans. Endocr Rev. 2006;27:710–718.
12. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res. 1985;29:71–83.
13. Provencher V, Drapeau V, Tremblay A, Després JP, Lemieux S. Eating behaviors and indexes of body composition in men and women from the Québec family study. Obes Res. 2003;11:783–792.
14. Gallant AR, Tremblay A, Pérusse L, Bouchard C, Després JP, Drapeau V. The three-factor eating questionnaire and BMI in adolescents: results from the Québec Family Study. Br J Nutr. 2010;7:1–6.
15. Steinle NI, Hsueh WC, Snitker S, et al. Eating behavior in the Old Order Amish: heritability analysis and a genome-wide linkage analysis. Am J Clin Nutr. 2002;75:1098–1106.
16. Bouchard L, Drapeau V, Provencher V, et al. Neuromedin beta: a strong candidate gene linking eating behaviors and susceptibility to obesity. Am J Clin Nutr. 2004;80:1478–1486.
17. Dotson CD, Shaw HL, Mitchell BD, Munger SD, Steinle NI. Variation in the gene *TAS2R38* is associated with the eating behavior disinhibition in Old Order Amish women. Appetite. 2010;54:93–99.
18. Choquette AC, Lemieux S, Tremblay A, et al. GAD2 gene sequence variations are associated with eating behaviors and weight gain in women from the Quebec family study. Physiol Behav. 1998;4:505–510.
19. Rolls ET. Taste, olfactory, and food texture processing in the brain, and the control of food intake. Physiol Behav. 2005;85:45–56.
20. Bartoshuk LM, Duffy VB, Miller IJ. PTC/PROP tasting: anatomy, psychophysics, and sex effects. Physiol Behav. 1994;56:1165–1171.
21. Drewnowski A, Henderson SA, Shore AB, Barratt-Fornell A. Nontasters, tasters, and supertasters of 6-n-propylthiouracil (PROP) and hedonic response to sweet. Physiol Behav. 1997;62:649–655.
22. Duffy VB, Bartoshuk LM. Food acceptance and genetic variation in taste. J Am Diet Assoc. 2000;100:647–655.
23. Tepper BJ, Nurse RJ. Fat perception is related to PROP taster status. Physiol Behav. 1997;61:949–954.
24. Tepper BJ, Nurse RJ. PROP taster status is related to fat perception and preference. Ann N Y Acad Sci. 1998;855:802–804.
25. Duffy VB, Peterson JM, Bartoshuk LM. Associations between taste genetics, oral sensation and alcohol intake. Physiol Behav. 2004;82:435–445.
26. Goldstein GL, Daun H, Tepper BJ. Adiposity in middle-aged women is associated with genetic taste blindness to 6-n-propylthiouracil. Obes Res. 2005;13:1017–1023.
27. Bartoshuk LM, Duffy VB, Hayes JE, Moskowitz HR, Snyder DJ. Psychophysics of sweet and fat perception in obesity: problems, solutions and new perspectives. Philos Trans R Soc Lond B Biol Sci. 2006;361:1137–1148.
28. Golding J, Steer C, Emmett P, Bartoshuk LM, Horwood J, Smith GD. Associations between the ability to detect a bitter

taste, dietary behavior, and growth: a preliminary report. Ann N Y Acad Sci. 2009;1170:553–557.
29. Johnston FE, Hertzog KP, Malina RM. Phenylthiocarbamide taste sensitivity and its relationship to growth variation. Am J Phys Anthropol. 1966;24:253–255.
30. Enoch MA, Harris CR, Goldman D. Does a reduced sensitivity to bitter taste increase the risk of becoming nicotine addicted? Addict Behav. 2001;26:399–404.
31. Scott K. Taste recognition: food for thought. Neuron. 2005;48:455–464.
32. Kim UK, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. Science. 2003;299:1221–1225.
33. Mennella JA, Pepino MY, Reed DR. Genetic and environmental determinants of bitter perception and sweet preferences. Pediatrics. 2005;115:e216–222.
34. Timpson NJ, Christensen M, Lawlor DA, et al. TAS2R38 (phenylthiocarbamide) haplotypes, coronary heart disease traits, and eating behavior in the British Women's Heart and Health Study. Am J Clin Nutr. 2005;81:1005–1111.
