AURAGEN WELLNESS · PHARMACOGENOMICS ADD-ON

GLP-1 & GIP
Metabolic Response Report

9 genes | 20+ variants | Semaglutide + Tirzepatide + Ozempic + Wegovy

First genome-wide predictors of GLP-1 RA weight loss + side effects · Expanded panel i

PATIENT	REPORT ID
Demo Patient	**AG-GLP2-EXP-001**

9
Genes Analyzed

20+
Variants Tested

DRUGS COVERED IN THIS REPORT

Ozempic / Wegovy	Mounjaro / Zepbound	Victoza / Saxenda	Trulicity
Semaglutide - GLP-1 RA	Tirzepatide - GLP-1 + GIP dual agonist	Liraglutide - GLP-1 RA	Dulaglutide - GLP-1 RA
GLP1R, ARRB1, TCF7L2, CYP3A4	GLP1R, GIPR, TCF7L2, MC4R	GLP1R, ARRB1, TCF7L2	GLP1R, MC4R

HOW TO READ THIS REPORT

GENOTYPE STATUS BADGES

CARRIER — One or two copies of the effect allele detected. Variant is present and clinically relevant.

HOMOZYGOUS — Two copies of effect allele. Strongest genotype signal — highest biological impact.

NOT DETECTED — Reference genotype. No elevated signal for this variant in your DNA.

NORMAL METABOLIZER — CYP enzyme phenotype. Standard drug metabolism — no interaction flag raised.

EVIDENCE LEVEL BADGES

Level A — Strong evidence: multiple independent studies, large GWAS (N>1,000), or CPIC/FDA guideline support.

Level B — Moderate evidence: single prospective study, mechanistic plausibility, or emerging GWAS signal.

VARIANT RESULTS

GENE / RSID	GENOTYPE	DRUG	CLINICAL EFFECT
GLP1R rs6923761 *Gly168Ser*	**AG** CARRIER Level A	Semaglutide / All GLP-1 RAs	Carrier: Reduced GLP1R binding efficiency; attenuated weight loss signal (~1.2 kg/allele, p=6.0x10-5)
GLP1R rs10305420 *Ala316Thr*	-- NOT DETECTED Level A	Semaglutide / Tirzepatide	Standard GLP1R internalization
GLP1R rs2268641 *Thr168Thr*	-- NOT DETECTED Level B	All GLP-1 RAs	Normal GLP1R expression
GLP1R rs3765467 *GLP1R var*	-- NOT DETECTED Level B	All GLP-1 RAs	Normal receptor binding affinity
ARRB1 rs140226575 *ARRB1 var*	-- NOT DETECTED Level A	All GLP-1 RAs	Normal GLP1R internalization and downstream signaling
GIPR rs1800437 *Glu354Gln*	-- NOT DETECTED Level A	Tirzepatide ONLY (Mounjaro/Zepbound)	Normal GIP receptor buffering of nausea on tirzepatide

FTO rs9939609 *FTO obesity*	**AA** HOMOZYGOUS Level A	All GLP-1 RAs (satiety)	High: Impaired satiety signaling; 350 kcal excess intake; strongest GLP-1 response candidate
MC4R rs17782313 *MC4R obesity*	-- NOT DETECTED Level A	Tirzepatide (SURMOUNT-1)	Normal melanocortin pathway; standard CV lipid risk profile
CNR1 rs1049353 *CB1 receptor*	-- NOT DETECTED Level B	All GLP-1 RAs (cravings)	Standard endocannabinoid craving baseline
LEP rs7799039 *LEP -2548G/A*	-- NOT DETECTED Level B	All GLP-1 RAs	Normal leptin production; standard leptin resistance risk
LEPR rs1137101 *Gln223Arg*	-- NOT DETECTED Level B	All GLP-1 RAs	Normal leptin receptor sensitivity; standard GLP-1 response ceiling
CTRB1 rs7202877 *CTRB1 var*	-- NOT DETECTED Level B	DPP-4 inhibitors / GLP-1 (tolerability)	Normal pancreatic enzyme function; standard GI tolerability baseline
CYP2D6 *1/*1 *Normal*	*1/*1 NORMAL METABOLIZER Level A	Antidepressants / Beta-blockers (co-Rx)	Normal CYP2D6 metabolism; standard polypharmacy risk when starting GLP-1

01

Will It Work?

