The Genetics of Pediatric Obesity
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Obesity among children and adults has notably escalated over recent decades and represents a global major health problem. We now know that both genetic and environmental factors contribute to its complex etiology. Genome-wide association studies (GWAS) have revealed compelling genetic signals influencing obesity risk in adults. Recent reports for childhood obesity revealed that many adult loci also play a role in the pediatric setting. Childhood GWAS have uncovered novel loci below the detection range in adult studies, suggesting that obesity genes may be more easily uncovered in the pediatric setting. Sheding light on the genetic architecture of childhood obesity will facilitate the prevention and treatment of pediatric cases, and will have fundamental implications for diseases that present later in life.

Childhood Obesity: Definition and Epidemiology
The World Health Organization (WHO) defines obesity as ‘abnormal or excessive fat accumulation that may impair health’ [1]. Indeed, it is a complex trait that originates from both environmental and genetic factors. An imbalance between calories ingested versus how much energy is expended results in excess adipose tissue, and sedentary behaviors combined with high-calorie diets characteristic of modern societies are considered the major environmental factors driving the pathogenesis of obesity. However, this trait – excess fuel storage in adipose tissue – could have originally represented a survival advantage in previous times when food was relatively scarce and physical activity was a natural component of everyday life [2].

Obesity has reached epidemic levels in modern societies, with more than 65% of adults in the USA and about 30% of youth being overweight or obese in 2011–2012 [3]. Obesity-related complications lead to huge medical costs for healthcare systems, a consequence of preventable common co-morbidities including type 2 diabetes (T2D), cardiovascular disease, and some forms of cancer [1]. Worldwide obesity rates have climbed steeply among children and adolescents in the past 40 years, and tripled in the USA where, despite a recent decline among preschool-aged children, rates are still high at about 17% [3]. This is particularly troubling given that being overweight in childhood not only causes direct adverse effects such as orthopedic complications, breathing problems, and psychosocial disorders [4], but is associated with obesity, cardiovascular and digestive problems, as well as increased overall mortality in adult life [5].

From an operative point of view, obesity is almost always defined using body mass index (BMI), the weight (in kg) divided by height squared (in m²). BMI is strongly correlated with fat content in adults (where BMI corresponding to 25–30 is defined as overweight and BMI >30 is considered obese). In children and adolescents this definition is less useful because of the large variations in BMI owing to pubertal status, age, and gender. BMI-for-age percentiles are instead used to ascertain pediatric adiposity in children aged 2 years and older. The Center for Disease Control and Prevention defines overweight as age-adjusted BMI in the bandwidth of the 85th to the 95th

Trends
More 65% of adults in the USA and about 30% of youth were overweight or obese in 2011–2012.

Before the GWAS era, family-based linkage scans, animal models, and candidate gene approaches – while successful in identifying loci operating in syndromic forms of extreme childhood obesity – had limited success in isolating genes contributing to the more common form of obesity.

In the past 7 years, GWAS has helped to identify nearly 100 loci implicated for BMI in adults.

Several of these adult BMI and/or obesity loci also play a role in childhood obesity.

Childhood GWAS have uncovered novel loci below the detection range in adult studies, demonstrating that the pediatric setting, owing to higher heritability estimates and less environmental exposure, is optimal for uncovering obesity genes. One should keep in mind, however, that some loci (FTO, MC4R) show an age-dependent effect and might operate differently in early childhood compared to adulthood.

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percentile, while a BMI equal or in excess of the 95th percentile is defined as obese [6]. Once a child reaches late adolescence, the percentiles start to correlate well with the adult definition, with the 95th BMI-for-age percentile equating approximately to a BMI of 30 kg/m² [4]. Another possible approach is the use of height-adjusted BMI, in other words BMI_adj = weight/height², with x being dependent on age. Suggested values for the least correlation of BMI_adj with height are x = 1.5 at 12 months and x = 3.1 between 8 and 12 years of age [7]. For infants less than 2 years of age there is a widely accepted definition to help to identify excess adiposity in the clinical setting; the weight-for-length percentile curves that are often used by practitioners [3] do not take into account age-based changes in weight and length, which is problematic considering the dynamic pattern of infant growth [8].

