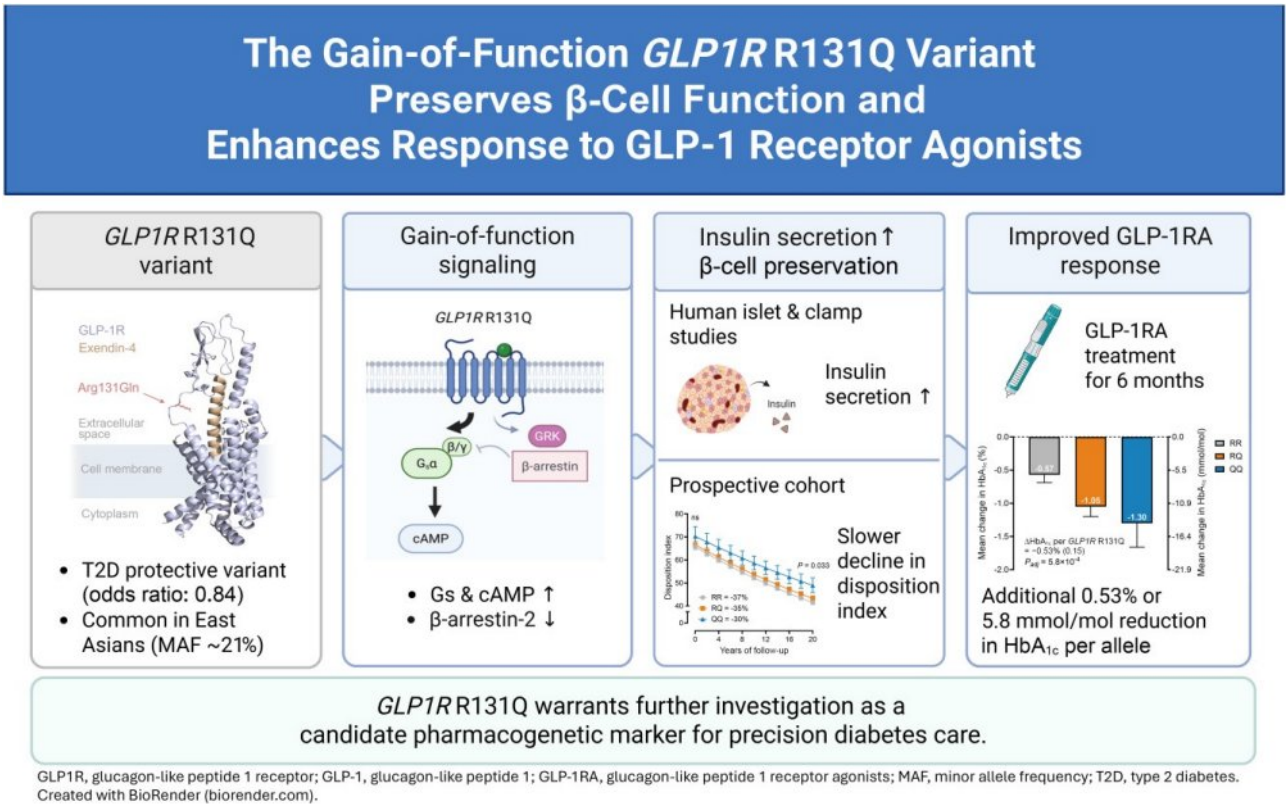
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The Gain-of-Function *GLP1R* R131Q Variant Preserves β-Cell Function and Enhances Response to GLP-1 Receptor Agonists

Hyunsuk Lee, Hannah E. Christie, Ji Seon Lee, Woo-Il Kwon, Min Kyong Moon, Sung Hee Choi, Dae Ho Lee, Seunggeun Lee, Hyunbeom Lee, Minjung Kho, Federica Boscolo, Chiara Dalla Man, Nam H. Cho, Jaewon Choi, Jeongeun Lee, Jongseok Park, Yeeun Jo, Sangwon Lee, Adrian Vella, Soo Heon Kwak, Jong-Il Kim, and Kyong Soo Park

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GLP1R, glucagon-like peptide 1 receptor; GLP-1, glucagon-like peptide 1; GLP-1RA, glucagon-like peptide 1 receptor agonists; MAF, minor allele frequency; T2D, type 2 diabetes. Created with BioRender (biorender.com).

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Genetic variation in the glucagon-like peptide 1 receptor (*GLP1R*) has been implicated in type 2 diabetes (T2D) risk and treatment response.
- **What are the specific questions we wanted to answer?**
  Is the common missense variant *GLP1R* R131Q associated with β-cell function and glucagon-like peptide 1 receptor agonist treatment response, and what is the underlying mechanism?
- **What did we find?**
  GLP1R R131Q is associated with preservation of β-cell function and greater HbA_{1c} reduction. Mechanistically, *GLP1R* R131Q is a gain-of-function variant that enhances cAMP production in cell-based assays and glucagon-like peptide 1 receptor agonist–stimulated insulin secretion in hyperglycemic clamp and human islet experiments.
- **What are the implications of our findings?**
  GLP1R R131Q warrants further investigation as a candidate pharmacogenetic marker for precision diabetes management.

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The Gain-of-Function *GLP1R* R131Q Variant Preserves β-Cell Function and Enhances Response to GLP-1 Receptor Agonists

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Hyunsuk Lee,[1,2] Hannah E. Christie,[3] Ji Seon Lee,[4] Woo-Il Kwon,[5] Min Kyong Moon,[6] Sung Hee Choi,[7] Dae Ho Lee,[8] Seunggeun Lee,[1,9] Hyunbeom Lee,[10] Minjung Kho,[9] Federica Boscolo,[11] Chiara Dalla Man,[11] Nam H. Cho,[12] Jaewon Choi,[2,13] Jeongeun Lee,[2] Jongseok Park,[2,13] Yeeun Jo,[2,13] Sangwon Lee,[2,13] Adrian Vella,[3] Soo Heon Kwak,[2] Jong-Il Kim,[1,13] and Kyong Soo Park[4]

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OBJECTIVE

Genetic variation in the glucagon-like peptide 1 receptor (*GLP1R*) has been implicated in type 2 diabetes (T2D) risk and treatment response. We investigated whether *GLP1R* R131Q, which was previously reported as a T2D-protective variant in genome-wide association studies, alters receptor signaling, β-cell function, and response to glucagon-like peptide 1 receptor agonists (GLP-1RAs).

RESEARCH DESIGN AND METHODS

Trajectory of β-cell function was evaluated in a 20-year community-based prospective cohort in Korea (*n* = 6,373), where participants underwent biennial 2-h 75-g oral glucose tolerance tests, and disposition index was used as surrogate marker. Pharmacogenetic response to GLP-1RAs was assessed in a hospital-based T2D cohort in Korea (*n* = 177). Hyperglycemic clamp studies (*n* = 17), human islet experiments (*n* = 21), and in vitro assays were conducted to characterize *GLP1R* R131Q effects on receptor signaling and islet function.

