Published in final edited form as:

Surg Obes Relat Dis. 2016 February ; 12(2): 377–378. doi:10.1016/j.soard.2015.10.083.

Comment on: Comparative physiogenomic analyses of weight loss in response to two modes of bariatric surgery: demonstration with candidate neuropsychiatric and cardiometabolic genes

Tooraj Mirshahi, Ph.D. and Peter N. Benotti, M.D.

Geisinger Clinic, Danville, PA

Precision medicine, a recently popularized term, aims to use patient-specific information to improve clinical practice [1]. A major part of precision medicine that has attracted particular attention involves use of genetic information for patient care. Genetic and genomics data are becoming more cost-effective and readily available. In this context, Seip et al. have performed a timely “physiogenomic” analysis of patients with different extremes of weight loss outcomes after bariatric surgery. The study focused on patients in the top and bottom quartiles of weight loss after 2 different types of surgery: laparoscopic adjustable gastric banding (LAGB) and Roux-en-Y gastric bypass (RYGB). The study tested the association of 384 single nucleotide polymorphisms (SNP) with 1-year weight loss outcomes.

The authors tested the association of select variants in or close to several genes with lowest and highest quartiles of weight loss outcome. Many of the selected genes play critical roles in either the metabolic or neuropsychiatric pathways contributing to obesity. Genetics play a role in both obesity [2] and weight loss after surgery [3]. Previous studies on genetics of postsurgery weight loss have looked at both common [4,5], typically defined as >1% to 5% frequency, and rare genetic variants [6–8] but are limited to RYGB weight loss outcomes. The Seip et al. study did not discover any variants that are significantly associated with differential weight loss among the RYGB subgroup. This is not surprising because previously identified genetic variants that contribute to weight loss outcomes were not included in the SNP panel used in the study. In addition, the study likely was underpowered to find such differences.

So far, most genetic analyses have found limited effect size for specific genetic factors [4–6,9] with regard to weight loss, limiting their utility in predicting outcomes or in patient selection. A major value of studies on genetic association with weight loss outcomes after bariatric surgery is in identification of biologic targets and pathways that may be critical for weight loss. For example, a very common variant close to *MC4R* is associated with obesity and predicts slightly poorer RYGB outcomes [4], and a coding variant in *MC4R* is negatively associated with obesity and predicts slightly better RYGB outcomes [9]. These findings do not warrant genetic testing for *MC4R* before surgery, per se; however, they point to the critical role of the *MC4R* physiologic pathway in weight loss [7,8] and the potential for targeting *MC4R* for pharmacotherapy in improving weight loss outcomes.

The authors' findings in the LAGB cohort did reach significance for 1 SNP in apolipoprotein E (*APOE*) after Bonferroni correction for multiple testing. The *APOE* findings and clarification of a role for genes in the neuropsychiatric and cardiometabolic pathways in LAGB are important. However, LAGB surgeries are performed less frequently, possibly limiting the clinical value of these findings.

Seip et al. found different genetic contributors to weight loss after RYGB and LAGB. A next obvious step is to compare genetic contributors to outcomes after the 2 most common bariatric procedures, RYGB and laparoscopic sleeve gastrectomy. Comprehensive approaches using the latest available data, from whole exome and genome sequencing and other "omics" approaches (including proteomic, transcriptomic, epigenomic, metabolomic, and microbiome analyses), will continue to identify critical "players" in bariatric surgery outcomes. Clinical predictors of weight loss after surgery have been reported [10] and will continue to improve with larger and new studies. Combining the "omics" data with clinical predictors promises to further improve our ability to more accurately forecast surgical weight loss outcomes and resolution of co-morbidities, which, as the authors point out, may improve patient selection and allocation of resources. Finally, although these "omics" findings may not always lead to new predictive tests for bariatric outcomes, they do provide a clearer picture for the physiologic basis of surgical outcomes.

References

1. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015; 372(9):793–5. [PubMed: 25635347]
2. Bouchard C, Tremblay A, Despres JP, et al. The response to long-term overfeeding in identical twins. *N Engl J Med*. 1990; 322(21):1477–82. [PubMed: 2336074]
3. Hatoum IJ, Greenawalt DM, Cotsapas C, Reitman ML, Daly MJ, Kaplan LM. Heritability of the weight loss response to gastric bypass surgery. *J Clin Endocrinol Metab*. 2011; 96(10):E1630–3. [PubMed: 21832118]
4. Still CD, Wood GC, Chu X, et al. High allelic burden of four obesity SNPs is associated with poorer weight loss outcomes following gastric bypass surgery. *Obesity (Silver Spring)*. 2011; 19(8):1676–83. [PubMed: 21311511]
5. Hatoum IJ, Greenawalt DM, Cotsapas C, Daly MJ, Reitman ML, Kaplan LM. Weight loss after gastric bypass is associated with a variant at 15 q26.1. *Am J Hum Genet*. 2013; 92(5):827–34. [PubMed: 23643386]
6. Moore BS, Mirshahi UL, Yost EA, et al. Long-term weight-loss in gastric bypass patients carrying melanocortin 4 receptor variants. *PLoS One*. 2014; 9(4):e93629. [PubMed: 24705671]
7. Hatoum IJ, Stylopoulos N, Vanhoose AM, et al. Melanocortin-4 receptor signaling is required for weight loss after gastric bypass surgery. *J Clin Endocrinol Metab*. 2012; 97(6):E1023–31. [PubMed: 22492873]
8. Zechner JF, Mirshahi UL, Satapati S, et al. Weight-independent effects of Roux-en-Y gastric bypass on glucose homeostasis via melanocortin-4 receptors in mice and humans. *Gastroenterology*. 2013; 144(3):580–90.e7. [PubMed: 23159449]
9. Mirshahi UL, Still CD, Masker KK, Gerhard GS, Carey DJ, Mirshahi T. The MC4 R(I251 L) allele is associated with better metabolic status and more weight loss after gastric bypass surgery. *J Clin Endocrinol Metab*. 2011; 96(12):E2088–96. [PubMed: 21976721]
10. Still CD, Wood GC, Chu X, et al. Clinical factors associated with weight loss outcomes after Roux-en-Y gastric bypass surgery. *Obesity (Silver Spring)*. 2014; 22(3):888–94. [PubMed: 23804287]