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Mini Review

Hereditary Obesity: Causes and Genetic Relevance

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Abstract

Obesity is a multi-featured disease characterized by an abnormal rise in body fat content, owing to several factors which cannot be traced down to a single determinant but often a combination of them. The article discusses these causes which are broadly classified as biological, environmental, and behavioral factors. Biological factors are supplemented by metabolic modifications of the normal body cycle, which include genetics, gut microbiota (loss or gain of some species may impair fat metabolism or absorption), hormonal effects (for instance steroid hormones are closely related to acquiring an obese body), use of medications and alcohol consumption. On the other hand, environmental effects encompass the societal or cultural ambiance, presence of certain obesity-related chemicals, and obesogenic environment (surroundings encouraging weight gain and unfavorable to loss of weight). Sedentary lifestyles and inadequate exercise correspond to behavioral factors [4]. Genetic factors are the highlight of the article, which reviews various genes related to conferring obesity, the associated complications, and possible solutions.

Keywords: Obesity; Hereditary Obesity; Genetics; BMI

Introduction

Obesity is a disorder or condition of the body based on multiple factors and is characterized by excessive accumulation of fats in the body which damages health. Recent years witnessed a dramatic elevation in obesity cases. Its contribution to the population's overall health is not to be underestimated since obesity is the underlying cause of several disorders ranging from cardiovascular diseases to hormonal imbalances. Body mass index (BMI) is the determinant for obesity in adults and children, however, for the latter, age is considered as well. Adults with a BMI of 30 or more fall under the obese category. In 2019, WHO reported approximately 38.2 million cases of obese or overweight children under the age of 5. These conditions, infamous in high-income countries, have now seeped their way into low - or middle-income countries, specifically in urban areas [1].

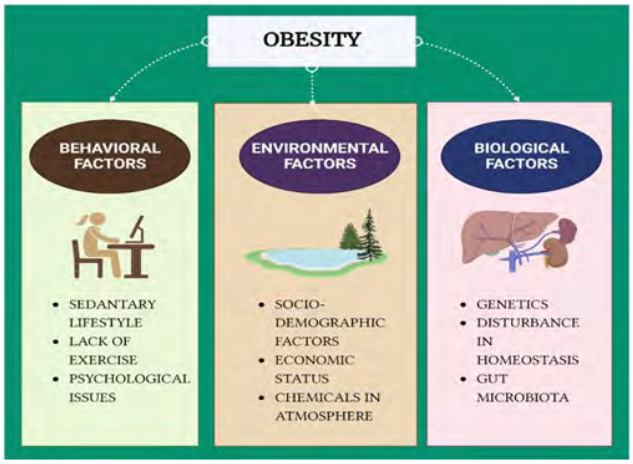

Figure 1: Various Causes of Obesity.

Several studies have shown that the cause of weight gain doesn't solely depend on environmental and lifestyle factors, but also on genetic factors which define an individual's affinity and body's disposition to gain weight and develop obesity. Concerning molecular genetics behind obesity and its subsequent inheritance, numerous genetic variants have been analyzed with the help of the genome-wide association studies (GWAS) approach [2]. The following article discusses these genes and their complications, and their impact on individuals' health and future generations is investigated. At the fundamental level, obesity is instigated by an energy imbalance within the body, wherein the uptake of calories is more than its expenditure. It is also noteworthy, that the progression of obesity in adults and children, despite having similar contributing factors, is different. In children, due to active growth, their energy expenditure is varied. Furthermore, obesity in children is also interrelated to psychological issues such as peer pressure, low self-esteem, or marginalization [3].

Figure 2: BMI and type of body.

Experimental evidence has asserted that genetics do play an important role in determining a body's predisposition to be obese. BMI as mentioned before is a determinant of obesity (Figure 2). A study highlights that around 30-40% of the variance in BMI inclining toward obesity is due to genetic factors and the rest 60-70% is attributed to environmental factors [2]. The interaction of genetic factors, comprising of mutations that can be inherited, with the environment, often governs the expression of those obesity-related genotypes. These mutations are further discussed ahead. A study on weight gain of young adult twins revealed the genetic acquisition of obesity. It showed that upon treatment with high-calorie food to the participants (including twins among others) the variance in weight gain was significantly lower in twins, that is, their results were quite similar, compared to others who shared similar BMI, fat percentages, etc. [5]. In simple terms, it can be implied that if two individuals of similar build (fat and muscle ratio) and BMI are taken, then one with obese/overweight parents have a higher chance to become obese/overweight than one with normal parents.