RESULTS

***GLP1R* R131Q was associated with slower decline in disposition index in individuals without T2D, with reductions from baseline of 30% in homozygous carriers, 35% in heterozygotes, and 37% in wild-type individuals. In people with T2D, each allele conferred an additional 0.53% or 5.8 mmol/mol reduction in HbA_{1c} after 6 months of GLP-1RA treatment ($P = 5.8 \times 10^{-4}$). Hyperglycemic clamp and human islet experiments demonstrated allele-dependent enhancement of GLP-1RA–stimulated insulin secretion ($P = 0.050$ and $P = 0.037$, respectively). In vitro, *GLP1R* R131Q increased GLP-1RA–stimulated cAMP production with directional observations consistent with pathway bias.**

CONCLUSIONS

***GLP1R* R131Q is a gain-of-function variant associated with preservation of β-cell function and enhanced glycemic response to GLP-1RA treatment, supporting further investigation as a candidate pharmacogenetic marker for precision diabetes care.**

Glucagon-like peptide 1 (GLP-1) is secreted from intestinal L cells after nutrient intake and regulates glucose homeostasis by enhancing glucose-stimulated insulin secretion, suppressing glucagon release, and reducing appetite (1). These actions are

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ORIGINAL ARTICLE

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mediated through GLP-1 receptor (GLP-1R), a class B G protein–coupled receptor expressed in pancreatic islets and other tissues. Upon activation, GLP-1R engages with heterotrimeric G proteins, leading to cAMP production and intracellular Ca^{2+} mobilization, promoting insulin secretion (1). GLP-1R also recruits β-arrestins involved in receptor desensitization and non–G protein signaling (2–4). The relative engagement between G protein versus β-arrestins, referred to as biased agonism (4), influences the magnitude and duration of GLP-1R signaling, raising the possibility that coding variants in GLP-1R may shift this balance and modulate incretin responsiveness (5).

Previous studies on rodents and humans demonstrated that GLP-1 receptor agonists (GLP-1RAs) preserve β-cell function by reducing apoptosis, mitigating glucolipotoxic stress, and promoting β-cell proliferation (6). Through these and other metabolically beneficial actions (6), GLP-1RAs have emerged as central therapies for type 2 diabetes (T2D), offering potent glucose lowering, weight reduction, and cardiovascular and renal benefits (7–9). However, therapeutic response varies substantially between individuals, underscoring the need for biomarkers to guide incretin-based treatments.

Genetic studies have identified genetic variants in the *GLP1R* gene that are associated with glycemic traits and drug response (10,11). Among these, our group previously reported that the nonsynonymous variant *GLP1R* R131Q (rs3765467, chr6:39,065,819:G:A [GRCh38], p.Arg131Gln), which results in an amino acid change in the extracellular domain, is associated with lower fasting glucose (12), reduced risk of T2D (12), improved response to GLP-1 during hyperglycemic clamp (13), and greater HbA_{1c} reduction by dipeptidyl peptidase-4 inhibitors (14). The variant is common in East Asians (minor allele frequency 21%) but rare in Europeans (0.29%) (15), suggesting a population-specific contribution to diabetes risk and therapeutic response. While statistical associations have been replicated (16), the underlying functional mechanism remains incompletely understood. Prior in vitro (10,17–20) and clinical studies (13,14,21,22) have reported conflicting results, and the impact of the variant in human pancreatic islets and clinical settings has not been fully resolved.

In this study, we comprehensively characterized the *GLP1R* R131Q variant across multiple levels of evidence. We first analyzed data from a 20-year community-based prospective cohort to evaluate whether the variant is associated with long-term preservation of β-cell function. We then assessed pharmacogenetic response to GLP-1RAs in a hospital-based cohort of people with T2D. To provide mechanistic insights, we performed in vivo hyperglycemic clamp studies, ex vivo human islet experiments, and in vitro cell studies to define the functional mechanism of the *GLP1R* R131Q variant.

RESEARCH DESIGN AND METHODS

Cohort Study Population

To characterize β-cell function trajectories in individuals without T2D, we used data from the Ansan-Ansung Cohort Study, a prospective community-based cohort in South Korea that is part of the Korean Genome and Epidemiology Study (KoGES) (23,24). The study was designed to evaluate genetic and environmental determinants of chronic complex disorders, including diabetes. Residents aged 40–69 years were enrolled between 2001 and 2002 and followed biennially through 2022. Among 8,840 genotyped participants, 6,373 individuals without T2D at baseline and with at least two oral glucose tolerance tests (OGTTs) were included in longitudinal analyses. Study protocols were approved by the Korean Disease Control and Prevention Agency and the institutional review board of Seoul National University Hospital (SNUH) (Seoul, Republic of South Korea) (IRB 1801-095-916), and all participants provided written informed consent.

At each visit, a 2-h 75-g OGTT was performed, with glucose and insulin measured at 0, 60, and 120 min. Participants with known diabetes or on glucose-lowering medications were exempted from OGTT. Insulinogenic index at 60 min (IGI_{60}), Matsuda insulin sensitivity index (ISI), and disposition index (DI = $IGI_{60} \times$ ISI) were calculated as described in Supplementary Methods.

To assess pharmacogenetic response, we analyzed data from a multicenter hospital-based T2D cohort comprising SNUH (12,25), Seoul National University Bundang Hospital, Seoul Metropolitan Government–Seoul National University Boramae Medical Center, and Gachon University Gil Medical Center. People with T2D were recruited between 2016 and 2024, and those aged 20 years or older who had been treated with GLP-1RAs for ≥6 months were included in the analysis. T2D was diagnosed according to American Diabetes Association guidelines. Study protocols were approved by the institutional review board of SNUH (IRB 2303-170-1417).

Genotype Data

Participants of the Ansan-Ansung cohort were genotyped using Affymetrix Genome-Wide Human SNP Array 5.0 (23,24). In the hospital-based T2D cohort, genotyping was performed with Affymetrix Axiom Biobank Plus Genotyping Array (JS Link, Seoul, South Korea) and spike-in whole exome sequencing (JS Link). Imputation was performed using the Trans-Omics for Precision Medicine r2 reference panel (26), and the *GLP1R* R131Q variant showed high imputation quality (Rsq >0.95).

Statistical Analysis

For cohort analyses, categorical variables are presented as counts (percentages), and continuous variables are presented as means (SD). Skewed variables were log-transformed. Group differences were assessed using χ^2 tests or ANOVA, as appropriate.

Longitudinal trajectories of $\log_2$-transformed DI, IGI_{60}, and composite ISI were analyzed using linear mixed-effects models to estimate mean parameter

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S.H.K., J.-I.K., and K.S.P. jointly directed this work and contributed equally as corresponding authors.

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levels over time according to *GLP1R* genotype for up to 20 years of follow-up. DI was defined a priori as the primary outcome, and IGI_{60} and ISI were analyzed as secondary outcomes, to support physiological interpretation. Fixed effects included time, genotype, and their interaction, and participants were modeled as a random effect. The model was adjusted for age, sex, BMI, and the first 10 principal components of ancestry. OGTT measurements were censored at diabetes onset. There were no differences in the mean number of OGTT data or follow-up duration across genotype groups (Supplementary Table 1). Sensitivity analyses were performed by restricting the follow-up window to 18, 16, and 14 years.

For pharmacogenetic analyses, HbA_{1c} change was defined from treatment initiation to 6 months using prespecified windows (baseline: −3 to 1 months; follow-up: 3–9 months) (11). Genotype effects on HbA_{1c} change, HbA_{1c} target achievement, and weight change were assessed using regression models adjusted for age, sex, baseline value, T2D duration, GLP-1RA type, and the first 10 principal components of ancestry. Analyses were performed with R software version 4.5.1.