From birth, BMI increases and reaches a peak around 9 months of age (‘infancy peak BMI’ or ‘adiposity peak’), then gradually drops to a low point in the range of 4–6 years of age (‘adiposity rebound’) [9,10], and after that continues to rise up through adolescence until adulthood. An alternative promising approach is the use of infancy BMI trajectories (and associated characteristics such as the magnitude and timing of infancy BMI peak), which have been shown by several studies to be predictive of adiposity in children and in adulthood [9–13].

**Childhood Obesity – The Genetic Component**

Environmental and societal changes over the past three decades, in particular with the availability of convenient, high-calorie foods together with the advent of a sedentary lifestyle, can partly explain the rising rates of obesity in Western societies. Nonetheless, it is abundantly clear that there is also a pronounced genetic component to this disease: studies of twins reared either together or apart have revealed that genetic factors account for between 32 and 70% of variation in BMI between individuals; concordance rates among monozygotic twins for fat mass are ~ 80% but only ~ 40% in dizygotic twins [14]. Adoption and family studies have provided further complementary evidence showing that the BMI of adopted children correlates strongly with biological parent and/or sibling BMI, but not with adoptive parent BMI [15,16]. Further indication of the role of genetics in obesity is from observations of obesity prevalence differences between ethnic groups; for instance, the obesity rate in European and Asian populations is less than 35% while it is as high as 50% in Pima Indian and Pacific Island populations [17].

**Before the Dawn of GWAS: Family Studies and Animal Models**

Familial studies of common forms of childhood obesity have reported several loci detected by linkage, but the underlying corresponding causative genetic lesion has yet to be elucidated. Instead, this approach has proven particularly useful to identify chromosomal loci causing rare familial syndromes of childhood obesity, such as Prader–Willi syndrome [18], Alstrom’s syndrome [19], and Bardet–Biedl syndrome [20].

Animal models, in particular severely obese mouse strains, have provided the earliest insight into the genetics of obesity in humans: the two obese mouse strains ob/ob and db/db were shown to contain mutational events within the leptin gene [21] and in its receptor [22], respectively. These observations point to a fundamental role of networks related to hormonal and neural mechanisms in modulating excess adiposity, especially pertaining to appetite control, via the hypothalamus. Variants within these two genes (LEP and LEPR) and other genes in the hypothalamic leptin–melanocortin pathway (POMC–AGY3, PCSK1, MC4R, BDNF) have subsequently been reported in humans with obesity-related traits and in children specifically (Tables 1 and 2; full gene names are given in Table 2) [23,24]. Other loci implicated in severe childhood obesity are NTRK2B and SIM1 [25,26]. MC4R in particular is the first established gene that confers dominantly inherited obesity when mutated, and was the most frequently observed genetic factor for obesity in humans characterized before the advent of **genome-wide association studies** (GWAS; see **Glossary**) [27,28].
GWAS in Adults

Although very fruitful for the discovery of the genetic causes of rare familial syndromic forms of obesity, linkage studies are not well suited to identify the numerous genetic variants of small effect that underlie the more common form of obesity. Candidate gene approaches, by contrast, have the drawback of relying on previous knowledge of the pathways relevant for disease, and are unlikely to discover new biology.

The GWAS approach has allowed investigators to search for causal genetic variants in a comprehensive and unbiased manner, and has proven very successful in yielding robust and replicable associations [29].

In the past 9 years, nearly 100 BMI loci have been discovered by GWAS, the majority of which were found in adults. INSIQ2 (insulin-induced gene 2) was the first such locus to be described [30]. This locus was implicated in obesity risk for both children and adults of European and African American ancestry, but largely failed to replicate in subsequent studies [31–35]. The second obesity locus to be reported, FTO (fat mass- and obesity-associated gene) [36], has instead been extensively replicated [37], including in children [38], and is now widely viewed as being the most strongly associated obesity locus reported to date. Interestingly, this locus was initially implicated in type 2 diabetes by GWAS [39,40], but subsequently it became evident that its primary role involves governing BMI, and thus in turn only secondarily influences glucose levels [36].

