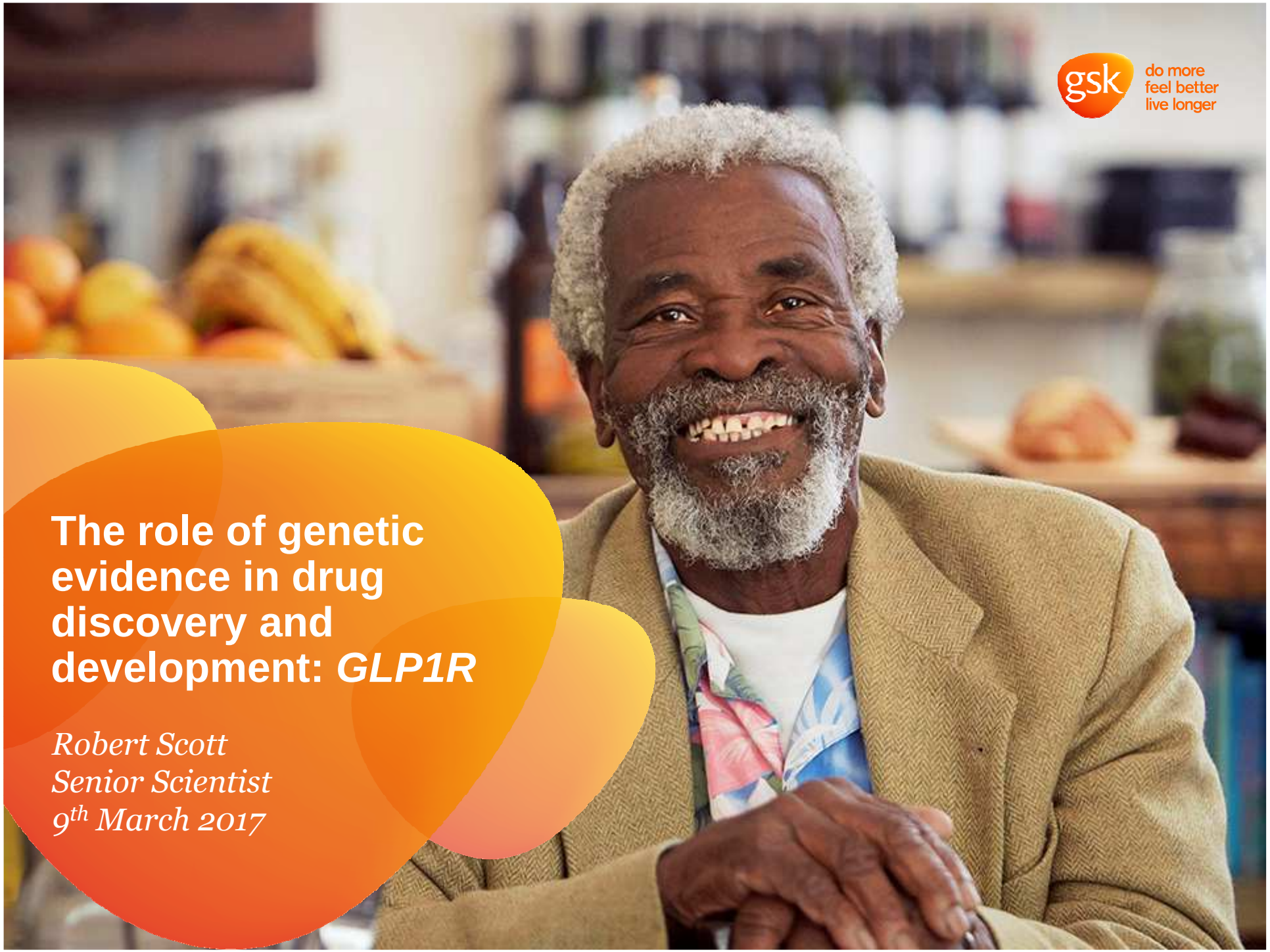


gsk do more feel better live longer

The role of genetic evidence in drug discovery and development: *GLP1R*

Robert Scott
Senior Scientist
9th March 2017

Overview

Why study genetics?

Genetics can aid drug development process…

Example of *GLP1R*

- Aims and approaches
- Findings
- Broader implications
- Challenges and opportunities in future

Why study genetics of complex disease?

Understand the biology of disease

- Powerful experiments of nature in *Homo sapiens*
- No reverse causality, less confounding
- Can use genetics to gain causal insight into disease aetiology

Predict disease?

Identify novel therapeutic targets or better understand existing ones

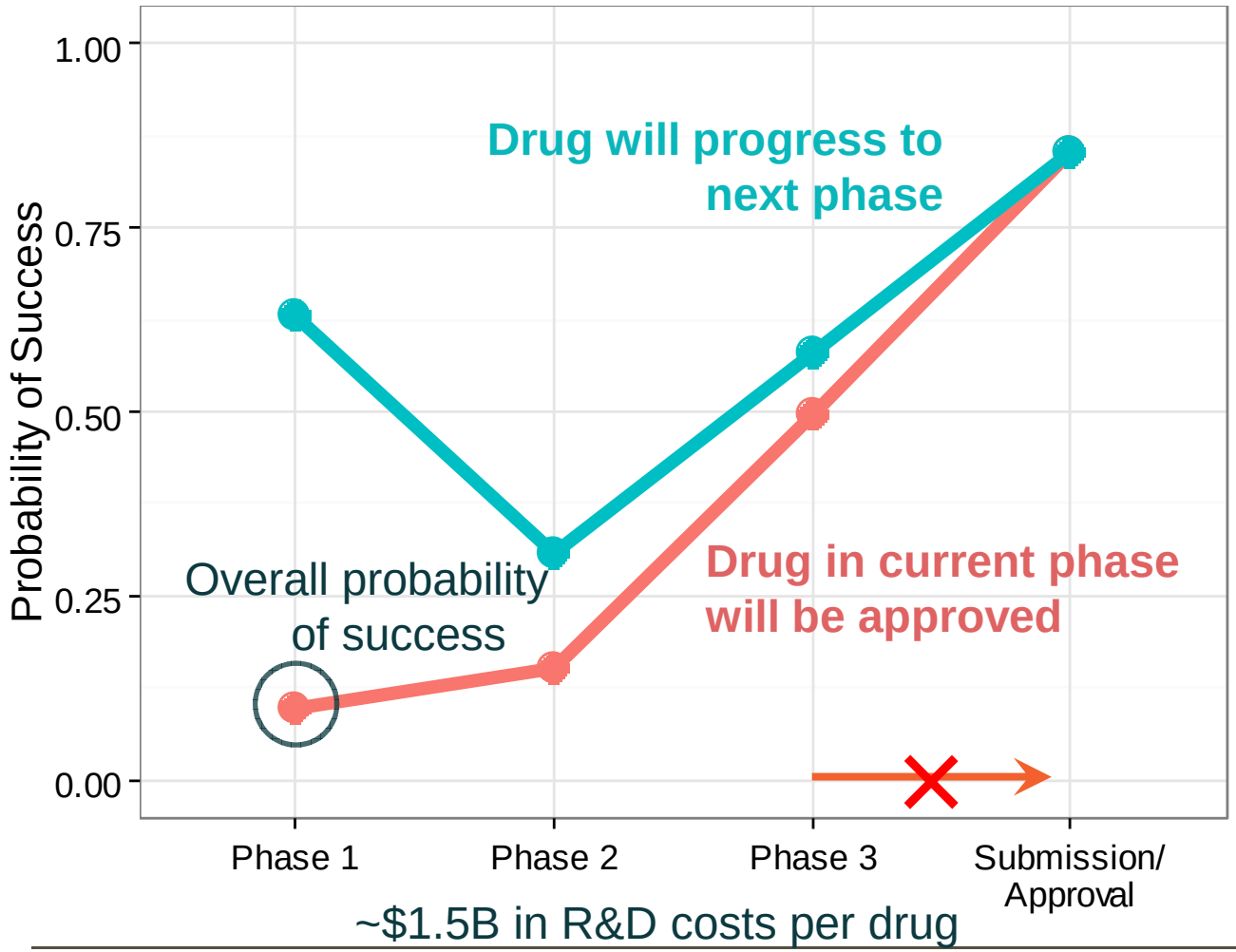
- Genes elucidate novel pathways to T2D – perturbation of which alters disease risk

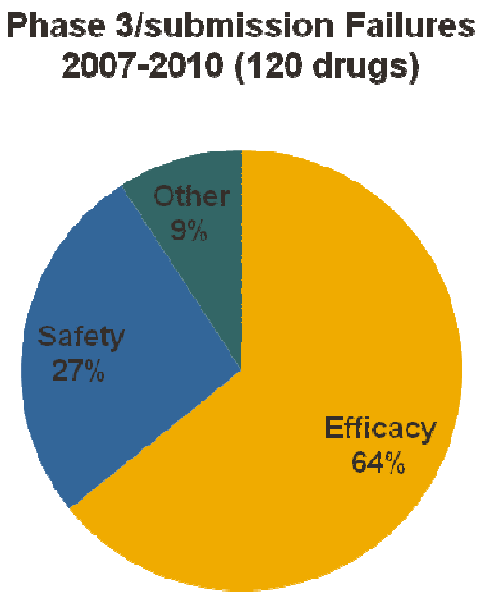
Background

Genetics can aid drug development process

- Identify new targets
- Validate existing targets
  - Increase or reduce enthusiasm
  - Insight into safety profile
  - Identify opportunities for repositioning