35. Bell KI, Tepper BJ. Short-term vegetable intake by young children classified by 6-npropylthoiuracil bitter-taste phenotype. Am J Clin Nutr. 2006;84:245–251.
36. Tepper BJ, Koelliker Y, Zhao L, et al. Variation in the bitter-taste receptor gene *TAS2R38*, and adiposity in a genetically isolated population in Southern Italy. Obesity (Silver Spring). 2008;16:2289–2295.
37. Sausenthaler S, Rzehak P, Wichmann HE, Heinrich J. Lack of relation between bitter taste receptor TAS2R38 and BMI in adults. Obesity (Silver Spring). 2009;17:937–938.
38. Lin HF, Juo SH, Cheng R. Comparison of the power between microsatellite and single-nucleotide polymorphism markers for linkage and linkage disequilibrium mapping of an electrophysiological phenotype. BMC Genet. 2005;6(Suppl 1):S7.
39. Hinrichs AL, Wang JC, Bufe B, et al. Functional variant in a bitter-taste receptor (hTAS2R16) influences risk of alcohol dependence. Am J Hum Genet. 2006;78:103–111.
40. Nie Y, Hobbs JR, Vigues S, Olson WJ, Conn GL, Munger SD. Expression and purification of functional ligand-binding domains of T1R3 taste receptors. Chem Senses. 2006;31:505–513.
41. Nie Y, Vigues S, Hobbs JR, Conn GL, Munger SD. Distinct contributions of T1R2 and T1R3 taste receptor subunits to the detection of sweet stimuli. Curr Biol. 2005;15:1948–1952.
42. Dyer J, Salmon KS, Zibrik L, Shirazi-Beechey SP. Expression of sweet taste receptors of the T1R family in the intestinal tract and enteroendocrine cells. Biochem Soc Trans. 2005;33:302–305.
43. Sternini C, Anselmi L, Rozengurt E. Enteroendocrine cells: a site of "taste" in the gastrointestinal chemosensing. Curr Opin Endocrinol Diabetes Obes. 2008;15:73–78.
44. Wu SV, Rozengurt N, Yang M, Young SH, Sinnett-Smith J, Rozengurt E. Expression of bitter taste receptors of the T2R family in gastrointestinal tract and enteroendocrine STC-1 cells. Proc Natl Acad Sci USA. 2002;99:2392–2397.
45. Gautier JF, Choukem SP, Girard J. Physiology of incretins (GIP and GLP-1) and abnormalities in type 2 diabetes. Diabetes Metab. 2008;34(Suppl 2):S65–S72.
46. Dotson CD, Zhang L, Xu H, et al. Bitter taste receptors influence glucose homeostasis. PLoS ONE. 2008;3:e3974.
47. Nakazato M, Murakami N, Date Y, et al. A role for ghrelin in the central regulation of feeding. Nature. 2001;409:194–198.
48. Callahan HS, Cummings DE, Pepe MS, Breen PA, Matthys CC, Weigle DS. Postprandial suppression of plasma ghrelin level is proportional to ingested caloric load but does not predict intermeal interval in humans. J Clin Endocrinol Metab. 2004;89:1319–1324.
49. Zhang JV, Ren PG, Avsian-Kretchmer O, et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science. 2005;310:996–999.
50. Korbonits M, Gueorguiev M, O'Grady E, et al. A variation in the ghrelin gene increases weight and decreases insulin secretion in tall, obese children. J Clin Endocrinol Metab. 2002;87:4005–4008.
51. Hinney A, Hoch A, Geller F, et al. Ghrelin gene: identification of missense variants and a frameshift mutation in extremely obese children and adolescents and healthy normal weight students. J Clin Endocrinol Metab. 2002;87:2716–2719.
52. Steinle N, Pollin T, O'Connell J, Mitchell B, Shuldiner A. Variants in the ghrelin gene are associated with metabolic syndrome in the Old Order Amish. J Clin Endocrinol Metab. 2005;90:6672–6677.
53. Monteleone P, Tortorella A, Castaldo E, Di Filippo C, Maj M. The Leu72Met polymorphism of the ghrelin gene is significantly associated with binge eating disorder. Psychiatr Genet. 2007;17:13–16.
54. Dockray GJ. Cholecystokinin and gut-brain signalling. Regul Pept. 2009;155:6–10.
55. de Krom M, van der Schouw YT, Hendriks J, et al. Common genetic variations in CCK, leptin, and leptin receptor genes are associated with specific human eating patterns. Diabetes. 2007;56:276–280.
