Genetic and epigenetic mechanisms involved in bariatric surgery

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Morbid obesity (BMI>40 kg/m^2) is a challenging health condition with an increasing incidence in the last decades. Conventional therapy which consists in diet and lifestyle interventions, along with pharmaceutical therapy, has a limited effect on morbidly obese patients. In this context, bariatric surgery is the most effective approach, leading to significant weight loss, along with other beneficial effects like type 2 diabetes resolution or improvement of cardiovascular status. The bariatric surgery outcomes can widely vary among individuals, with a significant percentage of patients having small benefits from the operation. These variations may be partially explained by the genetic background of each individual.
During the last years, several studies have been conducted in order to determine the genetic and epigenetic factors involved in bariatric surgery outcomes. Many genes involved in different molecular pathways were found to be associated with weight loss after bariatric surgery. Epigenetic studies revealed that genes methylation may be influenced by weight loss interventions.
All these findings suggest that there is an intimate connection between genetic and epigenetic factors and the bariatric surgery outcomes. Further studies are required in order to better understand if genetics can be used in order to predict the operation results.

KEY WORDS: Bariatric surgery, Body-mass index, Epigenetic, Genetic

Introduction

Obesity (defined by a body mass index higher that 30Kg/m^2) is one of the most common disease worldwide. According to the World Health Organization, more than 650 million adults were obese in 2016 [1]. Due to obesity comorbidities, like type 2 diabetes (T2D), cardiovascular diseases, sleep apnea, depression, etc., this health condition represents a major cause of morbidity and mortality, having a great impact on public he.alth with social and economic consequences [2].

The conventional treatment for obesity consists of diet therapy, pharmaceutical therapy and lifestyle change interventions [3]. However, these methods are not efficient in treating morbid obesity (BMI>40Kg/m^2). By contrast, bariatric surgery proved to be a good path for treating morbidly obese patients on a long term period [4,5]. The most frequently used bariatric surgery procedures are Roux en Y gastric bypass (RYGB) and sleeve gastrectomy (SG). These procedures lead not only to weight loss, but also to a significant improvement of the obesity comorbidities outcome, with resolution or a better control of T2DM, obstructive sleep apnea, hypertension or hyperlipidemia [6].

The molecular mechanisms which lead to these health improvements are not yet well established. The malabsorptive effects of some bariatric surgery techniques were believed to be responsible for the anti-T2DM effect [7]. SG

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on the other hand is a restrictive and nonmalabsorptive operation that also results in resolution of T2DM, sometimes before weight reduction takes place [8]. Thus, other mechanisms should also be involved in bariatric surgery outcomes.

An important heterogeneity in patient's response to weight loss surgical interventions was observed. Up to 30% of patients fail to lose at least 50% of the excess body weight [9] and there is also a high variability in terms of the resolution of obesity comorbidities. This heterogeneity may be explained by environmental factors, but also by genetic variability among individuals. Therefore, genetic polymorphisms and different epigenetic signatures are possible explanations for different responses among patients. This hypothesis has been confirmed by animal studies, where gene expression was found to be influenced by sleeve gastrectomy [10].

Our aim was to review the clinical studies that tried to determine the impact of genetic and epigenetic factors on bariatric surgery outcomes.

Genetics of Bariatric Surgery

Considering the fact that obesity has an important genetic component, with a heritability estimated between 40-70% [11] it would make biological sense for weight loss interventions outcomes to be also influenced by genetic factors. Twin studies conducted on diet [12] and bariatric surgery [13] confirmed this hypothesis, showing a greater weight loss variation between unrelated controls than in twins. A study conducted on first degree relatives who underwent bariatric surgery also showed that related patients have a smaller difference in excess weight loss than cohabitating patients genetically unrelated [13,14].

Understanding how these genetics factors influence the effect of weight loss interventions will advance our knowledge about the biological mechanisms of weight loss at a molecular level and also help identify patients who will benefit the most from each type of intervention.

Candidate-gene Approach Studies

Single nucleotide polymorphisms (SNPs) are the most common genetic variants in the human genome and 97 SNPs were previously associated with a high BMI and estimated to be responsible for 20% of the BMI variation [15]. In order to find if these variants could also affect the outcomes of bariatric surgery, several studies based on a candidate gene approach were conducted (Table I). Some SNPs were associated with weight loss following bariatric surgery. Most of the studies were conducted on patients that underwent Roux en Y gastric bypass (RYGB) and laparoscopic gastric banding. Despite the evidence that genetic factors also play an important role in sleeve gastrectomy [16], few studies have been conducted on this procedure.

One of the most studied genes regarding this topic is the MC4R. This gene encodes the melanocortin 4 receptor and MC4R mutations lead to one of the most common forms of monogenic obesity [17]. Multiple studies showed that MC4R variant rs17782313 is also involved in the common multifactorial obesity [18]. Interestingly, the same polymorphism predicted a lesser weight loss in patients that underwent RYGB [19,20]. On the other hand, another MC4R variant (rs52820871), which is a protective factor against obesity [21], was associated with a higher weight loss, a lesser weight regain and also the improvement of metabolic status in patients 1 year after RYGB [22].

FTO gene is also strongly associated with obesity [23-25]. Despite the fact that many studies have been conducted on this gene, the mechanism by which FTO variants increase the risk of obesity is still unknown. A link was found however between FTO variants and increased food intake [26]. Physical activity has been found to reduce the influence of FTO variants on obesity risk [27]. Therefore, several scientific papers aimed to establish if FTO genotype could predict the bariatric surgery outcomes. At 6 months after gastric bypass, patients carrying the rs9939609 risk allele (A allele) were found to lose more weight and have a decreased HbA1c [28]. An opposite effect was observed in long term follow-up, where rs9939609 risk allele predicted a poor weight loss outcome [20,29]. Intriguingly, a meta-analysis which evaluated the relation between the FTO genotype and the response to diet and lifestyle interventions showed that the patients with the obesity-risk rs9939609 genotypes (TA and AA) have a greater weight loss than those carrying the wild variant [30]. These findings may suggest that patients with this variant could benefit more from dietary and lifestyle interventions, and less from bariatric surgery, but further research is required in order to confirm this idea.

