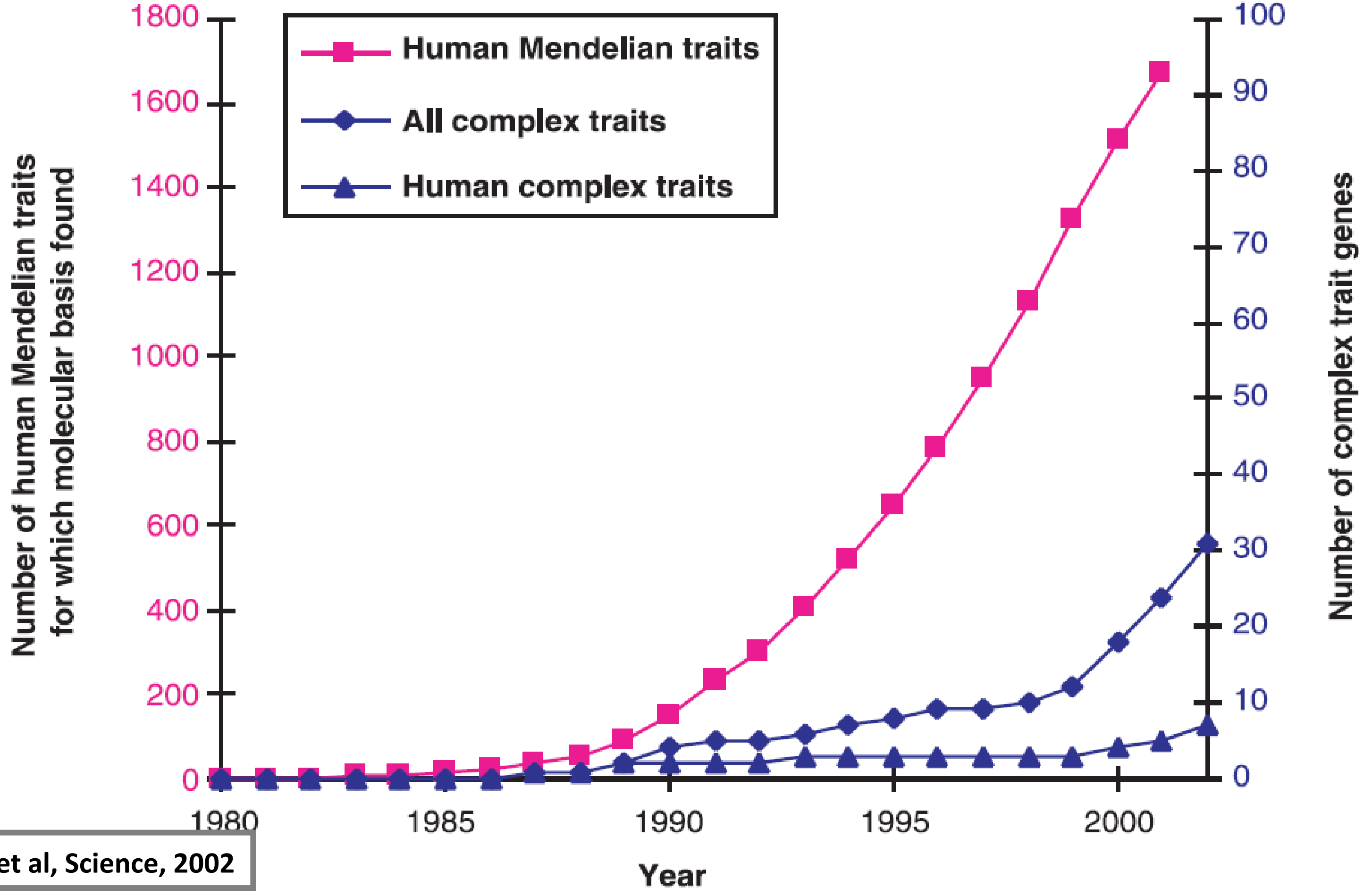
Thinking big: Finding more and (more) genes influencing glycaemic and anthropometric traits