Subsequent larger meta-analyses combining datasets from different groups to increase statistical power, again primarily in adults, uncovered many additional signals, first of which was the well-known MC4R gene [41]. Of note, the additional loci uncovered by meta-analyses have considerably smaller effects than FTO, but do provide additional crucial insights into the biology of the obesity.

Following larger and larger GWAS and meta-analyses [42–44], including other ethnicities [45–47], the largest meta-analysis reported to date, by the GIANT consortium, reported a total of 97 BMI loci (56 of which were novel) in a study involving 339,224 adult individuals, accounting for less than 3% of BMI variation, and suggesting that up to 21% of adult BMI variation is due to common genetic variation [48]. This latest study also was able to come closer to the causal variant at some of these loci by defining “credible sets” of SNPs that represent a reduced shortlist of which one must be the functional lesion.
<table>
<thead>
<tr>
<th>Gene name</th>
<th>Locus</th>
<th>Full Name</th>
<th>Pattern of Expression</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB5</td>
<td>7p21.1</td>
<td>ATP-binding cassette, subfamily B (MDR/TAP), member 5</td>
<td>Ubiquitous</td>
<td>Participates in ATP-dependent transmembrane transport of structurally diverse molecules</td>
</tr>
<tr>
<td>ARL15</td>
<td>5p15.2</td>
<td>ADP-ribosylation factor-like 15</td>
<td>Ubiquitous</td>
<td>GTP binding (predicted)</td>
</tr>
<tr>
<td>BDNF</td>
<td>11p4</td>
<td>Brain-derived neurotrophic factor</td>
<td>Brain</td>
<td>Nerve growth factor</td>
</tr>
<tr>
<td>EDIL3</td>
<td>5q14</td>
<td>EGF-like repeats and discodin I-like domains 3, DEL1</td>
<td>Ubiquitous</td>
<td>Integrin ligand, plays an important role in angiogenesis and may be important in vessel wall remodeling and development and endothelial cell behavior</td>
</tr>
<tr>
<td>EPHA6</td>
<td>3q11.2</td>
<td>EPH receptor A6</td>
<td>Brain, testis</td>
<td>Receptor tyrosine kinase</td>
</tr>
<tr>
<td>FAIM2</td>
<td>12q13</td>
<td>Fas apoptotic inhibitory molecule 2</td>
<td>Ubiquitous</td>
<td>Not known</td>
</tr>
<tr>
<td>FOXP2</td>
<td>7q31</td>
<td>Forkhead box P2</td>
<td>Ubiquitous</td>
<td>Transcription factor, required for proper development of speech and language</td>
</tr>
<tr>
<td>FTO</td>
<td>16q12</td>
<td>Fat mass- and obesity-associated gene</td>
<td>Brain</td>
<td>Nuclear protein of the AlkB-related non-heme iron and 2-oxoglutarate-dependent oxygenase superfamily</td>
</tr>
<tr>
<td>GNPDA2</td>
<td>4p12</td>
<td>Glucosamine-6-phosphate deaminase 2</td>
<td>Ubiquitous</td>
<td>Catalyzes the reversible conversion of D-glucosamine-6-phosphate into D-fructose-6-phosphate and ammonium</td>
</tr>
<tr>
<td>HHEX-IDE</td>
<td>10q23.33</td>
