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Review
EPIDEMIOLOGY/GENETICS

Obesity

Genetics of Obesity: What We Have Learned Over Decades of Research

Claude Bouchard

There is a genetic component to human obesity that accounts for 40% to 50% of the variability in body weight status but that is lower among normal weight individuals (about 30%) and substantially higher in the subpopulation of individuals with obesity and severe obesity (about 60%-80%). The appreciation that heritability varies across classes of BMI represents an important advance. After controlling for BMI, ectopic fat and fat distribution traits are characterized by heritability levels ranging from 30% to 55%. Defects in at least 15 genes are the cause of monogenic obesity cases, resulting mostly from deficiencies in the leptin-melanocortin signaling pathway. Approximately two-thirds of the BMI heritability can be imputed to common DNA variants, whereas low-frequency and rare variants explain the remaining fraction. Diminishing allele effect size is observed as the number of obesity-associated variants expands, with most BMI-increasing or -decreasing alleles contributing only a few grams or less to body weight. Obesity-promoting alleles exert minimal effects in normal weight individuals but have larger effects in individuals with a proneness to obesity, suggesting a higher penetrance; however, it is not known whether these larger effect sizes precede obesity or are caused by an obese state. The obesity genetic risk is conditioned by thousands of DNA variants that make genetically based obesity prevention and treatment a major challenge.

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Introduction

Obesity continues to be a major public health concern. The prevalence of obesity in adults aged 20 years and older, defined as BMI ≥ 30 kg/m^2, reached 30.5% in 2000 and 39.8% 15 years later (1). There are currently about 93 million American adults with obesity. The situation is just as alarming in youth (age 2-19 years old), as the prevalence increased from 13.9% in 2000 to 18.5% in 2016. The prevalence of severe obesity (BMI > 40) increased at an even more alarming pace in adults, going from 3.9% in 2000 to 6.6% in 2010. About 15.5 million adult American individuals were classified as having severe obesity a decade ago. Importantly, the prevalence of BMI > 50 cases increased at an even faster rate (2). The future looks bleak, as some recent projections have shown (3). By 2050, it has been estimated that 50% of the adult population will have obesity. BMI > 35 will be the most common BMI category in female, non-Hispanic, Black, and low-income adults. Notably, the obesity epidemic is increasingly more apparent in rural areas of the world (4).

Research on the causes of obesity has about a 100-year-long history (5). One of the first attempts to understand the inheritance of body weight and body build, including obesity, was reported in 1923 by Davenport (6). He measured height and weight in 528 pairs of parents and their 986 male and 746 female offspring, 606 of which were adults. Based on the weight divided by height squared (Quetelet Index, or BMI as we call it now), he explored the segregation pattern from the parental to the offspring generation using five classes of BMI. In brief, he found some evidence for a parental-transmission effect of body mass on adult offspring. However, all five classes of mating produced a highly heterogeneous progeny in terms of body weight. For instance, when both parents had obesity, some of their adult descendants were either normal weight or had overweight or obesity, but none of them was lean or very lean.

Here, the status of our understanding of the genetic predisposition to obesity is reviewed. The lessons learned from genetic epidemiology are summarized. The contribution of single-gene defects to the risk of obesity and the protection against obesity is summarized. The impact of common and low-frequency genomic variants on the predisposition to obesity is evaluated based largely on the evidence accumulated from genome-wide association studies (GWAS). The potential contribution of obesity alleles to the morbidities commonly observed with obesity (pleiotropic effects) will not be covered herein. This review is greatly influenced by the author's personal view on what are the most important findings and trends based on the overall body of literature on the subjects discussed. An apology is offered to all those who have contributed to this field but whose work could not be cited because of space limitations and journal guidelines.

Genetic Epidemiology

Genetic epidemiology relies mainly on observational data obtained on relatives, by descent or by adoption, and specific statistical methods in

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order to decompose the total phenotypic variance of a trait into various components, including the fraction of the trait variance owing to genetic transmission. Commonly investigated issues include testing for maternal and paternal effects, sex-specific effects in an offspring generation, assortative mating, and other circumstances of interest.

Heritability is a population parameter

It is important to appreciate that heritability is a population estimate of the relative contribution of genetic differences to a given trait. As such, knowing the heritability level for a trait, such as BMI, does not provide information applicable to an individual. For instance, consider the data depicted in Figure 1 as drawn from data of the Québec Family Study. The narrow sense heritability (additive genetic variance) is of particular interest, and it can be estimated, among other approaches, by comparing the regression of a trait between both parents (midparent value) and their offspring in nuclear families (7). The figure illustrates the distribution of individual scores for a level of heritability of 29%. This low genetic component to BMI can be explained by the fact that the individuals of phase 1 of the Québec Family Study were generally of normal weight (see later text regarding this topic). Note that there were large interindividual differences in the relation between the midparent value for the trait and the values of their offspring. This is an illustration of the fact that the heritability level is an average population value and not a parameter that can be used to specify the level of risk for a given individual. For the interested reader, an informative presentation of the concept of heritability and its applications can be found in Visscher and collaborators (7).

Emerging consensus on heritability of BMI

Although there were attempts to quantify the genetic component of obesity prior to the 1980s, most of the research activities on this topic began in the 1980s. The research reported up to about the mid-1990s has been summarized earlier (8,9), and the evidence up to the early 2010s has been reviewed elsewhere (10). In brief, very high heritability (genetic variance over the total phenotypic variance × 100) estimates are found when studies are based solely on the comparison of pairs of monozygotic (MZ) and dizygotic (DZ) twins, reared apart or together (11-14). Values range from about 50% to 90%, clustering around 70% to 80%. Nuclear family studies yield intermediate levels of heritability, whereas adoption studies produce the lowest estimates, although the heritability levels generated by both designs overlap to a large extent, with a range of 10% to 50%. Table 1 provides a summary of the ranges in heritability values reported for each type of study.

The reasons why the twin study designs lead to higher heritability estimates than other study types are debated and beyond the scope of this review. However, of critical importance is the role of the common environment in twin resemblance. For instance, MZ brothers and sisters share a single placenta during fetal life about 75% of the time, whereas DZ twins reside in two placentas during pregnancy. Moreover, MZ twins are treated during postnatal life more similarly than DZ twins or regular siblings by parents, relatives, and friends. Such conditions could translate into a higher common environmental effect in MZ twins. However, most twin studies of BMI report no substantial common environmental effect, which has the potential to inflate heritability estimates if untrue. In contrast, family and adoption studies often report a common or shared environmental effect on BMI or other indicators of obesity. A comparison of within-pair difference in identical twins, same-sex fraternal twins, and same-sex non-twin siblings could potentially shed light on this issue. These comparisons were undertaken with data from the Longitudinal Survey of Youth 1979 (15). Members of MZ pairs were found to differ, on average, by 12 BMI percentile points, whereas same-sex fraternal twins differed by 16 points and opposite-sex fraternal twins and same-sex and opposite-sex regular pairs of siblings differed by 29 points, all of which, just like DZ twins, share 50% of their genes by descent. This pattern is compatible with a shared environmental effect enhancing within-pair similarity beyond genetic covariance. It is an important point, as the shared environmental effect, if not properly quantified, is aggregated with the genetic variance in conventional twin studies. Indirect evidence also comes from a pooled analysis of about 140,000 twin pairs showing that the heritability of BMI decreases from young adulthood to old age (when cotwins are less likely to be living in the same environment), with the role of nongenetic factors becoming progressively more important (16).

Many studies accumulated over the last few years have generated population estimates of the BMI or risk of obesity genetic component that are more aligned with the familial and adoption designs. Moreover, genetic heritability estimates for BMI derived from such studies have been concordant with the percentage of the variance in BMI accounted

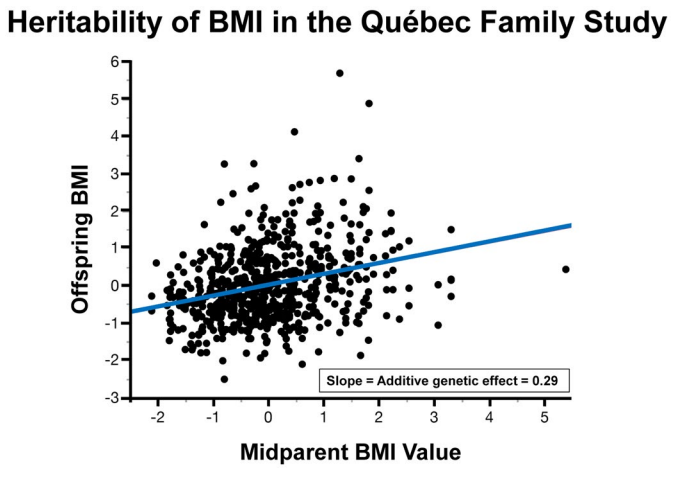

Figure 1 In this figure, the regression of offspring phenotype on the average phenotype value of the parents (midparent value) is depicted. The midparent value associates poorly with the phenotype in the offspring (low slope of the regression line). There are wide interindividual differences, as shown by the scatter of individual values in the presence of a heritability level accounting for 29% (additive genetic effect) of the age- and sex-adjusted values (BMI of offspring = 0.29 × midparent BMI). BMI scores were standardized after adjustment for age and sex within each generation. The heritability was derived from data on 667 trios. Unpublished data courtesy of Dr. Louis Pérusse.

TABLE 1 Overview of commonly observed ranges in heritability estimates for BMI, adiposity, or risk of obesity

	Heritability, %
Nuclear families	30-50
Adoption studies	10-35
Twin studies	50-90

Modified from Bouchard et al. (8).

for by common and rare alleles, as shown in several recent genomic exploration studies and reviewed in a subsequent section.

Heritability in heterogeneous populations. In a review of 25 family studies, it was shown that there was heterogeneity in the heritability estimates but that they clustered around 40% to 50% of the BMI variance with no detectable effect of sample size, age of individuals, and study setting (10). Many family studies were not included in the latter review, but the findings of the missing reports are quite concordant with the aforementioned conclusion (17-19). Comparable BMI heritability levels were reported for the Tecumseh Community Health Study, the Muscatine Ponderosity Study, the Lipid Research Clinic, and the Québec Family Study (8,20). Two large studies illustrate the case of a moderate heritability level of BMI. In one of the largest studies to date, a Norwegian sample of 23,936 pairs of spouses, 43,586 parent-offspring pairs, 19,157 sibling pairs, 2,400 second-degree relatives, as well as substantial numbers of pairs of twins and of other more remote relatives, the heritability of BMI reached 39% (21). In an adoption study, Vogler et al. used BMI data on adult adoptees ($N=660$) and their biological parents, adoptive parents, biological siblings, and maternal and paternal half-siblings from the Danish Adoption Study and found that the BMI genetic component reached 34% (95% CI: 31%-37%) (22).

Interestingly, from serial measurements of BMI in the Framingham Study families, the mean BMI over 35 years and more was characterized by a heritability level of 37%, whereas the maximal BMI heritability reached 40% (23). However, lower heritability levels were observed for 7-year changes in BMI (14%) and estimates of subcutaneous fat (12%) in 521 nuclear families of the Canada Fitness Survey (17). Maternal and paternal effects on the BMI levels of sons and daughters are quantitatively comparable even though some studies have reported slightly higher maternal effects (24). In some of the studies on the latter topic, the slight difference in maternal versus paternal effects could be explained by paternity issues.