Mark McCarthy, Oxford

Slow progress in finding multifactorial genes…



Glazier et al, Science, 2002

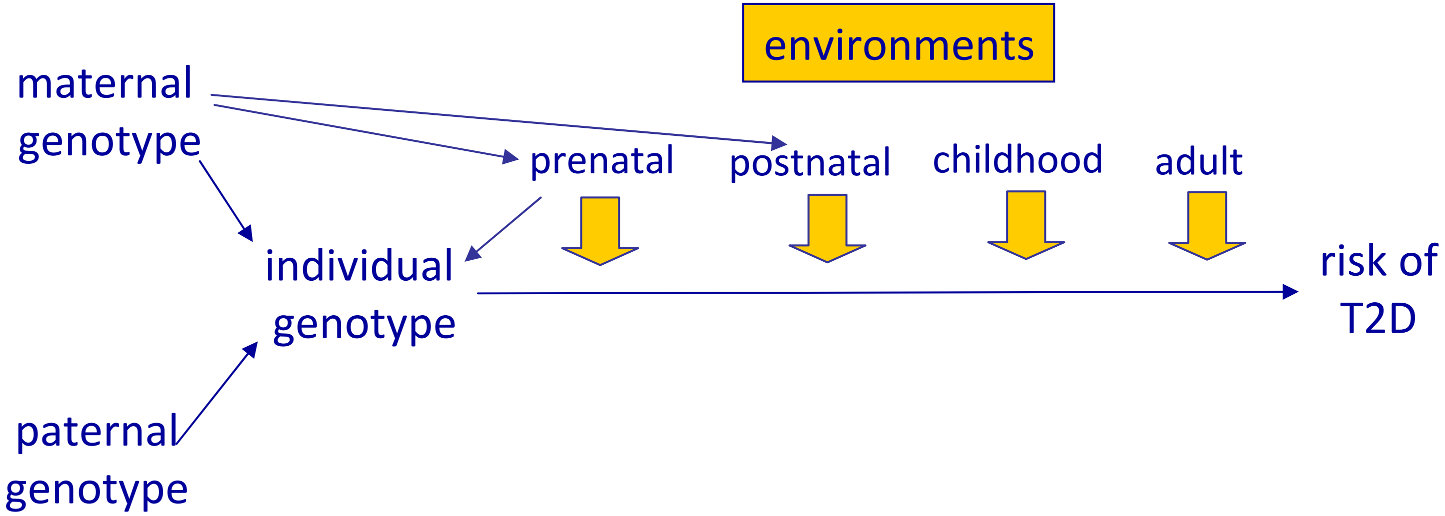
Why? - biological complexity

Genes

- familial clustering
- twin studies
- adoption studies
- migration studies
- admixture studies
- gene discovery

Environment

- secular trends
- migration studies
- twin studies
- transgenerational effects
- intervention studies