<td>Hematopoietically expressed homeobox/insulin-degrading enzyme</td>
<td>Ubiquitous</td>
<td>Zinc metalloendopeptidase that degrades intracellular insulin, glucagon, amylin, bradykinin, and kallidin. Deficiencies in the function of this protein are associated with Alzheimer’s disease and T2D</td>
</tr>
<tr>
<td>HOX8B5</td>
<td>17q21.3</td>
<td>Homeobox B5</td>
<td>Ubiquitous</td>
<td>Sequence-specific transcription factor, part of a developmental regulatory system that provides cells with specific positional identities on the anterior–posterior axis</td>
</tr>
<tr>
<td>INSIG2</td>
<td>2q14.2</td>
<td>Insulin induced gene 2</td>
<td>Ubiquitous</td>
<td>Regulation of cholesterol biosynthesis by SREBP (SREBF)</td>
</tr>
<tr>
<td>KC7D15</td>
<td>19q13</td>
<td>Potassium channel tetramerization domain containing 15</td>
<td>Pituitary</td>
<td>During embryonic development, interferes with neural crest formation (by similarity). Inhibits AP2 transcriptional activity by interaction with its activation domain</td>
</tr>
<tr>
<td>KIF2B</td>
<td>17q22</td>
<td>Kinesin family member 2B</td>
<td>Ubiquitous</td>
<td>Plus end-directed microtubule-dependent motor required for spindle assembly and chromosome movement. Has microtubule depolymerization activity</td>
</tr>
<tr>
<td>LEPR</td>
<td>1p31</td>
<td>Leptin receptor</td>
<td>Isoform A: ubiquitous. Isoform B: hypothalamus</td>
<td>Receptor for obesity factor (leptin). On ligand binding, mediates signaling through JAK2/STAT3. Involved in the regulation of fat metabolism</td>
</tr>
<tr>
<td>MC4R</td>
<td>18q21</td>
<td>Melanocortin receptor 4</td>
<td>Brain, placenta and intestinal tissue</td>
<td>Receptor specific to the heptapeptide core common to adrenocorticotropic hormone and α-, β-, and γ-MSH. Plays a central role in energy homeostasis and somatic growth</td>
</tr>
<tr>
<td>NEGR1</td>
<td>1p31</td>
<td>Neuronal growth regulator-1</td>
<td>Brain</td>
<td>Member of the immunoglobulin superfamily, with a role in cell adhesion and neurite outgrowth in the developing brain</td>
</tr>
<tr>
<td>NR0N3</td>
<td>14q31</td>
<td>Neurexin 3, C14orf60</td>
<td>Brain</td>
<td>Member of a family of proteins that function in the nervous system as receptors and cell adhesion molecules. Genetic variation at this locus has been associated with behavioral phenotypes</td>
</tr>
<tr>
<td>OLFM4</td>
<td>13q14.3</td>
<td>Olfactomedin 4</td>
<td>Prostate, small intestine and colon</td>
<td>Anti-apoptotic factor that promotes tumor growth and is an extracellular matrix glycoprotein that facilitates cell adhesion</td>
</tr>
<tr>
<td>OR4P4–OR4S2–OR4C6</td>
<td>11q12.1</td>
<td>Olfactory receptor, family 4, subfamily P, member 4/2/6</td>
<td>Ubiquitous/not known</td>
<td>Olfactory receptors</td>
</tr>
</tbody>
</table>
### Table 2. (continued)