Heritability levels have also been reported for fat mass and body fat percentage. The heritability of fat mass and body fat percentage reached 39% and 47%, respectively, in the Québec Family Study (25). In extended pedigrees from 22 families comprising 2,506 individuals from a Dutch genetic isolate, the heritability of dual x-ray absorptiometry (DXA) fat mass was 46% (39% for fat mass index), whereas it reached 42% for fat mass percentage (26). Globally, the genetic component of total adiposity is comparable with that of BMI.

Another approach to the quantification of genetic factors and shared environment on the risk of obesity is to compute the familial risk level, defined as the ratio of the risk of having obesity when a biological relative has obesity compared with the prevalence of obesity in the population at large (λ coefficient or standardized relative risk ratio) (27). It is generally computed based on nuclear family or twin data. The familial risk of obesity (>90th percentile of BMI distribution) is about three times higher for individuals from families with a history of obesity (28,29). In contrast, the familial risk for severe obesity (>95th percentile) reaches five to eight times compared with the level seen in relatives with family members of normal weight (28-31). These data provided the first evidence that there may be a lower genetic component to BMI among normal weight individuals than among individuals with obesity.

The genetic component of variability of weight or weight for height is known to be low at birth, but it increases steadily during the first few years of life (11,32). The BMI heritability around the prepubertal period tends to be comparable with the levels observed in adulthood (33). Importantly, however, only about 50% of school-age children with obesity continue to have obesity during adulthood (34). Tracking is stronger in people with high BMI levels during the growing years than in those in the middle and lower part of the BMI distribution (35). However, childhood BMI level correlates only mildly with the level observed after 60 years of age ($r\sim0.25$) (36).

We conclude that the genetic component of BMI in a population comprising the whole range of BMI values accounts for about 40% to 50% of the variance adjusted for age and sex.

Heritability varies across the BMI range. Over the last decade, data have accrued to show that the genetic component of BMI varies across the BMI range, with higher heritability levels observed in the subpopulation of individuals with obesity and severe obesity. In brief, the heritability of BMI or adiposity traits is stronger in the subpopulation of those who have obesity compared with the subpopulation of individuals in the normal body weight or even overweight range (37-39). This was illustrated recently based on parent-offspring pairs from the Framingham Heart Study. The heritability levels of BMI or DXA fat mass adjusted for height squared at the 90th percentile of their distributions were more than threefold higher than the heritability levels observed at the 10th percentile levels (40). Overall, these studies strongly suggest that global population heritability levels underestimate the genetic load impacting the susceptibility to gain an excessive amount of weight and adiposity in the subpopulation of people with obesity. This generalization is supported by the evidence on effect size at obesity alleles across the BMI range, as will be reviewed later in this review. It is also well supported by evidence on the familial risk for obesity when probands are selected from an increasing level of BMI, ranging from having normal weight to having severe obesity (28-31).

Whereas the heritability level for a large heterogenous population, in terms of body weight, reaches about 40% to 50%, the heritability is lower (about 30% to 35%) in the subgroup of individuals with normal BMI, reflecting trends from available studies but increases to about 50% in the subpopulation of individuals with overweight, 60% to 65% for the obesity class I subgroup, and 80% and more for the severe obesity strata (Figure 2).

In summary, the studies on the heritability of BMI or obesity have generated findings that are highly heterogeneous. Some variability is to be expected given potential differences among populations, study designs, and sample sizes. The true heritability component of the BMI variance after adjustment for age, sex, and other appropriate concomitants reaches about 40% to 50%, but it is substantially higher in the subgroup of individuals in which having overweight and obesity is endemic. In contrast, heritability of BMI is lower among adults who are lean and normal weight. It is important to keep in mind that these population estimates could be substantially altered by major environmental disruptions or major behavior changes.

Body fat distribution

Is there a genetic component to the profile of fat deposition beyond the well-established sex dimorphism characteristic of subcutaneous and deep fat depots? To address this question, we rely on studies that have controlled for the high correlations between total adiposity and indicators of fat distribution (8,41,42). Suggestive evidence of the

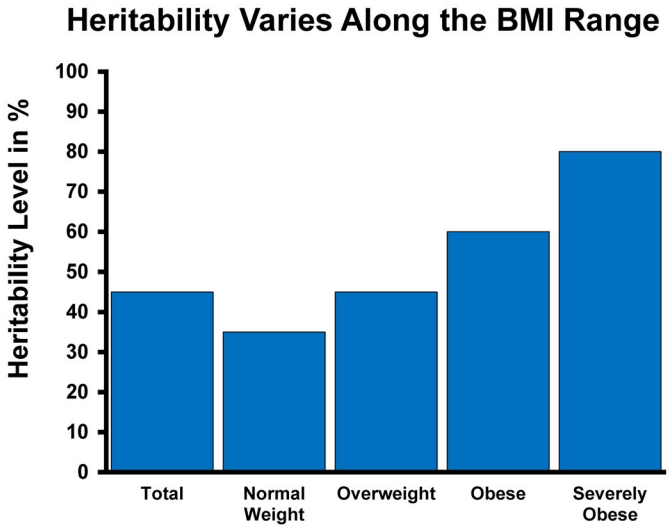

Figure 2 Overview of heritability estimates of BMI across the BMI range. Although the heritability of BMI in a heterogeneous population in terms of body mass or adiposity is in the 40% to 50% range, it is lower in the subgroup characterized by BMI in the normal weight range. The heritability level appears to increase almost linearly across the range of body weight classes, reaching a maximal level around >80% in the subgroup of adults characterized by severe obesity.

involvement of specific genes in the patterns of fat deposition is found in genetic deficiencies resulting in partial or generalized lipodystrophies (43). Several twin and family genetic epidemiology studies have been reported on subcutaneous fat distribution traits with adjustment for total adiposity or BMI or body mass, with twin studies recording the highest heritability levels (44). An early review of familial and adoption data based on anthropometric measurements suggested that the heritability was less than 50% (45). Globally, family and extended pedigree studies suggest that indicators of adipose tissue distribution, such as abdominal fat, upper body fat, lower body fat, waist-hip ratio, extremities-trunk skinfold ratio, subcutaneous fat relative to total fat mass, DXA android fat mass, DXA gynoid fat mass, and DXA android to gynoid fat mass ratio, are characterized by heritability estimates ranging from about 30% to 50% (18,25,26,46).

Visceral and liver fat

Two specific fat depots are of particular importance because of their potential implications in the etiology of morbidities associated with excess adiposity, namely abdominal visceral fat and liver fat. Here again, studies that have controlled for total adiposity or BMI are retained because of the strong correlation between the latter with visceral fat or liver fat (8,41,47-49). Visceral adipose tissue (VAT) cross-sectional area was measured by computed tomography in the Québec Family Study (50) and the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study (51). After adjustment for total fat mass, heritability levels ranging from 48% to 56% were reported. In a study of 521 adults from five large families, visceral fat was measured by magnetic resonance imaging and adjusted for height squared (visceral fat index, kilograms per meters squared) (52). The heritability of the visceral fat index reached 36%. Visceral fat is also a trait in which the heritability appears to be substantially higher (threefold higher) in the subgroup, with the highest level of computed tomography visceral fat (90th percentile) among those at the low end of the visceral fat distribution (10th percentile), although the visceral fat data were apparently not adjusted for total adiposity (40).

Studies on the heritability of hepatic fat are few and generally based on small sample sizes. Nonetheless, useful information on the potential role of genetic differences on liver fat has been reported. A familial aggregation study was undertaken in children with overweight with and without nonalcoholic fatty liver disease, with liver fat assessed by magnetic resonance imaging (48). There were 33 children with nonalcoholic fatty liver disease and 153 first- and second-degree relatives in the study. After adjustment for BMI, the heritability of liver fat fraction reached 39%. In the Insulin Resistance Atherosclerosis (IRAS) Family Study, the liver density was quantified from computed tomography scans in 795 Hispanic American individuals and 347 African American individuals (49). The heritability of liver density adjusted for age, sex, and insulin sensitivity (but not adjusted for adiposity) ranged from 32% to 35%.

Of importance to the metabolic dysfunctions associated with obesity is the ectopic lipid deposition in skeletal muscle. In a study of muscle density (a surrogate for muscle fat infiltration) based on 471 individuals from eight multigeneration Afro-Caribbean families (3,535 relative pairs), the heritability level reached 35% with adjustment for multiple covariates, including BMI (53). Interestingly, one report based on the Framingham Study has found that renal sinus fat level was characterized by a genetic component of the order of 40% after adjustment for BMI or visceral fat (54).

The trends of the genetic-epidemiology estimates of heritability levels for several adipose tissue distribution indicators are depicted in Figure 3. After controlling for age, sex, and total adiposity, the heritability levels cluster around moderate values ranging from 30% to 55%. VAT levels tend to exhibit slightly higher genetic variance (with a peak at about 55%) than markers of subcutaneous fat topography. The lowest values seem to be found for ectopic fat deposition in liver and skeletal muscle, with heritability levels around 35%.

Assortative mating

One potential path that could contribute and, in the long term, increase the genetic component of obesity is via assortative mating, which is when mate selection is influenced by corpulence as opposed to complete independence from body size (55,56). Assortative mating for corpulence has the potential to increase the concentration of obesity alleles among people who are in the upper segment of the BMI distribution over time (and concentrate the leanness alleles in the middle and lower parts of the distribution). One approach to quantify assortative mating is simply to compute the correlation between spouses. The spousal correlation for BMI is typically ranging from about 0.1 to 0.4, with most common values of the order of 0.15 to 0.20 (55-58). Interestingly, it has been suggested that assortative mating for high and very high BMI has become more prevalent from the period preceding the worldwide obesity epidemic to the most recent decades (59). In one study based on a Swedish cohort, the following three findings were reported: 1) in parents with obesity, the obesity prevalence reached 20% in their offspring, whereas it was only 1% when parents had normal weight; 2) there was no relation between the BMI of parents and that of their adopted offspring; and 3) simulation studies suggested that positive assortative mating for corpulence could lead to an increase in the prevalence of obesity over multiple generations (57). The finding that

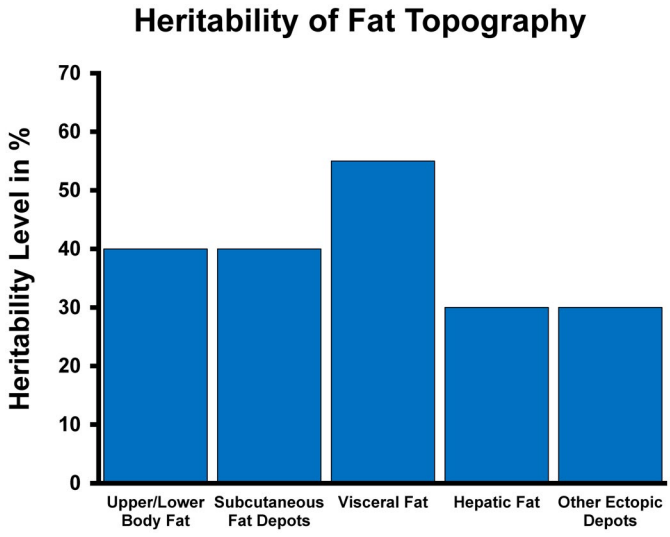

Figure 3 Overview of heritability estimates for several indicators of fat topography, including subcutaneous fat distribution traits, visceral fat, and ectopic fat depots. Whereas the estimates for upper versus lower body fat and subcutaneous fat depots are based on multiple studies, those pertaining to visceral adipose tissue, hepatic, and ectopic fat levels are supported by fewer studies.

spouse concordance for obesity translates into a twentyfold higher risk for obesity in adult offspring compared with biological offspring of normal weight parents emphasizes the importance of including assortative mating in obesity risk models. Because the genetic component of BMI is higher in adults with obesity compared with normal weight people, a small to moderate degree of assortative meeting can have a sizable impact on the risk of obesity in offspring from parents with obesity.

