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The impact of genetic polymorphisms on weight regain after successful weight loss

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Abstract

Obesity is associated with an increased risk of various diseases and mortality. Although nearly 50 % of adults have been reported trying to lose weight, the prevalence of obesity has increased. One factor that hinders weight loss-induced decrease in obesity prevalence is weight regain. Although behavioural, psychological and physiological factors associated with weight regain have been reviewed, the information regarding the relationship between weight regain and genetics has not been previously summarised. In this paper, we comprehensively review the association between genetic polymorphisms and weight regain in adults and children with obesity after weight loss. Based on this information, identification of genetic polymorphism in patients who undergo weight loss intervention might be used to estimate their risks of weight regain. Additionally, the genetic-based risk estimation may be used as a guide for physicians and dietitians to provide each of their patients with the most appropriate strategies for weight loss and weight maintenance.

Key words: **Genetic polymorphisms: Obesity: Weight regain: Weight loss**

Obesity is associated with an increased risk of numerous chronic diseases. These include the metabolic syndrome, CHD, obstructive sleep apnoea, cancer, depression and infertility[1]. Although nearly 50 % of adults worldwide were reported to be trying to lose weight[2], obesity prevalence has doubled in seventy-three countries since 1980[3] and adult obesity exceeded 50 % in several countries[1]. Moreover, the increase in obesity prevalence resulted in a 28·3 % increase in the rate of obesity-related mortality and a 35·8 % increase in the rate of disability-adjusted life years from 1990 to 2015[3], which led to a substantial economic burden conferred by obesity in both developed and developing countries[3,4]. One factor that hinders weight loss-induced decrease in obesity prevalence is weight regain. In fact, about half of the weight lost is regained in the first year following weight loss and the weight regain continues thereafter[5,6]. In the 3- to 5-year period following weight reduction, many subjects (about 85 %) have returned to, or exceeded, their initial weight[5,6]. Factors that are associated with weight regain have been reviewed in many previous articles. These include large initial weight loss[7,8], high levels of orexigenic peptides after weight loss[8,9], increased consumption of high glycaemic index food and beverages[10,11], low levels of exercise[8,9], sedentary activities including excessive television watching[8,12], infrequent self-weighing[9], internal disinhibition of eating[8,9] and dichotomous thinking[5,8]. Indeed, it is widely accepted that weight regain is multifactorial involving physiological, psychological and behavioural factors. However, the information regarding the association between weight regain and genetics, which play an important role in obesity[13,14], has not been previously summarised.

Abbreviations: *ADRB2*, β-2 adrenergic receptor; *BDNF*, brain-derived neurotrophic factor; *COL23A1*, collagen type XXIII α1 chain; *DRD2*, dopamine receptor D2; *FBLN5*, fibulin 5; *FN1*, fibronectin 1; *FTO*, fat mass and obesity-associated protein; *GRL*, glucocorticoid receptor; *KCTD15*, K channel tetramerisation domain containing 15; *LAMB1*, laminin subunit β1; *MTIF3*, mitochondrial translational initiation factor 3; *NEGR1*, neuronal growth regulator 1; *PLIN*, perilipin; *POSTN*, periostin; *PPM1K*, protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1K; *TMEM18*, transmembrane protein 18; *TNFRSF11A*, TNF receptor superfamily member 11a.

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Heritability estimates of BMI and/or the development of obesity are between 40 and 80 %[13,14], and therefore, genetic polymorphisms have been believed to be one of the key determinants of weight regain in individuals with obesity following successful weight loss. Genetic polymorphism is defined as the inheritance of a trait controlled by a single genetic locus with two alleles, in which the least common allele has a frequency of about 1 % or greater[15]. In this article, we have reviewed genetic polymorphisms associated with weight regain in adults and children with obesity after successful weight loss.

Search strategy and selection criteria

A literature search was performed using PubMed from database inception to April 2020. Only articles written in English are included. The search terms included weight regain, gene and obese. Only relevant articles pertaining to the topic of interest are included. Finally, we identified thirty-one polymorphisms from twenty genes that are associated with weight regain and categorised them depending on their functions, including: (1) nutrient metabolism, (2) food intake and energy expenditure, (3) adipocyte differentiation and (4) inflammation, extracellular matrix and bone metabolism.

Nutrient metabolism-related genes and their association with weight regain

It has been shown that nutrient-related metabolite levels in plasma differ between lean subjects and individuals with obesity. These include branched-chain amino acids, aromatic amino acids, NEFA and acylcarnitine intermediates of fatty acid oxidation and branched-chain amino acid catabolism[16]. Additionally, a study into skeletal muscle revealed lower levels of citric acid cycle metabolites, end products of nutrient metabolism, in rats with obesity compared with their lean counterparts[17]. Moreover, they found impaired switching from fat to carbohydrate utilisation during the fasted-to-fed transition in the skeletal muscle of rats with obesity[17]. Those results suggest that obesity is associated with alteration in nutrient metabolism; therefore, it is not surprising that the polymorphisms of several nutrient metabolism-related genes are also associated with weight regain. These include perilipin (*PLIN*), brain-derived neurotrophic factor (BDNF), leptin, PPARγ2, protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1K (PPM1K), β-2 adrenergic receptor (ADRB2), IL-6 and glucocorticoid receptor (*GRL*). A comprehensive summary of the reports describing these genes is shown in Table 1.

PLIN coats intracellular lipid droplets and regulates adipocyte lipolysis[18]. Soenen and colleagues identified the linkage equilibria between *PLIN1* and *PLIN4* and between *PLIN5* and *PLIN7*[19]. They also revealed that males carrying the C-allele of *PLIN1* plus the A-allele of *PLIN4* had a lower BMI and body fat at baseline, weight loss phase and weight maintenance phase, whereas females carrying these alleles had larger weight loss and fat loss at both weight loss and weight maintenance periods[19]. In the case of *PLIN6*, males with the T/T genotype had a lower BMI and body fat at all time points[19]. In females, those who carried the G allele of *PLIN5* plus the A/A genotype of *PLIN7* showed greater reduction on fat mass after weight loss and during weight maintenance[19]. These findings indicate an association between *PLIN* gene polymorphisms and risks of weight and fat mass regain in a sex-specific manner. These sex-specific effects of *PLIN* on obesity risk suggest a particular characteristic of *PLIN* in obesity-related conditions. A further in-depth study regarding the association between *PLIN* and sex hormones on obesity and weight regain could be useful in the identification of molecular mechanisms responsible for this association.

