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Journal of Endocrinology Research
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ARTICLE

Evaluation of Genetics of Obesity and MC4R Deficiency: A Gene-oriented Approach to Obesity

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ARTICLE INFO

Article history
Received: 17 March 2021
Accepted: 29 March 2021
Published Online: 31 March 2021

Keywords:
Obesity
Genetics of obesity
MC4R
Mutation

ABSTRACT

Obesity is a multifactorial and complex health problem that is affected by several factors including genetic, environmental, social, behavioural, and biological aspects. Even though the influence of other environmental and behavioural factors such as sedentary lifestyle, high-calorie nutritional intake, and the inadequate expenditure of energy are acknowledged as important aspects that cause obesity, the issue of inheritance is indisputable. The study aims to investigate the effects of inheritance on obesity and examine how understanding and detecting genetic reasons behind obesity may benefit the treatment and prevention of the obesity epidemic. The relationship between common gene variants and obesity is now being studied through the emergence of GWAS. It is undeniable that genetic mutations and gene deficiencies particularly MC4R deficiency are significant factors. The process of detecting genes that create a tendency to obesity is currently being studied. It may be possible to prevent and treat obesity with the detection of certain genes.

1. Introduction

Obesity is a public health concern worldwide. Obesity cases show a significant increase in both developed and developing countries. The disease is now considered an epidemic since it threatens public health in a global sense. Not only obesity influence societies in terms of health, but also social and economic terms [1]. Obesity is known to be a factor that induces several other diseases such as stroke, hypertension, reflux, several cancer types, liver cirrhosis, T2D, depression, etc. Therefore, it is argued that obesity decreases average lifetime [2 3 4]. Exercise has many beneficial effects, leads to less telomere attrition and may diminish the risk of cancer, these two outcomes are possible resulted by a reduction in oxidative stress and chronic inflammation [5]. Hippocrates was the first to recognize the need for a balanced diet and exercise and the fact that different age has different needs [6]. Hippocrates' innovative spirit laid the foundations of modern medicine and the wellbeing movement: Exercise Is Medicine (EIM) ®, which has been inspired-adopted by scientific institutions such as the American College of Sports Medicine (ACSM), the American Medical Association (AMA) and Harvard Medical School [7].

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 DOI: https://doi.org/10.30564/jer.v3i1.2977

Obesity is a multifactorial and complex health problem. Even though a wide number of studies indicate that genetics played a role for 40 to 70% of obese patients by provoking weight gain, it cannot be suggested that genetics only cause this disease [8 9]. Obesity is affected by several factors including genetic, environmental, social, behavioural, and biological aspects. In this sense, it is important to emphasize that one factor only does not directly lead to obesity. For instance, it is possible for an individual who has a genetic tendency to obesity, to stay healthy and have a normal BMI by adjusting their physical and nutritional habits [10]. In fact, in a study, Xiang et al. compared those who carry a genetic variant that may cause obesity and the control group without the variant. The study indicated that following the right nutrition program and with adequate physical activity, a person with the genetic variant can reach a normal weight and live a healthy life [11]. For this reason, while it is severely important to examine the impact of inheritance on obesity, it is also important to understand the interaction of the genes with the environment and other aspects.

1.1 Types of Obesity

In a general sense, obesity can be divided into categories based on its etiology. These categories include monogenic obesity, syndromic obesity, and polygenic/common obesity. Monogenic obesity, which is also known as single gene obesity, is not a common but quite severe type of obesity. The reason for monogenic obesity is a single gene mutation or deficiency. Syndromic obesity is considered to be linked to mental retardation and certain abnormities in the development of organs. Polygenic obesity is caused by multiple polymorphic genes. It is a common type of obesity that is known to be seen more frequently in society and increases the risk for other diseases [12].

1.2 Genetic Basis of Obesity

The importance of inheritance in the practice of medicine and community health has gained quite significance. Since inheritance is considered an issue significant to community health, genetics pose a crucial factor for urgent health problems that threaten people's health. Obesity, being of those public health problems, is considered a

Table 1. Single genes are known to be linked to obesity

NAME	GENE	MIM	MODE of INHERITANCE	CHROMOSOMAL POSITION
Leptin	*LEP*	164160	AR	7q32.1
Leptin receptor	*LEPR*	601007	AR	1p31.2
Proopiomelanocortin	*POMC*	176830	AR	2p23.2
Melanocortin 4 receptor	*MC4R*	155541	AD/AR	18q21.32
Single-minded Drosophila Homologue-1	*SIM1*	603128	AD	6q16.3
Nurotrophic Tyrosine Kinase Receptor Type 2	*NTRK2*	600456	AD	9q21.33
Kinase suppressor of Ras2	*KSR2*	610737	AD	12q24.22-q24.23
Carboxypeptidase	*CPE*	114855	AD	4q32.3
Proconvertase 1	*PCSK1*	162150	AR	5q15
Brain Derived Neurotropic factor	*BDNF*	113505	AD	11p14.1
SH2B adaptor protein	*SH2B1*	608937	AD	16p11.2
Tubby, Homogue of Mouse	*TUB*	601197	AR	11p15.4

AD= Autosomal dominant, AR = Autosomal recessive.