Response to experimental challenges

Further support for the notion that genetic differences contribute to human variability in adiposity comes from proof-of-concept experimental studies. As proof-of-concept experimental studies are based on small sample sizes and owing to the difficulties and costs associated with the execution of such studies, they are mainly used to provide evidence for or against a genetic role in modulating changes in adiposity or BMI in response to an experimental intervention, as opposed to an exact quantification of the magnitude of the genetic effect. Four types of intervention of interest to this review have been reported: chronic experimental overfeeding, negative energy balance caused by an exercise regimen or very low-calorie diet, and response to bariatric surgery.

In one overfeeding protocol conducted in an inpatient setting with the participation of 12 pairs of MZ twins exposed to a caloric surplus of 84,000 kcal over 100 days, there was 3 times more variability among the 12 pairs compared with the variability seen between twin brothers for

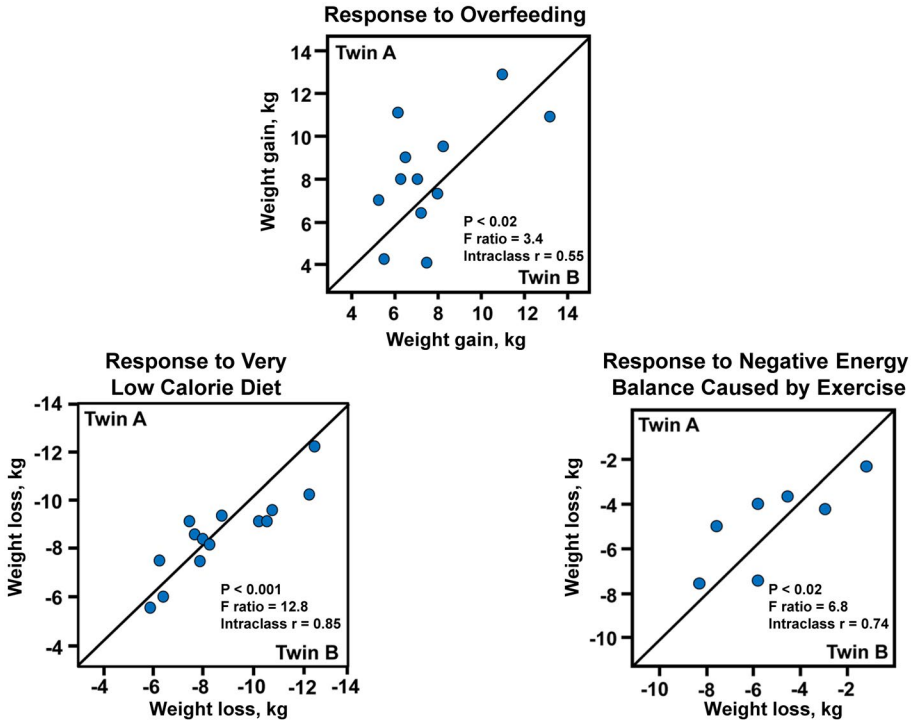

Figure 4 Changes in body weight in three protocols altering energy balance in pairs of identical twins. The upper panel depicts the changes in body weight in response to experimental overfeeding (from Bouchard et al.) (60). The lower left panel illustrates the response of female identical twins to 28 days of a very low-calorie diet (from Hainer et al.) (61). The bottom right panel shows the response of identical twins to a standardized exercise intervention; caloric intake and nutrient composition were clamped at baseline level (from Bouchard et al.) (62).

the gain in body weight (see "F ratio" in the top panel of Figure 4) (60). There was also significant within-pair resemblance for the overfeeding-induced changes in fat mass, visceral fat, and other indicators of fat distribution. These results strongly suggest that there are genetic factors contributing to adaptation to experimental overfeeding.

Two studies have dealt with the potential role of genetic differences in adaptation to standardized negative energy balance protocols. One weight loss study using a very low-calorie diet (about 400 kcal/d) for 28 days was performed in 14 pairs of premenopausal identical twins with obesity in an inpatient setting (see lower left panel in Figure 4) (61). Individuals lost an average of 8.8 kg of body weight. There was very strong within-pair resemblance in the amount of weight and fat mass losses, with F ratios of 12 and more. In another experiment, seven pairs of male identical twins were exposed to a negative energy balance protocol in which they exercised on cycle ergometers twice a day over a period of 93 days while their caloric intake and macronutrient composition were clamped at the baseline weight maintenance level (62). The total energy deficit reached 58,000 kcal, and the mean weight loss was 5 kg. Again, significant within-pair resemblance was observed for the changes in body weight (F ratio = 6.8) and total adiposity (F ratio = 14.1) (see lower right panel in Figure 4).

Finally, one study has explored whether there was an inherited component to the variability in weight loss response to bariatric bypass surgery (63). The investigators identified 13 pairs of first-degree relatives, 10 pairs of patients living together but who were biologically unrelated by descent, and 397 randomly generated pairs of patients who were not cohabitating and were biologically unrelated. The first-degree relative patients exhibited a within-pair mean excess weight loss difference of 9%, whereas the difference for both the cohabitating pairs and the unrelated pairs of patients reached 25%, respectively. These data are suggestive of a genetic component to the weight loss response to gastric bypass surgery, but these observations could not be replicated in another study (64). Further studies of this issue are clearly warranted.

Obesity at the Genome Level

Genetic epidemiology has provided ample evidence for the presence of a substantial genetic component to human obesity and related adiposity phenotypes. The next important question is whether we can explain the observed heritability levels in terms of genomic variants. Single-gene defects resulting in obesity are first introduced. Then, the focus shifts to common, low-frequency, and rare variants, the biology represented by these genomic variants, and interactions between weight loss under standardized conditions and genomic variants. Finally, genomic markers related to adipose tissue distribution and specific fat depot traits are reviewed.

Single-gene defects

There are obesity genes with large effect sizes that exhibit recognizable Mendelian transmission patterns. These cases are commonly referred to as cases of Mendelian obesity in which excess adiposity is a predominant trait. They are typically characterized by endocrine disorders and hyperphagia. Most (but not all) Mendelian obesity cases are due to deficiency in a gene of the leptin-melanocortin signaling pathway, a major player in the regulation of energy balance (65). Thus far, defects in 16 genes have been identified in monogenic obesity: adenylate cyclase 3 (*ADCY3*), brain-derived neurotrophic factor (*BDNF*), dual-specificity tyrosine phosphorylation-regulated kinase 1A (*DYRK1B*), kinase suppressor of ras 2 (*KSR2*), leptin (*LEP*), leptin receptor (*LEPR*), melanocortin 4 receptor (*MC4R*), melanocortin-2 receptor accessory protein 2 (*MRAP2*), nuclear receptor subfamily 0 group B member 2 (*NR0B2*), neurotrophic receptor tyrosine kinase 2 (*NTRK2*), proprotein convertase subtilisin/kexin type 1 (*PCSK1*), proopiomelanocortin (*POMC*), peroxisome proliferator-activated receptor γ (*PPARG*), SH2B adaptor protein 1 (*SH2B1*), SIM BHLH transcription factor 1 (*SIM1*), and TUB bipartite transcription factor (*TUB*) (66,67). Table 2 provides a list of genes most frequently identified as causal of Mendelian obesity along with their prevalence and notes on phenotypic manifestations (68). Although the prevalence estimates of these Mendelian disorders vary across studies, they individually account for a small percentage of obesity cases. However, in the aggregate, they are responsible for 5% to 10% of obesity cases in populations of European descent, but it could be higher depending on the population and the extent of the diagnosis effort (69). The prevalence of severe obesity cases can be markedly higher in inbred populations as shown in a recent study of consanguineous families from Pakistan in which 59% of cases in a cohort of 225 children with severe obesity were shown to have a likely genetic cause (70). It has been estimated that one person in 24,000 of the United States population carries a deficient allele at *LEPR*, *POMC*, or *PCSK1* (71). One feature that these single-gene defects have in common is that the excess weight is manifested early in life and tends to be severe. Another important characteristic is that the weight status of carriers of monogenic obesity alleles can be influenced by the overall polygenic obesity risk level of the individual, as was recently shown for pathogenic mutations in *MC4R* (72). To illustrate, carriers of *MC4R* mutations known to cause obesity weigh approximately 14 kg less (for a body height of 1.7 m) if they have a low polygenic risk score compared with those with a high score in the UK Biobank population.

Some rare variants with large effect sizes may increase BMI, total adiposity, and the risk of obesity, such that carriers of these variants may be undistinguishable from true cases of Mendelian obesity, as suggested by a screen for such variants in a large population (73). However, such cases do not exhibit the other clinical features commonly observed in cases of single-gene defects. Many more Mendelian obesity cases will likely be uncovered as whole-genome sequencing becomes increasingly used in clinical studies. For instance, explorations on the number of loss-of-function variants at protein-coding genes have suggested that a person of European descent carries almost 100 alleles causing loss of function, with 18 of them in the homozygous state (74). Some of these naturally occurring human gene knockouts should be of relevance to obesity.

In addition to these Mendelian obesity genes, there are Mendelian disorders in which excess weight is a secondary condition. They are commonly referred to as syndromic obesity cases, and there are dozens of them (75). One interesting subset of these patients with syndromic obesity is grouped under the Bardet-Biedl syndrome (BBS). The BBS is heterogeneous, and 19 genes have been implicated in its etiology thus far. Abnormal ciliary function is a common feature of BBS cases, but the relation with the upper body obesity observed in these patients varies with the gene involved and is not always understood (76).

Common, low-frequency, and rare DNA variants

Most obesity cases are not caused by single-gene defects with recognizable Mendelian transmission patterns. Rather, they arise from a

TABLE 2 Examples of single-gene defects responsible for human Mendelian obesity cases

Gene	Mutation type	Prevalence	Associated phenotypes
Leptin	Autosomal recessive inheritance	<100 patients worldwide	Hyperphagia Gonadotropic and thyrotrophic insufficiency Alteration in immune function
LEPR	Autosomal recessive inheritance	<3% of patients with severe early-onset obesity	Hyperphagia Gonadotropic, thyrotrophic, and somatotropin insufficiency Alteration in immune function
MC4R	Heterozygous or homozygous loss of function	About 5% of children with severe obesity, 1% of adults with severe obesity, and 0.1% of the general population	Hyperphagia Hyperinsulinemia High lean mass and bone mineral density
NTRK2	Heterozygous missense mutation	<10 patients worldwide	Hyperphagia Developmental delay Behavioral disturbance Blunted response to pain
PCSK1	Autosomal recessive inheritance or compound heterozygotes	<20 patients worldwide	Hyperphagia Adrenal, gonadotropic, somatotropin, and thyrotrophic insufficiency Postprandial hypoglycemia
POMC	Autosomal recessive inheritance or compound heterozygotes	<10 patients worldwide	ACTH insufficiency Mild hypothyroidism Pale skin and red hair in Caucasian individuals
SIM1	Translocation between chromosome 1p22.1 and 6q16.2 or dominant inheritance	<50 patients worldwide	Neurobehavioral abnormalities Memory deficit, emotional lability, or autism-like behavior

Modified and amplified from Huvenne et al. (68).
ACTH, adrenocorticotropic hormone.

combination of genetic predisposition, environmental exposures, and obesogenic behavior. Such a genetic predisposition has a complex genomic anatomy, as revealed by advances of the last decade based on the exploration of the whole genome with large panels of single-nucleotide polymorphisms (SNPs). It is useful to distinguish among three classes of SNPs: a common SNP with a minor allele frequency (MAF) of 5% or more, a low-frequency SNP with a MAF in the range of <5% to 1%, and a rare variant in which the minor allele has a frequency of <1% (77). It is important to appreciate that microarray-based chips used in past GWAS provide generally good coverage of common and low-frequency SNPs depending on the platform and chip used. However, rare variants are not adequately covered in the majority of GWAS reported to date. It is expected that a whole-genome sequencing approach will ensure more complete coverage of all three types of variants in the future.

