REVIEW

From genetics and epigenetics to the future of precision treatment for obesity

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Abstract

Obesity has become a major global health problem, epitomized by excess accumulation of body fat resulting from an imbalance between energy intake and expenditure. The treatments for obesity range from modified nutrition and additional physical activity, to drugs or surgery. But the curative effect of each method seems to vary between individuals. With progress in the genetics and epigenetics of obesity, personalization of the clinical management of obesity may be at our doorstep. This review presents an overview of our current understanding of the genetics and epigenetics of obesity and how these findings influence responses to treatments. As bariatric surgery is the most effective long-term treatment for morbid obesity, we pay special attention to the association between genetic factors and clinical outcomes of bariatric surgery. Finally, we discuss the prospects for precision obesity treatment.

Key words: morbid obesity; genetics; epigenetics; bariatric surgery

Introduction

Metabolic diseases, especially obesity, have become a serious chronic disease affecting human health. Generally, obesity is epitomized by excess accumulation of body fat resulting from an imbalance between energy intake and expenditure. Ranging from lifestyle adjustment to medication and even surgery, various weight-loss programs have emerged in response; however, other than bariatric surgery, which is comparatively a more effective long-term treatment for morbid obesity [1], most other treatments are barely satisfactory. Even the effects of surgery vary between different individuals; under such circumstances, a lot of patient undergoing surgery might experience substantial short-term weight loss but later regain some or all of that weight. It should be noticed that the body weight loss after

surgery varies from person to person [2]. Almost 20% of patients fail to achieve or maintain sufficient weight loss [3].

For these reasons, it is important to establish a method of screening the most suitable subjects for surgery, as well as other candidate treatments. Currently, without a full understanding of the reasons behind this variability, there is no practicable method of profiling patients to predict the outcome; only with a more accurate method of classifying patients could we implement more effective, personalized treatment. Although these clinical, demographic, psychological, and surgical predictors, such as age, sex, baseline weight and so on, have been used for predicting the variation of the therapeutic effects of surgery, these phenotype factors explain only a small part of the variation and fall short of identifying patients with good efficiency

[4, 5]. There has been consensus in academia that not only the phenotype but also the genotype should be used for customized treatment. With progress in the understanding of the genetics and epigenetics of obesity, more studies have been carried out to identify the association between outcomes and treatments in order to implement more personalized therapeutic options.

Numerous studies on the genetics of obesity have been reported. Researchers have found that the body mass index (BMI) can be influenced by genetic variations in the melanocortin 4 receptor (MC4R), neuropeptide Y receptor Y2 (Npy2R), fat mass and obesity-associated (FTO) and neuropeptide FF receptor 2 (NPFFR2) in adult populations [6]. For paediatric obesity, a recent study suggested that the leptin receptor (LEPR) and protein kinase C (PRKCH) could influence the obesity of infants [7]. A great number of in-depth studies of these main genes can be found. A study of nearly 250 000 individuals and 2.8 million polymorphisms confirmed 14 loci that were already known to be associated with BMI and revealed 18 new loci [8]. Another meta-analysis of associations between BMI and approximately 2.4 million single nucleotide polymorphisms (SNPs) was conducted among 27 715 East Asians, and identified 10 BMI-associated loci at the genome-wide significance level [9]. Findings from these studies may shed light on new pathways involved in obesity. Still many pathways warrants further clarification. The proposed molecular mechanism that could mediate this control is epigenetics.

Epigenetics is the study of changes in DNA that regulate gene expression patterns without alterations in the nucleotide sequence, which are potentially transmitted to an individual's descendants [10]. As to obesity, the epiobesigenic genes also play important roles, including controlling processes such as adipogenesis, inflammation, appetite and glucose tolerance [11]. Development of high-throughput techniques made epigenetic-wide association studies (EWAS) a reality, which helps us to find new loci of obesity. Dick et al. conducted an analysis of 450 million CpG (5′-C-phosphate-G-3′) sites, and made an association between BMI with raised DNA methylation at hypoxia-inducible transcription factor 3A (HIF3A) [12]. Another study of 4 million CpG sites in 74 individuals showed that variable methylated regions may be used in the prediction of disease [13]. Furthermore, a twin-based study has shown an association between the serotonin transporter SLC6A4 promoter hyper-methylation in blood leucocytes, and increased BMI and waist circumference levels [14].

