Onset of obesity has been anticipated at earlier ages, and prevalence has dramatically increased worldwide over the past decades. Epidemic obesity is mainly attributable to modern lifestyle, but family studies prove the significant role of genes in the individual’s predisposition to obesity. Advances in genotyping technologies have raised great hope and expectations that genetic testing will pave the way to personalized medicine and that complex traits such as obesity will be prevented even before birth. In the presence of the pressing offer of direct-to-consumer genetic testing services from private companies to estimate the individual’s risk for complex phenotypes including obesity, the present review offers pediatricians an update of the state of the art on genomics obesity in childhood. Discrepancies with respect to genomics of adult obesity are discussed. After an appraisal of findings from genome-wide association studies in pediatric populations, the rare variant–common disease hypothesis, the theoretical soil for next-generation sequencing techniques, is discussed as opposite to the common disease–common variant hypothesis. Next-generation sequencing techniques are expected to fill the gap of “missing heritability” of obesity, identifying rare variants associated with the trait and clarifying the role of epigenetics in its heritability. Pediatric obesity emerges as a complex phenotype, modulated by unique gene–environment interactions that occur in periods of life and are “permissive” for the programming of adult obesity. With the advent of next-generation sequencing techniques and advances in the field of exposomics, sensitive and specific tools to predict the obesity risk as early as possible are the challenge for the next decade. Pediatrics 2012;130:123–133
Prevalence of overweight and obesity has dramatically increased worldwide in children and adolescents over the past 3 decades. Recent estimates suggest that 1 child in 2 in the United States and 1 in 3 in Europe is overweight. Therefore, childhood obesity has turned into a major health problem in Western countries, despite policies targeted at reducing its prevalence.

Obesity is a complex trait that stems from a complicated network of contributory components, encompassing genomic (see glossary in Table 1) and environmental factors, which in aggregate increase the probability of disease. Sedentary behaviors and high-calorie diets are major environmental factors driving epidemic obesity. Studies in twins, nontwin siblings, and adoptees have shown that genetic components contribute from 40% to 70% to the interindividual variation in common obesity. With no doubt, the obese phenotype runs prevalently in families, but most of the causative genes are still undiscovered. Findings from genome-wide association studies (GWAS) explain a very few of the obesity heritability. The most recent meta-analysis of GWAS data identified 18 new loci associated with BMI, thus setting the number of genes likely associated with obesity up to 42. It is disappointing that each of these alleles explained only a very small portion of the interindividual variability in BMI, contributing to an increase in BMI of \(-0.17 \text{ kg/m}^2\). Shortcomings of GWAS in explaining such heritability are often referred to as the “missing heritability.”

As estimated by GWAS, the genetic component of obesity encompasses the small contribution of many single-nucleotide polymorphisms (SNPs; Table 1). Apart from common variants, rare and private variants determine jointly the human genetic variation of BMI, but they cannot be identified by current GWAS. As far as the role of copy number variants is concerned, there is no evidence supporting their role in explaining some of the BMI variation. Evidence is also lacking on gene-by-gene or, more specifically, variant-by-variant interactions (a phenomenon also termed “epistasis”) that contribute to BMI variability. Indeed, analyses to detect epistatic interactions suffer from a substantially increased multiple testing burdens that hamper detection and interpretation. To date, these investigations have focused only on those SNPs with significant marginal effects, but future collaborative studies should provide evidence on gene-by-gene interactions.

The cumulative risk to develop the disease relies not only on the individual’s genotype, but also on nongenetic determinants, mainly epigenetic (Table 1) and environmental factors.

As to environmental factors, the notion of “environment” has been evolving beyond the classic idea of parental and nonparental influences on the child’s lifestyle, mood, and behavior. Maternal influences on the child’s phenotype originate before birth (in the intrauterine environment) and continue during the first 6 years of life, when BMI trajectories are programmed by the mother’s genetic, hormonal, and behavioral factors. Intraterine and early postnatal life are “permissive” windows when maternal and nonmaternal environmental factors will up or down modulate the phenotypic expression of the child’s genotype. Similarly, age of adiposity rebound and puberty are “permissive” periods.