For detailed information and references, refer to Online Mendelian Inheritance in Man using the MIM number: https://www.omim.org

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DOI: https://doi.org/10.30564/jer.v3i1.2977

severe risk factor for other diseases such as coronary heart disease (CHD) [14 15].

The fact that obesity has a genetic origin is indisputable. Even though the influence of other environmental and behavioural factors such as sedentary lifestyle, high-calorie nutritional intake, and the inadequate expenditure of energy are acknowledged as important aspects that cause obesity, the issue of inheritance is a considerable factor.

Earliest findings of the association between obesity and inheritance date back to 2007 [16 17]. Along with the improvements in technic and analysis methods, genome-wide association studies (GWAS) started. GWAS is an approach that helps scientists to reveal and discover the genetic reasons behind certain diseases. According to GWAS, common variants altogether can pass on through the family (International HapMap Consortium, 2005) [18]. With this information, scientists were able to detect nearly 80% of common gene variations [19 20].

1.2.1 MC4R Deficiency

The melanocortin-4-receptor (*MC4R*) is encoded by the MC4R gene. It is a G-protein coupled seven-transmembrane receptor G protein-coupled receptor and is proven to be associated with obesity disease. It regulated the nutritional behaviour in the hypothalamus [22]. α-melanocyte-stimulating hormone (α-MSH) binds and activates MC4R and this helps control appetite. Appetite regulation is linked to MC4R [23]. Thus, one of the most common reasons for obesity based on genetics is certain mutations in MC4R. This type of obesity is quite prevalent in societies at a rate of 0.5-6% [24 25 26].

2. Discussion

Many researchers are studying genetics' influence on obesity and twin studies are quite common. These studies suggest that a similar phenotype is observed in the other twin or either of the parents, indicating the inheritability of obesity [27 28 29]. According to several studies conducted on families, twins, and adopted family members, BMI is affected by genetics by 70-80% [30 31 32 33]. Similar findings are seen in studies conducted on societies from various ethnic groups [34].

According to the studies in the field of epidemiology, as the degree of affinity lowers, so does the risk of obesity. Therefore, it is argued that inheritance is an important factor. In twin studies, it is indicated that dizygotic twins demonstrate a concordance rate by less than half of the monozygotic twins (~ 0.68 vs~0.28) [35 36].

Similarly, in studies conducted on families with adopted children, it was observed that the adopted children's BMI is more proximate to their biological parent compared to the BMI of their legal parents. This significantly emphasizes that environmental factors such as a mutual home environment are still important but the influence of inheritance on obesity is undeniable [37 38].

Farooqi et al. examined the MC4R deficiency or mutations and obesity relationship in a study conducted with families. Endocrine and metabolic analyses were performed on subjects. The study reported that 5.8% of the patients that suffered from obesity showed MC4R mutations. Farooqi et al. indicated in this wide-ranging study that the monogenic type of obesity is associated with MC4R deficiency. However, it is noted that in similar studies conducted on diverse ethnic populations, this rate

Table 2. Comparison of phenotypic features of monogenic forms of obesity

Gene	Obesity	Birth weight	Endocrine abnormalities	Hyperphagia	Inheritance	Chromosome
LEP	Severe	Normal	Low leptin Hypogonadism High thyroid-stimulating hormone High insulin	+	Recessive	7q31.3
LEPR	Severe	?	High leptin Pituitary dysfunction Hypogonadotrophic hypogonadism Hypothalamic hypothyroidism Sympathetic dysfunction High insulin	+	Recessive	1p31
POMC	Severe	Normal	Red hair pigmentation ACTH deficiency, hypocortisolism Lowa-MSH	+	Recessive	2p23.3
PC1	Severe	?	Hypogonadotrophic hypogonadism Hypocortisolism High proinsulin, low insülin Postprandial hypoglycemia High POMC	?	Recessive	5q1.5–2.1
MC4-R	Severe	Normal	Not observed	+	Dominant	18q22
NROB2	Mild	High	Mild hyperinsulinemia	-	Dominant	1p36.1

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 DOI: https://doi.org/10.30564/jer.v3i1.2977

was lower [39].

Bonnefond et al. reported that even though obese individuals that have monogenic MC4R mutations are suitable for bariatric operations. These patients lose less weight after the operation compared to people that have common obesity. Bonnefond et al. Lapsen et al. [40 41] Collet et al. conducted a study on patients with MC4R mutations and a control group. While the group carrying the mutation was treated with Setmelanotide which is known to be an MC4R agonist, they lost an average weight of 3,5 kilograms. However, the control group receiving placebo treatment lost 0,85 kilograms within the same period [42].

3. Conclusions

Obesity is a multifactorial epidemic and it is the result of various factors. Genetics plays a crucial role in the occurrence of the disease. The relationship between common gene variants and obesity is now being studied through the emergence of GWAS. Regarding our extensive literature review, it is understood that it is undeniable that genetic mutations and gene deficiencies particularly MC4R deficiency are significant factors. The process of detecting genes that create the tendency to obesity is currently being studied. It may be possible to prevent and treat obesity with the detection of certain genes. Investigation of genetic factors on obesity should be further studied for future and current patients to maintain a healthier life.

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