Human Hyperglycemic Clamp Studies

Hyperglycemic clamp studies were conducted at Mayo Clinic's Clinical Research and Trials Unit (IRB 20-003984; NCT04466566), and *GLP1R* genotype was determined using TaqMan assays. Detailed protocols of the hyperglycemic clamp are provided in Supplementary Methods. In brief, participants completed three study visits in randomized order at least 1 week apart. After an overnight fast, a variable glucose infusion was initiated at 09:00 h (0 min) to maintain plasma glucose at ∼160 mg/dL and continued for 210 min, with [3-^{3}H] glucose infusion for assessment of endogenous glucose production and glucose disappearance. A 1-mg intravenous glucagon bolus was administered at 180 min. The three conditions were *1*) saline infusion (−120 to 210 min), *2*) subcutaneous liraglutide 1.2 mg at −180 min, and *3*) exendin 9-39 infusion (300 pmol/kg/min, −120 to 210 min). The intended recruitment was 40 participants, but, due to the low prevalence of this genotype, a total of 17 participants (9 RR, 6 RQ, 2 QQ) were enrolled (Supplementary Fig. 1). All 17 participants completed the saline study, one participant did not complete the liraglutide study, and another did not complete the exendin 9-39 study.

Fasting values were calculated as the mean from −30 to 0 min. Within-group differences across conditions were assessed using two-sided paired *t* tests and test for trend using linear regression.

Human Islet Experiments

Human pancreatic islets were obtained from surgical donors with no diabetes through the SNUH Human Islet Multi-Omics Study (IRB 2309-070-1465), and *GLP1R* genotype was determined using Sanger sequencing (Bionics, Seoul, South Korea).

Detailed human islet isolation and experiment details are described in Supplementary Methods. In brief, pancreatic tissue (typically ∼1 g) was collected during surgery and processed using a density gradient method. Islets were sequentially exposed to low glucose (2.8 mmol/L), high glucose (16.8 mmol/L), and high glucose plus exendin-4 (50 ng/mL) for 30 min each. Insulin secretion was quantified using human insulin ELISA (Alpco, Salem, NH) and expressed relative to basal secretion. Test for trend was performed using linear regression adjusting for donor's age, sex, and BMI.

In Vitro Receptor Assays

Isogenic Flp-In T-REx 293 (Thermo Fisher Scientific, Waltham, MA) cell lines stably expressing wild-type (WT) or *GLP1R* R131Q were generated to evaluate receptor function. Receptor surface expression was quantified following tetracycline induction using SNAP-tag labeling and flow cytometry. Ligand-induced cAMP production was assessed in real time using a luciferase-based GloSensor reporter system (Promega, Madison, WI) after stimulation with GLP-1RAs. Dose-response relationships were analyzed using nonlinear regression models.

To examine pathway bias, G protein activation and β-arrestin-2 recruitment were quantified using NanoBiT complementation assays (Promega) measuring mini-G_s and β-arrestin-2 recruitment following agonist stimulation. Data represent independent biological replicates, and statistical comparisons were performed using two-sided unpaired *t* tests. Detailed experimental procedures, plasmid constructs, reagents, and assay conditions are provided in Supplementary Methods.

Data and Resource Availability

The Ansan-Ansung Cohort Study data are available from the Korean National Institute of Health (https://biobank.nih.go.kr). The data sets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

RESULTS

GLP1R R131Q Is Associated With Slower Decline in β-Cell Function in a Prospective Cohort

To determine whether the *GLP1R* R131Q variant is associated with long-term preservation of β-cell function in the general population, we analyzed 6,373 individuals without diabetes from the Ansan-Ansung community-based prospective cohort in South Korea (23,24), who underwent biennial 2-h 75-g OGTTs over 20 years (41,950 OGTT measurements in total, mean 6.6 per person). Participants had a mean age of 51.5 years, 47% were male, and had a mean BMI of 24.5 kg/m^2 (Supplementary Table 2). HbA_{1c} and fasting glucose were significantly lower in people with *GLP1R* R131Q, consistent with our previous report (12).

At baseline, DI, IGI_{60}, and ISI were comparable across genotypes (Supplementary Table 2). During follow-up, ISI declined over time and was accompanied by a compensatory increase in IGI_{60}, resulting in an overall decline in DI. Individuals carrying the *GLP1R* R131Q variant showed a slower decline in DI over time (Fig. 1*A*). IGI_{60} tended to increase more among the variant carriers, although this difference did not reach statistical significance (Fig. 1*B*). In contrast, the trajectory of ISI was comparable between groups during follow-up (Fig. 1*C*). Although DI was similar at baseline, a significant difference was observed at year 20 (P = 0.033), with carriers of the *GLP1R* R131Q variant showing a more gradual decline in DI (RR −37%, RQ −35%, and QQ −30% change from baseline). Sensitivity analyses restricted to earlier follow-up windows showed directionally consistent results (Supplementary Table 3). These findings indicate that the *GLP1R* R131Q variant is

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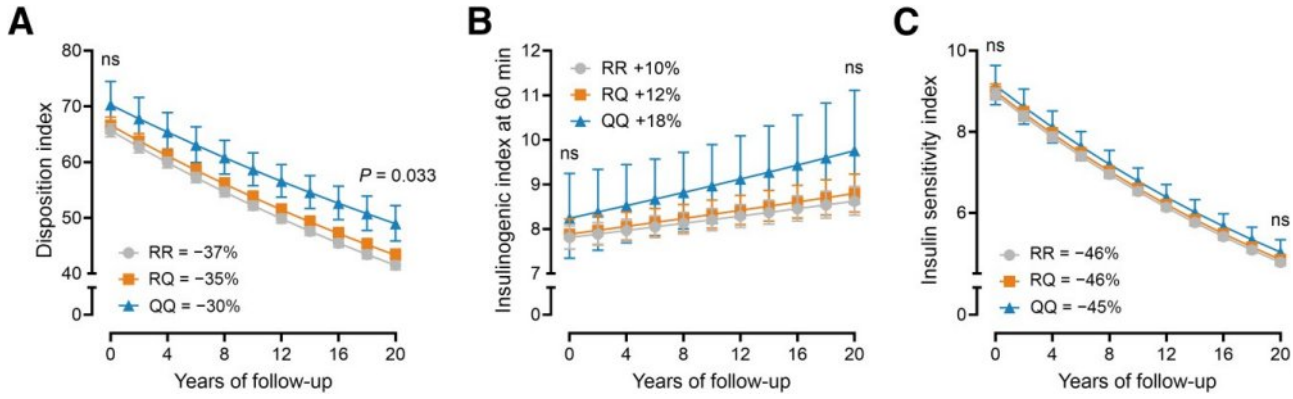


Figure 1—Individuals carrying the *GLP1R* R131Q variant exhibit slower decline in β-cell function in a prospective cohort. *A*–*C*: Longitudinal trajectories of DI (ISI × IGI_{60}) (*A*), insulinogenic index at 60 min (IGI_{60}) (*B*), and insulin sensitivity index (ISI) (*C*) over 20 years in individuals without diabetes from the Ansan-Ansung cohort (n = 6,373: 4,045 RR, 2,079 RQ, and 249 QQ). Longitudinal analyses were performed using linear mixed-effects models adjusted for age, sex, BMI, and the first 10 principal components of ancestry. The percentage change from baseline at the end of follow-up is shown next to the legend. Statistical comparison is by Welch ANOVA. Lines represent mean ± SEM. ns, not significant.

associated with long-term preservation of β-cell function in people without diabetes.

