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Supplementary appendix

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Contents

Description of cohorts

DIRECT

Three groups of subjects with type 2 diabetes from four IMI-DIRECT (DIabetes REsearCh on patient straTification) participating centres in the United Kingdom have been included in this cohort. The first group were recruited just before starting a GLP-1RA and followed up for 6 months. The second group were recruited after they had GLP-1RA treatment between 6 and 24 months and were still on treatment at the time of assessment. The third group were all patients who had ever been treated with a GLP-1RA where they had at least 4 months of GLP-1RA treatment and an HbA1c measurement within the 6 weeks prior to starting the GLP-1RA, and within 6 months (± 2 months) after starting the GLP-1RA in order to define HbA1c reduction. The inclusion criteria for all the groups were a) baseline HbA1c ≥ 7.5% (58mmol/mol) and HbA1c < 12% (108 mmol/mol), b) White European, c) Age ≥ 18 years and < 80 years. Written informed consent was signed by each participant and ethical approval was obtained from the respective participating centres.

PRIBA

The PRIBA (Predicting Response to Incretin Based Agents in Type 2 Diabetes) study recruited subjects with type 2 diabetes commencing GLP-1RA as part of routine care prospectively between April 2011 and October 2013 in the United Kingdom. Participants with baseline HbA1c ≥ 7.5% (58 mmol/mol) and estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73m^2 were included. Participants were assessed (including HbA1c) immediately prior to commencing treatment and after 3 and 6 months on therapy. All the participants signed informed consent and the Southwest National Research Ethics committee approved the study. Further study details, and details of previous publications, are available through https://clinicaltrials.gov/ct2/show/NCT01503112

GoDARTS

GoDARTS (Genetics of Diabetes Audit and Research in Tayside Scotland) is a longitudinal cohort study established to study the genetics of type 2 diabetes. Over 18,000 participants were enrolled between December 1998 and August 2012, of whom half of them are diagnosed with type 2 diabetes and the remaining age and sex matched non-diabetic controls identified from general practice records in Tayside, Scotland.[1] Comprehensive electronic medical records history dating back to 1990 including anthropometric, clinical, prescription and

biochemistry is available for each participant through a unique anonymised community health index number provided by the Health Informatics Centre (HIC) in partnership with the University of Dundee and the National Health Service (NHS).

From 659 incident GLP-1RA users in the GoDARTS cohort, we identified a study sample of 315 patients who had been started on liraglutide or exenatide as their second-line (added to metformin or sulphonylurea monotherapy) or third-line (added to metformin and/or sulphonylurea and/or thiazolidinediones, dual therapy) treatment according to the NHS guideline in Scotland. All the patients in the study had complete data with respect to age, gender, antidiabetic treatment history, regular HbA1c measurements and genotype. They all had a baseline HbA1c higher than 7% (53 mmol/mol). They were on stable treatment for 6 months after GLP-1RA was initiated (the index date), which meant they did not start or stop another antidiabetic drug within the study period. They were not treated with insulin before or during the study period. The study was approved by the Tayside Regional Ethics Committee and informed consent was obtained from all subjects.

PROMASTER

The PROMASTER (PROspective Cohort MRC ABPI STratification and Extreme Response Mechanism in Diabetes) is a longitudinal study designed to examine extreme responders to second- and third-line type 2 diabetes therapies using a prospective approach in the United Kingdom. All the participants were clinically diagnosed with type 2 diabetes aged between 18 and 90 years, had HbA1c > 7% (53 mmol/mol) and signed informed consent to participate. Data from 79 participants treated with GLP-1RA as part of their diabetes care were included for this meta-analysis. Further study information is available through https://www.clinicaltrials.gov/ct2/show/NCT02105792.

The HARMONY phase 3 trials

The HARMONY program for albiglutide includes eight phase III clinical trials designed to evaluate the efficacy and safety of albiglutide in patients with type 2 diabetes inadequately controlled on lifestyle and/or a combination of other glucose lowering drugs. Data from the GLP-1RA (Albiglutide) arm of seven of these trials is included in the current study.[2-8] Supplementary Table 1 shows the different studies included with numbers in each arm with background medication, duration for primary end points and study centres. Each study included male and nonpregnant, nonlactating female participants of 18 years of age or older, with a history of type 2 diabetes diagnosis currently on lifestyle and/or other hypoglycaemic

agents but experiencing inadequate glycaemic control. Patients were required to have baseline HbA1c between 7.0 and 10.0% (53–86 mmol/mol), BMI between 20 and 45 kg/m^2

Important exclusion criteria included a history of cancer (except non-melanoma skin cancers) not in remission for 3 years), treated diabetic gastroparesis, current symptomatic biliary disease or history of pancreatitis, significant gastrointestinal surgery, or recent significant cardiovascular or cerebrovascular events and history or family history of medullary carcinoma or multiple endocrine neoplasia type 2. Other study specific inclusion/exclusion criterion are available in the respective publications.[2-8] Informed consent was obtained from all participants.

For this study, participants randomized to the GLP-1RA arm who have genotypic and complete clinical data are included. Glycaemic response to GLP-1RA was modelled as the quantitative phenotype of HbA1c reduction between baseline HbA1c and treatment HbA1c. Baseline HbA1c was the HbA1c measure at randomization. The treatment HbA1c was the closest HbA1c measure to 6 months after initiation of GLP-1RA (between 3 and 9 months).

Supplementary Table 1: HARMONY phase 3 trials included in the current analysis.

Study	Treatment arm at randomization (n)	Comparator arm at randomization (n)	Background medication	Duration of primary end point (weeks)	Genotyped	Recruitment centres
HARMONY 1	Albiglutide (155)	Placebo (155)	Pioglitazone and/or metformin	52	244	United States, India, Republic of Korea, Peru, South Africa, United Kingdom
HARMONY 2	Albiglutide (204)	Placebo (105)	Diet and exercise	52	234	United States, Mexico, South Africa
HARMONY 3	Albiglutide (302)	Placebo(101)/Sitagliptin (302)/Glimepiride (307)	Metformin	104	730	United States, Albania, Germany, Hong Kong, Mexico, Peru, Philippines, Russia Federation, South Africa, Spain, United Kingdom
HARMONY 4	Albiglutide (504)	Insulin (241)	Metformin and/or sulfonylurea	52	584	United States, Russia Federation, South Africa, United Kingdom
HARMONY 5	Albiglutide (281)	Placebo(116)/Pioglitazone (288)	Metformin and glimepiride	52	490	United States, Germany, Hong Kong, India, Peru, Philippines, Russia Federation, Spain, United Kingdom
HARMONY 7	Albiglutide (422)	Liraglutide (419)	Any oral medication	32	638	United States, Australia, Israel, Republic of Korea, Peru, Philippines, Spain, United Kingdom
HARMONY 8	Albiglutide (254)	Sitagliptin (253)	Diet and or exercise and/or any oral medication	26	290	United States, Australia, Brazil, Colombia, Germany, India, Israel, Republic of Korea, Peru, Philippines, Russia Federation, South Africa, Spain, Taiwan, United Kingdom
Total	2, 122	2, 287			3210	