Personalized Obesity Treatment by Nutrition, Physical Activity and Drugs

Nutrition

Obesity is epitomized by excess accumulation of body fat resulting from an imbalance between energy intake and expenditure; thus an inappropriate amount of nutrition plays an important role in the development and progression of obesity. Several studies have provided evidence for the influences of nutrients and bioactive foods on the interaction between genome and epigenome [15]; for example, some nutrients and bioactive foods can regulate epigenetic processes by inhibiting enzymes, such as DNA methyltransferases and histone de-acetylases [15]; vitamin B12 and folate provide methyl groups for DNA methylation reaction [16, 17].

Since there is variability in metabolic responses to diet and food components in individuals, more studies have been conducted in the past few years, aimed at developing diagnostic tools based on genetic susceptible loci to provide a personalized

diet. One study found that the AA risk allele of the rs9939609 was associated with an excessive intake of fat and low fibre intake [18]. Another research showed that several obesity susceptibility genes influence the intake of dietary carbohydrates to increase BMI [19].

Above all, a personalized dietary intervention is a helpful preventative, but limitations exist in there having been insufficient studies, in ethnic background, and in the high cost of this form of intervention. Meanwhile the challenge may be that compliance with nutrient-based recommendations has been very poor.

Physical activity

It is known that regular exercise can prevent weight gain and reduce weight. Several studies have shown that physical activity can reduce the effects of FTO variants with obesity [20–22]. Another study found that physical activity could reduce the effect of the A risk allele of rs9939609, which could increase the odds ratio of obesity [23].

However, the propensity to do physically activity also has a strong genetic component: parents who are more physically active have more active children, relative to parents who avoid exercise. It seems that variations in genes could have an impact on variations in the level of physical activity. One investigation found that there is an association between common polymorphisms in the MC4R gene and self-reported physical inactivity [24, 25]; thus, more studies about the shortfall of physical activity may help to elucidate its role in the development of obesity.

Drugs

Individuals with a BMI greater than $30 \, kg/m^2$, with existing comorbidities such as diabetes, dyslipidaemia or hypertension could use drugs as a treatment for obesity. Up to now, only five drugs to combat obesity have been approved for continuous use in the USA—orlistat, lorcaserin, liraglutide, phentermine/topiramate, and bupropion/naltrexone [26]. In these drug treatments, significant consideration needs to be given to factors such as drug interactions, the risk of negative collateral effects and individualized treatments based on genetic make-up.

In the near future, with the development of pharmacogenetic and nutrigenetic strategies, it may be possible to allow more effective personalized pharmacological intervention. Pharmacogenetic studies should be conducted to identify differences in drug response, gene regulation, and epigenetic modifications, which could explain individual differences in responses to drugs beyond genetic variation.

Personalized Obesity Treatment by Bariatric Surgery

Bariatric surgery is the most effective long-term treatment for morbid obesity [1]. It results in a significant reduction in body weight, accompanied by improvement of several risk factors for cardiovascular disease [27]; however, patients do not all lose the same percentage of weight or enjoy the same clinical benefits after surgery.

The effects of candidate genes on the outcomes of bariatric surgery

The effect of different polymorphisms after bariatric surgery is an interesting area of investigation. Gene variants may

determine the outcomes of obesity treatment. As laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG) and bilio-pancreatic diversion (BPD) are the major bariatric procedures, we will begin our review according to the different types of surgery.