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Locus</th>
<th>Full Name</th>
<th>Pattern of Expression</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACS1</td>
<td>11q13.1</td>
<td>Phospholipid acid cluster sorting protein 1</td>
<td>Ubiquitous</td>
<td>Putative role in the localization of trans-Golgi network (TGN) membrane proteins</td>
</tr>
<tr>
<td>POMC-ADCY3</td>
<td>2p23.3</td>
<td>Proopiomelanocortin/adenylate cyclase 3</td>
<td>Pituitary, hypothalamus, placenta, and epithelium</td>
<td>Polypeptide hormone precursor that undergoes extensive, tissue-specific, post-translational processing via cleavage by subtilisin-like enzymes known as prohormone convertases</td>
</tr>
<tr>
<td>PRKCH</td>
<td>14q23.1</td>
<td>Protein kinase Cα</td>
<td>Epithelial tissues</td>
<td>Calcium-independent and phospholipid-dependent protein kinase, can regulate keratinocyte differentiation, mediates the transcription activation of the transglutaminase 1 (TGM1) gene</td>
</tr>
<tr>
<td>QPCTL</td>
<td>19q13.32</td>
<td>Glutamyl-peptide cyclotransferase-like</td>
<td>Ubiquitous</td>
<td>Responsible for the biosynthesis of pyroglutamyl peptides</td>
</tr>
<tr>
<td>RMST</td>
<td>12q23.1</td>
<td>Rhabdomyosarcoma 2 associated transcript (non-protein coding)</td>
<td>Ubiquitous</td>
<td>Long non-coding RNA (lncRNA), function not known</td>
</tr>
<tr>
<td>S1PR5</td>
<td>19p13.2</td>
<td>Sphingosine-1-phosphate receptor 5</td>
<td>Ubiquitous</td>
<td>Receptor for the lysosphingolipid sphingosine 1-phosphate (S1P)</td>
</tr>
<tr>
<td>SDCCAG8</td>
<td>1q43</td>
<td>Serologically defined colon cancer antigen 8</td>
<td>Thymus, prostate, testis, ovary, small intestine, colon, mucosa, colon and renal cancer tumors</td>
<td>Centrosome-associated protein that may be involved in organizing the centrosome during interphase and mitosis. Mutations in this gene are associated with retinal-renal ciliopathy</td>
</tr>
<tr>
<td>SEC16B</td>
<td>1q25</td>
<td>SEC16 homolog B, endoplasmic reticulum export factor</td>
<td>Ubiquitous</td>
<td>Organization of transitional endoplasmic reticulum sites and protein export</td>
</tr>
<tr>
<td>SH2B1</td>
<td>16p11.2</td>
<td>Src-homology-2 (SH2) domain containing putative adapter protein 1</td>
<td>Ubiquitous</td>
<td>Member of the SH2 domain, mediates activation of various kinases and may function in cytokine (i.e., leptin) and growth factor receptor signaling and cellular transformation</td>
</tr>
<tr>
<td>TBCA</td>
<td>5q14.1</td>
<td>Tubulin folding cofactor A</td>
<td>Ubiquitous</td>
<td>Tubulin-folding protein; involved in the early step of the tubulin folding pathway</td>
</tr>
<tr>
<td>TMEM18</td>
<td>2p25</td>
<td>Transmembrane protein 18</td>
<td>Brain, nucleus</td>
<td>Not known</td>
</tr>
<tr>
<td>TNKS-MSRA</td>
<td>8p23.1</td>
<td>Tankyrase 1 (TRF1-interacting ankyrin-related ADP-ribose polymerase/methionine sulfoxide reductase A</td>
<td>Ubiquitously expressed, abundant in kidney and nervous tissue</td>
<td>Enzymatic reduction of methionine sulfoxide to methionine; repair of oxidative damage to proteins to restore biological activity</td>
</tr>
<tr>
<td>TNNK3</td>
<td>1p31.1</td>
<td>TNNK3 interacting kinase</td>
<td>Heart</td>
<td>Belongs to the MAP kinase kinase kinase (MAPKKK) family of protein kinases and it is thought to play a role in cardiac physiology</td>
</tr>
<tr>
<td>ZPLD1</td>
<td>3q12.3</td>
<td>Zona pellucida-like domain containing 1</td>
<td>Placenta, kidney, lung, pancreas, and at very low level in other tissues</td>
<td>Not known</td>
</tr>
</tbody>
</table>

