CARDIOVASCULAR GENOMICS

A genomic approach to therapeutic target validation identifies a glucose-lowering *GLP1R* variant protective for coronary heart disease

All authors with their affiliations appear at the end of this paper.

Regulatory authorities have indicated that new drugs to treat type 2 diabetes (T2D) should not be associated with an unacceptable increase in cardiovascular risk. Human genetics may be able to guide development of antidiabetic therapies by predicting cardiovascular and other health endpoints. We therefore investigated the association of variants in six genes that encode drug targets for obesity or T2D with a range of metabolic traits in up to 11,806 individuals by targeted exome sequencing and follow-up in 39,979 individuals by targeted genotyping, with additional in silico follow-up in consortia. We used these data to first compare associations of variants in genes encoding drug targets with the effects of pharmacological manipulation of those targets in clinical trials. We then tested the association of those variants with disease outcomes, including coronary heart disease, to predict cardiovascular safety of these agents. A low-frequency missense variant (Ala316Thr; rs10305492) in the gene encoding glucagon-like peptide-1 receptor (*GLP1R*), the target of GLP1R agonists, was associated with lower fasting glucose and T2D risk, consistent with GLP1R agonist therapies. The minor allele was also associated with protection against heart disease, thus providing evidence that GLP1R agonists are not likely to be associated with an unacceptable increase in cardiovascular risk. Our results provide an encouraging signal that these agents may be associated with benefit, a question currently being addressed in randomized controlled trials. Genetic variants associated with metabolic traits and multiple disease outcomes can be used to validate therapeutic targets at an early stage in the drug development process.

INTRODUCTION

In 2008, the U.S. Food and Drug Administration issued guidance for industry on new therapies to treat type 2 diabetes (T2D), recommending that sponsors should demonstrate that these treatments are "not associated with an unacceptable increase in cardiovascular risk" (*1*). This mandate challenges drug developers to prove safety during clinical trials, which is an expensive and late-phase strategy for the identification of such concerns. Instead, genetic approaches may aid in the identification of possible drug side effects much earlier in the drug development process. Genetic variants can inform the treatment and prevention of human disease (*2*, *3*), by either reducing the prioritization of potential targets (*4*, *5*) or implicating new targets (*6*, *7*). Functional exonic variants can be useful surrogates for drug effects, when, for example, a loss-of-function (LoF) variant may be a useful tool to understand the consequences of pharmacological inhibition of a particular target protein (*7*). Recent sequencing efforts have identified a large number of potentially functional low-frequency and rare exonic variants in human populations, even among genes under purifying selection (*8*–*12*). Although such variants may influence susceptibility to disease, the high cost of these sequencing approaches has previously meant that they have not been performed in the sample sizes required to allow routine investigation of their association with complex disease and related traits.

A recent targeted exome sequencing study of 202 genes encoding potential drug targets identified an abundance of potentially functional exonic variants (*8*). Among these 202 genes, 6 genes encoding drug targets licensed or in development by GlaxoSmithKline (GSK) for treatment of obesity and/or T2D were included. Recognizing that these data could be used to test for genetic variants mimicking pharmacological manipulation of the encoded protein (drug target), we investigated six genes encoding targets of relevance to obesity and T2D. These variants could then serve as tools to aid a broader evaluation of drug-related risk for adverse events mediated via on-target effects.

As a proof of concept for use of genetic variants to evaluate the cardiovascular safety of antidiabetic agents, we evaluated the widely used glucose-lowering glucagon-like peptide-1 receptor (GLP1R) agonists (*13*). These agents are long-acting mimetics of the incretin hormone GLP-1, which increases insulin secretion after oral consumption of glucose but not after glucose administered intravenously. There are uncertainties over the role of these agents in the etiology of rare adverse pancreatic events that have been reported after their usage (*14*). These therapies have been associated with weight loss (*15*) and reduced cardiovascular risk factors, and while a recent trial reported noninferiority of GLP1R agonists in cardiovascular safety (*16*), multiple large trials evaluating cardiovascular safety have not yet been completed (*17*). We used a genetic variant in *GLP1R* that is associated with variation in fasting glucose levels and with T2D risk (*18*) to evaluate the cardiovascular safety of GLP1R agonists. The low-frequency variant protective for T2D was also protective for coronary heart disease (CHD). These findings support the notion that GLP1R agonists will not confer an increased cardiovascular risk in people. This study also demonstrates how genetic target validation approaches can be used early in the drug development process to evaluate efficacy and safety.

RESULTS

Association of genetic variants in genes encoding T2D and obesity drug targets

The study design consisted of initial discovery of variants with suggestive associations to targeted genotyping and in silico follow-up analyses (Fig. 1). We investigated the association of 121 variants

in six genes encoding therapeutic targets in use or in development for T2D or obesity (*CNR2*, *DPP4*, *GLP1R*, *SLC5A1*, *HTR2C*, and *MCHR1*)—drawn from a recent targeted exome sequencing study of 202 genes encoding drug targets (*8*)—with variation in the following traits: T2D, obesity, body mass index (BMI), waist circumference, fasting glucose, fasting insulin, and 2-hour glucose (Fig. 1). In the "discovery analysis," we identified seven variants potentially associated with T2D- or obesity-related traits (where $P < 0.001$ or which were in a target of interest to GSK and $P < 0.05$) (Table 1). For these seven variants, "follow-up analysis" was performed by targeted genotyping in up to 39,979 additional individuals of European ancestry. Where possible, in silico follow-up analysis was performed for traits and variants available in large-scale genetic consortia data.

Initial discovery analyses included 1331 tests of association, with the threshold specified to reach significance in combined analyses being $P < 3.8 \times 10^{-5}$. In a combined analysis of results from the different phases, we identified a low-frequency [~1% minor allele frequency (MAF)] missense variant Ala316Thr; rs10305492 in the *GLP1R* gene to be associated with fasting glucose (Fig. 2A). The variant was in Hardy-Weinberg equilibrium in all genotyped samples ($P > 0.2$). The effect size (that is, the difference per allele) of 0.09 mM was larger than most common variants previously reported for fasting glucose (Fig. 2B) and was recently found to be associated with fasting glucose in nonoverlapping samples from large-scale analyses of coding variant associations with glycemic traits (*18*). The combined analyses for the six other variants in Table 1 did not show evidence of association ($P > 3.8 \times 10^{-5}$, by linear or logistic regression) with the suggestively associated trait in the discovery analysis ("follow-up" P values >0.05; "combined" P values ≥0.005; Table 1).

The *GLP1R* gene encodes the GLP-1 receptor, the target for GLP-1, a hormone that mediates the augmented response to insulin secretion after oral glucose administration. This receptor is the target for the GLP1R agonist class of T2D therapeutics, and the association of this variant with fasting glucose mimicked a major effect of this class of agents. To further corroborate the utility of this variant as a surrogate indicator of pharmacological modulation of the receptor, we investigated its association with T2D and found that the minor allele was associated with lower risk of T2D [odds ratio (OR), 0.83; CI, 0.76 to 0.91; $P = 9.4 \times 10^{-5}$; in a fixed-effect meta-analysis of log-ORs from studies and consortia listed in table S1 and in the Supplementary Materials "Studies contributing to follow-up analyses of T2D and obesity-related traits"; n_{cases} = 25,868, $n_{controls}$ = 122,393]. However, we saw no association of this *GLP1R* variant (Ala316Thr; rs10305492) with fasting insulin nor with 2-hour glucose (Fig. 2A).

Although there were no individuals carrying putative LoF variants in *GLP1R* in the targeted sequencing study, a single individual in the cohort arm of the UK10K study had an LoF allele ($W^{297}*$) but did not have an extreme glycemic phenotype. This individual's fasting glucose and insulin concentrations were within the range of 95% of the values for this population. Nine high-confidence LoF variants in *GLP1R* were observed in the Exome Aggregation Consortium (ExAC) database (*19*). Eight were singletons, and the most common had a frequency of less than 1/10,000, highlighting the difficulty in restricting analyses to individual LoF variants.