Another gene which may play an important role in bariatric surgery is UCP2. This gene encodes the uncoupling protein 2, which is an anion carrier protein located in the mitochondrial membrane. The mentioned protein decreases the glucose stimulated insulin secretion, it is involved in the energetic cell metabolism and it may increase the energy expenditure and decrease the body weight [31]. Carriers of T allele of rs660339, which is a missense polymorphism in 4th exon, had a higher weight loss in three independent studies after 6 months, 1 and 2 years respectively [28,32,33]. Two other variants were also associated with a better outcome after gastric banding and RYGB [33,34]. Thus, this gene function may be involved in the mechanisms that lead to bariatric surgery induced weight loss.

The main limitation of these studies is the fact that tested variants are restricted to already known pathways and mechanisms, which in the case of bariatric surgery are

Table I - *SNPs associated with bariatric surgery outcomes in candidate-gene studies.*

Gene	SNP	Findings	Surgery type	Follow-up	Ref.
MC4R	rs17782313	C allele associated with treatment failure	RYGB	60 months	(19)
INSIG2	rs7566605	Poor weight loss outcome in patients with the obesity SNP alleles	RYGB	30 months	(20)
FTO	rs9939609				
MC4R	rs17782313				
PCSK1	rs6235				
MC4R	rs52820871	higher weight loss, less weight regain, metabolic status improvement	RYGB	12 months	(22)
FTO	rs16945088	Minor allele is associated with a poor outcome	Gastric banding	6 years	(35)
FTO	rs9930506	G allele is associated with a greater weight loss	Sleeve gastrectomy	6 months	(36)
UCP2	rs659366	A allele associated with better outcome	RYGB	1 year	(33)
	rs660339	T allele associated with better outcome			
UCP2	rs660339	T allele associated with better outcome	Gastric banding	12 and 24 months	(32)
FTO	rs9939609	Poor weight loss outcome in patients with the obesity SNP allele	RYGB	36, 48, 60 months	(29)
MTIF3	rs4771122	associated with weight loss trajectories, weight loss nadir, and long-term weight loss	RYGB	9.5 years	(37)
UCP2	rs660339	T allele associated with better outcome	Gastric banding	6 months	(28)
ESR1	rs712221	Risk allele associated with better outcome and decreased Hb1Ac	Mini-gastric bypass		
FTO	rs9939609	Risk allele associated with better outcome and decreased Hb1Ac			
PNPLA3	p.I148M	improvement of hepatic steatosis; greater weight loss	Gastric bypass	12 months	(38)
5-HT2C	rs3813929	TT genotype predicts better outcome in female patients	RYGB	12 months	(39)
FKBP5	rs1360780	T allele associated with poor outcome	RYGB	14 months	(40)
LYPLAL1	rs4846567	TT genotype associated with weight loss and decrease in hunger feelings	RYGB	2 years	(41)
IL-6	rs603573	GG genotype predicts greater weight loss	Gastric banding	6 months	(34)
UCP2	rs1800795	AA genotype predicts greater weight loss			
POMC	rs1042571	Higher weight loss	RYGB	12 months	(42)
TCF7L2	rs7903146	Decreased fasting blood glucose	RYGB	12 months	(43)

not yet well defined. Most of the studies tested variants that are linked with obesity, but there also may be genes involved in weight loss mechanisms, especially through bariatric surgery, which are not particularly in connection with obesity

Pathogenesis

Genome wide association studies (GWAS)

This type of studies have the advantage of testing a very large number of variants across the entire genome. Thus, the tested SNPs in this case are not limited to previously known mechanisms or hypotheses and may lead to discovery of new pathways involved in the organism's response to bariatric surgery.

Up to date, two studies used a GWAS approach in order to identify variants associated with bariatric surgery outcomes. Rinella et al. found 17 loci in 6 genes with different genotypes distribution between good and bad responders to RYBG [44]. One interesting finding of this study is a 6 SNPs PKHD1 haplotype CCAACT, which was strongly associated with the procedure outcome. PKHD1 gene is implicated in weight gain after antipsychotic therapy [45]. Other genes found in this GWAS are HTR1A, a gene known to be involved in appetite regulation [46], GUCY1A2, a gene previously associated with early-onset obesity [47], IGF1R, CENFP, and CITED2 which are involved in insulin and glucose metabolism[48-50].

Another GWAS study found and replicated an association between rs17702901 (a 15q26.1 locus near ST8SIA2 and SLCO3A1 genes) and weight loss after the RYBG procedure. ST8SIA2 expression in omental fat was also associated with weight loss after RYGB, but an association between this gene expression and rs17702901 was not found [51]. None of these studies confirmed any previously described association in candidate gene studies, possibly due to the small sample sizes.

Bariatric Surgery and Gene Expression

Several studies showed that bariatric surgery may impact the transcriptomic profile of different various tissues like subcutaneous adipose tissue, skeletal muscle or whole blood [52-57]. There is however an increased heterogeneity among studies, due to different time-points of the analysis, different tissue or different microarray platforms used. Another important variable among these studies is the surgery type they investigated, although in most of the

cases RYGB was performed. A computational analysis conducted by Freudenberg et al. showed that many genes which were previously associated with obesity and involved in pathways like inflammation, lipid metabolism, diabetes or amino acids metabolism, also showed different expressions after bariatric surgery [58].

One of the genes which was found to have an increased expression following bariatric surgery is IL-6 gene [58]. This gene encodes a cytokine which was previously shown to play a role in body-weight regulation [59]. Different results were observed however by Jürets et al, who showed that IL-6 expression in subcutaneous adipose tissue of obese patients decreased 1 year after bariatric surgery. The IL-6 expression was higher in the obese patients compared to controls at the baseline, but the post operatory IL-6 expression was even lower than in the control group [60]. Several other inflammatory cytokines like IL-1B, CCL-3 or IL-10 presented increased expression in like subcutaneous adipose fat of obese patients, with a marked decrease 1 year after the surgery. Interestingly, TNF gene presented an increased gene expression 1 year after the RYGB [60]. These findings point to a reduced inflammation in the adipose tissue after bariatric surgery. The high TNF expression may be explained by an increased lipolysis and adipose tissue catabolism.

