Is Genetic Testing of Value in Predicting and Treating Obesity?

Maggie C. Y. Ng, Donald W. Bowden

Obesity is a multifactorial disease resulting from the interaction between genetic factors and lifestyle. Identification of rare genetic variations with strong effects on obesity has been useful in diagnosing and designing personalized therapy for early-onset or syndromic obesity. However, common variants identified in recent genome-wide association studies have limited clinical value.

In the United States in 2009–2010, 35.7% of adults were obese, which is defined as having a body mass index (BMI) of 30 kg/m² or greater [1]. Concurrently, 16.9% of children and adolescents were obese, which is defined as being at or above the 95th percentile on the sex-specific BMI-for-age growth charts of the Centers for Disease Control and Prevention [2]. Obesity is a consequence of taking in more energy (through consumption of foods and beverages) than is expended (through exercise and other activities). Although the increasing prevalence of obesity is attributable in large part to the obesogenic environment and to lifestyle factors such as lack of physical activity and consumption of foods high in fat and sugar, individuals vary in their susceptibility to obesity, suggesting that genetic predisposition also plays a role. Family and adoption studies suggest that an estimated 20%-80% of population variance in BMI is due to genetic effects (ie, heritability) [3]. There is increasing interest in whether the genetic variants that have recently been associated with obesity are useful for predicting risk of obesity and/or for developing personalized therapy for obesity.

Identifying Genes Associated With Obesity

Both early rodent studies and targeted gene association studies in humans have identified rare genetic mutations associated with the development of early-onset severe obesity. The key features associated with these gene mutations (summarized in Table 1) can be found in the Online Mendelian Inheritance in Man database (OMIM.org), which catalogs diseases that have a genetic component and links these diseases to the relevant genes. Several of the genes associated with early-onset severe obesity belong to the leptin-melanocortin pathway, including the genes encoding leptin (LEP), leptin receptor (LEPR), melanocortin-4 receptor (MC4R), prohormone convertase 1 (PCSK1), proopiomelanocortin (POMC), single-minded homolog 1 (Drosophila) (SIM1), and brain-derived neurotrophic factor (BDNF). In addition to developing severe obesity at an early age, carriers of mutations in some of these genes also have intellectual disabilities and exhibit developmental delays, which suggests that there is an interplay between neurodevelopment and the hypothalamic functions of energy homeostasis and body-weight regulation.

The identification of genetic variants contributing to common forms of obesity has primarily been the result of recent genome-wide association studies (GWAS). The HapMap Project [4, 5] and the recent 1000 Genomes Project [6] have identified tens of millions of genetic variants, including single-nucleotide polymorphisms (SNPs) and copy number variations, and these studies have established patterns of chromosome structure in diverse populations. In GWAS, millions of these genetic variants in tens of thousands of individuals have been either directly genotyped or inferred from known patterns of chromosome structure using the HapMap and the 1000 Genomes data; GWAS have thus been able to test for associations between genetic variants and a variety of obesity-related traits. To date, at least 58 loci have been associated with various adiposity measures, including BMI, waist-hip ratio, percent body fat, subcutaneous fat, and visceral fat; these associations have primarily been made in individuals of European descent [7-9].

The first of these genetic loci to be identified is still the one most strongly associated with adiposity; it is located in intron 1 of the FTO gene on chromosome 16q12 [10]. Each copy of the risk allele is associated with a 1.2-fold increased risk for obesity and a 0.39 kg/m² increase in BMI in the general population [11]. The effect appears to be stronger (odds ratio = 1.67) in individuals with early-onset extreme obesity [12]. Association of FTO risk alleles with BMI is widely replicated across multiple populations, including Asians [13] and African Americans [14]. Overexpression or knockdown of FTO protein expression in mice leads to altered food intake, energy expenditure, body mass, and fat mass [15-17].
A homozygous Arg316Gln mutation was identified in a family in which 9 individuals had a polyalformance syndrome characterized by growth retardation and developmental delay [18], suggesting that FTO plays a role in the development of the central nervous system and the cardiovascular system.