environments

maternal genotype

prenatal

postnatal

childhood

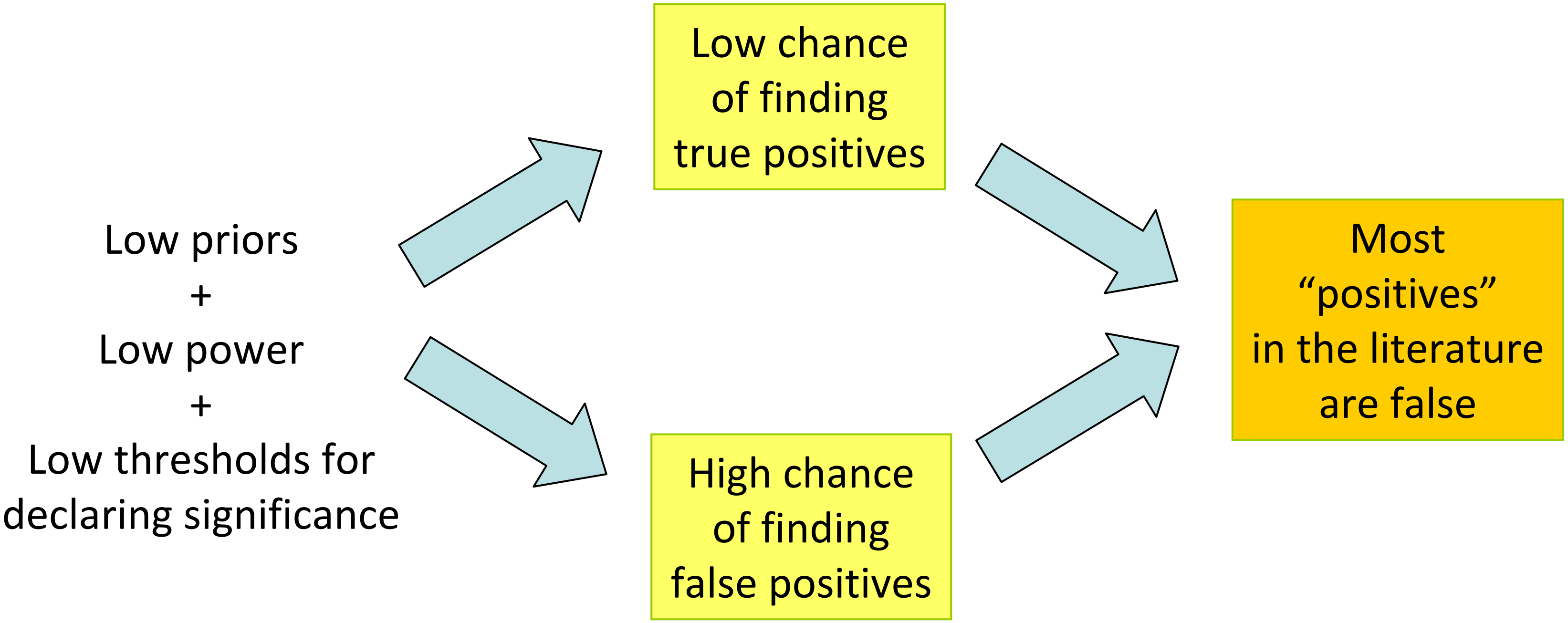
adult

individual genotype

risk of T2D

paternal genotype

Why? - inadequate study design



Low priors
+
Low power
+
Low thresholds for
declaring significance

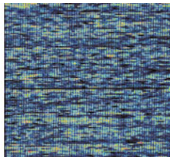
Low chance
of finding
true positives

High chance
of finding
false positives

Most
“positives”
in the literature
are false

Recent advances using GWA approach

Better understanding of patterns of human sequence variation



Advances in genotyping technology

Sample collections of adequate size

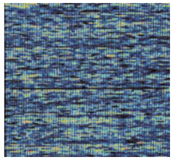
Genome-wide association scans

3,000,000,000 bases in human genome

~10,000,000 positions commonly variant in Europeans

80% of these captured by typing ~500k

Samples of interest



test for evidence of association

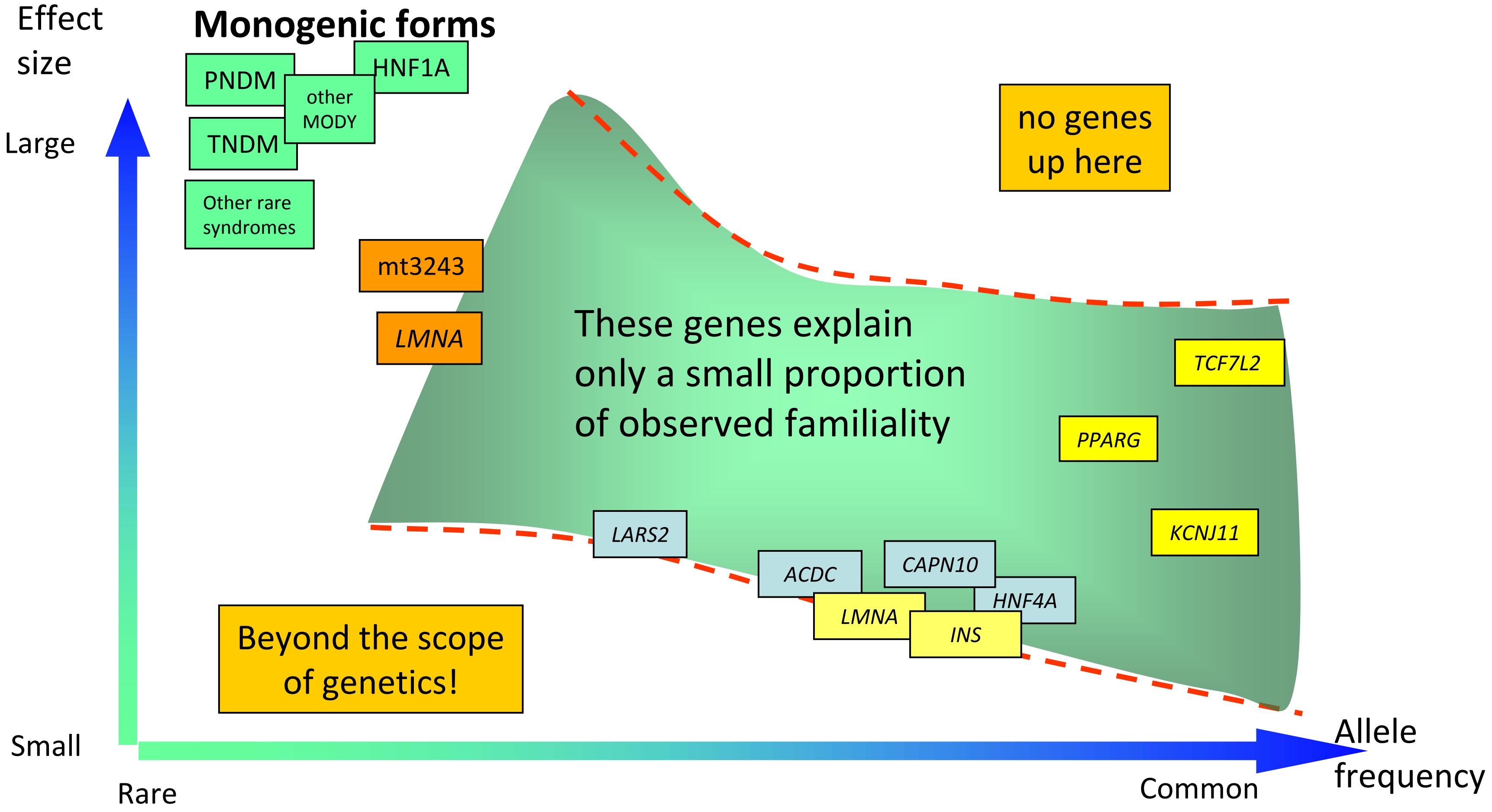
Summary of talk

 # common variant loci implicated

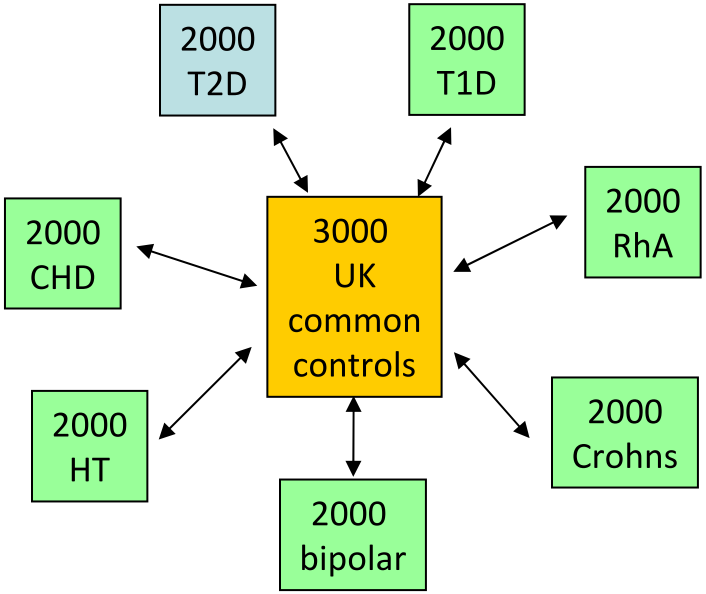
	2006		2008
T2D	3	→	20
BMI	0	→	10
glucose	1	→	5

Type 2 diabetes

Atlas of diabetes susceptibility (2006)



