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METABOLISM (A SÁNCHEZ-VILLEGAS, SECTION EDITOR)

Obesity: Underlying Mechanisms and the Evolving Influence of Diet

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Abstract Obesity is determined by both genetic and environmental factors. Since 2007, 52 genes have been associated with obesity and obesity-related measurements in genome-wide association studies (GWAS), among these the fat and obesity-associated gene (*FTO)*. Despite the success in identifying genes predisposing to obesity, these GWAS hits only account for approximately about 5 % of the estimated obesity heritability and do not predict who will become obese and who will not. The missing heritability might be accounted for by gene-gene and gene-environment interactions. Most consistently, physical activity has been shown to attenuate the effect of *FTO* on obesity. Several studies have examined gene-diet interactions in relation to obesity, but only a few suggestive interactions have been identified. This is most probably due to small effect sizes of the interactions and thereby a demand for large samples sizes and accurate measurements of exposures and outcomes. In addition to SNPs, epigenetic changes have been suggested to account for some of the missing heritability, and epigenetic changes have been shown to be induced by dietary intake of mothers, *in utero* conditions, and early nutrition and can lead to increased risk of developing obesity. Recently, the intestinal microbiome, the collected genome of the bacteria, also has been associated with obesity and with specific dietary profiles. The underlying mechanisms determining the susceptibility to obesity do not only include the genome but also the epigenome and the microbiome that can be modified by diet, and by genotype, adding to the complexity of determining the contributors to obesity.

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Introduction

Obesity is prevalent in westernized countries and has a high incidence in developing countries [1] and with the observed association with an increased overall mortality [2], obesity is a pandemic and a worldwide problem. The increase in the percentage of obese individuals in the population during the past 30 years has been mostly attributed to a change toward a more energy-dense diet and sedentary life, but other factors, including maternal age, infections, and sleep deprivation also have been suggested to contribute to the obesity pandemic [3]. Despite the apparent obesity-promoting environment and a general increase in overweight and obesity on the population level, the individual's response to the environment also is attributable to nonenvironmental factors. Studies of twins and adoptees have shown that monozygotic twins are more concordant for obesity than dizygotic twins, and adoptees are more similar in body mass index (BMI) to their biological, than to their adopted parents [4, 5], making it likely that there is a significant heritable component that determines susceptibility to obesity. The heritability (h^2) is estimated to be relatively high by twin studies and low by family studies, but a general estimate of obesity heritability is that it explains approximately 65 % of the variance in BMI [6]. Thus, in addition to the environmental factors giving a high rise in the worldwide prevalence of obesity, genetic predisposition may explain some of the inter-individual variance in the given environment. Yet, it has been suggested that the heritability of obesity has been overestimated due to interactions between genes and gene

and environment [7•] and that epigenetic factors, which affect gene transcription without changing the DNA sequence, might explain some of the estimated obesity heritability [8]. Alternatively, the common disease—common mutation theory might not apply, and more of the variation in BMI might be explained by relatively rare mutations. Additionally, it has been recently discovered that our other genome—the collected genome of the gut bacteria (microbiome)—is associated with obesity [9, 10], suggesting that nonhuman genetic factors also might influence obesity development.

Genetic Variation and Obesity

Because obesity is a common disease, it has been assumed that the major heritable part of obesity would be common genetic variants, or single nucleotide polymorphisms (SNPs). Still, mutations with a relatively low frequency, and possibly unique for the individual/family, have been shown to lead to severe obesity. Monogenic obesity is mostly caused by mutations in genes in the leptin-melanocortin signaling pathway or genes expressed in hypothalamic nuclei [11]. Mutations reducing the activity or expression of the melanocortin 4 receptor (*MC4R*) are the most common form of monogenic obesity occurring with a frequency of 2–6 % in individuals with obesity [11–14]. Even with an established link between molecular function (*in vitro*) of the *MC4R* mutations and *ad libitum* food intake [12], there is an age-dependent penetrance of the obese phenotype [14] and environmental factors do still influence *MC4R monogenic obesity [15]*.