BDNF influences various cell types involved in glucose metabolism. These include increased insulin production from pancreatic β-cells, decreased glucose production in hepatocytes and increased insulin sensitivity in skeletal muscle[20]. Deletions or mutations of the *BDNF* gene result in a phenotype of obesity[21,22]. Considering the effect on weight regain, it was observed that the G allele of the rs6265 SNP of the *BDNF* gene was positively associated with weight regain after successful weight loss using lifestyle intervention at two to four and a half years of follow-up[23,24]. However, there was no effect of that SNP on weight regain in subjects who underwent bariatric surgery at 6 years of follow-up[25]. These findings suggest that: (1) bariatric surgery overwhelms the effect of this polymorphism on weight regain and (2) the effects of this polymorphism on weight regain are not persistent. A shorter-term study in the bariatric surgery model and a longer-term study in the lifestyle intervention model are required to confirm these hypotheses.

Leptin also plays a critical role in glucose and lipid metabolism. *Leptin* has been shown to decrease glucose production and fat accumulation in the liver and to increase glucose uptake and fatty acid oxidation in skeletal muscle, in addition to increasing glucose uptake into brown adipocytes[26,27]. The G allele of rs4731426 SNP was found to be positively associated with weight regain, while the C allele of rs2071045 SNP was negatively associated with weight regain[28]. Additionally, a multivariate parsimonious model including rs4731426, rs2071045 and rs3828942 SNP showed a significant association with weight regain, and a model that included rs4731426, rs2071045, rs3828942, rs11763517 and 11760956 SNP also showed a significant association[28].

PPARγ2 regulates glucose metabolism by increasing transcription of GLUT2 and glucokinase genes, leading to increased glycolysis in the liver and increased insulin secretion by pancreatic β-cells, that is, *PPARγ2* improves insulin sensitivity[29]. In addition, *PPARγ2* is responsible for lipid metabolism by increasing fatty acid oxidation in skeletal muscle[30]. Previous studies investigated the effect of *PPARγ2* polymorphism on weight regain by identifying a correlation between rs1801282 SNP of the *PPARγ2* gene and weight regain. However, their results were inconsistent. In fact, a study in postmenopausal females demonstrated that the G (Ala) allele of rs1801282 showed a positive correlation with weight regain after diet-induced weight loss[31], whereas the other two studies in both males and females discovered a negative correlation[23,32]. Another study found that the weight regain group had more homozygous Pro alleles (C/C genotype) than the weight maintenance group did, but the relationship of the gene with weight regain was not significant after multiple corrections (body weight, BMI and waist circumference), and also there was only one subject who carried the

Table 1. SNP or the restriction fragment length polymorphisms (RFLP) of nutrient metabolism-related genes that are associated with weight regain

Genes	Subjects/average age	Total *n*	% Female	Sex-separation analysis	Samples	Follow-up time	Targeted alleles and SNP/RFLP		Findings: Correlation with weight regain +	–	None	Findings: Correlation with fat mass regain +	–	None	Interpretation	Reference
PLIN	Male and female/ 49 years	118	64·4	Yes	Peripheral blood leucocytes	1 year	C	rs2289487 SNP (*PLIN1*), located on position 89673865 on chromosome 15		√			√		The *PLIN* rs2289487 is negatively associated with weight regain and fat mass regain	(19)
	Male and female/ 49 years	118	64·4	Yes	Peripheral blood leucocytes	1 year	A	rs894160 SNP (*PLIN4*), located on position 89668592 on chromosome 15		√			√		The *PLIN* rs894160 is negatively associated with weight regain and fat mass regain	(19)
	Male and female/ 49 years	118	64·4	Yes	Peripheral blood leucocytes	1 year	T	rs1052700 SNP (*PLIN6*), located on position 89665079 on chromosome 15		√, Male	√, Female		√, Male	√, Female	The *PLIN* rs1052700 is negatively associated with weight regain and fat mass regain in males	(19)
	Male and female/ 49 years	118	64·4	Yes	Peripheral blood leucocytes	1 year	G	rs2304795 SNP (*PLIN5*), located on position 89667032 on chromosome 15					√, Female	√, Male	The *PLIN* rs2304795 is negatively associated with fat mass regain in females	(19)
	Male and female/ 49 years	118	64·4	Yes	Peripheral blood leucocytes	1 year	A	rs2304796 SNP (*PLIN7*), located on position 89667026 on chromosome 15					√, Female	√, Male	The *PLIN* rs2304796 is negatively associated with fat mass regain in females	(19)
BDNF	Male and female with IGT/51 years	1411/		No	Peripheral blood leucocytes	2–4·5 years	G	rs6265 SNP, located on position 27658369 on chromosome 11	√						The *BDNF* rs6265 is positively associated with weight regain	(23)
	Male and female with T2DM/49 years	2022	56·9	No	Peripheral blood leucocytes	4 years	G	rs6265 SNP, located on position 27658369 on chromosome 11	√						The *BDNF* rs6265 is positively associated with weight regain	(24)
	Male and female/ 47·2–47·4 years depending on the type of bariatric surgery	1443	70–73·4 depending on the type of bariatric surgery	No	Whole blood	6 years	G	rs6265 SNP, located on position 27658369 on chromosome 11			√				The *BDNF* rs6265 is not associated with weight regain	(25)
Leptin	Male and female/ 51·2 years	322	14	No	Whole blood	2 years	G	rs4731426 SNP, located on position 128242017 on chromosome 7	√						The *leptin* rs4731426 is positively associated with weight regain	(28)
	Male and female/51·2 years	322	14	No	Whole blood	2 years	C	rs11763517 SNP, located on position 128250009 on chromosome 7	√						The *leptin* rs11763517 is positively associated with weight regain	(28)
	Male and female/51·2 years	322	14	No	Whole blood	2 years	A	rs11760956 SNP, located on position 128251034 on chromosome 7	√						The *leptin* rs11760956 is positively associated with weight regain	(28)
	Male and female/51·2 years	322	14	No	Whole blood	2 years	C	rs2071045 SNP, located on position 128252927 on chromosome 7		√					The *leptin* rs2071045 is negatively associated with weight regain	(28)
	Male and female/51·2 years	322	14	No	Whole blood	2 years	A	rs3828942 SNP, located on position 128254252 on chromosome 7		√					The *leptin* rs3828942 is negatively associated with weight regain	(28)

