Genomic Variation and Disease

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Observation: disease clusters in families

If you have type 2 diabetes, what is the risk to:

Your neighbor (unrelated)?	≈10%
Your sibling?	≈30%
Your identical twin?	>80%

Variation in DNA sequence influences risk

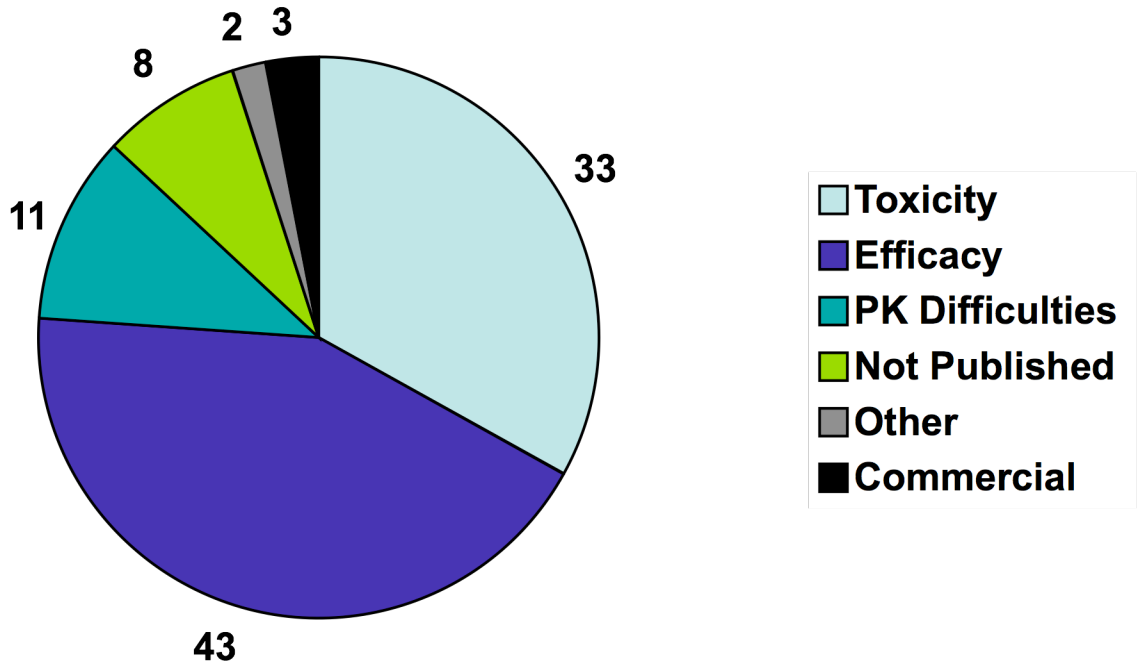
What are the pathways responsible?

Why study *inheritance* of disease?

To discover and validate pathways
(in my mind, uniquely powerful)

To predict disease risk
(one of many factors)

Why Drugs Fail: 1992 - 2002*

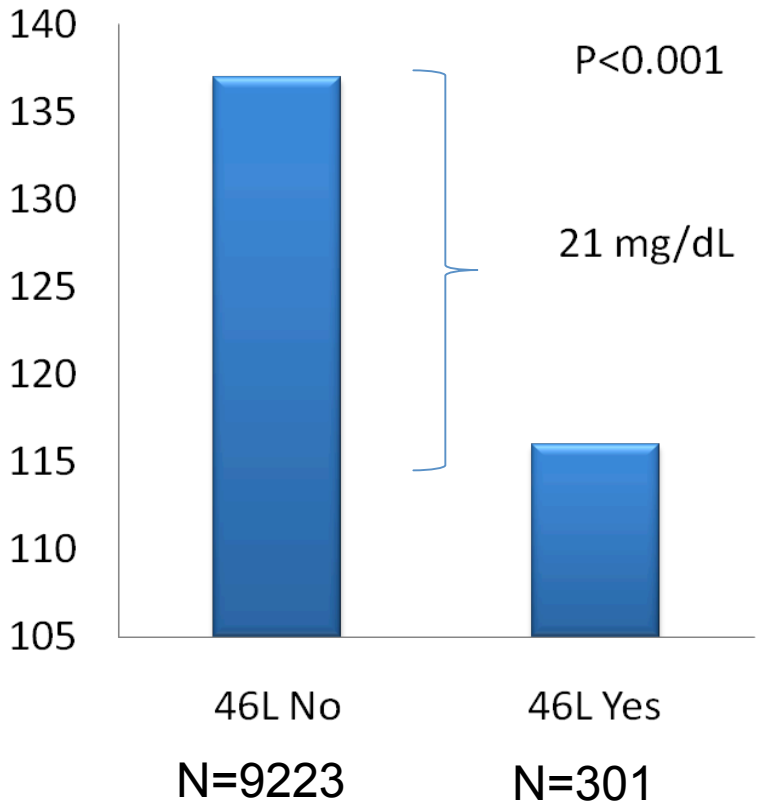


Projects Terminated in Clinical Phases 1 - 3, n=73

*Schuster *et al.,* Curr Pharm Des. 2005;11(27):3545-59;
Thanks to Robert Gould

PCSK9, LDL and coronary artery disease

Lipids



Outcome

Hazard Ratio for incident CHD:

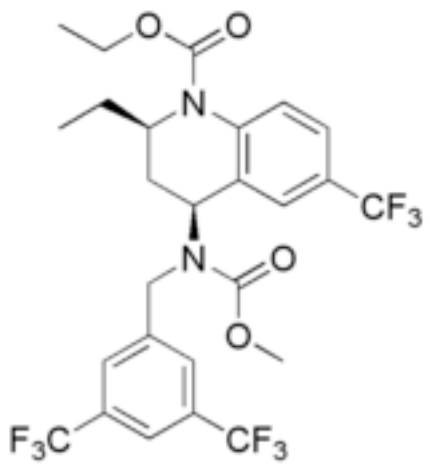
0.50 (0.32 – 0.79)

P=0.003

1108 events/9524

Cohen, *N Engl J Med* 2006

CETP, HDL and coronary heart disease



Torcetrapib

The NEW ENGLAND JOURNAL of MEDICINE

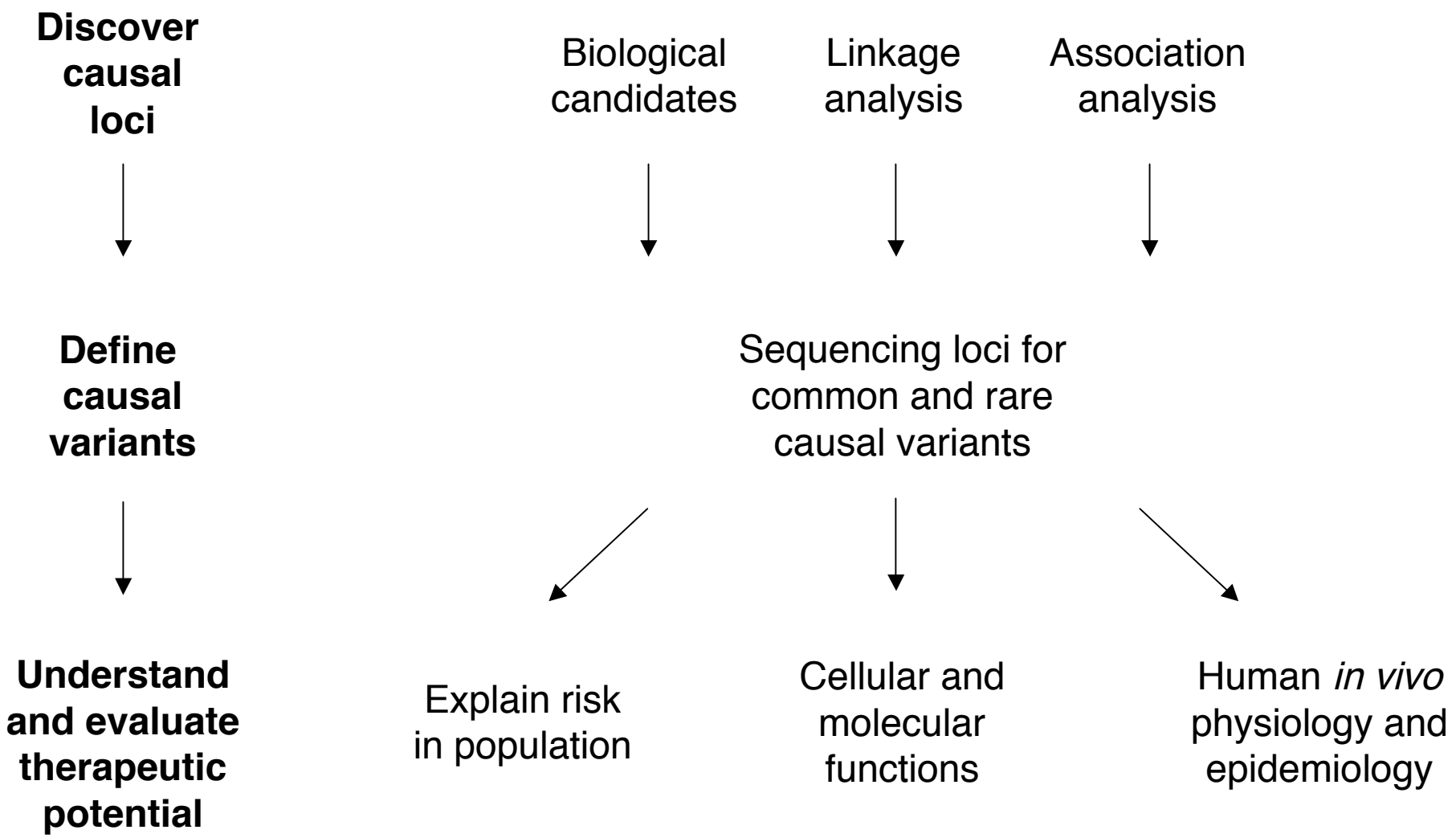
ORIGINAL ARTICLE

Effects of an Inhibitor of Cholesteryl Ester Transfer Protein on HDL Cholesterol

Margaret E. Brousseau, Ph.D., Ernst J. Schaefer, M.D., Megan L. Wolfe, B.S., LeAnne T. Bloedon, M.S., R.D., Andres G. Digenio, M.D., Ph.D., Ronald W. Clark, M.S., James P. Mancuso, Ph.D., and Daniel J. Rader, M.D.

