Review Article

Association Between Plausible Genetic Factors and Weight Loss from GLP-1 Receptor Agonists and Bariatric Surgery: A Review

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Abstract: Obesity has emerged as one of the most pressing public health challenges of the twenty-first century, with prevalence rates tripling globally since 1975 and now affecting over 650 million adults (World Health Organization, 2023). In response, a growing array of therapeutic modalities—including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and bariatric surgery—has demonstrated significant efficacy in achieving sustained weight reduction and metabolic improvements. Nevertheless, substantial inter-individual variability in treatment outcomes remains a formidable obstacle: while some patients experience dramatic and durable weight loss, others attain only modest benefit or encounter weight regain. Recent advances in human genetics have begun to illuminate the underlying sources of this heterogeneity, implicating inherited variants in key neuroendocrine and metabolic pathways. In this review, we synthesize evidence from genome-wide association studies (GWAS), targeted candidate-gene investigations, and prospective clinical cohorts to characterize how polymorphisms in melanocortin-4 receptor (MC4R), fat mass and obesity-associated (FTO), transcription factor 7-like 2 (TCF7L2), GLP-1 receptor (GLP1R), and other loci modulate responsiveness to both pharmacological and surgical interventions. We examine mechanistic insights—such as altered receptor expression, signaling efficacy, and appetite regulation—that link specific alleles to differential weight-loss trajectories, glycemic control, and long-term maintenance. Furthermore, we evaluate emerging strategies for integrating polygenic risk scores (PRS) and pharmacogenomic biomarkers into clinical decision-making, with the aim of enabling precision obesity medicine. By mapping the genetic determinants of GLP-1 RA efficacy and post-bariatric surgical outcomes, we highlight opportunities to tailor treatment selection, optimize dosing regimens, and ultimately enhance therapeutic success rates. Future research priorities include expanding multi-ethnic cohorts, harmonizing phenotype definitions, and conducting randomized trials of genotype-informed therapies. Understanding the genetic architecture of weight-loss response promises to transform obesity management from a one-size-fits-all paradigm to an individualized, data-driven approach.

Keywords: plausible, genetic factors, weight loss, glp-1 receptor, agonists, bariatric surgery

1. INTRODUCTION

Obesity represents one of the most intricate and pervasive health challenges facing modern societies, arising from a dynamic interplay of environmental exposures, lifestyle behaviors, and inherited genetic factors [1]. At its core, obesity develops when energy intake chronically exceeds energy expenditure, yet the drivers of this imbalance extend far beyond simple willpower or caloric counting. Urbanization has reshaped food environments across the globe, flooding communities with high-calorie, nutrient-poor options that stimulate palatable eating and undermine traditional dietary patterns; simultaneous

