GENETICS OF OBESITY

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ABSTRACT

Background: Obesity is a complex phenomenon that involves interactions between environmental and genetics factors. The genetic studies in animal models and humans has allowed great progress in the knowledge of body weight regulation. Identifying the hypothalamic leptin/melanocortin pathway as critical in many cases of monogenic obesity has permitted targeted, hypothesis-driven experiments to be performed, and has implicated new candidates as causative for previously uncharacterized clinical cases of obesity.
Data sources: Narrative review. PubMed, Lilacs and ScieLo databases were searched with the terms “obesity”, “genetics” and limited only for “ all child 0-18 years”.
Results: Numerous studies in children and adolescents, have tried to identify candidate genes. At present, the results are not conclusive. Thus, is yet premature genotype obese child on a large scale for predictive testing. Meanwhile, the effects of mutations in the melanocortin-4 receptor gene, for which the obese phenotype varies in the degree of severity among individuals, are now thought to be influenced by one's environmental surroundings. Molecular approaches have revealed that syndromes previously assumed to be controlled by a single gene are conversely regulated by multiple elements.
Conclusions: When specific treatments based on recent discoveries become available, genetic testing could help to discriminate different types of obesity that may respond differentially to therapeutic measures.

Key words: obesity; genetics; child; adolescent

Obesity has become a major health problem around the world, with an increasing incidence in children[1] . The genetic study of obesity is progressing with high velocity. This review discusses the relationships between genetics and obesity, and the role of genetics in potential obesity treatment.

Obesity is defined as an excess of body fat. In the practice, physicians use a body mass index (BMI = body weight in Kilograms divided by square of height in meters) > 30 to define obesity. BMI charts are now available for children by age and sex [2] .

In the last 20 years has yielded the tools necessary to explore the biochemistry underlying obesity, it has also demonstrated that interactions between genetic and environment are critical for the regulation of adipose mass function.

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Medical and nutritional recommendations based on genetically undefined and/or environmentally heterogeneous population-based studies have, not unsurprisingly, minimal success in treating common obesity. It is precisely this lack of success that is conducting for the discussed concepts of personalized medicine[3,4] and nutrition[5-7]. However, prior realizing these concepts, the genetic components underlying common obesity must be elucidated.

In the later ten years, the study of genetically complex diseases has benefited from the advances in molecular biology. While obesity was understand how a problem that obeys rules of genetic laws, new technologies have led to unsuspected developments. Obesity originated from a single dysfunctional gene (i.e., monogenic obesity) is both severe and rare when compared to the more common form of obesity, in which numerous genes make minor contributions in determining phenotype (i.e., polygenic obesities). Some genetic candidates underlying monogenic obesities in the mouse have been defined, transferring this knowledge to humans has led to more questions than answers. However, molecular approach has revealed novel candidate genes for the various types of human obesity, has suggested that several clinical cases previously defined as monogenic obesity are genetically more complex, and has show genetic and environmental interactions as fundamentally important to understanding the mechanisms involved in fat-mass pathophysiology.

However, a genetic approach may provide a useful framework for addressing the obesity epidemic, more research is needed before specific targeted health interventions can be effectively integrated in the clinical practice.

Genetics and environmental factors

Energy storage in the form of fat is a very important adaptation to survival. It is probable that a group of genes have been selected during evolution to favor energy storage ("thrifty gene hypothesis" [8]). In an actual context of increased food availability and decreased physical activity, these genes will confer susceptibility to develop obesity and its perpetuation[9]. The role of genes in body weight control is based on studies in monozygotic twins who show a high concordance in body composition and response to overfeeding[9] . The susceptibility in most cases is polygenic, and rarely monogenic.

Moreover, genetic factors can modulate nutrient storage, but also, nutrients modulate gene expression too[10]. Obesity results from very complex genetic and environmental interactions.

Interactions

Genomics is the study of the entire human genome and involves not only studying the actions of single genes but also the interactions of multiple genes with each other and with the environment. This review emphasizes the multifactorial nature of obesity, which is caused by the interaction of genes, environment, and lifestyle.

Separating genetic factors from other factors is difficult because genes are part of dynamic system that is constantly in flux in response to environmental cues, for this reason at the present is not sufficiently clear the causal relation between genes and body weight regulation.