Goals (a personal list)

- Identify mechanisms whereby *in vivo* perturbation in humans alters risk of disease
  - Phenotype-driven genome screening
  - Mendelian randomization to establish causality
- Exploit this information to illuminate disease pathophysiology and therapeutic potential
- Evaluate genetic testing for utility in clinical care


Discover causal loci
Biological candidates
Linkage analysis
Association analysis
Define causal variants
Sequencing loci for common and rare causal variants
Understand and evaluate therapeutic potential
Explain risk in population
Cellular and molecular functions
Human *in vivo* physiology and epidemiology

Systematic association testing of common human genetic variation

- Databases of common sequence variants
  - SNPs, haplotypes
  - Copy number variants
- Laboratory tools to test comprehensively
- Analytical methods to interpret the results

Progress identifying common variants that influence risk of common diseases

Cholesterol
Obesity
Myocardial infarction
QT interval
Atrial Fibrilliation
Type 2 Diabetes
Prostate cancer
Breast cancer
Colorectal cancer
Height
Uric Acid

Age Related Macular Degeneration
Crohns Disease
Type 1 Diabetes
Systemic Lupus Erythematosus
Asthma
Restless leg syndrome
Gallstone disease
Multiple sclerosis
Rheumatoid arthritis
Glaucoma
Celiac Disease

FGFR2 TBL2 ITGAM
TNRC9 TRIB1 BLK
MAP3K1 KCTD10 HMGA2
LSP1 ANGLPT3 GDF5-UQ(C
8q24 GRIN3A HMPG
CDKN2B/A MEIS1 CRAC1
8q24 (n=6) LBXCOR JAZF1
ATG16L1 BTBD9 CDC123
5p13 C3 ADAMTS9
10q21 8q24 THADA
IRGM ORMDL3 WSF1
NKX2-3 4q25 LOXL1
IL12B TCF2 GLUT9
3p21 GCKR L7R
1q24 FTO TRAF1/C5
PTPN2 C12orf30 STAT4
TCF2 ERBB3 4q27
CDKN2B/A KIAA0350 ABCG8
IGF2BP2 CD226 MLXIPL
CDKAL1 16p13 GALNT2
HHEX PTPN2 PSRC1
SLC30A8 SH2B3 NCAN

NOS1AP
IFIH1
PCSK9
CFB/C2
LOC387715
8q24
IL23R
TCF7L2

CD25
IRF5
PCSK9
CFH

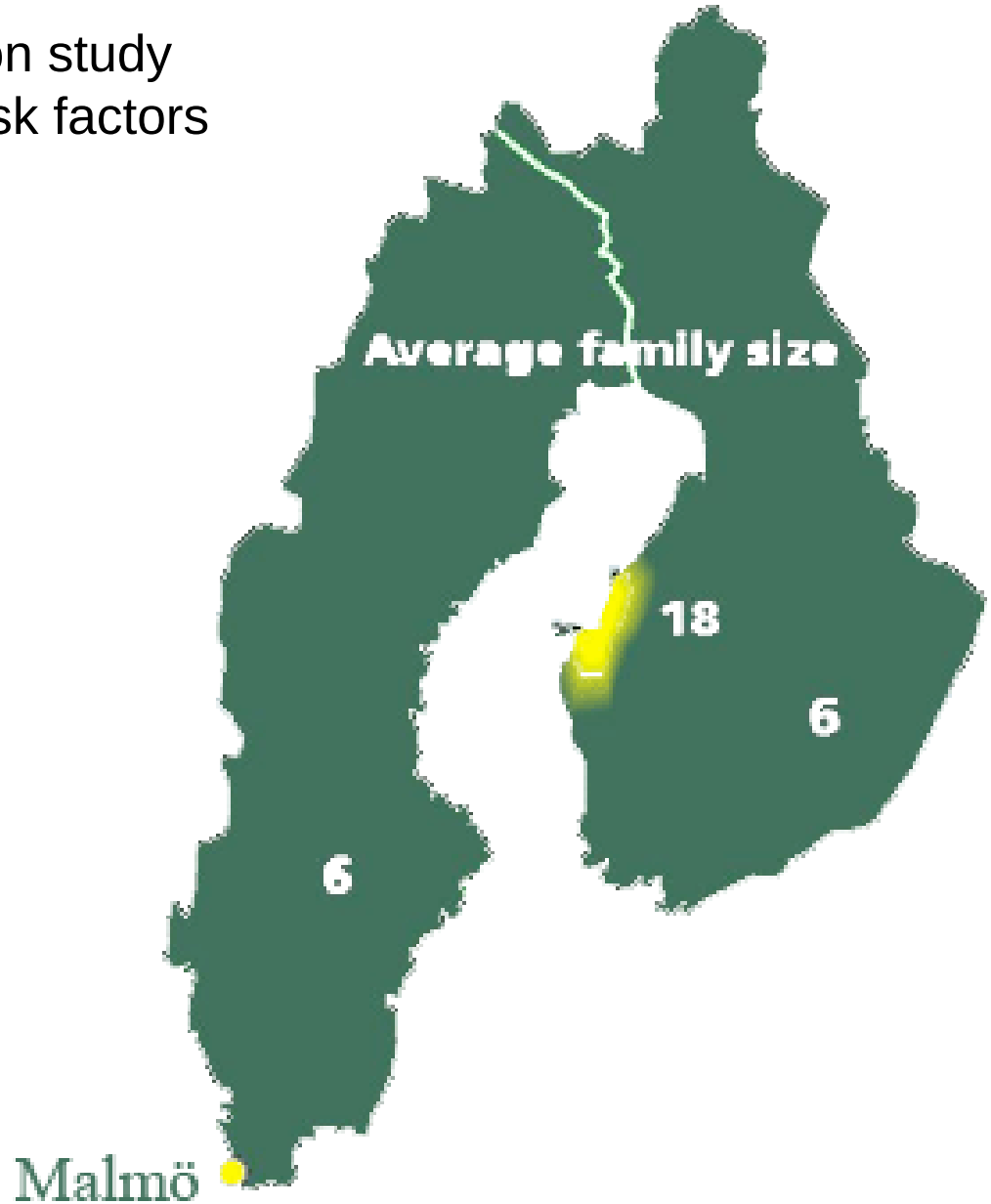
IBD5
NOD2

PPARγ
CTLA4
KCNJ11
PTPN22

2000 2001 2002 2003 2004 2005 2006 2007

Whole genome association study
T2D, 18 cardiovascular risk factors

1,464 participants with T2D
1,467 euglycemic controls



A genome-wide association study identifies novel risk loci for type 2 diabetes

Robert Sladek[1,2,4], Ghislain Rocheleau[1*], Johan Rung[4*], Christian Dina[5*], Lishuang Shen[1], David Serre[1], Philippe Boutin[5], Daniel Vincent[4], Alexandre Belisle[4], Samy Hadjadj[6], Beverley Balkau[7], Barbara Heude[7], Guillaume Charpentier[8], Thomas J. Hudson[4,9], Alexandre Montpetit[4], Alexey V. Pshezhetsky[10], Marc Prentki[10,11], Barry I. Posner[2,12], David J. Balding[13], David Meyre[5], Constantin Polychronakos[1,3] & Philippe Froguel[5,14]

A variant in *CDKAL1* influences insulin response and risk of type 2 diabetes

Valgerdur Steinthorsdottir[1,15], Gudmar Thorleifsson[1,15], Inga Reynisdottir[1], Rafn Benediktsson[2,3], Thorbjorg Jonsdottir[1], G Bragi Walters[1], Unnur Styrkarsdottir[1], Solveig Gretarsdottir[1], Valur Emilsson[1], Shyamali Ghosh[1], Adam Baker[1], Steinunn Snorradottir[1], Hjordis Bjarnason[1], Maggie C Y Ng[4], Torben Hansen[5], Yu Bagger[6], Robert L Wilensky[7], Muredach P Reilly[7], Adebowale Adeyemo[8], Yuanxiu Chen[8], Jie Zhou[8], Vilmundur Gudnason[3], Guanjie Chen[8], Hanxia Huang[8], Kerrie Lashley[8], Ayo Doumatey[8], Wing-Yee So[4], Ronald C Y Ma[4], Gitte Andersen[5], Knut Borch-Johnsen[5,9,10], Torben Jorgensen[10], Jana V van Vliet-Ostaptchouk[11], Marten H Hofker[11,12], Cisca Wijmenga[13,14], Claus Christiansen[6], Daniel J Rader[7], Charles Rotimi[8], Mark Gurney[1], Juliana C N Chan[4], Oluf Pedersen[5,9],Gunnar Sigurdsson[2,3], Jeffrey R Gulcher[1], Unnur Thorsteinsdottir[1], Augustine Kong[1] & Kari Stefansson[1]

Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels

Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes for BioMedical Research*†

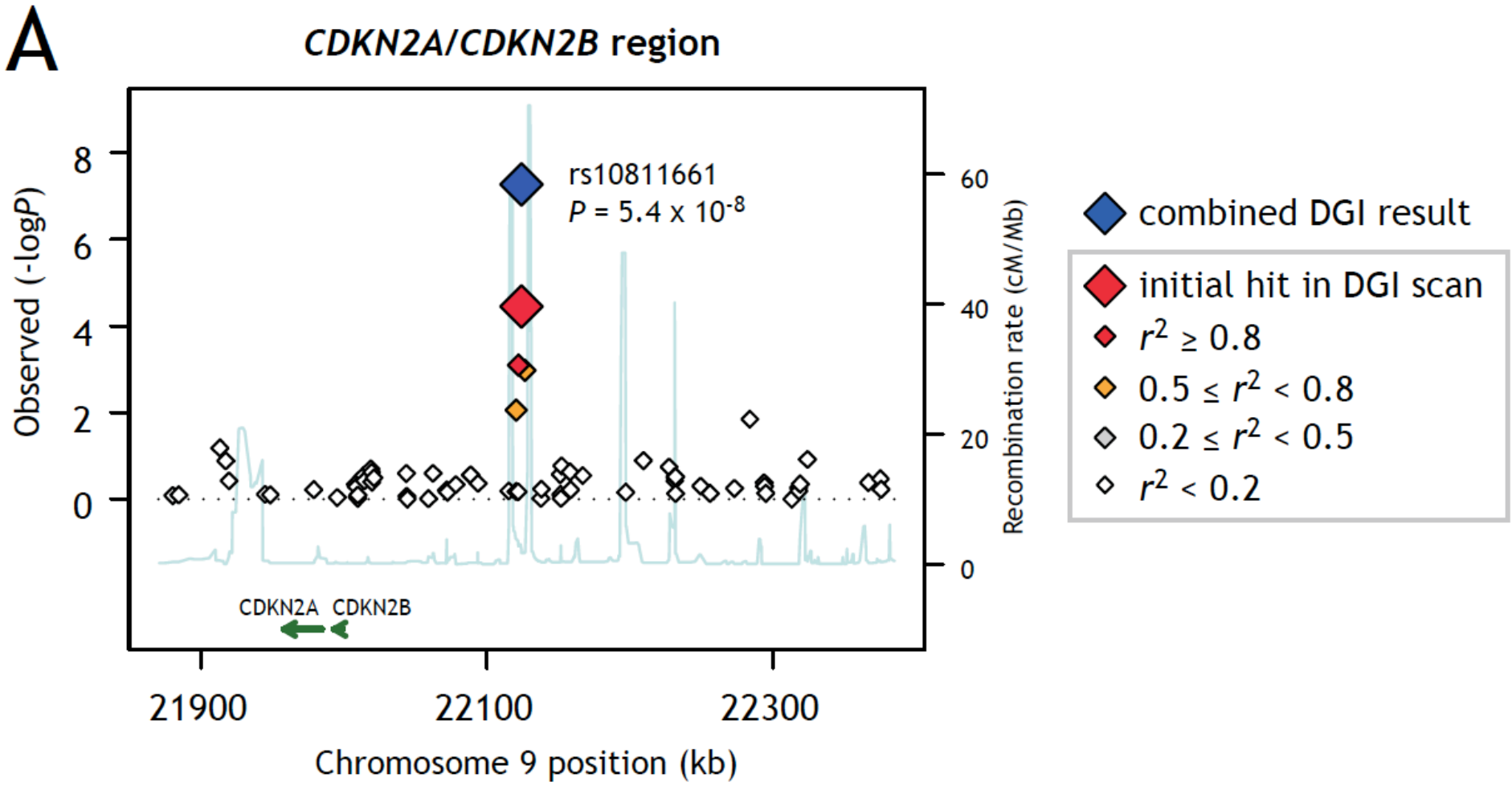
Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes

Eleftheria Zeggini,[1,2*] Michael N. Weedon,[3,4*] Cecilia M. Lindgren,[1,2*] Timothy M. Frayling,[3,4*] Katherine S. Elliott,[2] Hana Lango,[3,4] Nicholas J. Timpson,[2,5] John R. B. Perry,[3,4] Nigel W. Rayner,[1,2] Rachel M. Freathy,[3,4] Jeffrey C. Barrett,[2] Beverley Shields,[4] Andrew P. Morris,[2] Sian Ellard,[4,6] Christopher J. Groves,[1] Lorna W. Harries,[4] Jonathan L. Marchini,[7] Katharine R. Owen,[1] Beatrice Knight,[4] Lon R. Cardon,[2] Mark Walker,[8] Graham A. Hitman,[9] Andrew D. Morris,[10] Alex S. F. Doney,[10] The Wellcome Trust Case Control Consortium (WTCCC),† Mark I. McCarthy,[1,2‡§] Andrew T. Hattersley[3,4‡]

A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

Laura J. Scott,[1] Karen L. Mohlke,[2] Lori L. Bonnycastle,[3] Cristen J. Willer,[1] Yun Li,[1] William L. Duren,[1] Michael R. Erdos,[3] Heather M. Stringham,[1] Peter S. Chines,[3] Anne U. Jackson,[1] Ludmila Prokunina-Olsson,[3] Chia-Jen Ding,[1] Amy J. Swift,[3] Narisu Narisu,[3] Tianle Hu,[1] Randall Pruim,[4] Rui Xiao,[1] Xiao-Yi Li,[1] Karen N. Conneely,[1] Nancy L. Riebow,[3] Andrew G. Sprau,[3] Maurine Tong,[3] Peggy P. White,[1] Kurt N. Hetrick,[5] Michael W. Barnhart,[5] Craig W. Bark,[5] Janet L. Goldstein,[5] Lee Watkins,[5] Fang Xiang,[1] Jouko Saramies,[6] Thomas A. Buchanan,[7] Richard M. Watanabe,[8,9] Timo T. Valle,[10] Leena Kinnunen,[10,11] Gonçalo R. Abecasis,[1] Elizabeth W. Pugh,[5] Kimberly F. Doheny,[5] Richard N. Bergman,[9] Jaakko Tuomilehto,[10,11,12] Francis S. Collins,[3*] Michael Boehnke[1*]

Example: common SNP at 9p21
125-kb from *CDKN2B/A*



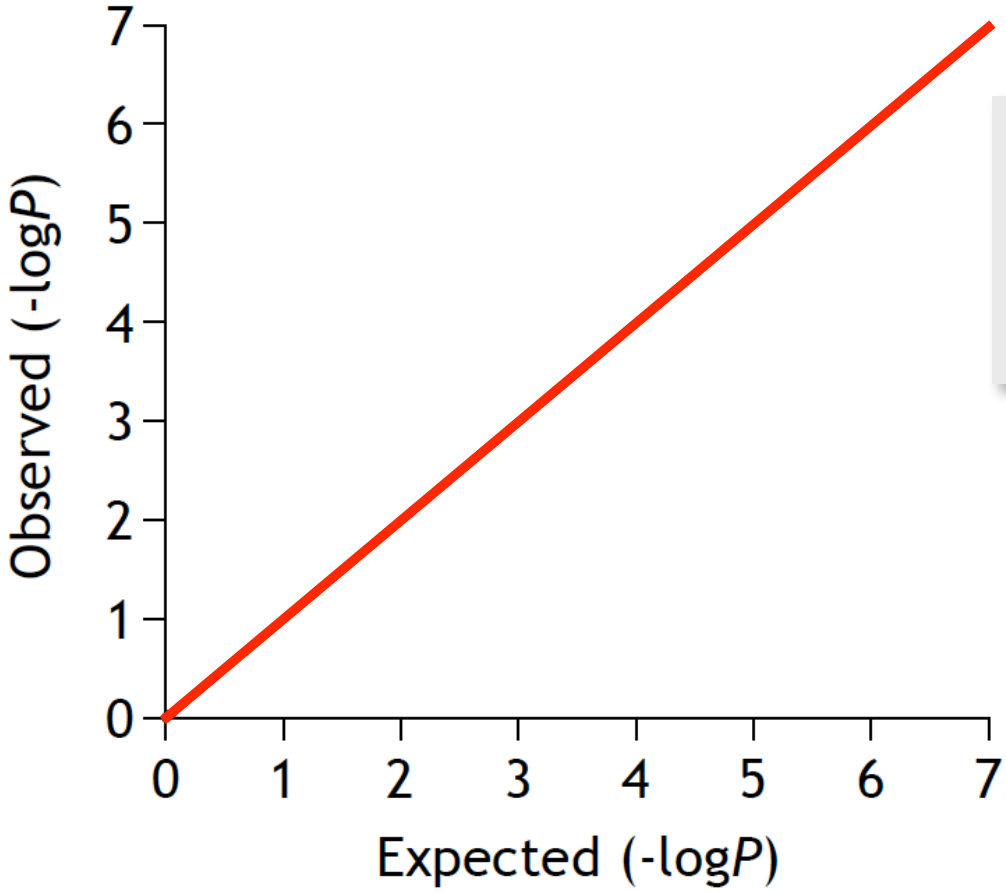
"Associated" with T2D,
or "influencing" T2D?

Association is locus-specific
and phenotype-dependent

"Associated" with T2D,
or "influencing" T2D?

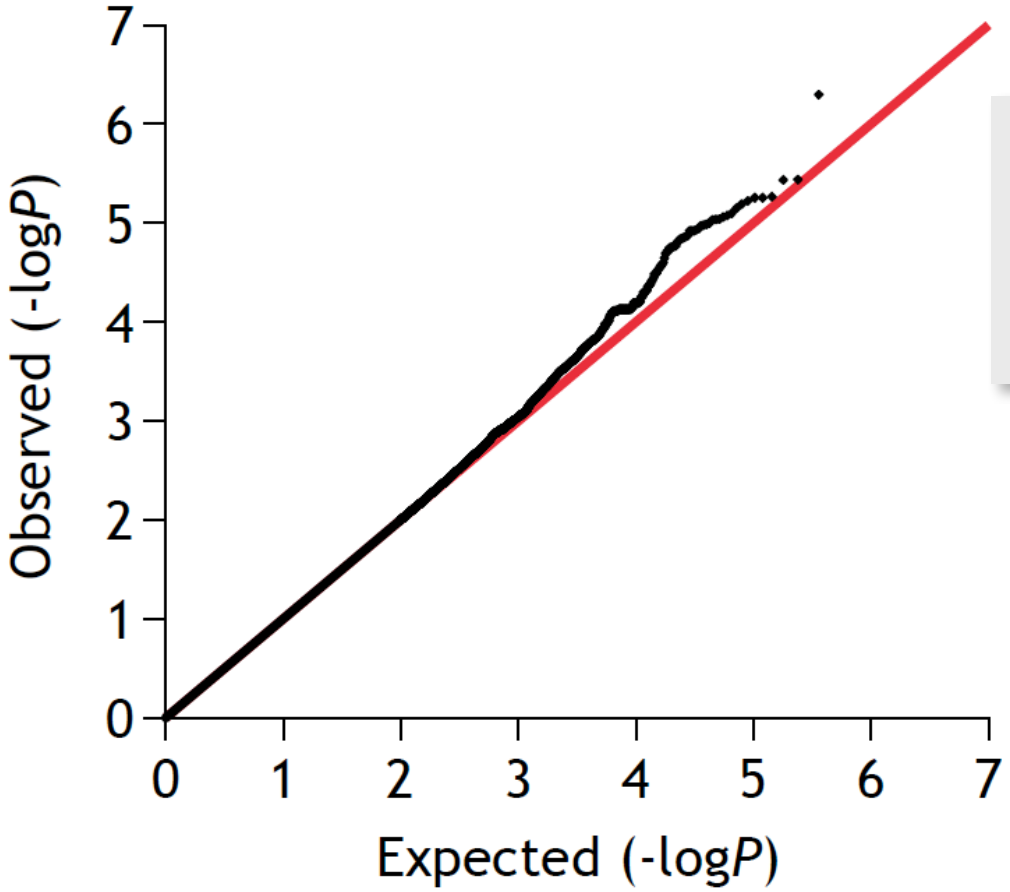
Genotypes are assigned at conception
unaltered by the disease process
and follow a null distribution

T2D *P*-value distribution: expected vs. observed



expected distribution under the null hypothesis

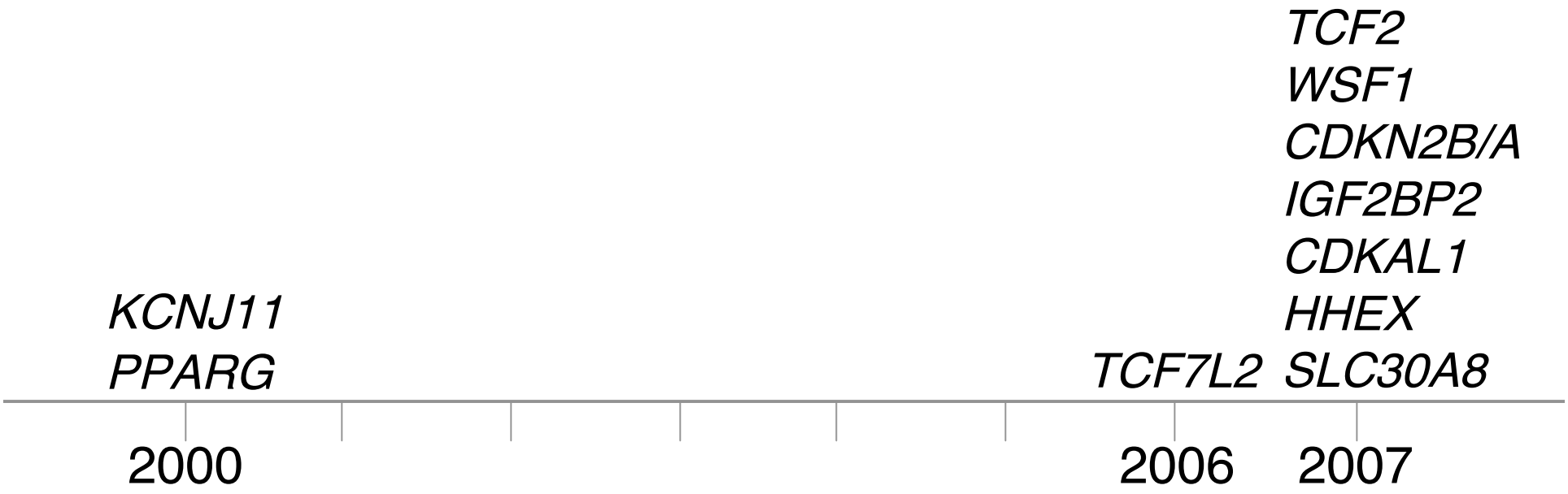
T2D *P*-value distribution: expected vs. observed



observed distribution in the WGAS data

Stringent quality control,
appropriate statistical thresholds,
and strong replication
are absolutely required
in any genome-scale screen