In addition to BMI, other phenotypes related to body fat distribution such as waist-to-hip ratio have been investigated by large GWAS in different ethnicities [49–52]. Although not focused on obesity per se, these studies may give important insights into body fat distribution, which in itself is associated with adverse outcomes.

**Testing Adult-Discovered Loci in Children**

Many common complex diseases observed in adults, in particular obesity, have their origin during development, in childhood, or even in utero [53,54]. As such, it is vital to understand how the BMI loci discovered in adults operate in childhood and if they confer risk for pediatric obesity.

A query of 32 loci reported by an earlier GIANT consortium meta-analysis of BMI in adults [43] in a pediatric Caucasian cohort of in excess of 1000 obesity cases (BMI ≥ 95th percentile) and
over 2500 lean controls (BMI ≤ 50th percentile) revealed evidence of association for nine of the loci, BDNF, FTO, GNPDA2, MC4R, NRXN3, OPCTL, SEC16B, TMEM18, and TNNI3K [55] (Tables 1 and 2). As a consequence, it became clear that all but four of the loci showed concordance in the direction of effects with the original adult BMI study. Several other studies have looked at the adult BMI loci (individually or combined in a genetic risk score) against BMI in childhood [56–62]. As such, it has become apparent that most of the loci related to obesity and/or BMI initially discovered in the adult setting also operate in childhood; however, because these loci collectively account for only a very small proportion of BMI variation in children (~1–2% [61,62]), many more pediatric loci remain to be discovered.

Following a similar approach, loci implicated by GWAS for T2D and adult bone mineral density (BMD) and/or osteoporosis risk were investigated in the context of childhood obesity. Interestingly, a single T2D locus (IDE–HHEX) (Tables 1 and 2) showed association, with the same variant that increases T2D risk also increasing pediatric BMI [63]. This finding suggests that this locus is more likely to operate in T2D via insulin resistance processes. Further, the same variant near the osterix gene that increases BMD also showed a gender-specific, positive association with pediatric BMI in girls [64], suggesting that body proportions and loading on the skeleton govern the ultimate BMD phenotype.

**FTO in the Pediatric Setting**

Being the first and most robust locus associated with obesity, FTO has received more attention than other reported loci and is the most studied in the pediatric setting.

Various study designs have clearly shown that the effect of genetic variation in FTO on pediatric BMI is age-dependent, strengthening initially in the age range of 3–7 years old and then rising to a peak at approximately 29 years of age, then weakening during adulthood [36,58]. A relatively small study of newborn infants (n = 234) showed that the adult obesity-associated risk genotype at rs9939609 in FTO had no impact on fetal growth or birth weight [65], while a larger study of over 4500 individuals showed an association with intrauterine growth restriction that was reversed in infants from smoking mothers [66]. In a meta-analysis of eight Caucasian pediatric cohorts (from very early in life to 13 years of age), the same adult obesity-associated FTO variant was associated with lower BMI in infancy (<2 years), earlier age of adiposity rebound, and higher BMI in childhood (>5 years), suggesting that variation at FTO influences adiposity through a developmental change in adiposity rebound timing, rather than though a sustained increased BMI throughout lifetime [67]. Specific developmental BMI trajectories are in turn known to lead to higher incidences of future obesity [68] and coronary heart disease [69].

The process by which FTO impacts on obesity pathogenesis has remained elusive. The gene encodes the enzyme 2-oxoglutarate-dependent nucleic acid demethylase [70], which is most highly expressed in the hypothalamus and other areas of the brain governing appetite and feeding behavior [71,72]. A role in metabolism and energy balance is supported by studies in mice, where knockout of Fto produces an animal that is relatively lean, while Fto overexpression leads to obesity [73,74].

However, recent studies have suggested that the key genetic signal does not influence FTO expression but rather the function of two genes flanking FTO, namely IRX3 and RPGRIP1L [75–77]. Indeed, exonic mutations in FTO were reported in Caucasian adults and African American children; however, these variants generally were not associated with obesity [78]. These data show that the exonic variants in FTO are unlikely to be causative, while the culprit variant(s) is more likely to be non-coding and affects the regulatory machinery of FTO or, as more and more data suggest, of a nearby gene(s). This is an important point to keep in mind when looking at Table 2, where the nearest gene corresponding to a GWAS signal is reported;
although many of the genes described make sense as obesity related genes, some do not – it is very possible that the causative variants regulate another nearby gene.

**GWAS Loci Uncovered in Children Specifically**

Despite the fact that mapping genes for early-onset monogenic obesity has proven relatively successful, much less effort has been placed on the less-severe common forms of obesity that have been on the rise in recent years. Unraveling the genetic component of common obesity should be easier in children than in adults, who are subject to a longer period of environment exposure.