Genetics of pediatric obesity is peculiar with respect to genetics of adult obesity. The joint effects of genes and environment change sizably from birth toward adulthood and are affected by sex-limited effects. Two phases of

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**TABLE 1** Glossary

<table>
<thead>
<tr>
<th>Copy number variants (CNVs)</th>
<th>They are variants that change the number of base pairs in the genome.</th>
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</thead>
<tbody>
<tr>
<td><strong>Less common variants</strong></td>
<td>Alleles with a minor allele frequency between 1% and 5%</td>
</tr>
<tr>
<td><strong>Effect size</strong></td>
<td>The increase in risk that is conferred by a given causal variants</td>
</tr>
<tr>
<td><strong>Epigenetics</strong></td>
<td>The study of heritable changes in gene expression that are not due to changes in DNA sequence. Epigenetic modifications include changes in the localized or global density of DNA methylation (also termed “methylome”), incorrect histone modifications, or altered distribution or function of chromatin-modifying proteins that, in turn, lead to aberrant gene expression. Three kinds of genomic targets are susceptible to gene-expression changes owing to environmental perturbations of epigenetic marks: the promoter region of certain housekeeping genes; genes with metastable epialleles, which are loci particularly sensible to environmental factors; and imprinted genes.</td>
</tr>
<tr>
<td><strong>Epistasis</strong></td>
<td>The phenomenon in which the effect of a gene or variant on a trait is not independent of the effect on the trait of another gene or variant.</td>
</tr>
<tr>
<td><strong>Exome</strong></td>
<td>The proportion of the genome that is translated into proteins (1% of the whole genome).</td>
</tr>
<tr>
<td><strong>Exosome</strong></td>
<td>It is the sum of all the individual’s exposures in his/her lifetime and estimates how those exposures relate to disease.</td>
</tr>
<tr>
<td><strong>Exposomics</strong></td>
<td>The science which aims at studying association among factors, the exposome, which can influence the individual’s health.</td>
</tr>
<tr>
<td><strong>Heritability</strong></td>
<td>It measures the fraction of the total phenotypic variance of a quantitative trait attributable to genes in a specified environment.</td>
</tr>
<tr>
<td><strong>Minor allele frequency</strong></td>
<td>The proportion of alleles at a locus, that consists of the less frequent alleles, and ranges from 0% to 50%.</td>
</tr>
<tr>
<td><strong>Private variants</strong></td>
<td>Alleles restricted to probands and immediate relatives.</td>
</tr>
<tr>
<td><strong>Rare variants</strong></td>
<td>Alleles with a minor allele frequency (&lt;1%)</td>
</tr>
<tr>
<td><strong>Single-nucleotide polymorphisms (SNPs)</strong></td>
<td>Single base changes in the DNA</td>
</tr>
<tr>
<td><strong>Very common variants</strong></td>
<td>Alleles with a minor allele frequency between 5% and 50%.</td>
</tr>
</tbody>
</table>
infancy, 0.5 to 1.5 years and 5 to 6 years, are considered as 2 particularly critical periods regarding BMI development, whose direction is crucially fixed during those time periods.\textsuperscript{3} Afterward, sex-limited genetic effects will add complexity to the dynamic picture of differential genetic expression of obesity as a function of age.\textsuperscript{8} The sets of genes contributing to BMI variation are not identical in men and women.\textsuperscript{9} Twin studies demonstrated that sex-specific effects modulate genetically driven growth patterns\textsuperscript{7} and influences of shared and nonshared environmental factors on BMI heritability.\textsuperscript{10} These effects become evident when fat mass distribution and hormonal milieu differentiate between the 2 genders.\textsuperscript{8}

Recognition of age- and gender-dependent gene effects is pivotal to explain some of the inconsistencies in GWAS findings between young and adult individuals.

The growing inventory of human genetic variation is facilitating an understanding of why susceptibility to common diseases varies among individuals and populations. It represents the rationale to the development of “personalized medicine.” Individuals, when presented with information about their personalized, gene-based "disease risk profile" seem to better adapt their lifestyles so as to reduce their chances of developing conditions for which they have an “increased” risk.\textsuperscript{11} In the presence of the pressing offer of direct-to-consumer genetic testing services from private companies to estimate the individual’s risk for complex phenotypes, ie, obesity, caution must be paid in interpreting results of such tests.

COMMON DISEASE–COMMON VARIANT HYPOTHESIS AND GWAS IN PEDIATRIC POPULATIONS

Based on the common disease–common variant hypothesis, which posits that multiple common alleles contribute to the disease risk, the approach to genetic studies of obesity has entailed prevalently GWAS. In GWAS, larger and larger samples of cases and controls have been genotyped for hundreds of thousands of common variants, typically 300 000 to 1 000 000 of SNPs with the aim of detecting the largest number of at risk variants.\textsuperscript{12} The allele or genotype frequencies have been evaluated for differences between groups or for correlations with continuous traits. Despite such apparent simplicity, results of GWAS may be subject to multiple-hypothesis testing because of typing a very large number of alleles. They need correction to exclude random association attributable to multiple testing, which can turn spurious associations out. Drawbacks to GWAS include also the need for replication of results in independent study populations and complementation with robust mechanistic studies to elucidate the biological mechanisms responsible for the genetic association.\textsuperscript{13} Despite shortcomings, GWAS have provided robust evidence for a role of some variants, particularly \textit{FTO}, \textit{MC4R}, and \textit{TMEM18} loci, in the development of obesity. Table 2 reports genes so far associated with pediatric obesity, their acronyms, and functions, whenever known.