A few studies, except for the treatment with recombinant leptin for leptin-deficient children [11], have examined treatment possibilities for individuals with monogenic mutations in the leptin-melanocortin pathway. The studies of lifestyle interventions for individuals with mutations in proopiomelanocortin *(POMC)* or *MC4R* show that weight loss on either diet or diet and physical activity was similar to obese individuals without mutations in these genes [15–17], but the children with *MC4R* mutations were not successful in maintaining their weight loss compared with noncarriers [17]. There are indications the MC4R deficiency also might decrease weight loss after bariatric surgery, whereas *MC4R* haploinsufficiency does not affect weight loss after Roux-en-Y gastric bypass (RYBG) [18, 19].

Before the genome-wide association study (GWAS) era, genome-wide linkage studies that used polymorphic markers to examine the entire genome for co-segregation with obesity in families, and candidate gene studies that used prior knowledge of the gene function to select and identify mutations in relevant genes, identified 52 genomic regions (replicated by at least two studies) and 426 mutations associated with obesity [20]. Compared with genome-wide linkage and candidate gene studies, GWAS have had a higher success rate of identifying robust associations between SNPs and obesity due to inclusion of a large number of SNPs covering the genome and a large number of individuals, and using a two-stage design with replication of the initial genome-wide significant SNPs ($p<5\times10^{-8}$) [21••]. Since the first GWAS that identified an association between fat mass- and obesity-associated gene (*FTO*) and BMI for a population of 4,892 British individuals with type 2 diabetes with replication in 38,759 individuals [22] and for an population of 4,741 Sardinian individuals with replication in 3,205 individuals [23], the number of published GWAS has increased greatly. Although with a smaller and smaller expected effect size of the next obesity-associated SNP, the next GWAS will need to include an even larger population to identify these SNPs [24–26].

In total, 32 SNPs (or loci) have been associated with BMI/obesity [21••, 24, 25] and additional loci have been associated with fat percentage, waist-to-hip ratio, and abdominal obesity [21••]. *FTO* rs9939609 that has the largest effect on obesity of all GWAS hits, only increases the risk of obesity by 1.2-fold and one risk-allele would give an average increase of 0.4 BMI units [21••]. If all 32 loci are considered to each give a small increased risk of obesity, loading all obesity risk alleles to give a combined risk estimate might explain more of the heritability of obesity. However, allele loading does not lead to better predictions of obesity risk than risk estimates based on parent or childhood obesity [21••]. It remains that only a fraction of the expected genetic contribution to obesity has been identified with the 32 confirmed loci for BMI accounting for 1.5 % of the inter-individual variation [21••, 25], corresponding to less than 5 % of the estimated heritability.

Genetic Variation and Food Preference

A change in food preference toward energy-dense foods could be one of the mechanisms by which common SNPs increase susceptibility to obesity. For the *FTO*, the rs9930609 A-allele has been associated with increased intake of fat (1.5 g/day) and total energy 25 kJ/day (based on 3-day unweighted food records) independently of BMI among the 3,641 children [27], and the A-allele is associated with an increased total energy intake among 76 children (based on three *ad libitum* lunch meals with different pre-load) independently of body weight [28]. Both of these studies suggest that A-allele carriers tend to have a higher intake of energy dense foods than noncarriers, which might precede the development of obesity. In addition, the *FTO* rs9939609 AA-genotype has been associated with diminish satiety among 3,337 children from the United Kingdom [29].

In adults, the A-allele of the *FTO* rs9930609 has been associated with a higher habitual intake of fat among 706 Canadians with different ethnicities [30], and a higher intake of dietary protein and of energy from fat [31], and the AA-genotype also with lower habitual carbohydrate intake but no interaction with protein or fibers were observed among 4,839 individuals [31]. Among 21,675 health women from the Women's Genome Health Study, the *FTO* rs8050136 A-allele, which is in complete linkage disequilibrium (LD) with rs9939609, and can as such act as a representative or tagSNP for rs9939609, has been significantly associated with a slightly higher habitual dietary intake of protein and cereal, but not total energy, fats, carbohydrates, legumes or fruit [32]. However, several studies have not identified associations between *FTO* and dietary intake or food preference. Among 756 healthy normal to overweight adult twin pairs, rs9930609 was not associated with habitual total energy intake, macronutrient composition, glycemic index/load, dietary energy density or energy from 20 different food group assessed by a 247-question food frequency questionnaire (FFQ) [33]. No effect of rs9939609 was observed on dietary intake assessed by 3-day food record during 3.2 years of follow-up of 470 overweight Finnish adults [34]. Among 6,024 overweight adults, there was no association between rs17817449 and total energy intake or macronutrient intake assessed with 140-item FFQ [35].