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Table 1. (*Continued*)

Genes	Subjects/average age	Total *n*	% Female	Sex-separation analysis	Samples	Follow-up time	Targeted alleles and SNP/RFLP		Findings: Correlation with weight regain +	–	None	Findings: Correlation with fat mass regain +	–	None	Interpretation	Reference
PPARγ2	Postmenopausal female/57–61 years depending on the genotype	70	100	No	Whole blood	1 year	G	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3	√						The *PPARγ2* rs1801282 is positively associated with weight regain	(31)
	Male and female/ 34·7 years	67	20·9	No	Peripheral blood leucocytes	1 year	G	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3		√					The *PPARγ2* rs1801282 is negatively associated with weight regain	(32)
	Male and female with IGT/51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	G	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3		√					The *PPARγ2* rs1801282 is negatively associated with weight regain	(23)
	Male and female/ 47·2–47·4 years depending on the type of bariatric surgery	1443	70–73·4 depending on the type of bariatric surgery	No	Whole blood	6 years	G	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3			√				The *PPARγ2* rs1801282 is not associated with weight regain	(25)
	Male and female/ 49 years	119/		No	Peripheral blood leucocytes	1 year	C	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3			√				The *PPARγ2* rs1801282 is not associated with weight regain	(33)
PPM1K	Male and female/ 51 years	734	60·9	No	Peripheral blood leucocytes	2 years	C	rs1440581 SNP, located on position 88305270 on chromosome 4	√						The *PPM1K* rs1440581 is positively associated with weight regain	(38)
ADRB2	Male/35–37 years depending on the genotype	154	0	No	Whole blood	2 years	G	rs1042713 (Arg16Gly) SNP, located on position 148826877 on chromosome 5	√						The *ADRB2* rs1042713 is positively associated with weight regain	(41)
IL-6	Male and female/ 34·7 years	67	20·9	No	Peripheral blood leucocytes	1 year	C	rs1800795 (-174 G > C) SNP, located on position 22727026 on chromosome 7		√					The *IL-6* rs1700795 is negatively associated with weight regain	(32)
GRL	Male and female/ 49 years	119/		No	Peripheral blood leucocytes	1 year	G	rs41423247 (BCl1) RFLP, located on position 143399010 on chromosome 5		√					The *GRL* Bcl1 is negatively associated with weight regain	(33)

+, Positively associated with; –, negatively associated with; *ADRB2*, *β*-2 adrenergic receptor; *BDNF*, brain-derived neurotrophic factor; *GRL*, glucocorticoid receptor; IGT, impaired glucose tolerance; *PLIN*, perilipin; *PPM1K*, protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1K; T2DM, type 2 diabetes.

G/G genotype in that study[33]. Six years after bariatric surgery, there was no effect of that SNP on weight regain as well[25]. Because there was no relationship between *PPARγ2* rs1801282 and weight regain in adults who underwent bariatric surgery at the 6-year follow-up but the relationship was established in other studies using lifestyle intervention-induced weight reduction at earlier stages of follow-up, these findings suggest that: (1) bariatric surgery overcomes the effect of *PPARγ2* rs1801282 on weight regain, and (2) the effect of *PPARγ2* rs1801282 on weight regain is inconsistent. As in the case of *BDNF* rs6265, both a shorter-duration study in the bariatric surgery model and a longer-duration study in lifestyle intervention model are necessary. Also of note, the association between weight regain and *PPARγ2* in postmenopausal females was different from other populations. *PPARγ* and oestrogen receptors have been shown to interact with each other in terms of vascular function and the treatment of cancer[34–36]. Therefore, oestrogen receptors may also mediate the effect of *PPARγ2* on weight regain, which may be responsible for differences in effect between pre- and postmenopausal females. Further investigation is required to clarify the relationships between *PPARγ2*, oestrogen receptor and weight regain.

The *PPM1K* gene encodes for the mitochondrial branched-chain α-ketoacid dehydrogenase phosphatase, which catalyses oxidative decarboxylation of branched-chain α-ketoacids from branched-chain amino acids[37]. At 24 months after the intervention, the C allele of the rs1440581 SNP of the *PPM1K* gene was related to smaller weight reduction in subjects with obesity who received a high-fat diet (40 % of fat), whereas no significant genetic effect was observed in a low-fat diet group (20 % of fat)[38]. These findings suggested that there was a gene-diet interaction on weight maintenance, and the C allele of the rs1440581 was positively associated with the risk of weight regain following high-fat diet intervention.

ADRB2 plays important roles in lipid and glucose metabolism by modulating lipolysis[39] and insulin secretion[40]. Masuo and colleagues investigated the effects of the rs1042713 SNP of the *ADRB2* gene and demonstrated that males with rebound weight gain had a significantly higher frequency of the Gly16 (G) allele compared with those who could maintain their weight loss[41].

IL-6 affects glucose and lipid metabolism through various mechanisms, including decreased glucose uptake into adipocytes, decreased glycogen synthesis in the liver and increased lipolysis, resulting in obesity and insulin resistance[42,43]. A previous study revealed that the C allele of the rs1800795 (–174 G > C) SNP of the *IL-6* gene protected against weight regain[32]. Moreover, the conjoined presence of the C allele of the rs1800795 and the G (Ala) allele of the rs1801282 SNP of the *PPARγ2* gene further improved the ability for weight maintenance[32].

GRL is a transcription factor that binds glucocorticoids and regulates the transcription of specific genes[44]. These *GRL* primary target genes further initiate the physiological and pathological responses of glucocorticoids, which include the homoeostasis involved in lipid metabolism[44]. A previous study showed that the G/G genotype of the Bcl1 (rs41423247) RFLP of the *GRL* gene was independently associated with successful weight maintenance[33].

In summary, evidence indicates that the polymorphisms of several genes related to lipid, glucose and branched-chain amino acid metabolism (*PLIN, BDNF, leptin, PPARγ2, PPM1K, ADRB2, IL-6* and *GRL*) are associated with weight regain.