In the study by Willer et al\textsuperscript{14} the first analysis was conducted in the Avon Longitudinal Study of Parents and Children (ALSPAC) study sample (\textit{N} = 4951 with BMI information at age 11) and confirmed significant associations of variants in/near \textit{FTO}, \textit{MC4R}, \textit{TMEM18}, \textit{KCTD15}, and \textit{GNPDA2} with BMI. Successively, data were replicated in the cohort of obese children (\textit{N} = 1038) from the Severe Childhood Onset Obesity Project United Kingdom cohort and an increased risk of extreme childhood obesity was revealed for the BMI-increasing alleles near \textit{TMEM18}, \textit{GNPDA2}, \textit{NEGR1}.\textsuperscript{14} In the European Youth Heart Study (1252 children and 790 adolescents), associations of 15 variants (\textit{NEGR1}, \textit{SEC16B}, \textit{LYPLAL1}, \textit{TMEM18}, \textit{ETV5}, \textit{GNPDA2}, \textit{TFAP2B}, \textit{MSRA}, \textit{BDNF}, \textit{MTCH2}, \textit{BCDIN3D}, \textit{NRXN3}, \textit{SH2B1}, \textit{FTO}, \textit{MC4R}, and \textit{KCTD15}) with BMI were similar to those observed in adults.\textsuperscript{15} In a meta-analysis of data from 13 071 children and adolescents significant associations with BMI were found for 9 of 13 variants and the near \textit{TMEM18} variant had the strongest effect. Effect sizes for BMI tended to be more pronounced for variants in/near \textit{SEC16}, \textit{TMEM18}, and \textit{KCTD15} in children and adolescents than in adults.\textsuperscript{16}

\textbf{FTO}

The association between \textit{FTO} polymorphisms and obesity-related traits (ie, BMI, adiposity, circulating leptin, energy intake, impaired control of energy balance, satiety sensitivity, and food responsiveness) is one of the most robust association reported for complex traits and has been firmly established in children.\textsuperscript{15–36} Nevertheless, functional relevance of \textit{FTO} for the pathogenesis of obesity remains elusive.\textsuperscript{17,18,21,25–31}

It is worth mentioning that this association shows clearly sex-limited effects\textsuperscript{19} and an age-dependent expression in that gene expression changes developmentally.\textsuperscript{15,19,24,29,34,36} At birth, no association exists between \textit{FTO} variants and birth weight,\textsuperscript{15,17,18,32,33} but it appears soon within the first weeks of life\textsuperscript{34} and persists through the passage from childhood into adolescence.\textsuperscript{17,19,29,35} In this regard, Hebebrand\textsuperscript{37} hypothesized that the intrauterine environment has a strong influence on anthropometric variables of newborns and infants, thus tempering the effect of \textit{FTO} variants on the infant's body weight, whereas, successively at 2 to 3 years, the effect of the genetic makeup becomes discernible. The association strengthens from 4 years of age onward over the lifespan.\textsuperscript{15,38} BMI development during infancy can influence later the adult BMI.\textsuperscript{29} In a Dutch cohort of children