Genome-wide association findings. This review begins with a summary of findings on genomics and body height, an important correlate of weight, because it has generated the largest GWAS explorations to date on the genomic architecture of a complex trait. Lessons learned on the genomics of human height are useful for the understanding of the genomics of human variability in BMI, adiposity, and risk of obesity. It may be hard to understand in our era, but, earlier in the 20th century, it was not uncommon to read in a textbook of human genetics that variability in human height was determined by alleles at a handful of genes. The view that most complex human traits were conditioned by alleles at a small number of genes prevailed up to the 1990s, when genome-wide linkage and later association studies could be undertaken as a result of technological advances. Height is variable (SD ~ 7 cm) among individuals in a given population and is one of the most heritable morphological traits in humans, with estimates around 80% (78,79). What are the most important lessons we have learned regarding the genomic architecture of human height?

In brief, a number of genes have been implicated in single-gene deficiencies causing short stature (e.g., insulin-like growth factor 1 [*IGF1*], insulin-like growth factor 1 receptor [*IGF1R*], natriuretic peptide receptor 2 [*NPR2*], short stature homeobox [*SHOX*], aggrecan [*ACAN*], SRY-box transcription factor 9 [*SOX9*], collagen type X alpha 1 chain [*COL10A1*], growth hormone receptor [*GHR*]) or acromegaly (e.g., growth hormone [*GH*], *IGF1*, fibrillin 1 [*FBN1*], aryl hydrocarbon receptor-interacting protein [*AIP*], menin 1 [*MEN1*], cyclin-dependent kinase inhibitor 1B [*CDKN1B*]). Several large-scale GWAS for height, with increasing sample sizes, have been published in the last decade (80-85), and they have reported growing numbers of common height-increasing or -decreasing alleles. When very large panels of SNPs are considered simultaneously in the analysis, common MAF variants account for more than half (45%) of the height heritability (83,86). When rare and low-frequency coding variants were investigated in more than 700,000 individuals, 83 coding variants associated with

height were identified, with 24 alleles affecting height by more than 1 cm plus 4 alleles (at *AR*, *CRISPLD2*, *IHH*, and *STC2*) with an effect size of at least 2 cm (87). It has been suggested that an excess of 10,000 genomic variants is necessary to account for the heritability of height, with the top 700 SNPs having a median effect size of about 1.4 mm per allele and the remaining loci having a median effect size of<0.1 mm per allele (81,88).

The lessons learned on the genomic architecture of height are relevant to the case of BMI and total adiposity even though the heritability of BMI is substantially lower than human height in a global population perspective; that is, in the range of 40% to 50% of age- and sex-adjusted variance as reviewed previously in this review. GWAS explorations aimed at identifying SNPs associated with BMI have been based on increasingly larger sample sizes (73,80,82,84,89-108). When only the SNPs significant at the genome-wide level ($P<5\times10^{-8}$) are considered, the variance in BMI accounted by the panel of SNPs remains low primarily because of the sample size limitations. Therefore, the BMI variance explained by mostly common SNPs was of the order of 2% in early studies (80,94,96) but increased to about 6% in more recent reports based on larger samples (84).

However, when very large panels of SNPs or all genotyped SNPs are included under the assumption that the sample size is extremely large, or when SNPs at a less-stringent threshold are considered with the requirement that the direction of the association for each minor allele is concordant with prior studies, then more than 20% of the BMI variance is accounted for (82,91,95,96,106). In support of this conclusion, the narrow-sense heritability of BMI was estimated at 42%, with common SNPs explaining 23% of the BMI variance in a study based on a population from Iceland using a combination of close and distant relatives combined with a genome-wide panel of SNPs (106). The notion that common SNPs account for about two-thirds of the BMI heritability has been supported by several studies. Yang et al. observed that the common SNPs explained 27% of the BMI variance, a figure that was exactly replicated by Ge and collaborators (82,91). It is also concordant with the findings derived from 2.1 million SNPs in about 120,000 middle-aged adults of the UK Biobank in which common SNPs accounted for 23% of the BMI variance (95). A useful observation is that there are hotspots in the human genome where clusters of SNPs associate with height or BMI (88).

If common SNPs account for approximately two-thirds of the BMI heritability, then low-frequency and rare variants could potentially explain the missing fraction of the heritability estimate. No compelling data, to our knowledge, have been published to date on this topic, but strong support for this notion is being reported in an unpublished paper in which whole-genome sequencing was performed on 21,620 unrelated individuals of European ancestry (Wainschtein et al. bioRxiv, doi:10.1101/588020, unpublished data). The whole heritability (40%) of BMI was recovered, with about one-third of the heritability explained by rare variants in genomic regions of low linkage disequilibrium. Taken together, the most recent data suggest that the heritability of BMI can be fully explained by a large number of common SNPs combined with low-frequency and rare variants.

How many DNA variants does it take to account for the heritability of BMI? It is too early to be able to address this question with confidence. However, some rough indications can be obtained from findings on the genomic architecture of height and exploration of the same issue for BMI. In the case of height, it requires an excess of 10,000 DNA variants to account for the heritability level, with effect sizes decreasing as

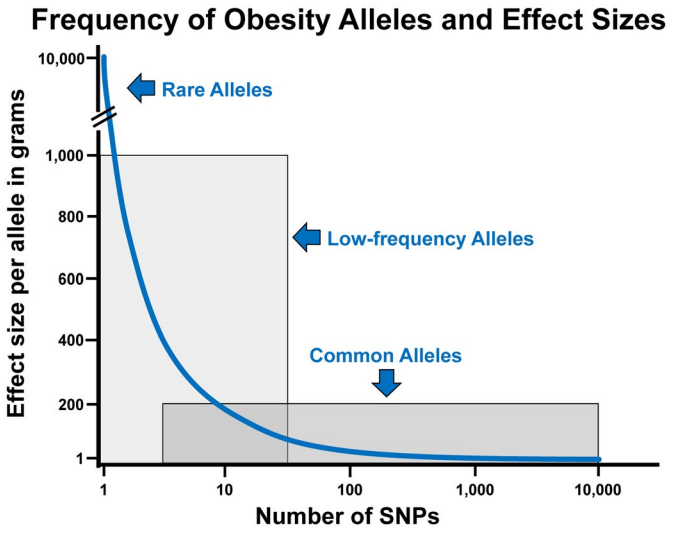

Figure 5 Schematic illustration of the relation between effect size on weight and the number of SNPs accounting for the heritability of BMI across the three classes of allele frequencies. SNP, single-nucleotide polymorphism.

additional SNPs are incorporated into the polygenic system. It is very likely that the same scenario will apply to BMI. For instance, Locke and colleagues estimated that about 1,000 SNPs were true BMI SNPs in a first attempt to address this question (96). A similar effect-size pattern as for height is emerging for BMI, with an alpha-ketoglutarate-dependent dioxygenase (*FTO*)-risk allele (the most strongly associated SNP) accounting for about 0.4 kg/m^2 but with the effect size decreasing rapidly to about 0.1 kg/m^2 for associated SNP number 20 and 0.05 kg/m^2 for SNP number 30 (80). Diminishing effect sizes should be expected with the growing number of variants, with most variants contributing BMI-increasing or -decreasing alleles with effect sizes of a few grams or less. This scenario is illustrated schematically in Figure 5. Even though there are rare alleles increasing or decreasing body mass by kilograms, most alleles impact weight much more subtly, often by a few grams or one gram and less.

An important observation is that the effect size of obesity alleles increases at the upper end of the BMI distribution compared with the low and middle range of the same distribution. For instance, the effect size of an *FTO*-risk allele on BMI was more than six times greater at the 90th percentile compared with the 10th percentile of the BMI distribution in a study based on the Framingham Heart Study population (39). The genotypic risk score based on obesity-promoting alleles at eight loci was more strongly associated with BMI in the upper end of the BMI distribution in a large pediatric population (109). The notion that the top obesity alleles have uniform effect sizes across the BMI range was also dispelled in a large study based on more than 75,000 adults of European ancestry (37). The effects of nine SNPs at eight obesity loci (*FTO*; *PCSK1*; transcription factor 7-like 2 [*TCF7L2*]; *MC4R*; FA complementation group L [*FANCL*]; gastric inhibitory polypeptide receptor [*GIPR*]; mitogen-activated protein kinase 5 [*MAP2K5*]; and 5′-nucleotidase, cytosolic II [*NT5C2*]) increased across the BMI distribution, suggesting that obesity alleles exert minimal effects in lean and normal weight individuals but carry growing deleterious effects in individuals with a proneness to overweight or obesity. Attempts to uncover a similar pattern regarding the effects of height-impacting alleles across

the body height distribution were not successful (37,40). Globally, these observations reveal that obesity-promoting alleles have greater penetrance in people who have a proneness toward overweight and obesity (Figure 6). However, the available data do not establish whether the larger effect size of obesity-promoting alleles results from the prevailing physiological and metabolic environment of people with obesity or whether the larger effect sizes preceded weight gain and obesity.

Low-frequency and rare variants. One important issue is whether low-frequency and rare variants can offer insights into the genomic architecture of BMI or the risk of obesity. Most common DNA variants captured by the usual genotyping platforms cluster in noncoding genomic regions. In contrast, low-frequency and rare variants could impact coding and regulatory elements more often, as suggested by the 1000 Genomes Project (110). Low and rare MAF variants tend to have larger effect sizes and to be of more recent origin than common alleles (schematically illustrated in Lupski and colleagues) (111). Importantly, only about 68% of the low-frequency and rare variants (defined here as MAF < 0.01) is captured by imputation (82).

A search for rare coding variants associated with BMI was undertaken in 718,734 individuals from 125 studies with exome-genotyping arrays yielding 14 rare coding variants in 13 genes (73). One coding variant was found in each of the following genes: zinc finger and BTB domain-containing 7B (*ZBTB7B*), rap guanine nucleotide exchange factor 3 (*RAPGEF3*), *RAB21*, member RAS oncogene family, zinc finger homeobox 3 (*ZFHX3*), ectonucleoside triphosphate diphosphohydrolase 6 (*ENTPD6*), zinc finger RNA-binding protein 2 (*ZFR2*), and zinc finger protein 169 (*ZNF169*). Two coding variants were identified in *GIPR*, one in *MC4R*, and one in kinase suppressor of ras 2 (*KSR2*). The largest effect size was observed in the carrier of a stop-codon mutation in *MC4R* in which the carrier weighed 7 kg more than noncarriers. Overall, the effect size of the coding variants is about 10 times larger than that of common variants (73).