LAGB is a therapeutic method of inducing a durable weight loss in obese patients [28]. Some studies have focussed on whether genetic factors of body weight homeostasis may account for differences in the therapeutic effects of LAGB. One study of 167 unrelated obese subjects, with a 6-month follow-up, showed that carriers of the G-174G IL-6 genotype had lost more weight than those with G-174C or C-174C. Carriers of the A866A uncoupling protein 2 genotype lost more weight after LAGB than those with G866G; however, the researchers did not observe that, after LAGB, there was any statistically significant difference in subjects with obesity carrying the Gly972Arg polymorphism of the insulin receptor substrate-1 (IRS1) gene and Pro12Ala polymorphism of the peroxisome-proliferator-activated receptor (PPARG) gene, when compared with non-carriers [27]. Another study showed similar effects [29]. Sarzynski *et al.* tested the association of SNPs in 11 obesity candidate genes, including ADIPOQ, BDNF, FTO, GNB3, LEP, LEPR, MC4R, NR3C1, PPARG, PPARGC1A and TNF, with weight loss and weight regain: among the 11 SNPs, only FTO rs16945088 was associated with maximum weight loss after gastric banding [30]. To our knowledge, Chen *et al.* performed the first study of genetic susceptibility testing in weight-loss prediction in the Chinese population, while most other studies were performed in Caucasian populations [31]; they found that the rs660339 (Ala55Val), on exon 4 of the uncoupling proteins 2 (UCP2), was associated with morbid obesity ($P = 0.049$), and played an important role in obesity development and weight loss after LAGB. These results suggest that genetic markers may be useful new clinical tools to guide obesity therapies.

RYGB is an effective therapy for patients with extreme obesity [32]. In a study of 1011 white individuals who underwent RYGB surgery, the variants in or near obesity genes, such as FTO (fat mass and obesity-associated), INSIG2 (insulin induced gene 2), MC4R (melanocortin 4 receptor), and PCSK1 (proprotein convertase subtilisin/kexin type 1), were associated with poorer weight loss outcomes after RYGB [33]. Another study of 1433 RYGB patients who were studied for 2 years before and after surgery showed that patients with the MC4R (I251L) common allele could achieve better weight loss over a longer period after surgical interventions [34].

LSG has become increasingly popular around the world since 2000 [35]. LSG has been an effective, stand-alone therapy for morbidly obesity, with stable weight loss and resolution of obesity-associated comorbidities [36, 37], but there have been few studies of the association between genetic factors and the outcomes of LSG. In 2016, Shanti *et al.* found that, after LSG, patients in the family group, in which patients had a family member who has undergone LSG, experienced significantly greater weight loss than the control group, while family members living together showed no advantage over those who lived separately [38]. This suggests that genetic factors may have a great influence on the outcomes of LSG. Another study aimed to explore the effects of the rs9939609 FTO gene polymorphism after LSG [39]. Although the rs9939609 FTO gene polymorphism was thought to have a positive effect on weight loss after lifestyle intervention, LAGB and BPD, the studies did not find any differences between mutant and wild-type groups after LSG [40–42]. More studies are needed to evaluate the association between genetic factors and the outcomes of LSG.

BPD is a mixed operation that has shown good results regarding weight loss [43]. De Luis *et al.* have made numerous studies to evaluate the influence of genetic factors on the outcomes of BPD in obese patients; they did not find that polymorphism Ala54Thr of FABP had any effect on clinical outcomes [44]. A similar conclusion was reached in the study of G308A polymorphism in the TNF-alpha gene, the polymorphism 55CT of UCP3 [45, 46], while another study by the team showed that weight loss was greater in subjects with the mutant group of leptin receptor gene (Lys656Asn and Asn656Asn) than in those with the wild-type group (Lys656Lys) [47]. They found that the rs6923761 gene variant in the gucagon-like peptide 1 receptor gene did have an effect on clinical outcomes after BPD, with a greater weight loss, at 12 and 18 months, in patients with the GG variant than in patients with the A allele [48].

The studies above suggest that different types of bariatric surgery may interact with particular gene variants. Chen *et al.* found that the rs660339 (Ala55Val), on exon 4 of the uncoupling proteins 2 (UCP2), was associated with morbid obesity; however, this phenomenon was not observed in patients after laparoscopic mini-gastric bypass [31]. Sarzynski *et al.* performed a study estimating the effect of genetic factors on the outcome of the obesity surgery in 1443 patients (vertical banded gastroplasty: $n = 966$; banding: $n = 293$; gastric bypass: $n = 184$) [30]. Of the 11 SNPs, only FTO rs16945088 was associated with maximum weight loss after gastric banding: this phenomenon was not observed in patients after other types of the surgery. It seems that different types of bariatric surgery may take effect by different pathways, and this trait may help in choosing the most suitable type of surgery for individual patients.

Genome-wide association studies on bariatric surgery

With advances in genetic technology and the huge number of bariatric surgeries, it is feasible to perform genome-wide association studies (GWAS) of the variable clinical outcomes of bariatric surgery. These GWAS studies suggest that genetic variation can affect weight loss after surgery.