\textit{STATE-OF-THE-ART REVIEW ARTICLE}

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<table>
<thead>
<tr>
<th>Nearest Genes (Acronym)</th>
<th>Locus</th>
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<th>Major Cohort Studies and Meta-analyses</th>
<th>Functions (Whenever It Is Known)/Sites of Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCY5</td>
<td>3q13.2-q21</td>
<td>BW</td>
<td>Meta-analysis85</td>
<td>Adenylate cyclase 5. The gene encodes a member of the membrane-bound adenylyl cyclase enzymes. Adenylyl cyclases mediate G protein-coupled receptor signaling through the synthesis of the second messenger cAMP. Activity of the encoded protein is stimulated by the Gs α subunit of G protein-coupled receptors and is inhibited by protein kinase A, calcium, and Gi α subunits. Single-nucleotide polymorphisms in this gene may be associated with low BW and type 2 diabetes. Alternatively, spliced transcript variants that encode different isoforms have been observed for this gene.</td>
</tr>
<tr>
<td>BDNF</td>
<td>11p4</td>
<td>BMI/BW</td>
<td>EYHS16 Obeldicks intervention10 Beijing Child and Adolescent Metabolic Syndrome Study46 ABC40</td>
<td>Brain-derived neurotrophic factor. The protein encoded by this gene is a member of the nerve growth factor family. It is induced by cortical neurons, and is necessary for survival of striatal neurons in the brain. Expression of this gene is reduced in patients with Alzheimer's and Huntington disease. This gene may play a role in the regulation of stress response and in the biology of mood disorders. The gene has a complex pattern of expression in the brain. Its high expression in the ventromedial hypothalamus is regulated by nutritional state and MC4R signaling.</td>
</tr>
<tr>
<td>CCNL1</td>
<td>3q25.31</td>
<td>BW</td>
<td>Meta-analysis85</td>
<td>Cyclin L1 protein kinase binding. Nothing is currently known about the mechanism behind the association with obesity.</td>
</tr>
<tr>
<td>ETV5</td>
<td>3q27</td>
<td>BMI</td>
<td>EYHS16</td>
<td>Ets variant gene 5. It is a transcription factor that plays a role in development and cancer; highly expressed in brain and pancreas. Its transcript levels are tightly regulated during fetal development.</td>
</tr>
<tr>
<td>FAIM2</td>
<td>12q13</td>
<td>BMI</td>
<td>Beijing Child and Adolescent Metabolic Syndrome Study46</td>
<td>Fas apoptotic inhibitory molecule 2. Nothing is currently known about the mechanism behind the association with obesity.</td>
</tr>
<tr>
<td>FTO</td>
<td>16q12</td>
<td>BMI/BW</td>
<td>ALSPAC and SCOOP-UK14 EYHS16 Northern Finland Birth Cohort 196629 GINI and LISA24 National Longitudinal Study on Adolescent Health8,9 Obeldicks intervention10 GENESIS and GENDAI63,64 Meta-analysis84</td>
<td>Fat mass- and obesity-associated gene. This gene is a nuclear protein of the AlkB related non-heme iron and 2-oxoglutarate-dependent oxygenase superfamily but the exact physiologic function of this gene is not known. Studies in mice and humans indicate a role in nervous and cardiovascular systems and a strong association with BMI, obesity risk, and type 2 diabetes. The gene is involved in processes such as fatty acids metabolism, and highly expressed in the hypothalamic nuclei.</td>
</tr>
<tr>
<td>GNPDA2</td>
<td>4p12</td>
<td>BMI</td>
<td>ALSPAC and SCOOP-UK14 EYHS16</td>
<td>Glucosamine-6-phosphate deaminase 2. It catalyzes the reversible conversion of D-glucosamine-6-phosphate into D-fructose-6-phosphate and ammonium.</td>
</tr>
<tr>
<td>KCNJ1</td>
<td>11p15.1</td>
<td>BW</td>
<td>ABC40</td>
<td>Potassium inwardly rectifying channel, subfamily J, member 11 Potassium channels are present in most mammalian cells, where they participate in a wide range of physiologic responses. The protein encoded by this gene is an integral membrane protein and inward-rectifier type potassium channel.</td>
</tr>
<tr>
<td>KCTD15</td>
<td>19q13</td>
<td>BMI</td>
<td>ALSPAC and SCOOP-UK14 EYHS16</td>
<td>Potassium channel tetramerization domain containing 15 gene. It is expressed in the pituitary and carries out sulfation of carbohydrates, which confers highly specific functions on glycoproteins, glycolipids, and proteoglycans, pivotal for signal transduction and embryonic development.</td>
</tr>
<tr>
<td>MCR4</td>
<td>18q21</td>
<td>BMI</td>
<td>ALSPAC and SCOOP-UK14 EYHS16 Meta-analysis studies48,50 Obeldicks intervention19 Beijing Child and Adolescent Metabolic Syndrome Study46</td>
<td>Melanocortin receptor 4. The prepromelanocortin-derived α-melanocyte-stimulating hormone from the arcuate nucleus binds to MCR4 in the paraventricular nucleus of the hypothalamus and is responsible for increase in energy intake and decrease in food intake.</td>
</tr>
<tr>
<td>MTCH2</td>
<td>11p11.2</td>
<td>BMI/BW</td>
<td>EYHS16 Meta-analysis44</td>
<td>Mitochondrial carrier homolog 2. Nothing is currently known about the mechanism behind the association with obesity. Neuronal growth regulator-1 gene. The encoded protein is a member of the immunoglobulin superfamily. Through its function as cell adhesion molecule, the protein participates in the regulation of neurite outgrowth in the developing brain.</td>
</tr>
<tr>
<td>NEGR1</td>
<td>1p31</td>
<td>BMI</td>
<td>ALSPAC and SCOOP-UK14</td>
<td>Null.</td>
</tr>
</tbody>
</table>
TABLE 2 Continued