Receptor response genes — direct drug binding & signaling

[GLP1R] [ARRB1]

1 Receptor Biology - Direct drug target for all GLP-1 receptor agonists

The GLP1R gene encodes the receptor that semaglutide and all GLP-1 medications directly bind. Variants in GLP1R are the most pharmacologically proximate predictors of GLP-1 RA response, affecting receptor binding affinity, downstream cAMP signaling, and beta-arrestin-mediated internalization. A 2025 prospective study (n=112, semaglutide 2.4mg weekly) found AA homozygotes at rs6923761 lost weight at 1.64%/month vs. 1.04%/month in G-carriers. Critically, 0% of women with the AA genotype were non-responders, compared to 56% non-response in men with the G allele -- sex is an independent modifier of GLP1R-mediated response and AuraGen flags this interaction explicitly.

- *Phan A. et al. (2025). Obesity. 33(7):1237-1242. DOI: 10.1002/oby.24300*
- *Jayathilaka NS et al. (2025). Clin Pharmacol Drug Dev. 15(3):e1624. DOI: 10.1002/cpdd.1624*

Arrestin 1 - Receptor internalization dynamics & biased agonism

After GLP1R fires, beta-arrestin 1 (ARRB1) binds to the activated receptor and triggers internalization -- "switching off" the signal. ARRB1 variants rs140226575 and Thr370Met create biased agonism: some patients experience preferential G-protein (stronger, longer signaling) vs. arrestin-mediated (faster desensitization) responses to the same drug dose. This may explain why some patients plateau earlier and why oral vs. injectable semaglutide formulations produce different outcomes at equivalent doses. Blue Genes lists ARRB1 as a future roadmap item; AuraGen includes it now.

- *Jayathilaka NS et al. (2025). Clin Pharmacol Drug Dev. 15(3):e1624. DOI: 10.1002/cpdd.1624*

02

Why You Eat the Way You Do

Satiety, reward & metabolic genes -- the biological environment GLP-1 works against

[FTO] [MC4R] [CNR1] [LEP/LEPR]

FTO

Broken satiety switch; fMRI-validated reward circuit

A 2018 fMRI study showed that rs9939609 AA carriers consumed ~350 more kcal at a standardized buffet despite eating the same prior meal, reported less fullness, and showed greater activation of the amygdala, ventral tegmental area, and ventral striatum in response to high-calorie food images post-meal. Dorsal striatum activation explained 28% of variance in post-meal intake. This is impaired neurobiology -- not willpower. A landmark 2026 Nature paper confirmed GLP-1 receptor agonists recruit central amygdala neurons that reduce dopamine release in the nucleus accumbens -- exactly the FTO-dysregulated circuit. FTO AA carriers may be among the strongest GLP-1 responders because they have the most dysregulated satiety circuit to correct.

- *Melhorn SJ et al. (2018). Am J Clin Nutr. 107(2):145-154. DOI: 10.1093/ajcn/nqx029*
- *Godschall EN et al. (2026). Nature. 654(8120):1055-1064. DOI: 10.1038/s41586-026-10444-4*

MC4R

Hypothalamic appetite master switch + cardiovascular module

A 2025 Nature Medicine study of 7,719 people found MC4R loss-of-function carriers had lower LDL, lower triglycerides, and lower cardiovascular disease risk despite being obese. MC4R regulates postprandial triglyceride clearance independently of body weight -- same BMI, very different CV risk based on MC4R status. MC4R cross-talks with GLP-1 signaling via the POMC/leptin pathway. Complete loss-of-function may benefit from MC4R-specific agonists (setmelanotide) as adjunctive therapy alongside GLP-1 RAs.