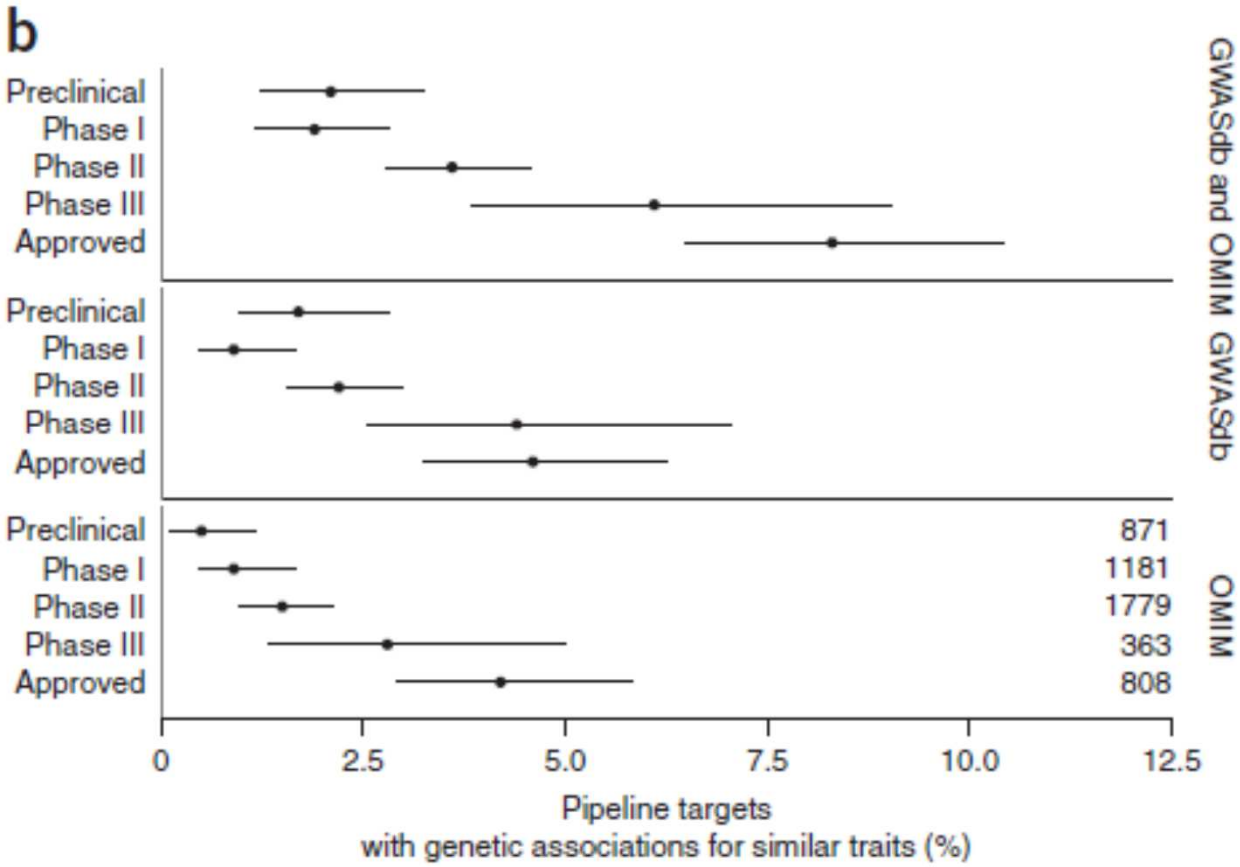
Failure due to lack of efficacy is a major challenge in drug development





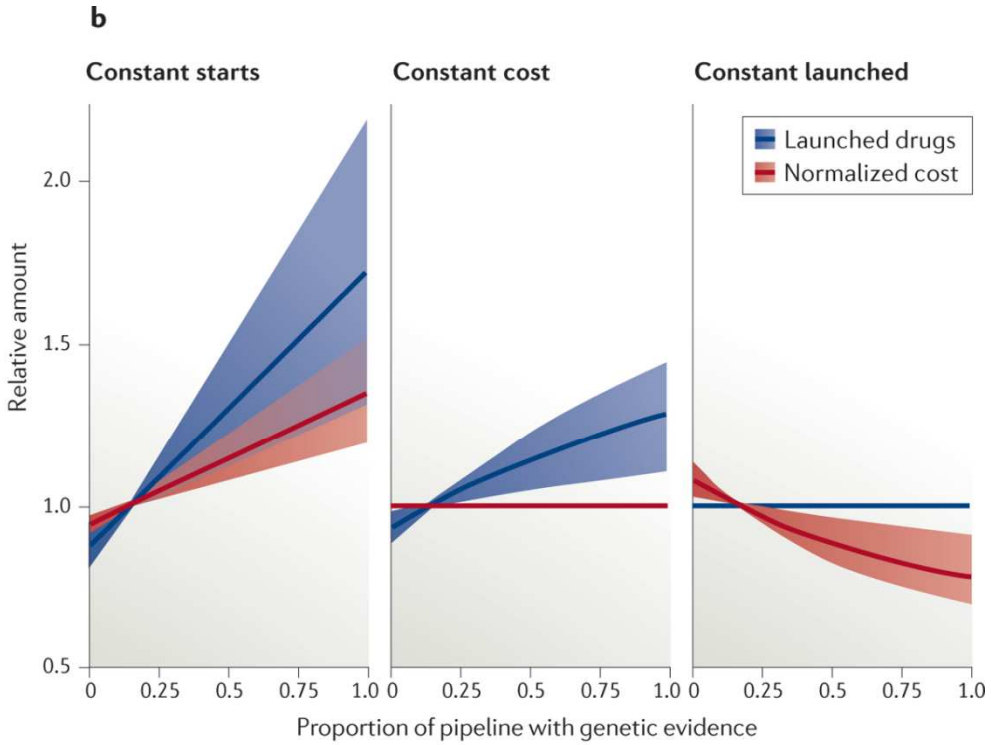
BIO (2016); Hay et al. (2014) Nat. Biotech. 32:40-51
Arrowsmith & Miller (2013) Nat. Rev. Drug. Disc. 12:569

Drugs with genetic support are more likely to become safe and effective targets



Nelson et al, Nat Gen 2015

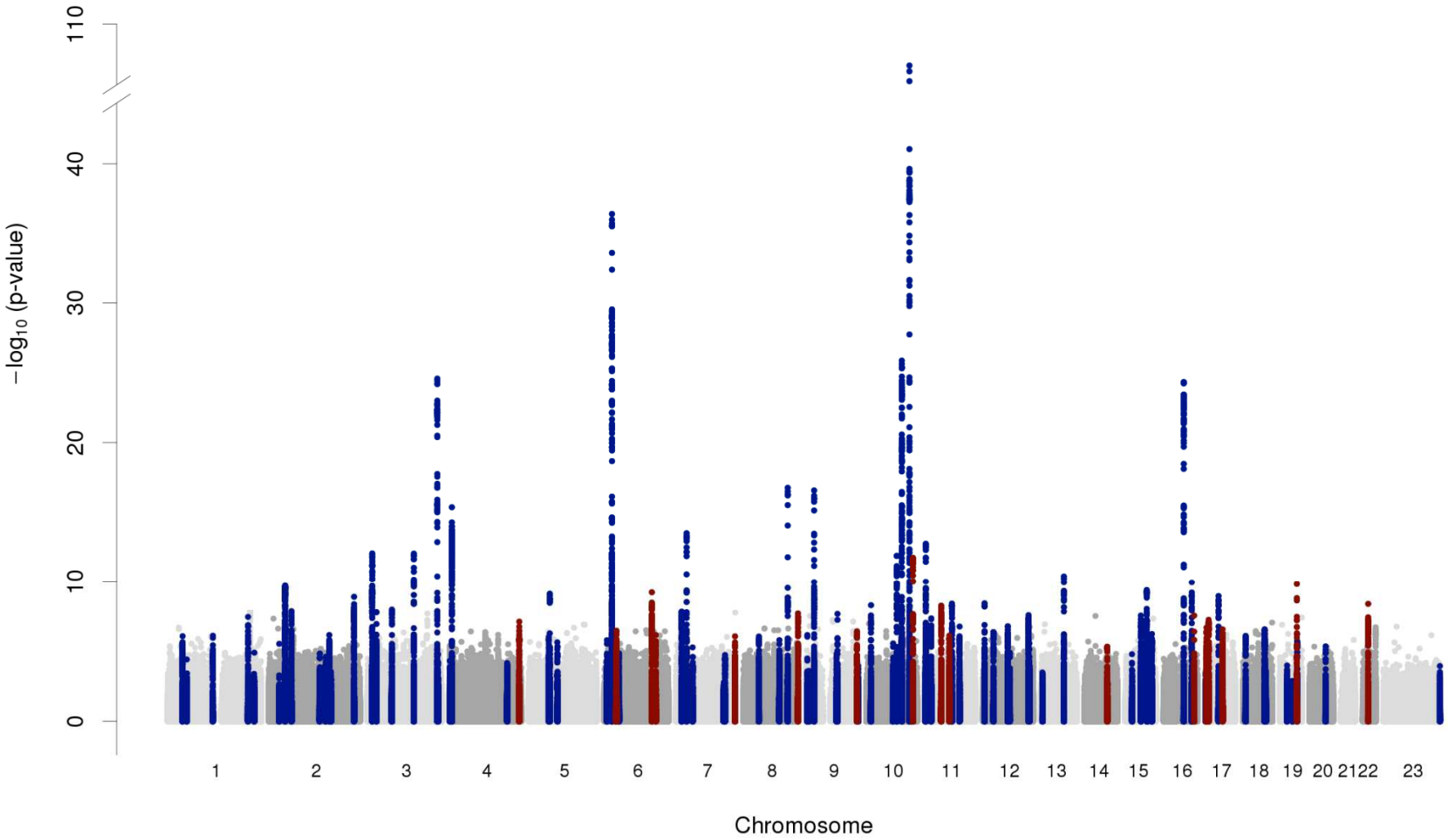
Even modest increases in clinical trial success rates can translate into substantial increases R&D efficiency



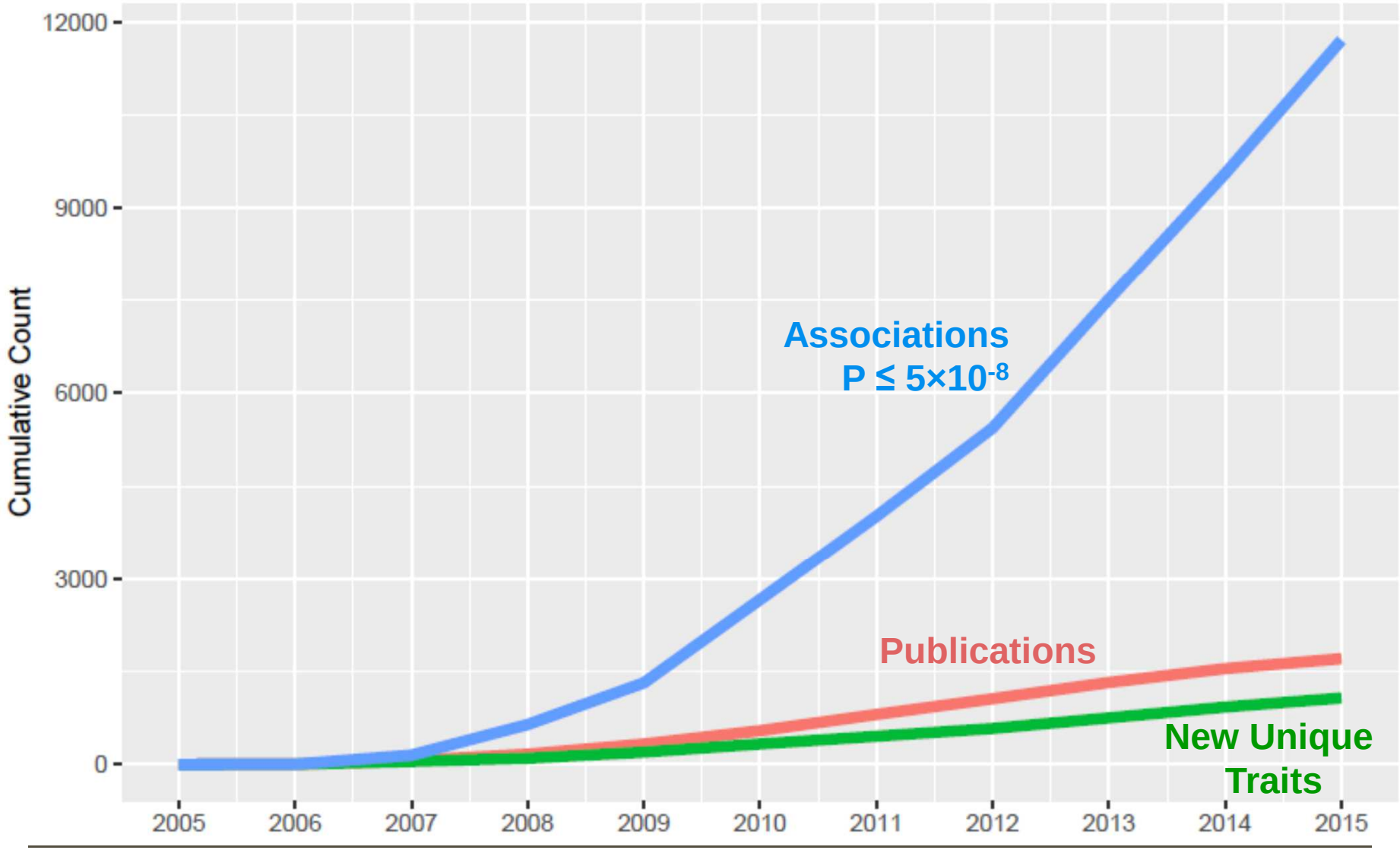
Impact of genetically supported target selection on R&D productivity