In the LOOK AHEAD study, SNPs that had been previously associated with obesity in GWAS or associated with weight loss were examined in relation to dietary intake in 2,075 individuals with overweight and type 2 diabetes using FFQs [36•]. In total, 16 SNPs in 11 genes were included: *FTO (4 SNPs), MC4R*, brain-derived neurotrophic factor (*BDNF, 3 SNPs)*, insulin induced gene 2 (*INSIG2)*, mitogen-activated protein kinase kinase 5 (*MAP2K5)*, mitochondrial translational initiation factor 3 (*MTIF3)*, nischarin/stabilin 1 (*NISCH/STAB1)*, peroxisome proliferator-activated receptor gamma (*PPARG)*, glutaminyl-peptide cyclotransferase-like/gastric inhibitory polypeptide receptor (*QPCTL/GIPR)*, SH2B adaptor protein 1 (*SH2B1),* and TNNI3 interacting kinase *(TNNI3K)*. *BDNF* rs6265 was associated with an increased energy intake of 100 kcal/day/allele, *TNNI3K* rs1514176 was associated with a lower percentage intake of dietary protein of 0.3E%/allele, and *FTO* rs1421085 with a higher E% from fat of 0.5E%/allele [36•]. Another analysis of 12 SNPs, previously associated with obesity in GWAS, and macronutrient preference among 1,700 Dutch individuals from the EPIC cohort showed that *SH2B1* was significantly associated with increased intake of fat (1.1 g/d/G-allele) and saturated fatty acids (SFA, 0.6 g/d/G-allele) after correction for multiple testing, while there were suggestive evidence for association between intake of fat (including SFA and monounsaturated fatty acids [MUFA]) for SNPs in potassium channel tetramerisation domain containing 15 (*KCTD15)* and neuronal growth regulator 1 (*NEGR1)*, and for association between carbohydrate intake and SNPs in *KCTD15* and mitochondrial carrier 2 (*MTCH2)* [37].

Despite these association between GWAS-identified SNPs and food intake/preference, genetic variation in taste receptors (*TAS1R* and *TAS2R*) that has been associated previously with taste perception of sweet, bitter, and umami have not been identified as GWAS hits [38]. Only a few studies have suggested an association between SNPs in taste receptors, taste perception, or food preference and obesity [38]. Nevertheless, it has been shown that consumption of fruit, vegetables, and protein has a moderate heritability and that there is a significant proportion of the genetic variance that was shared between fruit and vegetable intake and BMI [39]. These studies do suggest that genetic variation that influences taste perception or food preference might contribute to the development of obesity. A specific food preference has not been shown to precede obesity and only suggestive evidence for an association between *FTO* SNPs and an increase in energy dense foods has been observed in children.

Gene-diet Interactions in Obesity

Several common mutations in candidate genes involved in energy expenditure, adrenoceptor beta 3 (*ADRB3)*, uncoupling protein 1 (*UCP1)* and 2 (*UCP2*), appetite control, leptin (*LEP)*, leptin receptor (*LEPR)* and 5-hydroxytryptamine (serotonin) receptors (*HTR2*) and lipid metabolism, PPARG coactivator 1 alpha (*PPARGC1A)*, perilipin 1 (*PLIN1)*, hepatic lipase (*LIPC)*, fatty acid binding protein 2 (*FABP2) and PPARG,* have been shown to modify response to weight loss with and without interaction with diet or lifestyle [40, 41, 42••], whereas other studies have failed to identify such associations [40, 43]. From the candidate gene studies, the most investigated and consistently associated SNP *PPARG* Pro12Ala (rs1801282) [44, 45] has recently been shown to interact with dietary fat in determining obesity and weight loss among 1,465 subjects undergoing a life-style intervention study based on a Mediterranean diet [46]. In addition, another SNP in a candidate gene for obesity apolipoprotein A-II (*APOA2*) rs5082 has been shown to interact with high fat intake on weight (>22 g/d) loss success and this have been replicated in six independent studies, including more than 10,000 individuals [47, 48].