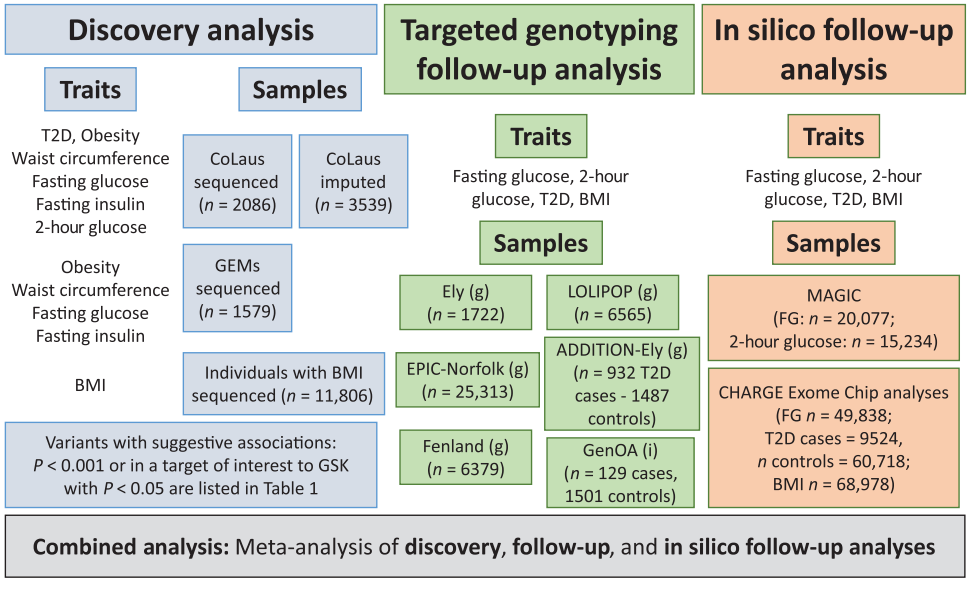

Fig. 1. Overall study design, participating studies, and consortia. Discovery analyses were performed using targeted exome sequencing of variation in six genes tested for association with seven traits. Variants were taken forward to follow-up by targeted genotyping. Additional in silico results were obtained using available association results. Combined results were obtained by fixed-effect meta-analysis of estimates from linear or logistic regression, as appropriate. On the basis of the 1331 statistical tests performed in the discovery analyses, $P < 3.8 \times 10^{-5}$ was used as the threshold for statistical significance. In targeted genotyping, (g) refers to studies that were directly genotyped for relevant markers, whereas (i) indicates those in which relevant variants were captured by imputation.

Association of the *GLP1R* variant with quantitative traits and comparison with effects observed in clinical trials of GLP1R agonists

To further characterize the extent to which the *GLP1R* variant associations mirrored the effects of GLP1R agonist therapy, we compared genetic associations to the metabolic effects observed in previously reported clinical trials (Fig. 3 and table S2). GLP1R agonist therapy can result in lower fasting and post-challenge glucose, weight loss, a reduction in systolic blood pressure, reduced total and low-density lipoprotein (LDL) cholesterol, and an increase in resting heart rate. The effects of GLP1R agonists on glycemic measures (fasting glucose and 2-hour glucose) were stronger than those on nonglycemic factors (Fig. 3), which have been detectable only in some meta-analyses of clinical trials (*20*–*23*).

Using fasting glucose as the benchmark, the per-allele association of the genetic variant with glucose [−0.15 SDs (0.20 to −0.11); from Fig. 2] was 3.3-fold weaker than the effect observed for GLP1R agonist treatment [−0.49 (−0.60 to −0.37); from Fig. 3]. We therefore rescaled the genetic

Table 1. Discovery, follow-up, and combined results for variants taken forward to follow-up. Seven variants in six genes reached $P < 0.001$ (or $P < 0.05$ in target of interest to GSK) in sequence-based discovery analyses (Fig. 1) and were taken forward to follow-up in additional samples, by targeted genotyping and by in silico lookup from existing consortia. Data and *P* values are from fixed-effect meta-analysis of linear regression for quantitative traits or logistic regression for binary disease status. 5′UTR, 5′ untranslated region.

Gene	Variant	Chr	Position (NCBI b37 genome alignment)	Consequence	Trait	Effect allele	Other allele	MAF	Stage	Study	*n* (case/control for binary trait)	β (odds ratio for binary trait)	SE (CI for OR)	*P*
GLP1R	rs10305492	6	39046794	A316T	Fasting glucose	A	G	0.015	Discovery	Sequenced CoLaus*	1,869	−0.28	0.14	0.04
									Targeted follow-up	Additional CoLaus, Ely, Fenland, LOLIPOP, GEMS	18,937	−0.13	0.04	1.5×10^{-3}
									In silico follow-up	MAGIC (*29*)	20,077	−0.16	0.03	1.1×10^{-7}
									Combined		40,883	−0.15	0.02	2.6×10^{-10}
DPP4	rs56179129	2	162890142	V266I	Fasting glucose	T	C	0.008	Discovery	GEMS	1,416	0.61	0.21	3.6×10^{-3}
									Targeted follow-up	CoLaus, Ely, LOLIPOP	12,934	0.00	0.07	0.95
									In silico follow-up	CHARGE Exome Chip (*18*)	49,838	0.00	0.03	0.16
									Combined		64,188	0.01	0.03	0.71
SLC5A1	rs200410750	22	32439209	5′UTR	Fasting glucose	T	C	0.001	Discovery	Sequenced and imputed CoLaus	5,210	1.44	0.33	1.7×10^{-5}
									Targeted follow-up	Ely, Fenland, LOLIPOP†	12,707	−0.16	0.27	0.56
									In silico follow-up	NA				NA
									Combined		18,059	0.51	0.19	0.01
CNR2	rs4649124	1	24201357	Synonymous	2-Hour glucose	A	G	0.420	Discovery	Sequenced and imputed CoLaus	505	0.18	0.06	0.01
									Targeted follow-up	Ely, Fenland	6,377	0.00	0.02	0.95
									In silico follow-up	MAGIC (proxy: rs10917431) (*49*)	15,234	−0.01	0.01	0.49
									Combined		22,106	0.00	0.01	0.88
CNR2	rs2229579	1	24201162	H316Y	T2D	T	C	0.110	Discovery	Sequenced and imputed CoLaus	385/5,241	0.73	(0.55–0.97)	0.03
									Targeted follow-up	ADDITION-Ely, NDS, LOLIPOP, GenOA	7,141/27,096	1.06	(0.99–1.14)	0.07

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Gene	Variant	Chr	Position (NCBI b37 genome alignment)	Consequence	Trait	Effect allele	Other allele	MAF	Stage	Study	*n* (case/control for binary trait)	β (odds ratio for binary trait)	SE (CI for OR)	*P*
									In silico follow-up	CHARGE Exome Chip (*18*)	9,524/60,718	0.96	(0.90–1.01)	0.10
									Combined		17,047/93,225	0.99	(0.95–1.04)	0.67
HTR2C	rs56372597	X	113951968	Intronic	BMI	A	G	0.150	Discovery	BMI	10,798	0.05	0.02	2.1×10^{-3}
									Targeted follow-up	Additional CoLaus, Ely, EPIC, Fenland, LOLIPOP	36,983	0.00	0.01	0.92
									In silico follow-up	NA				NA
									Combined		47,781	0.01	0.01	0.13
MCHR1	rs117372135	22	41075523	T25M	BMI	T	C	0.002	Discovery	BMI	10,952	0.62	0.15	4.5×10^{-5}
									Targeted follow-up	Additional CoLaus, Ely, EPIC, Fenland, LOLIPOP	37,240	0.08	0.10	0.40
									In silico follow-up	CHARGE adiposity Exome chip working group	68,978	−0.04	0.07	0.59
									Combined		117,170	0.08	0.05	0.13

*Analyzed in sequenced CoLaus participants only owing to low imputation quality ($R^2 < 0.5$) in additional CoLaus participants at the discovery stage. †Not analyzed in GEMS because of low number of carriers (<5 minor alleles).

associations to account for this difference, by multiplying the magnitude of all observed genetic associations by 3.3 (Fig. 3), and demonstrated that there was little difference between the magnitude of association of the *GLP1R* variant and the effects observed in clinical trials beyond that expected by chance ($\alpha = 0.0025$). An exception to this observation was the impact of GLP1R agonist therapy on weight in nondiabetic individuals when compared to the observed association between the variant and BMI ($P = 2.6 \times 10^{-4}$, Cochrane's *Q* test) (table S2). The genetic variant was not associated with BMI (Fig. 3), whereas the agonist therapy caused a reduction in body mass in nondiabetic individuals but not in individuals with T2D (fig. S1 and table S2). However, five of the six trials in nondiabetic individuals were performed in obese participants (table S3), whose higher starting weight may have enabled a greater weight loss.

