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Review Article

Genetics of Childhood Obesity

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Obesity is a major health problem and an immense economic burden on the health care systems both in the United States and the rest of the world. The prevalence of obesity in children and adults in the United States has increased dramatically over the past decade. Besides environmental factors, genetic factors are known to play an important role in the pathogenesis of obesity. Genome-wide association studies (GWAS) have revealed strongly associated genomic variants associated with most common disorders; indeed there is general consensus on these findings from generally positive replication outcomes by independent groups. To date, there have been only a few GWAS-related reports for childhood obesity specifically, with studies primarily uncovering loci in the adult setting instead. It is clear that a number of loci previously reported from GWAS analyses of adult BMI and/or obesity also play a role in childhood obesity.

1. Definition and Epidemiology of Childhood Obesity

Obesity is a major health problem in modern societies, with a prevalence of up to 25% in Western societies and an increasing incidence in children [1]. Obesity, plus the associated insulin resistance [2, 3], is also considered a contributor to the major causes of death in the United States and is an important risk factor for type 2 diabetes (T2D), cardiovascular diseases (CVD), hypertension, and other chronic diseases.

Approximately 70% of obese adolescents grow up to become obese adults [4–6]. The main direct adverse effects of childhood obesity include orthopedic complications, sleep apnea, and psychosocial disorders [7, 8]. Obesity present in adolescence has been shown to be associated with increased overall mortality in adults [9]; overweight children followed up for 40 [10] and 55 years [11] were more likely to have CVD and digestive diseases, and to die from any cause as compared with those who were lean.

Obesity is a complex disease that involves interactions between environmental and genetic factors. Excess in adipose tissue mass can be seen as a disruption in the balance between energy intake and expenditure. In modern times, this excess in adipose tissue fuel storage is considered a disease; however, a better viewpoint would be that obesity is a survival advantage that has gone astray that is, what is now considered a disease was probably advantageous when food was less available and a high level of energy expenditure through physical activity was a way of life [12].

The true prevalence of childhood obesity is difficult to empirically quantify as there is currently no internationally accepted definition; however, in general terms, childhood obesity is considered to have reached epidemic levels in developed countries.

Approximately 25% of children in the US are overweight and approximately 11% are obese. In the 10-year period between the National Health and Nutrition Examination Survey (NHANES) II (1976–1980) and NHANES III (1988–1991), the prevalence of overweight children in the USA had increased by approximately forty percent [1]. Examination of historical standards for defining overweight in children from many countries tells us that the distribution of BMI is becoming increasingly skewed [13]. The lower part of the distribution has shifted relatively little whereas the upper

part has widened substantially. This finding suggests that many children may be more susceptible (genetically or socially) to influence by the changing environment.

Although the definition of obesity and overweight has changed over time [14, 15], it can be defined as an excess of body fat. The definition of childhood obesity continues to be problematic due to the fact that almost all definitions use some variant of BMI (body mass index). A range of other methods are available which allow for accurate estimates of total body fat; however, none of these are widely available and/or are easily applicable to the clinical situation. Body weight is reasonably well correlated with body fat but is also highly correlated with height, and children of the same weight but different heights can have widely differing amounts of adiposity, but in adults BMI correlates more strongly with more specific measurements of body fat, that is, BMI is useful for depicting overweight in the population but is an imperfect approximation of excess adiposity [16].

In addition, the relation between BMI and body fat in children varies widely with age and with pubertal maturation. This in itself makes BMI definitions of overweight for children more complex than definitions for adults, which use a single cutoff value for all ages. Definitions of overweight that use BMI-for-age can be based on a number of different standards that all give slightly different results, and all are essentially statistical not functional definitions. However, useful percentile charts relating BMI to age have now been published in several countries [17]. The Center for Disease Control and Prevention defined overweight as at or above the 95th percentile of BMI for age and "at risk for overweight" as between 85th to 95th percentile of BMI for age [18, 19]. European researchers classified overweight as at or above 85th percentile and obesity as at or above 95th percentile of BMI [20]. A recent report from the Institute of Medicine has specifically used the term "obesity" to characterize BMI $\geq$ 95th percentile in children and adolescents [21]. By late adolescence, these percentiles approach those used for adult definitions; the 95th percentile is then approximately 30 kg/m^2 [8]. These statistical percentile definitions are now general guidelines for clinicians and others [19].