Another study showed that preoperative increased adipose expression of IL6, as well as TNF and CD11B were associated with a higher chance of type 2 diabetes resolution [61].

De Olivera et al showed that UCP2 expression was higher 6 months after RYGB. Moreover, preoperative UCP2 and PLIN1 expression in abdominal subcutaneous adipose fat levels could influence the weight loss, independent of variables like age or BMI. These findings support the role of UCP2 in obesity and bariatric surgery induced weight loss.

Although these findings are useful in order to determine the mechanisms which contribute to the bariatric surgery outcomes, they may have limited relevance for the development of molecular biomarkers, due to the high costs and difficulty of adipose tissue collection. On the other hand, peripheral white blood cells are much easier to obtain. Several studies showed changes in whole blood gene expression following bariatric surgery [52,54], but there are still limited data available regarding the correlation between different gene expression in blood and surgery outcome. A recent study showed different whole blood expression of FTO, FAS and CCL2 genes in whole blood 6 months after sleeve gastrectomy [62]. However, these changes were not correlated with the weight loss or comorbidities resolution. Another study found that increased GIP expression 3 months after bariatric surgery was associated with the type 2 diabetes resolution [63].

Epigenetics of Bariatric Surgery

Environmental factors can influence the gene expression through several epigenetic mechanisms, such as histone post-translational modifications, non-coding RNAs or DNA methylation [64]. There is an increasing interest in epigenetics in the scientific community, and many studies were conducted in order to find its role in chronic diseases development, obesity among them. The most studied epigenetic regulatory mechanism in obesity remains the DNA methylation, although other epigenetic mechanisms such as microRNAs [65] and long non-coding RNAs [66] may also play a role in body weight regulation and energy metabolism.

DNA methylation (DNAm) consists in the methylation of the carbon 5 position of cytosine base, and in mammals it occurs especially in CG dinucleotides. The regions with a high density of CG dinucleotides are often referred as CpG sites and can usually be found in promoter and other gene regulatory regions [67]. DNAm is typically associated with a decreased gene expression

Table II - *Impact of bariatric surgery on specific genes promoter methylation*

Gene	Tissue	Findings	Surgery/ follow-up	Ref
PDK4, IL1B IL-6 TNFA, PPARGC1A (n=18)	Whole blood	Increased PDK4, IL1B IL-6 TNFA methylation Decreased PPARGC1 methylation	RYGB/ 12 months	(74)
PPARGC1A, PDK4 (n=8)	Skeletal muscle	Increased methylation and decreased expression of PDK4 Decreased methylation and increased expression of PPARGC1A	6 months	(78)
IL-6 SERPINE1 (n=14)	Whole blood	Decreased DNAm in IL6 promoter; SERPINE1 methylation predicted weight loss	RYGB/ 6 months	(79)
SCD (n=120)	Whole blood	Increase	RYGB/ 6 months	(80)
LEP, GHRL, GHSR, IGF2	Whole blood	DNAm could not predict RYGB outcome	RYGB/ 12 months	(81)
LEP (8)	Adipose tissue	Decreased expression of LEP but no change in methylation level	RYGB/ 2 years	(82)

when it occurs in enhancers or gene promoters and with active gene expression when established within the gene body [68].

The association between DNAm and obesity has been confirmed by multiple epigenome-wide association studies (EWAS) [69-72], where more than 100 CpG sites where found to be linked with BMI and waist circumference. Wahl et al [69] provided evidence that these CpG sites were more likely to be a consequence of obesity, rather than a cause of it. Therefore, these epigenetic changes may be involved in obesity complications pathogenesis. Many of these CpG sites are found in genes involved in lipid metabolism, substrate transport and inflammatory pathways.

These findings suggested the hypothesis that epigenetic regulation of genes expression could explain the multiple benefits of bariatric surgery and encouraged the research on DNAm in the context of these interventions. Although bariatric surgery was showed not to affect the global methylation levels in blood or skeletal muscle [73,74], when only promoter-specific DNA methylation profile was tested, it was found that promoters methylation of obese individuals changed after RYGB procedure and resembled that of non-obese patients [75]. Global postoperative hypomethylation was also detected in EWAS studies where adipose tissue was tested [76, 77]. These studies followed an EWAS approach in order to find CpG sites that are differently methylated before and after bariatric surgery. Many small changes in different CpGs methylation levels were found in genes involved in obesity, blood pressure or type 2 diabetes [76], supporting the hypothesis that gastric surgery benefits may be partly explained by epigenetic changes.

Several candidate gene studies showed the impact of bariatric surgery on specific genes promoter methylation (Table II). These results however should be treated carefully, due to the lack of reproducibility and their small sample sizes. IL-6 and PPARGC1A genes promoters were found to be differently methylated in more than one study. The PPARGC1A methylation level decreased after bariatric surgery, and the results were consistent both in skeletal muscle and whole blood [74,78]. On the other hand, the results regarding the IL-6 promoter are contradictory, which may be explained by the differences in study design [74,79].

An interesting finding was made by Donkin et al who showed that the spermatozoal epigenome is dynamically remodeled after bariatric surgery. DNA methylation of central control of appetite genes in sperm varied between obese and non-obese subjects and RYGB surgery-induced weight loss [83]. This finding offers insight into how obesity may propagate metabolic dysfunction to the next generation. Strikingly, different methylation in inflammation and type 2 diabetes related genes were found between siblings born before and after maternal bariatric surgery [84]. Genes involved in glucoregulatory pathways were also differently methylated in a similar manner [85]. These studies demonstrate that bariatric surgery conducted on women of reproductive age may change the metabolic and inflammatory genes expression, and therefore reduce obesity risk in their offspring, potentially via epigenetic mechanisms [86].