Wellcome Trust Case Control Consortium



2000
T2D

2000
T1D

2000
CHD

3000
UK
common
controls

2000
RhA

2000
HT

2000
Crohns

2000
bipolar

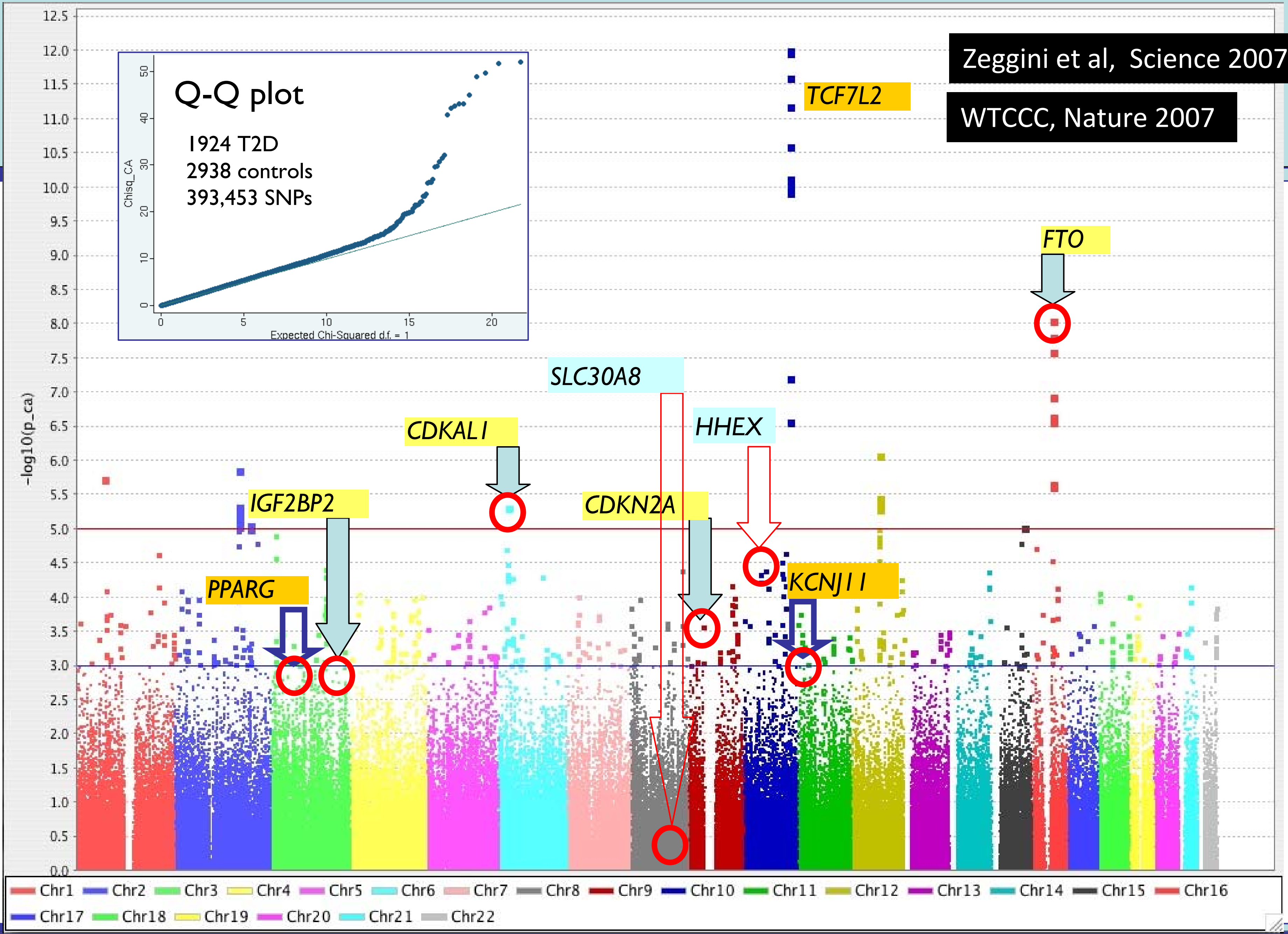
Main study with national cases/controls

Affymetrix 500k array

WTCCC, Nature 2007

	Cases	Controls	SNPs
UK (WTCCC)	1924	2938	500,000
FUSION	1200	1200	317,000
DGI (Broad/Malmo)	1559	1503	500,000
Total	4600	5600	~5 billion genotypes