Ten confirmed loci at which common variants associate with risk of type 2 diabetes



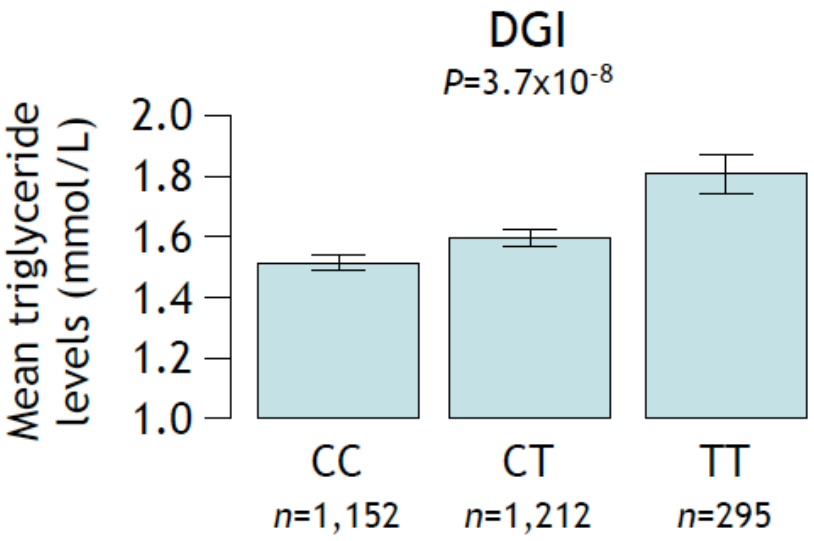
18 additional traits examined for association

- Insulin/Glucose:
  - Fasting glucose
  - Insulinogenic index
  - HOMA-IR
- Anthropometric:
  - BMI
  - Weight
  - Height
  - Waist hip ratio
  - Waist circumference
- Cardiovascular:
  - Systolic blood pressure
  - Diastolic blood pressure
  - Hypertension
  - LDL cholesterol
  - HDL cholesterol
  - Triglycerides
  - Triglyceride/HDL ratio
  - ApoA1
  - ApoA2
  - ApoB

Lipid loci exceeding genome-wide significance in the DGI study

LDL	HDL	TG
APOE cluster	CETP	GCKR

GCKR is a novel locus for triglyceride levels



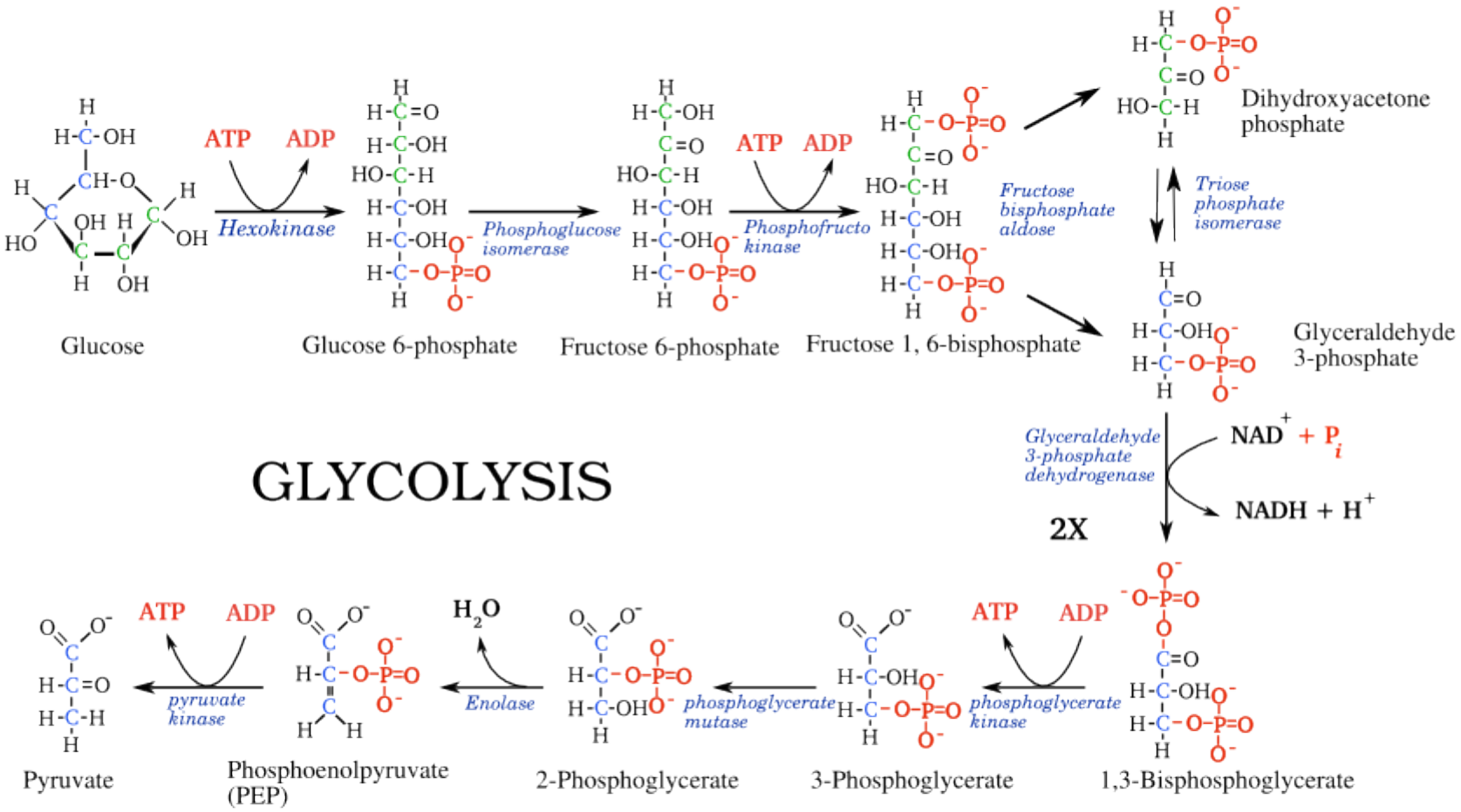
rs780094 (MAF=35%)

Replication in 5,217 Swedish individuals from Malmö Diet and Cancer –Cardiovascular Cohort:

$P = 8.7 \times 10^{-8}$

Combined $P < 10^{-13}$

Glucokinase (*GCK*) and *GCKR*



In liver, GCK activity regulated by GCKR binding

Lessons from epidemiology and physiology

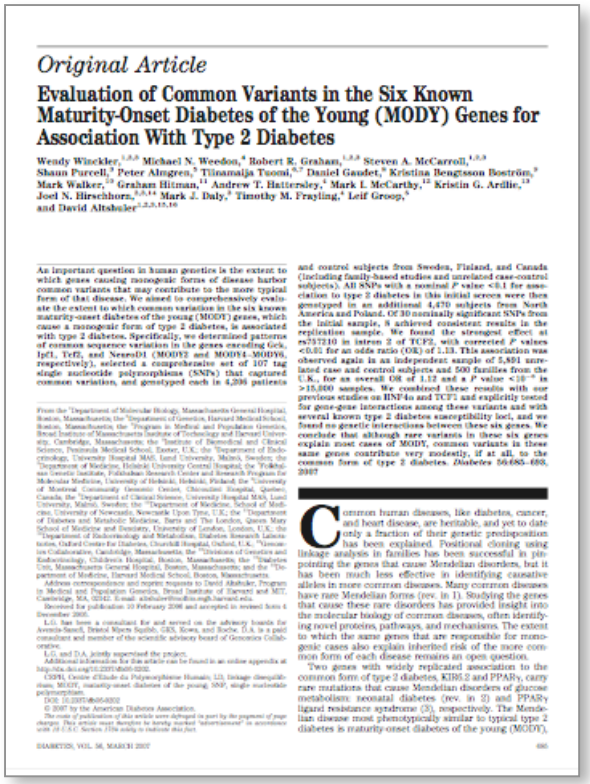
Type 2 diabetes and heart attack: 9p21

Type 2 diabetes
Odds ratio = 1.20
Risk allele frequency = 83%

Coronary heart disease/heart attack
Odds ratio = 1.26
Homozygote OR = 1.64
Risk allele frequency = 50%

Helgadottir et al., Science (2007)
McPherson et al., Science (2007)
WTCCC, Nature (2007)

T2D and prostate cancer: TCF2



Original Article

Evaluation of Common Variants in the Six Known Maturity-Onset Diabetes of the Young (MODY) Genes for Association With Type 2 Diabetes

Wendy Winckler,[1,2,3] Michael N. Weedon,[4] Robert B. Graham,[1,2,3] Steven A. McCarroll,[1,2,3] Shaun Purcell,[3] Peter Almgren,[5] Tiinamaija Tuomi,[6,7] Daniel Gaudet,[8] Kristina Bengtsson Boström,[9] Mark Walker,[10] Graham Hitman,[11] Andrew T. Hattersley,[4] Mark I. McCarthy,[12] Kristin G. Ardlie,[13] Joel N. Hirschhorn,[2,3,14] Mark J. Daly,[3] Timothy M. Frayling,[4] Leif Groop,[5] and David Altshuler[1,2,3,15,16]

An important question in human genetics is the extent to which genes causing monogenic forms of disease harbor common variants that may contribute to the more typical form of that disease. We aimed to comprehensively evaluate the extent to which common variation in the six known maturity-onset diabetes of the young (MODY) genes, which cause a monogenic form of type 2 diabetes, is associated with type 2 diabetes. Specifically, we determined patterns of common sequence variation in the genes encoding Gck, Hpf1, Tcf2, and Neurod1 (MODY2 and MODY4–MODY6, respectively), selected a comprehensive set of 107 tag single nucleotide polymorphisms (SNPs) that captured common variation, and genotyped each in 4,206 patients and control subjects from Sweden, Finland, and Canada (including family-based studies and unrelated case-control subjects). All SNPs with a nominal P value <0.1 for association to type 2 diabetes in this initial screen were then genotyped in an additional 4,470 subjects from North America and Poland. Of 30 nominally significant SNPs from the initial sample, 8 achieved consistent results in the replication sample. We found the strongest effect at rs757210 in intron 2 of TCF2, with corrected P values <0.01 for an odds ratio (OR) of 1.13. This association was observed again in an independent sample of 5,891 unrelated case and control subjects and 500 families from the U.K., for an overall OR of 1.12 and a P value $<10^{-6}$ in >15,000 samples. We combined these results with our previous studies on HNF4α and TCF1 and explicitly tested for gene-gene interactions among these variants and with several known type 2 diabetes susceptibility loci, and we found no genetic interactions between these six genes. We conclude that although rare variants in these six genes explain most cases of MODY, common variants in these same genes contribute very modestly, if at all, to the common form of type 2 diabetes. *Diabetes* 56:685–693, 2007

Common human diseases, like diabetes, cancer, and heart disease, are heritable, and yet to date only a fraction of their genetic predisposition has been explained. Positional cloning using linkage analysis in families has been successful in pinpointing the genes that cause Mendelian disorders, but it has been much less effective in identifying causative alleles in more common diseases. Many common diseases have rare Mendelian forms (rev. in 1). Studying the genes that cause these rare disorders has provided insight into the molecular biology of common diseases, often identifying novel proteins, pathways, and mechanisms. The extent to which the same genes that are responsible for monogenic cases also explain inherited risk of the more common form of each disease remains an open question.