<table>
<thead>
<tr>
<th>Nearest Genes (Acronym)</th>
<th>Locus</th>
<th>Association With BMI or BW</th>
<th>Major Cohort Studies and Meta-analyses</th>
<th>Functions (Whenever It Is Known)/Sites of Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFKP</td>
<td>10p15.3-p15.2</td>
<td>BW</td>
<td>ABC</td>
<td>The PFKP gene encodes the platelet isozyme of phosphofructokinase (PFK). PFK catalyzes the irreversible conversion of fructose-6-phosphate to fructose-1,6-bisphosphate and is a key regulatory enzyme in glycolysis. Phosphofructokinase. Nothing is currently known about the mechanism associated with obesity. Serologically defined colon cancer antigen 8. This gene encodes a centrosome-associated protein. This protein may be involved in organizing the centrosome during interphase and mitosis. Mutations in this gene are associated with retinal-renal ciliopathy. Located in intron 15 of the Mammalian Homolog of Saccharomyces cerevisiae.Sec1 gene. The protein encoded is required for organization of transitional endoplasmic reticulum sites and protein export. Scr-homology-2 (SH2) domain containing putative adapter protein 1. This gene encodes a member of the SH2 domain. The encoded protein mediates activation of various kinases and may function in cytokine (ie, leptin) and growth factor receptor signaling and cellular transformation.</td>
</tr>
<tr>
<td>SEC1B</td>
<td>1q25</td>
<td>BMI</td>
<td>EYHS</td>
<td>Transcription factor AP-2 (2 B) or activating enhancer-binding protein 2 B is a member of the AP-2 family of transcription factors. AP-2 proteins form homo- or heterodimers with other AP-2 family members and bind specific DNA sequences. They are thought to stimulate cell proliferation and suppress terminal differentiation of specific cell types during embryonic development. The encoded transcription factor is expressed in adipose tissue. Its overexpression leads to increased lipid accumulation and decreased expression of adiponectin. Thus, TFAP2B may have an effect on fat accumulation at multiple sites.</td>
</tr>
<tr>
<td>SH2B1</td>
<td>16p11.2</td>
<td>BMI</td>
<td>EYHS, ABC</td>
<td>Transmembrane protein 18. The gene is highly conserved among species and expressed in the brain, particularly at the nuclear site. This protein is ubiquitous and highly conserved. It carries out the enzymatic reduction of methionine sulfoxide to methionine. Human and animal studies have shown the highest levels of expression in kidney and nervous tissue. Its proposed function is the repair of oxidative damage to proteins to restore biological activity. Three transcript variants encoding different isoforms have been found for this gene.</td>
</tr>
<tr>
<td>TFAP2B</td>
<td>6p12</td>
<td>BMI</td>
<td>EYHS</td>
<td>Functions (Whenever It Is Known)/Sites of Expression</td>
</tr>
<tr>
<td>TMEM18</td>
<td>2p25</td>
<td>BMI</td>
<td>ALSPAC and SCOOP-UK</td>
<td></td>
</tr>
<tr>
<td>TNJK/MSRA1</td>
<td>8p23.1</td>
<td>BMI</td>
<td>EYHS</td>
<td></td>
</tr>
</tbody>
</table>

Functions and sites of expression are reported as in the Reference Sequence (RefSeq) collection. BW, body weight; ABC, Auckland Birth weight Collaborative study; EYHS, European Youth Heart Study; GINI, German Infant Nutritional Intervention; LISA, Lifestyle-related factors on the Immune System and the Development of Allergies in Childhood; SCOOP-UK, Severe Childhood Obesity Onset Project-United Kingdom; SGA, small-for-gestational birth weight.

followed with yearly collection of data on anthropometry from birth to age 7 and on anthropometry, body composition, leptin concentrations, physical activity (PA), hours watching television, and attitude toward eating from ages 12 to 17, researchers observed that at 17 years, 20% of the children were overweight/obese and 88% of the overweight/obese children had the A allele in contrast to 45% of the lean children. The A allele carriers had higher ratio of fat mass to height. The FTO allele was associated with higher BMI, fat ratio, and leptin concentrations from the age of 12 years, whereas the associations showed a dip at ages 13 to 14 years, probably because of the pubertal hormonal storm. The association became stronger at age 17 years. Such results were in keeping with reports from the German Infant Nutritional Intervention, the Lifestyle-related factors on the Immune System and the Development of Allergies in Childhood birth cohorts, and a twin study. In the German Infant Nutritional Intervention and Lifestyle-related factors on the Immune System and the Development of Allergies in Childhood birth cohorts, term newborns were genotyped (rs1558902 or rs9935401) and followed from birth up to age 6 years. BMI trajectories varied by genotype status and differences become recognizable again from the age of 3 years onward. In 3582 twin pairs, Haworth et al reported a progressively larger heritability estimate of BMI over time and, again, an age-dependent stronger association for the common variant rs9939609 of FTO with BMI, which became significant as of age 4. As to mechanisms of the association between FTO variants and fatness, in a sample of 2726 Scottish children (age 4–10 years), the variant rs9939609 was associated with both adiposity and food
intake, whereas no association was found with energy expenditure in a subgroup of 97 subjects. Scuteri et al suggested that the FTO variants might have a role in the control of food intake and food choice, because children carrying FTO variants are hyperphagic and prefer energy-dense foods. A more recent study in 655 European adolescents provided evidence for an association of the minor A allele of the FTO rs9939609 with increased levels of leptin, and this association was independent of adiposity. 