Obesity is a complex disorder with contribution of multiple genes and gene variants. Evidence suggests that genetics factors are involved in all aspects of weight regulation, including food intake, energy expenditure, hunger, appetite, eating behavior, taste, satiety, spontaneous physical activity, metabolic rate, thermogenesis, and motivation to exercise. Same genetic research gives a sight of the complex relations between genes, genes and age, and genes and environment. Genome wide association studies have led to rapid progress in the understanding of genetic basis of diseases and specially in genetics interactions.

A study[11] found a significant interaction between two gene variants, PPAR λ 2 and ADR β 3, in the risk of obesity in children and adolescents. After adjusting for family history of obesity, the researchers found that carriers of both gene variants were almost 20 times more likely to be obese than noncarriers, suggesting a synergistic effect between the two genes.

The effects of genes may vary depending on age. Investigator[12] reported an association between a mutation in the gene for agouti-related protein (a strong appetite stimulator) and obesity in older adults. The mutation was not associated with obesity in study subjects with a mean age of < 25 years, but was significantly associated with fat and abdominal adiposity in parents.

A great number of studies explored gene–environment–lifestyle interactions. Researchers[13] found that an interaction between diet and specific genes may affect obesity. Exist an increased obesity risk for women with a Glu27 variant and a diet with more than 49% of calories coming from carbohydrates. An alternate variant of that same gene was not associated with an increased obesity risk in relation to carbohydrate intake, given the same number of calories consumed. This finding suggests that the effect of diet on obesity depends on genetic factors. Changes in gene expression that result from epigenetic influences (modifications of DNA structure rather than DNA sequence) were also explored because of their potential role in obesity and associated chronic diseases. Associations between fetal environment (Barker theory) and adult-onset obesity may be due to epigenetic influences that promote fat storage, but possible mechanisms are not well understood[14,15].

Genes, metabolic disorders and secondary obesity

Distribution of fat, more than amount of total body fat, play a key role in metabolic consequences associated with obesity. Excess central (abdominal) fat is particularly associated with adverse effects. People with fat concentrated in the abdomen are more likely to develop diabetes than are people with the same amount of fat distributed throughout the body. A study in prepubertal children also suggests that genetics has a role in abdominal fat deposition[16].

There are near 30 genetics diseases in which patients are obese, with different grades of mental abnormalities, dysmorphic features, and organ-specific developmental dysfunction[17,18]. Such cases are called syndromic obesity. These syndromes arise from genetic defects or chromosomal abnormalities, and can be either autosomal or X-linked. The genetic component analysis suggests that multiple genes within a biological pathway may produce identical phenotypes [19] . The most common disorders known are Prader-Willi syndrome (PWS), Bardet-Biedl syndrome (BBS), and Alström syndrome, but many others have been reported too [19] .

The most frequent of these syndromes (1 in 25,000 births) is PWS, which is characterized by obesity, hyperphagia, diminished fetal activity, mental retardation, and hypogonadism. This disease is caused by an absence in the paternal segment 15q11.2–q12 through chromosomal loss. Several candidate genes in the 15q11–13 region of PWS patients have been studied; however, the molecular basis of hyperphagia remains undefined in part because of the fact that none of the currently available PWS mouse models have an obese phenotype[20]. One candidate protein that may mediate the severe hyperphagia of PWS is the gastric hormone ghrelin[21], via its regulation of hunger and stimulation of growth hormone [18] . Ghrelin's role is further implied by the positive findings that growth hormone supplementation is capable of reversing several dysfunctional processes associated with PWS[22-23]; however, in the absence of a suitable experimental model, identifying the genetic components of this syndrome will be difficult.