AWARD trials:

The **A**ssessment of **W**eekly **A**dminist**R**ation of LY2189265 (dulaglutide) in **D**iabetes (AWARD) is a phase 3 clinical study program that compared GLP1-RA dulaglutide (0.75 mg and/or 1.5 mg) to a variety of common antihyperglycemic medications. Studies were designed to assess efficacy, safety, and patient reported outcomes in patients across different stages of the T2D treatment. Eligible patients at screening were adults with an HbA1c of ≥7.0% (≥53 mmol/mol) experiencing inadequate glycaemic control with one, two, or three glucose lowering medications for at least 3 months. Patients were excluded from study participation if they had received chronic insulin therapy at any time in the past or had taken GLP-1 receptor agonists within 3 months of screening. Data from the dulaglutide arms along with two other active GLP1-RA comparators (exenatide and liraglutide) from five trials were included in this study[9-13]. Supplementary Table 2 shows different studies included with numbers in each arm, background medications and duration for primary end points. The primary outcome in AWARD studies was HbA1c change from baseline to the primary endpoint were mostly 26-52 weeks depending on the study. To achieve consistency in our analyses, we used 26 or 24 weeks HbA1c change from baseline as our primary endpoint. The participants with full consent and available genotypic and clinical data were only included in this analysis.

Supplementary Table 2: AWARD phase 3 trials included in the current analysis

Study	At randomization (n)	Comparator(s) (dose) - (n)	Background medication	Duration of primary end point (weeks)	Genotyped (n)	Analyzed (n)	Recruitment centres
AWARD-1 (GBDA)§	Dulaglutide (498)	Exenatide (10µg BID) - (249) Placebo	Pioglitazone (≥30 mg) Metformin (≥1500 mg)	26	Dulaglutide (341) Exenatide (166)	501	United States, Argentina, Mexico, Puerto Rico
AWARD-2 (GBDB)§	Dulaglutide (446)	Insulin Glargine (titrated to target)	Glimepiride (≥4 mg) Metformin (≥1500 mg)	52	Dulaglutide (187)	185	Argentina, Australia, Belgium, Brazil, Canada, Croatia, Czech Republic, France, Greece, Hungary, India, Italy, Republic of Korea, Mexico, Poland, Romania, Slovakia, Spain, Sweden, Taiwan
AWARD-5 (GBCF)§	Dulaglutide (606)	Sitagliptin (100 mg QD) Placebo	Metformin (≥1500 mg)	52	Dulaglutide (179)	178	United States, Canada, France, Germany, India, Republic of Korea, Mexico, Poland, Puerto Rico, Romania, Russian Federation, Spain, Taiwan,
AWARD-6 (GBDE)§	Dulaglutide (299)	Liraglutide (1.8 mg QD) - (300)	Metformin (≥1500 mg)	26	Dulaglutide (243) Liraglutide (233)	476	United States, Czech Republic, Germany, Hungary, Mexico, Poland, Puerto Rico, Romania, Slovakia, Spain,
AWARD-8 (GBDG)¶	Dulaglutide (239)	Placebo	Sulfonylurea (at least 50% of maximum tolerated dose)	24	Dulaglutide (225)	222	United States, Argentina, Austria, Croatia, Mexico, Romania, Slovenia, South Africa

§ Indicates that genetic analyses for HbA1c reduction were conducted at 26 weeks change from baseline (CFBL); ¶ Indicates that genetic analyses for HbA1c reduction were conducted at 24 weeks change from baseline (CFBL)

HARMONY outcome trial

The HARMONY outcome was a double-blind, randomised, placebo-controlled trial designed to evaluate the cardiovascular benefit of Albiglutide in patients with type 2 diabetes[14]. Recruitment was performed across the Americas, Europe, Asia and Africa. Each study included men and women aged 40 years or older with established disease of the coronary, cerebrovascular, or peripheral arterial circulation who had a glycated haemoglobin concentration of more than 7·0% (53 mmol/mol). Individuals with estimated glomerular filtration rate (eGFR) of less than 30 mL/min per 1·73 m^2, severe gastroparesis, previous pancreatitis or substantial risk factors for pancreatitis, a personal or family history of medullary carcinoma of the thyroid or multiple endocrine neoplasia type 2, a history of pancreatic neuroendocrine tumours, or current use of a GLP-1A were excluded[14]. Patients had study visits every four months - anthropometric and biochemical measures were collected. Informed consent was obtained from all participants and for this analysis ethical approval was obtained from the ethics committee by GSK.

For this study, participants randomized to the GLP-1RA arm with genotype data for rs140226575 and complete clinical data are included. Glycaemic response to GLP-1RA was modelled as the quantitative phenotype of HbA1c reduction between baseline HbA1c and treatment HbA1c. Baseline HbA1c was the HbA1c measure at randomization. The treatment HbA1c was the HbA1c measure at 8 months after initiation of GLP-1RA.

Genotyping and imputation

Genotypes for the DIRECT, PRIBA and PROMASTER studies were generated using the Illumina Human Core Exome chip v1.1 (HCE24 v1.1). Genotype calling for both common and low-frequency variants was performed using the GenCall algorithm in the GenomeStudio software supplied by Illumina. Data were subjected to a series of standard quality control analyses in order to highlight poorly performing genetic markers and samples prior to imputation. Individuals that had a call rate lower than 98% were excluded. The heterozygosity rate per sample was calculated using the formula (number of non-missing genotypes N (NM) - Number of homozygous genotypes O (Hom)) / N (NM). Cut-off for exclusion of outliers was 4 standard deviations from the mean heterozygosity rate. Gender check was ascertained to detect discrepancies between phenotypic and genotypic sex. Individuals with discordant sex information were removed. In order to avoid bias from duplicates and related individuals, estimates of pairwise identity by decent (IBD) were generated. Among the related samples, IBD > 0.2, the one with the lowest call rate was excluded. Accordingly, 10 participants from DIRECT, 30 from PRIBA and 4 from PROMASTER were excluded. Each dataset was then

imputed to the 1000 Genomes Phase 3 CEU reference panel with ShapeIt (v2.r790)[15] and Impute2 (v2.3.2).[16] Post-imputation, the final dataset has 6,912,896 common variants for DIRECT, 6,951,827 for PRIBA and 6,825,849 markers for PROMASTER. The DIRECT and PRIBA cohorts contributed to the gene-based analysis on low frequency and rare protein coding variants. Accordingly, 13,099 and 14,218 genes were included into the meta-analysis from the DIRECT and PRIBA studies, respectively.