GLP1R R131Q Is Associated With Enhanced Glycemic Response to GLP-1RA in Humans

We next examined the pharmacogenetic effect of *GLP1R* R131Q in 177 people with T2D treated with GLP-1RAs in a hospital-based cohort. Participants had a mean age of 58 years, diabetes duration of 15 years, and baseline BMI of 27.7 kg/m^2 and HbA_{1c} of 9.0%; 36% were on insulin. Baseline characteristics, including baseline HbA_{1c}, diabetes duration, and BMI, were comparable between groups (Supplementary Table 4). Most participants were treated with dulaglutide (80.2%), followed by insulin degludec/liraglutide (11.3%) and insulin glargine/lixisenatide (6.2%) in smaller proportions.

After a median 181 days of GLP-1RA treatment, HbA_{1c} decreased by a mean of 0.74 percentage points (8.1 mmol/mol), while body weight decreased by a mean of 0.79 kg. Carriers of the *GLP1R* R131Q variant showed a significantly greater reduction in HbA_{1c} compared with noncarriers (Fig. 2*A*) (RR −0.57% [−6.2 mmol/mol], RQ −1.05% [−11.5 mmol/mol], and QQ −1.30% [−14.2 mmol/mol]). In the adjusted analysis, each copy of the *GLP1R* R131Q variant was associated with an additional 0.53 percentage points (5.8 mmol/mol) reduction in HbA_{1c} ($P = 5.8 \times 10^{-4}$). When restricting the analysis to RR and RQ individuals, RQ carriers showed a greater reduction in HbA_{1c} compared with RR individuals (−0.59% [−6.4 mmol/mol], P = 0.0024), indicating that the association was not driven by the small number of QQ homozygotes. A greater proportion of participants achieved HbA_{1c} target after GLP-1RA treatment among carriers of the *GLP1R* R131Q variant in an additive manner (Fig. 2*B*) ($HbA_{1c} \leq 7\%$ [53 mmol/mol]: RR 8.4%, RQ 22%, and QQ 43%, P_{trend} = 0.0064; $HbA_{1c} \leq 8\%$ [64 mmol/mol]: RR 39%, RQ 57%, and QQ 71%, P_{trend} = 0.024). However, no significant difference in weight reduction was observed by genotype (P_{trend} = 0.390) (Supplementary Fig. 2), likely reflecting both the modest weight-lowering effect of the GLP-1RAs in this cohort (80.2% treated with dulaglutide) and the relatively low BMI at baseline (mean 27.7 kg/m^2). These findings indicate that the *GLP1R* R131Q variant is associated with enhanced glycemic response to GLP-1RA treatment in people with T2D, supporting its potential utility as a pharmacogenetic marker for treatment stratification.

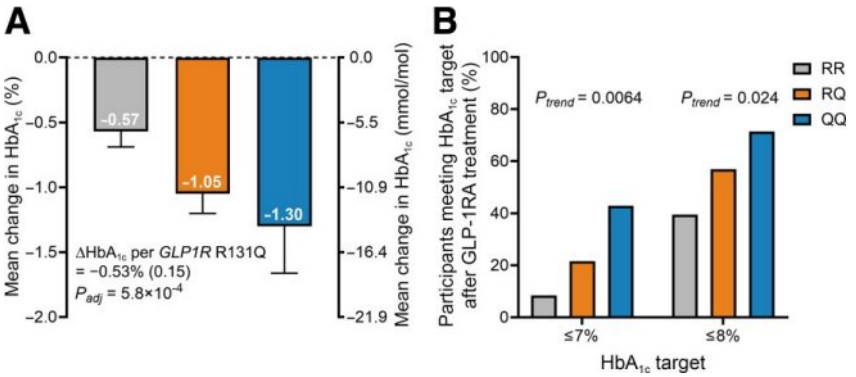


Figure 2—*GLP1R* R131Q is associated with enhanced glycemic response to GLP-1RA in people with T2D. *A*: People with T2D carrying the *GLP1R* R131Q variant showed greater reduction in HbA_{1c} after 6 months of GLP-1RA treatment (n = 177: 119 RR, 51 RQ, and 7 QQ) in a multicenter hospital-based cohort in South Korea. Association was tested with linear regression adjusted for age, sex, baseline HbA_{1c}, diabetes duration, GLP-1RA medication type, and the first 10 principal components of ancestry. *B*: Proportion of individuals achieving target HbA_{1c} after 6 months of GLP-1RA treatment, showing higher proportion among *GLP1R* R131Q carriers. Trends were tested with logistic regression adjusted for age, sex, baseline HbA_{1c}, diabetes duration, GLP-1RA medication type, and the first 10 principal components of ancestry. Data are presented as mean ± SEM.

GLP1R R131Q and Responsiveness to GLP-1RA During Hyperglycemic Clamp

To further evaluate the physiological relevance of the *GLP1R* R131Q variant, we performed hyperglycemic clamp studies in 17 individuals without diabetes (Fig. 3*A*). Baseline metabolic characteristics were comparable when stratified by *GLP1R* R131Q genotype, although sex distribution

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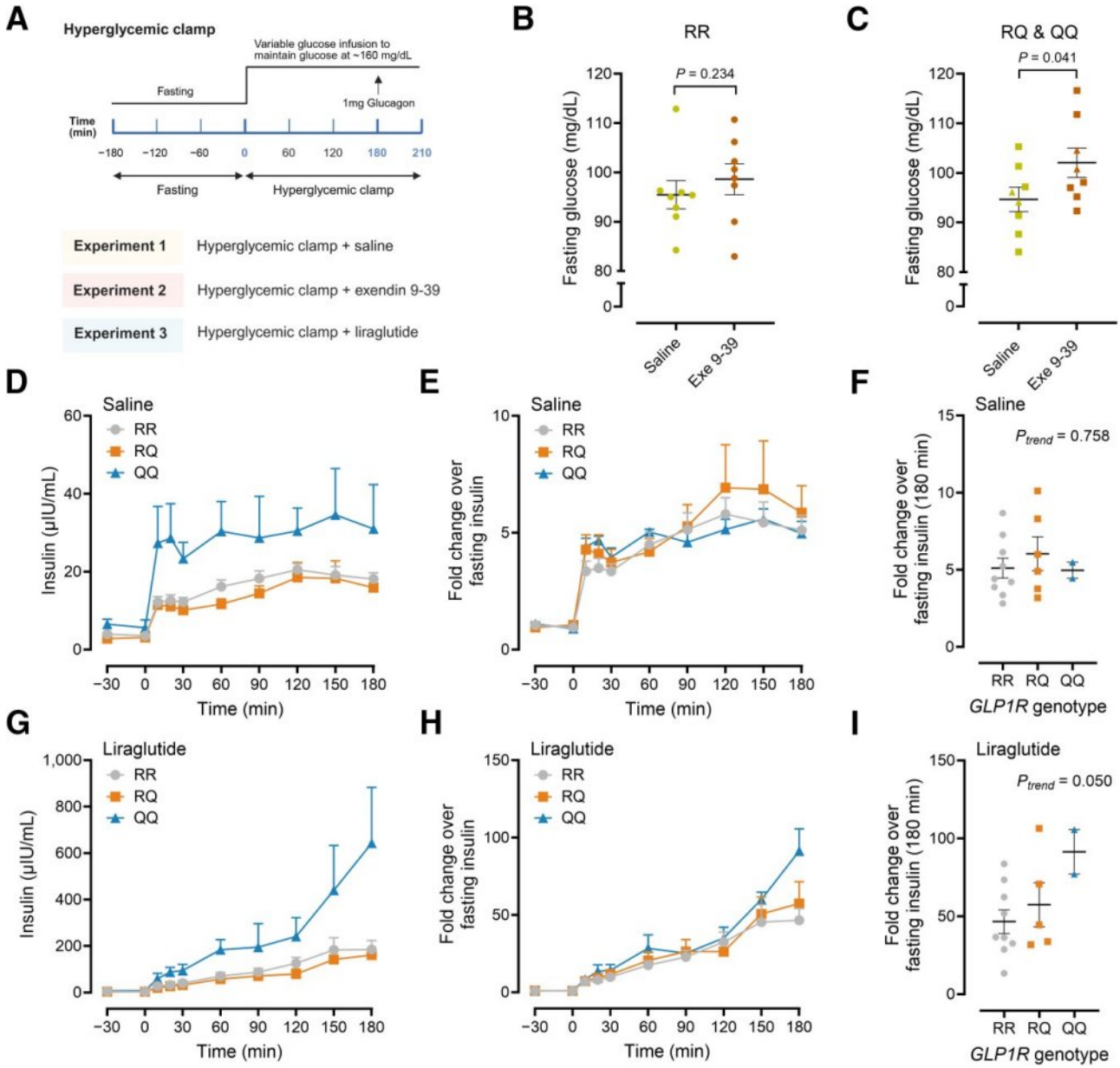