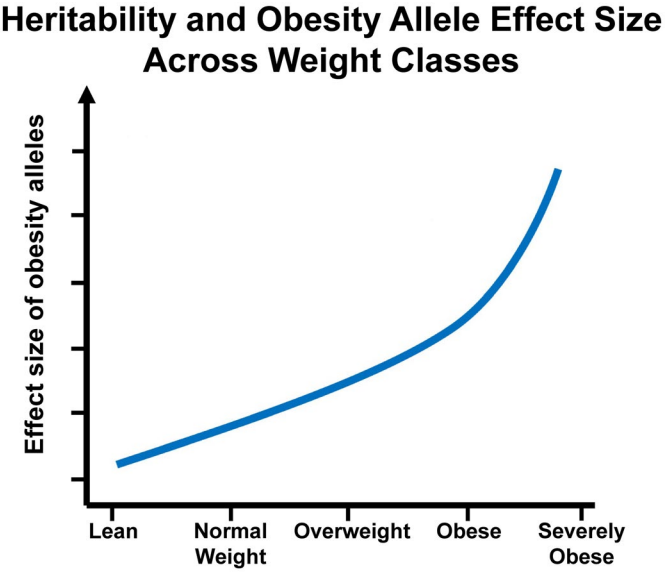

Figure 6 Schematic illustration of the effect size of obesity alleles across BMI classes. A typical obesity allele has a minimal effect in lean and normal weight individuals, but it has a much larger impact in individuals with excess weight, including those with severe obesity. The exact shape of the curve is currently unknown. Based on data reviewed in the text.

In a study comparing common and low-frequency variants associated with obesity in 1,509 children with obesity and 5,380 controls, it was found that both types of variants around the *BDNF*, *LEPR*, *MC4R*, *POMC*, and *SH2B1* loci were involved in the pathogenesis of early-onset obesity (104). It was also reported that rare copy number variants (CNVs) affecting genes participating in the neuronal regulation of energy balance contribute to severe cases of obesity, particularly CNVs impacting genes of the G protein–coupled receptors family. In an analysis of DNA sequence data in 119 genes performed in 2,548 children with obesity and 1,117 controls that excluded *MC4R* and leptin mutations, rare variants in angiopoietin-like 6 (*ANGPTL6*), BBS syndrome 1 (*BBS1*), BBS syndrome 2 (*BBS2*), clock circadian regulator (*CLOCK*), guanine nucleotide-binding protein Gs (*GNAS*), and McKusick-Kaufman syndrome (*MKKS*) were nominally and significantly associated with obesity (112). A total of 52 variants were identified, and they were found to contribute to obesity in 2% of cases compared with controls. One can make a strong case for a contribution of CNVs to obesity, as they play a large role in human genomic variability. This is well supported by data showing associations between CNVs from several genomic regions and obesity, including loci at 11q11, 1p21.1, 10q11.22, 10q26.3, 16q12.2, 16p12.3, and 4q25 (113).

Variants in monogenic obesity cases and in candidate genes contribute to common obesity forms. One important issue is whether loci of Mendelian obesity cases (rare, single-gene defects) harbor other alleles that are more common and whether they influence BMI or the risk of obesity. In one early paper, Farooqi and colleagues showed that heterozygotes for the deletion of a glycine residue (D G133) in the leptin gene, resulting in a partial leptin deficiency, was associated with lower serum leptin levels and higher levels of adiposity (114).

A search for the potential contribution of common BMI SNPs to severe obesity was undertaken by genotyping more than half a million SNPs across the autosomal genome in 775 severe obesity cases and 3,197 controls (115). Ten alleles shown to increase BMI in prior studies were also more prevalent in individuals with severe obesity. It is reasonable to conclude from the aforementioned and other data (116) that common variants in monogenic obesity loci are part of the common obesity polygenic profile and that common obesity SNPs are also contributing to the risk of obesity in severe single-gene defect cases.

In the early phase of obesity genetic research, the emphasis was on candidate genes of obesity (See Rankinen et al. for a review) (117). A literature search identified 547 candidate genes derived from multiple types of studies, and the contribution of SNPs located in ±10 kb flanking sequences around these genes was investigated (118). It was concluded that there is some evidence for enrichment of association between these candidate genes and BMI variation, but that the level of association is small. DNA variants at traditional candidate gene loci have generated some relevant findings, but most of the BMI variability is explained by sequence differences at noncandidate gene loci. Another line of evidence relates to CNV at candidate genes, as illustrated by studies on copy number at a locus encompassing the amylase alpha 1A (*AMY1*) gene and its association with obesity (119).

Polygenic risk scores and prediction. Who is at risk of developing obesity over time? This is a question generating a lot of attention because of its potential public health and clinical utility.

Given the evidence for a significant genetic transmission of BMI level or risk of obesity across generations, it is not surprising that there are attempts to use genomic variants to predict future levels of BMI or the risk of developing obesity with age. Multiple small and large companies are engaged in this process and are offering commercial products to the public even though there is no evidence to date that their panels of SNPs have appropriate sensitivity and specificity to qualify as useful predictors.

The research on genomic predictors of obesity traits has been closely linked to incremental progress in sample size and to the number of loci identified in reports on GWAS of BMI. One of the first reports was based on 12 loci, and it yielded an area under the curve (AUC) for the receiver operating characteristic (ROC) curve of about 0.57 (a random classification would generate an AUC of 0.50) (120). A similar AUC (0.57) was obtained when the panel of SNPs was augmented to 32, which is likely an indication that the added SNPs were characterized by small effect sizes (80). Subsequently, the number of SNPs significant at the genome-wide level was increased to 97 based on a larger sample size of 339,224 participants (96). When attempting to predict obesity (BMI ≥ 30), the AUC under the ROC curve reached 0.60. Even though the increase in prediction was very modest, a growing number of BMI-increasing alleles was associated with a higher body weight for height. For instance, individuals who were between 160 and 180 cm tall and who were carrying >104 BMI-increasing alleles were heavier by about 10 kg compared with those who carried <78 such alleles.

More recently, genome-wide polygenic predictors (GPS) based on more than 2 million variants accounting for 23% of the variance in BMI were developed (95). The GPS best correlated with BMI ($r = 0.29$) and validated in a large sample of the UK Biobank was retained for further testing. When BMI was investigated in relation to deciles of the GPS in a sample of 288,016 middle-aged individuals, there was a strong gradient with a mean BMI of 25.2 in the lowest decile compared with a BMI of 30 for those in the top GPS decile, with 83% of those in the upper decile having overweight or obesity (95). The prevalence of severe obesity (BMI > 40) reached 0.2% in the lowest GPS decile versus 5.6% in the highest decile. In 3,722 young adults from the Framingham Offspring and the Coronary Artery Risk Development in Young Adult studies who were followed for a median of 27 years, 16% of those in the top GPS decile developed severe obesity, whereas only 1.3% in the lowest GPS decile developed severe obesity. Finally, in 7,861 children followed from birth to 18 years of age from the Avon Longitudinal Study of Parents and Children study, the weight differences between the lowest and the top GPS deciles at 18 years of age reached 12 kg, suggesting that a prediction of future risk of obesity based on panels of genome-wide variants could eventually be implemented even in the growing years (95). AUC under the ROC curves were not available for these various GPS predictions of BMI levels, but they are likely below 0.80, a level that is often considered as a threshold for truly useful clinical applications. Despite the technical and practical challenges arising from predictors based on very large panels of SNPs, other genomic variants, and clinical variables, it may be possible, with more research, to generate future, powerful predictors of body weight trajectory and the risk of obesity over time.

Population differences in obesity genomics. Most of the findings summarized previously in the review were generated in populations of European ancestry. Is the genomic architecture of BMI level or obesity risk emerging in African or Asian individuals comparable with what is observed in people of European descent? Although the evidence is even more incomplete in other ethnic groups, the evidence accumulated thus far indicates that most common BMI SNPs have comparable effects among Asian, African, and White European individuals (99,102,103). For instance, 79% of BMI SNPs identified in European populations exhibited consistency in the direction of the MAF effect on BMI in people of African descent and 91% in samples of East Asian individuals (96). However, several BMI loci have been identified in people of African descent that were not found in populations of European descent (121). Comparisons of BMI-related loci between European and African individuals are especially useful for the understanding of its genomic architecture given the lower level of linkage disequilibrium observed in African populations.

Genomics and the biology of obesity. A high-altitude view posits that the risk of obesity is defined by physics, physiology, behavior, and the social and physical environment. What have we learned from obesity genomics that could inform us about the role of biological heterogeneity on the risk of obesity? This question is highly relevant, as we have a much better understanding of the extent of human genomic variability. More than 88 million genomic variants with a frequency > 1% have been identified, of which about 85 million are SNPs, 8 million of them have a frequency > 5%, 3.6 million are short insertions/deletions, and 60,000 are structural variants (110). In addition, a typical genome harbors about 2,500 structural or chromosomal variants, including up to 1,000 large DNA deletions and as many as 160 copy number variants. On average, each person carries about 150 DNA variants that yieldtruncated mRNAs leading to partial or complete knockout of gene products, and more than 10,000 variants alter the amino acid sequences of proteins. Based on the whole-genome sequencing of 185 genomes of the 1000 Genomes Project, it was estimated that a person of European descent carries about 100 variants causing a loss of function of the gene products, with 18 of them in the homozygous state (74). By some estimates, an individual selected at random carries from 200,000 up to 500,000 rare variants, which tend to be of recent origin and are often unique to a pedigree (111). Notably, the genome of a given person differs from the human reference genome at up to 5 million DNA sites.

What is the altered biology resulting from all this genomic variability that influences the risk of obesity? It is still too early in the research to be able to paint a complete picture depicting the complex connections between DNA sequence variants and the regulation of energy balance. The available data and insights are based on small subsets of the global panel of genomic variants defining the obesity genotype. However, as common variants identified in the early GWAS have larger effect sizes than variants uncovered later with larger sample sizes, valuable lessons can be derived from these early efforts.

In the GWAS report by Locke et al., 97 BMI loci were identified at the genome-wide significance level (96). These loci were interrogated via a bioinformatics pipeline to uncover tissues, gene sets, and pathways contributing to the predisposition to obesity. About 500 gene sets were found to be enriched for the genes indexed by the 97 BMI SNPs. Gene expression profiles in genes near BMI-associated SNPs revealed that there were 31 significantly enriched tissues, of which 27 were various brain regions. Strong gene enrichment was observed in the hypothalamus, pituitary gland, hippocampus, and limbic system. The most

significant gene sets revealed pathways related to synaptic function; glutamate signaling; noradrenaline, dopamine, and serotonin release cycles and γ-aminobutyric acid (GABA)-receptor activity (96). Other relevant pathways were related to physical activity, integration of energy metabolism, secretion and action of insulin, mechanistic target of rapamycin signaling and cell growth, neurotrophin signaling, calcium channels, mitogen-activated protein kinase activity, chromatin organization, and ubiquitin ligases. Gene prioritization was undertaken based on five lines of evidence. A panel of 64 potential obesity genes emerged, including several that overlap with central nervous system (CNS) processes (ELAV-like RNA-binding protein 4 [*ELAVL4*], glutamate ionotropic receptor delta type subunit 1 [*GRID1*], cell adhesion molecule 2 [*CADM2*], neurexin 3 [*NRXN3*], and secretogranin 3 [*SCG3*]), monogenic obesity syndromes (*MC4R*, *BDNF*, BBS syndrome 4 [*BBS4*], *SH2B1*, neuronal growth regulator 1 [*NEGR1*], and *POMC*), insulin, lipid and energy metabolism, adipogenesis (*TCF7L2*, *GIPR*, insulin receptor substrate 1 [*IRS1*], forkhead box O3 [*FOXO3*], ankyrin repeat and SOCS box containing 4 [*ASB4*], regulatory-associated protein of mTOR complex 1 [*RPTOR*], NPC intracellular cholesterol transporter 1 [*NPC1*], cAMP-responsive element binding protein 1 [*CREB1*], TLC domain containing 3B [TLCD3B], apolipoprotein B receptor [*APOBR*], and hydroxysteroid 17-β dehydrogenase 12 [*HSD17B12*]), RNA binding and processing (polypyrimidine tract binding protein 2 [*PTBP2*], *ELAVL4*, CUGBP Elav-like family member 1 [*CELF1*], and RALY RNA binding protein like [*RALYL*]), mitogen-activated protein kinase signaling pathway (*MAP2K5* and mitogen-activated protein kinase 3 [*MAPK3*]), and cell proliferation or cell survival (Fas apoptotic inhibitory molecule 2 [*FAIM2*], parkin RBR E3 ubiquitin protein ligase [*PRKN*], and olfactomedin 4 [*OLFM4*]).