Food intake and energy expenditure-related genes and their association with weight regain

Obesity is the result of an imbalance between food intake and energy expenditure[45]. For weight maintenance following weight loss, energy intake must match energy expenditure as well[46]. Unfortunately, weight reduction leads to decreased energy needs, but to an augmented drive to eat, which favours weight regain[45]. Previous studies have demonstrated that there were relationships between weight regain and polymorphisms of various genes that are related to food intake and energy expenditure, including *BDNF*, *leptin*, fat mass and obesity-associated protein (*FTO*), dopamine receptor D2 (*DRD2*), K channel tetramerisation domain containing 15 (*KCTD15*), transmembrane protein 18 (*TMEM18*), *ADRB2*, *IL-6*, neuronal growth regulator 1 (*NEGR1*) and mitochondrial translational initiation factor 3 (*MTIF3*). A comprehensive summary of those reports is shown in Table 2.

BDNF suppresses food intake by acting on neurons in the hypothalamus[47] and increases energy expenditure by increasing adaptive thermogenesis via the activation of a hypothalamic-adipocyte axis[48]. Deletions or mutations of the *BDNF* gene lead to impaired thermogenesis and clinical manifestations of hyperphagia and obesity[21,22]. An association between the G allele of the rs6265 SNP of the *BDNF* gene and weight regain was previously described in 'Nutrient metabolism-related genes and their association with weight regain'.

Similarly to *BDNF, leptin* acts on neurons in the hypothalamus and promotes satiety[26,27]. Several SNP of the *leptin* gene were previously found to be correlated with weight regain, including rs4731426, rs2071045, rs3828942, rs11763517 and rs11760956 SNP, as previously mentioned in 'Nutrient metabolism-related genes and their association with weight regain'.

Previous studies showed that polymorphisms of the *FTO* gene were associated with increased food intake[49,50] and obesity[49]. The SNP of the *FTO* gene that was commonly investigated regarding weight regain was rs9939609, but the results were inconsistent. Specifically, three previous studies, which include a study in children, showed that the A allele of that SNP was positively associated with weight regain[51–53]. On the other hand, a study in postmenopausal females and another two studies in subjects with impaired glucose tolerance and type 2 diabetes found there was no relationship of that SNP with weight regain[23,24,54]. The A allele of another SNP of the *FTO* gene, rs3751812, was also positively associated with weight regain in individuals who received diabetic support and education, but not in those who received the intensive lifestyle intervention[24]. All of these findings suggest that the impact of *FTO* rs9939609 on weight regain seems to have disappeared in postmenopausal females. There is evidence that oestrogen regulates *FTO* via the PI3K/AKT, MAPK and mTOR (mammalian target of rapamycin) signalling pathways, resulting in endometrial cancer

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Table 2. SNP or the restriction fragment length polymorphisms (RFLP) of food intake and energy expenditure-related genes that are associated with weight regain

Genes	Subjects/average age	Total *n*	% Female	Sex-separation analysis	Samples	Follow-up time	Targeted alleles and SNP/RFLP		Findings: Correlation with weight regain			Interpretation	Reference
							Alleles	SNP/RFLP	+	−	None		
BDNF	Male and female with IGT/ 51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	G	rs6265 SNP, located on position 27658369 on chromosome 11	√			The *BDNF* rs6265 is positively associated with weight regain	(23)
	Male and female with T2DM/ 49 years	2022	56·9	No	Peripheral blood leucocytes	4 years	G	rs6265 SNP, located on position 27658369 on chromosome 11	√			The *BDNF* rs6265 is positively associated with weight regain	(24)
	Male and female/47·2–47·4 years depending on the type of bariatric surgery	1443	70–73·4 depending on the type of bariatric surgery	No	Whole blood	6 years	G	rs6265 SNP, located on position 27658369 on chromosome 11			√	The *BDNF* rs6265 is not associated with weight regain	(25)
Leptin	Male and female/51·2 years	322	14	No	Whole blood	2 years	G	rs4731426 SNP, located on position 128242017 on chromosome 7	√			The *leptin* rs4731426 is positively associated with weight regain	(28)
	Male and female/51·2 years	322	14	No	Whole blood	2 years	C	rs11763517 SNP, located on position 128250009 on chromosome 7	√			The *leptin* rs11763517 is positively associated with weight regain	(28)
	Male and female/51·2 years	322	14	No	Whole blood	2 years	A	rs11760956 SNP, located on position 128251034 on chromosome 7	√			The *leptin* rs11760956 is positively associated with weight regain	(28)
	Male and female/51·2 years	322	14	No	Whole blood	2 years	C	rs2071045 SNP, located on position 128252927 on chromosome 7		√		The *leptin* rs2071045 is negatively associated with weight regain	(28)
	Male and female/51·2 years	322	14	No	Whole blood	2 years	A	rs3828942 SNP, located on position 128254252 on chromosome 7		√		The *leptin* rs3828942 is negatively associated with weight regain	(28)
FTO	Male and female/44·6 years	193	66·8	No	Whole blood	1 year	A	rs9939609 SNP, located on position 53786615 on chromosome 16	√			The *FTO* rs9939609 is positively associated with weight regain	(52)
	Boy and girl/10·6 years	346	55	No	Whole blood	1 year	A	rs9939609 SNP, located on position 53786615 on chromosome 16	√			The *FTO* rs9939609 is positively associated with weight regain	(53)
	Postmenopausal female/ 39·2–40·9 years depending on genotype	75	100	No	Whole blood	1 year	A	rs9939609 SNP, located on position 53786615 on chromosome 16			√	The *FTO* rs9939609 is not associated with weight regain	(54)
	Male and female with IGT/ 51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	A	rs9939609 SNP, located on position 53786615 on chromosome 16			√	The *FTO* rs9939609 is not associated with weight regain	(23)
	Male and female/41·7 years	146	82·2	No	Buccal mucosa or SC adipose tissue	2–5 years	A	rs9939609 SNP, located on position 53786615 on chromosome 16	√			The *FTO* rs9939609 is positively associated with weight regain	(51)
	Male and female with T2DM/ 49 years	2022	56·9	No	Peripheral blood leukocytes	4 years	A	rs9939609 SNP, located on position 53786615 on chromosome 16			√	The *FTO* rs9939609 is not associated with weight regain	(24)
	Male and female with T2DM/ 49 years	2022	56·9	No	Peripheral blood leucocytes	4 years	A	rs3751812 SNP, located on position 53784548 on chromosome 16	√, diabetic support and education group		√, intensive lifestyle intervention group	The *FTO* rs3751812 is positively associated with weight regain	(24)