Future Perspectives

Further research is needed in order to understand the full picture of genetics and epigenetics importance in bariatric surgery outcomes. More GWAS studies with larger sample sizes and inclusion of different ethnic groups would offer valuable information about the genes involved in weight loss surgical interventions mechanism of action. Regarding the candidate gene approach studies, more replication studies are needed to confirm the previously associated variants showed in GWAS or other candidate gene studies.

A very important aspect is the discovery of new prognostic factors. This will help determine whether the genetic background may have a different impact on the numerous types of surgical treatments and to improve the quality of the therapeutic act. Studies which tried to apply a genetic risk score in order to predict the surgery success or failure were already published, with conflicting results [20,87-89]. These scores were mostly based on variants associated with BMI or waist circumference, rather than bariatric surgery outcomes, due to the fact that little research was made on this particular topic. Another important idea is that none of the published studies were focused on the effect of weight loss surgery on cardiovascular or metabolic status improvement. This approach could help us understand the mechanism of these outcomes and could also reveal variants that could serve as predictive factors for health benefits other than weight loss.

Epigenetic studies should also focus on surgery outcome and try to compare good and bad responders in order to find the association between the methylation status of different loci and the treatment response. Up to date, only one candidate gene study used this approach, and has showed that SERPINE1 promoter gene methylation is associated with a better response [79]. No EWAS study compared good and bad responders, possibly due to the small sample sizes. It is important to mention that most of the epigenetic studies were conducted on small sample sizes, and replication is needed in order to confirm the results.

Conclusion

The increasing interest in genetic and epigenetic mechanisms involved in bariatric surgery revealed findings that could help in a better understanding of the impact of this therapeutic approach at a molecular level. Although

several studies showed new pathways which may be related with bariatric surgery outcomes, further studies are required in order to apply a more personalized approach regarding obesity treatment through bariatric surgery.

Riassunto

L'obesità patologica (BMI> 40 kg/m^2) è una condizione di salute difficile da gestire con un'incidenza crescente negli ultimi decenni. La terapia convenzionale che consiste in interventi sulla dieta e sullo stile di vita, insieme alla terapia farmaceutica, ha un effetto limitato sui pazienti con obesità di terzo grado. In questo contesto, la chirurgia bariatrica è l'approccio più efficace, che porta a una significativa perdita di peso, insieme ad altri effetti benefici come la risoluzione del diabete di tipo 2 o il miglioramento delle malattie cardiovascolari.

Gli esiti della chirurgia bariatrica possono variare ampiamente da individuo a individuo, con una percentuale significativa di pazienti che hanno piccoli benefici dall'operazione. Queste variazioni possono essere parzialmente spiegate dal background genetico di ogni individuo.

Negli ultimi anni sono stati condotti diversi studi per determinare i fattori genetici ed epigenetici coinvolti negli esiti della chirurgia bariatrica. Molti geni coinvolti in diversi percorsi molecolari sono stati identificati associati alla perdita di peso dopo la chirurgia bariatrica. Studi epigenetici hanno rivelato che la metilazione dei geni può essere influenzata da interventi per la perdita di peso.

Tutti questi risultati suggeriscono che esiste un'intima connessione tra fattori genetici ed epigenetici e gli esiti della chirurgia bariatrica. Sono necessari ulteriori studi per capire meglio se la genetica può essere utilizzata per prevedere i risultati dell'operazione.

Il nostro scopo e quello di rivedere gli studi clinici che hanno cercato di determinare l'impatto di fattori genetici ed epigenetici sugli esiti della chirurgia bariatrica

References

1. *Obesity and overweight*. [cited, 2020; April 1]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight.

2. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH: *The disease burden associated with overweight and obesity*. JAMA [Internet], 1999; Oct 27 [cited, 2019; May 23]; 282(16):1523. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.282.16.1523.

3. Tsigos C, Hainer V, Basdevant A, Finer N, Fried M, Mathus-Vliegen E, et al.: *Management of obesity in adults: european clinical practice guidelines.* Obes Facts [Internet], 2008 [cited, 2019; May 23]; 1(2):106-16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20054170.

4. Golzarand M, Toolabi K, Farid R: *The bariatric surgery and weight losing: a meta-analysis in the long- and very long- term effects of laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy on weight loss in adults.* Surg Endosc [Internet], 2017; 31(11):4331-45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28378086.

5. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al.: *Bariatric surgery versus non-surgical treatment for obesity: A systematic review and meta-analysis of randomised controlled trials.* BMJ [Internet], 2013; Oct 22 [cited, 2019; May 23]; 347:f5934. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24149519.

6. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al.: *Bariatric surgery*. JAMA [Internet], 2004; Oct 13 [cited, 2019; May 23]; 292(14):1724. Available from: http://jama.jamanetwork.com/article.aspx? doi: 10.1001/jama.292.14.1724.

7. Noel OF, Still CD, Gerhard GS: *Genetics of bariatric surgery outcomes.* Endocrinol Metab Clin North Am, 2016; 45(3):623-32.

8. Thaler JP, Cummings DE: *Hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery.* Endocrinology, [Internet], 2009; Jun [cited, 2020; Jan 8]; 150(6):2518-25. Available from: https://academic.oup.com/endo/article-lookup/doi/10.1210/en.2009-0367.

9. Eldar S, Heneghan HM, Brethauer SA, Schauer PR: *Bariatric surgery for treatment of obesity.* Int J Obes, [Internet], 2011; Sep 13, [cited, 2019; May 23]; 35(S3):S16-21. Available from: http://www.nature.com/articles/ijo2011142.

10. Du J, Tian J, Ding L, Trac C, Xia B, Sun S, et al.: *Vertical sleeve gastrectomy reverses diet-induced gene-regulatory changes impacting lipid metabolism.* Sci Rep, [Internet]; 2017; 7(1):1-10. Available from: http://dx.doi.org/10.1038/s41598-017-05349-2.

11. Farooqi S, O'rahilly S: *Recent advances in the genetics of severe childhood obesity*. [cited, 2019; May 13]; Available from: http://adc.bmj.com/.