Two genes with widely replicated association to the common form of type 2 diabetes, KIR6.2 and PPARγ, carry rare mutations that cause Mendelian disorders of glucose metabolism: neonatal diabetes (rev. in 2) and PPARγ ligand resistance syndrome (3), respectively. The Mendelian disease most phenotypically similar to typical type 2 diabetes is maturity-onset diabetes of the young (MODY),

LETTERS

nature genetics

Two variants on chromosome 17 confer prostate cancer risk, and the one in *TCF2* protects against type 2 diabetes

Julius Gudmundsson[1,30], Patrick Sulem[1,30], Valgerdur Steinthorsdottir[1], Jon T Bergthorsson[1], Gudmar Thorleifsson[1], Andrei Manolescu[1], Thorunn Rafnar[1], Daniel Gudbjartsson[1], Bjarni A Agnarsson[2], Adam Baker[1], Asgeir Sigurdsson[1], Kristrun R Benediktsdottir[2], Margret Jakobsdottir[1], Thorarinn Blondal[2], Simon N Stacey[1], Agnar Helgason[1], Steinunn Gunnarsdottir[1], Adalheidur Olafsdottir[1], Kari T Kristinsson[2], Birgitta Birgisdottir[1], Shyamali Ghosh[1], Steinunn Thorlacius[1], Dana Magnusdottir[1], Gerdur Stefansdottir[1], Kristleifur Kristjansson[1], Yu Bagger[3], Robert L Wilensky[4], Muredach P Reilly[4], Andrew D Morris[5], Charlotte H Kimber[6], Adebowale Adeyemo[7], Yuanxiu Chen[7], Jie Zhou[7], Wing-Yee So[8], Peter C Y Tong[8], Maggie C Y Ng[8], Torben Hansen[9], Gitte Andersen[9], Knut Borch-Johnsen[9–11], Torben Jorgensen[11], Alejandro Tres[12,13], Fernando Fuertes[14], Manuel Ruiz-Echarri[12], Laura Asin[13], Berta Saez[13], Erica van Boven[15], Siem Klaver[16], Dorine W Swinkels[16], Katja K Aben[17], Theresa Graif[18], John Cashy[18], Brian K Suarez[19], Onco van Vierssen Trip[20], Michael L Frigge[1], Carole Ober[21], Marten H Hofker[22,23], Cisca Wijmenga[24,25], Claus Christiansen[3], Daniel J Rader[4], Colin N A Palmer[6], Charles Rotimi[7], Juliana C N Chan[8], Olof Pedersen[9,10], Gunnar Sigurdsson[26,27], Rafn Benediktsson[26,27], Eirikur Jonsson[28], Gudmundur V Einarsson[28], Jose I Mayordomo[12,13], William J Catalona[18], Lambertus A Kiemeney[29], Rosa B Barkardottir[2], Jeffrey R Gulcher[1], Unnur Thorsteinsdottir[1], Augustine Kong[1] & Kari Stefansson[1]

We performed a genome-wide association scan to search for sequence variants conferring risk of prostate cancer using 1,501 Icelandic men with prostate cancer and 11,290 controls. Follow-up studies involving three additional case-control groups replicated an association of two variants on chromosome 17 with the disease. These two variants, 33 Mb apart, fall within a region previously implicated by family-based linkage studies on prostate cancer. The risks conferred by these variants are moderate individually (allele odds ratio of about 1.20), but because they are common, their joint population attributable risk is substantial. One of the variants is in *TCF2* (*HNF1β*), a gene known to be mutated in individuals with maturity-onset diabetes of the young type 5. Results from eight case-control groups, including one West African and one Chinese, demonstrate that this variant confers protection against type 2 diabetes.

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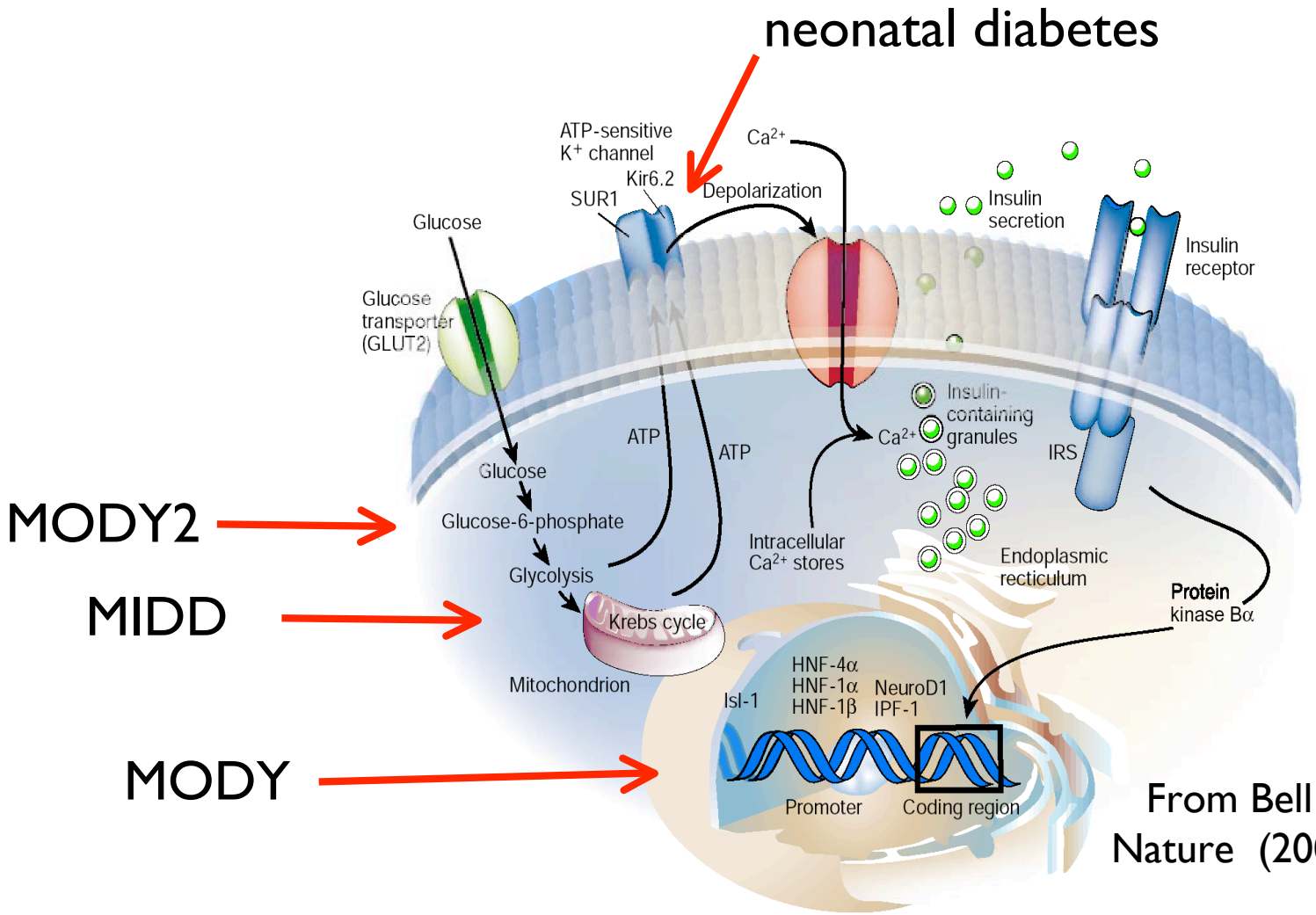
Received 21 March; accepted 8 May; published online 1 July 2007; doi:10.1038/ng2062

See also Bonnycastle et al., Diabetes (2006)

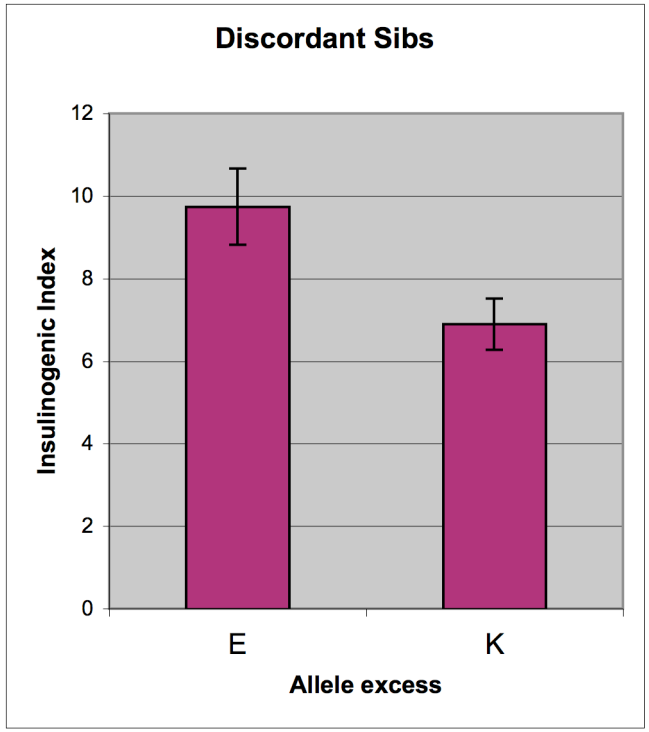
Mendelian and common T2D variants also decrease insulin secretion



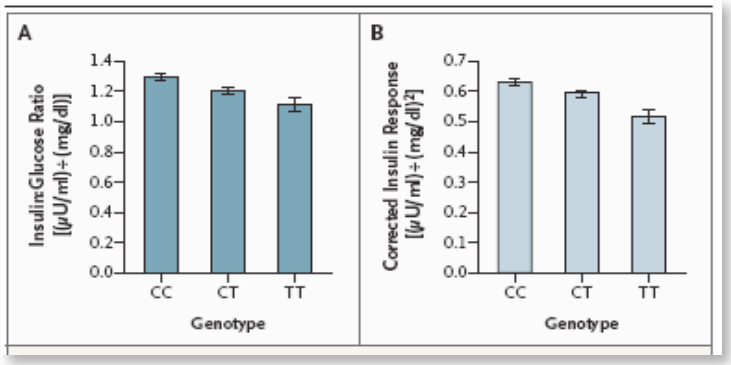
From Bell and Polonsky
Nature (2001) 414: 788-91

Kir6.2 and TCF7L2: reduced insulin secretion, but no increase in insulin resistance