Hatoum *et al.* have done several studies on this subject and provided persuasive evidence suggesting that there are strong genetic determinants of weight loss after RYGB [49, 50]. In a cohort study of 848 patients, by comparing weight loss after RYGB within pairs of genetically related and genetically unrelated individuals, they found similar weight loss within pairs of related individuals, whereas unrelated individuals exhibited far less similarity in weight loss outcomes after the same procedure [49]. Since part of this effect might be mediated through environmental factors, they also identified pairs of genetically unrelated individuals who were living together and found that their weight loss after RYGB was no more similar than completely unrelated pairs of individuals—and much greater than between first-degree relatives [49]. To identify genetic factors contributing to weight loss, the team performed a GWAS study of 693 genetically unrelated individuals undergoing RYGB and then replicated this analysis in an independent population of 327 individuals [50]. They found that a 15q26.1 locus near ST8SIA2 and SLCO3A1 was significantly associated with weight loss. An animal study performed later supported the above conclusion [50]. These findings provide strong evidence for specific genetic influences on weight loss after RYGB and underscore the biological nature of the response to this type of surgery.

In a cohort of 1143 patients, by comparing 86 obese patients who had the least percentage excess body weight loss (%EBWL) and 89 patients who had the greatest %EBWL at 2 years after

RYGB surgery, Rinella et al. tried to identify genetic factors contributing to this weight loss [51]. The first-stage cohort was genotyped for 730, 767 SNPs, and 111 SNPs were identified. In the validation stage, among these 111 SNPs, 17 SNPs are the most significant, covering 6 genes/regions: PKHD1, IPO11/HTR1A, CITED2/NMBR, GUCY1A2, IGF1R, and CENPF/KCNK2. In another examination of 34 obesity- and waist-to-hip ratio (WHR)-associated SNPs, rs4771122 in an intron of MTIF3 was the most significantly associated SNP with long-term weight loss after surgery [52]. Like most GWAS studies to date, the mechanism of action of rs4771122 through MTIF3 on obesity or weight loss after surgery is unknown. All these studies suggested that genetic variation can affect weight loss after surgery.

The genetic risk score predicting the clinical outcome of bariatric surgery

Genetic risk score (GRS) describes the collective impact of several potentially risk-contributing SNPs by creating one continuous variable that indicates the likelihood of developing a disease or a trait, such as weight loss [53]. GRS is calculated in a weighted or unweighted manner; however, the effect of the FTO allele variance explained was only 0.34% [8], meaning that the remaining individual variance in BMI may be attributed by other genetic and non-genetic factors, so GRS might be a more efficient and sensitive way of evaluating individual variance, including individual response after bariatric surgery.

Bandstein et al. identified two weighted GRSs, composed of BMI- and WHR-associated SNPs, which were based on a selection of genetic variants with significant impact on weight loss after RYGB surgery [54]. They found that patients with the lowest genetic risk scores had a significantly higher excess BMI loss than higher scoring patients. This observation supports the hypothesis that patients carrying none—or only a small number—of the risk alleles of obesity show more efficient weight loss after RYGB surgery than carriers of multiple risk variants. The GRS may be useful in pre-surgically evaluating the risks of patients undergoing RYGB surgery.

Conclusion and Prospects

This review attempts to provide an overview of the genetics and epigenetics associated with responses to obesity treatment, since the study of this field of medicine is rapidly growing and evolving. From the studies described above, we can see that genetic factors affect the outcomes of obesity treatment and, at the same time, that the current results are far from conclusive. Despite having a long way to go, the prospects are promising. With more and more studies being conducted, the introduction of precision obesity treatment is brought nearer. We can predict that, in the future, when receiving a new patient in our obesity department, we will be able to determine the patient's personal responses to the different treatments through genetic testing, so that we can choose the most appropriate method, from non-invasive to invasive. Also, in the future, genetic factors may provide a reliable pre-operative method of profiling patients who will successfully sustain weight loss. Such a prediction would be used for choosing the optimal treatment for patients, avoiding unnecessary adverse effects and costs. Moreover, understanding of the profound response to the prevention and treatment should illuminate key features of the normal regulation of energy balance and body weight. Identifying these mechanisms will facilitate the development of precision obesity treatment.

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