BBS is characterized by obesity, rod-cone dystrophy, morphological finger

abnormalities, learning difficulties, and renal disease, among other clinical manifestations. It was originally classified as a homogeneous syndrome, in the present BBS has been associated with at least 11 different chromosomal locations, with several mutations identified within some of the following locations: BBS1 on 11q13, BBS2 on 16q21, BBS3 on 3p13, BBS4 on 15q22.3, BBS5 on 2q31, BBS6 on 20p12, BBS7 on 4q27, BBS8 on 14q32.11, BBS9 on 7p14, BBS10 on 12q21.2, and BBS11 on 9q33.1 [24-27]. While BBS was considered to be autosomal-recessive, it has recently been found that the clinical symptoms of certain forms of BBS are related to recessive mutations at one of the BBS loci associated with a heterozygous mutation at a second locus, prompting, for the first time, the hypothesis of a triallelic mode of transmission[28]. Six genes are characterized in BBS. For the BBS6 locus, positional cloning identified the MKKS gene, which codes for a chaperone protein. Mutations identified in MKKS result in a shortened chaperone protein and are present in 5%–7% of BBS cases; however, the links between MKKS, its eventual target proteins, and the BBS clinical traits are largely unknown. A newly identified locus, BBS10, has recently been found to code for C12orf58, a vertebrate-specific chaperone-like protein, and was found to be mutated in 20% of the populations examined from various ethnic backgrounds [25]. Unlike BBS6 and BBS10, the genes associated with BBS1, BBS2, and BBS4 are very different from MKKS and C12orf58 genes, but it is reasonable that they code for protein substrates of these chaperones [29]. Recently, the gene encoding the E3 ubiquitin ligase TRIM32 was identified as the 11th locus associated with BBS, suggesting that the list of genetic components for this syndrome may yet remain incomplete [27]. Functional works performed in single-cell organisms have shown that certain BBS genes are specific to ciliated cells[30]. Ciliated cells have a role in mammalian development, contributing to right/left asymmetry, thus enabling the organs to be correctly positioned within the biological system. Dysfunction in processes affecting ciliated cells may contribute to the alterations in pigmentary epithelia and structural anomalies noted in certain organs in patients with BBS; however, the relationship between cilia and obesity remains unclear [31]. Recent findings suggest that cilia formation is not dependent on BBS gene functionality [32]; rather, the BBS genes may play an important role in intracellular signaling [31]. An article used *Caenorhabditis elegans* to demonstrate the regulation of fat storage by orthologs of both neuronal TUB and BBS1 genes, suggesting the existence of a currently unidentified intertissue signaling pathway that may link ciliated neurons and adipose cells[33,34].

While syndromic obesity was previously presumed to be under the control of a single gene, progress in genomic era has clearly distinguished this type of obesity, defining the contribution of multiple genetic factors in a syndrome is significantly more challenging than localizing the single gene involved in monogenic diseases.

Monogenic Obesity

Nearly 200 cases of human obesity have been associated with a single gene mutation. These cases, which obey Mendelian genetics, are characterized by severe phenotypes that present themselves in childhood and are often associated with additional behavioral, developmental, and endocrine disorders

The first gene identification was made in animal models of monogenic obesity. These rodents models mostly involved genes in regulatory pathway of food intake. Later, similar affected ways have been discovered in human monogenic obesity[35].

The present model have two integrated pathways: a leptin, leptin receptor (LR) and a melanocortin pathway. Leptin is produced by adipocytes . It bind to hypothalamic receptors in the arcuate nucleus and this induced an increased secretion and syntesis of α-melanocyte stimulating hormone (α-MSH) that is formed from pro-opiomelanocortin (POMC) through proteolitic cleavage

mediated by pro-hormone convertase 1(PC-1) . α-MSH binds to the melanocortin 4 receptor (MC4R) in the paraventricular nucleus. This in turn inhibit the effectors of food intake (see fig. 1).

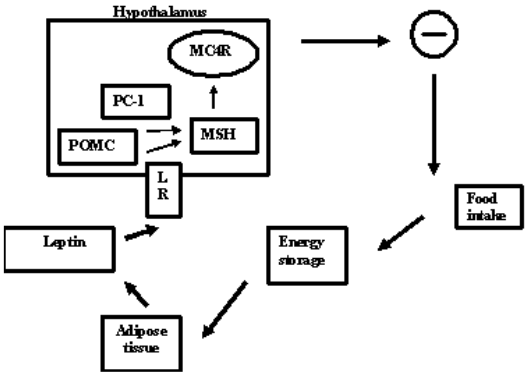

Fig 1. Schematic representation of leptin regulation food intake in monogenic obesity. Leptin is secreted by adopocytes. It bind to hypothalamic receptor (LR) and this induces an increased synthesis of melanocyte stimulating hormone (MSH), formed from pro-opiomelanocortin (POMC) through proteolytic cleavage mediated by pro-hormone convesrase 1 (PC-1). MSH binds to the melanocortin 4 receptor (MC4R). This, in turn, inhibit the effectors of food intake (-).