GLP1R agonists appeared to have a greater effect on 2-hour glucose than the magnitude of association observed for the variant ($P = 2.1 \times 10^{-12}$, Cochrane's *Q* test) (Fig. 3, fig. S2, and table S2). The difference was most pronounced in comparison to trials in individuals with T2D, among whom we observed heterogeneity in the effect of GLP1R agonists on 2-hour glucose, even within drug class ($I^2 = 97\%$) (fig. S2B). There was no significant difference between the magnitude of genetic association and the impact of GLP1R agonist therapy on 2-hour glucose in nondiabetic individuals (Fig. 3 and table S2), although the number of people included in such trials was much smaller than in trials including individuals with T2D (table S3).

Association of the *GLP1R* variant with disease outcomes

Our final aim was to describe the association of the *GLP1R* variant with CHD and other outcomes. In a large-scale international collaboration, we studied 61,846 individuals with CHD and 163,728 controls and found that the fasting glucose–lowering allele of *GLP1R* was associated with protection against CHD (Fig. 4). The association with CHD is greater than the 1% reduction in risk that would be predicted on the basis of the association of this variant with fasting glucose alone (*24*) (see "Calculating the reduction in coronary heart disease risk attributable to lower fasting glucose levels" in the Supplementary Materials), suggesting that lowering of fasting glucose alone is unlikely to explain the observed association between the *GLP1R* variant and lower risk of CHD. Although not significant, carriage of the minor allele was associated with lower LDL cholesterol, triglycerides, systolic blood pressure, and higher HDL (high-density lipoprotein) cholesterol.

Using data from international consortia, we found no evidence for association of the *GLP1R* variant with pancreatic cancer, although the CIs were wide owing to the comparatively small sample size (4987 cases

and 8627 controls) and low frequency of the allele (Fig. 4). There was no evidence of association with breast, ovarian, or prostate cancer risk. Given the interest in GLP1R agonist therapy for neurological diseases, including Parkinson's (*25*) and Alzheimer's (*26*), we also investigated the association of the *GLP1R* variant with those diseases but found no evidence of association (Fig. 4).

DISCUSSION

Anticipating the side effects of drugs before phase 3 clinical trials could support drug discovery and development, reducing attrition rates and saving considerable time and money. The promise of human genetics in this endeavor (*2*, *3*, *7*, *27*) depends on the availability of genetic variants that mimic pharmaceutical interventions. We undertook a systematic study to identify such genetic variants in the context of diabetes and obesity and identified an association between fasting glucose and T2D with a missense variant in *GLP1R*, the gene encoding the GLP-1 receptor—the target of the GLP1R agonist class of T2D therapies. Regulatory authorities require evidence that therapies for T2D are not associated with unacceptable increases in cardiovascular risk. The reduced risk associated with the glucose-lowering genetic variant in *GLP1R* provides evidence that not only will GLP1R agonists meet this regulatory hurdle but they may also reduce CHD events. Ongoing trials of GLP1R agonists are designed to resolve this uncertainty and will also augment the evidence on the broader validity of genetic approaches in drug target validation.

A key consideration in assessing whether genetic variants can be used to understand therapeutic effects is how well the genetic variant mirrors the effects of pharmacological intervention at the same target. Genetic association data, here and reported previously (*18*), suggest that lifelong carriage of the minor *GLP1R* allele (at rs10305492) is associated with lower fasting glucose and lower risk of T2D, although not with 2-hour glucose. Clinical trial data from individuals with T2D, who may have a diminished incretin effect, show that GLP1R agonists lower 2-hour glucose considerably (*28*), whereas the effect on 2-hour glucose is smaller in individuals without T2D (*29*), presumably because nondiabetic individuals are less likely to have an impaired incretin effect requiring therapeutic correction. Similarly, GLP1R agonists were associated with greater weight loss in obese than in nonobese individuals. Such a phenomenon has previously been suggested for the effects of GLP1R agonism on blood pressure, where GLP1R agonist therapy appears to lower blood pressure in individuals with high blood pressure but not in nonhypertensive individuals (*30*, *31*). This highlights a limitation in the use of genetic variants in target validation: that the association of genetic variants is often tested in individuals of "normal" physiology, whereas clinical trials are generally performed in individuals with prevalent disease.

An important step in evaluating the utility of genomics in target validation is to understand the functional consequences of variants. For potential novel targets, whether the variant confers gain or loss of function informs the development of either an agonist or an antagonist therapy. For example, LoF variants have been used to understand the consequences of antagonism of a novel drug target (*7*, *32*). However, researchers have gained insights using variants validated as instruments when their phenotypic associations mirrored pharmacological action, even in the absence of strong functional insights into the mechanism of those variants (*33*). GLP1R agonist therapy reduces