declines in occupational physical activity and the proliferation of sedentary leisure pursuits—such as long hours seated at desks or in front of screens—have compounded the imbalance, creating fertile ground for weight gain [2]. Behavioral determinants of obesity encompass not only caloric consumption and physical activity but also the psychological dimensions of eating: stress-induced bingeing, disrupted sleep that alters appetite-regulating hormones, ingrained habits formed in early childhood, and cultural norms that valorize larger body sizes in some contexts or, conversely, stigmatize weight gain in ways that drive cycles of dieting and rebound overeating. Overlaying this environmental and behavioral substrate is a robust genetic architecture: twin and family studies consistently estimate that 40–70% of interindividual variation in body mass index (BMI) can be attributed to heritable factors, while genome-wide association studies have uncovered over a hundred loci—most notably variants in the FTO and MC4R genes—that confer modest but cumulative effects on energy intake, satiety signaling, and adipocyte differentiation [3]. In light of these multifaceted influences, it is unsurprising that therapeutic interventions yield variable outcomes: pharmacological agents such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) harness incretin pathways to reduce appetite and slow gastric emptying, yet patient responses range from dramatic 15–20% reductions in baseline weight to more modest 5% losses, influenced in part by genetic polymorphisms that affect receptor sensitivity and downstream signaling cascades. Similarly, bariatric procedures—including Roux-en-Y gastric bypass and sleeve gastrectomy—deliver substantial and often sustained weight loss via mechanical restriction, hormonal shifts, and alterations in gut microbiota, but a nontrivial subset of patients experiences primary nonresponse or significant weight regain, with emerging evidence implicating inherited variations in genes governing neuropeptide Y, leptin receptor function, and energy homeostasis as modulators of post-surgical trajectories. Against this backdrop of heterogeneous efficacy, the promise of precision medicine has begun to galvanize efforts to decode the genetic determinants of treatment success and to translate these insights into individualized care pathways [4]. By systematically cataloguing single-nucleotide polymorphisms and haplotypes that influence drug metabolism, receptor expression, appetite regulation, and adipose tissue remodeling, researchers aim to develop predictive models—ranging from single-gene assays to composite polygenic risk scores—that can forecast which patients are likely to derive the greatest benefit from specific pharmacotherapies or surgical techniques. Implementation of such pharmacogenomic approaches could streamline clinical decision-making, sparing individuals from ineffective or poorly tolerated interventions, reducing time lost in trial-and-error cycles, and optimizing resource allocation within strained health care systems. Moreover, identifying genetic markers linked to weight-loss resistance may prompt early adjunctive measures—such as intensification of behavioral support, tailored nutritional counseling, or combination drug regimens—to preempt suboptimal outcomes [5]. However, realizing the full potential of personalized obesity treatment necessitates overcoming significant challenges: most pharmacogenetic associations have been identified in relatively small, ethnically homogeneous cohorts, limiting generalizability; effect sizes of individual variants are often modest, requiring aggregation into polygenic frameworks and integration with clinical variables (e.g., age, sex, baseline BMI, comorbidities) and environmental factors (e.g., diet quality, physical activity levels) to achieve clinically actionable predictive power [6]. Additionally, disparities in access to genetic testing and the ethical considerations around data privacy, potential stigmatization, and insurer use of genetic information must be thoughtfully navigated. Standardization of outcome measures—such as uniform definitions of clinically meaningful weight loss, protocols for follow-up duration, and metrics for weight regain—is essential to harmonize studies and facilitate the construction of robust, externally validated algorithms. Looking ahead, the integration of multi-omics datasets—including transcriptomic, proteomic, metabolomic, and microbiome profiles—with high-resolution phenotyping and real-world digital health monitoring platforms holds promise for unveiling novel biomarkers and mechanistic pathways underlying interindividual differences in treatment response [7]. Machine learning and advanced biostatistical methods can mine these rich data

streams to identify latent phenotypic clusters, predict longitudinal weight trajectories, and uncover gene–environment interactions that may inform combination therapies. Ultimately, by illuminating the complex genetic underpinnings of obesity treatment variability and leveraging this knowledge to tailor interventions, the field moves closer to a future in which each patient's therapeutic regimen is optimized not through trial and error, but through precise alignment of their unique biological blueprint with the most effective pharmacological, surgical, and behavioral strategies.

2. GLP-1 RECEPTOR AGONISTS AND WEIGHT LOSS

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have revolutionized the pharmacologic management of obesity by harnessing the body's own incretin system. Agents such as liraglutide (approved at 3.0 mg daily for weight management) and semaglutide (2.4 mg weekly) structurally mimic endogenous GLP-1, a hormone secreted by the intestinal L-cells in response to nutrient ingestion. After subcutaneous administration, these analogues bind to GLP-1 receptors on pancreatic β-cells, amplifying glucose-stimulated insulin secretion while simultaneously inhibiting α-cell glucagon release. Beyond glycemic control, GLP-1 RAs exert profound effects on gastric motility—delaying gastric emptying by up to 30–50%—and act centrally in the hypothalamus and brainstem to reduce hedonic and homeostatic appetite signals [8]. Clinical trials consistently demonstrate that GLP-1 RAs produce significant and sustained weight reductions in overweight and obese populations. In the landmark SCALE trial, liraglutide 3.0 mg yielded a mean placebo-adjusted weight loss of 8.0% at 56 weeks, with nearly two-thirds of participants achieving ≥5% body-weight reduction and one-third achieving ≥10% [9]. More recently, the STEP program showcased semaglutide's even greater potency: participants lost an average of 14.9% of baseline weight after 68 weeks, and 86% achieved at least 5% weight loss [10]. Real-world evidence echoes these findings but also underscores substantial interindividual heterogeneity: some patients experience dramatic 20–25% weight loss, whereas others lose less than 5%, and up to 20% may be classified as "non responders" (<5% weight loss) [11]. Emerging data suggest that this variability is not merely stochastic but is partly attributable to inherited genetic differences. The GLP1R gene itself harbors functional single-nucleotide polymorphisms (SNPs)—notably rs6923761 (Gly168Ser) and rs10305420 (promoter variant)—that influence receptor expression levels, ligand-binding affinity, and downstream cyclic AMP signaling. In several cohorts, carriers of the Ser allele at rs6923761 demonstrated 20–30% less weight loss and smaller improvements in glycemic indices when treated with liraglutide or semaglutide, compared to Gly homozygotes. Likewise, individuals with the T allele at rs10305420 exhibited reduced GLP1R mRNA in peripheral mononuclear cells and correspondingly blunted anorectic responses [12]. Beyond GLP1R, polymorphisms in other metabolic and neuroendocrine genes modulate GLP-1 RA efficacy. Variants in FTO (rs9939609) are associated with diminished satiety signaling and up to 15% lower weight reduction, potentially through altered hypothalamic demethylation pathways. MC4R noncoding SNPs (rs17782313) correlate with attenuated appetite suppression and may necessitate higher GLP-1 RA dosing for equivalent weight outcomes. TCF7L2 (rs7903146) variants influence endogenous incretin secretion and β-cell responsiveness, with T-allele carriers showing both reduced weight loss and glycemic benefit on liraglutide. Together, these pharmacogenetic insights underscore a polygenic framework in which multiple SNPs—each with modest effect size—collectively shape the magnitude and durability of weight loss achieved with GLP-1 receptor agonist therapy [13]. Understanding these genetic contributors holds promise for precision obesity medicine: integrating GLP1R, FTO, MC4R, and TCF7L2 genotypes into predictive models or polygenic risk scores could enable clinicians to anticipate patient-specific responses, tailor drug selection and dosing, and implement early adjunctive strategies in anticipated "poor responders." As genetic testing becomes more accessible, incorporating pharmacogenomic profiling into obesity management pathways may help optimize therapeutic success, minimize exposure to ineffective interventions, and ultimately improve long-term outcomes [14].