Figure 3—*GLP1R* R131Q and β-cell responsiveness to GLP-1R activation during hyperglycemic clamp. *A*: Schematic diagram of the hyperglycemic clamp protocol. Individuals without diabetes were recruited from the Mayo Clinic Clinical Research and Trials Unit (n = 17: 9 RR, 6 RQ, and 2 QQ). Each participant underwent three separate experiments during the hyperglycemic clamp, consisting of saline infusion, exendin 9-39 infusion, and liraglutide injection, performed in random order at least 1 week apart. All 17 participants completed the saline experiment; one participant did not complete the liraglutide experiment, and another did not complete the exendin 9-39 experiment. *B* and *C*: Fasting glucose during the saline and exendin 9-39 experiments in individuals without (*B*) (8 RR) and with (*C*) (6 RQ shown as squares, and 2 QQ shown as triangles) the *GLP1R* R131Q variant. A significant increase in fasting glucose was observed in carriers of the variant during the exendin 9-39 experiment compared with saline. *D–F*: Insulin secretion during the saline experiment and corresponding fold increase in insulin over fasting levels, which were comparable between genotypes (n = 17: 9 RR, 6 RQ, and 2 QQ). *G–I*: Insulin secretion during the liraglutide experiment showing a genotype-dependent increasing trend in insulin fold change over fasting levels in individuals carrying the *GLP1R* R131Q variant in the unadjusted analysis (n = 16: 9 RR, 5 RQ, and 2 QQ). Genotype differences should be interpreted with caution given the small sample size and imbalance in sex distribution across groups. Data are presented as mean ± SEM. Statistical comparisons were performed using two-sided paired t tests (panels *B* and *C*) or linear regression for trend (panels *F* and *I*).

differed between groups (Supplementary Table 5).

Fasting glucose was comparable between saline and exendin 9-39 experiments in individuals without the variant (Fig. 3*B*). In contrast, individuals carrying at least one copy of the variant showed a significant increase in fasting glucose during the exendin 9-39 experiment compared with saline (Fig. 3*C*). This amplified glycemic response to GLP-1R blockade suggests that the variant carriers had increased GLP-1R signaling by endogenous ligands in the fasting state.

In the hyperglycemic clamp, glucose concentrations did not differ between genotypes and were maintained at ~160 mg/dL by design (Supplementary Fig. 3). During the saline experiment, hyperglycemic clamp increased insulin secretion in all participants, and the fold

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increase over fasting levels was comparable between genotypes (Fig. 3*D*–*F*). The exendin 9-39 experiment also showed similar results (Supplementary Fig. 3). In contrast, during the liraglutide experiment, hyperglycemia markedly increased insulin secretion and elicited a stronger insulin secretory response in individuals carrying the *GLP1R* R131Q variant, with a marginally significant allele-dependent trend toward a greater fold increase in insulin over fasting levels (Fig. 3*G*–*I*) (P_{trend} = 0.050). A sex-adjusted model was explored, but its interpretation was limited by the small sample size and strong correlation between sex and genotype (Pearson r = 0.722, P = 0.0011). Glucagon-stimulated insulin secretion tended to be higher in people with the variant but did not reach statistical significance (P_{trend} = 0.237) (Supplementary Fig. 3). The [3-^{3}H] glucose-derived endogenous glucose production and glucose disappearance did not show a significant genotype-dependent trend (Supplementary Fig. 4).

GLP1R R131Q Is Associated With Enhanced GLP-1RA–Stimulated Insulin Secretion in Human Pancreatic Islets

Human pancreatic islets were isolated from 21 surgical donors with no diabetes and with comparable baseline characteristics across genotypes (n = 21) (Fig. 4*A* and Supplementary Tables 6 and 7).

Under high glucose (16.8 mmol/L) and/or exendin-4 (50 ng/mL) stimulation, all pancreatic islets demonstrated a robust increase in insulin secretion (Fig. 4*B*). The basal insulin secretion under low glucose (2.8 mmol/L) medium was comparable across genotypes (P_{trend} = 0.560, Supplementary Fig. 5). However, when stimulated with high glucose plus exendin-4, insulin secretion increased in an allele-dependent manner, with each additional *GLP1R* R131Q variant associated with a greater fold increase relative to baseline (Fig. 4*C*) (P_{trend} = 0.037). These results demonstrate that the *GLP1R* R131Q variant is associated with greater GLP-1RA–stimulated insulin secretion in human islets in an additive, per-allele manner.

GLP1R R131Q Enhances cAMP Production and Shows Signaling Changes Consistent With Pathway Bias

We generated isogenic human embryonic kidney 293 cell lines stably expressing either WT *GLP1R* or *GLP1R* R131Q, enabling direct comparison of the functional consequences of the amino acid substitution in the receptor extracellular domain. In our model, receptor surface expression was comparable between WT and *GLP1R* R131Q–expressing cells (hereafter referred to as R131Q cells) (Supplementary Fig. 6), consistent with previous reports (18,20). Upon exendin-4 stimulation, greater total cAMP production was observed in R131Q cells (Fig. 4*D*); the area under the curve (0–380 min) was 1.5-fold larger in R131Q cells compared with WT (Supplementary Fig. 6). Kinetic analysis demonstrated a significantly faster rate of cAMP accumulation in R131Q cells (Fig. 4*E*). The efficacy (E_{max}) of exendin-4 was 1.22-fold higher in R131Q cells, while the potency (half-maximal effective concentration, EC_{50}) was comparable between genotypes. Similar gain of function in the receptor efficacy was observed in response to GLP-1 (7-36) (1.43-fold) and semaglutide (1.28-fold) (Fig. 4*F*).