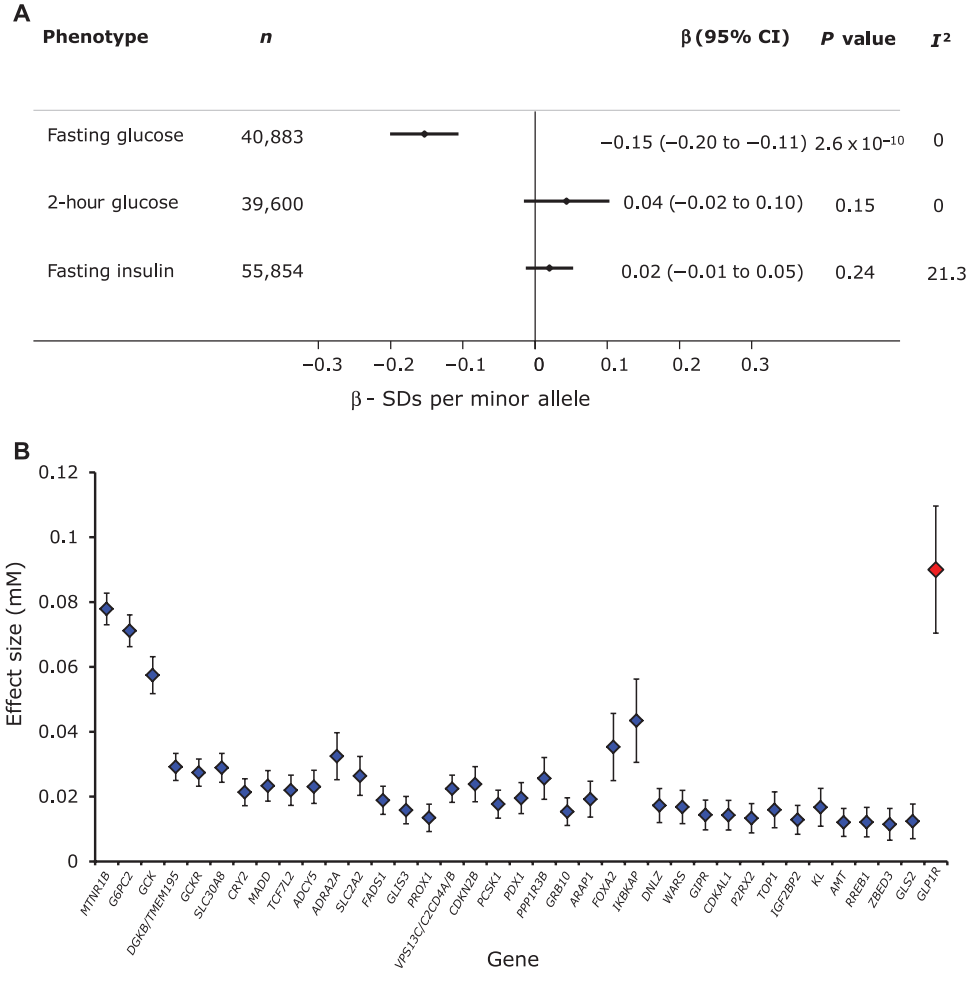

Fig. 2. Association of the *GLP1R* variant (rs10305492) with glycemic traits. (**A**) Genetic variant association with glycemic traits. Data are SDs per minor allele at rs10305492. Fasting glucose results are from the combined analysis (Table 1). Individual studies contributing to the associations for fasting insulin and 2-hour glucose are in table S4. All results reflect point estimates and 95% confidence intervals (CIs) from a fixed-effect meta-analysis of linear regression estimates. (**B**) Effect size of the *GLP1R* variant (in red) and loci previously reported to be associated with fasting glucose. Effect sizes are reported from discovery analyses of available MAGIC results (*50*) and from the combined estimate for the *GLP1R* variant in (A).

fasting glucose in humans, as does administration of GLP1, regardless of the duration or severity of T2D (*34*). In mice, the loss of GLP1R leads to fasting hyperglycaemia (*35*, *36*). Together, these findings in humans and in mice suggest that the glucose-lowering minor allele at rs10305492 confers gain of function. However, differences in basal activity of the human and murine GLP1R (*37*) limit our ability to extrapolate findings from *GLP1R* knockout mice to humans (*15*, *32*). Previous attempts to characterize the effect of this variant in cellular models have been inconclusive (*38*, *39*). The rarity of putative LoF alleles in the *GLP1R* impaired our ability to restrict analyses to such variants. Although the absence of definitive functional characterization is a limitation of this study, our observation that the minor allele is strongly associated with lower fasting glucose levels and is protective against T2D supports the validity of the variant as a genetic instrument for GLP1R agonist therapy. Future integration of large-scale human genetic data with functional characterization in appropriate cell models will allow a broader application of variants, other than those characterized as LoF, in target validation.

Although the *GLP1R* variant was not associated with any of the other nonglycemic or quantitative cardiovascular parameters, there was insufficient evidence to suggest that the genetic associations and pharmacological effects were different. Power calculations indicated that to detect the expected association with systolic blood pressure or resting heart rate, a sample size of more than 250,000 individuals would be required. This is considerably larger than most current genetic consortia, although this limitation could soon be overcome as larger studies become available (*40*), further strengthening the promise of genomics in target validation. Although we did not observe overall evidence for association of variants other than the *GLP1R* variant, the discovery phase, from which we selected variants for follow-up, was relatively small in comparison to the overall sample, and there remains a possibility of type II error in the discovery phase. As larger resources of genetic data become available, these limitations will also be reduced.

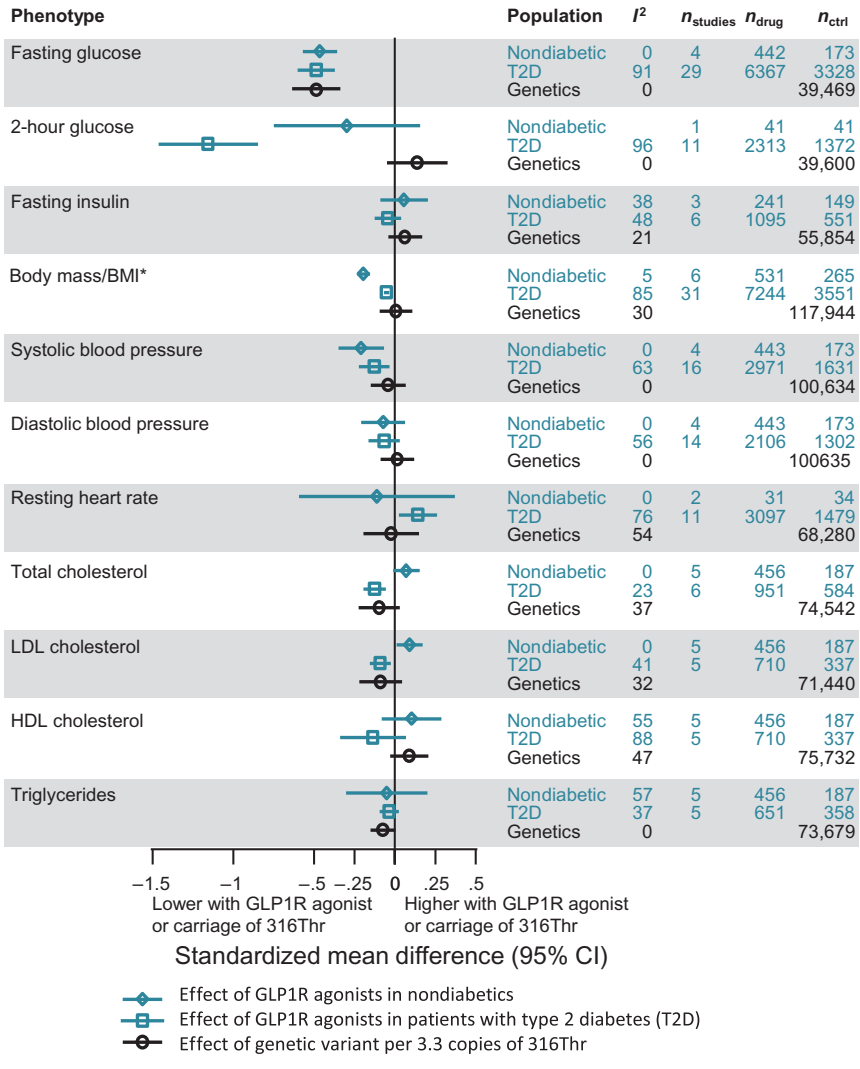

Fig. 3. Comparison of the *GLP1R* variant (rs10305492) associations with effects observed in clinical trials of GLP1R agonists in nondiabetic individuals and in individuals with T2D. Genetic associations are all scaled to match the effects of GLP1R-agonists on fasting glucose [that is, per 3.3 copies of the minor (A) allele]. Genetic variant results are β estimates and 95% CIs from fixed-effect meta-analysis of linear regression results. Trial results are estimates from fixed-effect meta-analyses of standardized mean differences between treatment and comparison groups of the individual trials listed in table S3. *Trials reported effects on body mass, whereas genetic associations were only available for BMI.

The detection of rare adverse effects of a drug remains a challenge. Pharmacoepidemiological approaches using routine database analysis may identify rare adverse outcomes associated with treatment, but the approach is rarely conclusive because of confounding, particularly by indication. Our demonstration that the *GLP1R* variant is not associated with pancreatic, breast, prostate, or ovarian cancer or with Parkinson's or Alzheimer's disease is limited by the upper bounds of CIs, which are too high to allow strong inference about the likely long-term safety of GLP1R agonists with regard to these outcomes. Although these data represent the largest resources available globally, the accumulation of studies with greater numbers of individuals with genetic data and robust disease outcome classification will considerably enhance the potential of this type of investigation. Comparisons of other traits and disease outcomes, beyond the primary indications, make the assumption that pharmacological effects are mediated via "on-target" effects and not "off-target" effects (that is, those mediated by effects of the agent on other nonspecific targets). Thus, while our results offer insight into the effects of GLP1R agonists, they do not necessarily apply to other agents targeting the incretin pathway through different mechanisms, such as by DPP-4 inhibition (*41*).