12. Hainer V, Stunkard A, Kunešová M, Parízková J, Štich V, Allison D: *Intrapair resemblance in very low calorie diet-induced weight loss in female obese identical twins*. Int J Obes, 2000; 248 [Internet], 2000; Sep 6 [cited, 2019; May 13]; 24(8):1051. Available from: http://www.nature.com/articles/0801358.

13. Hatoum IJ, Greenawalt DM, Cotsapas C, Reitman ML, Daly MJ, Kaplan LM: *Heritability of the Weight.* Loss Response to Gastric Bypass Surgery, 2015; 96(October):1630-3.

14. Boswell L, Jiménez A, Ortega E, Pané A, Hollanda A de, Moizé V, et al.: *Genetic background influences weight-loss trajectories on the mid-term after bariatric surgery*. Int J Obes [Internet], 2018; Oct 9 [cited, 2019; May 17]; 1. Available from: http://www.nature.com/articles/s41366-018-0229-4.

15. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature [Internet], 2015; Feb 12 [cited, 2019; May 13]; 518(7538):197-206. Available from: http://www.nature.com/articles/nature14177.

16. Shanti H, Obeidat F: *The impact of family members on weight loss after sleeve gastrectomy*. Surg Obes Relat Dis [Internet], 2016; Sep 1 [cited, 2019; May 17]; 12(8):1499-503. Available from: https://www.sciencedirect.com/science/article/pii/S1550728916300338.

17. Huvenne H, Dubern B, Clément K, Poitou C: *Rare genetic forms of obesity: Clinical approach and current treatments in 2016, obes facts* [Internet], 2016; [cited, 2019; May 17]; 9(3):158-73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27241181.

18. Xi B, Chandak GR, Shen Y, Wang Q, Zhou D: *Association between common polymorphism near the MC4R gene and obesity risk: A systematic review and meta-analysis*. PLoS One [Internet], 2012; [cited, 2019; May 17]; 7(9):e45731. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23049848.

19. Resende CMM, Durso DF, Borges KBG, Pereira RM, Rodrigues GKD, Rodrigues KF, et al.: *The polymorphism rs17782313 near MC4R gene is related with anthropometric changes in women submitted to bariatric surgery over 60 months*. Clin Nutr [Internet], 2018; Aug [cited, 2019; May 17]; 37(4):1286-92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28579220.

20. Still CD, Wood GC, Chu X, Erdman R, Manney CH, Benotti PN, et al.: *High allelic burden of four obesity SNPs is associated with poorer weight loss outcomes following gastric bypass surgery.* Obesity [Internet], 2011; Aug 10 [cited, 2019; May 17]; 19(8):1676-83. Available from: http://doi.wiley.com/10.1038/oby.2011.3.

21. Stutzmann F, Vatin V, Cauchi S, Morandi A, Jouret B, Landt O, et al.: *Non-synonymous polymorphisms in melanocortin-4 receptor protect against obesity: the two facets of a Janus obesity gene*. Hum Mol Genet [Internet], 2007; Aug 1 [cited, 2019; May 17]; 16(15):1837-44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17519222.

22. Mirshahi UL, Still CD, Masker KK, Gerhard GS, Carey DJ, Mirshahi T: *The MC4R(I251L) allele is associated with better metabolic status and more weight loss after gastric bypass surgery.* J Clin Endocrinol Metab [Internet], 2011; Dec 1 [cited, 2019; May 17]; 96(12):E2088-96. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2011-1549.

23. Scuteri A, Sanna S, Chen W-M, Uda M, Albai G, Strait J, et al.: *Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits*. PLoS Genet [Internet], 2007; [cited, 2019; May 16]; 3(7):e115. Available from: https://dx.plos.org/10.1371/journal.pgen.0030115.

24. Dina C, Meyre D, Gallina S, Durand E, Körner A, Jacobson P, et al.: *Variation in FTO contributes to childhood obesity and severe adult obesity.* Nat Genet [Internet], 2007; Jun 13 [cited, 2019; May 16]; 39(6):724-6. Available from: http://www.nature.com/articles/ng2048.

25. Herbert A, Gerry NP, McQueen MB, Heid IM, Pfeufer A, Illig T, et al.: *A common genetic variant is associated with adult and childhood obesity*. Science [Internet], 2006; Apr 14 [cited, 2019; May 16]; 312(5771):279-83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16614226.

26. Qi Q, Kilpeläinen TO, Downer MK, Tanaka T, Smith CE, Sluijs I, et al.: *FTO genetic variants, dietary intake and body mass index: Insights from 177 330 individuals*. Hum Mol Genet [Internet], 2014; Dec 20 [cited, 2019; May 16]; 23(25):6961-72. Available from: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddu411.

27. Kilpeläinen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, et al.: *Physical activity attenuates the influence of FTO variants on obesity risk: A meta-analysis of 218,166 Adults and 19,268 Children*. PLoS Med [Internet], 2011; Nov [cited, 2019; May 16]; 8(11):e1001116. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22069379.

28. Liou TH, Chen HH, Wang W, Wu SF, Lee YC, Yang WS, et al.: *ESR1, FTO, and UCP2 genes interact with bariatric surgery affecting weight loss and glycemic control in severely obese patients*. Obes Surg, 2011; 21(11):1758-65.

29. Rodrigues GK, Resende CMM, Durso DF, Rodrigues LAA, Silva JLP, Reis RC, et al.: *A single FTO gene variant rs9939609 is associated with body weight evolution in a multiethnic extremely obese population that underwent bariatric surgery*. Nutrition [Internet], 2015; 31(11-12):1344-50. Available from: http://dx.doi.org/10.1016/j.nut.2015.05.020.

30. Xiang L, Wu H, Pan A, Patel B, Xiang G, Qi L, et al.: *FTO genotype and weight loss in diet and lifestyle interventions: A systematic review and meta-analysis*. Am J Clin Nutr [Internet], 2016; Apr 1 [cited, 2019; May 16]; 103(4):1162-70. Available from: https://academic.oup.com/ajcn/article/103/4/1162/4662896.