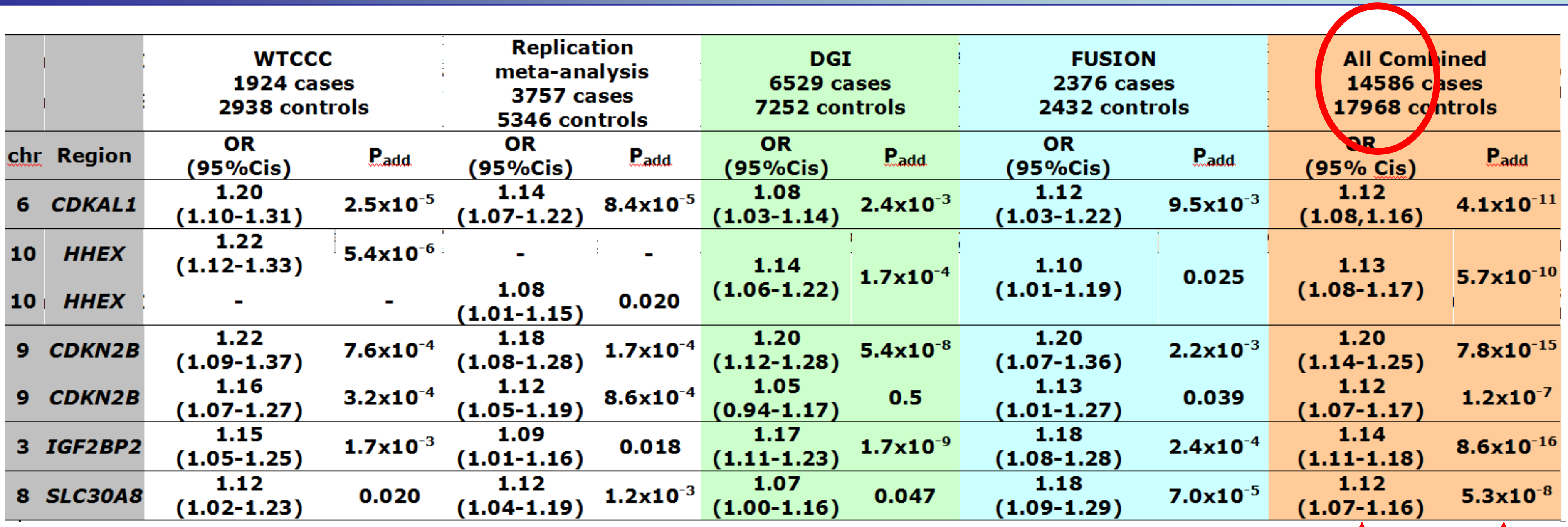
Replication in ~20,000 samples



Zeggini et al, Science 2007

WTCCC, Nature 2007

Back to the other T2D genes



		WTCCC 1924 cases 2938 controls		Replication meta-analysis 3757 cases 5346 controls		DGI 6529 cases 7252 controls		FUSION 2376 cases 2432 controls		All Combined 14586 cases 17968 controls	
chr	Region	OR (95%Cis)	P_{add}	OR (95%Cis)	P_{add}	OR (95%Cis)	P_{add}	OR (95%Cis)	P_{add}	OR (95% Cis)	P_{add}
6	***CDKAL1***	1.20 (1.10-1.31)	2.5×10^{-5}	1.14 (1.07-1.22)	8.4×10^{-5}	1.08 (1.03-1.14)	2.4×10^{-3}	1.12 (1.03-1.22)	9.5×10^{-3}	1.12 (1.08,1.16)	4.1×10^{-11}
10	***HHEX***	1.22 (1.12-1.33)	5.4×10^{-6}	-	-	1.14 (1.06-1.22)	1.7×10^{-4}	1.10 (1.01-1.19)	0.025	1.13 (1.08-1.17)	5.7×10^{-10}
10	***HHEX***	-	-	1.08 (1.01-1.15)	0.020						
9	***CDKN2B***	1.22 (1.09-1.37)	7.6×10^{-4}	1.18 (1.08-1.28)	1.7×10^{-4}	1.20 (1.12-1.28)	5.4×10^{-8}	1.20 (1.07-1.36)	2.2×10^{-3}	1.20 (1.14-1.25)	7.8×10^{-15}
9	***CDKN2B***	1.16 (1.07-1.27)	3.2×10^{-4}	1.12 (1.05-1.19)	8.6×10^{-4}	1.05 (0.94-1.17)	0.5	1.13 (1.01-1.27)	0.039	1.12 (1.07-1.17)	1.2×10^{-7}
3	***IGF2BP2***	1.15 (1.05-1.25)	1.7×10^{-3}	1.09 (1.01-1.16)	0.018	1.17 (1.11-1.23)	1.7×10^{-9}	1.18 (1.08-1.28)	2.4×10^{-4}	1.14 (1.11-1.18)	8.6×10^{-16}
8	***SLC30A8***	1.12 (1.02-1.23)	0.020	1.12 (1.04-1.19)	1.2×10^{-3}	1.07 (1.00-1.16)	0.047	1.18 (1.09-1.29)	7.0×10^{-5}	1.12 (1.07-1.16)	5.3×10^{-8}