2. Therapeutic Options

Data supporting the use of pharmacological therapy for pediatric overweight are limited and inconclusive [22].

Sibutramine has been studied in a randomized controlled trial of severe obesity [23]. It has been shown to be efficacious as compared with behavior therapy alone, but it may be associated with side effects including increases in heart rate and blood pressure [24]; recent clinical trial studies have concluded that subjects with preexisting cardiovascular conditions who were receiving long-term sibutramine treatment had an increased risk of nonfatal myocardial infarction and nonfatal stroke [25]; indeed, it was recently dropped from further development based on the results from such clinical trials.

Orlistat is approved for use in adolescence but its efficacy has not yet been tested extensively in young patients. Orlistat is associated with gastrointestinal side effects and requires fat-soluble vitamin supplementation and monitoring [26, 27].

Metformin, used to treat T2D, has been used in insulin-resistant children and adolescents who are overweight, but long-term efficacy and safety are unknown [28]. Additionally, surgical approaches to treat severe adolescent obesity are being undertaken by several centers [29].

For rare genetic and metabolic disorders, pharmacological treatment may be useful. For example, recombinant leptin is useful in hereditary leptin deficiency. Octreotide may be useful in hypothalamic obesity [30].

3. Evidence for a Genetic Component in Obesity

The rising prevalence of obesity can be partly explained by environmental changes over the last 30 years, in particular the unlimited supply of convenient, highly calorific foods together with a sedentary lifestyle. Despite these changes, there is also strong evidence for a genetic component to the risk of obesity [31, 32]; indeed, obesity is now considered a classic example of a complex multifactorial disease resulting from the interplay between behavioral, environmental and genetic factors which may influence individual responses to diet and physical activity.

A genetic component for obesity is reflected in prevalence differences between racial groups, from 5% or less in Caucasian and Asian populations to 50% or more among Pima Indians and South Sea Island populations [33]. In addition, the familial occurrences of obesity have been long noted with the concordance for fat mass among MZ twins reported to be 70–90%, higher than the 35–45% concordance in DZ twins; as such, the estimated heritability of BMI ranges from 30 to 70% [34–36].

4. Previous Genetic Studies in Obesity and the Need for GWAS Approaches

Genome-wide linkage scans in families with the common form of childhood obesity have yielded several loci, but the genes in these loci have yet to be elucidated. A number of families with rare pleiotropic obesity syndromes have been studied by linkage analysis where chromosomal loci for Prader-Willi syndrome [37], Alström's syndrome [38], and Bardet-Biedl syndrome [39–41] have been mapped but the underlying molecular mechanisms have yet to be determined.

Recent studies of genetic syndromes of obesity in rodents have provided insights in to the underlying mechanisms that may play a role in energy homoeostasis. In recent years, research has begun to identify human disorders of energy balance that arise from defects in these or related genes [42]. These mutations have been shown to result in morbid obesity in children without the developmental features that commonly accompany recognized syndromes of childhood obesity.

The severely obese ob/ob mouse strain [43] inherits its early-onset obesity autosomal recessively and weighs approximately three-times more than normal mice by maturity. Zhang et al. [44] cloned and characterized the *ob* gene

which is expressed primarily in white adipose tissue as the secreted protein, leptin, a mutation of which renders these mice leptin deficient. Administration of recombinant leptin is known to reverse the phenotypic abnormalities in these mice entirely [45–47] while there is no effect in another strain of severely obese mice, db/db, who instead have been characterized to have a mutation in the leptin receptor gene, which is primarily expressed in a different site, namely, the hypothalamus [48]. In human studies, serum leptin concentrations are widely recognized as being positively correlated with obesity-related traits [49].