In conclusion, through a targeted exome sequencing approach, we identified that a low-frequency missense variant in *GLP1R* was associated with lower fasting glucose and risk of T2D, similar to the effects of GLP1R agonist therapy. This variant was also associated with lower risk of CHD, thus providing supportive evidence that these agents are not likely to be

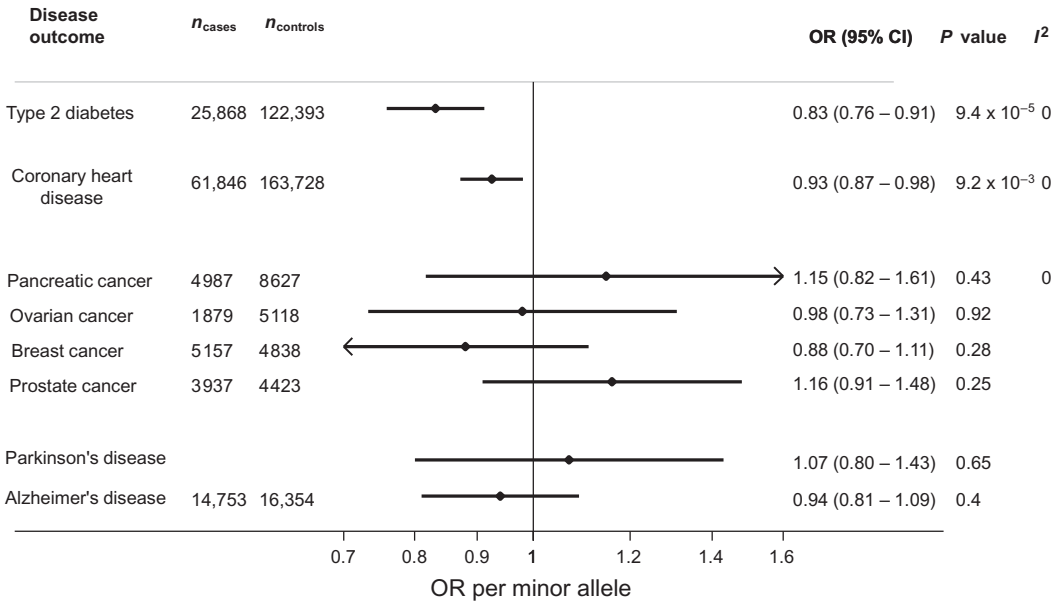

Fig. 4. Association of the *GLP1R* variant (rs10305492) with disease outcomes. Association with disease outcomes are reported per minor allele at rs10305492. Data show ORs and 95% CIs from logistic regression models.

associated with an unacceptable increase in cardiovascular risk and may indeed be associated with benefit, a question currently being addressed in randomized controlled trials. We propose that future drug development and investment decisions could be informed by genomic data much earlier in the development process, providing insight into both efficacy and side effects.

METHODS

Study design

We studied six genes encoding therapeutic targets licensed or in development for obesity or T2D (*CNR2*, *DPP4*, *GLP1R*, *SLC5A1*, *HTR2C*, and *MCHR1*), drawn from a recent targeted exome sequencing study of 202 genes encoding drug targets (*8*), which represented about 1% of the coding genome and 7% of all genes considered current or potential drug targets (*8*). In the "discovery analysis," we investigated the association of common and rare variants in these six genes with seven T2D- and obesity-related traits (Fig. 1). We analyzed all variants that had an (i) MAF ≥0.5% or well imputed ($R^2 > 0.5$) in CoLaus; (ii) MAF ≥0.5% in GEMS; or (iii) MAF ≥0.1% in BMI (given the larger sample size) in the CoLaus study (*42*), the GEMS study (*43*), or all individuals with BMI measurements. We examined 121 variants for association with six traits in the CoLaus study (6 × 121 = 726 tests), four traits in GEMS (4 × 121 = 484 tests), and one trait in the BMI study, comprising a total of 1331 tests of association. First, we analyzed a subset of the population-based CoLaus study (n = 2086) for T2D, obesity, waist circumference, fasting glucose, fasting insulin, and 2-hour glucose traits. Second, in the GEMS dyslipidemic case and normolipidaemic control study (n_{cases} = 787, $n_{controls}$ = 792), we analyzed obesity, waist circumference, fasting glucose, and fasting insulin traits. We performed discovery analyses in the CoLaus and GEMS studies separately because of the different study designs and traits analyzed in an attempt to maximize sensitivity to detect associations that might be masked by context-dependent associations. Third, BMI measures were available in a larger sample size from 11 studies (Fig. 1) and were analyzed together. We provide the sample sizes for the discovery analyses in Fig. 1 and trait-specific sample sizes in Table 1 (n = 505 to 11,806). We augmented the sequence data for the CoLaus study with imputed data in the remainder of the study (n = 3539), where variants were imputable ($R^2 > 0.5$), using a custom imputation process on individuals genotyped on the Affymetrix 500K chip but not included in the targeted sequencing experiment (Supplementary Materials).

Using results from the discovery analyses, we identified variants that were associated with T2D- or obesity-related traits at the $P < 0.001$ level or were located in genes encoding targets of strategic interest to GSK, including *GLP1R*, *DPP4*, *CNR2*, and *HTR2C* with a P value threshold of <0.05. To maximize sensitivity to detect associations in these genes of highest interest, we took forward to follow up those variants reaching $P < 0.05$ in the discovery analyses. However, this did not affect the threshold for statistical significance or overall α value (3.8×10^{-5}), for which we accounted for all association tests performed in the discovery analyses (n = 1331). The principal reason for prioritizing specific genes was to ensure a balance between sensitivity for targets of high priority to GSK and to maintain specificity: given that initial replication was performed by de novo large-scale targeted genotyping, we were practically unable to follow up vast numbers of variants. This does not bias the variants selected for follow-up nor raise the risk of type I error. The only variant we determined to be mimicking pharmacological manipulation was well beyond "genome-wide significance" even if all possible low-frequency and common variants in the genome had been tested.

We then genotyped seven variants in six genes in up to 39,979 follow-up participants of European ancestry drawn from multiple studies (Fig. 1): CoLaus (when GEMS was the discovery sample), GEMS (when CoLaus was the discovery set), Ely (*44*) (n = 1,722), EPIC-Norfolk (*45*) (n = 25,313), Fenland (*46*) (n = 6379), and LOLIPOP (*47*) (n = 6565) studies. The follow-up analysis of T2D included participants from the Norfolk Diabetes Study (n_{cases} = 5587 and $n_{controls}$ = 19,012), the GenOA study (n_{cases} = 129 and $n_{controls}$ = 1501), and individuals with T2D from the ADDITION study (*48*) (n_{cases} = 816) who were combined with additional cases from the Ely study (n_{cases} = 116) and compared to non-diabetic controls from the Ely study ($n_{controls}$ = 1,487).

We also performed additional in silico follow-up analysis to further evaluate associations in collaborative studies utilizing results from the MAGIC and CHARGE consortia. Five of the seven variants were available for in silico analysis (Table 1). Further details on each of the studies and consortia are provided in the Supplementary Materials and tables S1 and S4.

Statistical analyses

We carried out genetic association analyses on variants identified via targeted sequencing using an additive genetic model by linear or logistic regression, adjusting for age and sex and other study-specific covariates. We combined study-specific estimates using fixed-effect meta-analysis. We performed analyses on standardized variables (mean, 0; SD, 1) and, as such, expressed effect sizes as SDs for quantitative traits. In total, we analyzed 121 single nucleotide variants. Overall, we performed 1331 tests of association in the discovery analyses, and, as such, associations that were $P < 3.8 \times 10^{-5}$ in the combined analysis were deemed to be statistically significant.