The first GWAS of pediatric obesity involved the analysis of genotype data derived from France and Germany for early-onset extreme obesity (BMI ≥ 97th percentile, with most cases having BMI ≥ 99th percentile) [79]. The study reported two loci, namely SDCCAG8 and TNKS/MSRA (Tables 1 and 2). These loci were specifically associated with extreme obesity in children, while were only very mildly associated with BMI in adults in the most recent GIANT meta-analyses [43,48].

A subsequent large study addressed the more common form of pediatric obesity using a less extreme BMI cutoff (BMI ≥ 95th percentile) [80]. The study consisted of a meta-analysis of 14 existing GWAS datasets, consisting of ~5500 cases and ~8300 controls (BMI ≥ 50th percentile). Seven of the known adult loci (FTO, TMEM18, POMC-ADCY3, MC4R, FAIM2, TNNS3K, and SEC16B) were detected, together with two novel loci, OLFM4 and HOXB5 (Tables 1 and 2). These loci were both nominally significantly associated with BMI in the 2010 GIANT adult meta-analysis [43], with effects in the same direction, albeit that genome-wide significance was not formally achieved. As such, the pediatric approach was able to detect additional loci that were below the detection bandwidth within adult studies, and also ‘rediscovered’ loci such as TNNS3K using a much smaller cohort size than the one required in the adult setting. The increased power of the childhood studies is likely due to less environmental clouding. A comparison of the effect sizes of the BMI loci in adults versus children is not straightforward and requires more investigation because they often show a strong dependence on age (e.g., FTO) [56].

More recently, a GWAS of extreme obesity (BMI >3 standard deviations from the mean of the distribution) was performed in a cohort of ~1500 children plus ~5400 controls, and was followed-up for replication in an additional cohort of ~970 severely obese children and ~2000 controls [81]. The study identified four new loci, namely LEPR, PRKCH, PACS1, and RMST (Tables 1 and 2). These results are very different from what has been observed in studies of less severe forms of obesity, but nevertheless could be helpful in the future for sub-categorization of different forms of childhood obesity.

A recent GWAS study performed on a pediatric cohort of ~5800 children (mean age 10 years, from the ALSPAC study) looked at a different trait, in other words height-adjusted BMI, to account for height [7]. SNPs in the known adult locus POMC-ADCY3 achieved genome-wide significance levels in the association analyses with height-adjusted BMI, but not with conventional BMI. The findings were subsequently replicated in an independent cohort derived from the Dutch Generation R study. The data suggested that a missense variant in ADCY3 was driving the association signal and also correlated strongly with the expression of the gene.

Another recent study on the same cohort (ALSPAC) plus the Raine Study investigated BMI trajectories over childhood [82]. An association signal within the neighborhood of FAM120AOS was detected when these two cohorts were meta-analyzed, but was not replicated in an additional cohort, and further studies will therefore be necessary to establish FAM120AOS
as a true BMI locus. Indeed, this variant was not detected in the most recent GIANT meta-analysis of adult BMI [48]. Furthermore, three established adult BMI loci (FTO, MC4R, and POMC–ADcy3) and one locus detected in childhood obesity (OLFM4) also attained association at the genome-wide significance level.

GWAS in Other Populations

To date, most GWAS analyses of obesity and BMI have been carried out in Caucasians, the main reason being the relatively low genetic variation of Caucasian genomes, but also to avoid issues related to population admixture.

Studying population of different ancestry has proven very useful in identifying genes and pathways of global relevance that may represent more attractive targets for prevention, diagnosis, and therapeutic intervention in obesity. Furthermore, cohorts derived from African ancestral groups have been successfully leveraged to fine map loci down to the closest point to the underlying causal variant. This is possible because these populations are more ancient and thus have, on average, shorter stretches of linkage disequilibrium. For instance, the 2q37 locus TCF7L2 [83] has been refined utilizing a West African cohort [84]. In the case of FTO, the association with BMI is strongest in children of European ancestry [56], while the picture in cohorts of African ancestry has been less clear [85,86]; however, from recent large-cohort studies in both adults [87] and children [38] it is becoming increasingly clear that SNP rs3751812 in the FTO locus is associated with the trait in both ethnicities.