Monogenic obesity is generally characterized by gene deficiencies altering hypothalamic regulation, resulting in hyperphagia and disruption of energy homeostasis (122). In contrast, based on gene expression studies of 106 genes in more than 20 tissues, it has been reported that the expression of common obesity-susceptibility genes was particularly enriched in the insula and substantia nigra, brain regions involved in addiction and reward (123). Even though genome-wide explorations have emphasized that genes and pathways expressed in brain regions dominate the genomic signature of obesity, there is evidence that adipocyte biology disturbances in lipolysis and adipogenesis are also involved (96,124).

An important and consistent signal from GWAS reports relates to the strong associations between the *FTO* locus and obesity in humans across ethnicities. Variants in the first intron were first shown by Frayling et al. to be associated with BMI and obesity, with the homozygous for the most potent risk allele weighing up to 2 kg more than those without the risk allele (90). This finding has been replicated multiple times in different populations, and several alleles in the first intron shown to be in strong-linkage disequilibrium have also been found to be associated with obesity (125,126). Although *FTO* was found to have demethylase activity and to be expressed in hypothalamic regions, no clear connection could be established between the *FTO* variants, gene expression, and functional markers across a wide range of investigative strategies (127). This led to the study of other candidate genes encoded in the surrounding genomic region, including RPGR-interacting protein 1 like (*RPGRIP1L*), cut-like homeobox 1 (*CUX1*), and iroquois homeobox 3 (*IRX3*) as potential mechanistic links between the *FTO*-intronic variants and obesity. Reduced expression of *CUX1* decreased the expression of *FTO* and *RPGRIP1L*. *RPGRIP1L* may regulate ciliary signaling, suggesting potential similarities with aspects of the BBS and perhaps an involvement of ciliary deficiencies in common obesity forms. *In vitro* and *in vivo* studies in model organisms provided evidence that the *FTO*-risk alleles reduced expression levels of *FTO*, *RPGRIP1L*, and *CUX1*, leading to attenuated leptin signaling with higher food intake and fat mass (128,129). Another line of research has evidenced that the homeobox gene, *IRX3*, is a candidate for mediating the effects of the *FTO*-intronic variants. The *IRX3* promoter was found to interact over a long range with *FTO* genomic regions harboring obesity risk variants (130). Relevant *FTO* SNPs were shown to be associated with *IRX3* expression in the cerebellum of human brain samples. In *IRX3*-deficient mice, there is an increased sympathetic tone and activation of brown adipose tissue that seem to entrain the observed reduced energy expenditure and lower adiposity, a finding that has been confirmed by others in samples of patients and mice (131). More research is warranted before we reach a complete understanding of the mechanisms by which the *FTO*-risk alleles modulate the susceptibility to obesity.

Obesity-relevant DNA variants could also impact the biology of the predisposition to obesity via microRNAs and epigenetic events. These topics will not be fully reviewed here, but suffice it to say that there is growing evidence that both could contribute to the obesity risk profile. For example, it has been suggested that some obesity SNPs could result in DNA base changes altering microRNA binding to target sites (132) and that selected microRNAs were obesity biomarkers (133,134). A growing number of studies focused on the epigenetics of obesity have appeared in recent years (135). It is still too early to draw a conclusion on the true contribution of epigenetic signatures on the risk of obesity and on the potential modulation of epigenetic events of relevance to obesity by diet, physical activity level, smoking, alcohol intake, and other behaviors. However, the suggestion that BMI is associated with widespread changes in DNA methylation patterns (up to 187 genetic loci impacted) is of importance, as is the conclusion that alterations in DNA methylation profile are the consequence rather than the cause of obesity (136). Variation in the DNA methylome profile between members of pairs of identical twins discordant for BMI offers an opportunity to identify epigenetic signatures participating in the etiology of obesity (137). Equally important is the observation that older pairs of MZ twins exhibit more differences in methylation and histone acetylation content than young pairs of MZ twins (138). Advances in the genetic and epigenetic transcriptional regulation of energy homeostasis have highlighted the importance of the cross talk between them and their potential to illuminate further the etiology of obesity (139).

One relevant question is whether the advances in the genomics of obesity that have occurred over the last decade or so translate into insights into the biology of obesity that are concordant with the progress made over the last 70 years in classical laboratory research on the physiology, metabolism, and behavior of obesity. This question was addressed recently through a variety of approaches (140). The findings of three GWAS (96,141,142) were used as the basis for the derivation of a set of 110 unique SNPs significant at the genome-wide level, as well as 2,000 obesity SNPs significant at a lower threshold, that were subsequently interrogated for underlying genes, pathways, expression quantitative trait loci, tissue-specific networks, noncoding versus coding variants, epigenomic implications, and matching with relevant gene-knockout mouse models. The emerging biology was then compared with the panel of determinants of obesity arising from decades of experimental and clinical research as defined by 53 traits contributing to the etiology of obesity (140). Convergence of the evidence between both research tracks was observed for CNS processes, lipid metabolism, oxidative phosphorylation, as well as hormones, neuropeptides, and their receptors. *Cis*-expression quantitative loci (eQTL; association between an

allele at a locus and a gene expression trait) surveys found that, in about 50% of cases, obesity alleles affected gene expression of closest positional genes. Extensive overlap was observed between obesity SNPs and transcription binding sites, enhancers, and promoter sites, especially enhancer sites in brain regions. However, the evidence accumulated in physiological and behavioral research diverged from the GWAS findings and related inferences on the role of skeletal muscle metabolism, energy partitioning, and energy expenditure (140). It is entirely possible that the evidence gap between the two research tracks will be closed as the number of obesity SNPs expands.

Genomic research has generated thousands of DNA variants that define the biological and behavioral architecture of the risk of obesity. Fortunately, the large number of obesity loci is converging on a finite set of genes, pathways, and systems, as well as gene-regulatory elements. As the number of obesity SNPs and other variants expands and becomes more or less fixed, the focus should shift to a more complete delineation of the integrative biology defining the predisposition to common forms of obesity. The advances brought about by unbiased genome-wide exploration of sequence variants associated with obesity have been spectacular. They have dramatically changed our understanding of what constitutes the genomic architecture and molecular basis of the numerous paths by which people could be predisposed to obesity. It has also taught us that the risk of obesity results from the confluence of vulnerabilities across multiple genomic and epigenomic sites, genes, pathways, and tissues (139). Although an individual genomic barcode is unique, the obesity predisposition barcode overlaps considerably among individuals, as suggested by the contribution of common risk alleles (143). Although much progress has been made, no clinical screening algorithms, to our knowledge, have yet attained the predictive power needed, with sufficient levels of specificity and sensitivity, to be recommended for practical implementation. We expect that the number of GWAS-generated signals for the predisposition to obesity will quickly expand and reach its useful limit. This would set the stage for major efforts aimed at deciphering the underlying biology and the complex mechanisms involved. It is a daunting, but not unsurmountable, task.

Genomic variants and adipose tissue distribution

As reviewed previously in this review, indicators of subcutaneous fat distribution, visceral fat, hepatic fat content, and other fat deposition sites are characterized by a genetic component of about 30% to 55% based on data adjusted for age, sex, and markers of adiposity or weight status. Thus, there are genetic elements influencing fat topography over and above the genetic drivers of total adiposity level. Cases of monogenic lipodystrophies offer insights into the genomic factors contributing to body-fat distribution regulation. For instance, inherited defects in 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*); BSCL2 lipid droplet biogenesis associated, seipin (*BSCL2*); caveolin 1 (*CAV1*); and caveolae-associated protein 1 (*CAVIN1*) have been identified in congenital generalized lipodystrophies, whereas mutations in AKT serine/threonine kinase 2 (*AKT2*), lamin A/C (*LMNA*), perilipin 1 (*PLIN1*), and peroxisome proliferator-activated receptor γ (*PPARG*) have been found in familial partial lipodystrophies (43). Other genes that have been implicated include cell death-inducing DFFA-like effector C (*CIDEC*), zinc metallopeptidase STE24 (*ZMPSTE24*), and proteasome 20S subunit β 8 (*PSMB8*).

Adipose tissue distribution. Three major reports have dealt with the waist girth to hip girth ratio (WHR) adjusted for BMI. An initial GWAS effort was based on 32 studies comprising more than 77,000 participants, with the replication of 16 loci attempted in a panel of 29 new studies totaling 113,636 individuals (144). Fourteen loci were identified at the genome-wide significance level for their associations with the relative fat distribution between the upper and lower body segments (ADAM metallopeptidase with thrombospondin type 1 motif 9 [*ADAMTS9*]; cytoplasmic polyadenylation element binding protein 4 [*CPEB4*]; dynamin 3-phosphatidylinositol glycan anchor biosynthesis class C [*DNM3-PIGC*]; growth factor receptor bound protein 14 [*GRB14*]; homeobox C13 [*HOXC13*]; inositol 1,4,5-trisphosphate receptor type 2-sarcospan [*ITPR2-SSPN*]; lymphocyte antigen 86 [*LY86*]; lysophospholipase-like 1 [*LYPLAL1*]; nuclear factor, erythroid 2-like 3 [*NFE2L3*]; nischarin-stabilin 1 [*NISCH-STAB1*]; R-spondin 3 [*RSPO3*]; T-box transcription factor 15-tryptophanyl tRNA synthetase 2, mitochondrial [*TBX15-WARS2*]; vascular endothelial growth factor A [*VEGFA*]; and zinc and ring finger 3-kringle containing transmembrane protein 1 [*ZNRF3-KREMEN1*]). Seven of these loci had a stronger effect on WHR in women than in men. These WHR loci did not overlap with the common obesity loci, suggesting that they influence fat distribution as opposed to the total amount of adiposity (145). Subsequently, meta-analyses of GWAS data encompassing 245,549 individuals from the GIANT Consortium identified 49 loci associated with WHR adjusted for BMI, with 19 of these loci exhibiting a stronger effect in women and 1 locus with a stronger effect in men (146). Finally, a new meta-analysis of GWAS for WHR adjusted for BMI was performed in 694,649 individuals (147). There were 463 significant associations covering 346 loci, with 105 signals exhibiting sex dimorphism in the association pattern. The increasing number of significant SNPs is reminiscent of what has been reported on the genomic architecture of height and BMI. The 5% of individuals carrying the most WHR-increasing alleles were 60% more likely than the bottom 5% to have a WHR above the cutoff for metabolic syndrome (147).