**MC4R in Common and Monogenic Obesity**

The melanocortin pathway plays a pivotal role in the central regulation of energy homeostasis. MC4R deficiency resulting from the disruption of one or both MC4R alleles represents the most common monogenic form of early-onset obesity, affecting 4% to ~6% of severely obese French and British populations, respectively. More than 90 different obesity-associated mutations of MC4R, most of which are missense mutations, have been reported so far. Phenotype of carriers varies considerably. Homozygous individuals typically exhibit a more severe phenotype than heterozygous do, but penetrance and expressivity may vary in affected families, with variable age of onset and severity of obesity.

Children carrying MC4R mutations present with early-onset severe obesity, persistent food-seeking behavior from 6 months of age, increased fat and lean masses, hyperinsulinemia and hyperphagia, which ameliorate with aging, higher stature, increased growth velocity, and older bone age (ie, exceeding the chronological age by 1–5 years) than matched obese controls. Findings from GWAS have proved that variants in/near MC4R contribute frequently to complex obesity, with a non-negligible size effect in the general population. The increasing BMI size effect ranged from 18% to 31% for carriers of rs2229616 variant, whereas carriers of rs52820871 had ~20% reduced risk of obesity. A recent meta-analysis of data from 13,004 young Europeans demonstrated that each additional risk allele of the near/in MC4R locus increases BMI by ~7% SD. No association was found between variants in near MC4R gene and birth weight and/or early weight gain.

On the contrary, the association with BMI becomes significant by age 6 to 7 years.

**TMEM18**

The TMEM18 gene might be powerfully involved in the modulation of energy homeostasis, because it is widely expressed and detected in the majority of neurons in all major brain regions. Interestingly, variants near TMEM18 were significantly associated with BMI in adults and pediatric populations. The most recent case-control study of 502 obese and 525 control Swedish children (age 6–20 years) found a significant association of rs6548238 and rs756131 variants with obesity. In this study, the odds ratio for the locus near TMEM18 was as high as that reported for the FTO locus. Interestingly, homozygous carriers of the major alleles showed a trend for lower birth weight and length. Variants near TMEM18 were also significantly associated with weight gain in infancy and early-onset obesity.

**GENE-BY-PA AND DIET INTERACTIONS**

The obesity-increasing effect of some polymorphisms may be attenuated in individuals who are physically active. Variants in FTO have been the most frequently analyzed with respect to gene-by-PA interactions, but results have been contradictory. In population-based cohorts of 4762 Finnish adolescents, low PA was found to accentuate the effect of FTO variant (rs1421085), whereas no clear interactions with PA were seen in 3187 French adults, in a population of Danish children (rs7566605) stratified for PA, in young European and African American patients (rs9839609) in 1979, and in 19,268 children from a meta-analysis of 9 studies. The latter meta-analysis demonstrated that PA attenuates the influence of FTO variants on obesity risk by 30% in adults.

No significant interaction was observed as well between MC4R variant (rs17782313) and PA in the aforementioned Finnish cohort. The interactions of 10 SNPs at 5 loci (in/near FTO, MC4R, TMEM18, SDCCAG8, and TNJK/MSRA) with 1-year lifestyle intervention was explored in 401 overweight children and adolescents (“Obeldicks” intervention). Homozygous carriers of obesity risk alleles of SDCCAG8 lost less weight than heterozygous or homozygous carriers of other alleles. Such findings were not confirmed in adults. In the Beijing Child and Adolescent Metabolic Syndrome Study, the associations between FAIM2, NPC1, FTO, MC4R, BDNF, and GNPD42 and obesity risk was modulated by PA. A higher risk of obesity was observed in children who carried the high-risk alleles of the 6 SNPs and engaged in sedentary behavior ≥2 hours per day outside of school or participated in low or moderate PA.

Heterogeneity between study in genetic architecture and environmental factors, differences in methods of measuring PA, and accuracy of the phenotype measurements make it difficult to study interactions between gene variants and PA. Differences with reports in adults may be due to more intensive PA in young and age-related effects.

In relation to nutritional effects, no interaction was found between FTO allele (rs9839609) and dietary energy density in the ALSPAC study. On the contrary, fat intake modified the age-
gender-specific association of the Pro12Ala polymorphism with adiposity in preschoolers and periadolescents (data from the growth, exercise, and Nutrition Epidemiologic Study, GENESIS, and the Gene diet Attica Investigation on childhood obesity, GENDAI, respectively). In children, an age-dependent and gender-limited gene-by-diet effect was found at the age of 48 months when the gene-by-diet effect differentiated in the 2 genders.64

Ideally, future GWA studies should be performed in large study samples with superior characterization of lifestyle factors to take into account gene-by-environment interactions and thus facilitate the detection of low-impact gene variants, of which there are expected to be numerous variants with important but modest effects on obesity.