NATURE REVIEWS | DRUG DISCOVERY
Mark R. Hurle, Matthew R. Nelson, Pankaj Agarwal and Lon R. Cardon are at GlaxoSmithKline,
596 | SEPTEMBER 2016 | VOLUME 15

Genetics can identify new drug targets…

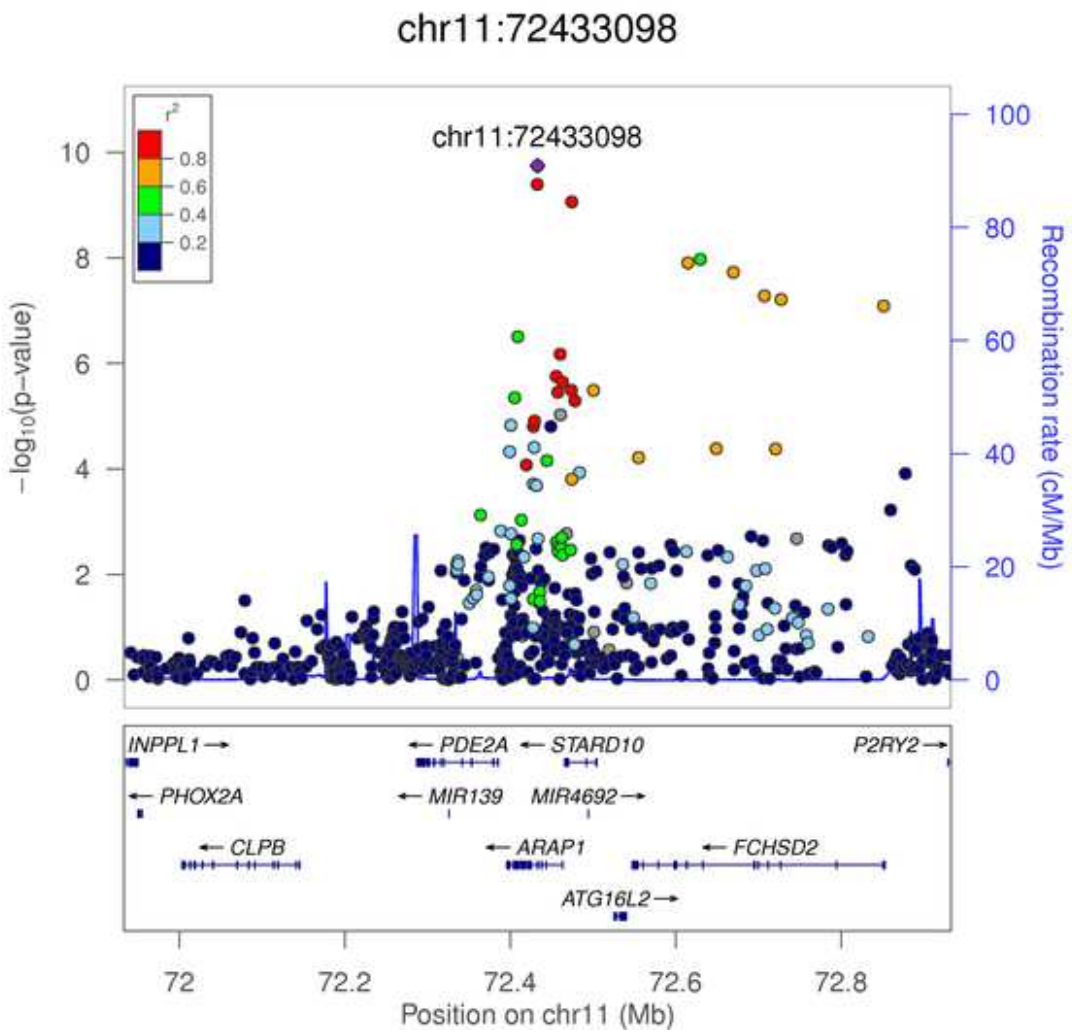


Genome-wide association studies have identified thousands of variants that influence human traits



Source: NHGRI/EBI GWAS Catalog, September 1, 2016

Genetics can identify new drug targets…ish



- To develop drugs based on genetic evidence, we need to know the effector gene
- Some suggest that the small effect sizes of genetic variants render the findings less relevant…

Common variants with modest effects do not equate to therapeutic potential

Statins

- LDL-lowering therapy used by millions
  - Prevent ~80,000 strokes and heart attacks each year
  - Inhibit HMG-CoA reductase (*HMGCR*)

Table 1 | Meta-analysis of plasma lipid concentrations in >100,000 individuals of European descent.

Locus	Chr	Lead SNP	Lead trait	Other traits	Alleles/MAF	Effect size	*P*	eQTL	CAD	Ethnic
SLC39A8	4	rs13107325	HDL		C/T/0.07	−0.84	7×10^{-11}	Y		+−?−
ARL15	5	rs6450176	HDL		G/A/0.26	−0.49	5×10^{-8}			−??+
MAP3K1	5	rs9686661	TG		C/T/0.20	+2.57	1×10^{-10}			++++
HMGCR	5	rs12916	TC	LDL	T/C/0.39	+2.84	9×10^{-47}			+++?
TIMD4	5	rs6882076	TC	LDL, TG	C/T/0.35	−1.98	7×10^{-28}			+++?
MYLIP	6	rs3757354	LDL	TC	C/T/0.22	−1.43	1×10^{-11}			+−−+
HFE	6	rs1800562	LDL	TC	G/A/0.06	−2.22	6×10^{-10}			++?+
HLA	6	rs3177928	TC	LDL	G/A/0.16	+2.31	4×10^{-19}	Y		+++?
		rs2247056	TG		C/T/0.25	−2.99	2×10^{-15}			+++−
C6orf106	6	rs2814944	HDL		G/A/0.16	−0.49	4×10^{-9}	Y		+++−
		rs2814982	TC		C/T/0.11	−1.86	5×10^{-11}		Y	−−+?
FRK	6	rs9488822	TC	LDL	A/T/0.35	−1.18	2×10^{-10}	Y		+++?
CITED2	6	rs605066	HDL		T/C/0.42	−0.39	3×10^{-8}			++−+
LPA	6	rs1564348	LDL	TC	T/C/0.17	−0.56	2×10^{-17}		Y	++?+

Genetics can alter enthusiasm for putative targets

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inactivating Mutations in *NPC1L1* and Protection from Coronary Heart Disease

The Myocardial Infarction Genetics Consortium Investigators

ABSTRACT

BACKGROUND

Ezetimibe lowers plasma levels of low-density lipoprotein (LDL) cholesterol by inhibiting the activity of the Niemann–Pick C1-like 1 (NPC1L1) protein. However, whether such inhibition reduces the risk of coronary heart disease is not known. Human mutations that inactivate a gene encoding a drug target can mimic the action of an inhibitory drug and thus can be used to infer potential effects of that drug.