Protein-coding variants contribute to variability in fat distribution. This was demonstrated in a study of 228,985 predicted-coding and splice variants in 334,369 individuals from five major ancestries in the discovery phase and in 132,177 persons of European descent in the validation phase for WHR adjusted for BMI (148). A total of 56 significant coding variants were identified, 43 of which were common variants. Notably, 25 of these variants were also associated with BMI, implying that 31 of them were specific to adipose tissue topography. On average, the 13 less-frequent variants had effect sizes three times greater than those of common variants. Of the 56 variants, 19 exhibited sex-specific effects, 16 of which had stronger associations with WHR in women. Among the genes identified as potential fat deposition profile genes, the following were highlighted: *RAPGEF3*; fibroblast growth factor receptor 2 (*FGFR2*); R3H domain containing like (*R3HDML*); H1.6 linker histone, cluster member (*HIST1H1T*); pecanex 3 (*PCNXL3*); activin A receptor type 1C (*ACVR1C*); aspartyl-tRNA synthetase 2, mitochondrial (*DARS2*); matrix metallopeptidase 14 (*MMP14*); dual serine/threonine and tyrosine protein kinase (*DSTYK*); angiopoietin-like 4 (*ANGPTL4*); UDP-glucose glycoprotein glucosyltransferase 2 (*UGGT2*); R-spondin 3-KIAA0408 (*RSPO3-KIAA0408*), ras responsive element binding protein 1 (*RREB1*); diacylglycerol lipase β (*DAGLB*); MLX-interacting protein like (*MLXIPL*); coiled-coil domain containing 92 (*CCDC92*); leucine rich repeat-containing 36 (*LRRC36*); and ubiquinol-cytochrome c reductase complex assembly factor 1 (*UQCC1*).

In a separate study, sex-specific loci and adiposity loci were reported for the profile of fat distribution relative to total body fat (149). A GWAS analysis was undertaken on more than 360,000 participants of the UK Biobank for the proportion of body fat to the arms, legs, and trunk (relative to total body fat) estimated from segmental bioelectrical

impedance. Of 98 independent associations observed with fat distribution indicators, 37 exhibited stronger effects in females.

VAT depot. One depot of particular interest is abdominal VAT. A number of genome-wide association reports on VAT have been published over the last decade (150-152). Considering the substantial correlation between VAT and BMI or total adiposity (42), only data for VAT adjusted for these covariates are summarized. Computed tomography was used to assess VAT in 5,560 women and 4,997 men, and VAT was adjusted for BMI (150). rs1659258 near threonine synthase-like 2 (*THNSL2*) was significantly associated with VAT in women but not in men. The same genomic marker was found to also be associated with waist circumference in women, but not in men, of the GIANT Consortium. Another study confirmed the *THNSL2* association with VAT in women and provided suggestive evidence for additional candidates, namely BBS syndrome 9 (*BBS9*) and CYCS pseudogene 30 (*CYCSP30*) (151). A recent study dealt with the colocalization of GWAS and eQTL signals for a number of traits, including VAT, in up to 18,332 participants (152). Ubiquitin-conjugating enzyme E2 E2 (*UBE2E2*) was found to be associated with the VAT-to-subcutaneous fat ratio, suggesting a contribution to the propensity to accumulate fat in the visceral cavity. Functional studies in primary mouse adipose progenitor revealed that an *UBE2E2* loss of function impairs adipocyte differentiation.

Ectopic fat depots. The genetics of ectopic fat deposition are also of considerable interest. In the study based on colocalization of GWAS and eQTL signals cited previously in this review, six ectopic fat depots, assessed by imaging, were considered (152). Genetic correlations among these traits were moderate, suggesting that there are common genetic drivers of ectopic fat deposition, as well as depot-specific determinants. Of particular interest are the findings about pericardial fat, with three loci (endosulfine α [*ENSA*], tribbles pseudokinase 2 [*TRIB2*], and EBF transcription factor 1 [*EBF1*]) associated with ectopic deposition around the heart but not with total adiposity or subcutaneous fat distribution. A GWAS analysis was also undertaken for liver fat based on bilirubin levels and liver biopsies in 2,300 individuals (153). A SNP at the UDP glucuronosyltransferase family 1 member A complex locus (*UGT1A*) was associated with total bilirubin levels, two SNPs at suppressor of cytokine signaling 2 (*SOCS2*) and receptor activity modifying protein 3 (*RAMP3*) loci were related to low-grade liver fat accumulation, and three SNPs in patatin-like phospholipase domain containing 3 (*PNPLA3*) and one in SURP and G-patch domain containing 1 (*SUGP1*) were associated with hepatic fat level. *SOCS2* and lisophosphatidic acid G protein coupled receptor 2 (*LAPR2*) were differentially expressed between fatty and normal liver.

Genomics and the biology of adipose tissue distribution. There are known differences among various human fat depots (154). Subcutaneous fat of the abdominal area shows a higher lipid turnover than the gluteofemoral fat depot. The half-life of abdominal fat tissue triglycerides reaches about 12 months but is 50% longer in the femoral depot (155). Abdominal fat accumulation is characterized mainly by increased fat cell size, whereas the lower body fat shows a higher capacity for recruitment of new adipocytes. Differences between upper and lower adipose tissue are not limited to morphology, as there are interdepot differences in apoptosis, inflammatory markers, adipokine secretion, lipolysis, and lipogenesis to name but a few (156).

GWAS of WHR adjusted for BMI have suggested that the genomic signals were enriched for adipocyte regulatory elements involving pathways related to adipogenesis, angiogenesis, adiponectin metabolism, regulation of transcription, and insulin resistance (146,148). Moreover, GWAS signals are often stronger in women compared with men (148,149). In the largest genome-wide screening for SNPs related to adipose tissue distribution to date, which identified 98 significant associations, the signals pertained to genes related to reproductive tissues, musculoskeletal tissues, chondrocytes, mesenchymal stem cells, and fibroblasts. Bioinformatics explorations suggested that a gynoid profile of fat distribution is driven by gonadal hormones on musculoskeletal and adipose tissue mesenchymal progenitors. In women, several genes relate to interactions between cells and the extracellular matrix (149). Gene expression studies of 96 fat distribution genes assessed in abdominal subcutaneous adipose tissue in women concluded that the profile of fat distribution in humans is largely governed by the morphology and function of adipocytes (157). In contrast to what has been reported for BMI, there is no indication that genomic variants in genes involved in CNS regulation are associated with the profile of fat distribution (149).

Figure 7 provides a simplified synopsis of tissues and pathways arising from the bioinformatics exploration of the biology underlying the statistical evidence from GWAS reports. The top panel is related to BMI, adiposity, and risk of obesity, as discussed previously in this review. The lower panel focuses on fat distribution, visceral fat, and ectopic fat traits, including hepatic fat content. Even though there is some degree of commonality between both sets of traits, there are clear differences regarding the biology driving excess adiposity versus fat topography.

Gene expression profiling of upper and lower body adipose tissue depots have highlighted marked differences in transcript abundance of developmental genes, including short stature homeobox 2 (*SHOX2*), iroquois homeobox 2 (*IRX2*), T-box transcription factor 5 (*TBX5*), *HOXC13*, T-box transcription factor 15 (*TBX15*), homeobox B5 (*HOXB5*), HOX transcript antisense RNA (*HOTAIR*), and several microRNAs (154). When the gene profiling was based on whole-blood RNA abundance, gene-set enrichment analyses revealed that the ATP-binding cassette transporters (ABC transporters), apoptosis, Janus Kinase- signal transducer and activator of transcription proteins signaling pathway (Jak-STAT signaling pathway), and p53 signaling pathway were significant for WHR adjusted for BMI, whereas ABC transporters, p53 signaling pathway, and ubiquitin-mediated proteolysis reached significance for VAT adjusted for BMI (158). An exploration of the transcriptomic profile of adipose tissue derived from 15 anatomical sites from five postmortem donors revealed that there are depot-specific gene expression profiles predicted to impact metabolism, inflammation, immune signaling, extracellular matrix, coagulation, thrombosis, beiging of adipose tissue, and apoptosis (159).

Genomics and response to weight loss interventions

As reviewed earlier, proof-of-concept data on gene-behavior interactions with body weight or fat distribution changes have been generated from standardized and fully monitored studies of MZ twins exposed to positive or negative energy balance protocols (60-62). Identifying the genomic drivers of these interactions in larger studies has proven to be challenging in part because they are typically based on behavioral changes examined under free living conditions in which individuals exhibit variable levels of compliance with intervention protocols, but also because the weight changes are generally small. Several studies have reported that genomic risk scores based on common obesity SNPs were not useful predictors of weight loss caused by behavioral interventions (160-163). These reports were

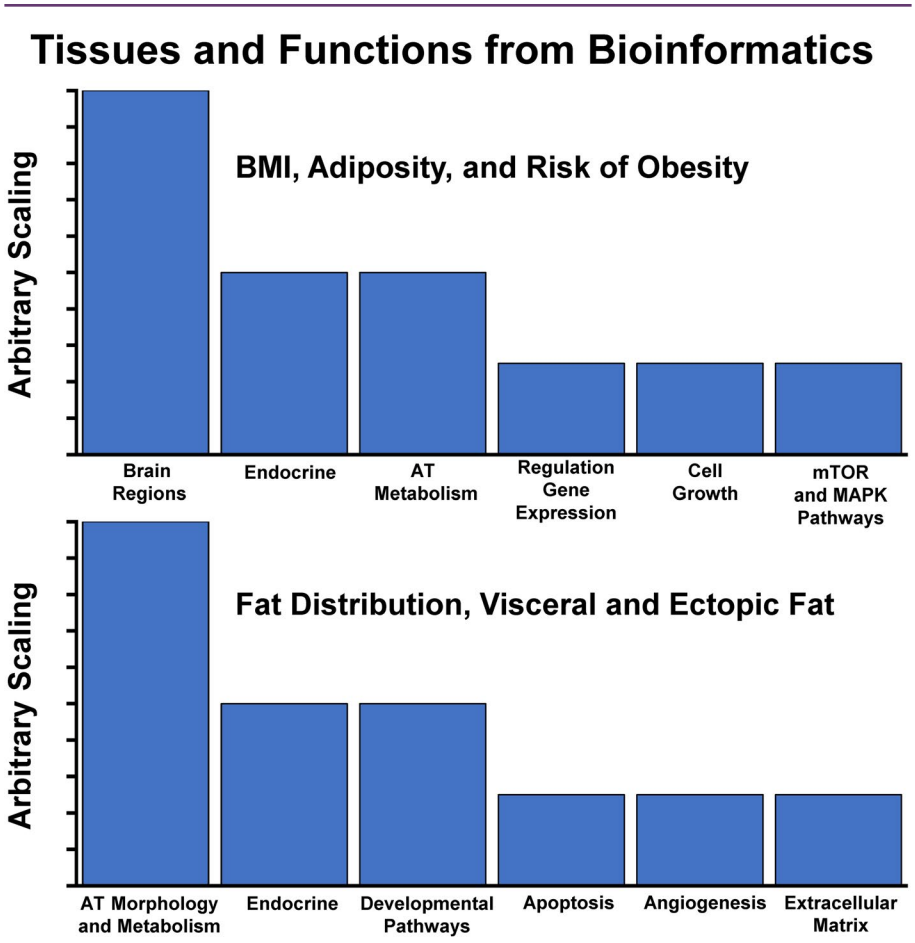

Figure 7 Overview of tissues and pathways contributing to individual differences in total adiposity versus adipose tissue distribution. The height of the bars in each panel reflects the trends from the bioinformatics exploration of the SNPs and positional genes identified in multiple GWAS. There are clear differences between the BMI, adiposity, and risk of obesity panel versus the fat distribution, visceral adipose tissue, and ectopic fat traits panel. AT, adipose tissue; GWAS, genome-wide association studies; SNP, single-nucleotide polymorphism.

based on relatively large sample sizes, but the weight loss was marginal, which is not ideal for uncovering small effect size genomic determinants of experimental weight loss. However, a few genes with allelic variants have been shown to be individually associated with variability in behaviorally induced weight loss, including neuromedin B (*NMB*) (164), LIM homeobox transcription factor 1 β (*LMX1B*) (160), mitochondrial translational initiation factor 3 (*MTIF3*) (163), ATP-binding cassette subfamily B member 11 (*ABCB11*), and TNF-receptor superfamily member 11a (*TNFRSF11A*) (165). In the POUNDS Lost Study, 19 loci were examined for their associations with weight loss induced by dietary interventions over 2 years. Individuals were randomized to one of four diets characterized by variable macronutrient compositions, all aiming at a reduction of 700 kcal per day from habitual caloric intake estimated from metabolic rate measurement and an activity factor (166). Among 19 loci tested, only 1 SNP (rs11185098) at the *AMY1-AMY2* locus was associated with weight loss at 6, 12, and 24 months independent of the diet.