Table 2. (*Continued*)

Genes	Subjects/average age	Total *n*	% Female	Sex-separation analysis	Samples	Follow-up time	Targeted alleles and SNP/RFLP		Findings			Interpretation	Reference
							Alleles	SNP/RFLP	Correlation with weight regain				
									+	–	None		
DRD2	Male and female/49 years	202	66·8	No	Whole blood	1 year	A1	rs1800497 (*Taq*IA) SNP, located on position 113400106 on chromosome 11	√ (21–40 years)		√ (41–60 years)	The *DRD2* rs1800497 is positively associated with weight regain in young adults	(62)
KCTD15	Male and female with IGT/ 51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	G	rs29941 SNP, located on position 33818627 on chromosome 19	√			The *KCTD15* rs29941 is positively associated with weight regain	(23)
TMEM18	Male and female with IGT/ 51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	C	rs6548238 SNP, located on position 634905 on chromosome 2	√			The *TMEM18* rs6548238 is positively associated with weight regain	(23)
ADRB2	Male/35–37 years depending on the genotype	154	0	No	Whole blood	2 years	G	rs1042713 (Arg16Gly) SNP, located on position 148826877 on chromosome 5	√			The *ADRB2* rs1042713 is positively associated with weight regain	(41)
IL-6	Male and female/34·7 years	67	20·9	No	Peripheral blood leucocytes	1 year	C	rs1800795 (–174 G > C) SNP, located on position 22727026 on chromosome 7		√		The *IL-6* rs1800795 is negatively associated with weight regain	(32)
NEGR1	Male and female with IGT/ 51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	A	rs2815752 SNP, located on position 72346757 on chromosome 1		√		The *NEGR1* rs2815752 is negatively associated with weight regain	(23)
MTIF3	Male and female with T2DM or at high risk of T2DM/ 50·7–59 years depending on the cohort	5730	60·9	No	Peripheral blood leucocytes	4 years	G	rs1885988 SNP, located on position 27436125 on chromosome 13		√		The *MTIF3* rs1885988 is negatively associated with weight regain	(76)

+, Positively associated with; –, negatively associated with; *ADRB2*, *β*-2 adrenergic receptor; *BDNF*, brain-derived neurotrophic factor; *DRD2*, dopamine receptor D2; *FTO*, fat mass and obesity-associated protein; IGT, impaired glucose tolerance; *KCTD15*, K channel tetramerisation domain containing 15; *MTIF3*, mitochondrial translational initiation factor 3; *NEGR1*, neuronal growth regulator 1; SC, subcutaneous; T2DM, type 2 diabetes mellitus; *TMEM18*, transmembrane protein 18.

cell proliferation[55,56]. Thus, it is possible that oestrogen regulates the effect of *FTO* on weight regain also and therefore oestrogen deficiency hinders the association between *FTO* and weight regain in postmenopausal females. A future study is needed to prove this possibility. Interestingly, studies in individuals with impaired glucose tolerance and type 2 diabetes demonstrated no correlation between *FTO* rs9939609 and weight regain following weight loss. However, a correlation was exhibited in studies in general populations and even in children, indicating the overwhelming effect of impaired glucose tolerance and type 2 diabetes on *FTO*-associated weight regain. Furthermore, *FTO* rs9939609 was reportedly associated with insulin resistance and the risk of type 2 diabetes[57,58]. Nevertheless, further studies are required to identify the molecular mechanisms responsible for the relationships between *FTO*, insulin resistance and weight regain.

DRD2 is known to be responsible for the circuit of food reward[59]. Genetic variations of the *DRD2* gene were previously found to be related to emotional eating[60,61]. It was shown that young adults (21–40 years old) carrying the A1 allele of the rs1800497 (*Taq*IA) SNP of the *DRD2* gene had greater weight regain during the weight maintenance phase, while there was no effect of that SNP on weight regain among older adults (41–60 years old)[62]. Particularly, age modulates the effect of the *DRD2* rs1800497 on weight regain. This might be due to age-induced improvement of response-inhibition capacities, alterations in several hormones and involvement of other acquired factors which are a result of the ageing process[62]. However, the reduction in D2 receptor binding and endogenous dopamine with age[63,64] may be another possible explanation.

KCTD15 plays an important role in the regulation of eating behaviour and reward[65]. A previous study observed treatment-specific effects of the *KCTD15* rs29941 SNP on weight regain[23]. Specifically, the G allele of that SNP was positively correlated with weight regain in subjects who underwent an intensive lifestyle modification programme[23].

A study in *TMEM18*-deficient mice found that the loss of *TMEM18* expression resulted in increased appetite[66]. Similarly to *KCTD15*, a treatment-specific effect of the *TMEM18* rs6548238 SNP on weight regain was exhibited[23]. Indeed, the C allele of that SNP was positively associated with weight regain in subjects who underwent an intensive lifestyle modification programme[23].

Not only does *ADRB2* modulate lipolysis, but it also regulates energy expenditure via the thermogenic effects of catecholamines[67,68]. A study in Japanese males revealed that the Gly16 (G) allele of the rs1042713 SNP of the *ADRB2* gene was positively related to weight regain[41].

IL-6 impacts regulation of energy expenditure through several mechanisms, including actions in the hypothalamic-pituitary-adrenal axis, and activation of the sympathetic nervous system[69,70]. A previous study demonstrated an association between the C allele of the rs1800795 (−174 G > C) SNP of the *IL-6* gene and weight regain[32], as previously described in 'Nutrient metabolism-related genes and their association with weight regain'.

Previous studies suggested that the expression of *NEGR1* in the hypothalamus was related to food intake[71,72]. Delahanty and colleagues demonstrated that the A allele of the rs2815752 SNP of the *NEGR1* gene was negatively associated with weight regain irrespective of treatment arms[23].

MTIF3 promotes the formation of the initiation complex on the mitochondrial 55S ribosome, which is essential for energy balance in the mitochondria[73]. This gene has also been identified as an obesity susceptibility gene due to its relationship with BMI[74,75]. Papandonatos and colleagues showed that the G allele of the *MTIF3* rs1885988 was associated with greater weight loss following lifestyle intervention over 4 years of follow-up[76]. In other words, their result implies that G allele of the *MTIF3* rs1885988 is related to lower-risk of weight regain.