3. GENETIC FACTORS MODULATING GLP-1RA RESPONSE

Genetic variation within the GLP1R locus—whose product is the glucagon-like peptide-1 receptor—has emerged as a key determinant of individual response to GLP-1 receptor agonists (GLP-1 RAs). Two of the most extensively studied single-nucleotide polymorphisms (SNPs) are rs6923761, which results in a Gly168Ser substitution in the receptor's extracellular domain, and rs10305420, a promoter-region variant that influences transcriptional activity. In clinical cohorts treated with liraglutide or semaglutide, carriers of the Ser allele at rs6923761 experience, on average, 20–30% less weight reduction and smaller improvements in glycemic indices than those homozygous for the Gly allele [15]. Similarly, individuals harboring the T allele of rs10305420 exhibit lower GLP1R mRNA expression in peripheral blood mononuclear cells, correlating with attenuated anorectic and insulinotropic responses. These observations suggest that altered receptor conformation, cell-surface trafficking, or signal transduction efficiency can substantially blunt both the metabolic and weight-loss effects of GLP-1 RAs. Beyond the GLP1R gene itself, polymorphisms in additional loci involved in energy homeostasis, appetite regulation, and nutrient sensing further modulate therapeutic outcomes. The fat mass and obesity-associated (FTO) gene, for example, carries the rs9939609 A risk allele, which has been linked to increased baseline hunger and diminished satiety signaling. In GLP-1 RA–treated subjects, A-allele carriers often report weaker appetite suppression and achieve up to 15% less weight loss compared to non-carriers, implicating altered hypothalamic demethylation processes in pharmacodynamic resistance [16]. Likewise, variants in the melanocortin-4 receptor (MC4R) gene—most notably the noncoding rs17782313 SNP—are associated with both higher obesity risk and a requirement for escalated GLP-1 RA dosing to obtain comparable anorectic effects, reflecting perturbations in central melanocortin signaling pathways. Transcription factor 7-like 2 (TCF7L2), a crucial regulator of Wnt signaling and pancreatic β-cell function, also exhibits impact on incretin biology. Carriers of the rs7903146 T allele demonstrate reduced endogenous GLP-1 secretion and attenuated insulin release, translating into both poorer glycemic control and approximately 25% less weight loss when treated with GLP-1 Ras [17]. Taken together, these findings underscore a polygenic architecture underlying response variability: rather than a single "master" gene, multiple SNPs across metabolic, neuroendocrine, and signaling pathways converge to shape individual trajectories of weight loss and metabolic improvement. Integrative approaches—such as constructing composite pharmacogenomic profiles or polygenic risk scores that weight each variant according to effect size—hold promise for forecasting which patients will derive the greatest benefit from GLP-1 RA therapy and for tailoring treatment regimens accordingly.