We performed targeted genotyping of selected variants from discovery analyses using Sequenom for the Ely, EPIC-Norfolk, Fenland, and ADDITION studies and KASPar for the LOLIPOP study. Imputed data were also available in the GenOA study using reference haplotypes from participants in the previous sequencing study (*8*). We carried out genetic association analyses in each study under an additive genetic model using linear or logistic regression, again adjusting for age-, sex-, and study-specific covariates. We sought further in silico follow-up from summary association results from the MAGIC and CHARGE consortia (Table 1). We converted summary association result effect sizes to SDs using the SD of fasting glucose from the population-based Fenland study (SD, 0.65 mM) (*46*). We meta-analyzed results from the discovery analysis, follow-up analysis, and in silico follow-up analysis using a fixed-effect inverse-variance weighted approach. The discovery analysis of the CoLaus study included association results from the sequence variants and imputed variants (Table 1). In the entire CoLaus study, we later directly genotyped (KASPar technology) variants that had been imputed in the unsequenced CoLaus participants study as part of the original follow-up analysis. The combined analysis results in Table 1 therefore represent those from the directly genotyped data.

For variants that showed statistically significant associations in the combined analysis ($P < 3.8 \times 10^{-5}$), we investigated their association with a range of anthropometric, metabolic, and cardiovascular risk factors and disease outcomes in the studies described previously, as well as in additional studies described in tables S1 and S4 and in the Supplementary Materials. We also investigated the association of variants reaching statistical significance after follow-up ($\alpha < 3.8 \times 10^{-5}$) with CHD through targeted genotyping and collaboration with large-scale exome chip consortia (table S1). For these variants, we also investigated association with a range of other disease outcomes (table S1), with a particular focus on diseases previously suggested as potential opportunities for repositioning (that is, where existing drugs might be used for alternative indications). However, as the variant reaching statistical significance was not well covered on existing GWAS (genome-wide association study) arrays or in HapMap, we were limited to those disease outcomes for which we could obtain association data. For genes that contained variants with $P < 3.8 \times 10^{-5}$ in the combined analysis, we investigated the presence of putative LoF alleles in individuals in whom we had performed targeted sequencing (*8*) and in individuals with whole-genome sequencing from the UK10K study (www.uk10k.org).

Comparison of clinical trial effects and genetic associations. Randomized clinical trials of GLP1R agonists were identified through previous systematic reviews and by performing a supplementary literature search, as detailed in the Supplementary Materials. Only trials with placebo or no-drug comparison groups (that is, no trials with active comparison groups) with ≥4 weeks of drug treatment (that is, no single-dose studies) and ≥10 participants per trial arm were included. Treatment effects were expressed in SDs before pooling across trials using random-effects meta-analysis (see table S3 for details of clinical trials included). *P* values derived from Cochrane's *Q* test were used as a guide to assess whether there were pairwise differences between the rescaled genetic and trial estimates.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/8/341/341ra76/DC1
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Methods
Fig. S1. Effects of GLP1R agonists on body weight.
Fig. S2. Effects of GLP1R agonists on 2-hour glucose.
Table S1. Study characteristics for disease traits.
Table S2. Comparison of heterogeneity between trial and rescaled genetic estimates.
Table S3. Details of randomized trials contributing to analyses of GLP1R agonist effects included in Fig. 2.
Table S4. Study characteristics for quantitative traits.
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Authors and affiliations

Robert A. Scott,[1*†] Daniel F. Freitag,[2,3*] Li Li,[4*‡] Audrey Y. Chu,[5] Praveen Surendran,[2] Robin Young,[2] Niels Grarup,[6] Alena Stancáková,[7] Yuning Chen,[8] Tibor V. Varga,[9] Hanieh Yaghootkar,[10] Jian'an Luan,[1] Jing Hua Zhao,[1] Sara M. Willems,[1,11] Jennifer Wessel,[12,13] Shuai Wang,[8] Nisa Maruthur,[14,15,16] Kyriaki Michailidou,[17] Ailith Pirie,[17] Sven J. van der Lee,[18] Christopher Gillson,[1] Ali Amin Al Olama,[17] Philippe Amouyel,[19] Larraitz Arriola,[20,21,22] Dominique Arveiler,[23] Iciar Aviles-Olmos,[24] Beverley Balkau,[25,26] Aurelio Barricarte,[22,27] Inês Barroso,[3,28] Sara Benlloch Garcia,[17] Joshua C. Bis,[29] Stefan Blankenberg,[30] Michael Boehnke,[31] Heiner Boeing,[32] Eric Boerwinkle,[33,34] Ingrid B. Borecki,[35] Jette Bork-Jensen,[6] Sarah Bowden,[36] Carlos Caldas,[37] Muriel Caslake,[38] The CVD50 consortium, L. Adrienne Cupples,[8,39] Carlos Cruchaga,[40] Jacek Czajkowski,[41] Marcel den Hoed,[42] Janet A. Dunn,[43] Helena M. Earl,[44] Georg B. Ehret,[45] Ele Ferrannini,[46] Jean Ferrieres,[47] Thomas Foltynie,[24] Ian Ford,[38] Nita G. Forouhi,[1] Francesco Gianfagna,[48,49] Carlos Gonzalez,[50] Sara Grioni,[51] Louise Hiller,[43] Jan-Håkan Jansson,[52,53] Marit E. Jørgensen,[54,55] J. Wouter Jukema,[56] Rudolf Kaaks,[57] Frank Kee,[58] Nicola D. Kerrison,[1] Timothy J. Key,[59] Jukka Kontto,[60] Zsofia Kote-Jarai,[61] Aldi T. Kraja,[41] Kari Kuulasmaa,[60] Johanna Kuusisto,[62,63] Allan Linneberg,[64,65,66] Chunyu Liu,[67] Gaëlle Marenne,[3] Karen L. Mohlke,[68] Andrew P. Morris,[69,70] Kenneth Muir,[71,72] Martina Müller-Nurasyid,[73,74,75] Patricia B. Munroe,[76] Carmen Navarro,[22,77] Sune F. Nielsen,[78] Peter M. Nilsson,[79] Børge G. Nordestgaard,[78] Chris J. Packard,[38] Domenico Palli,[80] Salvatore Panico,[81] Gina M. Peloso,[82,83,84] Markus Perola,[60,85] Annette Peters,[75,86] Christopher J. Poole,[72,87] J. Ramón Quirós,[88] Olov Rolandsson,[89] Carlotta Sacerdote,[90,91,92] Veikko Salomaa,[60] María-José Sánchez,[22,93] Naveed Sattar,[38] Stephen J. Sharp,[1] Rebecca Sims,[94] Nadia Slimani,[95] Jennifer A. Smith,[96] Deborah J. Thompson,[17] Stella Trompet,[56] Rosario Tumino,[97] Daphne L. van der A,[98] Yvonne T. van der Schouw,[99] Jarmo Virtamo,[60] Mark Walker,[100] Klaudia Walter,[3] GERAD_EC Consortium,[§] Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), Alzheimer's Disease Genetics Consortium,[§] Pancreatic Cancer Cohort Consortium, European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease (EPIC-CVD), EPIC-InterAct, Jean E. Abraham,[101] Laufey T. Amundadottir,[102] Jennifer L. Aponte,[103‡] Adam S. Butterworth,[2] Josée Dupuis,[8] Douglas F. Easton,[17,101] Rosalind A. Eeles,[61,104] Jeanette Erdmann,[105] Paul W. Franks,[9,53,106] Timothy M. Frayling,[10] Torben Hansen,[6] Joanna M. M. Howson,[2] Torben Jørgensen,[107,108,109] Jaspal Kooner,[110,111,112] Markku Laakso,[113] Claudia Langenberg,[1] Mark I. McCarthy,[70,114] James S. Pankow,[115] Oluf Pedersen,[6] Elio Riboli,[116] Jerome I. Rotter,[117] Danish Saleheen,[118] Nilesh J. Samani,[119,120] Heribert Schunkert,[75,121] Peter Vollenweider,[122] Stephen O'Rahilly,[28,123,124] CHARGE consortium, The CHD Exome+ Consortium, CARDIOGRAM Exome Consortium, Panos Deloukas,[125] John Danesh,[2,3] Mark O. Goodarzi,[126] Sekar Kathiresan,[83,127,128] James B. Meigs,[129,130] Margaret G. Ehm,[103] Nicholas J. Wareham,[1†] Dawn M. Waterworth[131†]