The behavioral and neuroendocrine effects of leptin could potentially be mediated through its actions at hypothalamic leptin receptors. Proopiomelanocortin (POMC) is produced by the hypothalamus, which is subsequently cleaved by prohormone convertases to yield peptides (including α melanocyte stimulating hormone, αMSH) that play a role in feeding behavior. Forty percent of POMC neurons express mRNA for the long form of the leptin receptor, and POMC expression is positively regulated by leptin [50]. Work in rodents has demonstrated that αMSH acts as a suppressor of feeding behavior; recently, mutations in *POMC* associated with severe and early-onset obesity have been described in two unrelated German subjects [51]. A single patient with severe early-onset obesity was reported to have compound heterozygote mutations in the prohormone convertase 1 (PC1) gene, a key component in the proteolytic processing of POMC [52, 53].

One form of melanocortin receptor (MC4R) is highly expressed in areas of the hypothalamus involved in feeding; mice with disruption of the *MC4R* gene are severely obese [54]. More recently in humans, mutations in the *MC4R* gene have been associated with obesity [55–58]. The *MC4R* gene is the first locus at which mutations are associated with dominantly inherited morbid human obesity thus making it the commonest genetic cause of human obesity described before the era of GWAS.

5. Genome Wide Association Studies

Overall, linkage analysis studies conducted to date have achieved only limited success in identifying genetic determinants of obesity due to various reasons, importantly including the generic problem that the linkage analysis approach is generally poor in identifying common genetic variants that have modest effects [59, 60]. Comparably, a generic problem with the candidate gene association studies is their general reliance on a suspected disease-causing gene(s) whose identity derives from a particular biological hypothesis on the pathogenesis of obesity. Thus, since the pathophysiological mechanisms underlying obesity are generally unknown, continued use of the hypothesis-driven candidate gene association approach is likely to identify only a relatively small fraction of the genetic risk factors for the disease.

The GWAS approach serves the critical need for a more comprehensive and unbiased strategy to identify causal genes related to obesity. It is also well established that in noncoding regions of the genome there are important regulatory elements, such as enhancers and silencers, and genetic variants that disrupt those elements could equally confer susceptibility to complex disease.

The human genome and International HapMap projects have enabled the development of unprecedented technology and tools to investigate the genetic basis of complex disease. The HapMap project, a large-scale effort aimed at understanding human sequence variation, has yielded new insights into human genetic diversity that is essential for the rigorous study design needed to maximize the likelihood that a genetic association study will be successful [59–61]. Genome-wide genotyping of over 500,000 SNPs can now be readily achieved in an efficient and highly accurate manner [62, 63]. Since much of human diversity is due to single base pair variations together with variations in copy number [64] throughout the genome, current advances in single-base extension (SBE) biochemistry and hybridization/detection to synthetic oligonucleotides now make it possible to accurately genotype and quantitate allelic copy number [63, 65].

There is now a revolution occurring in SNP genotyping technology, with high-throughput genotyping methods allowing large volumes of SNPs (10^5-10^6) to be genotyped in large cohorts of patients and controls, therefore enabling large-scale GWAS in complex diseases. Already with this technology compelling evidence for genetic variants involved in type 1 diabetes [66–68], type 2 diabetes [68–72], age-related macular degeneration [73], inflammatory bowel disease [74, 75], heart disease [76, 77], and breast cancer [78] has been described.

6. Findings from First GWAS Analyses of Obesity

In the past four years, many genetic loci have been implicated for BMI from the outcomes of GWAS, primarily in adults.

Insulin-induced gene 2 (*INSIG2*) was the first locus to be reported by this method to have a role in obesity [79] but replication attempts have yielded inconsistent outcomes [80–84]. A common genetic variant with modest relative risk (RR = ~1.2), rs7566605, near the *INSIG2* gene has been described to be associated with both adult and childhood obesity from a GWAS employing 100,000 SNPs [79]. This variant, present in 10% of individuals, was subsequently replicated in four separate cohorts in the same study, including individuals who were Caucasian, African American, and children; however, three subsequent technical comments to *Science* [80–82] disagreed with this observation.