For the GoDARTs data, a single time point blood sample was collected from each participant for DNA extraction and genotyping. Each of the Illumina Omni-express (Illumina, San Diego, USA) and the Affymetrix 6.0 SNP (Affymetrix, Santa Clara, USA) genotyping arrays were used to genotype participants with T2D. After standard quality control of the genotypic data, haplotypes were estimated using ShapeIt (v2.r790)[15] and imputation of the missing genotypes was performed using the 1000 Genomes Phase 3 CEU reference panel with Impute2 (v2.3.2).[16] Missing alleles were imputed by running a forward-backward algorithm with a certain probability. More details on genotyping, QC, imputation and processing have been published previously (1). The final dataset has 6,522,145 markers (MAF > 5%).

HARMONY phase 3: Samples from consented participants were genotyped with the Affymetrix Axiom Array with custom content (GSKBB1_v1). Genotypes were reported on the forward strand of the GRCH37/hg19 assembly. Participants with call rates < 96% and discrepancies in reported sex were removed. Samples with extra heterozygosity (more than 4 standard deviation away from the mean) or correlated with another sample (identity by descent [IBD]>0.2) were filtered out. Variants that are monomorphic or with call rates < 95% were removed. Data was available on 607,517 markers and 1869 GLP-1RA treated subjects. Autosomes were imputed to the 1000G panel using Michigan Imputation Server and converted to hard calls using default PLINK threshold settings. Non-biallelic SNPs were filtered out and SNPs with imputation quality (R^2) less than 0.3. SNPs with genotyping rates < 0.95, Hardy Weinberg Equilibrium P-value less than $10x10^{-6}$ were excluded. Individuals with call rates less than 0.96 were excluded. The final dataset contains 6,823,695 markers with MAF > 5%. The gene-based analysis on low frequency and rare protein coding variants had 17,237 genes. A GWAS was performed using SNPTEST[17] including sex, baseline HbA1c, baseline BMI, duration of diabetes, study, and the first 10 principal components as covariates.

AWARD phase 3

Human genomic DNA from 5 dulaglutide trials (AWARD 1, 2, 5, 6 and 8) enrolled participants was extracted using peripheral whole blood. Participant who consented for genetic analyses were only included in the study. Genome-wide data was generated using the Illumina's

HumanOmni-5 exome array (Santa Clara, CA, US) and standard quality control metrics of genome-wide association study were applied. Samples with call rate < 95% across all variants and discrepancies in reported sex were removed. Identity-by-state (IBS) score for all possible pairs of subjects was calculated and subjects with unusually high IBS scores were excluded from the analyses. Variants that were monomorphic or with call rates < 95% were removed. Samples that passed QC were later used as an input to perform genome-wide imputation. Chromosomal phasing was performed with Beagle v.4.1 using GRCh37/hg19 map reference file, and later genome-wide data imputation was performed using Minimac3 algorithm (https://genome.sph.umich.edu/wiki/Minimac3). The 1,000 Genomes Project phase 3 data from various ethnic groups (ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/phase3/data/) was used as the reference for the imputation. The imputation accuracy was evaluated using metrics generated by minimac3. The empirical correlation (Pearson correlation coefficient between Leave-One-Out dosages and known genotypes) was used to evaluate the imputation accuracy for genotyped variants. The average empirical correlation for variants that belong to different MAF bins was calculated to check the impact of MAF on imputation accuracy. For all downstream analyses, only biallelic autosomal variants were considered and optimal thresholds for Rsq were recommended given evaluation with various MAF ranges: an Rsq threshold of 0.3 is recommended for MAF > 1%; and threshold of 0.8 is recommended for MAF ≤ 1%. The final dataset had 6, 266, 305 common variants (MAF >5%). The gene-based analysis on low frequency and rare protein coding variants had 16,092 genes.

Seven separate GWASs (5 dulaglutide, 1 liraglutide and 1 exenatide) were performed using a model that consist of HbA1c (change from baseline) as response variable, and genotype, baseline HbA1c and the first 3 principal components as fixed effect variables, whereas study was used as random effect in the model. Treatment dose was used as a covariate if multiple doses were used in the study.

For each of the cohorts, the number of principal components to include into the model were decided from a scree plot by which the first n principal components to the point where the proportion of variance explained by each subsequent principal component drops off. In addition, this was triangulated by using the total variance explained method where the first n principal components explain at least 80% of the total variance (https://doi.org/10.1007/978-3-642-04898-2_455).

Power calculation

With a mean baseline HbA1c of 8% (64 mmol/mol) and standard deviation of 1% (10 mmol/mol), 4571 patients in the meta-GWAS provide 80% power to detect a genetic variant

of 12% minor allele frequency (MAF) responsible for a change in 0.2% (2.5 mmol/mol) at a GWAS significance threshold of 5×10^{-8}.

Supplementary Table 3: Models used in each cohort

Cohort	Covariates included in the model
DIRECT	Baseline HbA1c, sex, age at diagnosis, duration of diabetes, baseline BMI, Insulin use at GLP-1RA start, number of oral glucose lowering drugs, the first 3 principal components.
PRIBA	Baseline HbA1c, sex, age at diagnosis, duration of diabetes, baseline BMI, Insulin use, the first 3 principal components.
GoDARTS	Baseline HbA1c, sex, age at diagnosis, duration of diabetes, baseline BMI, number of oral glucose lowering drugs, the first 3 principal components.
PROMASTER	Baseline HbA1c, sex, baseline BMI, number of oral glucose lowering drugs, the first three principal components.
HARMONY PHASE 3	Baseline HbA1c, sex, baseline BMI, duration of diabetes, study, and the first 10 principal components.
AWARD	Baseline HbA1c, study, treatment dose, the first 3 principal components.
HARMONY outcomes	Baseline HbA1c, sex, baseline BMI, duration of diabetes, study, and the first 10 principal components.