METHODS

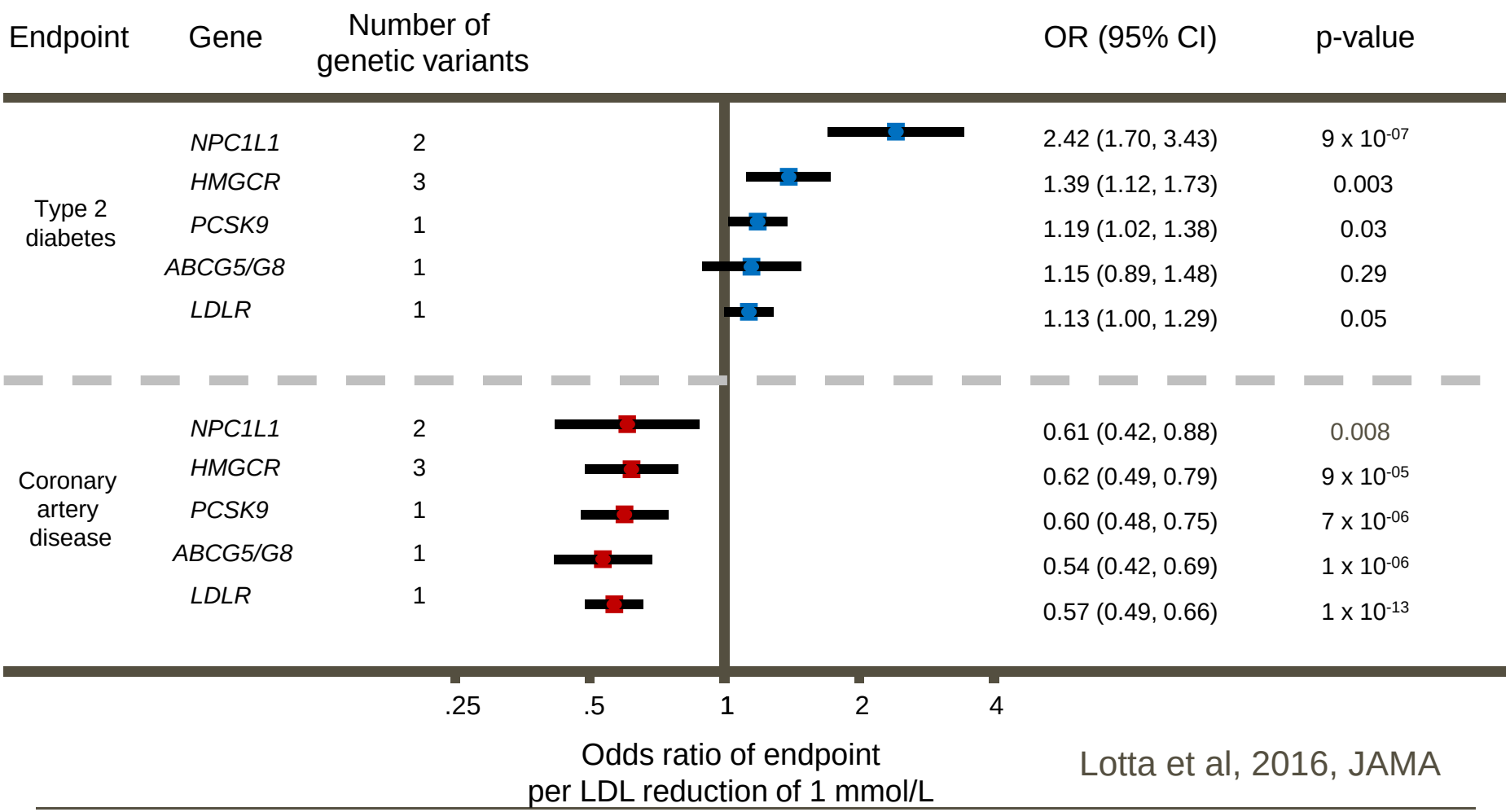
We sequenced the exons of *NPC1L1* in 7364 patients with coronary heart disease and in 14,728 controls without such disease who were of European, African, or South Asian ancestry. We identified carriers of inactivating mutations (nonsense, splice-site, or frameshift mutations). In addition, we genotyped a specific inactivating mutation (p.Arg406X) in 22,590 patients with coronary heart disease and in 68,412 controls. We tested the association between the presence of an inactivating mutation and both plasma lipid levels and the risk of coronary heart disease.

RESULTS

With sequencing, we identified 15 distinct *NPC1L1* inactivating mutations; approximately 1 in every 650 persons was a heterozygous carrier for 1 of these mutations. Heterozygous carriers of *NPC1L1* inactivating mutations had a mean LDL cholesterol level that was 12 mg per deciliter (0.31 mmol per liter) lower than that in

- Ezetimibe inhibits *NPC1L1*
- Inactivating mutations in *NPC1L1* are associated with lower LDL and risk of CHD
- Thus, suggest that inhibition of NPC1L1 will be effective therapy
- Published the week before randomised controlled trial

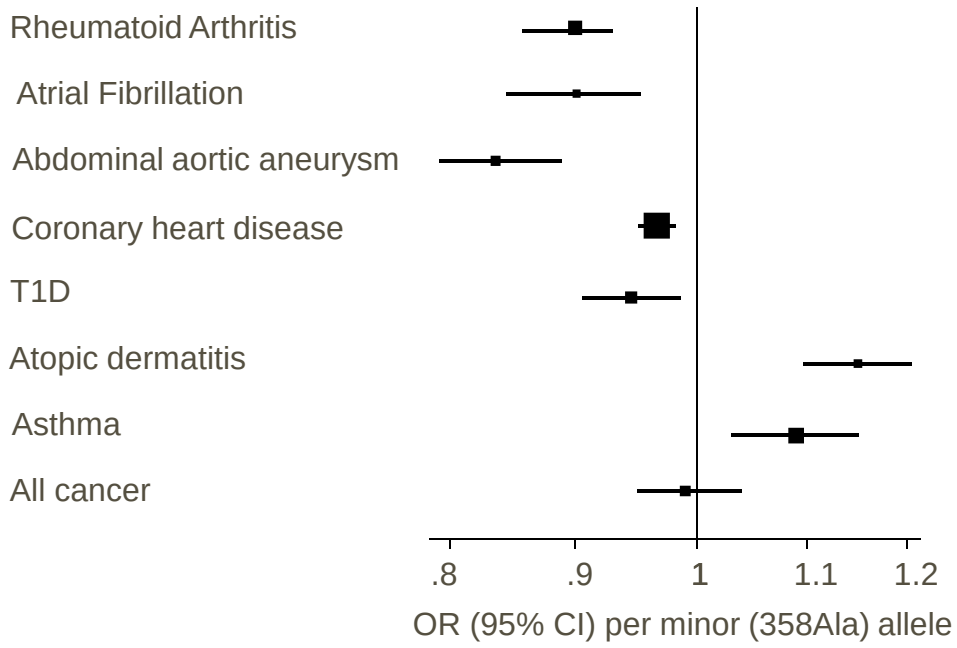
Genetics can inform safety profile for existing drugs



Lotta et al, 2016, JAMA

Identify opportunities for repositioning

- IL-6R antagonism already licensed for rheumatoid arthritis
- Potential for prevention of other diseases e.g. coronary heart disease?
- Caution for other outcomes



IL6R-GC *Lancet* 2012
Schnabel *Circ Cardiovasc Genet* 2011
Harrison et al *Eur Heart J* 2012
Eyre et al *Nat Genet* 2012
Ferreira et al *PLoS Genet* 2013
Esparza-Gordillo et al, *J Allerg Clin Immunol* 2013
Ferreira et al *Lancet* 2012
IL6MR *Lancet* 2012

Exome sequencing studies can identify functional variants in genes encoding drug targets

An Abundance of Rare Functional Variants in 202 Drug Target Genes Sequenced in 14,002 People

Matthew R. Nelson,[1*†] Daniel Wegmann,[2*] Margaret G. Ehm,[1] Darren Kessner,[2] Pamela St. Jean,[1] Claudio Verzilli,[3] Judong Shen,[1] Zhengzheng Tang,[4] Silviu-Alin Bacanu,[1] Dana Fraser,[1] Liling Warren,[1] Jennifer Aponte,[1] Matthew Zawistowski,[5] Xiao Liu,[6] Hao Zhang,[6] Yong Zhang,[6] Jun Li,[7] Yun Li,[4] Li Li,[1] Peter Woollard,[3] Simon Topp,[3] Matthew D. Hall,[3] Keith Nangle,[1] Jun Wang,[6,8] Gonçalo Abecasis,[5] Lon R. Cardon,[9] Sebastian Zöllner,[5,10] John C. Whittaker,[3] Stephanie L. Chissoe,[1] John Novembre,[2†‡] Vincent Mooser[9‡]

Rare genetic variants contribute to complex disease risk; however, the abundance of rare variants in human populations remains unknown. We explored this spectrum of variation by sequencing 202 genes encoding drug targets in 14,002 individuals. We find rare variants are abundant (1 every 17 bases) and geographically localized, so that even with large sample sizes, rare variant catalogs will be largely incomplete. We used the observed patterns of variation to estimate population growth parameters, the proportion of variants in a given frequency class that are putatively deleterious, and mutation rates for each gene. We conclude that because of rapid population growth and weak purifying selection, human populations harbor an abundance of rare variants, many of which are deleterious and have relevance to understanding disease risk.

Understanding the genetic contribution to human disease requires knowledge of the abundance and distribution of functional genetic diversity within and among populations. The "common-disease rare-variant" hypothesis posits that variants affecting health are under purifying selection and thus should be found only at low frequencies in human populations (*1*–*3*). This hypothesis has become increasingly credible because very large genome-wide association studies of common variants have explained only a fraction of the known heritability of most traits (*4*, *5*). Investigating the role of rare variants for complex trait mapping has led to tests that aggregate rare variants (*6*) and determine the abundance, distribution, and phenotypic effects of rare variants in human populations (*7*, *8*).

Population genetic models predict that mutation rates, the strength of selection, and demography affect the abundance of rare variants, although the relative importance of each is a long-standing question (*9*–*11*). To understand rare variant diversity in humans, we sequenced 202 genes in a sample of 14,002 well-phenotyped individuals (table S1). These genes represent approximately 1% of the coding genome and approximately 7% of genes considered current or potential drug targets (*12*) and are enriched for cell-signaling proteins and membrane-bound transporters (table S2). A total of 864 kb were targeted, including 351 kb of coding and 323 kb of untranslated (UTR) exon regions (database S1). More than 93% of target bases were successfully

[1]Department of Quantitative Sciences, GlaxoSmithKline (GSK), Research Triangle Park, NC 27709, USA. [2]Department of Ecology and Evolutionary Biology, University of California–Los Angeles, Los Angeles, CA 90095, USA. [3]Department of Quantitative Sciences, GSK, Stevenage SG1 2NY, UK. [4]Department of Genetics and Biostatistics, University of North Carolina–Chapel Hill, Chapel Hill, NC 27599, USA. [5]Department of Biostatistics, University of Michigan–Ann Arbor, Ann Arbor, MI 48109, USA. [6]BGI, Shenzhen 518083, China. [7]Department of Human Genetics, University of Michigan–Ann Arbor, Ann Arbor, MI 48109, USA. [8]Department of Biology, Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen 3393 9524, Denmark. [9]Department of Quantitative Sciences, GSK, Upper Merion, PA 19406, USA. [10]Department of Psychiatry, University of Michigan–Ann Arbor, Ann Arbor, MI 48109, USA.

*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: matthew.r.nelson@gsk.com (M.R.N); jnovembre@ucla.edu (J.N.)
‡These authors contributed equally to this work.

Aims:

Using a large-scale systematic approach for genes encoding targets for T2D/Obesity, could we:

i) Identify variants that mimic drug effects?
- i.e. does a variant in a gene encoding a receptor have the same effects as a drug binding to that receptor?

ii) Use those to evaluate risk profile of T2D/obesity drugs and opportunities for repositioning?