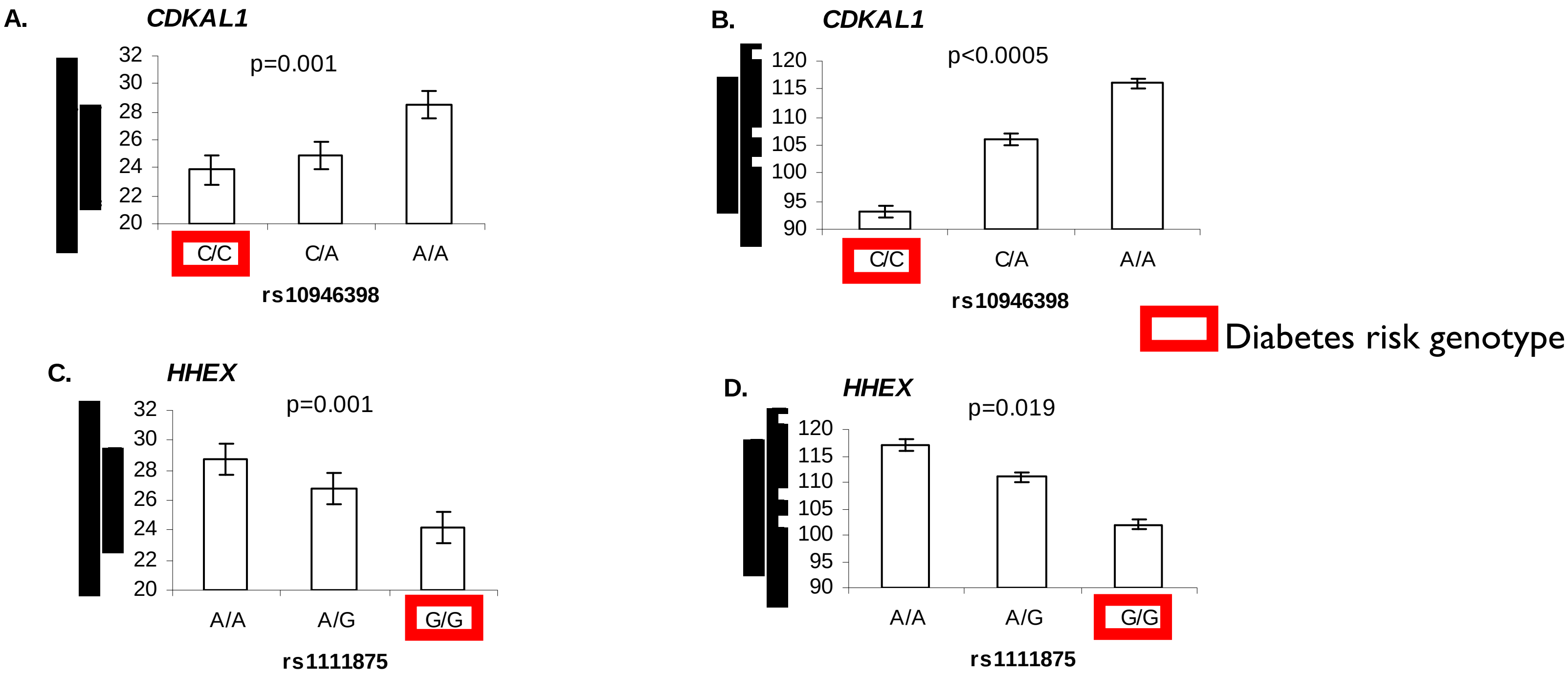
Large sample size

Modest odds ratios

Highly significant

Sladek et al, *Nature*
Zeggini et al, *Science*
Wellcome Trust Case Control Consortium, *Nature*
DGI Consortium, *Science*
Scott et al, *Science*
Steinthorsdottir et al, *Nature Genetics*

Beta-cell reigns supreme…..

