Genetics of Bariatric Surgery Outcomes

Olivier F. Noel, BS[a,b,c], Christopher D. Still, DO[d], Glenn S. Gerhard, MD[e,*]

KEYWORDS

• Bariatric surgery • Genetics • Weight loss • Type 2 diabetes mellitus • NAFLD

KEY POINTS

- Outcomes after bariatric surgery can vary widely and seem to have a significant genetic component.
- Only a small number of candidate gene studies and genome-wide association studies (GWAS) have analyzed bariatric surgery outcomes.
- The role of bile acids in mediating the beneficial effects of bariatric surgery implicate genes regulated by the farnesoid X receptor (FXR) transcription factor.

INTRODUCTION

The lack of adequate medical therapies for morbid or extreme obesity (body mass index [BMI] >40 kg/m^2) and type 2 diabetes mellitus (T2D) has led to the use of bariatric surgery, in particular the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) procedures. Several large observational studies have shown lasting (>5 years) weight loss and dramatic improvements in T2D after bariatric surgery,[1] which also seems to improve lipid parameters and decrease long-term cardiovascular events. Several clinical factors have been identified that can affect weight loss after RYGB[2] but few studies have addressed genetic influences on these outcomes.

The beneficial metabolic effects of bariatric surgery have been observed for more than 50 years[3] and have been confirmed by numerous subsequent studies in humans

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[a] Lewis Katz School of Medicine, Temple University, 3500 North Broad Street, Philadelphia, PA 19140, USA; [b] Penn State College of Medicine, 500 University Drive, Hershey, PA 17033, USA; [c] DNAsimple, Philadelphia, PA, USA; [d] Department of Gastroenterology and Nutrition, Geisinger Clinic, 100 North Academy Avenue, Danville, PA 17822, USA; [e] Department of Medical Genetics and Molecular Biochemistry, Lewis Katz School of Medicine, Temple University, 960 Medical Education and Research Building (MERB), 3500 North Broad Street, Philadelphia, PA 19140, USA
* Corresponding author.
E-mail address: gsgerhard@Temple.edu

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and animal models, but the molecular mechanisms underlying these effects are not yet well delineated. Much attention has also focused on incretins, in particular glucagon-like peptide 1 (GLP-1), although comprehensive reviews attributed only some or none of the antidiabetic effects to GLP-1.[4] The other main classes of hypotheses[5] are based on alterations in the flow and anatomic routing of ingested nutrients. The foregut hypothesis posits that bypass and exclusion from contact with ingested nutrients of the proximal small intestine (foregut), primarily the duodenum, changes the production of a mediator that produces direct anti-T2D effects. Procedures that cause malabsorption through intestinal bypass have dramatic effects on T2D. The lower intestinal or hindgut hypothesis is based on the premise that inappropriate delivery of ingested nutrients and/or digestive juices to more distal regions of the small intestine induces a putative molecular mediator that ameliorates T2D. Bile acids have been implicated as key molecules in this hypothesis.[3,4] A seeming confounder to this hypothesis is the SG, a restrictive and nonmalabsorptive operation that is increasingly used instead of RYGB, which is a partial gastrectomy in which the stomach becomes a vertical tube or sleeve. The SG also results in resolution of T2D, which seems to contradict the inappropriate delivery of nutrients and digestive components to the distal intestine hypothesis. Gastric transit is substantially increased in SG, however, expediting delivery of digesta, including bile acids through the duodenum into the distal intestine.[4]

Bile acids can bind to the G protein–coupled TGR5 cellular receptor to mediate signaling.[6] Bile acids also function as a ligand for a specific nuclear transcription factor, the FXR, which forms a heterodimeric complex with retinoid X receptor α that binds to an inverted repeat sequence in gene promoters.[7] Recently, FXR has been shown to be required for weight loss and improvements in glucose metabolism after SG in mice.[8] Further delineation of the molecular mechanisms underlying these beneficial effects could provide targets for the development of new nonsurgical treatments.

HERITABILITY OF WEIGHT LOSS OUTCOMES

Although RYGB surgery is among the most successful interventions for long-term weight loss in extreme obesity, the degree of weight loss after surgery is variable, with an estimated 20% of patients failing to achieve or maintain greater than 50% loss of their excess body weight.[9] Clinical factors affecting weight loss after RYGB include higher initial BMI and T2D.[2] Studies of twins and close relatives have provided strong evidence of a genetic component to dietary and surgical weight loss.[10] These data indicate that genetic factors may influence weight loss after bariatric surgery.

CANDIDATE GENES AND BARIATRIC WEIGHT LOSS

Several studies have analyzed the association of polymorphisms in candidate genes with weight loss after bariatric surgery. For example, patients with melanocortin-4 receptor (MC4R) mutations achieve superior weight loss outcomes from procedures, such as RYGB, that produce neurohormonal changes rather than gastric restriction alone, possibly through effects on appetite and satiety regulation.[11] Polymorphisms near the growth hormone secretagogue receptor gene, or ghrelin receptor, have been studied in association with weight loss outcomes 30 months after RYGB. Patients homozygous for the rs490683-CC genotype – located in the promoter region of the growth hormone secretagogue receptor gene – exhibited significantly more weight loss than those who carried the T allele.[12] An association between the variant rs9939609 located in the fat mass and obesity-associated protein (FTO) gene and