Scott et al., *Sci.Trans.Med.* 2016

Aim 1: identify variants that mimic drug effects

Discovery

Exome sequencing of genes encoding targets of relevance to T2D/obesity (*N*≤11,806) – 6 genes tested for association with T2D/obesity and related phenotypes

Replication

Targeted genotyping of 7 promising* variants (*N*≤39,979)
In silico analysis where possible (*N*≤70,242)
*(p<0.001, p<0.05 and strategic interest)

Follow up

In silico analyses of replicated variants to evaluate risk profile for a range of traits and diseases (*N*≤225,574)

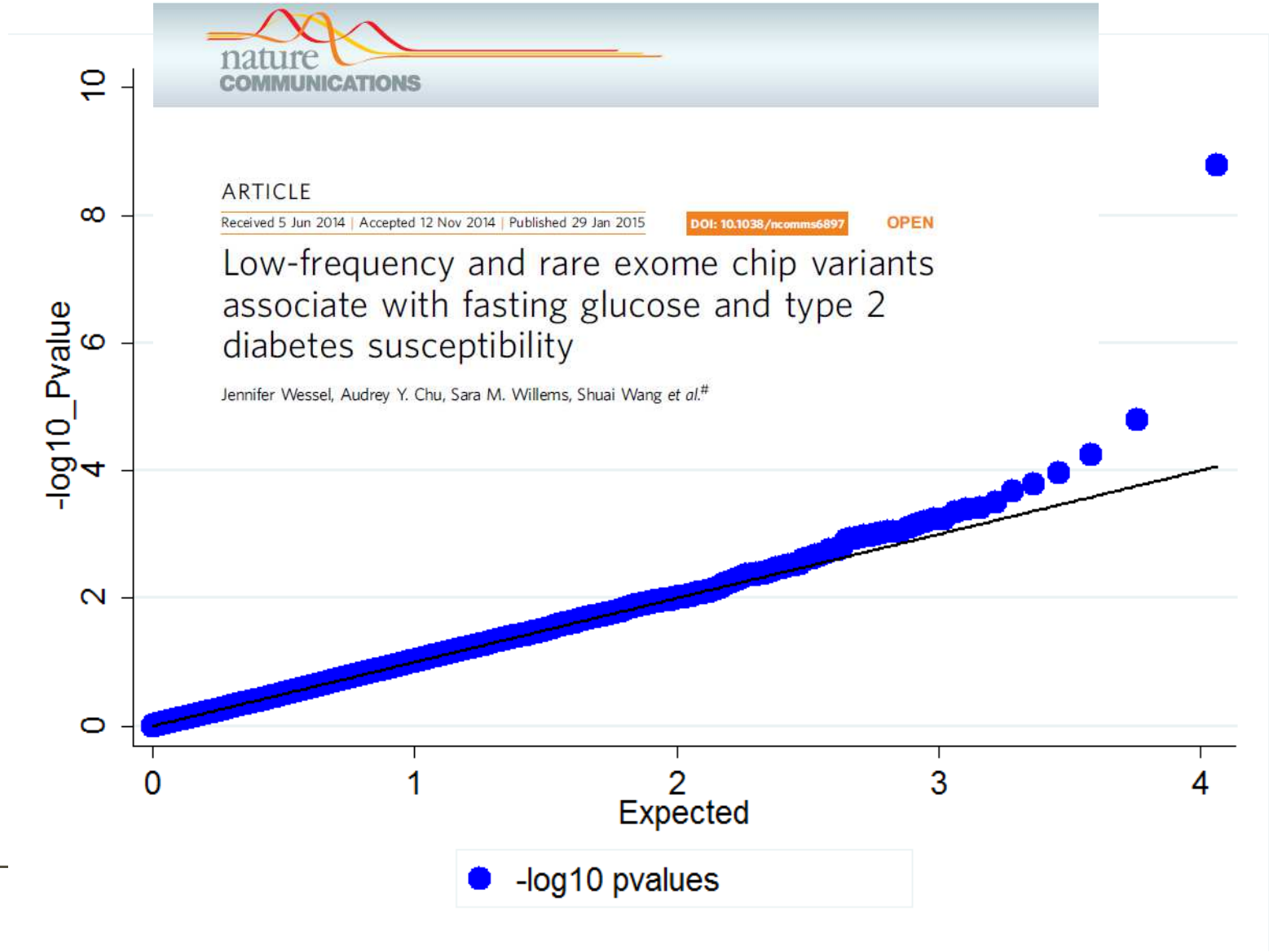
Discovery analyses

GENE	VARIANT	Consequence	Trait	Effect allele	MAF	Stage	N (case/control)	Beta (OR)	P-value
GLP1R	rs10305492	A316T	Fasting Glucose	A	0.015	Discovery	1869	-0.28	0.04
DPP4	rs56179129	V266I	Fasting Glucose	T	0.008	Discovery	1416	0.61	3.6E-03
SLC5A1	rs200410750	5' UTR	Fasting Glucose	T	0.001	Discovery	5210	1.44	1.7E-05
CNR2	rs4649124	Synon	2 hour glucose	A	0.420	Discovery	505	0.18	0.01
CNR2	rs2229579	H316Y	T2D	T	0.110	Discovery	385/5241	(0.73)	0.03
HTR2C	rs56372597	Intronic	BMI	A	0.150	Discovery	10798	0.05	2.1E-03
MCHR1	rs117372135	T25M	BMI	T	0.002	Discovery	10952	0.62	4.5E-05

Combined analyses

GENE	VARIANT	Consequence	Trait	Effect allele	EAF	Stage	N (case/control)	Beta (OR)	P-value
GLP1R	**rs10305492**	**A316T**	**Fasting Glucose**	**A**	**0.015**	Discovery	1869	-0.28	0.04
						Replication	18937	-0.13	1.5E-03
						In silico lookup	20077	-0.16	1.1E-07
						Combined	**40883**	**-0.15**	**2.6E-10**
DPP4	rs56179129	V266I	Fasting Glucose	T	0.008	Discovery	1416	0.61	3.6E-03
						Replication	12934	0.00	0.95
						In silico lookup	49838	0.00	0.16
						Combined	**64188**	**0.01**	**0.71**
SLC5A1	rs200410750	5' UTR	Fasting Glucose	T	0.001	Discovery	5210	1.44	1.7E-05
						Replication	12707	-0.16	0.56
						In silico lookup			NA
						Combined	**18059**	**0.51**	**0.01**
CNR2	rs4649124	Synonymous	2 hour glucose	A	0.420	Discovery	505	0.18	0.01
						Replication	6377	0.00	0.95
						In silico lookup	15234	-0.01	0.49
						Combined	**22106**	**0.00**	**0.88**
CNR2	rs2229579	H316Y	T2D	T	0.110	Discovery	385/5241	0.73	0.03
						Replication	7141/27096	1.06	0.07
						In silico lookup	9524/60718	0.96	0.10
						Combined	**17047/93225**	**0.99**	**0.67**
HTR2C	rs56372597	Intronic	BMI	A	0.150	Discovery	10798	0.05	2.1E-03
						Replication	36983	0.00	0.92
						In silico lookup			NA
						Combined	**47781**	**0.01**	**0.13**
MCHR1	rs117372135	T25M	BMI	T	0.002	Discovery	10952	0.62	4.5E-05
						Replication	37240	0.08	0.40
						In silico lookup	68978	-0.04	0.59
						Combined	**117170**	**0.08**	**0.13**

4 weeks later…



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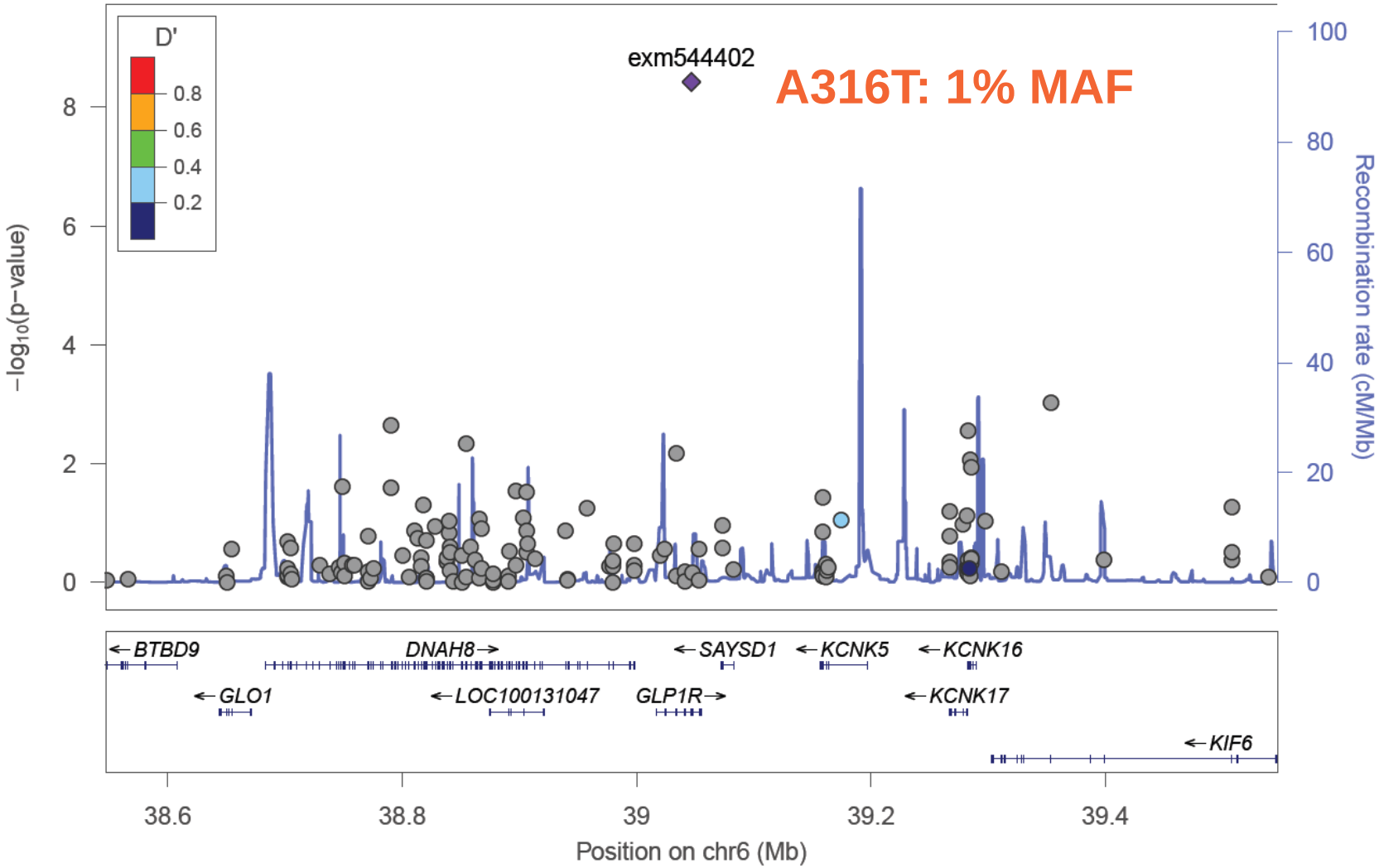
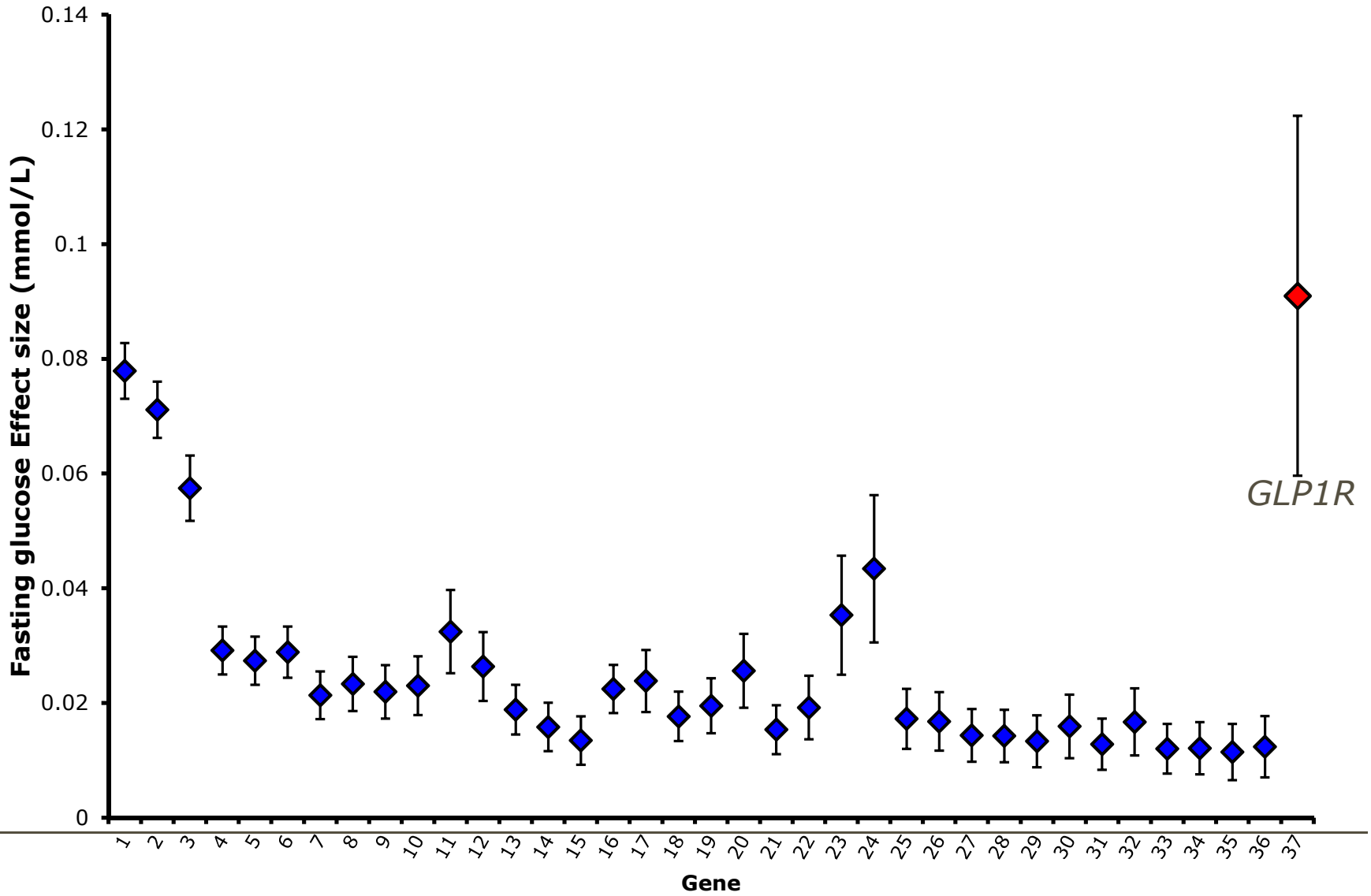