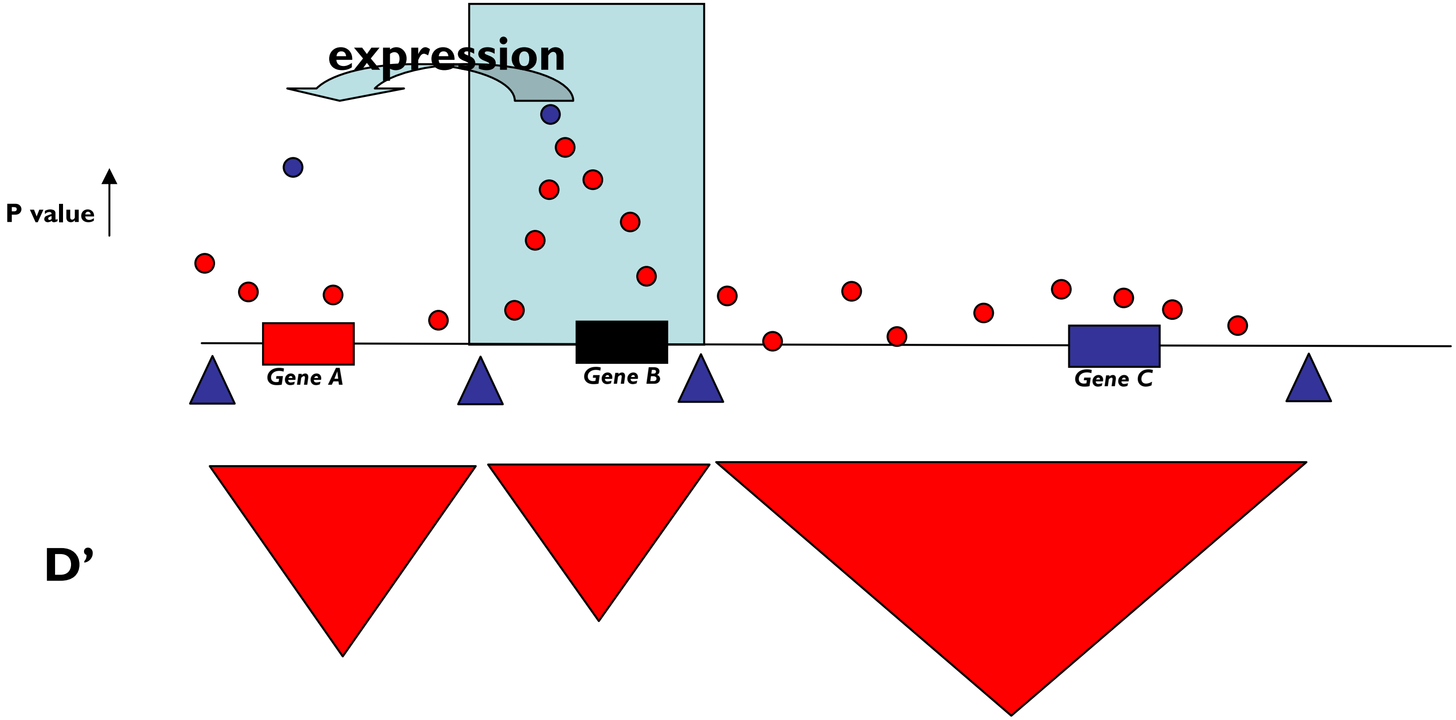


Beta-cell: *KCNJ11, TCF7L2, CDKAL1, CDKN2A/B, IGF2BP2, HHEX, SLC30A8, TCF2*

Insulin action: *PPARG, FTO, ??WFS1*

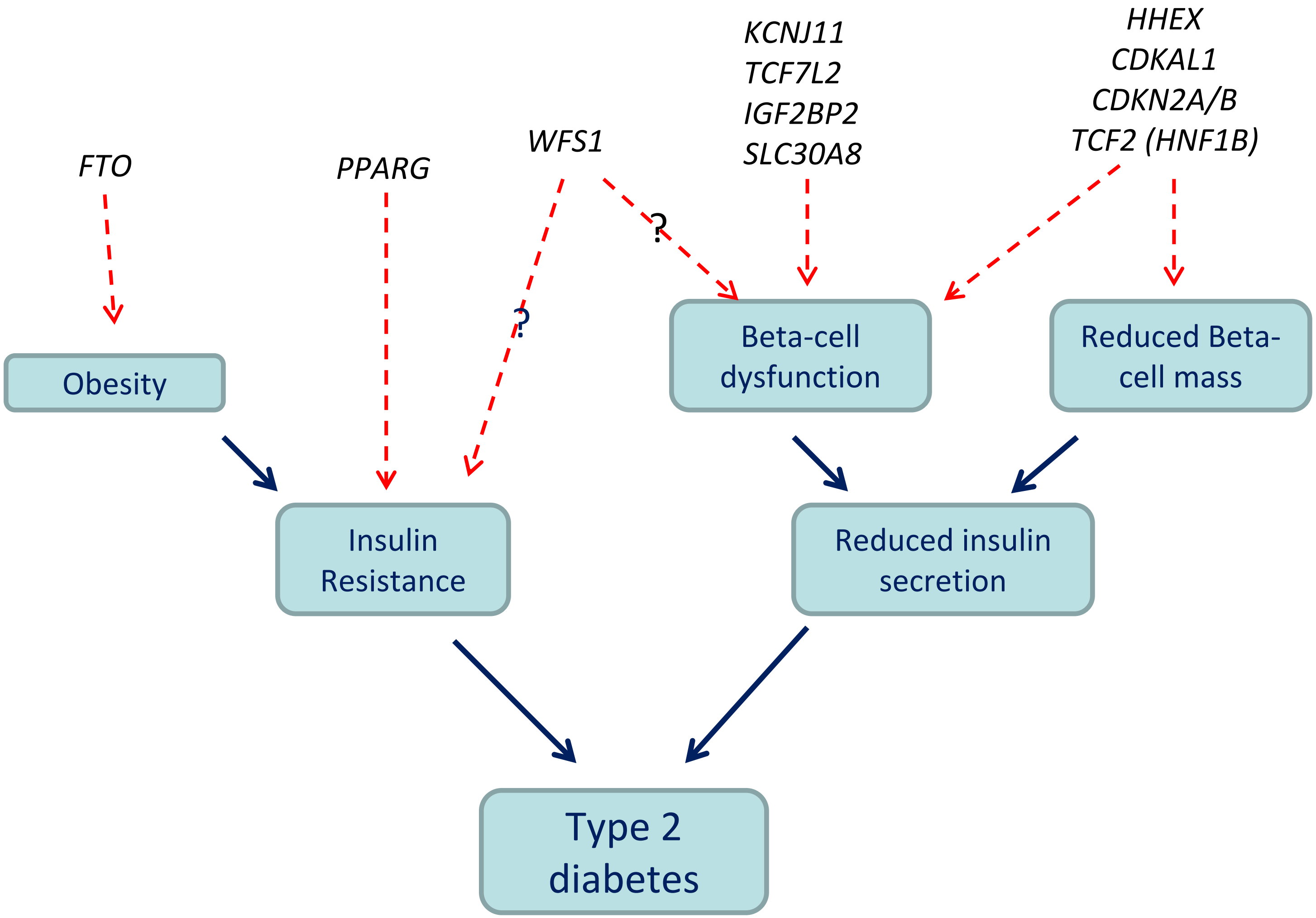
Pascoe et al, Diabetes, 2007
Garup et al, Diabetes, 2007