31. Fisler JS, Warden CH: *The Ala55Val and -866G>t: A polymorphisms of the UCP2 gene could be biomarkers for weight loss in patients who had Roux-en-Y gastric bypass*. Nutrition [Internet], 2017; Jan 1 [cited, 2019; May 17]; 33:326-30. Available from: https://www.sciencedirect.com/science/article/pii/S0899900716301630.

34. Sesti G, Perego L, Cardellini M, Andreozzi F, Ricasoli C, Vedani P, et al.: *Impact of common polymorphisms in candidate genes for insulin resistance and obesity on weight loss of morbidly obese subjects after laparoscopic adjustable gastric banding and hypocaloric diet*. J Clin Endocrinol Metab [Internet], 2005; Sep 1 [cited, 2019; May 17]; 90(9):5064-9. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2005-0404.

35. Sarzynski MA, Jacobson P, Rankinen T, Carlsson B, Sjöström L, Bouchard C, et al.: *Associations of markers in 11 obesity candidate genes with maximal weight loss and weight regain in the SOS bariatric surgery cases*. Int J Obes [Internet], 2011; May 24 [cited, 2019; May 17]; 35(5):676-83. Available from: http://www.nature.com/articles/ijo2010166.

36. Figueroa-Vega N, Jordán B, Pérez-Luque EL, Parra-Laporte L, Garnelo S, Malacara JM: *Effects of sleeve gastrectomy and rs9930506 FTO variants on angiopoietin/Tie-2 system in fat expansion and M1 macrophages recruitment in morbidly obese subjects*. Endocrine [Internet], 2016; Dec 31 [cited, 2019; May 17]; 54(3):700-13. Available from: http://link.springer.com/10.1007/s12020-016-1070-y.

37. Rasmussen-Torvik LJ, Baldridge AS, Pacheco JA, Aufox SA, Kim KYA, Silverstein JC, et al.: *rs4771122 predicts multiple measures of long-term weight loss after bariatric surgery*. Obes Surg, 2015; 25(11):2225-9.

38. Krawczyk M, Jiménez-Agüero R, Alustiza JM, Emparanza JI, Perugorria MJ, Bujanda L, et al.: *PNPLA3 p.I148M variant is associated with greater reduction of liver fat content after bariatric surgery.* Surg Obes Relat Dis [Internet], 2016; Dec [cited, 2019; May 17]; 12(10):1838-46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27576208.

39. Novais PFS, Weber TK, Lemke N, Verlengia R, Crisp AH, Rasera-Junior I, et al.: *Gene polymorphisms as a predictor of body weight loss after Roux-en-Y gastric bypass surgery among obese women*. Obes Res Clin Pract [Internet], 2016; Nov 1 [cited, 2019; May 17]; 10(6):724-7. Available from: https://www.sciencedirect.com/science/article/pii/S1871403X1630059X.

40. Hartmann IB, Fries GR, Bücker J, Scotton E, von Diemen L, Kauer-Sant'Anna M: *The FKBP5 polymorphism rs1360780 is associated with lower weight loss after bariatric surgery: 26 months of follow-up*. Surg Obes Relat Dis [Internet], 2016; Sep [cited, 2019; May 17]; 12(8):1554-60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27421688.

41. Bandstein M, Mwinyi J, Ernst B, Thurnheer M, Schultes B, Schiöth HB: *A genetic variant in proximity to the gene LYPLAL1 is associated with lower hunger feelings and increased weight loss following Roux-en-Y gastric bypass surgery*. Scand J Gastroenterol [Internet], 2016; Sep [cited, 2019; May 17]; 51(9):1050-5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27181159.

42. Velázquez-Fernández D, Mercado-Celis G, Flores-Morales J, Clavellina-Gaytán D, Vidrio R, Vidrio E, et al.: *Analysis of gene candidate SNP and ancestral origin associated to obesity and postoperative weight loss in a cohort of obese patients undergoing RYGB*. Obes Surg [Internet], 2017; Jun 29 [cited, 2019; May 17]; 27(6):1481-92. Available from: http://link.springer.com/10.1007/s11695-016-2501-9.

43. Rouskas K, Cauchi S, Raverdy V, Yengo L, Froguel P, Pattou F: *Weight loss independent association of TCF7 L2 gene polymorphism with fasting blood glucose after Roux-en-Y gastric bypass in type 2 diabetic patients.* Surg Obes Relat Dis [Internet], 2014; Jul [cited, 2019; May 18]; 10(4):679-83. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1550728914000082.

44. Rinella ES, Still C, Shao Y, Wood GC, Chu X, Salerno B, et al.: *Genome-wide association of single-nucleotide polymorphisms with weight loss outcomes after roux-en-Y gastric bypass surgery.* J Clin Endocrinol Metab [Internet], 2013; Jun [cited, 2019; May 18]; 98(6):E1131-6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23633212.

45. Müller DJ, Kennedy JL: *Genetics of antipsychotic treatment emergent weight gain in schizophrenia.* Pharmacogenomics [Internet], 2006; Sep [cited, 2019; May 18]; 7(6):863-87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16981847.

46. Yadav VK, Oury F, Suda N, Liu Z-W, Gao X-B, Confavreux C, et al.: *A serotonin-dependent mechanism explains the leptin regulation of bone mass, appetite, and energy expenditure*. Cell [Internet], 2009; Sep 4 [cited, 2019; May 18]; 138(5):976-89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19737523.

47. Bochukova EG, Huang N, Keogh J, Henning E, Purmann C, Blaszczyk K, et al.: *Large, rare chromosomal deletions associated with severe early-onset obesity*. Nature [Internet], 2010; Feb 6 [cited, 2019; May 18]; 463(7281):666-70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19966786.

48. Coletta DK, Balas B, Chavez AO, Baig M, Abdul-Ghani M, Kashyap SR, et al.: *Effect of acute physiological hyperinsulinemia on gene expression in human skeletal muscle in vivo*. Am J Physiol Metab [Internet], 2008; May [cited, 2019; May 18]; 294(5):E910-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18334611.

49. Gallagher EJ, LeRoith D: *The proliferating role of insulin and insulin-like growth factors in cancer*. Trends Endocrinol Metab [Internet], 2010; Oct [cited, 2019; May 18]; 21(10):610-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20663687.

