If you aren’t losing weight with GLP-1s, this may be one reason why

washingtonpost.com/health/2026/04/08/glp1-gene-weight-loss-response-side-effects

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The GLP-1 weight loss drugs revolutionizing the treatment of obesity, diabetes and a slew of other diseases come with a major caveat: They don’t work for everyone.

Some people experience profound weight loss; others barely see the scale budge. Some tolerate the drugs, but others experience nausea and vomiting so unpleasant that they stop taking them. In clinical trials, around 10 to 15 percent of the people who take the drugs are considered “non-responders” because they did not lose at least 5 percent of their body weight.

A new study published Wednesday in the journal Nature finds that part of the reason people’s responses to the drugs vary so widely may be in their DNA.

Researchers at the nonprofit 23andMe Research Institute pinpointed two versions of genes that help predict whether people will lose a few extra pounds on the drugs or will be more prone to nausea and vomiting. Genetics are only one piece of how people respond to GLP-1s, but when

coupled with other factors, such as age, sex and other medical conditions, the researchers created a model to predict the potential weight loss benefit and risk of side effects.

“There are a lot of factors that are influencing people’s experiences on GLP-1s. ... We’ve been able to show that genetics is also playing a role,” said Adam Auton, vice president of human genetics at 23andMe Research Institute and one of the authors of the study. 23andMe is integrating a report based on the findings into its “Total Health” product, a $499 genetic testing service that includes supervision by a clinician.

G. Caleb Alexander, an epidemiologist at Johns Hopkins Bloomberg School of Public Health, who was not involved in the study, said that it was aimed at an important and underrecognized question.

“A lot of clinicians and patients don’t seem to recognize that GLP-1s don’t work in everybody,” Alexander said in an email. “It’s not clear why a substantial minority of individuals don’t lose weight when taking a GLP-1 – this is a question of tremendous scientific and clinical importance.”

His own recent study in JAMA Internal Medicine suggests that the drugs work similarly across patient groups based on factors such as age, race and whether people have diabetes, but he said “it’s entirely plausible that there are genetic determinants of GLP-1 effectiveness that have yet to be identified.”

Precision medicine for obesity

For years, “personalized medicine” has been one of the biggest buzzwords in health care, heralding a new era in which treatments are not one-size-fits-all, but matched to a person’s biology. The field of pharmacogenomics — using genetic information to target medicines — could allow doctors to deliver treatments more likely to work and avoid ones that could have harmful effects. There have been successes, but most of medicine continues to operate with trial and error and a certain amount of guesswork.

The new study is a step toward creating precision obesity tools to guide the use of a powerful, expensive class of medicines. Giving patients more realistic expectations of their potential for weight loss could save time, frustration and money spent learning whether a drug works.

Robert C. Green, a medical geneticist at Harvard Medical School, praised the study as well done. He said it serves as a reminder of the tremendous promise of genomics to improve medicine, not just in diagnosing and treating rare diseases, but by improving routine clinical care.

“The promise of pharmacogenomics is out there waiting to be fulfilled,” Green said. “Now to fulfill the promise of pharmacogenomics in our health care system, we have to find a way to incorporate some degree of genomics into every patient encounter.”

Pinpointing two genes that influence GLP-1 response

In the new study, scientists scoured the genome of 15,000 people who have taken the drugs. DNA is a 3-billion-long string of letters, and each person carries distinct variations in the spelling. The team examined the code, looking for changes that were shared among people who reported losing more weight or experiencing side effects such as nausea and vomiting.

That approach flagged variants of two genes — GLP1R and GIPR — both of which are directly targeted by the drugsthat mimic the effects of our natural gut hormones. The semaglutide drugs, such as Ozempic and Wegovy, target the GLP-1 pathway, which is involved in insulin secretion, appetite and stomach emptying. The tirzepatide drugs, such as Mounjaro and Zepbound, target the GLP-1 pathway along with a second one, the GIP pathway.

The study showed that some people carry a specific version of the GLP1R gene that creates a protein in which one of the amino acid building blocks is different. People with this variant were more likely to lose weight on GLP-1s. The overall effect was relatively modest. People carry two copies of every gene, one from each parent. Those who had one copy of the GLP1R gene variant lost a little more than 1.5 pounds more than people with the regular version. With two copies of the variant, they lost more than three additional pounds.

The authors propose that the alternate version of GLP1R gene creates a protein that is functionally the same, but is moved more efficiently through the cell to the surface, where it can be targeted by the drug.

That same GLP1R variant linked to weight loss was also associated with an increased risk of nausea and vomiting. The scientists also found a variant of a different GIPR gene that was common in people who reported those side effects, when taking tirzepatide drugs. The rare people who carry two copies of both variants were particularly likely to have a rough time on the tirzepatide drugs, with a 15-fold increased chance of vomiting.

Ruth Loos, a genetic epidemiologist at the University of Copenhagen, who was not involved in the study, noted that the extra weight loss, on average, may not seem like a lot, but that for those with two copies of the GLP1R variant, it was more than 10 percent of the total weight loss that people experienced in the study population.

She said it was good to see the findings replicated in a separate database, from the National Institutes of Health's All of Us database, but would like to see more followup, because some other studies have not found a similar effect.

Andres Acosta, an obesity expert at Mayo Clinic who was not involved in the study, said that not one, but many genetic variants contribute to the differences in how people respond to these drugs. He has co-founded a startup called Phenomix Sciences that has commercialized a different test that also uses genetics to predict response to GLP-1s.

“This paper builds into decades of work from us and others into the understanding of genetics of obesity and predictors of response to obesity intervention,” Acosta said. “It validates the importance of precision obesity as a tool to improve outcomes at the individual level.”