Hereditary obesity, or loosely termed genetic obesity, is sorted as syndromic obesity; that which is clinically associated with Mendelian or chromosomal disorders (such as Down's Syndrome), and non-syndromic obesity; obesity pertaining to mutation followed by metabolic alteration, with no significant effect on mental or physical growth. The non-syndromic genetic obesity, further mentioned in this article, is divided into monogenic and polygenic obesity. Variations in the single gene lead to a monogenic form and many such genes are responsible for obesity development in childhood, whereas polygenic obesity is defined by the participation of many genes or several members of gene families. Polygenic obesity can also have instances of syndromic forms, as several genes are involved [6].

Therefore, genetic factors that are behind obesity are key components in the regulation of metabolism and appetite. Consequently, several pieces of evidence indicated the role of the hypothalamus in metabolism adaptation including behavioral appetite. These genes either show a deletion or certain modifications (mutations) entailing altered metabolic characteristics and thereby increasing the risk of obesity in individuals. Figure 3 provides an overview of the molecular regulation of obesity and genes, when mutated, causing obesity.

To acquire more knowledge about the nature of the inheritance of these genes, comprehensive and thorough investigations are required. Obesity and its associated inheritance largely depend on the bank of data we have on human genetics. Various approaches are adopted to analyze the genes related to obesity, the most prominent being next-generation sequencing (NGS) and genome-wide associated studies (GWAS). GWAS assesses innumerable SNPs (Single Nucleotide Polymorphism) against thousands of polymorphic DNA markers (for obesity) and equates their

Obesity-related genes	Effect on Obesity	Remarks
FTO	Increased appetite and decreases satiety.	Polymorphisms in the obesity-susceptibility gene affect BMI and metabolic processes
Leptin and Leptin receptor (LEPR)	Affects hypothalamus. Decrease appetite and increase energy expenditure	A protein secreted by white adipose tissue crosses the blood-brain barrier. Deficiency in patients caused severe early-onset obesity
Melanocortin- 4 receptor (MC4R)	Activates or inhibits leptin and its receptor	An important role in energy homeostasis and food intake behavior.
POMC deficiency	Appetite-inhibitory gene	Deficient in obese individuals, causes hyperphagia and low resting metabolic rate.
NPY (Neuropeptide Y)	Appetite stimulator	Increase the feeding behavior, body weight and adiposity in rats and limited to humans
Prohormone convertase 1 (PCSK1)	Linked to monogenic early-onset obesity	Responsible for post-translation modification of POMC. Additionally displays postprandial hypoglycemia, hypogonadism, and hypocortisolaemia.
Single-minded homolog 1 (SIM1)	Early onset of obesity and increased sensitivity to a high-fat diet.	Extensive studies on mouse model confirmed positive role in obesity and hyperphagia.
Brain-derived neurotrophic factor (BDNF)	Modulates energy homeostasis affecting food intake	Relatively fewer data are available but is hypothesized to affect obesity.
Ghrelin receptor gene	Regulates various physiological processes, including food intake and energy expenditure	Has opposite effect than leptin. Involved in glucose metabolism, cardiovascular functions, gastric acid secretion and motility, and immune function.
ADRB1, ADRB2, and ADRB3 (b1, 2, 3-adrenergic receptor)	Obesity Phenotypes	Plays a role in the catecholamine-induced energy homeostasis. It helps in the energy expenditure and lipolysis in adipose tissues.

Figure 3: Molecular Genetics of Obesity.

significance in the occurrence of obesity. Presently, around eight genes have been identified as causative of obesity (Figure 3) out of 500 known obesity-related genes [2,6].