50. Pooley RD, Moynihan KL, Soukoulis V, Reddy S, Francis R, Lo C, et al.: *Murine CENPF interacts with syntaxin 4 in the regulation of vesicular transport*. J Cell Sci [Internet], 2008; Oct 15 [cited, 2019; May 18]; 121(20):3413-21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18827011.

51. Hatoum IJ, Greenawalt DM, Cotsapas C, Daly MJ, Reitman ML, Kaplan LM. *Weight loss after gastric bypass is associated with a variant at 15q26*.1. Am J Hum Genet [Internet], 2013; May 2 [cited, 2019; May 18]; 92(5):827-34. Available from: https://www.sciencedirect.com/science/article/pii/S0002929713001705.

52. Berisha SZ, Serre D, Schauer P, Kashyap SR, Smith JD: *Changes in whole blood gene expression in obese subjects with type 2 diabetes following bariatric surgery: A pilot study*. PLoS One, 2011; 6(3).

53. González-Plaza JJ, Gutiérrez-Repiso C, García-Serrano S, Rodriguez-Pacheco F, Garrido-Sánchez L, Santiago-Fernández C, et al.: *Effect of roux-en-Y gastric bypass-induced weight loss on the transcriptomic profiling of subcutaneous adipose tissue*. Surg Obes Relat Dis, 2016; Feb 1; 12(2):257-63.

54. Pinhel MA de S, Noronha NY, Nicoletti CF, de Oliveira BAP, Cortes-Oliveira C, Pinhanelli VC, et al.: *Changes in global transcriptional profiling of women following obesity surgery bypass.* Obes Surg, 2018; 28(1):176-86.

55. Poitou C, Perret C, Mathieu F, Truong V, Blum Y, Durand H, et al.: *Bariatric surgery induces disruption in inflammatory signaling pathways mediated by immune cells in adipose tissue: A RNA-seq study*. PLoS One, 2015; 10(5):1-23.

56. Dankel SN, Fadnes DJ, Stavrum AK, Stansberg C, Holdhus R, Hoang T, et al.: *Switch from stress response to homeobox transcription factors in adipose tissue after profound fat loss*. PLoS One [Internet], 2010; [cited, 2020; Sep 8]; 5(6). Available from: /pmc/articles/PMC2882947/?report=abstract.

57. Park JJ, Berggren JR, Hulver MW, Houmard JA, Hoffman EP: *GRB14, GPD1, and GDF8 as potential network collaborators in weight loss-induced improvements in insulin action in human skeletal muscle*. Physiol Genomics [Internet], 2006; Oct 11 [cited, 2020; Sep 8]; 27(2):114-21. Available from: http://physiolgenomics.physiology.org.

58. Freudenberg JM, Rajpal N, Way JM, Magid-Slav M, Rajpal DK: *Gastrointestinal weight-loss surgery: Glimpses at the molecular level*. Drug Discov Today [Internet], 2013; 18(13-14):625-36. Available from: http://dx.doi.org/10.1016/j.drudis.2012.12.006.

59. Gregor MF, Hotamisligil GS: *Inflammatory mechanisms in obesity*. Annu Rev Immunol [Internet], 2011; Apr 23 [cited, 2020; Sep 8]; 29(1):415-45. Available from: http://www.annualreviews.org/doi/10.1146/annurev-immunol-031210-101322.

60. Jürets A, Itariu BK, Keindl M, Prager G, Langer F, Grablowitz V, et al.: *Upregulated TNF expression 1 year after bariatric surgery reflects a cachexia-like state in subcutaneous adipose tissue*. Obes Surg, 2017; 27(6):1514-23.

61. Garrido-Sánchez L, Tomé M, Santiago-Fernández C, García-Serrano S, García-Fuentes E, Tinahones FJ: *Adipose tissue biomarkers involved in early resolution of type 2 diabetes after bariatric surgery*. Surg Obes Relat Dis, 2017; 13(1):70-7.

62. Beisani M, Pappa S, Moreno P, Martínez E, Tarascó J, Granada ML, et al.: *Laparoscopic sleeve gastrectomy induces molecular changes in peripheral white blood cells*. Clin Nutr, 2020; 39(2):592-8.

63. Moran-Atkin E, Brody F, Fu SW, Rojkind M: *Changes in GIP gene expression following bariatric surgery*. Surg Endosc, 2013; 27(7):2492-7.

64. Xu W, Wang F, Yu Z, Xin F: *Epigenetics and cellular metabolism*. Genet Epigenet [Internet], 2016; Jan 25 [cited, 2019; May 18]; 8:GEG.S32160. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27695375.

65. Heneghan HM, Miller N, Kerin MJ: *Role of microRNAs in obesity and the metabolic syndrome*. Obes Rev [Internet], 2010; May 1 [cited, 2019; May 18]; 11(5):354-61. Available from: http://doi.wiley.com/10.1111/j.1467-789X.2009.00659.x.

66. Giroud M, Scheideler M: *Long non-coding RNAs in metabolic organs and energy homeostasis*. Int J Mol Sci [Internet], 2017; Nov 30 [cited, 2019; May 18]; 18(12):2578. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29189723.

67. Tollefsbol TO: *An overview of medical epigenetics*. In: Medical Epigenetics [Internet], Academic Press, 2016 [cited, 2019; May 18], p. 3-7. Available from: https://www.sciencedirect.com/science/article/pii/B9780128032398000016.

68. Jones PA: *Functions of DNA methylation: islands, start sites, gene bodies and beyond*. Nat Rev Genet [Internet], 2012; Jul 29 [cited, 2019; May 18]; 13(7):484-92. Available from: http://www.nature.com/articles/nrg3230.

69. Wahl S, Drong A, Lehne B, Loh M, Scott WR, Kunze S, et al.: *Epigenome-wide association study of body mass index and the adverse outcomes of adiposity*. Nature [Internet], 2017; Jan 21 [cited, 2019; May 18]; 541(7635):81-6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28002404.

