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The Genetics of Pediatric Obesity

Alessandra Chesi¹ and Struan F. A. Grant^{1,2}

¹Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

²Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA19104, USA

Abstract

Obesity among children and adults has notably escalated over recent decades and represents a global major health problem. We now know that both genetics 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. Shedding light on the genetic architecture of childhood obesity will facilitate 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 United States and about 30% of youth being overweight or obese in 2011–2012 [3]. Obesity-related complications lead to huge medical costs for health care 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 last 40 years, and tripled in the U.S. where despite a recent decline among preschool-aged children is still high at about 17% [3]. This is

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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 and 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 does not work as well, given the large variations in BMI due to pubertal status, age and gender. BMI-for-age percentiles are instead used to ascertain pediatric adiposity in children aged two 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 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, i.e. $BMI_{adj} = weight / height^x$, with x 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 two years of age there is no widely accepted definition to help 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 old (“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, 10, 11, 12, 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 30% and 70% of variation in BMI between individuals; concordance rates among monozygotic twins for fat mass are ~80% while 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 a number of 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-Will 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 impacting excess adiposity, especially when it comes to appetite control, via the hypothalamus. Variants within these two genes (*LEP* and *LEPR*) and other genes in the hypothalamic leptin-melanocortin pathway (*POMC-ADCY3*, *PCSK1*, *MC4R*, *BDNF*) have subsequently been reported in humans with obesity-related traits and in children specifically (Tables 1 and 2) [23, 24]. Other loci implicated in severe childhood obesity are *NTRK2B* and *SIMI* [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 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 genes approaches, on the other end, 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 7 years, nearly a hundred BMI loci have been discovered by GWAS, the majority of which were found in adults. *INSIG2* (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, 32, 33, 34, 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 involved impacting BMI, and thus in turn secondarily influenced 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 in to the biology of the obesity.

Following larger and larger GWAS and meta-analyses [42, 43, 44], including other ethnicities [45, 46, 47], the largest meta-analysis reported to date, by the ⁱGIANT 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 get closer to the causal variant at some of these loci by defining ‘credible sets’ of single nucleotide polymorphisms (SNPs) that represent a reduced shortlist of which one must be the functional lesion.

Besides BMI, other phenotypes related to body fat distribution such as waist-to-hip ratio have been investigated by large GWAS in different ethnicities [49, 50, 51, 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 1,000 obesity cases (BMI greater than or equal to 95th percentile) and over 2,500 lean controls (BMI less than or equal to 50th percentile) revealed evidence of association for nine of the loci, *BDNF*, *FTO*, *GNPDA2*, *MC4R*, *NRXN3*, *QPCTL*, *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. A number of other studies have looked at the adult BMI loci (individually or combined in a genetic risk score) against BMI in childhood [56, 57, 58, 59, 60, 61, 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, since these loci collectively account for only a very small proportion of BMI variation in children (~1–2% [61, 62]), many more pediatric loci are out there 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,

ⁱGenetic Investigation of ANthropometric Traits (GIANT) www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium

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 gene *Osterix* that increases BMD also showed a gender-specific, positive association with pediatric BMI in girls [64], suggesting body proportions and loading on the skeleton is the process by which the ultimate BMD phenotype is impacted.

***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 onwards to reach a peak at approximately twenty years old, 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 4,500 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 old), the same adult obesity-associated *FTO* variant was associated with lower BMI in infancy (<2 years old), earlier age of adiposity rebound, and higher BMI in childhood (>5 years old), suggesting that variation at *FTO* influences adiposity through a developmental change in adiposity rebound timing, rather than through 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 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 knock-out of *FTO* produces an animal that is relatively lean, while *FTO* over-expression 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, 76, 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 non-coding and affects the regulatory machinery of *FTO* or, as more and more data suggests, 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 well possible that the causative variants regulate another nearby gene.