After identification in GWAS, the most consistently obesity-associated SNPs, including *FTO*, *MC4R,* and transcription factor 7-like 2 (*TCF7L2*) have been investigated for their influence on weight loss and for gene-environment interactions in obesity and weight changes. For gene-environment interactions, SNPs in *FTO* have most consistently been shown to interact with physical activity to attenuate the effect of the association between *FTO* and obesity

[49]. Yet, most studies have not found a direct effect of *FTO* rs9939609/rs17817449 or rs17818902 on weight loss [50–54], and among these a large study of 41,504 Scandinavians that did not find that the *FTO* rs9939609 was associated with weight change [55•]. However, the rs9939609 AA-genotype was associated with better maintenance of weight loss during 40-weeks of weight maintenance diet [56], and A-allele carriers have an increased weight loss (0.83 kg) when eating a Mediterranean diet with a high content of virgin olive oil or nuts than independently of diet allocation (0.69 kg) over 3 years [57].

The *FTO* rs9930609 A-allele have been shown to interact with high intakes of SFA to give a higher BMI [58] or larger waist circumference [59••] and also with a low polyunsaturated fatty acids (PUFA):SFA ratio to give a larger waist circumference [59••]. The *FTO* rs9930609 AA-genotype interacts with energy-adjusted fat intake (AA-genotype gives a higher BMI with high fat intake) and carbohydrate intake (AA-genotype gives a higher BMI with low carbohydrate intake) to determine obesity [31]. This indicates that the observations of a preference for energy-dense food independently of obesity degree that was made in children might be more specific for SFAs in adults, as studies suggest an interaction between SFAs and FTO in modifying obesity. However, a recent study showed no significant interactions for fat E%, protein E%, carbohydrate E%, or glycemic index (GI) on BMI or waist circumference or changes among 6,566 individual of European descent [60], and no effect of an interaction between rs9939609 and fat intake on overall mortality or cardiovascular mortality among 22,799 individuals from the population-based Malmö diet and cancer cohort [61]. Interestingly, the *FTO* rs9939609 is associated with underreporting [31, 52]. Because the underreporting might be due to a general tendency of underreporting of energy dense and likely "unhealthy" food items, this could attenuate the identification of interactions between FTO and total energy intake or SFAs on obesity in some of the reported studies.

MC4R rs12970134, rs17700633, and rs17782313 has been investigated for associations with habitual total energy intake, macronutrient composition, glycemic index/load, dietary energy density, or energy from 20 different food group (assessed by a 247-question FFQ) among 756 healthy, normal-to-overweight, adult, twin pairs and only a suggestive association with energy from whole grains was identified [33]. The *MC4R* rs17782313 was associated with a higher intake of total energy, total fat, and protein, but there was no interaction between the SNP and these food preferences in determining weight increase over 10 years among 5,724 women [62]. A previously identified SNP in *MC4R* rs2229616 (Val103Ile), which has been associated with decreased weight [44], also has been associated with increased total energy intake (364 kcal/d) and carbohydrate (57 g/d) among 926 individuals with severe obesity (BMI≥33 kg/m^2) using FFQs [63].

In the *TCF7L2,* which was identified in GWAS for type 2 diabetes, rs7903146 and rs10885406, making up the haplotype HapA, was found to interact with dietary protein to attenuate weight change for carriers compared with noncarries; for carriers there was no dependence on dietary protein and weight change, whereas noncarriers gained more weight per year at higher protein intakes [64•]. They also investigated interaction with GI, but found no interactions with *TCF7L2* on weight change. Another study found that *TCF7L2* rs7903146 TT-genotype was associated with a lower weight loss of 2.8 kg on a high-fat diet than a low-fat diet for 10 weeks [65].

GIPR rs2287019 showed a trend for an interaction with dietary fat intake on weight loss after 6 months in participants who were on a low fat diet compared with a high fat diet among 737 overweight adults in the POUNDS LOST study [66], suggesting that the T-allele interacts with dietary fat content to determined weight loss response. There were no significant interactions between the SNP and diet after 2 years, suggesting that the proposed effect might only be true for weight loss periods and not prolonged periods where most individuals returns to weight maintenance or regain.