GWAS meta-analyses for BMI and obesity are now starting to appear for other ethnicities [46,47], and the first African American study [45] also included a pediatric cohort of the same ethnicity to support the findings. This study, in addition to detecting 32 of 36 loci discovered in Europeans, also reported two novel signals at GALNT10 and MIR148A–NFE2L3, plus suggestive support for association at KLHL32. GALNT10 and MIR148A–NFE2L3 were nominally significantly associated with BMI in European-ancestry populations from the 2010 GIANT meta-analysis [43], while KLHL32 was not, although directionally consistent. A comparison of the effect sizes of these loci among different ethnicities cannot be done in a systematic way until the causal variants or proper trans-ethnic tags have been identified.

Concluding Remarks and Future Perspectives

Despite great advances in the past decade, with the uncovering of well-established genetic signals affecting BMI, the combined results of the various approaches described above have only explained the tip of the iceberg regarding variation in childhood obesity, suggesting that there is still much of the genetic component to find (missing heritability; see Outstanding Questions). Recent estimates suggest that common variation accounts for ~20% of BMI variation, and new approaches such as larger and larger meta-analyses and the use of whole-genome sequencing technologies will be needed to discover rare variants conferring small effects. For instance, following a candidate gene approach, a rare SNP within intron 4 of NAMPT (which would not be detected with standard high-throughput genotyping methods) was uncovered for severe obesity [88]. Another area of investigation that is the focus of active research is that of copy-number variations (CNVs). To date, rare CNVs have been identified mostly in patients with syndromic obesity in early life plus developmental delay [89–91], but studies of rare and common CNVs in childhood obesity are starting to emerge [81,92,93].

On the quest for the missing heritability, it is important to look beyond the DNA sequence and also consider epigenetic changes due to DNA methylation and histone modification. Although the contribution of epigenetics to heritability is still subject to some debate [94], a recent study in Arabidopsis thaliana convincingly showed that, at least in plants, epigenetic changes are stable over several generations and contribute strongly to the heritability of complex traits [95]. In
relation to obesity, there are several indications that epigenetic mechanisms might be important. For instance, Prader–Willi syndrome, characterized by extreme life-threatening obesity, occurs through the deletion of a paternal copy of a region at 15q11–q13, while methylation can inactivate the maternal copy [96,97], and several other obesity-related genetic loci also have different parent-of-origin effects [98]. Progress in this area is rapid, thanks to recent technological advances, including leveraging whole-genome sequencing and ChiP-Seq (chromatin immunoprecipitation combined with high-throughput sequencing), which will help us to shed light into global methylation patterns and histone modifications in the context of childhood obesity.

It is also possible that current missing heritability estimates have been inaccurately quantified, where the estimated portion not detected by GWAS may in fact be hugely overinflated owing to the fact that SNP-by-SNP (epistatic) interactions have not been considered until now in GWAS studies because of the inherent increased multiple-testing burden that these analyses require [99]. Future large collaborative studies and new statistical methods will hopefully help to address this issue. Another important point to keep in mind is that genetic factors influencing childhood obesity deviate from what is seen in adults owing to the fact that the influences of genes and environment change greatly during childhood and are also heavily sex-specific [100]. For this reason, gene-by-age and gene-by-sex, and, in general, gene-by-environment interactions need to be considered.

Finally, it is well established that the reported variants to date from current GWAS (which are designed with representative tag-SNPs on the array) cannot be concluded to be causal, and to elucidate the culprit events (both at the variant and at the gene level) continues to be challenging for the complex-trait research community, especially when one does not know the culprit tissue where these loci primarily act. New approaches and functional studies will be required to address this problem and produce better treatments, guiding us to the ultimate goal of precision medicine.

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**Resources**

1  Genetic Investigation of Anthropometric Traits (GIANT);  [www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium](www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium)
2  Avon Longitudinal Study of Parents and Children (ALSPAC);  [www.bristol.ac.uk/alspac](www.bristol.ac.uk/alspac)
3  Generation R study;  [www.generationr.nl](www.generationr.nl)
4  Raine study; [www.rainestudy.org.au](www.rainestudy.org.au)

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