(Wessel et al. Nat Comms, 2015)

Sequencing and genotyping identified a missense variant in *GLP1R* associated with glucose levels



GLP1R – the gene and the receptor

- Receptor for glucagon-like peptide-1
  - Hormone which stimulates insulin release
- Target for major drug class for T2D
  - GLP1R agonists
  - Effective and widely used for diabetes

- **FDA, 2008:** any new T2D agent should be shown to be "not associated with an unacceptable increase in cardiovascular risk"
- Some (controversial) suggestions that GLP1R-agonists associated with an increase in rare adverse pancreatic events
- Suggested for use in a range of other disease outcomes

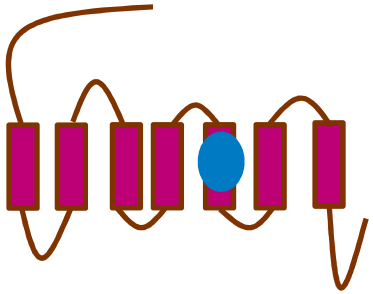
Key questions

III. Evaluate safety profile of GLP1R agonists?

II. Investigate opportunities for alternative indications?

I. Was our variant mimicking GLP1R-agonism?

What do we know about the *GLP1R* variant?
Previous experimental evaluation



- rs10305492; Ala316Thr;MAF=1.5%)
  - SIFT, POLYPHEN, CADD: damaging

- Function uncertain from previous small studies in cell models (CHO and HEK293 cells)
  - No effect on dose response to GLP1

Fortin et al, *J Pharmacol Exp Ther* 2010

  - Lower surface expression of GLP1R
  - Reduced intracellular signalling

Koole et al, *Mol Pharmacol* 2011

How reliably can we use bioinformatic prediction of missense variant function?

PNAS

Rare variants in *PPARG* with decreased activity in adipocyte differentiation are associated with increased risk of type 2 diabetes

Amit R. Majithia[a,b,c], Jason Flannick[a], Peter Shahinian[a], Michael Guo[d], Mark-Anthony Bray[a], Pierre Fontanillas[a], Stacey B. Gabriel[a], GoT2D Consortium[2], NHGRI JHS/FHS Allelic Spectrum Project[2], SIGMA T2D Consortium[2], T2D-GENES Consortium[2], Evan D. Rosen[c,e], and David Altshuler[a,b,c,d,f,1]

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Edited[1] by Edward Scolnick, Massachusetts Institute of Technology, Cambridge, MA, and approved July 21, 2014 (received for review June 5, 2014)

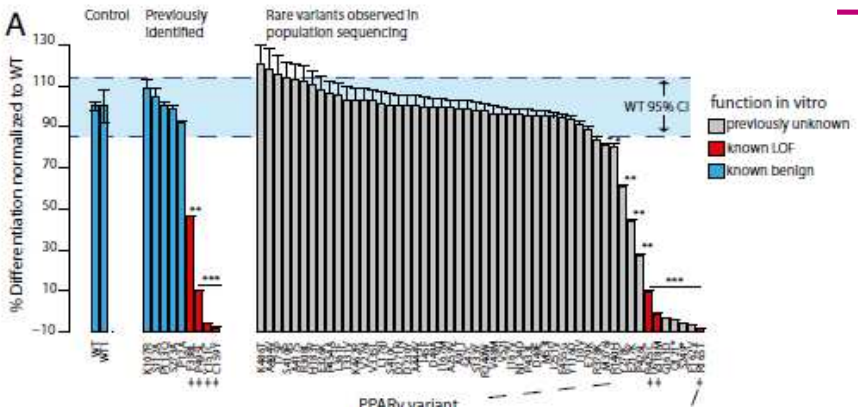


Table 1. Rare, nonsynonymous variants in *PPARG* identified from 19,752 T2D case/controls

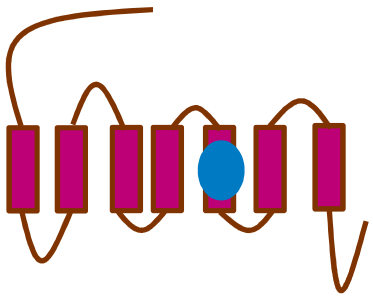
Location on chromosome 3	Base change	Amino acid change	Ancestral geography	Counts in controls	Counts in T2D cases	Bioinformatic prediction[†]	OR (95% CI)	P
12458632	G > T	A417S	European	0	1	Deleterious		
12447449	G > T	D230Y	South Asian	0	1	Deleterious		
12447410	G > A	R217K	Hispanic	0	1	Deleterious		
12458359	G > A	E326K	Hispanic	0	1	Deleterious		
12434116	T > G	F162V	European	0	1	Deleterious		
12434114	G > A	G161D	European	0	2	Deleterious		
12434179	C > T	H183Y	Hispanic	1	0	Deleterious		
12434133	C > G	I167M	European, European American	1	1	Deleterious		
12458374	A > G	I331V	South Asian	1	0	Deleterious		
12475511	A > G	K462R	Hispanic	0	1	Deleterious		
12475583	A > C	K486T	South Asian	1	1	Deleterious		
12434164	C > A	L178I	European	1	5	Deleterious		
12458466	G > C	L361F	European American	1	1	Deleterious	2.11 (0.82–5.45)	0.12
12475403	C > T	P426L	European	0	1	Deleterious		
12475486	C > G	P454A	Hispanic	4	2	Deleterious		
12422871	C > T	Q121*	European American	1	0	Deleterious		
12422929	G > A	R141H	Hispanic, African American	1	1	Deleterious		
12434126	G > C	R165T	European	0	2	Deleterious		
12447479	C > T	R240W	South Asian	1	0	Deleterious		
12458306	G > T	R308L	European	0	1	Deleterious		
12458516	G > A	R378K	European	0	1	Deleterious		
12475399	C > T	R425C	European	0	1	Deleterious		
12422908	C > A	S133Y	European	0	1	Deleterious		
12447507	C > G	S249T	European	0	1	Deleterious		
12458613	C > A	S410R	Hispanic	1	0	Deleterious		
12421260	C > G	S47C	East Asian	0	1	Deleterious		
12458335	G > A	V318M	European	0	1	Deleterious		
12447537	C > T	A259V	European American	1	0	Benign		
12458594	C > T	A404V	Hispanic	0	1	Benign		
12475457	C > T	A444V	European American	1	0	Benign		
12421391	G > A	A91T	African American	3	0	Benign		
12447572	G > A	D271N	European	0	1	Benign		
12421266	A > C	D49A	Hispanic	1	0	Benign		
12421267	T > G	D49E	African American	2	2	Benign		
12475490	A > G	E455G	European American	1	0	Benign		
12421355	G > A	E79K	European, East Asian	1	4	Benign		
12393119	A > G	I10V	South Asian	1	1	Benign		
12434131	A > G	I167V	European	0	1	Benign		
12447512	A > G	I251V	Hispanic	0	1	Benign		
12421253	A > T	I45F	African American	3	0	Benign		
12458511	G > A	M378I	European	0	2	Benign		
12421279	G > A	M53I	South Asian	1	0	Benign		
12422880	A > G	N124D	South Asian	1	0	Benign		
12475424	C > T	P433L	Hispanic, European	0	2	Benign		
12458611	A > T	S410C	European	0	1	Benign		
12421343	A > C	T75P	Hispanic	1	3	Benign		
12458209	G > A	V276I	European, Hispanic, African American, East Asian	5	6	Benign		
12458386	G > C	V335L	African American, Hispanic	11	9	Benign		
12421262	G > A	V48M	European American	1	0	Benign		
12421274	G > A	V52I	African American, East Asian, European	3	2	Benign		
12422856	T > G	Y116D	South Asian	1	0	Benign		
12458216	A > G	Y278C	European	0	1	Benign		

The variant position is based on human genome build NCB136/hg18, and the amino acid position is based on the NCBI protein reference sequence NP_005028.4. Release notes for this genome build are available at www.ncbi.nlm.nih.gov/genome/guide/human/release_notes.html#b36. CI, confidence interval.