The identification of the second locus, the fat mass- and obesity-associated gene (*FTO*) [85], which has been more robustly observed by others [86–89], including by us [90]. Interestingly, its role in obesity pathogenesis was actually made indirectly as a consequence of a GWAS of T2D [68, 71], but it became quite clear that its primary influence is on BMI determination which then in turn impairs glycemic control [85]. However, the mechanism by which the variant in *FTO* influences the risk of obesity is largely unknown.

Studies from both *FTO* knockout and *FTO* overexpression mouse model support the fact that *FTO* is directly involved in the regulation of energy intake and metabolism

in mice, where the lack of *FTO* expression leads to leanness while enhanced expression of *FTO* leads to obesity [91, 92].

A French sequencing effort in Caucasians (primarily adults) has reported a set of exonic mutations in *FTO*; however, due to the lack of significant difference in the frequencies of these variants between lean and obese individuals, this study was largely negative [93].

7. Meta-Analyses

Subsequent larger studies have uncovered eleven additional genes [94–96], again primarily in adults, firstly melanocortin 4 receptor (*MC4R*) from a multicenter meta-analysis [94], then the GIANT consortium revealed six more genes (transmembrane protein 18 (*TMEM18*), potassium channel tetramerisation domain containing 15 (*KCTD15*), glucosamine-6-phosphate deaminase 2 (*GNPDA2*), SH2B adaptor protein 1 (*SH2B1*), mitochondrial carrier 2 (*MTCH2*), and neuronal growth regulator 1 (*NEGR1*)) [96], five of which were confirmed in the GWAS reported from Iceland (but not *GNPDA2* due to an unavailable proxy SNP), who also uncovered and reported loci on 1q25, 3q27 and 12q13 [95] and verified association with the brain-derived neurotrophic factor (*BDNF*) gene [97].

The latest GIANT meta-analysis revealed multiple new loci associated with body mass index in a study involving a total of 249,796 individuals [98]. A total of 32 loci reached genome wide significance, which included ten known loci associated with BMI, four known loci associated with weight and/or waist-hip ratio, namely, *SEC16B*, *TFAP2B*, *FAIM2*, *NRXN3*, and eighteen new BMI loci, namely, *RBJ-ADCY3-POMC*, *GPRC5B-IQCK*, *MAP2K5-LBXCOR1*, *QPCTL-GIPR*, *TNNI3K*, *SLC39A8*, *FLJ35779-HMGCR*, *LRRN6C*, *TMEM160-ZC3H4*, *FANCL*, *CADM2*, *PRKD1*, *LRP1B*, *PTBP2*, *MTIF3-GTF3A*, *ZNF608*, *RPL27A-TUB*, and *NUDT3-HMGA1*. Besides association to SNPs, a correlated copy number variation (CNV), that is, a 21 kb deletion, was identified 50 kb upstream of *GPRC5B*. This study also leveraged a pediatric cohort to lend further support for their findings.

8. Testing Adult-Discovered Loci in Children

As described above, a number of genetic determinants of adult BMI have already been established through GWAS. One obvious question is how do these loci operate in childhood with respect to the pathogenesis of obesity? We have an ongoing GWAS of BMI variation in children so we are in position to query these SNPs in our dataset of in excess of 6,000 children with measures of BMI [99]. To date nine such loci have yielded evidence of association to BMI in childhood, of which variants at the *FTO* locus yielded the strongest association. With a similar magnitude of association to *FTO* was *TMEM18* followed by *GNPDA2*. The remaining loci with evidence for association were *INSIG2*, *MC4R*, *NEGR1*, 1q25, *BDNF*, and *KCTD15* (Table 1). This is very much in line with the observations made with the pediatric cohort utilized by Willer et al. [96].