Besides the above-described, single-gene studies of GWAS hits, gene-diet interaction studies have included several SNPs trying to mimic GWAS but most often selecting a limited number of SNPs/genes from a combination of biological candidate genes and GWAS hits for obesity-related phenotypes (Table 1). The EU-funded Pan-European Nutrient and Genes in Obesity (NUGENOB) study examined the gene-diet interactions for 42 SNP in 26 genes identified as possible candidate genes from previous obesity association or gene expression studies [43]. The study did not find significant interactions between the SNPs and fat content of the hypo-energetic diet on weight loss response during a 10-week intervention in 648 participants. Detailed analyses of the food intake among 549 women from the NUGENOB study showed a gene-diet interaction between *LIPC* and fiber intake [67]. A study of 38 genes, including 1,086 SNPs in 1,173 African Americans and 897 SNPs in 1,165 Caucasians in relation to several lifestyle factors, including dietary intake, found no consistent interaction between the SNPs and energy intake between the two ethnic populations but found suggestive associations ($p<0.001$) for *IL6* rs2069824 and *GHSR* rs9819506 and rs11918879 and dietary intake for Africans American and Caucasians, respectively [68]. In the MONICA/KORA study, seven SNPs in the GWAS hits transmembrane protein 18 (*TMEM18)*, *NEGR1*, *MTCH2*, *FTO*, *MC4R*, *SH2B1*, and *KCTD15* were investigated in 12,462 individuals, but no modification of carbohydrate and fat dietary intake on the effect of any of the SNPs on BMI was observed [69].

Table 1 Overview of gene-diet studies with multiple genes and SNPs in relation to BMI and weight change

	N	W (%)	Population	Duration	Diet	Outcome	SNPs	Genes	Gene/SNP selection	Interaction
Edwards et al [68]	1173	84	African	N/A	Energy intake	BMI	1086	38	Candidate genes with at least two previous studies indicating association with obesity	*IL6* rs2069824[1]
	1165	84	European	N/A	Energy intake	BMI	897	38		*GHSR* rs9819506[1] *GHSR* rs11918879[1]
Holzapfel et al [69]	12,462	50	European	N/A	Carbohydrates Fat	BMI	7	7	GWAS hits (*NEGR1*, *TMEM18*, *MTCH2*, *FTO*, *MC4R*, *SH2B1*, *KCTD15*)	None
Scherag et al [70]	401	55	European[2]	52 weeks	Life-style[3]	Weight loss	10	5	GWAS hits (*TMEM18*, *FTO*, *MC4R*, *SDCCAG8*, *TNKS/MSRA*)	*SDCCAG8* rs10926984, rs12145833 and rs2783963[4]
Sørensen et al [43]	648	75	European	10 weeks	Fat Carbohydrate	Weight loss	42	26	Candidate genes	None
Du et al [71••]	6,566	46	European	6.9 years	Protein Glycemic index	Weight gain	123	15	Hypothalamic candidate genes with coverage of genetic loci ± 5 kb and r^2> 0.7	*NMB* rs7180849[5]
Larsen et al [75]	742	65	European	26 weeks	Protein Glycemic index	Weight gain	651	69	Candidate genes with coverage of genetic loci ± 5 kb and r^2>0.7	None

[1] Suggestive evidence (no consistent results for the two populations), [2] Children and adolescents, [3] Life-style includes a low fat, low sugar weight loss diet, increased exercise and behavior therapy, [4] The diet-gene interaction was not significantly associated with weight loss in adults [43], [5] Interaction with glycemic index. W, women; SNP, single nucleotide polymorphism; BMI, body mass index; *IL6,* interleukin 6*; GHSR,* growth hormone secretagogue receptor; *NEGR1*, neuronal growth regulator 1; *TMEM18*, transmembrane protein 18; *MTCH2*, mitochondrial carrier 2; *FTO*, fat mass- and obesity-associated gene; *MC4R*, melanocortin 4 receptor; *SH2B1*, SH2B adaptor protein 1*, KCTD15,* potassium channel tetramerisation domain containing 15; *SDCCAG8,* serologically defined colon cancer antigen 8; *TNKS/MSRA,* tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase/methionine sulfoxide reductase A; *NMB,* neuromedin B