It is encouraging to note that some of the GWAS loci contain genes previously reported to be associated with monogenic obesity, including LEPR, MC4R, PCSK1, POMC, and the peroxisome proliferator-activated receptor gamma gene, PPARG (Table 1). This suggests that there is a wide spectrum of disease susceptibility; carrying highly penetrant rare variants of these genes leads to severe forms of obesity, while the common variants predisposes a person to more common forms of obesity. Additional GWAS loci—including neuronal growth regulator 1 (NEGR1), neurexin 3 (NRXN3) and SH2B adaptor protein 1 (SH2B1)—are expressed in the brain, which suggests that they may play a role in the neurological regulation of energy homeostasis.

In contrast, the genes and the respective causal genetic variants in many loci, particularly the novel ones, are unclear. The associated genetic variants are often located in noncoding or nongenic regions and are unlikely to be causal by themselves; rather, they are correlated with (ie, in close proximity to) unidentified causal variants. Studies in populations with different ancestries, and thus different genetic architectures, have revealed both shared and unique genetic susceptibility with varying effects; these studies may help to refine the location of causal genetic variants [19]. Analysis of the previously reported SNPs at FTO and MC4R has yielded consistent associations across East Asians, South Asians, Pima Indians, Hispanics, and African Americans. About half of the European-derived BMI variants are nominally significant (P<.01) in East Asians and African Americans, and additional variants have also demonstrated nominal significance in locus-wide analysis [14, 19]. Further bioinformatics analyses and functional annotation of coding variants [20] and noncoding variants may help to prioritize experimental validation of the putative functional variants.

### Clinical Applications

There is increasing interest in the question of whether genetic findings can be applied in the clinical setting to improve risk prediction and facilitate personalized therapy for obesity. Despite the discovery of a large number of genetic loci, the effect size of each variant is modest. The most strongly associated variant at FTO only explains 0.34% of the phenotypic variance for BMI in the general population; summing 32 GWAS variants increases the explained variance to 1.45%, with each additional risk allele increasing BMI by 0.17 kg/m² [11]. Individuals carrying the lowest number of risk alleles have a BMI that is 2.73 kg/m² lower, on average, than those carrying the highest number of risk alleles [11].

The current set of identified common variants has poor specificity and poor sensitivity for predicting obesity in both cross-sectional and longitudinal studies. In the Atherosclerosis Risk in Communities (ARIC) study, the area under the receiver operating characteristic curve (AUCROC) for predicting risk of obesity using the demographic variables age and sex was 0.515, compared with the null value of 0.5 [11]. Addition of a genetic risk score based on 32 genetic

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### TABLE 1.

**Genes Implicated in Monogenic Obesity and the Traits Found To Be Associated With Them in Genome-Wide Association Studies (GWAS)**

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Phenoype</th>
<th>Associated traits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BDNF</strong></td>
<td>Brain-derived neurotrophic factor</td>
<td>Wilms tumor, aniridia, genitourinary anomalies, mental retardation, and obesity (WAGRO syndrome)</td>
<td>Obesity, BMI, weight</td>
</tr>
<tr>
<td><strong>CART</strong></td>
<td>Cocaine- and amphetamine-regulated transcript</td>
<td>Severe obesity</td>
<td></td>
</tr>
<tr>
<td><strong>LEP</strong></td>
<td>Leptin</td>
<td>Morbid obesity due to leptin deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>LEPR</strong></td>
<td>Leptin receptor</td>
<td>Severe obesity due to leptin receptor deficiency</td>
<td>Serum level of C-reactive protein, serum level of leptin receptor</td>
</tr>
<tr>
<td><strong>MC4R</strong></td>
<td>Melanocortin-4 receptor</td>
<td>Early-onset severe obesity</td>
<td>Obesity, BMI, waist circumference, height, serum level of HDL cholesterol</td>
</tr>
<tr>
<td><strong>NTRK2</strong></td>
<td>Neurotrophic tyrosine kinase, receptor, type 2</td>
<td>Early-onset severe obesity, hyperphagia, developmental delay</td>
<td></td>
</tr>
<tr>
<td><strong>PCSK1</strong></td>
<td>Proprotein convertase subtilisin/kexin type 1 gene, or prohormone convertase 1</td>
<td>Early-onset severe obesity</td>
<td>BMI, serum proinsulin level, fasting serum glucose level (interaction with BMI)</td>
</tr>
<tr>
<td><strong>POMC</strong></td>
<td>Proopiomelanocortin</td>
<td>Early-onset severe obesity, adrenal insufficiency, red hair</td>
<td>Obesity, height</td>
</tr>
<tr>
<td><strong>PPARG</strong></td>
<td>Peroxisome proliferator-activated receptor gamma</td>
<td>Severe obesity, insulin resistance, lipodystrophy</td>
<td>Type 2 diabetes, fasting serum insulin level (interaction with BMI), plasma level of plasminogen activator inhibitor type 1</td>
</tr>
<tr>
<td><strong>SIM1</strong></td>
<td>Single-minded homolog 1 (Drosophila)</td>
<td>Early-onset severe obesity, Prader-Willi syndrome</td>
<td></td>
</tr>
</tbody>
</table>