The positive results for *FTO* and *MC4R* come as no surprise as we previously reported their association with the CDC-defined 95th percentile of BMI, that is, obesity, in our pediatric cohort, but limited to ages 2–18 years old [90, 106]. One of the more notable results is the positive association with *INSIG2*. This association with pediatric BMI, albeit at just the nominal level, contributes to the ongoing debate on the relative contribution of *INSIG2* in BMI determination.

However, these nine loci only explain 1.12% of the total variation for BMI. In addition, testing pair-wise interactions between the fifteen significant SNPs, none of the interaction effects were significant suggesting that these loci act additively on pediatric BMI [99]. As such, we do observe a cumulative effect but not as striking as reported by the GIANT consortium in their adult cohorts [96].

A number of studies have found that body mass index (BMI) in early life influences the risk of developing type 2 diabetes (T2D) later in life. Indeed, the same variant in *IDE-HHEX* that increases the risk of developing the disease later in life turns out to be also associated with increased BMI in childhood [100].

9. Loci Specifically Identified in Childhood Obesity GWAS Analyses

Two new loci for body-weight regulation were identified in a joint analysis of GWAS data for early-onset extreme obesity, that is, BMI ≥ 99th, in French and German study groups [101], namely, *SDCCAG8* and *TNKS/MSRA* (Table 1). In the discovery step, association was examined in a combined French and German sample of 1,138 extremely obese children and adolescents and 1120 normal or underweight controls with screening of 2,339,392 genotyped or imputed SNPs and testing ultimately 1,596,878 SNPs. In the replication cohort, all SNPs with strong evidence for association were genotyped in independent samples of 1,181 obese children and adolescents and 1,960 normal or underweight controls and in up to 715 nuclear families with at least one extremely obese offspring. However the two loci were, at most, only marginally associated with adult BMI in the latest GIANT study [98], suggesting their influence may be limited to extreme obesity in children.

The biochemistry employed in the current genome wide SNP arrays allows also for the accurate genotyping and quantitation of allelic CNV genome-wide [62, 63, 65]. Neurological disorders have proven the most challenging complex disease to address using genome wide SNP approaches, primarily as a consequence of the need for strict, uniform phenotyping across very large, multicenter cohorts. However, they have led the way in the uncovering of CNVs in common disorders such as autism [107–110], attention-deficit hyperactivity disorder [111], and schizophrenia [112–114].

Genomic copy number variations (CNVs) have been strongly implicated in subjects with extreme obesity and coexisting developmental delay (Table 1). Two groups in the UK plus collaborators independently reported deletions on chromosome 16p11.2 to be present at much higher in extreme obese cases than normal and obese individuals [102, 103]. These deletions, estimated to range in size from

Table 1: Childhood obesity loci that have been identified to date and the route through which they were implicated.

Category	Loci	Citations
Adult BMI GWAS loci also associated with childhood BMI/obesity in independent studies	*FTO, TMEM18, GNPDA2, INSIG2, MC4R, NEGR1, 1q25, BDNF, KCTD15*	[99]
Adult 2 type diabetes GWAS loci also associated with childhood BMI/obesity	*HHEX-IDE*	[100]
GWAS of extreme childhood obesity—novel loci	*SDCCAG8, TNKS-MSRA*	[101]
CNV analyses of childhood obesity—novel loci	*SH2B1, EDIL3, S1PR5, FOXP2, TBCA, ABCB5, ZPLD1, KIF2B, ARL15, EPHA6-UNQ6114, OR4P4-OR4S2-OR4C6*	[102–105]

220 kb to 1.7 Mb, encompass several genes. Bochukova et al. [102] pointed out that the *SH2B1* gene is within the deleted region that is common to all five cases studied. *SH2B1* may be the culprit as its role in leptin and insulin signaling and energy homeostasis is well described [102], plus common SNPs near *SH2B1* locus have already been associated with BMI in GWAS reports [96, 102].