In 401 German children and adolescents with obesity undergoing a 1-year lifestyle intervention program, 10 SNPs in *FTO*, *MC4R*, *TMEM18*, serologically defined colon cancer antigen 8 *(SDCCAG8)* and tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase/methionine sulfoxide reductase A (*TNKS/MSRA)* from GWAS hits for childhood obesity were analyzed, and three SNPs—rs10926984, rs12145833 and rs2783963—in *SDCCAG8* were associated with reduced weight loss [70]. This association was not confirmed in an adult population (NUGENOB) with 10 weeks of weight loss diet either low or high in dietary fat [70].

In the Diet and Genes (DIOGENES) epidemiological study, 123 SNPs (tagSNPs with LD (r^2)=0.7-0.8 for the gene ± 5 kb, MAF ≥0.05) in 15 candidate genes involved in hypothalamic control of food intake were examined for interaction with dietary protein or GI in determining weight changes in 6,566 individuals [71••]. Of the 123 SNPs, only *NMB* rs7180849 interacted with GI to give an increase in weight gain of 25 g/year per allele per GI unit after correction for multiple testing. Two SNPs *LEP* rs7788818 and *NMB* rs7180849 showed a trend for interaction with dietary protein and seven SNPs ghrelin (*GHRL)* rs35683, nucleobindin 2 (*NUCB2)* rs214075, *POMC* rs67565427, *NMB* rs2292462, and *LEPR* rs1137101, rs2025805, and rs7180849 for interaction with GI. Other studies also have suggested that genetic variation in *NMB* is associated with eating behaviors, habitual food intake and increased body fat gain [72, 73]. *NMB* belongs to the bombesin-like peptide family and is involved in gut-brain signaling and expressed in adipose tissue and therefore might act as a short-term satiation signal or as a long-term energy balance regulator [74]. The DIOGENES study also included an intervention study with a 2×2 factorial design with low- and high-dietary protein and low and high GI to examine the interaction with 651 SNPs genes related to obesity, selected with the same criteria as in the epidemiological part (above), on weight maintenance during 6 months after a minimum of 8 % weight loss [75]. We did not find a significant interaction between *NMB* rs7180849 and GI on weight maintenance, nor did we identify any significant interactions between the SNPs and either GI or dietary protein intake on weight regain after correction of multiple testing.

The DIOGENES study provides an example of replicating findings from epidemiological studies with a large population without randomization, with less detailed phenotypes and dietary assessments, and few follow-ups, and applying them to intervention studies with randomization to a specific diet, separation of low and high intakes of the examined nutrient, detailed phenotypic characterization of the participants,

several follow-ups and use of detailed dietary assessments including biomarkers of protein intake, but with a relatively small samples size and very often a short intervention period. Still, the replication between the epidemiological and intervention parts of DIOGENES did not result in identification of robust gene-diet interactions with effect on weight regain. Likewise the *SDCCAG8* SNPs associated with weight loss in children over 1 year was not replicated in adults undergoing 10 weeks of weight loss [70] and no consistency for interactions between SNPs in 38 genes and dietary intake in African American and Caucasian populations was observed [68].

For the above gene-diet interaction studies (Table 1), the gene-diet analyses are used retrospectively. One published study [76] used the genetic profile to adjust dietary and physical activity advice based on genotypes for 24 SNPs in 19 genes (from a direct to consumer genetic profile company). The study found that supplementing a low saturated fat, low GI Mediterranean diet with an exercise program for weight loss with genetic profile-based advice increased weight loss success, compared with following standard dietary advice (73 % vs. 32 %). For example, carriers of SNPs in vitamin D (1,25-dihydroxyvitamin D3) receptor (*VDR)* were recommended to increase their intake of dairy products. However, the study only included 50 individuals in the genetic profile group; they were not all obese, and the follow-up time varied, and not all the carriers of the SNPs received modified dietary advice. In addition, SNPs from GWAS or candidate genes studies with suggestive evidence of an interaction with diet on weight changes were not included [76].