In summary, evidence indicates that the polymorphisms of the genes that regulate satiety, food reward, eating behaviour, as well as energy expenditure (*BDNF, leptin, FTO, DRD2, KCTD15, TMEM18, ADRB2, IL-6, NEGR1* and *MTIF3*) are associated with the ability of long-term weight maintenance.

Adipocyte differentiation-related genes and their association with weight regain

Adipocytes are a key regulator of body weight, and obesity is a condition characterised by excess adipose tissue[77]. The generation of new adipocytes consists of two steps: the proliferation of preadipocytes and the differentiation from preadipocytes to adipocytes (adipocyte differentiation)[78]. Taken together, adipocyte differentiation is a process that determines body weight and obesity[79]. The polymorphisms of adipocyte differentiation-related genes that are associated with weight regain were previously evidenced, including *BDNF, PPARγ2, TMEM18* and *NEGR1*. A comprehensive summary of these relevant reports is shown in Table 3.

A previous study demonstrated that *BDNF* gene expression was down-regulated during adipocyte differentiation and knockdown of *BDNF* inhibited adipocyte differentiation[80]. There was an association between the G allele of the rs6265 SNP of the *BDNF* gene and weight regain as previously described in 'Nutrient metabolism-related genes and their association with weight regain'.

It is widely known that *PPARγ2* is a master regulator of adipocyte differentiation[30,81]. The effect of *PPARγ2* polymorphism on weight regain was focused on the rs1801282 SNP, but the results were inconsistent, as previously mentioned in 'Nutrient metabolism-related genes and their association with weight regain'.

Knockdown of *TMEM18* inhibited adipocyte differentiation[80]. Delahanty and colleagues demonstrated that there was a treatment-specific effect of the *TMEM18* rs6548238 SNP on weight regain. In other words, the C allele of that SNP showed a positive correlation with weight regain in individuals who underwent an intensive programme of lifestyle modification[23].

Unlike *BDNF, NEGR1* gene expression was up-regulated during adipocyte differentiation, yet knockdown of *NEGR1* did also inhibit adipocyte differentiation[80]. As previously mentioned, a negative correlation between the A allele of the rs2815752 SNP of the *NEGR1* gene and weight regain was observed regardless of treatment arms[23].

Table 3. SNP or the restriction fragment length polymorphisms (RFLP) of adipocyte differentiation-related genes that are associated with weight regain

Genes	Subjects/average age	Total *n*	% Female	Sex-separation analysis	Samples	Follow-up time	Targeted alleles and SNP/RFLP		Findings: Correlation with weight regain			Interpretation	Reference
							Alleles	SNP/RFLP	+	–	None		
BDNF	Male and female with IGT/ 51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	G	rs6265 SNP, located on position 27658369 on chromosome 11	√			The *BDNF* rs6265 is positively associated with weight regain	(23)
	Male and female with T2DM/ 49 years	2022	56·9	No	Peripheral blood leucocytes	4 years	G	rs6265 SNP, located on position 27658369 on chromosome 11	√			The *BDNF* rs6265 is positively associated with weight regain	(24)
	Male and female/47·2–47·4 years depending on the type of bariatric surgery	1443	70–73·4 depending on the type of bariatric surgery	No	Whole blood	6 years	G	rs6265 SNP, located on position 27658369 on chromosome 11			√	The *BDNF* rs6265 is not associated with weight regain	(25)
PPARγ2	Postmenopausal female/57–61 years depending on the genotype	70	100	No	Whole blood	1 year	G	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3	√			The *PPARγ2* rs1801282 is positively associated with weight regain	(31)
	Male and female/34·7 years	67	20·9	No	Peripheral blood leucocytes	1 year	G	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3		√		The *PPARγ2* rs1801282 is negatively associated with weight regain	(32)
	Male and female with IGT/ 51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	G	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3		√		The *PPARγ2* rs1801282 is negatively associated with weight regain	(23)
	Male and female/47·2–47·4 years depending on the type of bariatric surgery	1443	70–73·4 depending on the type of bariatric surgery	No	Whole blood	6 years	G	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3			√	The *PPARγ2* rs1801282 is not associated with weight regain	(25)
	Male and female/49 years	119		No	Peripheral blood leucocytes	1 year	C	rs1801282 (Pro12/Ala) SNP, located on position 12351626 on chromosome 3			√	The *PPARγ2* rs1801282 is not associated with weight regain	(33)
TMEM18	Male and female with IGT/ 51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	C	rs6548238 SNP, located on position 634905 on chromosome 2	√			The *TMEM18* rs6548238 is positively associated with weight regain	(23)
NEGR1	Male and female with IGT/ 51 years	1411		No	Peripheral blood leucocytes	2–4·5 years	A	rs2815752 SNP, located on position 72346757 on chromosome 1		√		The *NEGR1* rs2815752 is negatively associated with weight regain	(23)

+, Positively associated with; –, negatively associated with; *BDNF*, brain-derived neurotrophic factor; IGT, impaired glucose tolerance; *NEGR1*, neuronal growth regulator 1; T2DM, type 2 diabetes mellitus; *TMEM18*, transmembrane protein 18.

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Table 4. SNP or the restriction fragment length polymorphisms (RFLP) of inflammation, extracellular matrix and bone metabolism-related genes that are associated with weight regain

