DOI: https://doi.org/10.25121/PNM.2018.31.2.117 Post N Med 2018; XXXI(2): 117-119

*Elwira Siewiec[1], Urszula Puchta[1], Lukasz Szczerbinski[1], Anna Citko[2], Hady Razak Hady[3], Adam Jacek Kretowski[1, 2]

Genetics in obesity

Predyspozycje genetyczne rozwoju otyłości

[1]Department of Endocrinology, Diabetology and Internal Medicine, Faculty of Medicine, Medical University of Bialystok, Poland
[2]Clinical Research Center, Faculty of Medicine, Medical University of Bialystok, Poland
[3]I[st] Department of General and Endocrinological Surgery, Faculty of Medicine, Medical University of Bialystok, Poland

Keywords
obesity, genome-wide association study, genetics, genome, body mass index

Słowa kluczowe
otyłość, GWAS, genetyka, genom, BMI

Conflict of interest
Konflikt interesów
None
Brak konfliktu interesów

Address/adres:
*Elwira Siewiec
Klinika Endokrynologii, Diabetologii
i Chorób Wewnętrznych
Uniwersytecki Szpital Kliniczny
w Białymstoku
ul. Marii Skłodowskiej-Curie 24a
15-276 Białystok
tel. +48 (85) 831-81-56
elwira.siewiec@umb.edu.pl

Summary

Obesity is one of the biggest problems of modern medicine. Recently it has evolved from epidemic to a global pandemic. Previously obesity was generally considered as a disease induced mostly by environmental factors but in recent years a lot of studies has shown that genetics may play important role in the development of the disease.

In this review we describe current knowledge of the genetics of obesity. We discuss monogenic forms of obesity, characterize polygenic or "common" obesity, and emphasize genome-wide association studies for obesity-related traits, which provided new insights into the genetics and physiology of obesity.

Pubmed was searched for articles relevant to genetic background of obesity published between 2005 and 2018. Some earlier applicable articles were also consulted.

Knowledge of obesity genetics has still to be explored, to enable an understanding the molecular mechanisms of a disorder that affects hundreds of millions of people, providing new advances in the management of a disease for which no effective treatment, apart from surgery, currently exists.

Streszczenie

Otyłość jest jednym z najistotniejszych problemów współczesnej medycyny na całym świecie. Dotychczas uważano, iż rozwój otyłości jest ściśle uwarunkowany czynnikami środowiskowymi, jednak aktualne badania wykazały znaczenie genetycznych czynników w rozwoju choroby.

Praca poglądowa przedstawia aktualny stan wiedzy na temat genetycznych predyspozycji rozwoju otyłości. Przedyskutowano mono- i poligenową formę otyłości oraz podkreślono znaczenie badań asocjacyjnych całego genomu (GWAS), które dostarczają nowych informacji dotyczących patomechanizmu choroby.

Baza Pubmed została przeszukana pod względem artykułów odnoszących się do tematu podłoża genetycznego rozwoju otyłości, które ukazały się w latach 2005-2018.

Niezbędne jest dalsze pogłębianie wiedzy z zakresu genetyki otyłości, co pozwoli na zrozumienie mechanizmów molekularnych rozwoju choroby, która dotyczy milionów ludzi na całym świecie, jednocześnie pozwalając na rozwój nowoczesnych sposobów leczenia.

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 inflected 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 explication 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).

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

(a) Gene	Chromosomes position
Leptin (LEP)	7q32.1
Leptin receptor (LEPR)	1p31.3
Proprotein convertase subtilisin/kexin type 1 (PCSK 1)	5q15
Melanocortin 4 receptor (MC4R)	18q21.32
Pro-opiomelanocortin (POMC)	2p23.3
Single-minded homolog 1 (SIM1)	6q16.3
(b) Gene	**Chromosomes location**
FTO	16q12.2
MC4R	18q21.32
NPC1	18q11.2
MAF	16q23.1

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).