To complement these previous CNV studies on extreme obesity, we addressed CNVs in common childhood obesity by examining children in the upper 5th percentile of BMI but excluding any subject greater than 3 standard deviations from the mean to reduce severe cases in the cohort [104] (Table 1). We performed a whole-genome CNV survey of our cohort of European American (EA) childhood obesity cases ($n = \sim 1,000$) and lean controls ($n = 2,500$) who were genotyped with 550,000 SNP markers. We identified 34 putative CNVR loci (15 deletions and 19 duplications) that were exclusive to EA cases; however, three of the deletions proved to be false positives during the validation process with quantitative PCR (qPCR). Only 17 of these CNVR loci were unique to our cohort that is, not reported in controls by the Database of Genomic Variants. Positive findings were evaluated in an independent African American (AA) cohort ($n = \sim 1,500$) of childhood obesity cases and lean controls ($n = \sim 1,500$). Surprisingly, eight of these loci, that is, almost half, also replicated exclusively in AA cases (6 deletions and 2 duplications). Replicated deletion loci consisted of *EDIL3, S1PR5, FOXP2, TBCA, ABCB5, and ZPLD1* while replicated duplication loci consisted of *KIF2B* and *ARL15*. We also observed evidence for a deletion at the *EPHA6-UNQ6114* locus when the AA cohort was investigated as a discovery set.

The majority of genes harboring at the loci uncovered in this study have not been implicated in obesity previously. However, the most notable finding is with *ARL15,* which was recently uncovered in a GWAS of adiponectin levels, with the same risk allele also being associated with a higher risk of CVD and T2D [115].

We also evaluated large rare deletions present in <1% of individuals and >500 kb in size as set previously [104] and did not observe excess of large rare deletions genome-wide. This is not unexpected given that previous reports only found significance when including developmental delay subjects but not when severe early-onset obesity was evaluated alone [102, 103].

More recently, a novel common copy number variation for early-onset extreme obesity was reported on chromosome 11q11, harboring the *OR4P4*, *OR4S2*, and *OR4C6* genes using a similar approach [105] (Table 1). Indeed, as higher and higher resolution genome wide scans are carried out, one would expect further reports of such findings.

10. Other Ethnicities

Studying populations of different ancestry will also help us to globally identify and understand the genetic and environmental factors associated with estimates of obesity, as variants found in populations of both African and Caucasian ancestry may represent more universally important genes and pathways for subsequent diagnosis, prevention, and treatment of obesity and its complications. In addition, a cohort of African ancestry in many instances can aid in refining the anticipated association(s) made in with the GWAS approach due to lower LD in this ethnicity, for example, the association of T2D with *TCF7L2* [116] has been refined utilizing a West African patient cohort [117].

To date, most obesity GWAS reports have come from investigations of populations of European origin. This is partly due to the relatively low haplotypic complexity of Caucasian genomes and partly to get around admixture concerns. Indeed, like many of the other replication efforts, *FTO* shows the strongest association with BMI in our large European American pediatric cohort [98]. However, the role of the *FTO* locus in influencing BMI and obesity predisposition in populations of African ancestry has been previously less clear [88, 118], but consensus is emerging from large cohort studies, both in adults [119] and in our own pediatric cohort [90], that SNP rs3751812 captures the *FTO* association with the trait in both ethnicities; this finding is comparable to similar outcomes working with loci in asthma [120] and T2D [117].

11. Conclusions

While these recently discovered loci unveil several new biomolecular pathways not previously associated with obesity, it is important to note that these well-established genetic associations with obesity explain very little of the genetic risk for this pediatric phenotype, suggesting the existence of additional loci whose number and effect size remain unknown.

These findings have left the genetics community to ponder how we are going to finally uncover the full repertoire of

the genetic component of given traits in order to explain the "missing heritability" [121]. Thus, it is clear that in addition to larger and larger cohorts combined in to meta-analyses, new whole genome sequencing technologies will be a large part of the solution. With new advances in sequencing, one would expect further variants to be characterized in this condition so collectively they could build up to a meaningful contribution to the missing heritably for this trait.

Taken together, the unbiased genome wide approach to assess the entire genome has revealed genes that underpin the pathogenesis of childhood obesity. Further functional studies will be needed to fully characterize the function of the genes at these loci in relation to childhood obesity.

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