Supplementary Table 4: Baseline characteristics of participants included in each cohort

Characteristics		DIRECT	PRIBA	GoDARTS	PROMASTER	HARMONY Phase 3	AWARD	HARMONY outcomes
n		365	471	323	79	1771	1562	3748
Age (years)		59.72 ± 9.95	55.99 ± 10.18	59.16 ± 8.82	54.61 ± 11.43	55.81 ± 10.08	55.93 ± 9.59	64.29 ± 8.64
Duration of diabetes (years)		12.73 ± 6.58	10.02 ± 6.56	10.64 ± 4.72	-	8.00 ± 6.11	8.07 ± 5.36	14.12 ± 8.49
Sex (% women)		148 (40.6%)	216 (45.6%)	138 (42.7%)	35 (44.3%)	830 (46.9%)	773 (49.5%)	1103 (29.4%)
Pre-treatment weight (kg)		111.21 ± 22.08	114.47 ± 22.86	110.60 ± 22.04	106.12 ± 18.96	93.8 ± 20.51	92.21 ± 18.66	92.94 ± 19.86
Pre-treatment BMI (kg/m^2)		38.69 ± 6.94	39.77 ± 7.49	38.33± 6.71	36.99 ± 6.91	33.14 ± 5.62	32.77 ± 5.23	32.50 ± 5.98
Pre-treatment HbA1c (DCCT-%)		9.39 ± 1.20	9.76 ± 1.58	9.42 ± 1.39	9.85 ± 1.59	8.16 ± 0.67	8.14 ± 1.04	8.69 ± 1.41
On-treatment weight (kg)		107.14 ± 22.47	110.10 ± 21.78	112.85 ± 22.15	104.09 ± 20.13	92.98 ± 20.46	90.41 ± 18.81	91.87 ± 19.72
On-treatment BMI (kg/m^2)		37.25 ± 7.09	38.10 ± 7.05	39.07 ± 6.68	36.25 ± 6.94	32.84 ± 5.56	32.12 ± 5.29	32.13 ± 5.96
On-treatment HbA1c (DCCT-%)		8.19 ± 1.45	8.38 ± 1.59	8.67 ± 1.65	8.94 ± 1.82	7.26 ± 0.95	6.83 ± 0.99	7.40 ± 1.35
Weight fall (kg)[#]		4.00 [1.00-7.28]	3.45 [0.90-6.90]	4.45 [1.85-8.15]	2.75 [0.28-4.45]	0.84 [-1.0 – 2.40]	1.6 [-0.05 - 4.00]	0.80 [-1.00 – 2.80]
BMI fall (kg/m^2)[#]		1.47 [0.38-2.59]	1.17 [0.31-2.37]	1.72 [0.67-2.86]	0.88 [0.10-1.55]	0.24 [-0.39-0.91]	0.6 [-0.16 – 1.40]	0.27 [-0.35 – 0.99]
HbA1c fall (DCCT-%)		1.20 ±1.34	1.38 ±1.55	0.75 ± 1.71	0.89 ± 1.64	0.90 ± 0.89	1.31 ± 1.00	0.98 ± 1.33
Ethnicity - White Europeans		365 (100%)	471 (100%)	323 (100%)	79 (100%)	950 (54%)	1151 (74%)	2784 (74%)
Ethnicity - Hispanics		-	-	-	-	386 (22%)	63 (4%)	546 (15%)
Ethnicity - American Indians/Alaska Native		-	-	-	-	123 (7%)	189 (12%)	231 (6%)
Ethnicity - Others		-	-	-	-	312 (17%)	159 (10%)	187 (5%)
GLP-1RA type (%)	Liraglutide	64%	64%	77%	-	17%	-	-
	Exenatide	36%	36%	23%	-	-	-	-
	Albiglutide	-	-	-	-	83%	-	100%
	Dulaglutide	-	-	-	-	-	100%	-

BMI, body mass index. [#] Median [IQR]

Supplementary Table 5: Results for index variants at suggestive loci ($p<1\times10^{-5}$) associated with glycaemic response identified in a GWAS meta-analysis of GLP-1RA users with type 2 diabetes.

RSID	Chr	Position	EA	NEA	EAF	beta	se	Nearest gene	p.value	n
rs61800555	1	165220705	A	G	0.195	-0.142	0.025	*LMX1A*	2.5×10^{-7}	4462
rs2268640	6	39050384	A	G	0.608	0.100	0.020	*GLP-1R*	2.5×10^{-7}	4462
rs7687008	4	139268507	C	T	0.404	0.104	0.020	*LINC00499*	1.6×10^{-6}	4462
rs10224036	7	77106630	G	A	0.190	0.133	0.026	*PTPN12*	2.0×10^{-6}	4462
rs1969320	2	131027031	G	C	0.612	0.104	0.021	*MTND1P29*	3.5×10^{-6}	4150
rs11072298	15	71854982	C	A	0.688	-0.106	0.021	*THSD4*	5.2×10^{-6}	4462
rs4986076	17	81027889	A	G	0.086	0.171	0.035	*METRNL*	5.3×10^{-6}	4463
rs2048020	16	32375625	T	G	0.062	0.321	0.065	*LOC105371191*	5.9×10^{-6}	2406
rs2298192	10	132915050	A	G	0.148	-0.137	0.028	*TCERG1L*	6.6×10^{-6}	4462
rs10561032	19	5742326	G	T	0.153	0.143	0.029	*CATSPERD*	7.2×10^{-6}	4150
rs56354900	16	77451045	T	A	0.604	-0.100	0.020	*ADAMTS18*	7.5×10^{-6}	4150
rs11746176	5	78987399	G	C	0.208	0.119	0.024	*CMYA5*	7.5×10^{-6}	4462
rs40182	5	1350397	A	G	0.382	-0.099	0.020	*CLPTM1L*	7.8×10^{-6}	4462
rs5767119	22	48758497	T	C	0.133	0.139	0.029	*LOC105373081*	9.0×10^{-6}	4462
rs2286414	7	157475020	T	C	0.053	0.202	0.042	*PTPRN2*	9.2×10^{-6}	4463
rs75941546	3	187866416	A	G	0.082	0.171	0.036	*LPP*	9.6×10^{-6}	4462

*EA: Effective allele, †NEA: Non-effective allele, EAF: Effective allele frequency, A negative beta implies that the effective allele is associated with reduced response to GLP-1RA.