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

1. Roberto CA, Swinburn B, Hawkes C et al.: Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. Lancet 2015; 385: 2400-2409.
2. NCD Risk Factor Collaboration (NCD-RisC): Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016; 387: 1377-1396.
3. Kopelman P: Health risks associated with overweight and obesity. Obes Rev 2007; 8(1): 13-17.
4. Calle EE, Rodriguez C, Walker-Thurmond K et al.: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348(17): 1625-1638.
5. Maes HH, Neale MC, Eaves LJ: Genetic and environmental factors in relative body weight and human adiposity. Behav Genet 1997; 27: 325-351.
6. French SA, Story M, Jeffery RW: Environmental influences on eating and physical activity. Annu Rev Public Health 2001; 22: 309-335.
7. El Sayed Moustafa JS, Froguel P: From obesity genetics to the future of personalized obesity therapy. Nat Rev Endocrinol 2013; 9: 402-413.
8. Stunkard AJ, Foch TT, Hrubec Z: A twin study of human obesity. JAMA 1986; 256: 51-54.
9. Day FR, Loos RJF: Developments in obesity genetics in the Era of Genome--Wide Association studies. J Nutrigenet Nutrigenomics 2011; 4: 222-238.
10. Walley AJ, Asher JE, Froguel P: The genetic contribution to non-syndromic human obesity. Nature Rev Genet 2009; 10: 431-442.
11. Oswal A, Yeo G: Leptin and the control of body weight: a review of its diverse central targets, signaling mechanisms, and role in the pathogenesis of obesity. Obesity (Silver Spring) 2010; 18: 221-229.
12. Clement K, Vaisse C, Lahlou N et al.: A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998; 392(6674): 398-401.
13. Fischer-Posovszky P, von Schnurbein J, Moepps B et al.: A new missense mutation in the leptin gene causes mild obesity and hypogonadism without affecting T cell responsiveness. J Clin Endocrinol Metab 2010; 95(6): 2836-2840.
14. Cheung WW, Mao P: Recent advances in obesity: genetics and beyond. ISRN Endocrinol 2012; 2012: 536905.
15. Saeed S, Butt TA, Anwer M et al.: High prevalence of leptin and melanocortin-4 receptor gene mutations in children with severe obesity from Pakistani consanguineous families. Mol Genet Metab 2012; 106: 121-126.
16. Bell CG, Walley AJ, Froguel P: The genetics of human obesity. Nat Rev Genet 2005; 6: 221-234.
17. Farooqi IS, Keogh JM, Yeo G et al.: Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med 2003; 348: 1085-1095.
18. Krude H, Gruters A: Implications of proopiomelanocortin (POMC) mutations in humans: the POMC deficiency syndrome. Trends Endocrinol Metab 2000; 11: 15-22.
19. Locke AE, Kahali B, Berndt SI et al.: Genetic studies of body mass index yield new insights for obesity biology. Nature 2015; 518: 197-206.
20. Frayling TM, Timpson NJ, Weedon MN et al.: A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007; 316: 889-894.
21. Pigeyre M, Yazadi FT, Kaur Y et al.: Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clin Sci 2016; 130: 943-986.
22. Speliotes EK, Willer CJ, Berndt SI et al.: Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 2010; 42: 937-948.
23. Goodarzi MO: Genetics of obesity: what genetic association studies have taught us about the biology of obesity and its complications. Lancet Diabetes Endocrinol 2018; 6: 223-236.
24. Shungin D, Winkler TW, Croteau-Chonka DC et al.: New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015; 518: 187-196.
25. Saeed S, Arslan M, Froguel P: Genetics of Obesity in Consanguineous Populations: Toward Precision Medicine and the Discovery of Novel Obesity Genes. Obesity 2018; 26(3): 474-484.

received/otrzymano: 2.03.2018
accepted/zaakceptowano: 26.03.2018