$K_{ir}6.2$ E23K



Florez et al. (2004) *Diabetes*

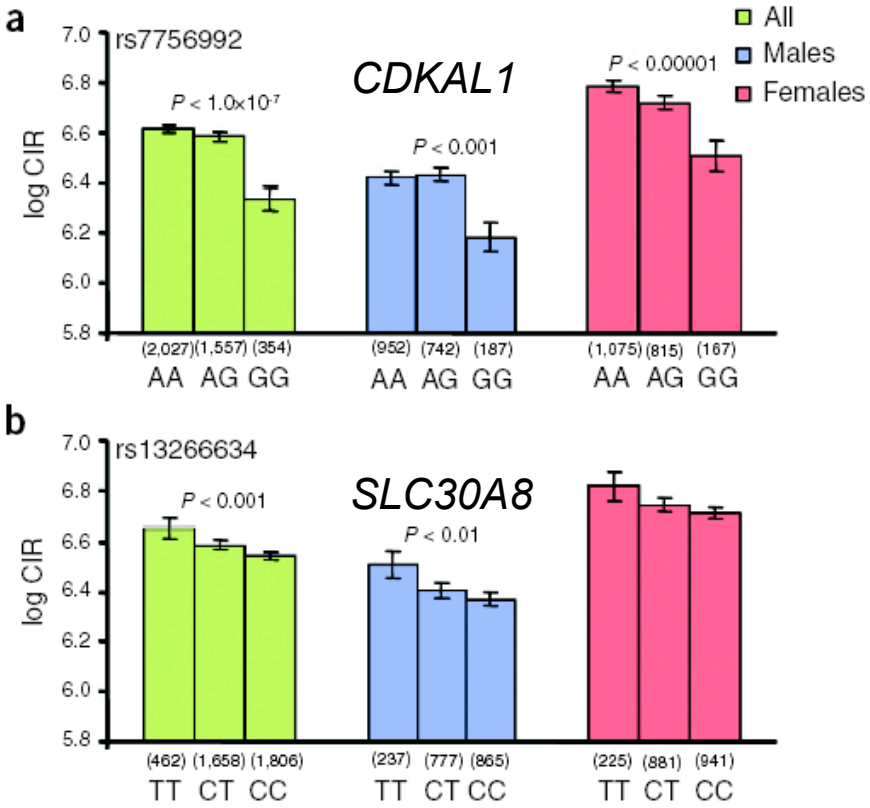


Florez et al. (2006) *NEJM*

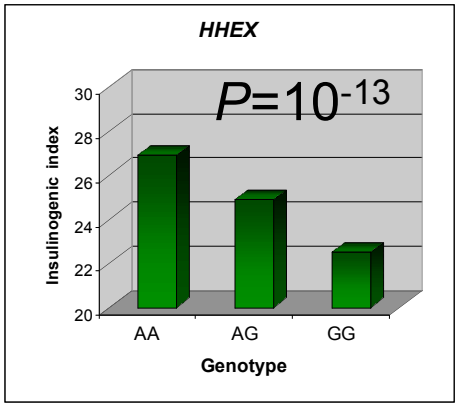
	N	*P value*
Insulin secretion measures		
Insulinogenic Index	995	**0.0030**
Disposition index	995	**0.0044**
AUCins / AUCgluc	721	**0.0023**
Insulin resistance measures		
Fasting insulin	995	0.3423
HOMA-IR	995	0.2561

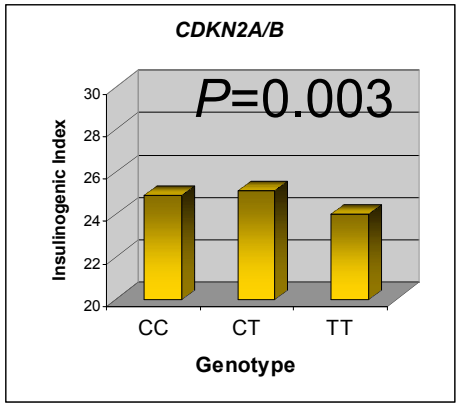
Saxena et al (2006) *Diabetes*

CDKAL1, *SLC30A8*, *HHEX* and *CDKN2A/B*: reduced insulin secretion in non-diabetics



Steinthorsdottir *et al.*, *Nat Genet* 2007





Grarup *et al.*, *Diabetes* online 9/7/2007

In some cases, associations to known pathways:
eg, complement in AMD, autophagy in Crohns,
TNF signaling in RA, interferon in SLE, etc

But the vast majority of associated loci are novel, highlighting the importance of unbiased approaches

New biological clues, and a lot of work to do

Nearly all of the new associations are common (this is to be expected, given the design), and each has a very modest association to disease risk

In aggregate, they explain only a small fraction (5%) of the inherited risk of T2D

What about the rest of the heritability?

For each disease,
only a small fraction
of the causal *loci*

At each locus,
an incomplete survey
for causal *mutations*

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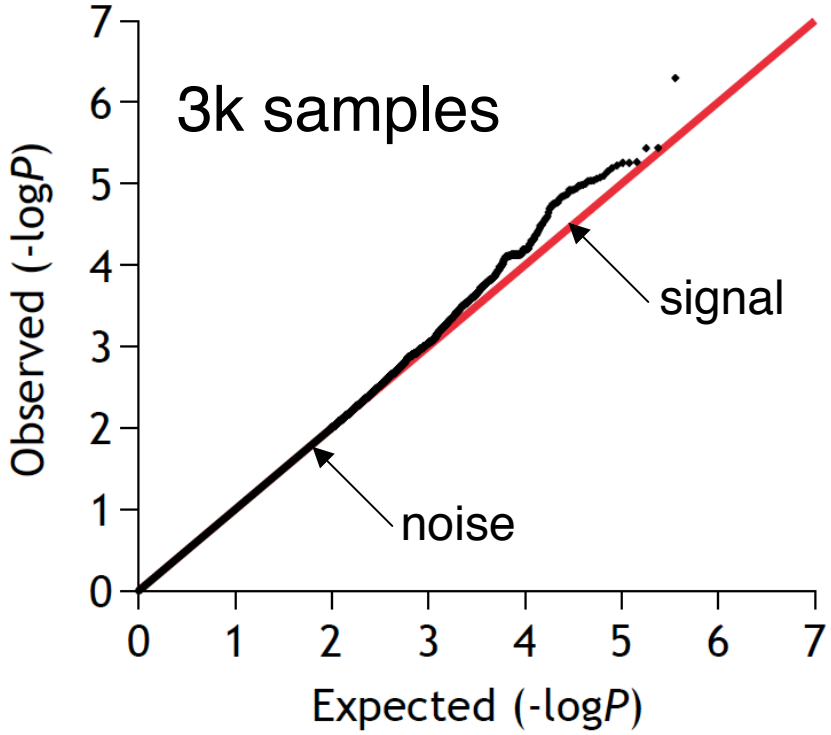
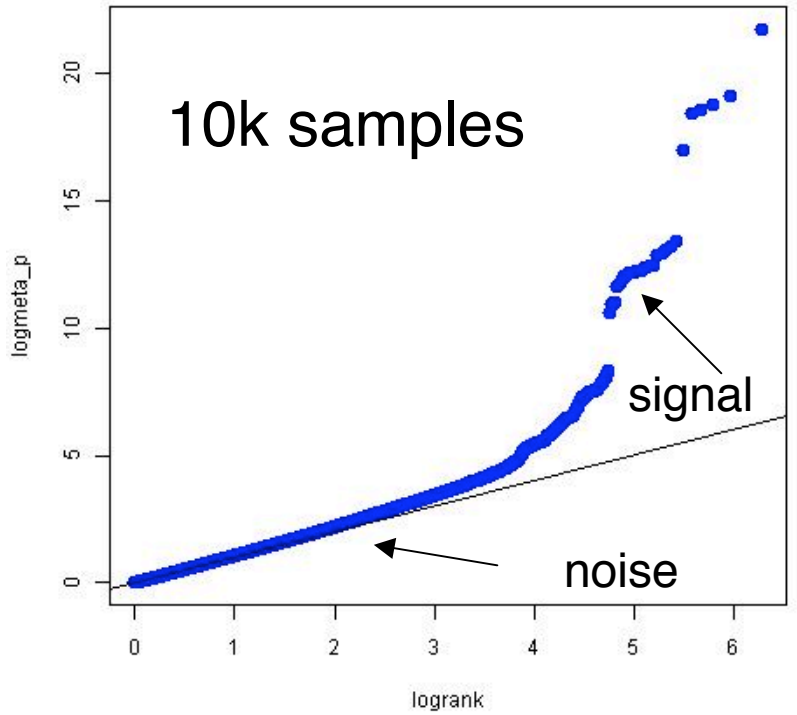
Unpublished: T2D meta-analysis

Stage	Study	Genotyping platform	$N_{effective}$ Samples	N SNPs
1*	FUSION WTCCC DGI	Illumina 300K Affymetrix 500K Affymetrix 500K	9,562	2,205,727
2	FUSION UKT2DGC DGI	Sequenom KASPar/TaqMan Sequenom	21,461	58
3	deCODE, Steno KORA, HUNT	Illumina 300K/ Nanogen, Sequenom	18,066	11

Zeggini, Scott, Saxena, Voigt for DIAGRAM, In review

Effect of increasing sample size on signal vs noise distribution





Zeggini, Scott, Saxena, Voigt for DIAGRAM, In review

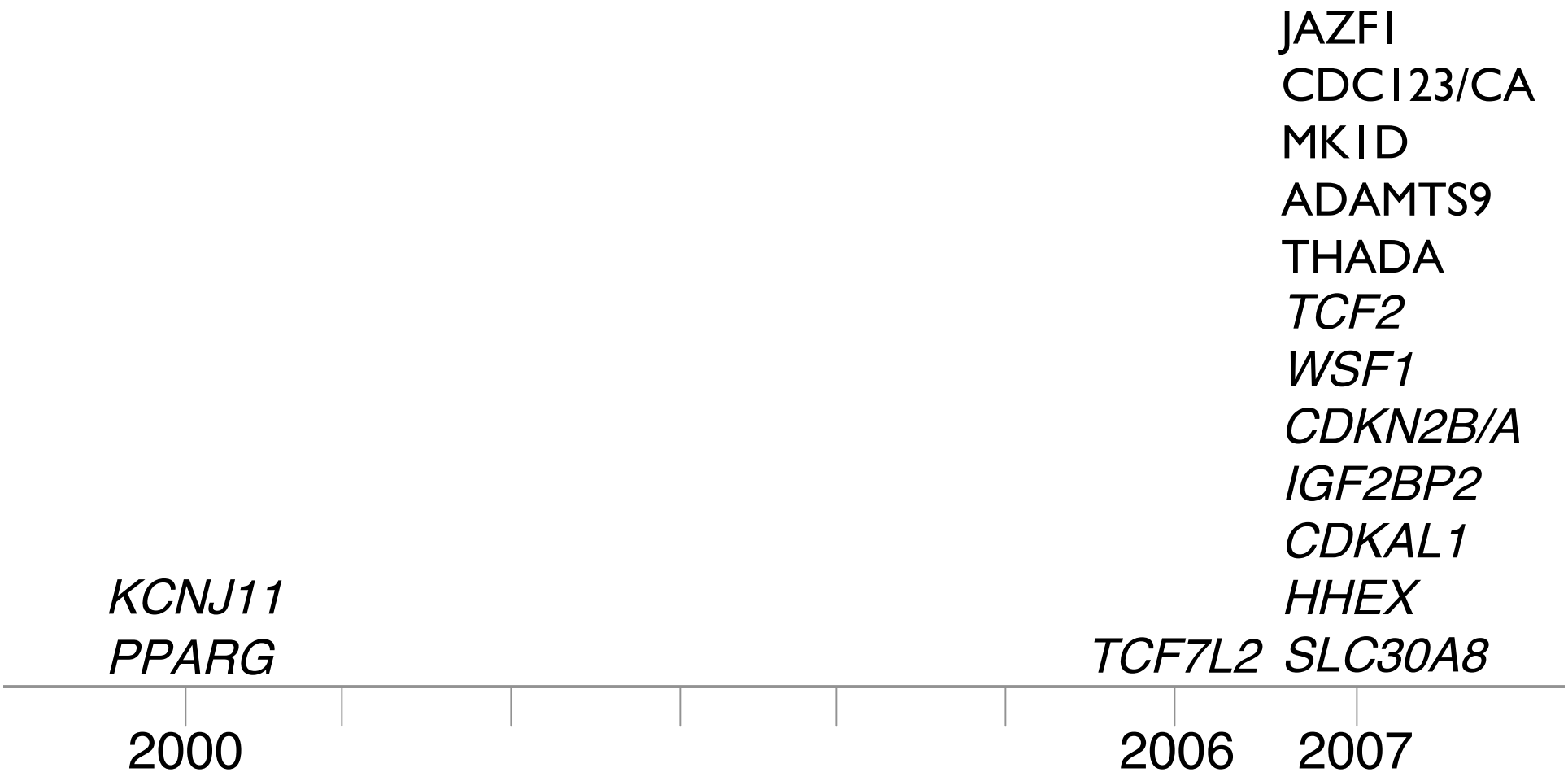
Four more T2D loci with P<5 x 10^{-8}

SNP	Stage 1 N=9,562 OR	p	Stage 2 N=21,461 OR	p	Stage 3 N=18,066 OR	p	Nearest gene
rs864745	1.14	1E-04	1.08	8E-05	1.13	2E-05	*JAZF1*
rs12779790	1.15	4E-04	1.11	5E-05	1.09	0.009	*CDC123/CAMK1D*
rs4607103	1.25	5E-04	1.10	1E-04	1.09	0.007	*ADAMTS9*
rs7578597	1.25	1E-04	1.15	.001	1.16	0.004	*THADA*