Genes	Subjects/average age	Total *n*	% Female	Sex-separation analysis	Samples	Follow-up time	Targeted alleles and SNP/RFLP		Findings: Correlation with weight regain +	–	None	Interpretation	Reference
IL-6	Male and female/34·7 years	67	20·9	No	Peripheral blood leucocytes	1 year	C	rs1800795 (-174 G > C) SNP, located on position 22727026 on chromosome 7		√		The *IL-6* rs1800795 is negatively associated with weight regain	(32)
POSTN	Male and female/41–43 years depending on sex and group of subjects	469	66·1	Yes	Peripheral blood leucocytes	6 months	C	rs7323378 SNP, located on position 37579214 on chromosome 13	√, Male		√, Female	The *POSTN* rs7323378 is positively associated with weight regain in males	(87)
	Male and female/41–43 years depending on sex and group of subjects	469	66·1	Yes	Peripheral blood leucocytes	6 months	C	rs9547947 SNP, located on position 37557856 on chromosome 13	√, Male		√, Female	The *POSTN* rs9547947 is positively associated with weight regain in males	(87)
	Male and female/41–43 years depending on sex and group of subjects	469	66·1	Yes	Peripheral blood leucocytes	6 months	C	rs9315503 SNP, located on position 37565123 on chromosome 13	√, Male		√, Female	The *POSTN* rs9315503 is positively associated with weight regain in males	(87)
COL23A1	Male and female/41–43 years depending on sex and group of subjects	469	66·1	Yes	Peripheral blood leucocytes	6 months	A	rs2672826 SNP, located on position 178527515 on chromosome 5	√, Male		√, Female	The *COL23A1* rs2672826 is positively associated with weight regain in males	(87)
FBLN5	Male and female/41–43 years depending on sex and group of subjects	469	66·1	Yes	Peripheral blood leucocytes	6 months	A	rs12589592 SNP, located on position 91911458 on chromosome 14	√, Male		√, Female	The *FBLN5* rs12589592 is positively associated with weight regain in males	(87)
LAMB1	Male and female/41–43 years depending on sex and group of subjects	469	66·1	Yes	Peripheral blood leucocytes	6 months	A	rs2158836 SNP, located on position 107940394 on chromosome 7	√, Male		√, Female	The *LAMB1* rs2158836 is positively associated with weight regain in males	(87)
FN1	Male and female/41–43 years depending on sex and group of subjects	469	66·1	Yes	Peripheral blood leucocytes	6 months	A	rs17516906 SNP, located on position 215414550 on chromosome 2	√, Female		√, Male	The *FN1* rs17516906 is positively associated with weight regain in females	(87)
TNFRSF11A	Male and female with T2DM/59·1 years	3899	56·2	No	Peripheral blood leucocytes	4 years	A	rs17069904 SNP, located on position 62365716 on chromosome 18		√		The *TNFRSF11A* rs170069904 is negatively associated with weight regain	(90)

+, Positively associated with; –, negatively associated with; *COL23A1*, collagen type XXIII α1 chain; *FBLN5*, fibulin 5; *FN1*, fibronectin 1; *LAMB1*, laminin subunit β1; *POSTN*, periostin; T2DM, type 2 diabetes mellitus; *TNFRSF11A*, TNF receptor superfamily member 11a.

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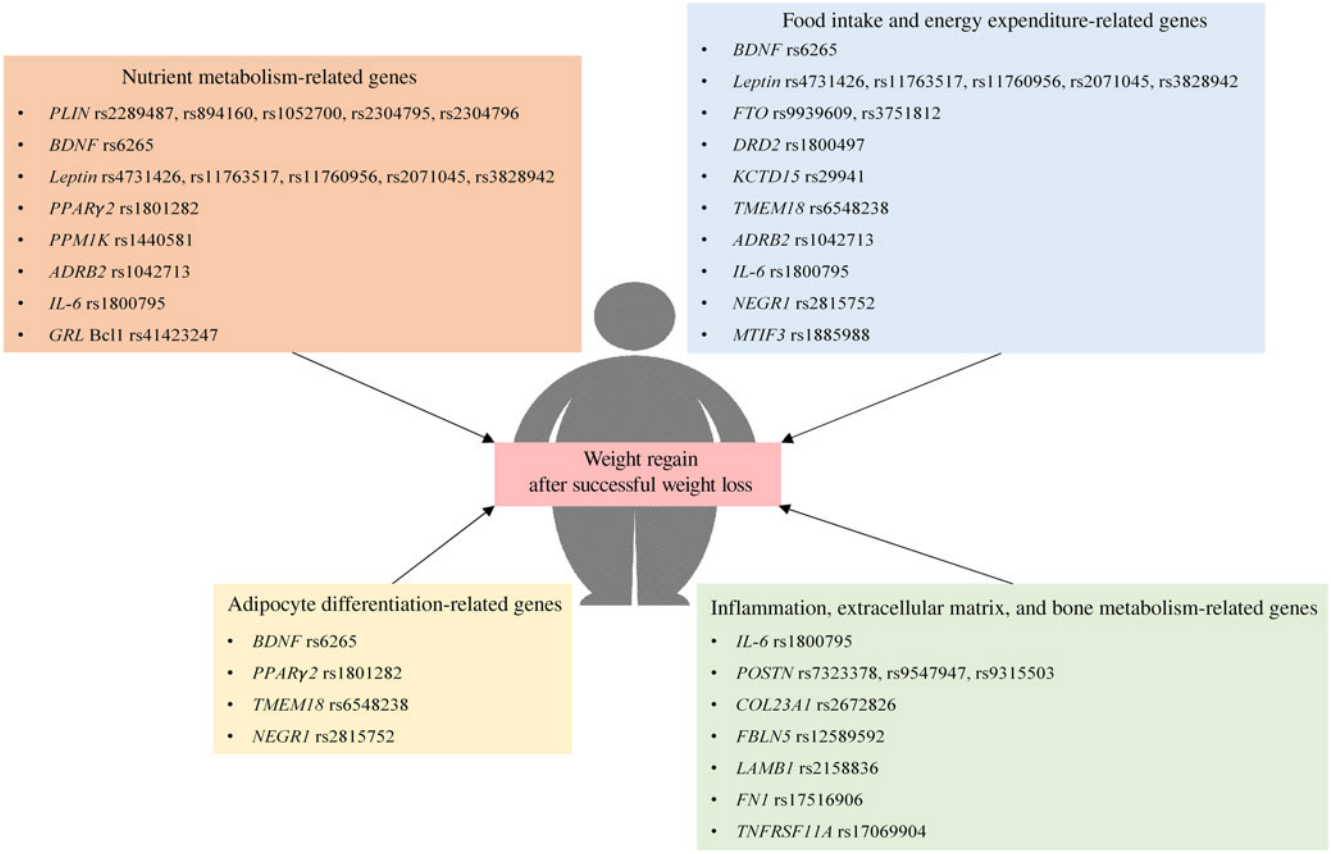

Fig. 1. Polymorphism of genes that are associated with weight regain after successful weight loss. *ADRB2*, β-2 adrenergic receptor; *BDNF*, brain-derived neurotrophic factor; *COL23A1*, collagen type XXIII α1 chain; *DRD2*, dopamine receptor D2; *FBLN5*, fibulin 5; *FN1*, fibronectin 1; *FTO*, fat mass and obesity-associated protein; *GRL*, glucocorticoid receptor; *KCTD15*, K channel tetramerisation domain containing 15; *LAMB1*, laminin subunit β1; *MTIF3*, mitochondrial translational initiation factor 3; *NEGR1*, neuronal growth regulator 1; *PLIN*, perilipin; *POSTN*, periostin; *PPM1K*, protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1K; *TMEM18*, transmembrane protein 18; *TNFRSF11A*, TNF receptor superfamily member 11a.