Supplementary Table 6: Genes most strongly associated with HbA1c reduction in a gene-based analysis, with $p < 1.0\times10^{-4}$.

gene	Extended gene name	p_burden	p_skat	p_skato	nsnps
ARRB1	Arrestin beta 1	1.1×10^{-7}	3.4×10^{-7}	6.7×10^{-8}	4
TAS2R1	Taste receptor type 2-member 1	4.3×10^{-5}	5.3×10^{-6}	5.2×10^{-6}	3
NANOGNB	NANOG Neighbor Homeobox	1.1×10^{-5}	4.7×10^{-4}	9.7×10^{-6}	2
PYGL	Glycogen Phosphorylase L	2.8×10^{-5}	9.2×10^{-5}	1.4×10^{-5}	11
PRRX1	Paired Related Homeobox 1	3.7×10^{-6}	2.8×10^{-5}	2.3×10^{-5}	3
TSPAN33	Tetraspanin 33	5.8×10^{-4}	2.5×10^{-5}	2.3×10^{-5}	2
BIRC3	Baculoviral IAP Repeat Containing 3	1.6×10^{-5}	4.3×10^{-5}	2.7×10^{-5}	7
KCNJ1	Potassium Inwardly Rectifying Channel Subfamily J Member 1	5.3×10^{-5}	3.5×10^{-5}	3.9×10^{-5}	6
TNFSF14	TNF Superfamily Member 14	1.5×10^{-3}	3.3×10^{-5}	4.0×10^{-5}	5
RNF4	RING finger protein 4	1.3×10^{-2}	3.9×10^{-5}	5.4×10^{-5}	4
TRIM21	Tripartite motif containing-21	0.59	3.9×10^{-5}	6.0×10^{-5}	9
GPRC5A	G Protein-Coupled Receptor Class C Group 5 Member A	1.0×10^{-4}	1.3×10^{-4}	7.9×10^{-5}	12
SLC6A5	Solute carrier family 6 member 5	4.9×10^{-3}	1.6×10^{-5}	9.2×10^{-5}	9
EHD1	EH domain-containing protein 1	8.2×10^{-3}	8.9×10^{-5}	9.2×10^{-5}	2

Supplementary Table 7: Association of *GLP-1R* variants and *ARRB1* with HbA1c reduction after treatment with different glucose lowering drugs.

SNP	Beta ± SE	p
Metformin (n = 11933)		
rs6923761G>A	0.007 ± 0.012	0.54
rs10305420C>T	0.017 **±** 0.013	0.20
Sulphonylureas (n = 5479)		
rs6923761G>A	-0.004 ± 0.021	0.87
rs10305420C>T	-0.011 ± 0.024	0.65
	Placebo (315)	
rs6923761G>A	0.115 ± 0.098	0.24
rs10305420C>T	0.121 ± 0.086	0.16
ARRB1 genetic score	0.135 ± 0.222	0.54
Pioglitazone (n = 191)		
rs6923761G>A	-0.115 ± 0.104	0.27
rs10305420C>T	0.059 ± 0.092	0.52
ARRB1 genetic score	0.329 ± 0.255	0.20
Glimepiride (n = 207)		
rs6923761G>A	0.068 ± 0.115	0.56
rs10305420C>T	0.052 ± 0.106	0.63
ARRB1 genetic score	-0.167 ± 0.277	0.55
Insulin (n = 187)		
rs6923761G>A	-0.078 ± 0.132	0.60
rs10305420C>T	-0.002 ± 0.117	0.99
ARRB1 genetic score	-1.017 ± 0.706	0.15

Supplementary Table 8: Association of *GLP-1R* variants and *ARRB1* with BMI reduction after treatment with GLP-1RA.

	Baseline BMI			**Treated BMI**			**BMI fall**	
SNP	**Beta ± SE**	**p**		**Beta ± SE**	**p**		**Beta ± SE**	**p**
rs6923761G>A	-0.12 ± 0.17	0.48		0.06 ± 0.23	0.78		-0.003 ± 0.05	0.95
ARRB1 genetic score	0.24 ± 0.42	0.56		0.39 ± 0.56	0.49		0.07 ± 0.13	0.58
GLP1R_ARRB1 genetic score: D	-	-		-	-		-	-
C	0.77 ± 0.53	0.15		0.58 ± 0.54	0.29		0.11 ± 0.12	0.36
B	0.33 ± 0.53	0.53		0.25 ± 0.54	0.65		0.05 ± 0.12	0.69
A	0.80 ± 0.79	0.31		0.48 ± 0.80	0.55		0.16 ± 0.18	0.37

A: ≤1 Ser allele at p.Gly168Ser and ≥ 1 *ARRB1* variant allele, B: wild type at both *GLP1R* and *ARRB1*, C: 1 Ser allele at *GLP1R* and wild type at *ARRB1*, D: two variant alleles at *GLP1R* and wild type at *ARRB1*. Comparisons are made by taking the least responding group (D) as a reference.

Supplementary Table 9: Association between *GLP1R/ARRB1* SNPs and metabolic traits using summary GWAS from published studies (https://t2d.hugeamp.org/).