G protein–coupled receptors mediate signals through G proteins and β-arrestins, and the relative balance between these pathways can modulate receptor function and downstream physiological response (4). Protein complementation assays demonstrated that, compared with WT cells, R131Q cells displayed enhanced mini-G_s recruitment (Fig. 4*G*), a surrogate marker for G_s protein activation (27), together with reduced β-arrestin-2 recruitment (Fig. 4*H*) upon stimulation with exendin-4. These findings are consistent with previous reports showing that stimulation with the endogenous ligand GLP-1 enhances G_s protein signaling (10) and reduces β-arrestin-2 recruitment (20) in in vitro models expressing *GLP1R* R131Q relative to WT. Given that G_s signaling promotes cAMP generation and insulinotropic activity (1), whereas β-arrestin–mediated pathways are associated with receptor desensitization and internalization (2–4), this provides a mechanistic explanation for the enhanced cAMP response observed in R131Q cells and increased responsiveness to GLP-1RAs in our ex vivo, in vivo, and cohort studies. Together, these findings indicate that *GLP1R* R131Q is a gain-of-function variant with directional changes in signaling consistent with pathway bias.

CONCLUSIONS

Our study provides a comprehensive functional and clinical characterization of the common *GLP1R* missense variant, *GLP1R* R131Q, which has been identified as a T2D-protective variant in genome-wide association studies. By integrating cellular signaling assays, human islet experiments, human hyperglycemic clamp studies, long-term prospective cohort analyses, and pharmacogenetic evaluation in individuals with T2D, we provide evidence that *GLP1R* R131Q enhances GLP-1R–mediated cAMP signaling with directional changes consistent with pathway bias. Our use of a real-time cAMP reporter (28) allowed assessment of time-resolved signaling output, which may explain differences from prior peak cAMP measurements (10,17–20) in which no significant difference was observed. This functional enhancement is associated with increased GLP-1RA–stimulated insulin secretion, preservation of β-cell function over time, and enhanced glycemic response to GLP-1RA treatment. Together, these findings support *GLP1R* R131Q as a gain-of-function variant and underscore its potential as a pharmacogenetic marker for precision treatment strategies in diabetes.

The results from our study support three notable conclusions. First, the *GLP1R* R131Q variant represents an example of genetic heterogeneity in T2D, contributing to differences in pharmacologic response between populations. Prior clinical studies have reported stronger glycemic responses to incretin-based therapies in Asians compared with other populations. For instance, a post hoc analysis of semaglutide randomized trials demonstrated an HbA_{1c} reduction ranging from −1.69 to −2.49 percentage points in the Japanese population versus −1.32 to −1.85 percentage points in the overall population (29). The *GLP1R* R131Q variant is relatively common in East Asians (minor allele frequency 0.21), carried by ∼40% of individuals, and is also present in South Asians (0.087), but is rare in Europeans and Africans (<0.01) (15). Consistent with this, systematic reviews and meta-analyses comparing GLP-1RA efficacy between Asians and other populations have suggested greater glycemic or cardiovascular benefit in Asians (30–32). Our findings provide genetic support for the possibility that population-specific variants such as *GLP1R* R131Q may contribute to this variability.

Second, our study highlights the physiological importance of GLP-1R signaling across both fasting and hyperglycemic

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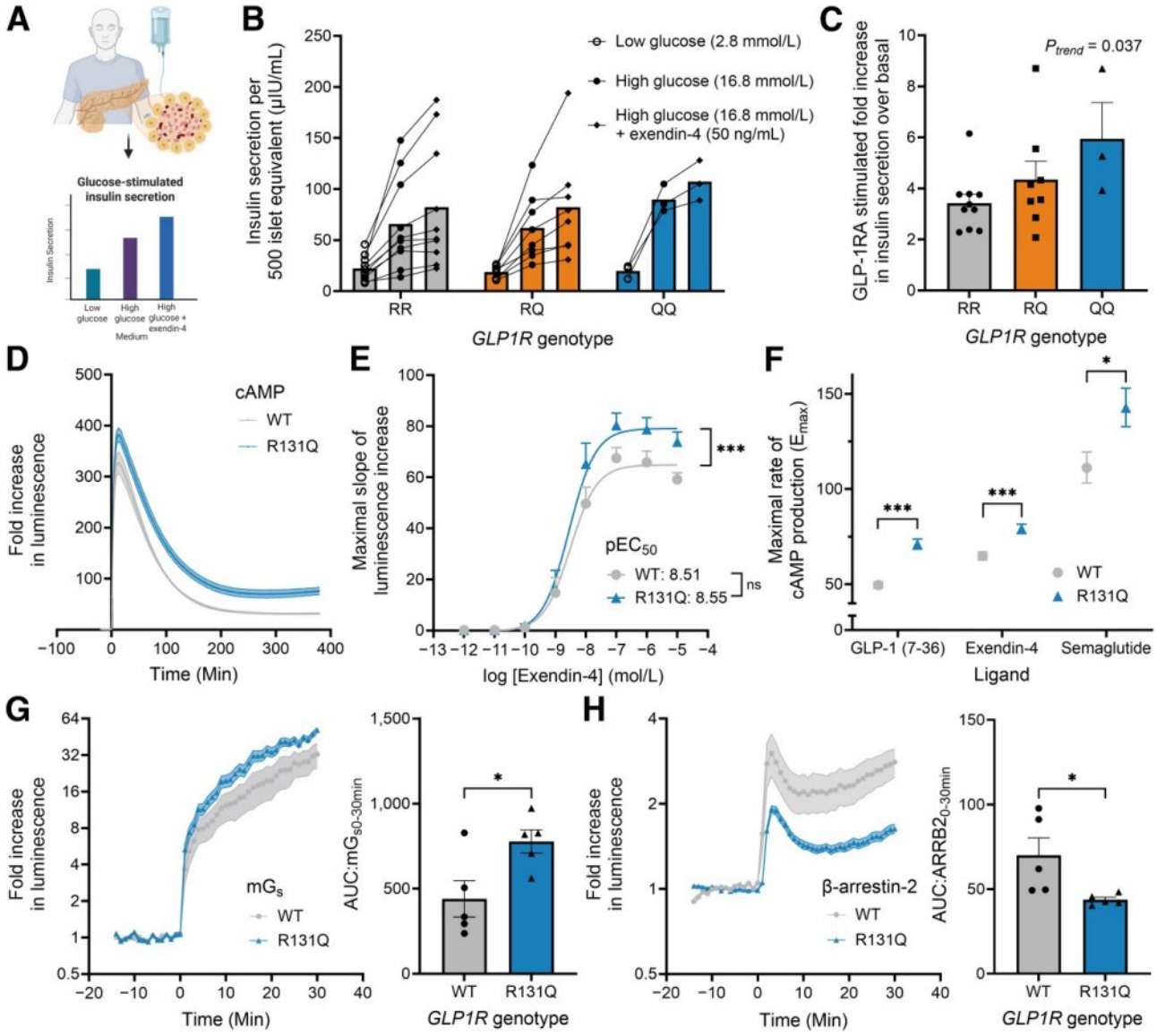