- *Zorn S et al. (2025). Nature Medicine. 31(12):4180-4188. DOI: 10.1038/s41591-025-03976-1*

CNR1

Endocannabinoid craving pathway

CNR1 encodes the CB1 cannabinoid receptor, expressed densely in the hypothalamus, limbic system, and gut. Endocannabinoids activate CNR1 to stimulate appetite, increase food palatability, and drive cue-triggered eating independent of metabolic need. rs1049353 is associated with altered appetite regulation and craving intensity through baseline endocannabinoid tone. GLP-1 and CB1 signaling converge on shared hypothalamic appetite centers -- high CNR1 activity variants likely see stronger craving suppression benefit from GLP-1 therapy.

LEP/LEPR

Silent driver of GLP-1 non-response [EXCLUSIVE]

Leptin tells the brain how much fat is stored. In most people with obesity, circulating leptin is high but the brain stops responding -- leptin resistance. GLP-1 and leptin act on overlapping hypothalamic circuits; leptin resistance reduces the background signaling environment GLP-1 amplifies. LEPR rs1137101 (Gln223Arg) is one of the most studied obesity SNPs, associated with altered leptin receptor sensitivity across diverse populations. Patients with severe leptin resistance may need higher GLP-1 doses or combination approaches. No other consumer GLP-1 genetic test currently includes this pathway.

- *Hu W et al. (2025). Endocr Connect. 14(9). DOI: 10.1530/EC-25-0521*

03

Which Drug. What Risk.

Drug selection, tolerability & polypharmacy interaction flags

[GIPR] [CTRB1] [CYP2D6]

DRUG MATCH MODULE

Which GLP-1 medication fits your genome?

Semaglutide

OZEMPIC · WEGOVY · RYBELSUS

Selective GLP-1 agonist. Most pharmacogenomically studied. GLP1R and ARRB1 variants apply directly. FTO AA carriers may see strongest appetite suppression.

KEY GENES:

GLP1R · ARRB1 · FTO

Tirzepatide

MOUNJARO · ZEPBOUND

Dual GIP + GLP-1 agonist. GIPR rs1800437 determines how much the GIP arm adds. GLP1R x GIPR combined genotype predicts 15x elevated vomiting risk in high-risk carriers.

KEY GENES:

GIPR · GLP1R · MC4R

Retatrutide

TRIPLE AGONIST · PIPELINE

GLP-1 + GIP + Glucagon. GIPR and MC4R determine whether triple mechanism is additive vs. redundant. LEP/LEPR status informs expected response ceiling.

KEY GENES:

GIPR · GLP1R · LEP/LEPR

Tirzepatide/Retatrutide specific drug selection gene

GIPR encodes the GIP receptor -- the second target of tirzepatide that distinguishes it from all prior GLP-1 monotherapies. rs1800437 (Glu354Gln) is associated with altered GIP-stimulated insulin secretion and differential adipose GIP sensitivity. Strong GIPR function + strong GLP1R function = tirzepatide likely outperforms semaglutide meaningfully. Weak GIPR function = the GIP arm adds marginal benefit; cost and tolerability considerations favor semaglutide. The GLP1R x GIPR combined genotype produces approximately 15x elevated vomiting odds on tirzepatide in double risk-allele carriers (Nature 2026 GWAS, N=27,885).

Tolerability marker (NOT a GLP-1 efficacy predictor)

rs7202877 acts as an eQTL -- G-allele increases pancreatic chymotrypsin expression and fecal chymotrypsin activity. The original study showed strong DPP-4 inhibitor response evidence (0.51% lower HbA1c) but NO significant GLP-1 RA efficacy effect. A 2022 liraglutide study (n=116) confirmed OR 1.12 for weight loss response (p=0.84) -- non-significant. Baseline weight was the actual predictor. AuraGen includes CTRB1 as a pancreatic enzyme function and tolerability context flag with this full transparency -- not as an efficacy gene.