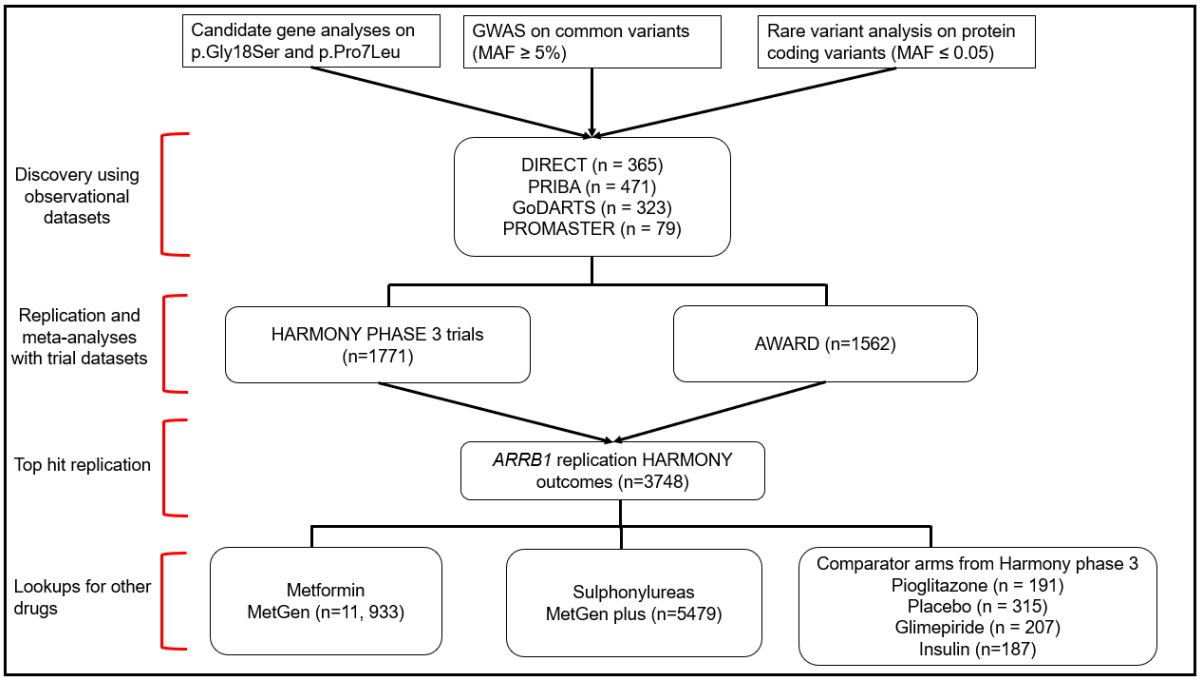
Gene	SNP	EA/NEA	Trait	Beta/OR	p	n
GLP1R	rs6923761	A/G	Type 2 diabetes	1.005*	0.27	581,605
			Fasting glucose adj BMI	-0.010	3.3×10^{-7}	165,284
			HbA1c	0.001	0.47	87,940
			HOMA-ß	0.009	0.01	58,767
			BMI	0.001	0.57	718,734
			HDL	0.003	0.02	1,769,370
			Non-HDL cholesterol	0.002	0.10	1,257,960
			TG	-0.0003	0.73	1,733,460
			SBP	-0.002	0.32	1,625,510
			DBP	-0.001	0.60	1,643,300
ARRB1	rs140226575	A/G	Type 2 diabetes	0.959*	0.29	257,033
			Fasting glucose adj BMI	-0.003	0.63	55,854
			HbA1c (mmol/l)	0.005	0.54	11,821
			HOMA- ß	0.225	0.06	9,349
			BMI	0.081	0.003	718,734
			HDL cholesterol	-0.003	0.53	957,313
			Non-HDL cholesterol	0.471	0.02	566,342
			TG	0.006	0.60	981,971
			SBP	0.007	0.84	662,111
			DBP	-0.009	0.82	662,108

*Odds ratio, HbA1c: glycated haemoglobin, HOMA-ß: homeostasis model assessment of β-cell function, BMI: body mass index, HDL: high-density lipoprotein, TG: triglycerides, SBP: systolic blood pressure, DBP: diastolic blood pressure.

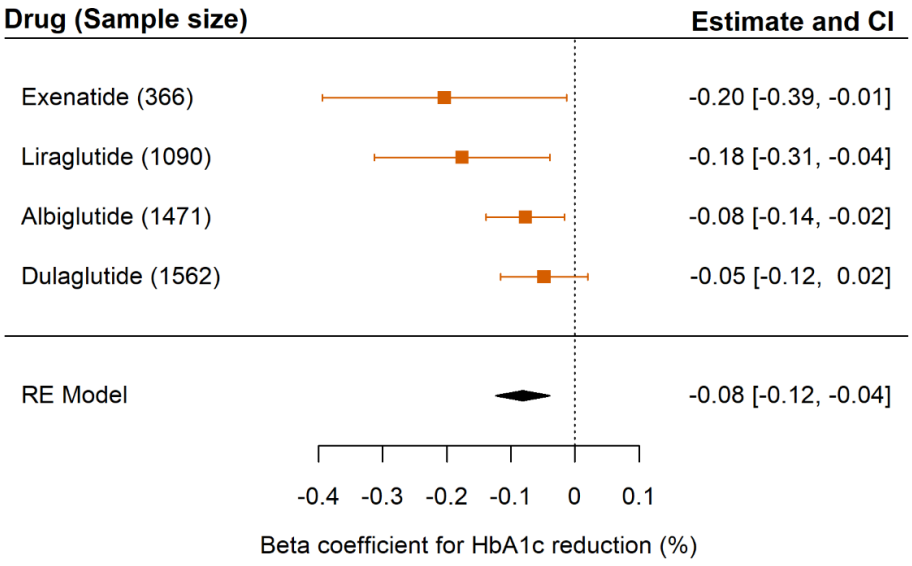
Supplementary Table 10: Comparison between included and excluded due to missingness in the HARMONY phase 3 trials

Variable	**Non missing (n=1771)**	**Missing (n=98)**	
	Mean ± sd	Mean ± sd	p
Age (years)	55.80 ± 10.08	54.43 ± 10.11	0.19
Sex (% women)	46.9%	47.0%	1
Baseline BMI (kg/m^2)	33.14 ± 5.62	32.91 ± 6.10	0.72
Duration of diabetes (years)	8.00 ± 6.12	7.71 ± 5.57	0.62
Baseline HbA1c (%)	8.16 ± 0.87	8.25 ± 0.93	0.33
Baseline Weight (kg)	93.79 ± 20.52	94.59 ± 19.67	0.70
Weight at six months (kg)	92.96 ± 20.46	90.58 ± 20.77	0.64
BMI at six months (kg/m^2)	32.84 ± 5.56	33.20 ± 6.39	0.82
BMI reduction at six months (kg/m^2)	0.31 ± 1.21	0.51 ± 1.40	0.56
Ethnicity (% White Europeans)	56.4%	53.4%	0.32