4. BARIATRIC SURGERY AND GENETIC INFLUENCE ON OUTCOMES

Bariatric surgery—including Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG)—remains the most potent and durable intervention for achieving clinically meaningful weight loss in individuals with severe obesity. RYGB combines restrictive and malabsorptive elements by creating a small gastric pouch and bypassing the proximal small intestine, thereby limiting caloric intake and altering nutrient absorption. SG, by contrast, reduces stomach volume by approximately 80% along the greater curvature, decreasing ghrelin production and inducing early satiety [18]. Although average excess weight loss (EWL) at one to two years postoperatively falls between 60% and 80%, there is striking inter-individual variability: some patients lose more than 100% of their excess weight, while up to one in five may experience suboptimal weight loss (<50% EWL) or significant weight regain after initial success. Emerging pharmacogenetic research points to inherited variants that may help explain this heterogeneity. The melanocortin-4 receptor (MC4R) gene—central to hypothalamic regulation of hunger and energy expenditure—houses both rare loss-of-function mutations and common noncoding polymorphisms such as rs17782313. Carriers of deleterious MC4R alleles have been found, in certain cohorts, to achieve 15–20% less EWL at 12 months post-RYGB and to exhibit higher rates of long-term

weight recidivism, although these associations are not uniformly replicated across ethnic groups. Transcription factor 7-like 2 (TCF7L2), a key modulator of Wnt signaling and insulin secretion, also emerges as a candidate: the rs7903146 T allele correlates with blunted postoperative improvement in glycemic indices and modestly reduced EWL, possibly through attenuated endogenous GLP-1 release and β-cell responsiveness [19]. Other genes implicated include the leptin receptor (LEPR), where the Gln223Arg variant may alter satiety signaling after SG, and PPARG Pro12Ala, which has been linked to enhanced early postoperative fat oxidation and weight loss. Collectively, these findings underscore a polygenic architecture in which multiple loci—each exerting modest effect—converge to shape the magnitude and durability of weight reduction following bariatric procedures. Integrating genetic screening into preoperative evaluation may one day enable surgeons and endocrinologists to better stratify patients by likelihood of success, tailor postoperative nutritional and behavioral support, and ultimately improve long-term outcomes [20].

5. CANDIDATE GENES AND PREDICTIVE GENETIC MODELS

In addition to the well-characterized loci in GLP1R, FTO, MC4R, and TCF7L2, researchers have turned their attention to a broader network of genes that govern energy balance, adipogenesis, and enteroinsular signaling. The leptin receptor gene (LEPR), which mediates the satiety effects of the adipocyte-derived hormone leptin, harbors variants—such as Gln223Arg—that have been linked to altered receptor sensitivity and differential postoperative weight trajectories following bariatric surgery. Peroxisome proliferator–activated receptor gamma (PPARG), a nuclear transcription factor central to adipocyte differentiation and lipid storage, carries the Pro12Ala polymorphism; Ala-allele carriers often exhibit enhanced early weight loss and improved insulin sensitivity, likely due to shifts in adipocyte gene expression profiles [21]. Meanwhile, the glucose-dependent insulinotropic polypeptide receptor (GIPR) gene influences incretin-mediated insulin secretion and fat deposition, with specific SNPs (e.g., rs10423928) correlating with blunted postprandial insulin responses and diminished weight loss on GLP-1 RA therapy. Recognizing the modest effect size of any single variant, investigators have pioneered the construction of polygenic risk scores (PRS) that synthesize information across dozens—or even hundreds—of obesity- and metabolism-related SNPs. By weighting each polymorphism by its effect on BMI or treatment response, these composite scores aim to stratify patients into risk strata that predict therapeutic efficacy. Early studies suggest that individuals in the highest PRS decile for obesity susceptibility exhibit approximately 10–15% less weight reduction with GLP-1 RAs and are twice as likely to have suboptimal excess weight loss (<50% EWL) after Roux-en-Y gastric bypass [22]. When combined with clinical variables such as baseline BMI, age, sex, and comorbidity burden, PRS-based models achieve area-under-the-curve values approaching 0.75–0.80 for forecasting treatment outcomes. Although these predictive frameworks remain in developmental stages—pending validation in larger, multiethnic cohorts and real-world settings—they represent a critical step toward truly personalized obesity management, in which genetic insights inform the selection, dosing, and combination of both pharmacological and surgical interventions.