Homozygous carriers of loss or mutation in the leptin gene exhibit early obesity onset, hypogonadotrophic hypogonadism and central hypohyroidism. The treatment with recombinant human leptin is in this case looks promising[35].

The homozygous mutation of leptin receptor, abolish leptin signaling, leading to a similar picture that individuals with leptin deficiency , but also display growth retardation.

Because α-MSH is involved in the regulation of food intake and also in hair pigmentation, defects in POMC function include obesity, red hair and ACTH deficiency.

Mutations of PC-1 have obesity, ACTH deficiency and hyperproinsulinemia, because PC-1 is involved in the conversion of proinsulin into insulin in pancreatic β-cells.

Mutations in MC4R cause dominant an recessive inherited nonsyndromic obesity, with incomplete penetrance and variable expression. It is similar to more common forms of obesity, with a early age onset. MC4R mutations represents a important cause of obesity between children (1-6%)[36].

Obesity in which a single gene can be can be identified as the major cause of disease is rarely found.

Polygenetic obesity

Polygenic or common obesity arises when an individual genetic profile develop in an environment that promotes energy consumption over energy expenditure. Every time more societies have an environment that favors weight gain rather than loss because of food abundance and lack of physical activity, thus positioning common obesity as a major epidemic currently challenging these societies. Many very good reviews have been published in which the genetic complexity and the challenges in dissecting the perturbed biology underlying common obesity have been outlined [17,37,38-40]. While independent replication of a novel association is mandatory, it is important to stress that our current degree of understanding of genetics and environment (G&E) interactions should prevent an unreplicated result from immediately being discarded. Complex traits are highly dependent on G&E interactions; however, a question persists: how can one account for and control all possible influences within an experimental design that may affect data interpretation and ultimately experimental conclusions? The individual complexity in humans relates to the alleles that influence common diseases in different genetic ways, and to variable genetic combinations eventually influenced by different epigenetic (including in utero) or environmental factors during an individual's lifetime (the role of epigenetics has been thoroughly reviewed in[41,42]). The precise degree to which genes eventually contribute to complex traits remains poorly defined, and the importance of subtle environmental factors may simply not be appreciated.

Studies of polygenic obesity are based on the analysis of single nucleotide polymorphisms (SNPs) or repetition of bases (polyCAs or microsatellites) located within or near a candidate gene, where a candidate gene is one that meets a number of criteria, such as its proximity to a quantitative trait locus or its having a phenotypic effect following genetic manipulation (e.g., knock-out and knock-in

models) [43]. Should a candidate-gene variant appear promising based on results derived from in vitro and animal-model studies, its association with the obese phenotype is then examined in case-control and family studies[44]; however, many genes and chromosomal regions contribute to defining the common obese phenotype [45,46]. These genes have been implicated in a wide variety of biological functions, such as energy expenditure, the regulation of food intake, glucose and lipid metabolism, and adipose tissue development.

Not only the number of genes associated with obesity is high, but variants in some of these genes are demonstrating the importance of polymorphisms in the "interpretation" of environmental stimuli [5]. In contrast to animal models whose environments can be rigorously controlled, the genetic and environmental diversity in humans has proved problematic for data replication [44,45,47] and the result can be conflicting, for example, an association between three SNPs of GAD2, which codes for the 65-kDa subunit of the glutamic acid decarboxylase enzyme, and morbid obesity was identified in a French population following a genome-wide scan[48]; however, independent replication in a German population could not be achieved[49]. Although this example raises questions concerning the role of GAD2 in obesity, it would be premature to discount GAD2*'s* involvement entirely[50]. This notion may also apply to additional candidates emerging from genome-wide scans, as they may also face replication issues.