Weight loss induced by bariatric surgery could potentially provide a stronger setting to identify genomic variants contributing to variability in weight loss, as the latter is much more substantial. Based on 1,443 individuals in the Swedish Obese Subjects bariatric arm, *FTO* rs16945088 was associated with maximal weight loss reached, on average, 2 years following surgery (167). No SNPs at 10 loci were related to maximal weight loss or weight loss at 6 years following surgery. A GWAS analysis of weight loss response to bariatric surgery was undertaken on low versus high weight losers (168). In a first stage, 111 SNPs were different between the two groups, and 17 SNPs were retained in the replication phase. These SNPs clustered around biologically relevant loci, such as fibrocystin (*PKHD1*), 5-hydroxytryptamine receptor 1A (*HTR1A*), neuromedin B receptor (*NMBR*), and *IGF1R*. In patients with a BMI > 50, the weight loss at 2 years following surgery was comparable in 30 patients who had clinically significant mutations in *MC4R*, *POMC*, or *PCSK1* compared with the weight loss achieved in 827 patients lacking these mutations (169). In a study of 865 patients followed for a mean of 4 years, the inclusion of a polygenic risk score based on 186 obesity SNPs to a weight loss prediction model based on age, sex, initial BMI, and surgery modality improved the prediction marginally but significantly and reduced the false-negative rate from 20% to 10% (170). Genetic

risk scores were tested in 577 patients following bariatric surgery for their associations with the excess BMI loss (171). The excess BMI loss reached 81% in the high tertile versus 74% in the low tertile of genetic risk scores, suggesting that patients genetically predisposed to a low BMI experienced marginally less weight loss with bariatric surgery.

Finally, there is an abundant body of literature on gene-nutrition and gene–physical activity interactions on BMI, adiposity or risk of obesity, and their changes over time. Although these observational studies will not be reviewed here, they offer mixed results, with positive and negative findings commonly reported. An important lesson for this line of research is that, if such interactions impacting BMI or obesity risk exist, their effect sizes at relevant alleles are small. Detecting such interactions in observational studies requires a large sample size and the proper analytical framework (172).

Lessons from the genetics of thinness

Understanding the genetics of thinness could potentially illuminate the genetics of obesity. The predisposition to be and remain lean over time is characterized by familial aggregation (173-176). Lean parents are known to have lean and normal weight offspring who become, more frequently, lean or normal weight adults compared with offspring from parents with obesity (57,177). The familial risk ratio (λ coefficient), defined as the risk of being thin (percentile < 10 of BMI distribution) when a relative is thin divided by the population prevalence of thinness, reached three in several large population samples of siblings, which is about the same ratio as that of class I obesity (173). Compared with regular siblings or DZ twins, the ratio for pairs of MZ twins was of the order of five in a large sample of twins, suggesting a substantial genetic component to thinness. Importantly, lean mass, assessed by a variety of techniques, is characterized by a significant heritability level of the order of 30% to 60% (25,178-180).

Several studies have focused on the identification of loci and alleles that are associated with leanness. Here, we do not refer to loci associated with conditions such as anorexia nervosa, but rather to thinness or leanness in healthy individuals. For instance, nine SNPs at three loci (C-terminal binding protein 2 [*CTBP2*], cyclin E1 [*CCNE1*], and calcium responsive transcription factor/neurobeachin like-1 [*CARF/NBEAL1*]) have been shown to be related to anorexia nervosa (181), but these loci have not been implicated in healthy thin individuals thus far. Likewise, a duplication of an approximately 600 kb region on chromosome 16 (16:29.5-30.1) is associated with low body weight in children and adults who tend to exhibit developmental disabilities or psychiatric disorders (182). Although there are mutations in *MC4R* known to cause early-onset and severe obesity, some other variants at the same locus are related to lower BMI and risk of obesity. For instance, the V103I polymorphism reduces the risk of obesity by about 20% to 30% based on several meta-analyses, whereas the I251L variant reduces the risk level by about 50% (183). In a comprehensive study on gain-of-function *MC4R* variants, 11 such mutations were identified (184). Among the latter, four variants exhibited preferential β-arrestin recruitment and enhanced signaling via the *MAPK* pathway. Among more than 27,000 UK Biobank individuals, 1 in 16 carried one of these gain-of-function alleles, and 1 in about 1,100 was homozygote for such an allele. Both heterozygotes and homozygotes had a lower BMI and reduced risk of obesity. In a GWAS exploration of genomic differences between thin individuals and individuals with obesity combined with observations in large cohorts, several loci were associated with thinness, including *PKHD1*, *FAM150B*, and *PRDM6/CEP120* (185). Recently, a GWAS analysis was performed on healthy thin Estonian individuals ($N = 881$, BMI < 18), Estonian individuals with severe obesity ($N = 555$, BMI > 95th percentile), and age- and sex-matched controls ($N = 3{,}173$) (186). Five loci were associated with thinness: interactor of little elongation complex ELL subunit 1/mediator complex subunit 10 (*ICE1/MED10*), AP activator protein 1/transmembrane p24 trafficking protein 10 (*FOS/TMED10*), DEP domain containing MTOR interacting protein (*DEPTOR*), anaplastic lymphoma kinase (*ALK*), and a long noncoding RNA (AC013652.1). Functional studies of *ALK* were pursued in drosophila and knockout mice. *ALK* is a member of the insulin receptor family highly expressed in the hypothalamus, and its genetic deletion in mice conferred protection against obesity. Mice with the *ALK* genetic deletion displayed increased energy expenditure, elevated sympathetic tone, and higher adipose tissue lipolysis. This study provides evidence that *ALK* inhibition may promote thinness.

Conclusion

A central message from the global body of obesity genetics research is that people do not all have the same predisposition to gaining weight and developing obesity. The genetic component of BMI in a population comprising the whole range of BMI values accounts for about 40% to 50% of its variance adjusted for age and sex. However, the heritability of BMI and adiposity traits is lower among individuals with normal weight (30%-35%) but higher in the subpopulation of individuals with obesity and severe obesity (60%-80%). The appreciation that the heritability level varies across classes of BMI represents an important advance that may go a long way toward explaining some of the variability observed among genetic epidemiology studies. Overfeeding and negative energy balance experiments conducted with pairs of identical twins support the conclusion that there is a genetic component to variability in body weight and adiposity, as reported by observational cross-sectional and longitudinal genetic epidemiology studies. Very importantly, heritability is a population parameter that does not specify the level of obesity risk for a given person. Assortative mating for BMI is low across the whole range of BMI, but it can nonetheless increase the frequency of obesity alleles among parents with obesity and overweight over multiple generations.

After controlling for BMI or total adiposity, the profile of fat distribution is characterized by heritability estimates ranging from about 30% to 55% depending on the trait. VAT levels exhibit higher genetic variance (50%-55%) than markers of subcutaneous fat topography or ectopic fat deposition in liver and skeletal muscle (30%-35%). Therefore, the size of any given fat depot is characterized by a moderate level of heritability once the data are adjusted for total adiposity.

There are obesity genes with large effect sizes that exhibit a recognizable Mendelian transmission pattern. Thus far, defects in 15 genes have been identified in monogenic obesity, and they are typically characterized by endocrine disorders and hyperphagia, with most cases resulting from a deficiency in a gene of the leptin-melanocortin signaling pathway. In addition, there are many conditions commonly referred to as syndromic obesity, in which excess weight is a secondary condition. Abnormal ciliary function is one of the most common features of these syndromic obesity cases. Globally, Mendelian and syndromic obesity represent perhaps as many as 10% of severe obesity cases around the world.

Genomic research has generated thousands of DNA variants that define the genetic risk of obesity. When genome-wide explorations are based on large populations with a wide range of BMI values, approximately two-thirds of the BMI heritability result from the contribution of common DNA variants, whereas low-frequency and rare variants explain the remaining fraction of the heritability estimate (ranging from 40% to 50%). Most common BMI SNPs seem to have comparable effects among Asian, African, and White European individuals. Diminishing effect sizes are observed with the growing number of variants, with most BMI-increasing or -decreasing alleles contributing a few grams or less. An important finding is that obesity-promoting alleles exert minimal effects in lean and normal weight people but carry growing deleterious effects in individuals with a proneness to obesity, suggesting a higher penetrance in individuals with a proneness to obesity. However, it is not known if this higher penetrance precedes obesity or is caused by the obese state.

The progress resulting from the unbiased genome-wide exploration of sequence variants associated with obesity has been remarkable. Genomic research has generated thousands of DNA variants defining the biological and behavioral architecture of the risk of obesity, and these obesity loci converge on a finite set of tissues, regulatory sequences, genes, pathways, and systems. Such advances are making it possible to shift the focus more onto the integrative biology of the predisposition to obesity. They have taught us that the biological and behavioral predisposition to obesity is shared by most people with obesity, as evidenced by the large number of common alleles that contribute to the genetic vulnerability. We have also learned that the predisposition to obesity seldom arises from a single locus but, rather, is caused by convergence of vulnerabilities entrained by multiple genomic and epigenomic sites and their impact on gene expression ultimately affecting pathways, tissues, and functions. An important line of research is based on the recognition that there are family lines in which obesity is nonexistent, with a strong indication that there is a genetic component to this apparent protection. Some studies have reported on loci and alleles associated with leanness or thinness in otherwise healthy individuals. This is a promising area of research that has the potential to enhance our understanding of the genetic predisposition to obesity in various segments of the population.

No genetically based clinical screening algorithms have yet attained the predictive power needed to be recommended for practical implementation. As the number of GWAS markers of the predisposition to obesity expands and reaches its useful limit, more powerful screening tools are likely to emerge. Because of the larger effect sizes seen in obesity alleles among people with obesity, there is growing optimism that valid genomic screening tools may eventually emerge, especially if the larger effect size of these alleles precedes the development of obesity. Even though the genomics of adipose tissue distribution and ectopic fat deposition has not reached the same level of development as obesity genomics, one can expect major advances in the coming years. Such advances could have implications for our understanding of some of the comorbidities of obesity.

Recent progress in our understanding of the genetic predisposition to obesity has confirmed that such a vulnerability ranges from very low to very high. The obesity genetic risk is determined by hundreds and thousands of DNA variants, a fact that makes genetically based obesity prevention and treatment a major challenge.**O**

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