*Stop codon.

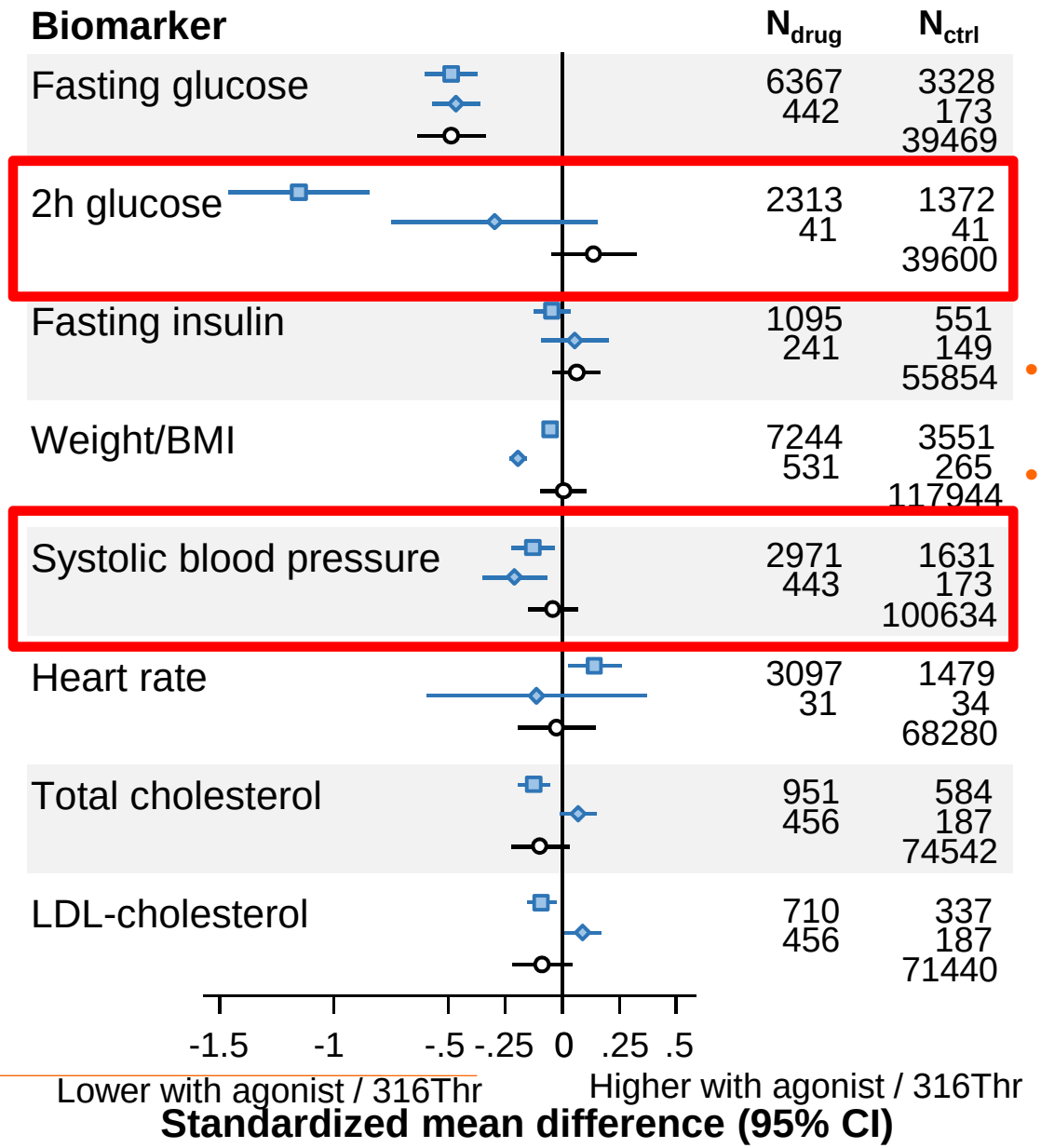
[†]Criteria for deleterious: A variant must have a mammalian conservation LOD score >10 and be categorized as damaging by Condel (17) (*Methods*).

What do we know about the *GLP1R* variant?
Human, mouse and trial data



- Minor allele = lower fasting glucose
- Agonist = lower fasting glucose
- GLP1R KO mouse is hyperglycaemic
- Human loss of function variants (LoF) too rare to allow any inference
- **Minor allele = gain of function?**

Ala316Thr compared to GLP1R-agonists



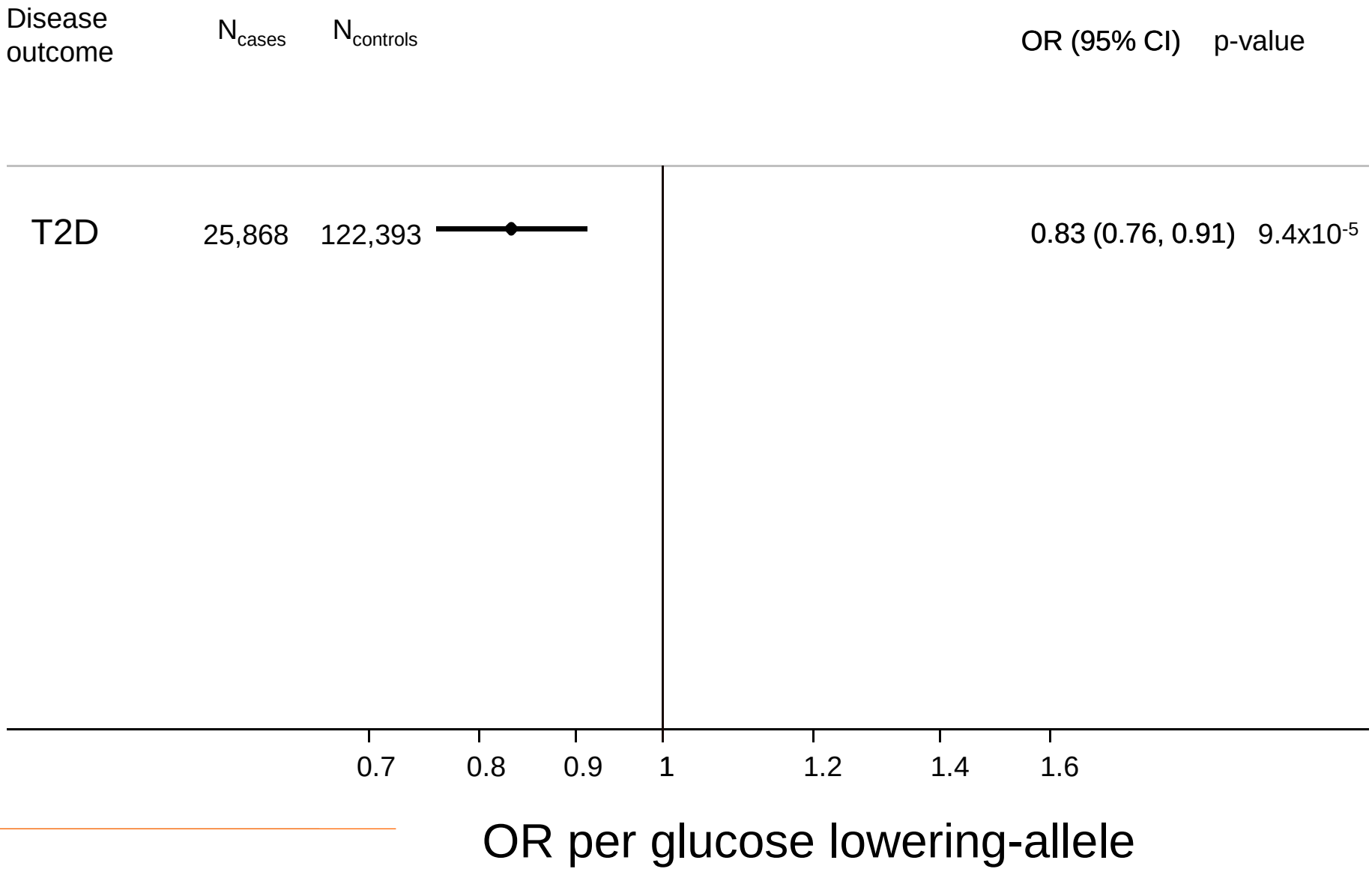
GLP1R agonists in T2D patients

GLP1R agonists in Non-diabetics

Genetic variant, per 3.3 alleles (*rescaled to match FG effect of GLP1R agonists*)

- Effects on non-glycaemic traits smaller than glycaemic
- Effects consistent between drug/variant
  - Different for 2hGlu (T2D), and weight (non-T2D)
    - Physiology vs pathophysiology
  - Unable to detect difference for others (low power)
  - Good instrument?