Five other loci with p values between 10^{-6} and $5x10^{-8}$

Zeggini, Scott, Saxena, Voigt for DIAGRAM, In press

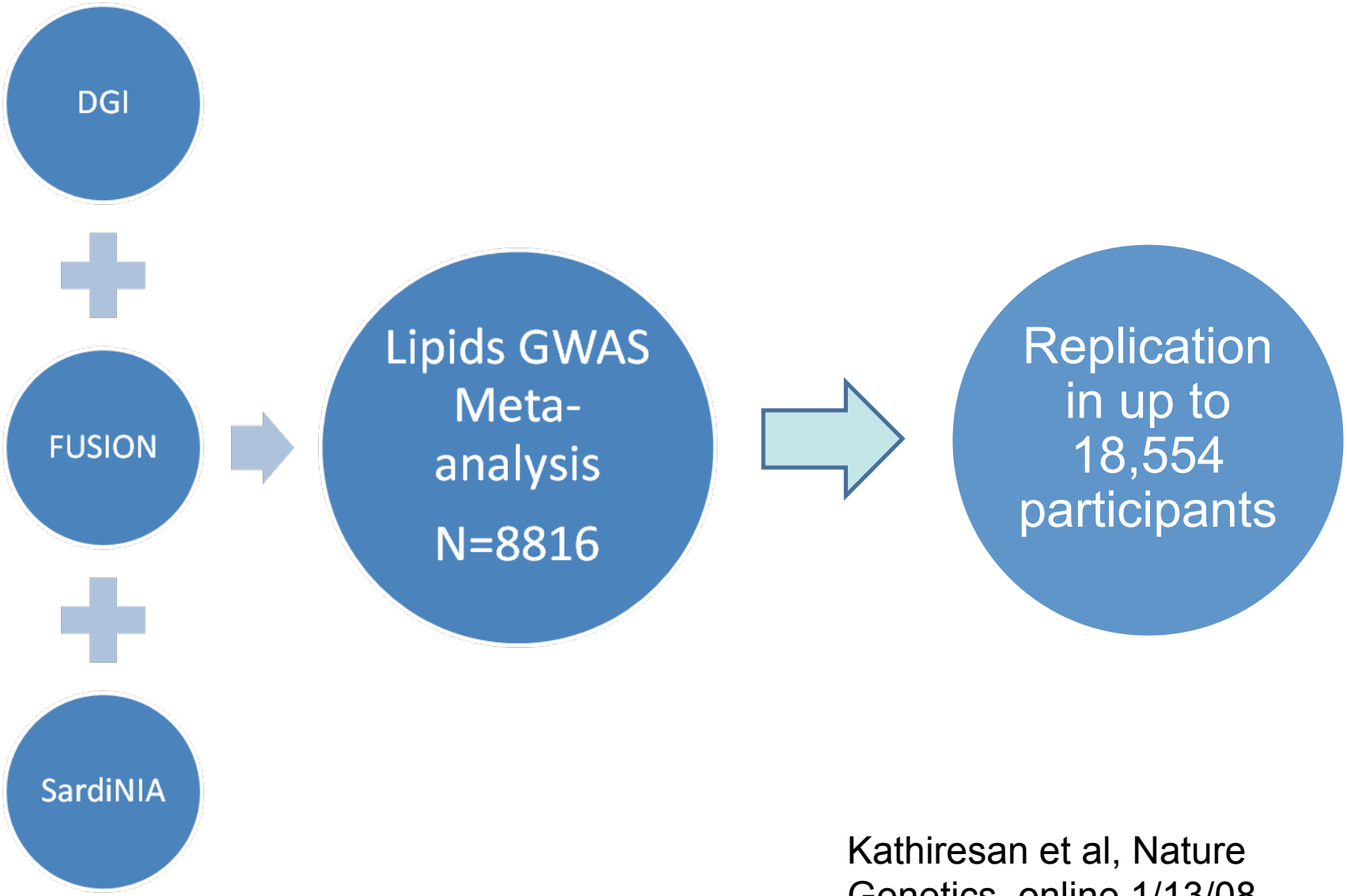
Fourteen confirmed loci at which common variants associate with risk of type 2 diabetes



DGI + literature: 9 lipid loci with validated common variants

LDL	HDL	TG
APOE cluster	CETP	APOA5
APOB	LPL	GCKR
PCSK9	LIPC	
	ABCA1	

Increasing power for discovery



Kathiresan et al, Nature Genetics, online 1/13/08

18 loci affecting blood lipids at $P<5x10^{-8}$

LDL-C	HDL-C	TG
APOE cluster	CETP	APOA5
APOB	LPL	GCKR
LDLR	LIPC	MLXIPL
SORT1	ABCA1	TRIB1
CSPG3/PBX4/CILP2	GALNT2	ANGPTL3
PCSK9	LIPG	
HMGCR		

Kathiresan et al, Nature Genetics, online 1/13/08

Genetic variation in HMGCR

The frequency and effect size
of genetic variation
bears no clear relationship
to the size of the population
or therapeutic impact of
of mechanism-driven intervention

Novel locus on chromosome 1: same SNP associated to heart attack

Table 3. Additional Loci Associated with Coronary Artery Disease from Combined Analysis of Data from the WTCCC and German MI Family Studies.*

Chromosome	Lead SNP	Minor Allele in Controls	Risk Allele	WTCCC Study		German Study		Combined Analysis	
				Frequency of Minor Allele among Controls	Odds Ratio for Risk Allele (95% CI)	Frequency of Minor Allele among Controls	Odds Ratio for Risk Allele (95% CI)	Odds Ratio for Risk Allele (95% CI)	P Value
1	rs599839	G	A	0.23	1.24 (1.12–1.38)	0.22	1.39 (1.19–1.63)	1.29 (1.18–1.40)	4.05×10^{-9}
1	rs17465637	A	C	0.29	1.23 (1.12–1.34)	0.26	1.15 (1.01–1.32)	1.20 (1.12–1.30)	1.27×10^{-6}
10	rs501120	C	T	0.13	1.24 (1.09–1.41)	0.16	1.54 (1.28–1.86)	1.33 (1.20–1.48)	9.46×10^{-8}
15	rs17228212	C	C	0.30	1.19 (1.09–1.30)	0.26	1.26 (1.11–1.44)	1.21 (1.13–1.30)	1.98×10^{-7}

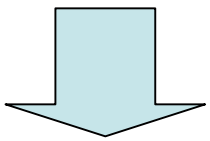
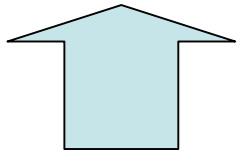
AA genotype → 16 mg/dL↑ LDL-C → 1.7-fold ↑ risk CHD

Samani, *N Engl J Med* 2007

For each disease,
only a small fraction
of the causal *loci*

At each locus,
an incomplete survey
for causal *mutations*

The frequency spectrum of mutations influencing disease

Deleterious	Neutral	Positive
		
Mutations are very likely to be rare	mutations can become common	mutations can become fixed

We've only identified the alleles at each locus that are of small enough effect to become very common

Nine of 18 lipid loci found by GWAS have known Mendelian mutations

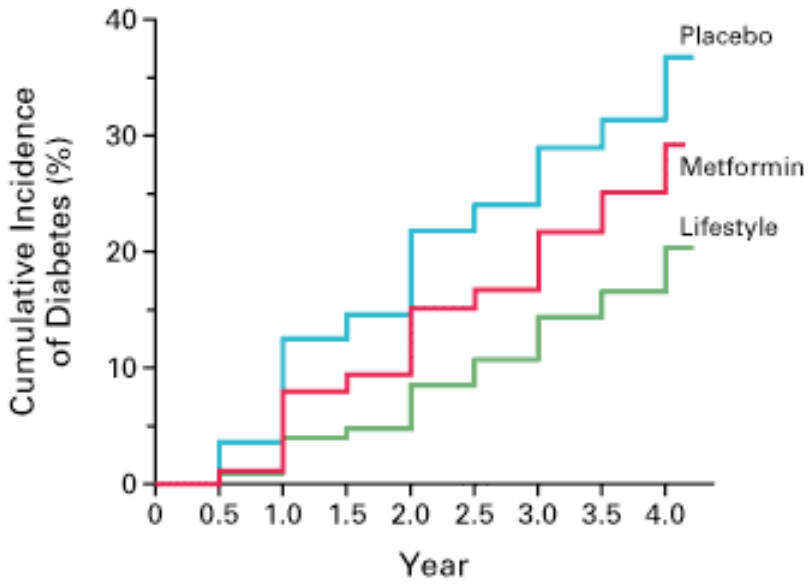
Many T2D genes with both common variants and rare mutations (Kir6.2, TCF2, WSF1, etc)

We need to identify causal mutations
(both common and rare) at each locus
newly identified by GWAS
before we can begin to estimate
the overall effect on disease

Prior to working out the biology,
can prediction inform clinical medicine?