GWAS loci uncovered in children specifically

Despite the fact that mapping of 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, which 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 $\geq$ 97th percentile, with most cases having BMI $\geq$ 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 $\geq$ 95th percentile) [80]. The study consisted of a meta-analysis of 14 existing GWAS datasets, consisting of ~5,500 cases and ~8,300 controls (BMI $\leq$ 50th percentile). Seven of the known adult loci (*FTO*, *TMEM18*, *POMC-ADCY3*, *MC4R*, *FAIM2*, *TNNI3K*, 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 like *TNNI3K* 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, since 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 ~5,400 controls, and 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*, *PACSI* 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 ~5,800 children [mean age 10 years, from the ⁱⁱALSPAC study] looked at a different trait, i.e. height-adjusted BMI, in order 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 ⁱⁱⁱGeneration R study. The data suggested that a missense

ⁱⁱAvon Longitudinal Study of Parents and Children (ALSPAC) www.bristol.ac.uk/alspac/

ⁱⁱⁱGeneration R study <http://www.generationr.nl/>

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 ^{iv}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, so further studies are needed 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 of obesity. Furthermore, cohorts derived from African ancestral groups have been successfully leveraged to fine map loci down to the closest point to the underlying causative variant. This is possible because these populations are more ancient and thus have, on average, shorter stretches of linkage disequilibrium. For instance, the T2D 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's 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, besides detecting 32 out 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 last decade, with the uncovering of well-established genetic signals impacting BMI, the combined results of the various approaches described above

^{iv}Raine study www.rainestudy.org.au

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 Box). 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, 90, 91], but studies of rare and common CNVs in childhood obesity are starting to emerge [81, 92, 93].

OUTSTANDING QUESTIONS BOX

- Where does the “missing heritability” in common childhood obesity reside? GWAS findings explain only very little of the genetic risk, suggesting that more loci are out there to find.
- Is the rare variant-common disease hypothesis correct? If so, whole-genome sequencing will help elucidate the full repertoire of the genetic component of childhood obesity.
- What is the role of epigenetics? ChIP-seq and whole-genome sequencing will provide insight in to global methylation patterns and histone modifications in the context of childhood obesity.
- What is the role of gene-by-gene (epistatic) and gene-by-environment (i.e. age, sex, physical activity, diet) interactions?
- Which are the underlying causal variants and genes at the loci identified by GWAS? GWAS is designed with representative tag-SNPs that are in no way to be considered the true causative variants, and new approaches and functional studies will be required to address this problem.

On the quest for the missing heritability, it’s 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 object of some debate [94], a recent study in *Arabidopsis thaliana* convincingly showed that at least in plants epigenetic changes are stable over a number of 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, which will help us 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 over-inflated, due 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 address this issue. Another important point to keep in mind is that genetic factors influencing childhood obesity deviate from what is seen in adults due to the fact that the influences of genes and environment change greatly during childhood and are also heavily sex-specific [100]. As such, 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 even 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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GLOSSARY BOX

Copy number variations (CNVs)	genomic rearrangements (deletions, duplications, inversions, and translocations) resulting in an alternation in the number of copies of a certain section of DNA
Effect size	the amount of phenotypic variation that can be ascribed to a genetic variant
Epigenetics	alternative study of DNA that does not involve sequence changes but rather cellular and physiological influences on how a given gene is expressed
Epistatic interactions	the phenomenon in which the effect of a variant or gene on the trait is not independent of the effect of another variant or gene
Genome-wide association study (GWAS)	a study whereby many hundreds of thousands of common genetic variants are assessed between study subjects, in order to attempt to identify association with a given trait at genomic locations within the genome

Heritability	the proportion of observed differences (variance) on a phenotypic trait among individuals of a population that are due to genetic differences
Meta-analyses	statistical methods for contrasting and combining results from different GWAS studies to increase statistical power
Missing heritability problem	the fact that single genetic variations discovered until now cannot explain the bulk of the genetic component to most common, complex phenotypes
Rare variants	alleles that yield a population-level frequency less than 1%

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TRENDS BOX

- More 65% of adults in United States 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 identify nearly a hundred loci implicated for BMI, in adults.
- Several of these adult BMI and/or obesity loci also play a role in childhood obesity.
- Childhood GWAS has uncovered novel loci below the detection range in adult studies, demonstrating that the pediatric setting, due 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.