GLP1R Ala316Thr associations



Aim 2: evaluate safety profile and opportunities for repositioning

Discovery

Exome sequencing of genes encoding targets of relevance to obesity/T2D ($N \leq 11{,}806$) – tested 6 genes for association with T2D/obesity and related phenotypes

Replication

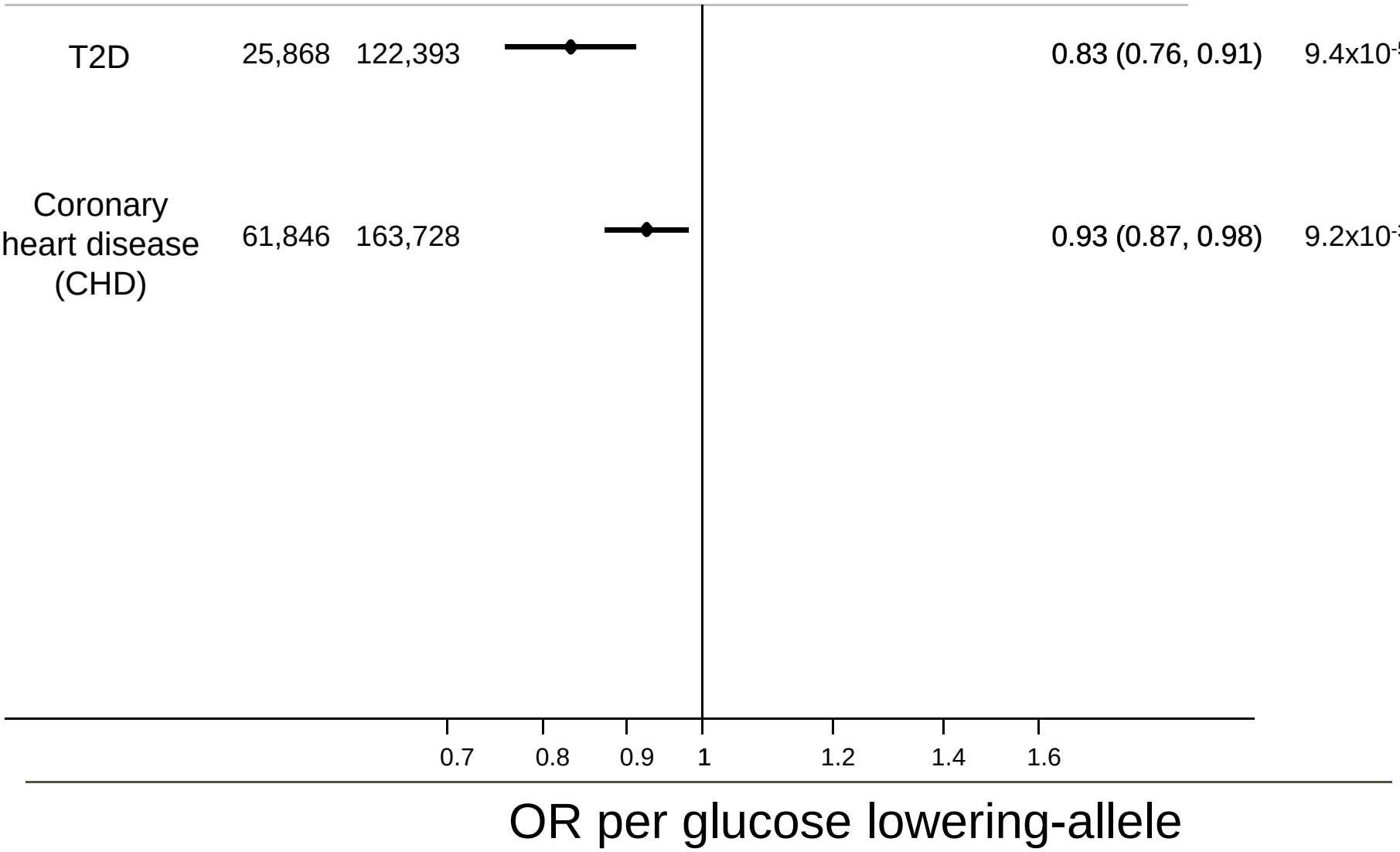
Targeted genotyping of promising variants ($N \leq 39{,}979$)
In silico analysis where possible ($N \leq 70{,}242$)
$\alpha = 3.8 \times 10^{-5}$

Follow up

Analyses of replicated variants to evaluate risk profile for a range of traits and diseases ($N \leq 225{,}574$)

GLP1R Ala316Thr associations

Disease outcome	N_{cases}	$N_{controls}$	OR (95% CI)	P-value
T2D	25,868	122,393	0.83 (0.76, 0.91)	9.4×10^{-5}
Coronary heart disease (CHD)	61,846	163,728	0.93 (0.87, 0.98)	9.2×10^{-3}



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Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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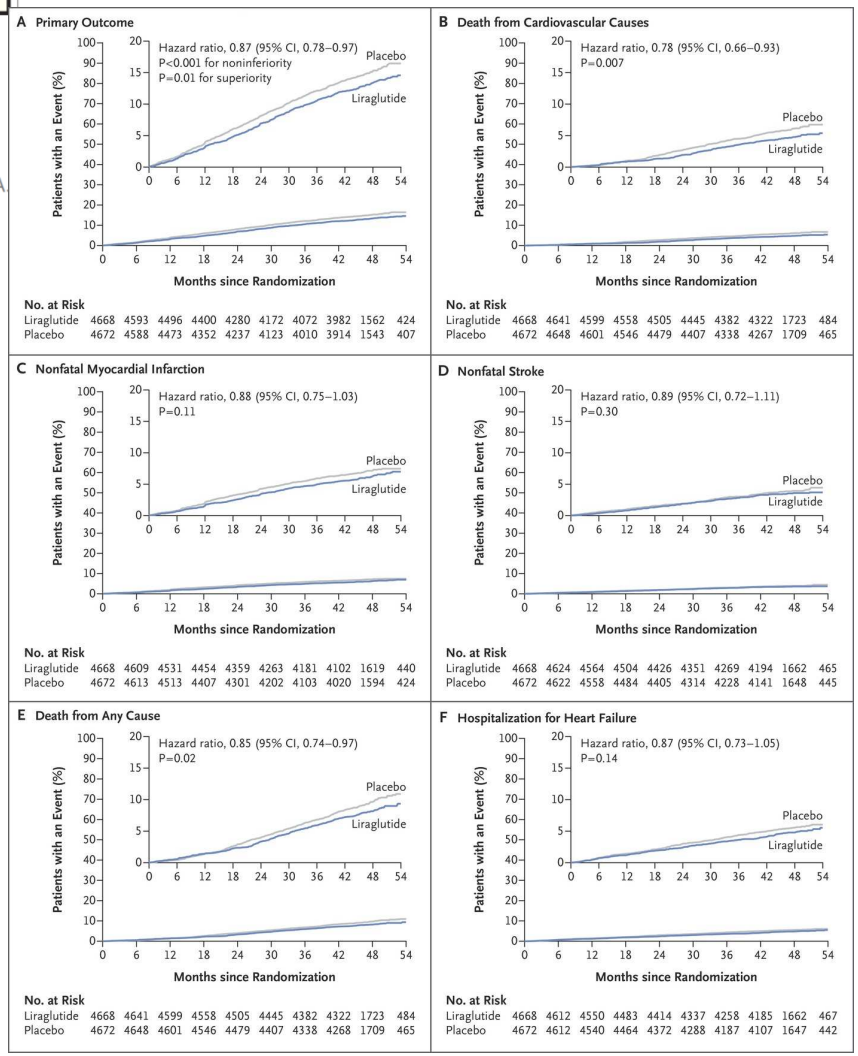
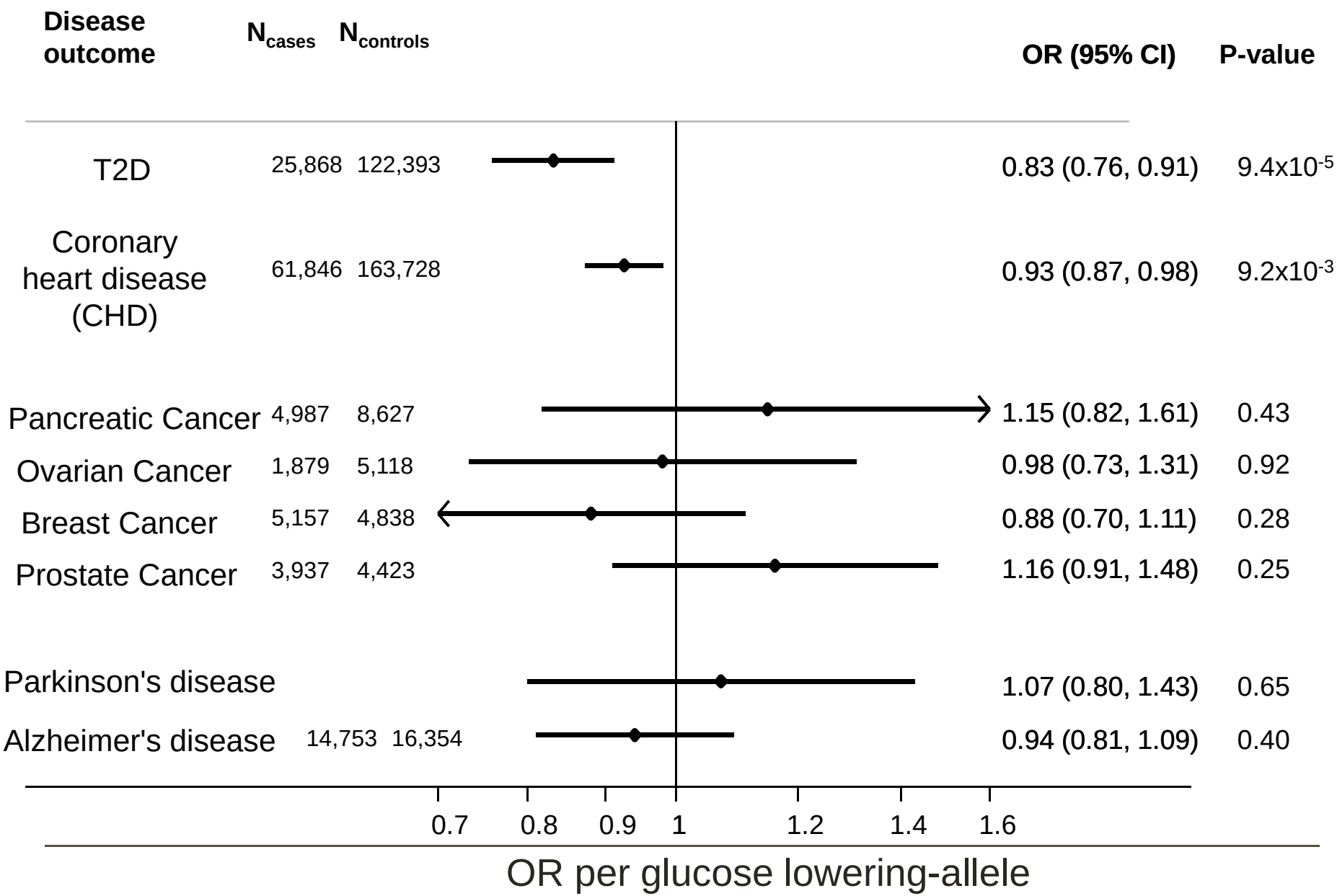
for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*



- Genetic **prediction** supported trial finding of cardiovascular safety
- Provides further support for utility of genetics in target validation, if we have
  - the right variants
  - the right outcomes

Opportunities for alternative indications?



Conclusions

- Systematic approach: missense variant in *GLP1R* associated with
  - lower fasting glucose and lower risk of T2D
  - lower risk of coronary heart disease - increasing confidence in cardiovascular safety of GLP-1R agonists
    - Prediction later supported by trial data

- Further demonstrates potential in leveraging human genetics to inform therapeutics
  - Highlights the challenges involved, including the scale of data and collaboration required
  - Months of negotiation required to access results
  - Move toward results sharing and large biobanks with deep phenotyping and genetic data likely to enable

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