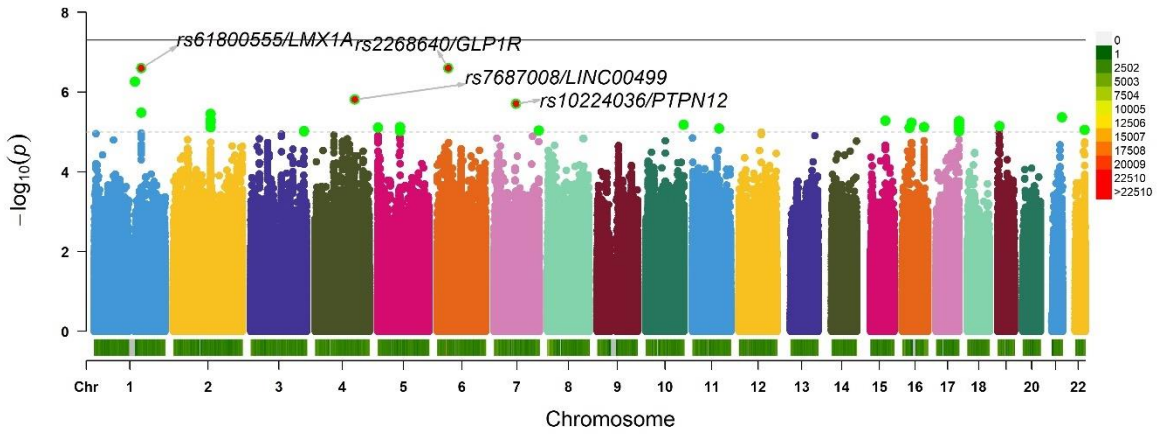
Supplementary Figures



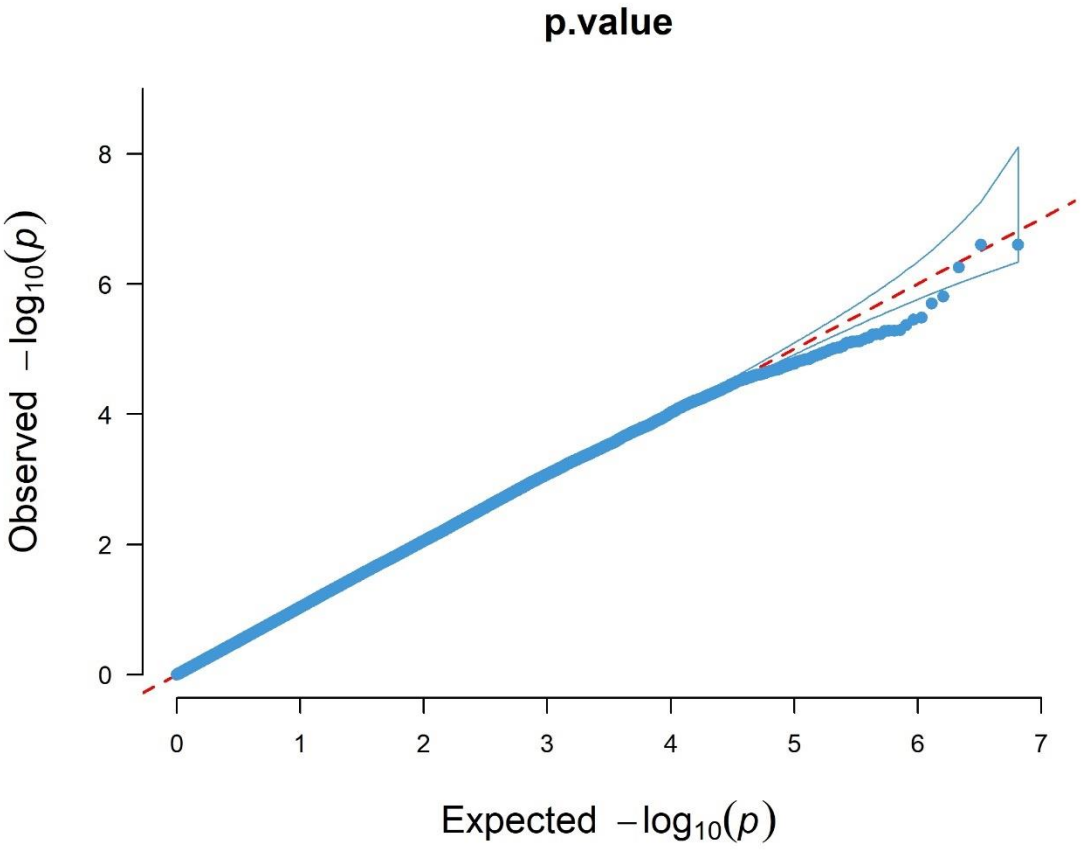
Supplementary Figure 1: The study design flowchart.



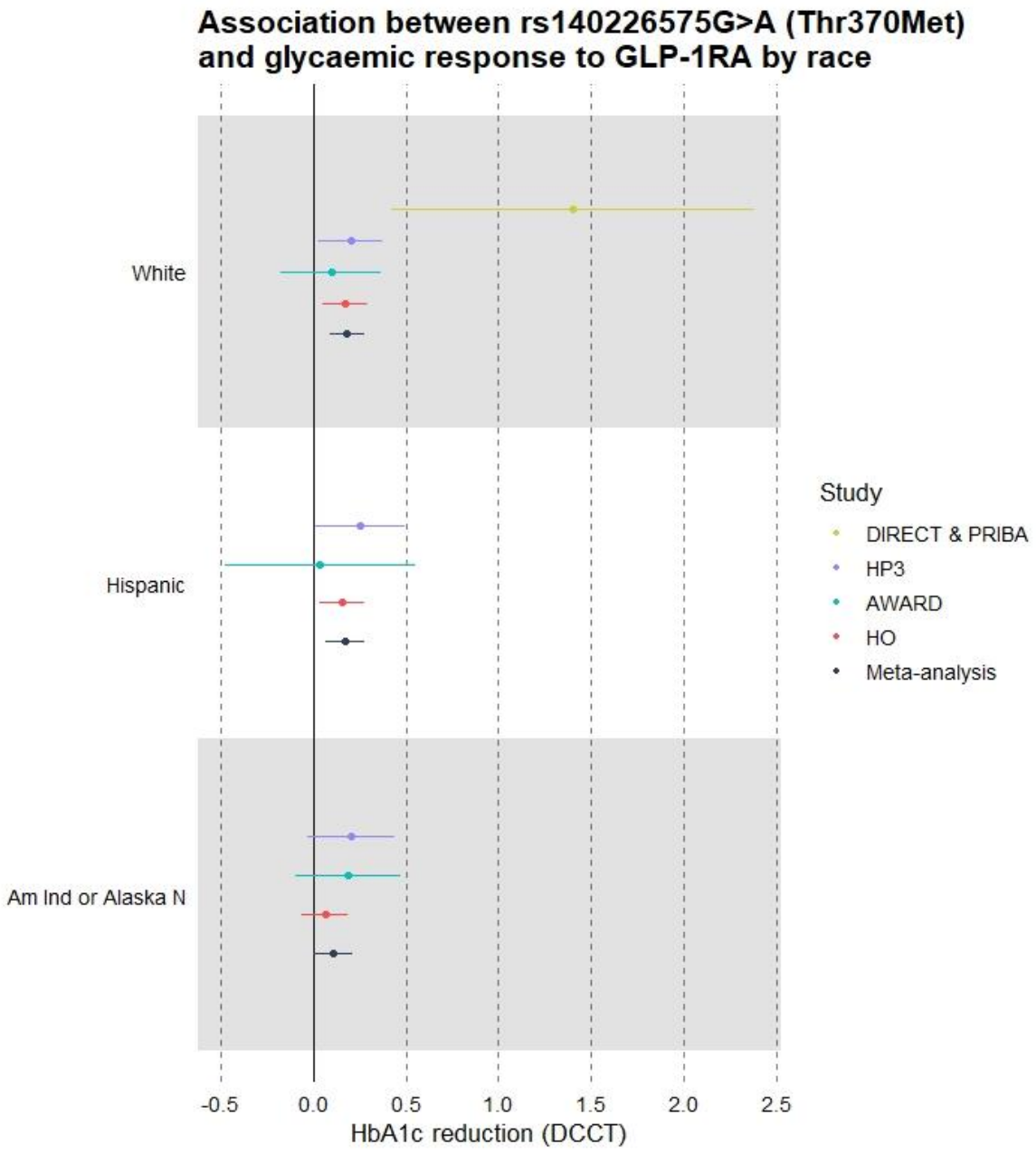
Supplementary Figure 2: Association between Gly168Ser and HbA1c reduction stratified by GLP-1RA type.