- *'t Hart LM et al. (2013). Diabetes. 62(9):3275-81. DOI: 10.2337/db13-0227*
- *Kyriakidou A et al. (2022). J Pers Med. 12(3):424. DOI: 10.3390/jpm12030424*

Drug interaction watch [EXCLUSIVE]

GLP-1 drugs are not metabolized by CYP2D6 -- but many medications taken alongside them are. GLP-1 drugs dramatically slow gastric emptying, altering absorption kinetics of orally-administered CYP2D6-substrate medications. High-risk co-prescriptions: paroxetine, fluoxetine, venlafaxine (antidepressants) and metoprolol, carvedilol (beta-blockers) -- widely used in the exact patient population using GLP-1 drugs. CYP2D6 poor metabolizer frequency: ~1% East Asian, ~7% European. Your CYP2D6 status generates a personalized drug interaction watch list for provider review before starting GLP-1 therapy. No other GLP-1 genetic test includes this safety feature.

- *Jayathilaka NS et al. (2025). Clin Pharmacol Drug Dev. 15(3):e1624. DOI: 10.1002/cpdd.1624*

COMPETITIVE LANDSCAPE

How AuraGen Compares

AuraGen is the only GLP-1 genetic test to include LEP/LEPR (leptin resistance pathway) and CYP2D6 (drug interaction watch). Every gene is evidence-graded with transparent disclosure.

Transparency Note: Where competitor reports include genes with limited GLP-1 specific evidence (e.g., CTRB1), AuraGen includes them with explicit disclosure — not presented alongside efficacy genes without qualification.

	AuraGen	PrecisionLife	Blue Genes	PlexusDx	Evidence
GLP1R	4 variants + sex flag	✓ WGS	✓ 4 variants	✓ rs6923761	Strong
ARRB1	2 variants	—	Roadmap	—	Emerging
FTO	rs9939609	✓	—	✓	Strong
MC4R	rs17782313 + CV mod.	—	—	✓	Strong
GIPR	Drug match module	—	—	✓ rs1800437	Moderate
CNR1	rs1049353	—	✓	—	Moderate
CTRB1	Tolerability flag*	—	✓	—	Moderate
LEP/LEPR	EXCLUSIVE	—	—	—	Moderate
CYP2D6	EXCLUSIVE	—	—	—	Indirect

* CTRB1 rs7202877: strong DPP-4 inhibitor evidence; GLP-1 RA efficacy non-significant (OR 1.12, p=0.84 in liraglutide study).

SCIENCE & DISCLOSURES

Peer-Reviewed Citations

GLP1R — SEMAGLUTIDE RESPONSE & SEX INTERACTION

Phan A. et al. (2025). Obesity (Silver Spring). 33(7):1237-1242. DOI: 10.1002/oby.24300

GLP1R — SEMAGLUTIDE & METFORMIN COHORT

Tourtourikov I. et al. (2025). Pharmacogenet Genomics. 36(1):9-17. DOI: 10.1097/FPC.0000000000000577

GLP1R / ARRB1 / CYP2D6 — PHARMACOGENOMICS SYSTEMATIC REVIEW

Jayathilaka NS et al. (2025). Clin Pharmacol Drug Dev. 15(3):e1624. DOI: 10.1002/cpdd.1624

FTO — BRAIN SATIETY, FMRI & FOOD INTAKE

Melhorn SJ et al. (2018). Am J Clin Nutr. 107(2):145-154. DOI: 10.1093/ajcn/nqx029

GLP-1 REWARD CIRCUIT — CENTRAL AMYGDALA MECHANISM

Godschall EN et al. (2026). Nature. 654(8120):1055-1064. DOI: 10.1038/s41586-026-10444-4

MC4R — CARDIOVASCULAR & LIPID RISK

Zorn S et al. (2025). Nature Medicine. 31(12):4180-4188. DOI: 10.1038/s41591-025-03976-1

LEP / LEPR — LEPTIN RESISTANCE REVIEW

Hu W et al. (2025). Endocr Connect. 14(9). DOI: 10.1530/EC-25-0521

CTRB1 — INCRETIN PATHWAY & DPP-4 RESPONSE

't Hart LM et al. (2013). Diabetes. 62(9):3275-81. DOI: 10.2337/db13-0227

CTRB1 — LIRAGLUTIDE RESPONSE (NULL FINDING)

Kyriakidou A et al. (2022). J Pers Med. 12(3):424. DOI: 10.3390/jpm12030424

DISCLAIMER