56. den Hoed M, Westerterp-Plantenga MS, Bouwman FG, Mariman EC, Westerterp KR. Postprandial responses in hunger and satiety are associated with the rs9939609 single nucleotide polymorphism in FTO. Am J Clin Nutr. 2009;90:1426–1432.
57. Hoffstedt J, Eriksson P, Mottagui-Tabar S, Arner P. A polymorphism in the leptin promoter region (-2548 G/A) influences gene expression and adipose tissue secretion of leptin. Horm Metab Res. 2002;34:355–359.
58. Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CN. An obesity-associated FTO gene variant and increased energy intake in children. N Engl J Med. 2008;359:2558–2566.
59. Tanofsky-Kraff M, Han JC, Anandalingam K, et al. The FTO gene rs9939609 obesity-risk allele and loss of control over eating. Am J Clin Nutr. 2009;90:1483–1488.
60. Stutzmann F, Cauchi S, Durand E, et al. Common genetic variation near MC4R is associated with eating behaviour patterns in European populations. Int J Obes. 2009;33:373–388.
61. DelParigi A, Chen K, Salbe AD, Reiman EM, Tataranni PA. Sensory experience of food and obesity: a positron emission tomography study of the brain regions affected by tasting a liquid meal after a prolonged fast. Neuroimage. 2005;24:436–443.
62. Edwards BG, Barch DM, Braver TS. Improving prefrontal cortex function in schizophrenia through focused training of cognitive control. Front Hum Neurosci. 2010;4:32.
63. Bokde AL, Karmann M, Born C, Teipel SJ. Altered brain activation during a verbal working memory task in subjects with amnestic mild cognitive impairment. J Alzheimers Dis. 2010;21(1):103–118.

64. Porubska K, Veit R, Preissl H, Fritsche A, Birbaumer N. Subjective feeling of appetite modulates brain activity: an fMRI study. Neuroimage. 2006;32:1273–1280.
65. Goldstone AP, de Hernandez CG, Beaver JD, et al. Fasting biases brain reward systems towards high-calorie foods. Eur J Neurosci. 2009;30:1625–1635.
66. Stoeckel LE, Weller RE, Cook EW, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage. 2008;41:636–647.
67. Le DS, Pannacciulli N, Chen K, et al. Less activation of the left dorsolateral prefrontal cortex in response to a meal: a feature of obesity. Am J Clin Nutr. 2006;84:725–731.
68. Malik S, McGlone F, Bedrossian D, Dagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab. 2008;7:400–409.
69. Ahima RS. Revisiting leptin's role in obesity and weight loss. J Clin Invest. 2008;118:2583–2591.
70. Siep N, Roefs A, Roebroeck A, Havermans R, Bonte ML, Jansen A. Hunger is the best spice: an fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. Behav Brain Res. 2009;198:149–158.
71. Stice E, Spoor S, Bohon C, Small DM. Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. Nutrition. 2009;25:132–133.
72. Martin LE, Holsen LM, Chambers RJ, et al. Neural mechanisms associated with food motivation in obese and healthy weight adults. Obesity. 2010;18:254–260.
73. Haase L, Cerf-Ducastel B, Murphy C. Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. Neuroimage. 2009;44:1008–1021.
74. Felsted JA, Ren X, Chouinard-Decorte F, Small DM. Genetically determined differences in brain response to a primary food reward. J Neurosci. 2010;30:2428–2432.
75. Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosomeband 11q23.1. Hum Mutat. 2004;23:540–545.
76. Waite RL, Williams L, Braverman ER, et al. LG839: anti-obesity effects and polymorphic gene correlates of reward deficiency syndrome. Adv Ther. 2008;25:894–913.
77. Florez JC, Jablonski KA, Bayley N, et al. Diabetes prevention program research group. N Engl J Med. 2006;355:241–250.
78. Ruiz JR, Labayen I, Ortega FB. Attenuation of the effect of the FTO rs9939609 polymorphism on total and central body fat by physical activity in adolescents: the HELENA study. Arch Pediatr Adolesc Med. 2010;164:328–333.
79. Mitchell JA, Church TS, Rankinen T, Earnest CP, Sui X, Blair SN. FTO genotype and the weight loss benefits of moderate intensity exercise. Obesity. 2010;18:641–643.