Figure 4—*GLP1R* R131Q enhances GLP-1RA-stimulated insulin secretion and shows signaling changes consistent with pathway bias. *A*: Schematic diagram of the human pancreatic islet experiment. Pancreatic tissue was collected during surgery at Seoul National University Hospital. Human islets were isolated from surgical specimens and tested for glucose-stimulated insulin secretion. *B*: Summary of glucose-stimulated insulin secretion results (n = 21 donors: 10 RR, 8 RQ, and 3 QQ). All islets demonstrated a robust increase in insulin secretion under high-glucose conditions (16.8 mmol/L) and in the presence of exendin-4 (50 ng/mL). *C*: Fold change in insulin secretion under high glucose (16.8 mmol/L) plus exendin-4 (50 ng/mL) relative to basal (2.8 mmol/L). *GLP1R* R131Q carriers showed an additive, allele-dependent trend toward higher exendin-4–stimulated secretion. *D*: Real-time cAMP production in isogenic human embryonic kidney 293 cells expressing WT *GLP1R* or homozygous *GLP1R* R131Q after stimulation with exendin-4 (10^{-7} mol/L). Data are shown as mean ± SEM from n = 3 independent biological replicates. Error bands represent SEM. No statistical comparisons were performed on the kinetic curves; statistical analyses were conducted on summary measures (e.g., area under the curve) as shown in Supplementary Fig. 6. *E*: Concentration-response curves for exendin-4. cAMP production rate was quantified as the maximal slope from the response vs. time curves, using three consecutive data points (n = 3). Curves were fit by nonlinear regression to a three-parameter logistic model with Hill slope constrained to 1.0. Best-fit potency (half-maximal effective concentration) and efficacy (E_{max}) were compared between WT and R131Q using the extra sum-of-squares F test. *F*: Comparison of efficacy (E_{max}) in WT and R131Q cells, stimulated with GLP-1, exendin-4, or semaglutide (n = 3 each). *G*: NanoBiT assay of mini-G_s recruitment showing enhanced recruitment in R131Q cells compared with WT after stimulation with exendin-4 (10^{-7} mol/L) (n = 5). *H*: NanoBiT assay of β-arrestin-2 recruitment showing reduced recruitment in R131Q cells compared with WT after stimulation with exendin-4 (10^{-7} mol/L) (n = 5). Data are presented as mean ± SEM. Statistical comparisons by linear regression were adjusted for age, sex, and BMI (panel *C*), extra sum-of-squares F test (panels *E* and *F*), and two-sided unpaired t tests (panels *G* and *H*). *P < 0.05; **P < 0.01; ***P < 0.001. Arg, arginine; ARRB2, β-arrestin-2; AUC, area under the curve; mG$_s$, mini-G$_s$; ns, not significant; Tet, tetracycline.

states. In the fasting state, blockade of GLP-1R with exendin 9-39 led to a greater increase in fasting glucose among individuals carrying the *GLP1R* R131Q variant. Because GLP-1R exhibits minimal basal activity in both the WT and R131Q receptors (17,33), and circulating GLP-1 has a short half-life (∼3 min) (1), emerging evidence suggests that glucose regulation by GLP-1R during fasting is likely driven by intra-islet GLP-1 or glucagon (34,35). Our in vitro and human islet findings showing

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enhanced GLP-1R signaling in *GLP1R* R131Q carriers, along with our prior observation that GLP-1R blockade impairs islet insulin secretion and glucose metabolism (34), collectively support the idea that intraislet GLP-1R activation contributes to basal islet function. Importantly, this augmented signaling was not limited to the fasting state: the gain-of-function phenotype persisted under hyperglycemia, a condition in which β-cell activation is already strongly engaged by glucose. Both our previous hyperglycemic clamp study with exogenous GLP-1 infusion (13) and the current study with liraglutide showed directionally consistent increases in insulin secretion among carriers. The persistence of this enhanced signaling was further demonstrated in people with T2D, where chronic GLP-1RA treatment resulted in an additive, allele dose-dependent improvement in HbA_{1c}. Together, these findings demonstrate that *GLP1R* R131Q amplifies GLP-1R signaling under both basal and glucose-stimulated conditions, providing a physiological explanation for the variant's association with lower fasting glucose (12,16) and enhanced therapeutic response (14).

Third, our findings extend an emerging pharmacogenomic framework in which genetic variation across the incretin axis contributes to interindividual variability in response to GLP-1–based therapies. Prior pharmacogenomic analysis in people with T2D identified low-frequency coding variants in *ARRB1*, a key regulator of GLP-1R desensitization and signaling, that were associated with glycemic response to GLP-1RAs (11). In addition, hypomorphic T2D risk alleles in the gene encoding peptidyl-glycine α-amidating monooxygenase (*PAM*), the enzyme responsible for amidation of GLP-1 and other bioactive peptides, have been shown to alter GLP-1 biology and attenuate glycemic response to GLP-1RA therapy (36). More recently, a large genome-wide association study of GLP-1RA medication response identified the *GLP1R* p.Pro7-Leu variant as a predictor of weight loss efficacy, further supporting the concept that genetic variation in the incretin axis can modify therapeutic outcomes (37). Together with these studies, our data provide mechanistic and translational evidence that the common East Asian enriched *GLP1R* R131Q variant contributes to GLP-1RA treatment response and further supports the potential for precision medicine approaches in GLP-1–based therapies.

The major strength of this study is in the integration of multiple layers of evidence to establish the functional consequence of the naturally occurring human genetic variant in the *GLP1R* gene. We demonstrate consistent results of the *GLP1R* R131Q variant across in vitro human cell models, ex vivo human pancreatic islets, in vivo human hyperglycemic clamp studies, and longitudinal cohort studies in individuals with and without diabetes. Despite these strengths, several limitations should be acknowledged. First, the in vitro functional analyses were performed in a heterologous system (human embryonic kidney 293 cells) with a limited number of replicates (n = 3–5 throughout), and a direct causal relationship between the observed signal changes and long-term β-cell preservation cannot be established. Second, the hyperglycemic clamp study was limited by a marked imbalance in sex distribution across genotype groups, a very small number of homozygous carriers, and an experimental design focused on GLP-1R–mediated β-cell responsiveness rather than extrapancreatic GLP-1 actions such as appetite regulation or gastric emptying. Both the hyperglycemic clamp and human islet experiments assessed multiple end points and were not powered for definitive inference, and these findings should be considered hypothesis-generating rather than confirmatory. Third, the trajectory analysis may be affected by censoring due to differential incidence of T2D across genotype groups. Although the number of observations and follow-up duration were similar across groups, and sensitivity analyses restricted to earlier follow-up windows showed directionally consistent results, this possibility cannot be fully excluded. Fourth, the analysis of GLP-1RA treatment response was based on observational cohorts, which may be affected by residual confounding and heterogeneity in clinical practice. Randomized pharmacogenetic trials will be needed to definitively establish the clinical impact of *GLP1R* R131Q on GLP-1RA efficacy.

In summary, by integrating multiple lines of evidence, we show that *GLP1R* R131Q is a gain-of-function variant associated with preserved β-cell function and enhanced glycemic response to GLP-1RA treatment. These findings provide mechanistic and translational evidence that common genetic variation in *GLP1R* may contribute to interindividual heterogeneity in T2D pathophysiology and treatment outcomes, supporting its potential role as a candidate pharmacogenetic marker for precision diabetes management.