[1]Medical Research Council (MRC) Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK. [2]Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge CB1 8RN, UK. [3]The Wellcome Trust Sanger Institute, Cambridge CB10 1SA, UK. [4]Statistical Genetics, Projects, Clinical Platforms, and Sciences (PCPS), GlaxoSmithKline, Research

Triangle Park, NC 27709, USA. [5]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA. [6]The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark. [7]Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, FI-70211 Kuopio, Finland. [8]Department of Biostatistics, Boston University School of Public Health, Boston, MA 02118, USA. [9]Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, SE-205 Malmö, Sweden. [10]Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, Exeter EX1 2LU, UK. [11]Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center, 3000 CE Rotterdam, Netherlands. [12]Department of Epidemiology, Fairbanks School of Public Health, Indianapolis, IN 46202, USA. [13]Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA. [14]Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. [15]Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, MD 21205, USA. [16]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD 21205, USA. [17]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Laboratory, Worts Causeway, Cambridge CB1 8RN, UK. [18]Department of Epidemiology, Erasmus University Medical Center, 3000 CA Rotterdam, Netherlands. [19]University of Lille, INSERM, Centre Hospitalier Régional Universitaire de Lille, Institut Pasteur de Lille, UMR 1167, RID-AGE, F-59000 Lille, France. [20]Public Health Division of Gipuzkoa, San Sebastian 20013, Spain. [21]Instituto BIO-Donostia, Basque Government, San Sebastian 20014, Spain. [22]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid 28029, Spain. [23]Department of Epidemiology and Public Health (EA3430), University of Strasbourg, 67085 Strasbourg, France. [24]Sobell Department of Motor Neuroscience, UCL Institute of Neurology, London WC1N 3BG, UK. [25]INSERM, Centre de Recherche en Epidémiologie et Santé des Populations (CESP), 94807 Villejuif, France. [26]Univeristy of Paris-Sud, F-94805 Villejuif, France. [27]Navarre Public Health Institute (ISPN), Pamplona 31003, Spain. [28]University of Cambridge Metabolic Research Laboratories, Wellcome Trust–MRC Institute of Metabolic Science, Cambridge CB2 0QQ, UK. [29]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA 98101, USA. [30]Department of General and Interventional Cardiology, University Heart Center Hamburg, 20246 Hamburg, Germany. [31]Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI 48109–2029, USA. [32]German Institute of Human Nutrition, Potsdam-Rehbruecke, 14558 Nuthetal, Germany. [33]Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX 77025, USA. [34]Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX 77030, USA. [35]Department of Genetics, Division of Statistical Genomics, Washington University School of Medicine, St. Louis, MO 63108, USA. [36]Cancer Research UK Clinical Trials Unit, Institute for Cancer Studies, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. [37]Cancer Research UK Cambridge Institute and Department of Oncology, Li Ka Shing Centre, University of Cambridge, Cambridge CB2 0RE, UK. [38]University of Glasgow, Glasgow G12 8QQ, UK. [39]Framingham Heart Study, National Heart, Lung, and Blood Institute (NHLBI), Framingham, MA 01702–5827, USA. [40]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA. [41]Division of Statistical Genomics, Department of Genetics and Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St. Louis, MO 63108, USA. [42]Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, SE-752 37 Uppsala, Sweden. [43]Warwick Clinical Trials Unit, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, UK. [44]University of Cambridge and National Institute of Health Research Cambridge Biomedical Research Centre, Cambridge University Hospitals National Health Service Foundation Trust, Cambridge CB2 0QQ, UK. [45]McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD 21205, USA. [46]Consiglio Nazionale delle Ricerche (CNR), Institute of Clinical Physiology, 56124 Pisa, Italy. [47]Department of Epidemiology, UMR 1027, INSERM, Centre Hospitalier Universitaire (CHU) de Toulouse, 31000 Toulouse, France. [48]Department of Clinical and Experimental Medicine, Research Centre in Epidemiology and Preventive Medicine, University of Insubria, 21100 Varese, Italy. [49]Department of Epidemiology and Prevention, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS), Istituto Neurologico Mediterraneo Neuromed, 86077 Pozzilli, Italy. [50]Catalan Institute of Oncology (ICO), Barcelona 08908, Spain. [51]Epidemiology and Prevention Unit, 20133 Milan, Italy. [52]Research Unit, 931 41 Skellefteå, Sweden. [53]Department of Public Health & Clinical Medicine, Umeå University, 901 85 Umeå, Sweden. [54]Steno Diabetes Center, 2820 Gentofte, Denmark. [55]National Institute of Public Health, Southern Denmark University, DK-1353 Odense, Denmark. [56]Leiden University Medical Center, 2333 ZA Leiden, Netherlands. [57]German Cancer Research Centre (DKFZ), 69120 Heidelberg, Germany. [58]UK Clinical Research Collaboration (UKCRC) Centre of Excellence for Public Health, Queen's University Belfast, Northern Ireland, Belfast BT12 6BJ, UK. [59]University of Oxford, Oxford OX1 2JD, UK. [60]National Institute for Health and Welfare, FI-00271 Helsinki, Finland. [61]The Institute of Cancer Research, London SM2 5NG, UK. [62]Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, FI-70211 Kuopio, Finland. [63]Kuopio University Hospital, FL 70029 Kuopio, Finland. [64]Research Centre for Prevention and Health, Capital Region, DK-2600 Copenhagen, Denmark. [65]Department of Clinical Experimental Research, Rigshospitalet, 2100 Glostrup, Denmark. [66]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark. [67]Framingham Heart Study, Population Sciences Branch, NHLBI/National Institutes of Health (NIH), Bethesda, MD 20892, USA. [68]Department of Genetics, University of North Carolina, Chapel Hill, NC 27599–7264, USA. [69]Department of Biostatistics, University of Liverpool, Liverpool L69 3GL, UK. [70]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK. [71]Centre for Epidemiology, Institute of Population Health, University of Manchester, Oxford Road, Manchester M13 9PT, UK. [72]University of Warwick, Coventry CV4 7AL, UK. [73]Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, D-85764 Neuherberg, Germany. [74]Department of Medicine I, Ludwig Maximilians University Munich, 80336 Munich, Germany. [75]DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, 80802 Munich, Germany. [76]Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK. [77]Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia 30008, Spain. [78]Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, 2730 Copenhagen, Denmark. [79]Lund University, 20502 Malmö, Sweden. [80]Cancer Research and Prevention Institute (ISPO), 50141 Florence, Italy. [81]Dipartimento di Medicina Clinica e Chirurgia, Federico II University, 80131 Naples, Italy. [82]Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA 02114, USA. [83]Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA 02114, USA. [84]Program in Medical and Population Genetics, Broad Institute, Cambridge, MA 02142, USA. [85]Institute of Molecular Medicine Finland (FIMM), University of Helsinki, FI-00014 Helsinki, Finland. [86]Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, D-85764 Neuherberg, Germany. [87]Department of Medical Oncology, Arden Cancer Centre, University Hospital Coventry and Warwickshire, West Midlands CV2 2DX, UK. [88]Public Health Directorate, 33006 Oviedo, Asturias, Spain. [89]Umeå University, 90187 Umeå, Sweden. [90]Unit of Cancer Epidemiology, Citta' della Salute e della Scienza Hospital, University of Turin, 10126 Torino, Italy. [91]Center for Cancer Prevention (CPO), 10126 Torino, Italy. [92]Human Genetics Foundation, 10126 Torino, Italy. [93]Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria ibs.GRANADA. Hospitales Universitarios de Granada/Universidad de Granada, Granada 18012, Spain. [94]Institute of Psychological Medicine and Clinical Neuroscience, MRC Centre, Cardiff University, Cardiff CF24 4HQ, UK. [95]International Agency for Research on Cancer, 69372 Lyon, France. [96]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109–2029, USA. [97]Cancer Registry and Histopathology Unit, "Civic–M.P. Arezzo" Hospital, ASP Ragusa, 97100 Ragusa, Italy. [98]National Institute for Public Health and the Environment (RIVM), 3720 BA Bilthoven, Netherlands. [99]University Medical Center Utrecht, 3508 GA Utrecht, Netherlands. [100]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne NE2 4HH, UK. [101]Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Laboratory, Worts Causeway, Cambridge CB1 8RN, UK. [102]Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD 20892, USA. [103]Genetics, PCPS, GlaxoSmithKline, Research Triangle Park, NC 27709, USA. [104]Royal Marsden NHS Foundation Trust, Fulham and Sutton, London and Surrey SW3 6JJ, UK. [105]Institut für Integrative und Experimentelle Genomik, Universität zu Lübeck, 23562 Lübeck, Germany. [106]Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA 02115, USA. [107]Research Centre for Prevention and Health, DK-2600 Capital Region, Denmark. [108]Department of Public Health, Institute of Health Science, University of Copenhagen, 1014 Copenhagen, Denmark. [109]Faculty of Medicine, Aalborg University, 9220 Aalborg, Denmark. [110]National Heart and Lung Institute, Imperial College London, London SW3 6LY, UK. [111]Imperial College Healthcare NHS Trust, London W2 1NY, UK. [112]Ealing Hospital NHS Trust, Middlesex UB1 3HW, UK. [113]Department of Medicine, University of Kuopio, FI-70211 Kuopio, Finland. [114]Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), University of Oxford, Oxford OX3 7LE, UK. [115]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN 55455–0381, USA. [116]School of Public Health, Imperial College London, London W2 1PG, UK. [117]Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor–University of California, Los Angeles Medical Center, Torrance, CA 90502, USA. [118]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA 19104, USA. [119]Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester LE3 9QP, UK. [120]National Institute for Health Research, Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester LE3 9QP, UK. [121]Deutsches Herzzentrum München, Technische Universität München, 80636 Munich, Germany. [122]Department of Internal Medicine, BH10-462, Internal Medicine, Lausanne University Hospital (CHUV), CH-1011 Lausanne, Switzerland. [123]MRC Metabolic Diseases Unit, Cambridge CB2 0QQ, UK. [124]National Institute for Health Research Cambridge Biomedical Research Centre, Cambridge CB2 0QQ, UK. [125]William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK. [126]Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA. [127]Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA. [128]Cardiology Division, Center for Human Genetic Research, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA. [129]Division of General Internal Medicine, Department of Medicine, Massachusetts General Hospital, Boston, MA 02114, USA. [130]Department of Medicine, Harvard Medical School, Boston, MA 02115, USA. [131]Genetics, PCPS, GlaxoSmithKline, Philadelphia, PA 19104, USA.