6. PHARMACOGENOMICS AND PRECISION OBESITY THERAPY

Pharmacogenomics—the discipline dedicated to understanding how inherited genetic variation influences individual responses to medications—holds tremendous promise for transforming obesity management from a trial-and-error endeavor into a precision-based practice. In the context of GLP-1 receptor agonists (GLP-1 RAs), pharmacogenomic insights enable clinicians to anticipate which patients are most likely to experience robust weight loss and glycemic improvement, and conversely, to identify those at risk for suboptimal response [23]. For example, profiling polymorphisms in GLP1R (e.g., rs6923761, rs10305420), TCF7L2 (rs7903146), and other appetite-regulating genes can inform the choice between long-acting agents such as semaglutide versus shorter-acting compounds like

liraglutide, as well as optimal dosing strategies to maximize efficacy while minimizing adverse effects. Similarly, preoperative genetic screening before bariatric surgery offers the potential to tailor surgical recommendations and perioperative care. Patients harboring MC4R loss-of-function variants or high polygenic risk scores for obesity may benefit from enhanced nutritional counseling, closer metabolic monitoring, or combined pharmacotherapy to counteract genetic predispositions toward weight recidivism [24]. Genetic information could also guide the selection of specific procedures—such as favoring Roux-en-Y gastric bypass over sleeve gastrectomy in individuals whose genotypes predict stronger incretin responsiveness. Early proof-of-concept studies have already demonstrated that integrating genetic biomarkers into clinical decision pathways can improve prediction of weight-loss trajectories. For instance, retrospective analyses suggest that carriers of the FTO risk allele experience attenuated satiety responses to standard GLP-1 RA dosing, prompting investigators to explore higher initial doses or combination regimens with complementary agents (e.g., GIP agonists). Other groups have evaluated composite pharmacogenomic panels—incorporating variants across up to 100 loci—to stratify patients into "likely responders" versus "likely non responders," achieving predictive accuracies (area under the receiver-operator curve) in excess of 0.75 when combined with demographic and metabolic covariates [25]. Despite these encouraging developments, significant hurdles remain before pharmacogenomic testing becomes routine in obesity care. Most studies to date are limited by small sample sizes, retrospective designs, and homogeneity of participant ancestry, which restricts generalizability [26]. Furthermore, the clinical utility of any genetic marker hinges on prospective validation through well-powered randomized trials that compare genotype-guided therapy versus standard of care. Economic considerations—such as the cost of genetic assays, reimbursement policies, and cost-effectiveness analyses—must also be addressed, alongside ethical and regulatory issues around genetic privacy and potential discrimination. Looking forward, the field must prioritize large, multiethnic cohort studies and pragmatic trials that embed pharmacogenomic endpoints into trial protocols. Harmonization of phenotypic definitions—such as standardized metrics for "responder" status, uniform follow-up intervals, and agreed-upon thresholds for clinically meaningful weight change—will be critical for cross-study comparisons and meta-analyses [27]. Ultimately, by elucidating the genetic determinants of drug and surgical outcomes, pharmacogenomics lays the groundwork for a new era of personalized obesity therapy—one in which each patient's unique genomic profile helps guide the choice, timing, and intensity of interventions to achieve the best possible health outcomes.

7. CONCLUSION

The heterogeneous weight-loss outcomes observed with GLP-1 receptor agonists and bariatric surgery underscore the complex interplay between genetic predisposition, neuroendocrine regulation, and environmental influences in the pathogenesis and treatment of obesity. Robust evidence implicates polymorphisms in key loci—GLP1R, FTO, MC4R, TCF7L2, and others governing leptin signaling, adipocyte differentiation, and incretin pathways—as modulators of appetite, satiety, metabolic efficiency, and long-term weight maintenance. Collectively, these variants exert modest individual effects but, when aggregated into polygenic risk scores or integrated with clinical and behavioral covariates, offer increasingly accurate predictions of therapeutic response. Translating these insights into routine clinical practice will require several parallel advances. First, large-scale, multiethnic cohorts and harmonized phenotypic definitions are essential to validate genetic associations across diverse populations and to refine predictive algorithms. Second, embedding pharmacogenomic endpoints into prospective, genotype-stratified trials of GLP-1 RAs and surgical procedures will generate high-quality evidence regarding the cost-effectiveness and clinical utility of pre-treatment genetic screening. Third, integration of genomics with complementary "omics" layers—transcriptomics, metabolomics, proteomics, and microbiome profiling—coupled with machine-learning approaches, holds promise for unveiling novel biomarker panels and mechanistic insights that further personalize intervention

strategies. Ultimately, the integration of genetic and multi-omics data into decision-support tools—alongside patient-reported measures and real-world digital health metrics—can pivot obesity management toward a model of precision medicine. In this paradigm, clinicians can anticipate each individual's likely response to pharmacological and surgical therapies, tailor treatment selection and dosing, and implement early adjunctive measures for those at risk of suboptimal outcomes. As genetic databases expand and analytical technologies mature, personalized obesity therapy will shift from empirical trial-and-error to data-driven optimization, enhancing efficacy, minimizing adverse effects, and improving long-term health and quality of life for patients living with obesity.

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