Table 1

Obesity and BMI loci described to date in the context of these traits in childhood

Category	Loci	REF
Adult BMI GWAS loci subsequently shown to be also associated with childhood BMI/obesity	<i>BDNF, FAIM2, FTO, GNPDA2, INSIG2, KCTD15, MC4R, NEGR1, NRXN3, POMC-ADCY3, QPCTL, SEC16B, TMEM18, TNNI3K</i>	[55, 56, 80, 82]
Adult type 2 diabetes GWAS loci subsequently shown to be also associated with childhood BMI/obesity	<i>HHEX-IDE</i>	[63]
Novel extreme childhood obesity loci revealed by GWAS	<i>SDCCAG8, TNKS-MSRA, LEPR, PRKCH, PACS1, RMST</i>	[79]
Novel common childhood obesity (BMI 95 th percentile) loci revealed by GWAS	<i>HOXB5, OLFM4</i>	[80]
Novel childhood obesity loci revealed by CNV assessments	<i>ABCB5, ARL15, EDIL3, EPHA6-UNQ6114, FOXP2, KIF2B, OR4P4-OR4S2-OR4C6, S1PR5, SH2B1, TBCA, ZPLD1</i>	[89, 90, 92, 93]

Table 2

Expression patterns and functions of the described childhood obesity and BMI loci

Gene Name	Locus	Full Name	Pattern of Expression	Function
<i>ABCB5</i>	7p21.1	ATP-binding cassette, sub-family B (MDR/TAP), member 5	ubiquitous	Participate in ATP-dependent transmembrane transport of structurally diverse molecules
<i>ARL15</i>	5p15.2	ADP-ribosylation factor-like 15	ubiquitous	GTP binding (predicted)
<i>BDNF</i>	11p4	brain-derived neurotrophic factor	brain	Nerve growth factor
<i>EDIL3</i>	5q14	EGF-like repeats and discoidin I-like domains 3, DEL1	ubiquitous	Integrin ligand, plays an important role in angiogenesis and may be important in vessel wall remodeling and development and endothelial cell behavior
<i>EPHA6 (UNQ6114)</i>	3q11.2	EPH receptor A6	brain, testis	Receptor tyrosine kinase
<i>FAIM2</i>	12q13	Fas apoptotic inhibitory molecule 2	ubiquitous	Not known
<i>FOXP2</i>	7q31	forkhead box P2	ubiquitous	Transcription factor, required for proper development of speech and language
<i>FTO</i>	16q12	Fat mass- and obesity-associated gene	brain	Nuclear protein of the AlkB related non-heme iron and 2-oxoglutarate-dependent oxygenase superfamily
<i>GNPDA2</i>	4p12	Glucosamine-6-phosphate deaminase 2	ubiquitous	Catalyzes the reversible conversion of D-glucosamine-6-phosphate into D-fructose-6-phosphate and ammonium
<i>HHEX-IDE</i>	10q23.33	insulin-degrading enzyme	ubiquitous	Zinc metalloproteinase that degrades intracellular insulin, glucagon, amylin, bradykinin, and kallidin. Deficiencies in this protein's function are associated with Alzheimer's disease and T2D
<i>HOXB5</i>	17q21.3	homeobox B5	ubiquitous	Sequence-specific transcription factor, part of a developmental regulatory system that provides cells with specific positional identities on the anterior-posterior axis
<i>INSIG2</i>	2q14.2	insulin induced gene 2	ubiquitous	Regulation of Cholesterol Biosynthesis by SREBP (SREBF)
<i>KCTD15</i>	19q13	Potassium channel tetramerization domain containing 15	pituitary	During embryonic development, interferes with neural crest formation (By similarity). Inhibits AP2 transcriptional activity by interaction with its activation domain
<i>KIF2B</i>	17q22	kinesin family member 2B	ubiquitous	Plus end-directed microtubule-dependent motor required for spindle assembly and chromosome movement. Has microtubule depolymerization activity