*These authors contributed equally to this work.
†Corresponding author. Email: dawn.m.waterworth@gsk.com (D.M.W.); robert.scott@mrc-epid.cam.ac.uk (R.A.S.); nick.wareham@ mrc-epid.cam.ac.uk (N.J.W.)
‡Present address: PAREXEL, Durham, NC 27713, USA.

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Robert A. Scott, Daniel F. Freitag, Li Li, Audrey Y. Chu, Praveen Surendran, Robin Young, Niels Grarup, Alena Stancáková, Yuning Chen, Tibor V. Varga, Hanieh Yaghootkar, Jian'an Luan, Jing Hua Zhao, Sara M. Willems, Jennifer Wessel, Shuai Wang, Nisa Maruthur, Kyriaki Michailidou, Ailith Pirie, Sven J. van der Lee, Christopher Gillson, Ali Amin Al Olama, Philippe Amouyel, Larraitz Arriola, Dominique Arveiler, Iciar Aviles-Olmos, Beverley Balkau, Aurelio Barricarte, Inês Barroso, Sara Benlloch Garcia, Joshua C. Bis, Stefan Blankenberg, Michael Boehnke, Heiner Boeing, Eric Boerwinkle, Ingrid B. Borecki, Jette Bork-Jensen, Sarah Bowden, Carlos Caldas, Muriel Caslake, The CVD50 consortium, L. Adrienne Cupples, Carlos Cruchaga, Jacek Czajkowski, Marcel den Hoed, Janet A. Dunn, Helena M. Earl, Georg B. Ehret, Ele Ferrannini, Jean Ferrieres, Thomas Foltynie, Ian Ford, Nita G. Forouhi, Francesco Gianfagna, Carlos Gonzalez, Sara Grioni, Louise Hiller, Jan-Håkan Jansson, Marit E. Jørgensen, J. Wouter Jukema, Rudolf Kaaks, Frank Kee, Nicola D. Kerrison, Timothy J. Key, Jukka Kontto, Zsofia Kote-Jarai, Aldi T. Kraja, Kari Kuulasmaa, Johanna Kuusisto, Allan Linneberg, Chunyu Liu, Gaëlle Marenne, Karen L. Mohlke, Andrew P. Morris, Kenneth Muir, Martina Müller-Nurasyid, Patricia B. Munroe, Carmen Navarro, Sune F. Nielsen, Peter M. Nilsson, Børge G. Nordestgaard, Chris J. Packard, Domenico Palli, Salvatore Panico, Gina M. Peloso, Markus Perola, Annette Peters, Christopher J. Poole, J. Ramón Quirós, Olov Rolandsson, Carlotta Sacerdote, Veikko Salomaa, María-José Sánchez, Naveed Sattar, Stephen J. Sharp, Rebecca Sims, Nadia Slimani, Jennifer A. Smith, Deborah J. Thompson, Stella Trompet, Rosario Tumino, Daphne L. van der A, Yvonne T. van der Schouw, Jarmo Virtamo, Mark Walker, Klaudia Walter, GERAD_EC Consortium, Neurology Working Group of the Cohorts for Heart, Aging Research in Genomic Epidemiology (CHARGE), Alzheimer's Disease Genetics Consortium, Pancreatic Cancer Cohort Consortium, European Prospective Investigation into Cancer and Nutrition-Cardiovascular Disease (EPIC-CVD), EPIC-InterAct, Jean E. Abraham, Laufey T. Amundadottir, Jennifer L. Aponte, Adam S. Butterworth, Josée Dupuis, Douglas F. Easton, Rosalind A. Eeles, Jeanette Erdmann, Paul W. Franks, Timothy M. Frayling, Torben Hansen, Joanna M. M. Howson, Torben Jørgensen, Jaspal Kooner, Markku Laakso, Claudia Langenberg, Mark I. McCarthy, James S. Pankow, Oluf Pedersen, Elio Riboli, Jerome I. Rotter, Danish Saleheen, Nilesh J. Samani, Heribert Schunkert, Peter Vollenweider, Stephen O'Rahilly, CHARGE consortium, The CHD Exome+ Consortium, CARDIOGRAM Exome Consortium, Panos Deloukas, John Danesh, Mark O. Goodarzi, Sekar Kathiresan, James B. Meigs, Margaret G. Ehm, Nicholas J. Wareham and Dawn M. Waterworth (June 1, 2016)

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Editor's Summary

At risk by association

Genetics could soon routinely tell clinicians whether certain drugs are putting patients at risk of developing heart disease or cancer. Scott *et al.* looked at six genes that encode the targets of various drugs for type 2 diabetes or obesity, to see whether any genetic variations were linked to metabolic traits like body mass index and fasting glucose levels. Using several cohorts totaling more than 50,000 individuals, they landed on one particular variant in *GLP1R*––the gene encoding glucagon-like peptide-1 receptor, which is the target for certain glucose-lowering drugs frequently used in the clinic, like exenatide and liraglutide––associated with fasting glucose. The authors then compared this variant against disease outcomes, like coronary heart disease (CHD). In more than 200,000 individuals––some with heart disease, some as controls––the *GLPR1* variant was actually protective against CHD, rather than causing any additional risk, and was not associated with various cancers or neurological diseases.

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