Possibly a failure to replicate data is related to the sample size in which the association was first detected. Indeed, because the contribution of any given gene to the phenotype of a complex trait is often minimal, a large cohort size is required if statistical significance is to be achieved; however, the caveat is that the more associations examined, the greater the risk of type-I errors. Statistical approaches such as linkage of disequilibrium threshold values and permutation analyses have proven useful, but an ingenious approach recently described will undoubtedly provide a template for future association studies[51] . Using a multi-stage design, in which the number of SNPs considered is reduced at each step without sacrificing genome-wide significance, the authors selected the first ten SNPs for further analysis, and only one, a SNP variant near the INSIG2 gene, was associated with obesity. While more common statistical tests (Bonferroni corrections), did not identify this variant, the multi-stage approach employed by the authors proved accurate, as this variant was replicated in four out of five independent populations [44,51].

What can we learn from genetic investigations on obesity

Over the past year important efforts has been invested in the search for genes that predispose to common obesity, among these, the major breackthough in obesity research was the discovery of FTO[52] gene, where variants located in the first intron of FTO were associated with 1.7 fold increased risk of obesity, and TCF7 a synembryon-like developmental gene[52].

It is unclear at the present stage whether counseling and genetic testing will be integrated into the practice of obesity prevention and treatment. Before this can occur, answers to several questions are needed, in addition to a response to the more general questions such psychological, social, and ethical. We are able to define the predictive risk related to obesity for gene variations or mutations in candidate genes? Although the genetic prediction for monogenic diseases is very high, the predictive risk is small and difficult to determine for the common causes of obesity. We face here more probability than predictive medicine.

Deficient growth during fetal life and infancy is associated with an increased risk of obesity, lipids abnormalities, coronary disease, metabolic syndrome and type 2 diabetes later in life. This early pattern of growth is associated with an increased disease risk especially when followed by a relative gain in body size later in childhood. Genetic factors are closely involved in growth and disease pathogenesis and gene-early life environmental interactions affect health outcomes[53].

Are we able to specifically treat or prevent obesity in carriers of allelic variants or mutations conferring a defined risk? Actually, there is no specific and efficient drug treatment for obesity. Conventional therapy in children can lead to excessive pressure and inexorably conducts to worsening obesity. Is it then reasonable to target a specific population-particularly children-for prevention?

In patients with MC4R mutations, the frequency and relative risk for obesity (100-fold higher) could lead us to consider mutation screening at a population scale. MC4R agonists are now under development and might be used in the future in patients with decreased melanocortinergic activity.

However, the expression of the disease in mutation carriers is variable and the penetrance incomplete, emphasizing the role of environment as well as other genetic contributors.

With all these uncertainties, it seems premature to promote the detection of the mutation on a large scale. Although scientists hope that personalized health care based on genetic profiling will help people recognize their risk and improve their behavior, additional evidence is needed to support this possibility. The present revision, as all narrative review, could be limited for selection search bias.

Neuroendocrinology and genes

Fat mass is an energy storehouse but also an endocrine organ. A deregulation of the sympathetic nervous system (SNS) might generate obesity. After stress SNS fibers liberate neuropeptide Y (NPY) that directly increases visceral fat. Adrenergic receptors are the major regulators of lipolisis. In severe obesity the adrenergic receptors subtypes are differentially expressed in different fat depots. Liver and visceral fat share a common sympathetic pathway. The neuroendocrine melanocortinergic system and gastric gherlin are greatly deregulated in obesity. The specific mutation of type 4 melanocortin receptor induces early obesity onset, hyperphagia and insulin resistance. The recently discovered prohormone convertase mutation simultaneously produces in 1/3 of cases severe gastrointestinal dysfunction and obesity[54,55].

Conclusion

One of the major interests of the of clinical genetic studies in patients, is to provide breakthroughs in the understanding of molecular mechanisms involved in body weight regulation[9]. This fact could provide new tools for the development of common obesity therapies, an objective that will be reached in the near future. Predictive genetics is problematic in common forms of obesity and does not justify large-scale testing until specific treatments are not available. However, once these therapies are developed, genetic testing could allow classification of patients in subgroups for which the efficacy of different treatments could be proved[9] .

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