The gene-diet interaction studies only provide suggestive evidence for a few relevant SNPs in determining obesity or weight changes, and the lack of results is most probably due to the relative small samples sizes, even for epidemiological studies, used for detecting gene-diet interaction effects. With the current published papers on gene-diet interaction in determining obesity, the effect of the interaction seem to be small, with effect sizes close to effect sizes for direct effects of SNPs from the last wave of obesity GWAS [21••]. Determining gene-diet interaction would, compared with GWAS populations, require sample sizes that are higher than 125,000 individuals, with replication in just as many individuals [77]. However, applying accurate measurements of exposure, such as using dietary biomarkers instead of FFQs, and accurate measurements of outcome to detect gene-lifestyle interactions might reduce the number of individuals, compared with to large studies with less accurate measurements, and using optimized study designs, such as replication within the same age group and ethnicity, and with the same nutrients in a sufficiently large population [77, 78].

Thus far, the gene-diet interaction analyses have not substantially explained more of the missing heritability than the 32 loci identified by GWAS. Because the GWAS hits for obesity only accounts for 1.5 % of the inter-individual variation, other possibilities than genetic variation in the linear DNA have been considered to identify other heritable contributions to obesity.

Epigenetics, Diet, and Obesity

Epigenetics refers to changes in DNA that are not in the linear DNA sequence but instead DNA methylation of CpG island and histone modifications leading to changes in the transcription of genes [8]. Studies of mice have shown that intrauterine conditions, maternal weight and nutrition, and early nutrition can influence development of obesity through epigenetic modifications [79]. Specifically, a study in mice has shown that high-fat diets decrease methylation of the *MC4R*, changing the expression of *MC4R* and thereby changing the regulation of energy metabolism [80]. The methylation did not correlate with *MC4R* expression, and this might suggest that there are other mechanisms in addition to methylation that regulates the *MC4R* gene expression. However, a change in the methylation of the *MC4R* promoter is a compelling explanation for the different penetrance of the *MC4R* mutations [14, 15]. A study in sheep has shown that maternal undernutrition and twinning result in decreased methylation of *POMC* and the glucocorticoid receptor that are both involved in regulation of energy metabolism [81], suggesting that maternal undernutrition or twinning might influence later disposition to obesity through expression changes of hypothalamic genes.

In humans, epigenetic changes are involved in the Prader-Willie Syndrome (PWS), a relatively rare form of early-onset obesity syndrome that is associated with extreme hyperphagia [82], and epigenetic changes also might affect monogenic obesity forms in human as *POMC* hypermethylation also has been shown to be associated with childhood obesity [83]. Likewise, promoter methylation of the serotonin transporter gene (*SLC6A4*) has been shown to be associated with intrapair difference in obesity between 84 monozygotic twin pairs [84].

FTO has been suggested to demethylate single-stranded DNA and RNA [85], and a recent study has shown that homozygous carriers of *FTO* rs9939609 differ in their degree of methylation at two genes lysyl-tRNA synthetase/ telomeric repeat binding factor 2, interacting protein (*KARS*/*TERF2IP*), which is proposed to be involved in regulation of telomere length and nuclear factor of kappa light polypeptide gene enhancer in B-cells (NF-kB) activity, and dexamethasone-induced transcript (DEXI) [86]. However, both of the genes are located on the same chromosome as *FTO* and the observed effect might not be due to protein level interactions but to structural changes in the DNA.

Studies of mothers who have undergone bariatric surgery show that infants born post-surgery were smaller and less likely to be severely obese than infants born presurgery [79], and maternal dietary intake has been associated with gene methylation leading to adiposity in the children [87]. Furthermore, methylation patterns of cord blood DNA suggested an association between CpG methylation of cyclin-dependent kinase inhibitor 1C (*CDKN1C)*, EPH receptor A1 (*EPHA1)* and caspase 10 (*CASP10)* and BMI at age 9 years [88••].

Obesity *per se*, or habitual diet in obese individuals, induce methylation changes in peripheral blood lymphocytes of two genes ubiquitin associated and SH3 domain containing A (*UBASH3A*) and tripartite motif containing 3 (*TRIM3*) involved in immune function, and these changes might lead to increased/decreased expression of genes, and thereby increase the inflammatory state often associated with development of obesity-related metabolic diseases [89].