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Author Contributions. Hyuns.L. performed cell experiments; analyzed the data from human islet experiments, human hyperglycemic clamp studies, and human cohort studies; and wrote the manuscript. H.E.C. researched data, ran the human hyperglycemic clamp experiments, performed statistical analysis, contributed to discussion, and reviewed/edited manuscript. J.S.L. and W.-I.K. performed the pancreatic islet experiments and reviewed the manuscript. M.K.M., S.H.C., and D.H.L. provided hospital-based T2D cohort data and reviewed the manuscript. F.B. and C.D.M. analyzed human hyperglycemic clamp data, contributed to the discussion, and reviewed/edited the manuscript. Se.L., Hyunb.L., M.K., J.C., J.L., J.P., Y.J., and Sa.L. integrated hospital-based T2D cohort data and reviewed the manuscript. N.H.C. provided population-based cohort data and reviewed the manuscript. A.V. designed the human

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hyperglycemic clamp study, oversaw its conduct, researched data, and reviewed/edited manuscript. S.H.K., J.-I.K., and K.S.P. collected data, contributed to the study design and wrote the manuscript. J.-I.K. and K.S.P. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 2013;17:819–837
2. Zhu L, Almaça J, Dadi PK, et al. β-arrestin-2 is an essential regulator of pancreatic β-cell function under physiological and pathophysiological conditions. Nat Commun 2017;8:14295
3. Bitsi S, El Eid L, Manchanda Y, et al. Divergent acute versus prolonged pharmacological GLP-1R responses in adult β cell-specific β-arrestin 2 knockout mice. Sci Adv 2023;9:eadf7737
4. Wootten D, Christopoulos A, Marti-Solano M, et al. Mechanisms of signalling and biased agonism in G protein-coupled receptors. Nat Rev Mol Cell Biol 2018;19:638–653
5. El Eid L, Reynolds CA, Tomas A, et al. Biased agonism and polymorphic variation at the GLP-1 receptor: implications for the development of personalised therapeutics. Pharmacol Res 2022; 184:106411
6. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 2018;27:740–756
7. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
8. Frías JP, Davies MJ, Rosenstock J, et al.; SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med 2021;385:503–515
9. Rosenstock J, Hsia S, Nevarez Ruiz L, et al.; ACHIEVE-1 Trial Investigators. Orforglipron, an oral small-molecule GLP-1 receptor agonist, in early type 2 diabetes. N Engl J Med 2025;393:1065–1076
10. Lagou V, Jiang L, Ulrich A, et al.; Meta-Analysis of Glucose and Insulin-Related Traits Consortium (MAGIC). GWAS of random glucose in 476,326 individuals provide insights into diabetes pathophysiology, complications and treatment stratification. Nat Genet 2023;55:1448–1461
11. Dawed AY, Mari A, Brown A, et al.; DIRECT consortium. Pharmacogenomics of GLP-1 receptor agonists: a genome-wide analysis of observational data and large randomised controlled trials. Lancet Diabetes Endocrinol 2023;11:33–41
12. Kwak SH, Chae J, Lee S, et al. Nonsynonymous variants in PAX4 and GLP1R are associated with type 2 diabetes in an East Asian population. Diabetes 2018;67:1892–1902
13. Sathananthan A, Man CD, Micheletto F, et al. Common genetic variation in GLP1R and insulin secretion in response to exogenous GLP-1 in nondiabetic subjects: a pilot study. Diabetes Care 2010;33:2074–2076
14. Han E, Park HS, Kwon O, et al. A genetic variant in GLP1R is associated with response to DPP-4 inhibitors in patients with type 2 diabetes. Medicine (Baltimore) 2016;95:e5155
15. Chen S, Francioli LC, Goodrich JK, et al.; Genome Aggregation Database Consortium. A genomic mutational constraint map using variation in 76,156 human genomes. Nature 2024;625:92–100
16. Suzuki K, Akiyama M, Ishigaki K, et al. Identification of 28 new susceptibility loci for type 2 diabetes in the Japanese population. Nat Genet 2019;51:379–386
17. Fortin JP, Schroeder JC, Zhu Y, et al. Pharmacological characterization of human incretin receptor missense variants. J Pharmacol Exp Ther 2010;332:274–280
18. Koole C, Wootten D, Simms J, et al. Polymorphism and ligand dependent changes in human glucagon-like peptide-1 receptor (GLP-1R) function: allosteric rescue of loss of function mutation. Mol Pharmacol 2011;80:486–497
19. Li W, Li P, Li R, et al. GLP1R single-nucleotide polymorphisms rs3765467 and rs10305492 affect β cell insulin secretory capacity and apoptosis through GLP-1. DNA Cell Biol 2020;39:1700–1710
20. Melchiorsen JU, Sørensen KV, Bork-Jensen J, et al. Rare heterozygous loss-of-function variants in the human GLP-1 receptor are not associated with cardiometabolic phenotypes. J Clin Endocrinol Metab 2023;108:2821–2833
21. Yu M, Wang K, Liu H, et al. GLP1R variant is associated with response to exenatide in overweight Chinese type 2 diabetes patients. Pharmacogenomics 2019;20:273–277
22. Guan Z, Du Y, Li R, et al. Association between glucagon-like peptide-1 receptor gene polymorphism and treatment response to GLP1R agonists in Chinese patients with type 2 diabetes: a prospective cohort study. Eur J Clin Pharmacol 2022;78:793–799
23. Ohn JH, Kwak SH, Cho YM, et al. 10-year trajectory of β-cell function and insulin sensitivity in the development of type 2 diabetes: a community-based prospective cohort study. Lancet Diabetes Endocrinol 2016;4:27–34
24. Lee H, Choi J, Kim JI, et al. Higher genetic risk for type 2 diabetes is associated with a faster decline of β-cell function in an East Asian population. Diabetes Care 2024;47:1386–1394
25. Lee H, Choi J, Kim NY, et al. Earlier age at type 2 diabetes diagnosis is associated with increased genetic risk of cardiovascular disease. Diabetes Care 2023;46:1085–1090
26. Taliun D, Harris DN, Kessler MD, et al.; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed program. Nature 2021;590: 290–299
27. Wan Q, Okashah N, Inoue A, et al. Mini G protein probes for active G protein-coupled receptors (GPCRs) in live cells. J Biol Chem 2018;293:7466–7473
28. Wang FI, Ding G, Ng GS, et al. Luciferase-based GloSensor™ cAMP assay: temperature optimization and application to cell-based kinetic studies. Methods 2022;203:249–258
29. Araki E, Harashima S, Nishida T, et al. Efficacy and safety of once-weekly semaglutide in Japanese individuals with type 2 diabetes in the SUSTAIN 1, 2, 5 and 9 trials: post-hoc analysis. J Diabetes Investig 2022;13:1971–1980
30. Kim YG, Hahn S, Oh TJ, et al. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab 2014;16:900–909
31. Lee MMY, Ghouri N, Misra A, et al. Comparative efficacy of glucagon-like peptide 1 receptor agonists for cardiovascular outcomes in Asian versus White populations: systematic review and meta-analysis of randomized trials of populations with or without type 2 diabetes and/or overweight or obesity. Diabetes Care 2025;48:489–493
32. Kang YM, Cho YK, Lee J, et al. Asian subpopulations may exhibit greater cardiovascular benefit from long-acting glucagon-like peptide 1 receptor agonists: a meta-analysis of cardiovascular outcome trials. Diabetes Metab J 2019;43:410–421
33. Chen G, Jayawickreme C, Way J, et al. Constitutive receptor systems for drug discovery. J Pharmacol Toxicol Methods 1999;42:199–206
34. Welch AA, Farahani RA, Egan AM, et al. Glucagon-like peptide-1 receptor blockade impairs islet secretion and glucose metabolism in humans. J Clin Invest 2023;133:e173495
35. Campbell SA, Johnson J, Light PE. Evidence for the existence and potential roles of intra-islet glucagon-like peptide-1. Islets 2021;13: 32–50
36. Umapathysivam MM, Araldi E, Hastoy B, et al. Type 2 diabetes risk alleles in peptidyl-glycine alpha-amidating monooxygenase influence GLP-1 levels and response to GLP-1 receptor agonists. Genome Med 2026;18:40
37. Su QJ, Ashenhurst JR, Xu W, et al.; 23andMe Research Team. Genetic predictors of GLP1 receptor agonist weight loss and side effects. Nature 2026; 653:770–775

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