One of the important genes associated with hereditary obesity is the FTO gene (Fat Mass and Obesity Associated Gene) which will be specially highlighted here. FTO is one of the first obesity-susceptible genes discovered through GWAS analysis and many validating and consequential studies revealed that FTO SNPs play a significant role in obesity. For instance, the SNPs; rs9939609, rs9930506, rs17817449, and rs12149832, observed in the FTO gene were found to be closely associated with BMI [7]. These associations (of FTO and obesity) have underlying factors involving increased appetite, reduced satiety, and thus compounded consumption of proteins, fat, and energy, all of which led to obesity [2]. Research demonstrated that SNPs in FTO and MC4R were significantly interconnected to BMI and PCOS; a hereditary condition related to hormonal disturbances., which often results in obese/overweight individuals.

Obesity being a multifactorial disease proves to be the causative factor of several other complications in the body. Adult obesity encounters several medical problems which pose a grave issue in the public health crisis. These risks essentially lead to lifestyle diseases encompassing hypertension, type 2 diabetes, osteoarthritis, sleep issues, and most importantly cardiovascular disorders (such as atrial fibrillation or outright heart failure) [8]. Studies have also analyzed certain neurodegenerative diseases associated with obesity, where obese individuals become more susceptible to diseases like Alzheimer's disease or Parkinson's disease. Diet-induced dysfunction in hereditary obesity can exacerbate the development of diseases in individuals carrying genetic variants for obesity. Investigating further, there is evidence that obesity coupled with environmental factors provides a favorable condition for the development of autoimmune diseases; rheumatoid arthritis, Hashimoto's thyroiditis, and inflammatory bowel diseases, to name a few. Obesity causes changes in the body's hormonal balance and structure and has been reported to be a major cause of mortality due to respiratory disorders and/or diabetes mellitus [6]. Obesity is not always the cause of abnormality in the body's function but is sometimes a consequence of a syndrome. Several studies have investigated chromosomal disorders which implicitly directed an individual to develop obesity through behavioral changes. A few of these include Prader–Willi Syndrome (PWS), Down Syndrome, Alstrom Syndrome, and Fragile X Syndrome (FXS) [6].

Figure 4: Portrayal of the associated complications with obesity.

Despite owning an extensive catalog of complications, obesity is manageable. The development of hereditary obesity, though unavoidable, greatly depends on environmental factors. For instance, smoking or a sedentary lifestyle provide gateways for obesity much more efficiently in hereditary obesity than acquired obesity. Genetics accounts for fraction of the variance in obesity and

the rest is controlled by the surroundings. Three broad therapeutic methods for genetic obesity are lifestyle modification, bariatric surgery, and medical treatment (use of hormonal treatment or agonists, like MC4 receptor agonists, depending on the genetic cause). Hyperphagia, being the most common outcome of obesity, can be treated by lifestyle changes [6]. One with genetics for obesity, can reduce the risk of it and manage the body's predisposition to it, by focusing on maintaining a stringent and healthy lifestyle throughout. Managing the external determinants regulating body weight, such as behavioral conduct, consumption of certain substances, or eating habits, may help in preventing obesity. However, such care must be taken meticulously, as individuals with genetic obesity are relatively more susceptible to external factors [9].

Conclusion

Obesity is a condition of the body attributed to abnormally high fat content leading to elevated BMI values. Currently, obesity is extremely common in adults and children. Though prevalent, it is governed by complex interactions of environmental and genetic causes, also contributing to an obesogenic environment. Obesity, which was once thought to be caused by excessive eating, has now shown hereditary evidence. Hereditary obesity is afflicted by genetic mutations in metabolism-regulating genes in the body which are then passed down through generations. Existing advanced studies such as GWAS and NGS, equipped our knowledge on these genes which influence our appetite and metabolism, thus paving way for obesity. For instance, studies have proven that the melanocortin system is crucial for the maintenance of the body's energy balance and thereby is a key element in the development of obesity. Be it hereditary or acquired obesity, the implications on an individual's health are vast, posing serious life-threatening risks. This condition is aggravated by a lack of exercise and improper and unhealthy food consumption. The only way to minimize the consequences of obesity on the body and our life is to maintain a healthy lifestyle, including less or no alcohol/junk food intake, energy expenditure via exercise, and sustaining mental well-being. Obesity inherited from parents requires exclusive caution in these habits since the individuals' bodies have the predisposition to get obese. To conclude, with the aim of managing obesity, keeping the body in shape, both physically and mentally, is crucial for the sustainable results of a healthy lifestyle.

Note

All the figures and table are original and created using the biorender app and MS Wordrespectively.

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