RARE VARIANT–COMMON DISEASE HYPOTHESIS AND NEXT-GENERATION SEQUENCING

As opposite to the common variant–common disease hypothesis, the rare variant–common disease hypothesis suggests that rare variants contribute significantly to complex traits. Common and rare variants are expected to exert their effects on adiposity by following a gradient ranging from negligible to severe along a continuum. In all probability, the obese phenotype is the consequence of additive effects and interactions among multiple alleles with varying magnitude of effect, variants acting as modifier alleles, noncoding RNA, microRNA, splice variants, and regulatory elements in trans by which the genome governs various biological processes.

Indeed, based on today’s knowledge, only 1% of the human genome is transcribed into mRNA and translated into proteins. An additional 0.5% serves as template for noncoding RNA and the regulatory regions that control gene expression. Functions of the remaining 98.5% of the genome remain unknown.12

GWAS, as they have been designed to date, are unable to detect rare and private variants and to provide information on the other genomic elements that modulate the phenotypic expression.12 On the contrary, rare and private variants might be identified by massive genotyping or deep sequencing in large families. Novel techniques that sequence millions of DNA strands in parallel and at low cost have been developed. These new technologies are collectively referred to as the next-generation sequencing techniques. In the next few years, a rapid shift from whole exome (Table 1) to whole genome sequencing as the desirable approach to identify obesity-associated variants is expected.

EPIGENETICS AND DEVELOPMENTAL ORIGIN OF OBESITY

Understanding the functional content of the genome necessitates knowledge beyond the complete genome sequence, including also information on epigenome (Table 1). Strong evidence is accumulating that the environment can alter gene expression and influence the individual’s phenotype mostly by modifying the epigenome.6 Interest in epigenetics has been increasing in the past few years, because it may provide a molecular mechanism for metabolic programming that links genes, prenatal environment, intrauterine growth, and subsequent susceptibility to disease.

Epigenetic changes occur most commonly during gestation, neonatal development, and puberty. They seem to carry “memory” of early life experiences, triggering reversible, but also inheritable disease susceptibility in later life. Indeed, they can be heritable across cell divisions in somatic cells and potentially inherited across several generations (“epimutations”).66

Studies in animal models support strongly the concept that experiences during the intrauterine life can modulate the phenotypes of progeny independently of its genotype. In particular, maternal nutrition67–70 and hormonal cues71 can influence the fetuses’ gene expression by altering the extent of DNA methylation in gene promoters and histone acetylation in the chromatin structure. This phenomenon continues immediately after the birth. Early modulation of the child’s phenotype may occur mostly through 2 mechanisms that encompass the effects of both the maternal epigenome and the epigenetic programming of the placenta in response to nutrient availability and hormonal cues (recently revised in ref 6). Epigenetic programming of the placenta, in turn, will result in structural and functional changes,72 which can up- or downmodulate nutrient transport to the fetus and, hence, to fetal growth restriction or vice versa to overgrowth.

However, evidence in humans of mechanisms by which epigenetics affect development of complex traits such as obesity and how such changes pass across generations are limited to a few clinical observations.73–76 In particular, the Dutch famine birth cohort represents a unique “natural” experience of heritability of epigenetic changes across generations due to a condition of maternal undernutrition.76 Very recently, Godfrey et al75 reported the first evidence that methylation status of gene promoters in utero affects related phenotypes later in the child’s development. The authors first measured the methylation status of CpGs in the promoters of 78 candidate genes in DNA extracted from umbilical cord tissue obtained at birth in children who were later assessed for adiposity at age 9 years. Measurements of perinatal DNA methylation were related to adiposity in later childhood and to information on...
mother’s diet during pregnancy. Associations of genes (retinoid X receptor-α, RXRA; endothelial nitric oxide synthase, eNOS; superoxide dismutase-1, SOD1; interleukin-8, IL8, and phosphoinositide-3-kinase, catalytic, δ-polypeptide, PI3KCD) that had associations of comparable strength between childhood body composition and both methylation of overall gene promoters and of individual oligomers, were replicated in a second and independent group of children. Methylation status of the promoter region of RXRA correlated strongly in the 2 cohorts and was inversely associated with maternal carbohydrate intake in the first months of pregnancy.

LOW BIRTH WEIGHT AND INCREASED RISK FOR OBESITY

Advances in the field of epigenetics shed new light on old concepts and hypotheses. Conditions of metabolic disadvantage associated with intrauterine growth retardation and low birth weight, a surrogate marker of such metabolic disadvantage, are significantly associated with adult obesity, diabetes, and cardiovascular disease as demonstrated by a number of epidemiological and clinical studies (reviewed in ref 8). Barker first hypothesized and demonstrated the disadvantaged conditions of intrauterine growth that result in a small-for-gestational birth weight, as having significant effects on a person’s weight over a lifetime. Even so, birth weight can depend on the individual’s predisposing genotype, because small-for-gestational birth weight births tend to cluster in families and to recur in successive generations.