70. Akinyemiju T, Do AN, Patki A, Aslibekyan S, Zhi D, Hidalgo B, et al.: *Epigenome-wide association study of metabolic syndrome in African-American adults*. Clin Epigenetics, 2018; 10(1):1-8.

71. Demerath EW, Guan W, Grove ML, Aslibekyan S, Mendelson M, Zhou Y-H, et al.: *Epigenome-wide association study (EWAS) of BMI, BMI change and waist circumference in African American adults identifies multiple replicated loci*. Hum Mol Genet [Internet], 2015; Aug 1 [cited, 2019; May 18]; 24(15):4464-79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25935004.

72. Meeks KAC, Henneman P, Venema A, Burr T, Galbete C, Danquah I, et al.: *An epigenome-wide association study in whole blood of measures of adiposity among ghanaians: The RODAM study*. Clin Epigenetics [Internet], 2017; Dec 21 [cited, 2019; May 18]; 9(1):103. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28947923.

73. Barres R, Kirchner H, Rasmussen M, Yan J, Kantor FR, Krook A, et al.: *Weight loss after gastric bypass surgery in human obesity remodels promoter methylation*. Cell Rep, 2013; 3(4):1020-7.

74. Kirchner H, Nylen C, Laber S, Barrès R, Yan J, Krook A, et al.: *Altered promoter methylation of PDK4, IL1 B, IL6, and TNF after roux-en Y gastric bypass*. Surg Obes Relat Dis [Internet], 2014; Jul 1 [cited, 2018; Dec 18]; 10(4):671-8. Available from: https://www.sciencedirect.com/science/article/pii/S1550728914000288.

75. Nilsson EK, Ernst B, Voisin S, Almén MS, Benedict C, Mwinyi J, et al.: *Roux-en Y gastric bypass surgery induces genome-wide promoter-specific changes in DNA methylation in whole blood of obese patients*. PLoS One, 2015; 10(2):1-11.

76. Benton MC, Johnstone A, Eccles D, Harmon B, Hayes MT, Lea RA, et al.: *An analysis of DNA methylation in human adipose tissue reveals differential modification of obesity genes before and after gastric bypass and weight loss*. Genome Biol, 2015; 16(1):1-21.

77. Dahlman I, Sinha I, Gao H, Brodin D, Thorell A, Rydén M, et al.: *Weight loss after gastric bypass surgery in human obesity remodels promoter methylation*. Cell Rep [Internet], 2013; Apr 25 [cited, 2019; May 19]; 3(4):1020-27. Available from: https://www.sciencedirect.com/science/article/pii/S2211124713001253.

79. Ferreira Nicoletti C, Barbosa Nonino C, Affonso Parenti de Oliveira B, Augusta de Souza Pinhel M, Luisa Mansego M, Ignacio Milagro F, et al.: *DNA methylation and hydroxymethylation levels in relation to two weight loss strategies: Energy-restricted diet or bariatric surgery*. Obes Surg [Internet], 2016 [cited, 2018; Dec 18]; 26:603-11. Available from: https://link.springer.com/content/pdf/10.1007%2Fs11695-015-1802-8.pdf.

80. Morcillo S, Martín-Núñez GM, García-Serrano S, Gutierrez-Repiso C, Rodriguez-Pacheco F, Valdes S, et al.: *Changes in SCD gene DNA methylation after bariatric surgery in morbidly obese patients are associated with free fatty acids*. Sci Rep [Internet], 2017; Dec 10 [cited, 2019; May 18]; 7(1):46292. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28393901.

81. Coppedè F, Seghieri M, Stoccoro A, Santini E, Giannini L, Rossi C, et al.: *DNA methylation of genes regulating appetite and prediction of weight loss after bariatric surgery in obese individuals*. J Endocrinol Invest [Internet], 2019; Jan 30 [cited, 2019; May 18]; 42(1):37-44. Available from: http://link.springer.com/10.1007/s40618-018-0881-5.

82. Marchi M, Lisi S, Curcio M, Barbuti S, Piaggi P, Ceccarini G, et al.: *Human leptin tissue distribution, but not weight loss-dependent change in expression, is associated with methylation of its promoter*. Epigenetics [Internet], 2011; Oct 27 [cited, 2019; May 18]; 6(10):1198-206. Available from: http://www.tandfonline.com/doi/abs/10.4161/epi.6.10.16600.

83. Donkin I, Versteyhe S, Ingerslev LR, Qian K, Mechta M, Nordkap L, et al.: *Obesity and bariatric surgery drive epigenetic variation of spermatozoa in humans*. Cell Metab, 2016; 23(2):369-78.

84. Toro-martín J De, Guénard F, Tchernof A, Pérusse L, Marceau S, Vohl M: *Polygenic risk score for predicting weight loss after bariatric surgery*. 2018; 1-12.

85. Guenard F, Deshaies Y, Cianflone K, Kral JG, Marceau P, Vohl M-C: *Differential methylation in glucoregulatory genes of offspring born before vs after maternal gastrointestinal bypass surgery*. Proc Natl Acad Sci [Internet], 2013; Jul 9 [cited, 2019; May 19]; 110(28):11439-44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23716672.

86. Patti ME: *Reducing maternal weight improves offspring metabolism and alters (or modulates) methylation*. Proc Natl Acad Sci [Internet], 2013; Aug 6 [cited, 2019; May 19]; 110(32):12859-60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23884649.

87. Bandstein M, Voisin S, Nilsson EK, Schultes B, Ernst B, Thurnheer M, et al.: *A genetic risk score is associated with weight loss following roux-en y gastric bypass* surgery. Obes Surg [Internet], 2016; Sep 30 [cited, 2019; May 23]; 26(9):2183-9. Available from: http://link.springer.com/10.1007/s11695-016-2072-9.

88. Käkelä P, Jääskeläinen T, Torpström J, Ilves I, Venesmaa S, Pääkkönen M, et al.: *A genetic risk score for the estimation of weight loss after bariatric surgery*. [cited, 2020; Sep 8]; Available from: https://doi.org/10.1007/s11695-019-04320-6.