Note. BMI, body mass index; HDL, high-density lipoprotein.
variants increased the AUCROC moderately in Europeans, to 0.575, but using the genetic risk score worked less well for African Americans, partly because of ethnic differences in effect size and allele frequencies of the tested variants [11, 21]. An analysis of the lifetime Northern Finland Birth Cohort 1986 showed that traditional risk factors—including parental BMI, birth weight, maternal gestational weight gain, and behavior and social indicators—had good predictive power for childhood obesity (AUCROC = 0.78); however, adding a genetic risk score based on 39 BMI-associated variants improved discrimination by 1% or less [22]. The lack of discrimination power for genetic variants is partly due to the small genetic effect, the use of surrogates rather than causal variants with larger effects, the presence of other unidentified common and rare genetic variants, and the lack of consideration of gene-gene and gene-environmental interactions. Clinical factors such as family history and birth weight are also influenced by genetic factors that contribute to the clinical prediction model.

Although the translation of genetic discovery into risk prediction is challenging at the population level, high penetrant variants associated with severe early-onset or syndromic forms of obesity may serve as a diagnostic tool and could assist in designing personalized therapy for individuals [23]. Mutations of the MC4R gene are most frequently found among children with nonsyndromic severe obesity, in whom the incidence ranges from less than 1% to 6% depending on nationality and variant [24]. These patients present with hyperphagia, severe hyperinsulinemia, tall stature, and high fat and lean mass. In patients with a syndromic form of obesity that is the result of single-variant mutations or large copy number variations—such as Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome, Albright hereditary osteodystrophy, or WAGRO (Wilms tumor, aniridia, genitourinary anomalies, mental retardation, obesity) syndrome—obesity often coexists with intellectual disabilities or developmental delays [23]. Powerful and cost-effective tools to identify the mutations and structural variants of chromosomes include sequencing of genes known to have medical implications, surveying of all coding sequences in an individual’s DNA using next-generation DNA sequencing, and using comparative genomic hybridization arrays. Screening of identified variants in family members also assists early diagnosis, which can allow clinicians to recommend preventive measures.

Only a few limited studies have examined the interaction between genetics and lifestyle and how this interaction affects risk prediction and therapeutic effects [25]. Nutrigenic studies have demonstrated that the Pro12Ala genetic variant in the PPARγ gene interacts with fat intake and obesity, with free fatty acids acting as natural agonists of this transcription factor. A Mediterranean diet has been reported to be associated with reversal of the effect of increased weight in 12Ala allele carriers; this reversal was not observed with a conventional low-fat diet [26]. Other studies have demonstrated that genetic risk has a lower impact in physically active individuals than in people with an unhealthy lifestyle [27-29]. Studies of the effect of genetic risk variants on weight reduction following bariatric surgery have had conflicting results; those who have higher-risk genetic variants may or may not have lower weight loss after surgery [30, 31]. Long-term follow-up studies will be necessary to evaluate the genetic interaction with therapeutic outcomes.

Taken together, advancements in genetic discovery and technologies have improved our understanding of the biological basis of obesity. Genetic testing of patients with early-onset or syndromic forms of obesity and their families is recommended to facilitate early diagnosis and personalized intervention. Clinical geneticists and physicians will need to work together to explain patients’ risk of obesity and to monitor their health. Cumulatively, the common genetic variants identified so far explain only a small proportion of the genetic contribution to obesity in the general population, and these variants exert differential effects in different populations. This limits their value in risk prediction compared with traditional clinical predictors, which can be measured easily and inexpensively. In the future, identifying additional genetic variants and understanding how they interact with lifestyle will improve the clinical applicability of these variants for risk prediction and personalized therapy. Overall, lifestyle modifications—including healthy diet and physical activity—remain the key to success in weight control, irrespective of an individual’s genetic profile.

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