Diabetes Prevention Program

- 3234 subjects with IGT
- Randomized to placebo, lifestyle or metformin
- 585 additional patients initially randomized to troglitazone
- Followed for 4 years
- DNA collected



DPP Research Group
NEJM 346:393-403, 2002

Risk reduction: 58% lifestyle
31% metformin

Implementing the lessons of the DPP

- The lifestyle intervention is highly effective
- Realizing this benefit requires expense and dedication by patient and caregivers
- While it might be good for everyone, we can't afford as a society to provide it

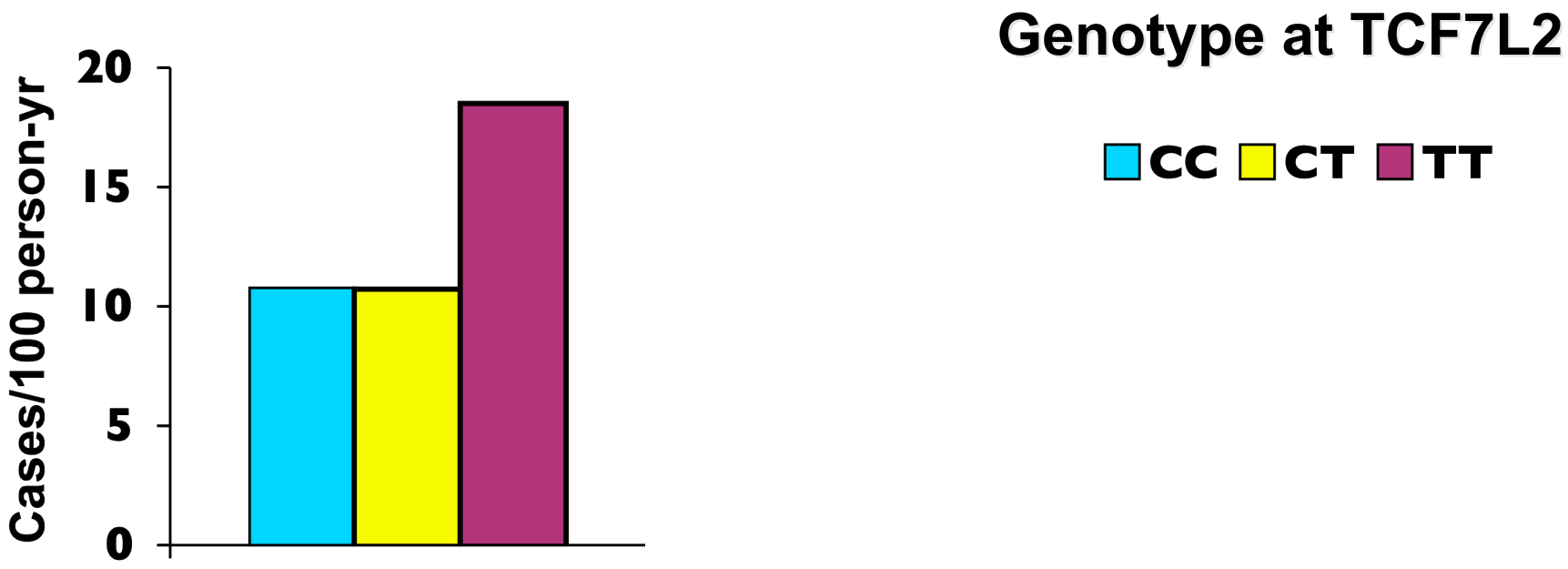
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 20, 2006 VOL. 355 NO. 3

TCF7L2 Polymorphisms and Progression to Diabetes in the Diabetes Prevention Program

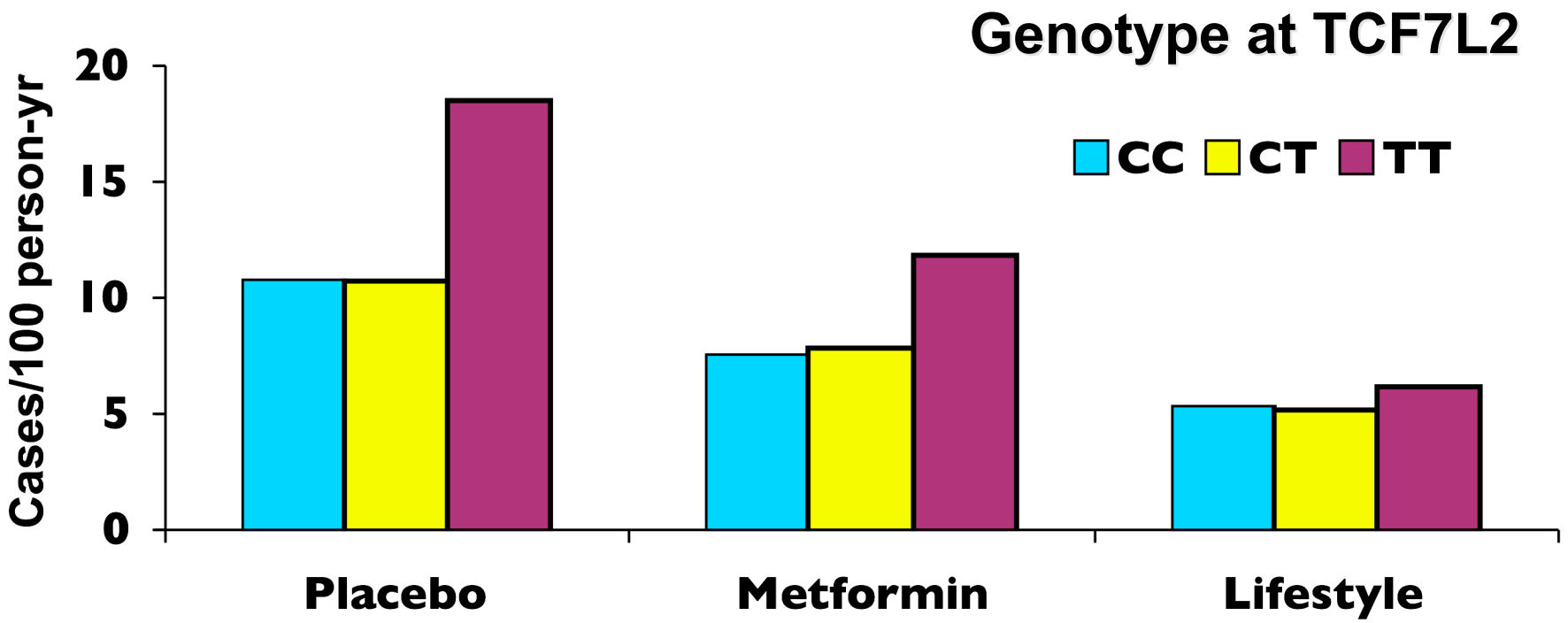
Jose C. Florez, M.D., Ph.D., Kathleen A. Jablonski, Ph.D., Nick Bayley, B.A., Toni I. Pollin, Ph.D., Paul I.W. de Bakker, Ph.D., Alan R. Shuldiner, M.D., William C. Knowler, M.D., Dr.P.H., David M. Nathan, M.D., and David Altshuler, M.D., Ph.D., for the Diabetes Prevention Program Research Group

TCF7L2 and risk of T2D in Diabetes Prevention Program



Florez et al, New England Journal of Medicine, 355 pp. 241-50 (2006)

TCF7L2 and risk of T2D in Diabetes Prevention Program



Florez et al, New England Journal of Medicine, 355 pp. 241-50 (2006)

June, 2007: $500 clinical test for TCF7L2

diagnostics home | deCODE T2™ | For physicians | For individuals | About deCODE

deCODE T2™

deCODE genetics – a global leader in applying human genetics to create better healthcare – offers deCODE T2™, a DNA-based test to help physicians assess the genetic risk of type 2 diabetes in their patients, and to enable lifestyle and therapeutic strategies that may reduce the risk of developing diabetes in the future.

deCODE genetics

Clinical trials of genetic information?

- Need to validate prediction in prospective studies
- Even valid predictive information does not guarantee improved outcome, and can harm
  - T2D: will patients with high risk genotype improve lifestyle more than low risk genotype worsen?
- Genetic determinism need be counterbalanced by hard data on beneficial interventions

"After my son tested positive for MODY, he continued to eat the same - wasn't going to let his genes stop him. My other son, who tested negative (but is overweight), was reassured by the test. He thinks that he can eat whatever he wants, since he doesn't have the gene."

— MODY patient and mother, presenting to students at a recent Harvard genetics class

By November, multiple companies offering genome-wide SNP data for ≈$1,000

Coverage on the front page of NYT

" My risk of breast cancer was no higher than average, as was my chance of developing Alzheimer's. I was 23 percent less likely to get Type 2 diabetes than most people. And my chance of being paralyzed by multiple sclerosis, almost nil…

I was in remarkably good genetic health, and I hadn't even been to the gym in months!"

Amy Harmon, NYT, 11/17/07

Why study *inheritance* of disease?

To discover and validate pathways
(in my mind, uniquely powerful)

To predict disease risk
(one of many factors)

To my mind, the frequency and effect of a genetic variant bears little relationship to the potential impact of intervention (which will not be genetic!)

This may be different than environmental / behavioral risk factors, where the intervention is directly aimed at the exposure (rather than the underlying biology)

For the first time, progress identifying inherited contributors to common human diseases

Long-term benefit will come from biological understanding and development of interventions

Typing of new genes variants (and the hyping of their potential value) will start immediately

Special thanks to…

Leif Groop

Stacey Gabriel

Mark Daly

Special thanks to…

Novartis Institutes for Biomedical Research
American Diabetes Association Pinnacle Award

BMS "Freedom to Discover" award
Doris Duke Charitable Foundation
National Institutes of Health
NHGRI, NIDDK, NCRR, NHLBI, NIAID, NCI
Charles E. Culpeper Scholarship
Burroughs Wellcome Fund


Study participants who made this work possible

In many cases, associated SNPs are far from any coding region

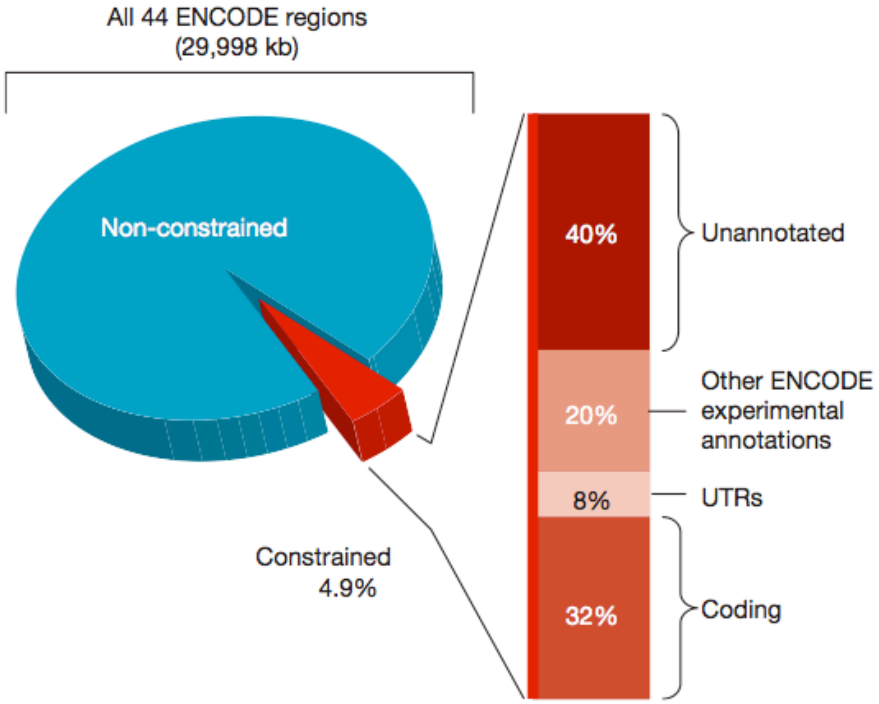


Figure 10 | Relative proportion of different annotations among constrained sequences. The 4.9% of bases in the ENCODE regions identified as constrained is subdivided into the portions that reflect known coding regions, UTRs, other experimentally annotated regions, and unannotated sequence.

ENCODE Consortium, Nature 2007