In summary, evidence indicates that there is a relationship between adipocyte differentiation and weight regain, which is mediated by the polymorphisms of adipocyte differentiation-related genes (*BDNF, PPARγ2, TMEM18* and *NEGR1*).

Inflammation, extracellular matrix and bone metabolism-related genes and their association with weight regain

Obesity is associated with chronic inflammation owing to NEFA-induced activation of inflammatory pathways[82,83]. This inflammatory response leads to increased extracellular matrix synthesis but reduced extracellular matrix degradation, resulting in increased deposition and remodelling of extracellular matrix, especially in adipocytes[84,85]. Bone metabolism is also correlated with body fat and lean mass[86]. In fact, bone has recently been determined as an endocrine organ that affects body weight regulation via the actions of bone-derived factors such as osteocalcin and osteopontin[86]. The associations between weight regain and polymorphisms of inflammation, extracellular matrix and bone metabolism-related genes include *IL-6*, periostin (*POSTN*), collagen type XXIII α1 chain (*COL23A1*), fibulin 5 (*FBLN5*), laminin subunit β1 (*LAMB1*), fibronectin 1 (*FN1*) and TNF receptor superfamily member 11a (*TNFRSF11A*). These reports are comprehensively summarised in Table 4.

IL-6 is an inflammatory mediator that is oversecreted in response to excessive macronutrients in adipose tissue[82]. A prior study demonstrated an association between the C allele of the rs1800795 (–174 G > C) SNP of the *IL-6* gene and weight regain[32], as previously described in 'Nutrient metabolism-related genes and their association with weight regain'.

Roumans and colleagues investigated the effects of one hundred and twenty-four extracellular matrix-related genes on weight regain, revealing six SNP (males) and one SNP (females) that were significantly associated with the weight maintenance score[87]. Indeed, they found that the risks of weight regain in males were increased in C-allele carriers of three SNP (rs7323378, rs9547947 and rs9315503) of the *POSTN* gene, A-allele carriers of the *COL23A1* rs2672826, A-allele carriers of the *FBLN1* rs12589592 and A-allele carriers of the *LAMB1* rs2158836[87]. In females, however, the risk of weight regain was higher in A-allele carriers of the *FN1* rs17516906[87]. As previously mentioned, obesity is associated with extracellular matrix remodelling in adipocytes[84,85] and adipocyte characteristics differ based on sex[88]. Altogether, these facts support the sex-specific effects of extracellular matrix-related genes on weight regain.

TNFRSF11A, or more commonly known as RANK, involves in a signalling pathway that regulates bone metabolism[89]. A previous study revealed that the A allele of *TNFRSF11A* rs17069904 was associated with greater weight loss in subjects who received intensive lifestyle intervention-induced weight reduction at 4 years of follow-up[90]. Indeed, the result from that study implies that A allele of *TNFRSF11A* rs17069904 is related to lower risk of weight regain.

In summary, not only inflammation, extracellular matrix and bone metabolism-related genes are associated with obesity but also the polymorphisms of these genes (*IL-6, POSTN, COL23A1, FBLN5, LAMB1*, *FN1* and *TNFRSF11A*) are also associated with weight regain in individuals with obesity after successful weight loss.

Conclusion

There is a growing body of evidence which suggests that genetic polymorphism is associated with weight regain in both adults and children with obesity. Specifically, these genes are responsible for the pathophysiology of obesity, including nutrient metabolism, regulation of food intake and energy expenditure, adipocyte differentiation, inflammation, structure of the extracellular matrix and bone metabolism as summarised in Fig. 1. Additionally, some of these genes affect weight regain in a distinct manner, such as intervention-specific, age-specific, sex-specific, oestrogen status-specific and insulin sensitivity status-specific.

Future directions and clinical applications

Since there is evidence that suggested relationships between genetic polymorphisms and weight regain, identification of genetic polymorphisms in patients with obesity who undergo weight loss intervention could provide useful information to estimate their risks of weight regain after successful weight reduction. However, the impact that any one of these genetic polymorphisms have on weight regain is still unclear due to short duration of follow-up in those reports. Because long-term follow-up is required for continued long-term weight loss success, it is essential that further studies with the longer duration of follow-up are needed to confirm the persistence of the impact of those genetic polymorphisms on weight maintenance. Furthermore, future studies in twins and siblings clarifying the contribution of each genetic polymorphism on weight regain are required to confirm a clinical valuable of genetic testing. Moreover, it is still controversial which genetic polymorphisms exhibit the maximum effect size on weight regain due to the difference of the design among studies. Therefore, further studies that directly compare the effect size of those polymorphisms are needed. Although most of the previous studies identified the correlations between genetic polymorphisms and weight regain after adjusting for several confounding factors (age, sex, ethnicity, study site, method of weight loss and baseline anthropometry), behavioural and psychological factors were not included in the multiple regression analyses. Adjusting for the degree of weight reduction, behavioural factors and psychological factors are necessary in future studies since these factors have been shown to be associated with weight regain[7–12]. In addition to the genetic polymorphisms, epigenetics could also play important roles on weight regain. Although the association between weight regain and DNA methylation of some genes, including proopiomelanocortin (*POMC*), neuropeptide Y (*NPY*), mal, T cell differentiation protein 2 (*MAL2*), family with sequence similarity 129, member A (*FAM129A*), periplakin (*PPL*), PDZ domain containing ring finger 4 (*PDZRN4*) and major facilitator superfamily domain containing 3 (*MFSD3*), has been reported[91–93], future epigenetic studies regarding the relationship between post-transcriptional modification and the impacts of genetic polymorphisms on long-term weight maintenance in different populations are also required.

After further investigation mentioned above, the genetic-based risk estimation might be used as a guide for physicians and dietitians to provide each of their own patients with the most appropriate strategies for weight loss and for long-term weight maintenance, which might result in a decreased prevalence of obesity, decreased risk of obesity-associated diseases and mortality, as well as decreased obesity-related economic burden.

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