Genetics in obesity

Predyspozycje genetyczne rozwoju otyłości

INTRODUCTION

The prevalence of overweight and obesity is escalating rapidly worldwide, emerging as one of the most serious public health challenges (1). Worldwide, roughly 40% of adults are overweight and 10-15% are obese (2). Overweight and obesity, respectively are associated with high risk of many chronic diseases, inclusive of type 2 diabetes, cancer, cardiovascular events (3, 4). The prodigious effort in the search to understand the physiological basis of obesity still needs to be taken.

Obesity emerges from the interactions between genetic profile and environmental risk factors. For instance, some of the “obesogenic environment” features are physical inactivity, excessive caloric intake, what results in an imbalance between energy intake and expenditure, and other such as medications, socioeconomic status, and feasibly novel factors like endocrine disruptors, the gastrointestinal microbiome or deficiency of sleep (5, 6). It is said that environmental factors are major causes of the obesity epidemic. The relative contribution between environmental aspects and genetic predisposition is still poorly understood. Wide interindividual discrepancy in body-mass index (BMI, the weight in kilograms divided by the square of the height
in meters) observed under comparable environmental conditions can only be ascribed to a genetic susceptibility to the condition. Therefore, obesity emerged as one of the most heritable human traits. However, this heritability can be inflicted by various environmental factors (7). The comprehension of the genetic causes linked to obesity susceptibility may explain some of the underlying biology and may give rise to possible prevention and new treatments methods. Although, studies that involve twins and family subjects, have suggested that 40-70% of the interindividual discrepancy in obesity risk and BMI can refer to genetic factors, the exploration of obesity susceptibility loci has only recently started to be prosperous (8, 9).

**REVIEW**

**Monogenic obesity**

Monogenic obesity is a complex term that refers to a number of uncommon forms of severe obesity, which is associated with mutations with large effect size in a particular gene or chromosomal region (tab. 1). Studies of monogenic forms of obesity underlying its genetic basis has made a considerable contribution to understanding of the pathogenesis of obesity and has outlined potential pathways and mechanisms involved in the development of this disorder (10). Furthermore, performed study of monogenic obesity, by emphasizing the influence of neurological factors to its development, has also amended our approach to obesity as an endogenous condition (7). The earliest evidence of individual-gene mutations that result in an increased susceptibility to obesity came from animal research. It was followed by discovery of the leptin gene and its receptor, what embarked on rare research activity in the field of the molecular and physiological basis of obesity and led to the expression of the hypothalamic leptin-driven melanocortin signaling pathway as the principal mechanism for the regulation of energy balance, appetite and body weight. Many of the known monogenic and some of the polygenic causes of obesity are related to alterations in the melanocortin pathway (11). Mild to extreme obesity phenotype in human population has been associated with mutations in leptin and leptin receptor genes (12-14). Uncommon homozygous mutations within leptin gene have also been identified in patients with severe early-onset obesity, which indicates of the importance of the leptin-melanocortin pathway in hyperphagia and obesity susceptibility (15). Autosomal-dominant forms of obesity can also be caused by mutations located in the gene that encodes MC4R (16). MC4R plays a substantial role in the regulation of food intake and energy homeostasis. Roughly 5% of extremely obese children carry mutations in the MC4R gene (17). Loss-of-function mutations in POMC have been associated with severe early-onset obesity coupled with a characteristic red-hair pigmentation in afflicted individuals (18).

**Common obesity**

Polygenic obesity known as “common obesity”, with its genetic background attributable to multiple susceptibility loci, acts in concert with environmental risk factors. The individual effect size of these contributing variants is rather small and so far can clarify only 2.7% of the BMI variation (7, 19). The discovery of the FTO (fat mass and obesity associated gene) was the first major breakthrough from three independent genome-wide association studies, becoming the locus that appeared to be consistently interrelated with common obesity (20). To date, the FTO locus is still the locus with the largest effect on BMI (9). Currently the most informative tool in studying polygenic diseases, including obesity, are genome-wide association studies (GWAS) focusing on finding variants associated with phenotype of the disease across whole genome, on large scale cohorts.

**Genome-wide association study**

Technology progress made genotyping individuals faster and low-priced, what means that researchers can focus on studying the majority of the common variants in the whole genome and in more individuals with the use of genome-wide association studies (GWAS). Currently genome-wide association studies are the most commonly used method to identify new loci associated with a trait or disease (9). A lot of genes implicated in monogenic obesity are in or near loci subsequently discovered by GWAS to be associated with obesity related traits, for instance MC4R, POMC, PCSK1, BDNF, SH2B1, LEPR, NTRK2 (21). Genome-wide association studies have focused on various obesity-related traits such as BMI, WHR (waist to hip ratio), as well as obesogenic environmental and lifestyle interactions such as diet, physical activity, age. 97 loci for BMI (among FTO, NEGR1, TMEM18, MC4R genes, for instance) where 56 of them were novel, has been identified by the Genetic Investigation of ANthropometric Traits consortium (GIANT) meta-analysis (19, 22, 23). A large-scale GWAS meta-analysis identified 49 loci for WHR adjusted for BMI (24).

### Tab. 1. Genes associated with monogenic (a) and common (b) obesity (7, 25)

<table>
<thead>
<tr>
<th>(a) Gene</th>
<th>Chromosomes position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin (LEP)</td>
<td>7p32.1</td>
</tr>
<tr>
<td>Leptin receptor (LEPR)</td>
<td>1p31.3</td>
</tr>
<tr>
<td>Proprotein convertase subtilisin/kexin type 1 (PCSK1)</td>
<td>5q15</td>
</tr>
<tr>
<td>Melanocortin 4 receptor (MC4R)</td>
<td>18q21.32</td>
</tr>
<tr>
<td>Pro-opiomelanocortin (POMC)</td>
<td>2p23.3</td>
</tr>
<tr>
<td>Single-minded homolog 1 (SIM1)</td>
<td>6q16.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) Gene</th>
<th>Chromosomes location</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTO</td>
<td>16q12.2</td>
</tr>
<tr>
<td>MC4R</td>
<td>18q21.32</td>
</tr>
<tr>
<td>NPC1</td>
<td>18q11.2</td>
</tr>
<tr>
<td>MAF</td>
<td>16q23.1</td>
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As an influential and successful approach, genome-wide association studies certainly will discover more sensitive genes or single nucleotide polymorphisms (SNPs) that influence body mass index and the risk of obesity in the future (14). A deep understanding of how identified locus affects phenotype is indispensable before genetic findings can be used to improve human health (23). The main obstacle in finding important signals in GWAS in aspect of polygenic diseases, including obesity, is still too low number of patients included in analyzes, which is major challenge in discovering new, significant loci.

CONCLUSIONS

The identification of genes that are involved in monogenic and polygenic obesity has greatly increased our knowledge of the mechanisms that underlie this condition. As is the case with other complex diseases, a substantial portion of the predicted heritability of obesity and inter-individual variability in BMI remains unexplained. The identification of new loci is only the beginning point of a new series of research to increase our understanding of the biological pathways they are involved in. There is no doubt that more genes and genetic loci associated with obesity remain to be discovered, given that currently only a fraction of the heritability is explained by the established loci. Genome-wide association studies have provided a remarkably valuable contribution to the field of obesity genetics with the discovery of a large number of genetic loci robustly associated with various obesity-related traits and generating new hypotheses to be tested in the future studies.

BIBLIOGRAPHY


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