Epigenetic changes influence the development of obesity and can be modified by diet or obesity *per se* or genetic mutations in the linear DNA. Likewise obesity or diet might lead to epigenetic changes that result in development of obesity-associated diseases. The epigenetic changes can exert their effect across generations.

Microbiome, Diet, and Obesity

The Human Microbiome Project has explored the microbiome from 15-18 body sites from five major body areas in health and disease [90], whereas the MetaHit Project has focused on the gut microbiome in relation to obesity and inflammatory bowel disease [10]. These projects have led to the discovery that human obesity is associated with a reduced bacterial diversity at phylum-level in the intestine with altered representation of bacterial genes and metabolic pathways [91].

Initial studies in both mice and humans suggested that obesity was associated with an altered balance between the two dominant bacterial phyla in the human gut, with a decline in *Bacteroidetes* and a correspondingly higher proportion of *Firmicutes* [92, 93], an alteration that appears to be reversible, as weight loss have been shown to re-establish a "lean" microbiota composition [92, 94]. However, later studies have suggested that there is most likely an association between obesity and the microbiome, but that phylum level analyses are not sufficiently detailed and that the obese microbiome should be defined on metabolic function of the expressed microbiome [9, 10, 95]. With the establishment of an obese genome that can differentiate between lean and obese individuals with high sensitivity and specificity, it can be speculated whether the microbiome composition is a side effect of a specific diet leading to obesity or if the microbiome itself causes obesity. Studies of mice have shown that transplantation of the microbiome is associated with rapid weight gain [96, 97], but that the microbiome composition also changes rapidly in response to dietary changes [97, 98].

In a recent publication from MetaHit, the investigators were able to define three dominant clusters of intestinal bacteria (enterotypes) that were similar in individuals from different populations, and these were dominated by *Bacteroides* (enterotype 1)*, Prevotella* (enterotype 2) or *Ruminococcus* (enterotype 3) [99••]. Nonetheless among less abundant bacteria species there are large inter-individual differences in the microbiome composition and bacteria abundance [90, 91, 99••].

It has been suggested that obesity might be associated with increased energy uptake due to changes in the microbiota [93], which is consistent with the earlier findings of changes in the phyla *Firmicutes* and *Bacteroidetes*. In humans, it was observed that varying caloric intake changed the microbiota already after 3 days, and an increase in *Firmicutes* and a decrease in *Bacteroidetes* were associated with an increased energy harvest of 150 kcal in lean individuals [100]. In addition, enterotypes 1 and 3 are associated with a long-term diet rich in protein and animal fat while enterotype 2 is associated with a carbohydrate-rich diet [101••]. A 10-day intervention with a low-fat, high-fiber diet or a high-fat, low fiber diet did change the microbiome composition, but not on the enterotype level [101••]. Among healthy individuals, the interindividuals variation only show a modest association with BMI, indicating that long-term dietary patterns shapes the composition of the gut microbiome [90].

Conclusions

The GWAS success in identifying genes associated with obesity has led to additional knowledge of the biological pathways involved in obesity. New genetic studies that include more individuals to search for smaller effect sizes, and exome or whole genome sequencing to identify rare variants or copy number variation (CNVs) aim to identify more of the proposed interindividual differences in obesity. The identification of new genetic variants associated with obesity allows for the study of their biological function and interaction with diet, and optimization of study design will help to identify robust gene-diet interactions. Emerging epigenetic studies show a strong interaction between epigenetic modifications and diet (and other environmental factors) starting *in utero*, or even across generations, and with possible interactions with mutations in the linear DNA. Besides genetic and epigenetic factors, the composition of the collected bacterial genome in our intestine has been associated with the development of obesity, and specific profiles, enterotypes, have been associated with dietary patterns. The underlying mechanisms determining the susceptibility to obesity do not only include variation in the

nucleotide sequence of the human genome but also variation in the epigenome and the microbiome. The epigenome and microbiome are more easily modified by diet, but also seem to interact with host genotype, adding to the complexity of determining the underlying mechanisms of obesity.

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