The Auckland Birth weight Collaborative and the ALSPAC studies identified common risk alleles associated with both low birth weight and obesity. The Auckland Birth weight Collaborative study explored the association of birth weight with 54 SNPs in candidate genes formerly associated with obesity. Genetic variation in KCNJ11, BDNF, PKP2, PTER, and SEC16B (Table 2) were associated with a small weight at birth. The ALSPAC investigated associations of 10 different risk alleles for obesity in n/near FTO; MC4R, TMEM18, GNPDA2, KCTD15, NEGR1, BDNF, and ETv5; Table 2) in 7146 children, whose anthropometrics were assessed from birth to age 11 years. An obesity–risk-allele score was derived for each child. The score was poorly associated with birth weight, but had an apparently much larger positive effect on early infancy weight gain, hence, suggesting that some variants, although they are effective against the newborn’s failure to thrive, conversely make the infant prone to develop obesity.

A meta-analysis of 6 GWAS, performed in 10 623 Europeans from pregnancy-birth cohorts, identified a significant association between 2 variants (ADcy5 and CCNL1) never implicated before with fetal growth and birth weight. The associations were independent of maternal intrauterine environment. A more recent meta-analysis of obesity susceptibility loci in 28 219 individuals confirmed an association only for MTCH2 and FTO with lower and higher birth weight, respectively. The associations, however, were no longer statistically significant after correction for multiple testing.

ENVIRONMENT AND EXPOSOMICS

Understanding heritability of obesity requires a deeper knowledge of the complex dynamic between gene-by-gene and gene-by-environment interactions. The extent of these associations varies significantly along the different periods of the human life. Studies on sibling and twin pairs have put attention on shared and nonshared environmental factors, mostly within the family, to try answering the question of how much genetics contributes to the complex trait. Environmental factors within the family have included parental eating and physical exercise behaviors, mental constructs, socioeconomical status, and other shared experiences of siblings and twins. In this light, twin studies allowed the estimate of the extent to which the family environment makes family members more similar than would be expected from their genetic relatedness (the shared-environment effect) and dissecting those nongenetic effects that come from environmental factors that are unique to each person (the nonshared-environment effects). However, because twins experience more commonality in indirect genetic effects than full siblings because they share both the stable and idiosyncratic parts of the home environment, but full siblings share only the common component, twin studies can have inflated heritability of obesity. The effect of the home environment clearly diminishes when children grow older and become more independent to make their own choices, which will reflect the effect of new specific environmental pressures. Perception of all these pressures may differ in each individual and in twins as well, hence, contributing significantly to the phenotype variance. Siblings generally attend the same school, but members of a sibling pair perceive their school and classroom experience differently, even identical twins in the same class room. Thus, the question becomes why siblings and twins are so different despite the common genetic background. Understanding how the individual’s exposures to the environmental factors (also termed as “exposome”) interact with its unique characteristics, such as its genetic makeup, resulting in the obese phenotype is pivotal to estimate heritability. “Omics” techniques and deep sequencing provide a huge amount of data, then, analyzed by data-mining techniques, with the aim of finding statistical associations between exposome, effects of exposures, and genetics.
CONCLUSIONS
Results from GWAS have strengthened the idea that the genetic heritage of obesity is strong, but still a wide gap exists between heritability, as demonstrated by family studies, and variance of body fatness, as estimated by numbers and odds ratios of identified risk alleles. Although some genes have been found for pediatric obesity, there is still a lot more to be learned, and the future involves looking at rare variants, gene-by-gene and gene-by-environment interactions, and epigenetic factors.

REFERENCES

Ruters F, Nieuwenhuizen AG, Bouwman F, Mariman E, Westerterp-Plantenga MS. Associations between a single nucleotide polymorphism of the FTO Gene (rs9939609) and obesity-related characteristics over time during puberty in a Dutch children cohort. *J Clin Endocrinol Metab*. 2011;96(6):E939–E942.


77. Barker DJ. The fetal and infant origins of adult disease. BMJ. 1990;301(6761):1111
81. Chung WK, Leibel RL. Considerations regarding the genetics of obesity. Obesity (Silver Spring). 2008;16(suppl 3):S33–S39
89. Exposome and exposomics. Atlanta, GA: Centers for Disease Control and Prevention. Available at: www.cdc.gov/niosh/topics/exposome/ Accessed September 6, 2011
# Genetics of Pediatric Obesity

Melania Manco and Bruno Dallapiccola

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