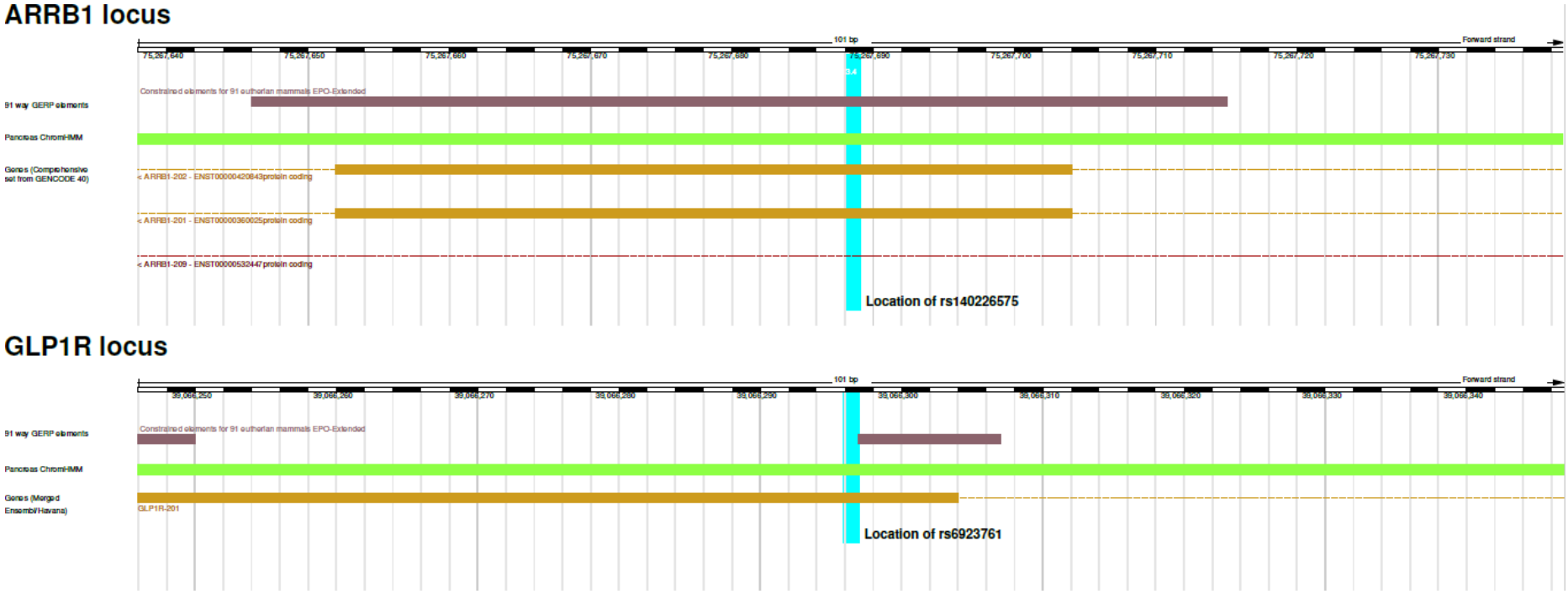
Supplementary Figure 3: Manhattan plot of single variant association results from a linear regression in the overall meta-analysis (n = 4,563). The–log10 p-values for each test are plotted against chromosomal position. A genome-wide significance threshold of 5×10^{-8} is indicated by the red horizontal bar.



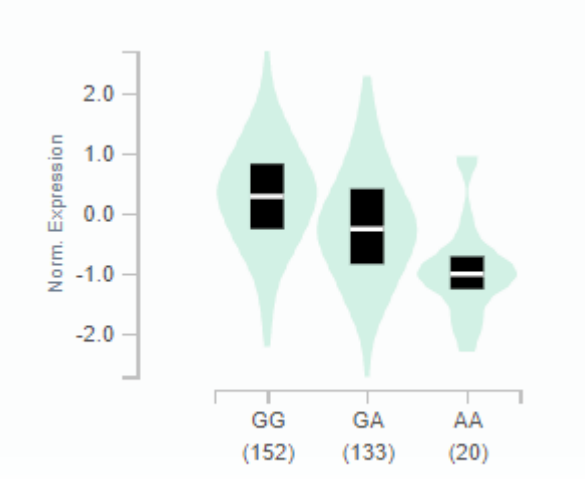
Supplementary Figure 4: The relationship between observed and expected p values (Q-Q plot) (λ = 1.04) and the 95% confidence interval.



Supplementary Figure 5: Association between *ARRB1*-rs140226575G>A (Thr370Met) and HbA1c reduction after treatment with GLP-1RAs stratified by ethnicity. Effect estimates represent HbA1c reduction (DCCT) per minor allele. Adjustment was made for baseline HbA1c, age, sex, and first 3 principal components. DIRECT: The DIRECT (DIabetes REsearCh on patient stratification) study; PRIBA: The PRIBA (Predicting Response to Incretin Based Agents in Type 2 Diabetes) study; HP3: Harmony Phase 3 trials; AWARD: AWARD (Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes) trials; HO: Harmony Outcomes; Am Ind or Alaska N: American Indian or Alaska Native; DCCT: Diabetes Control and Complications Trial unit (https://clinicaltrials.gov/ct2/show/NCT00360815).



Supplementary Figure 6: Genomic areas around GLP1R-rs6923761 and ARRB1-rs140226575 showing histone marks, conservation and eQTL[18,19].



Supplementary Figure 7: eQTL of GLP-1R variant, rs6923761 on GLP1R expression in the pancreas (Violin plot generated from the GTEx portal).

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