Gene Name	Locus	Full Name	Pattern of Expression	Function
<i>LEPR</i>	1p31	leptin receptor	Isoform A: ubiquitous. Isoform B: hypothalamus	Receptor for obesity factor (leptin). On ligand binding, mediates signaling through JAK2/STAT3. Involved in the regulation of fat metabolism
<i>MC4R</i>	18q21	Melanocortin receptor 4	brain, placenta and intestinal tissue	Receptor specific to the heptapeptide core common to adrenocorticotrophic hormone and α -, β -, and γ -MSH. Plays a central role in energy homeostasis and somatic growth
<i>NEGR1</i>	1p31	Neuronal growth regulator-1	brain	Member of the immunoglobulin superfamily, with a role in cell adhesion and neurite outgrowth in the developing brain
<i>NRXN3</i>	14q31	neurexin 3, C14orf60	brain	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
<i>OLFM4</i>	13q14.3	olfactomedin 4	prostate, small intestine and colon	Antiapoptotic factor that promotes tumor growth and is an extracellular matrix glycoprotein that facilitates cell adhesion
<i>OR4P4-OR4S2-OR4C6</i>	11q12.1	olfactory receptor, family 4, subfamily P, member 4/2/6	ubiquitous/not known	Olfactory receptors
<i>PACSI1</i>	11q13.1	phosphofurin acidic cluster sorting protein 1	ubiquitous	Putative role in the localization of trans-Golgi network (TGN) membrane proteins
<i>POMC-ADCY3</i>	2p23.3	proopiomelanocortin	pituitary, hypothalamus, placenta, and epithelium	Polypeptide hormone precursor that undergoes extensive, tissue-specific, post-translational processing via cleavage by subtilisin-like enzymes known as prohormone convertases
<i>PRKCH</i>	14q23.1	protein kinase C, eta	epithelial tissues	Calcium-independent and phospholipids-dependent protein kinase, can regulate keratinocyte differentiation, mediates the transcription activation of the transglutaminase 1 (TGM1) gene
<i>QPCTL</i>	19q13.32	glutaminyl-peptide cyclotransferase-like	ubiquitous	Responsible for the biosynthesis of pyroglutamyl peptides
<i>RMST</i>	12q23.1	rhabdomyosarcoma 2 associated transcript (non-protein coding)	ubiquitous	lncRNA, function not known
<i>S1PR5</i>	19p13.2	sphingosine-1-phosphate receptor 5	ubiquitous	Receptor for the lysosphingolipid sphingosine 1-phosphate (S1P)
<i>SDCCAG8</i>	1q43	serologically defined colon cancer antigen 8	thymus, prostate, testis, ovary, small intestine, colon, mucosa, colon and renal cancer tumors	Centrosome-associated protein that may be involved in organizing the centrosome during interphase and mitosis. Mutations in this gene are

Gene Name	Locus	Full Name	Pattern of Expression	Function
				associated with retinal-renal ciliopathy.
<i>SEC16B</i>	1q25	SEC16 homolog B, endoplasmic reticulum export factor	ubiquitous	Organization of transitional endoplasmic reticulum sites and protein export
<i>SH2B1</i>	16p11.2	Scr-homology-2 (SH2) domain containing putative adapter protein 1	ubiquitous	Member of the SH2 domain, mediates activation of various kinases and may function in cytokine (ie, leptin) and growth factor receptor signaling and cellular transformation
<i>TBCA</i>	5q14.1	tubulin folding cofactor A	ubiquitous	Tubulin-folding protein; involved in the early step of the tubulin folding pathway
<i>TMEM18</i>	2p25	Transmembrane protein 18	brain, nucleus	Not known
<i>TNKS-MSRA</i>	8p23.1	Methionine Sulfoxide Reductase A	ubiquitously expressed, abundant in kidney and nervous tissue	Enzymatic reduction of methionine sulfoxide to methionine; repair of oxidative damage to proteins to restore biological activity
<i>TNNI3K</i>	1p31.1	TNNI3 interacting kinase	heart	Belongs to the MAP kinase kinase kinase (MAPKKK) family of protein kinases and it is thought to play a role in cardiac physiology
<i>ZPLD1</i>	3q12.3	zona pellucida-like domain containing 1	placenta, kidney, lung, pancreas and at very low level in other tissues	Not known