Fine mapping: caution required…

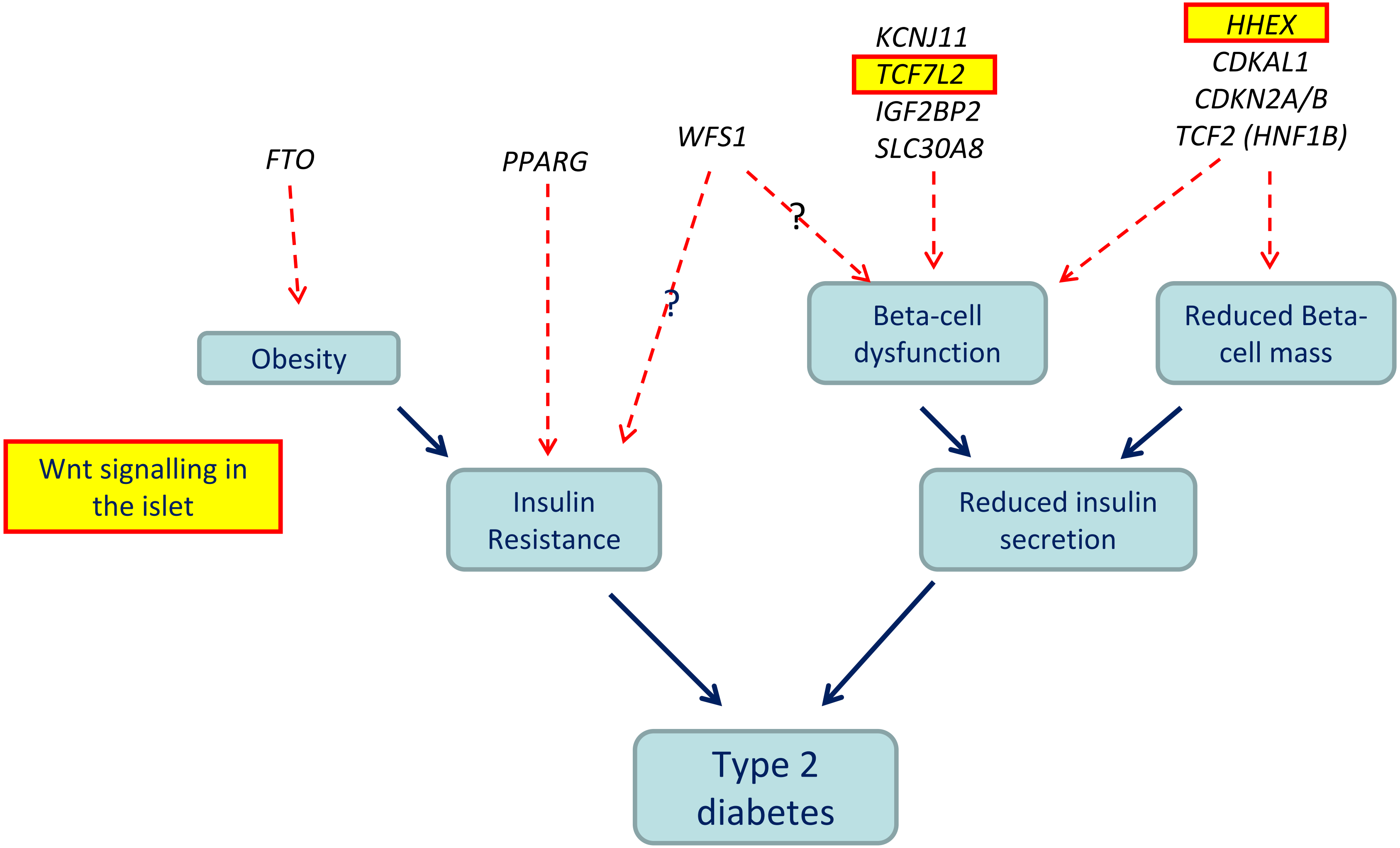


~~Gene B~~ → **Gene A**

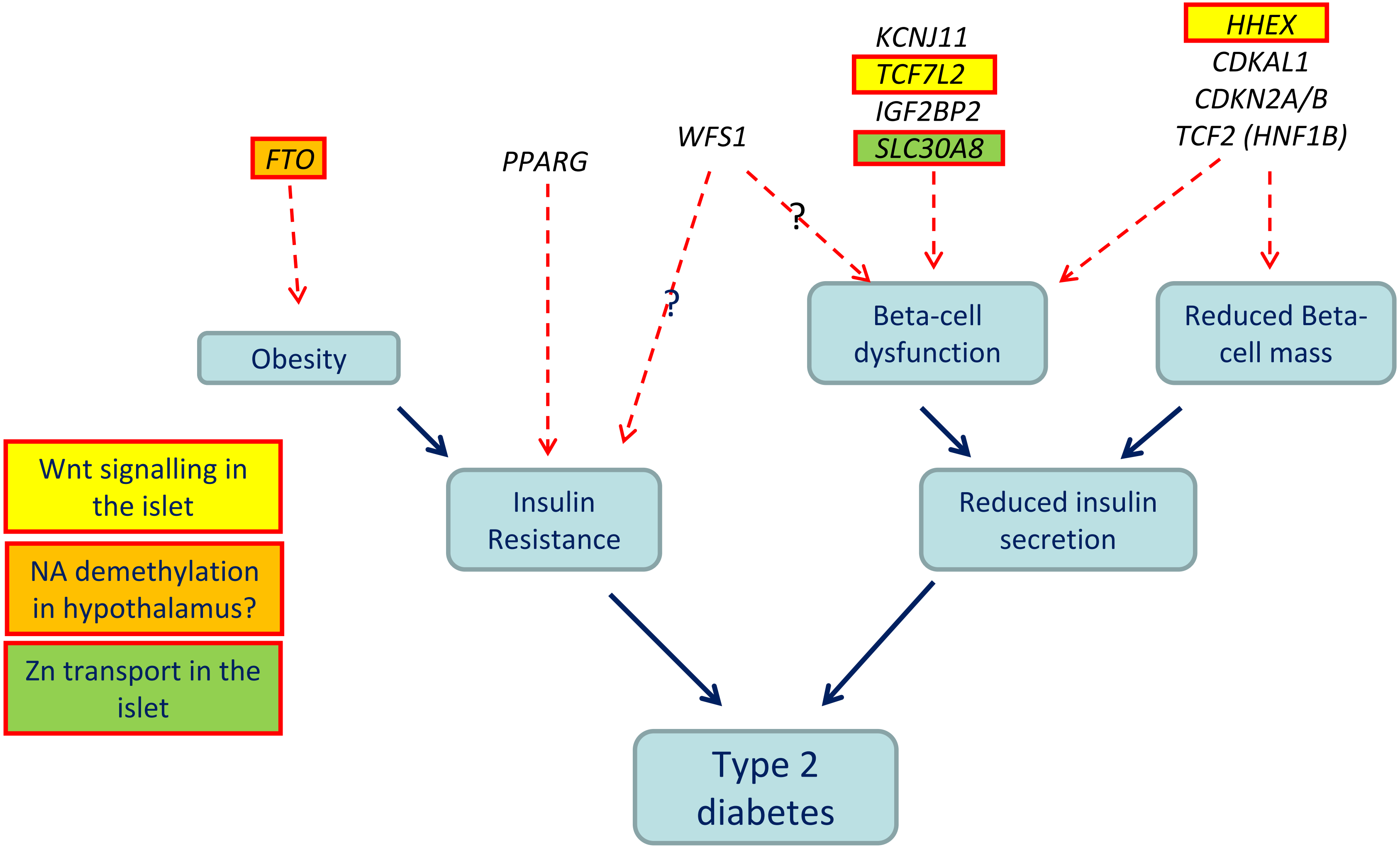
What do they do?



What do they do?



What do they do?



FTO

PPARG

WFS1

KCNJ11
TCF7L2
IGF2BP2
SLC30A8

HHEX
CDKAL1
CDKN2A/B
TCF2 (HNF1B)

?

?

Obesity

Insulin Resistance

Beta-cell dysfunction

Reduced Beta-cell mass

Reduced insulin secretion

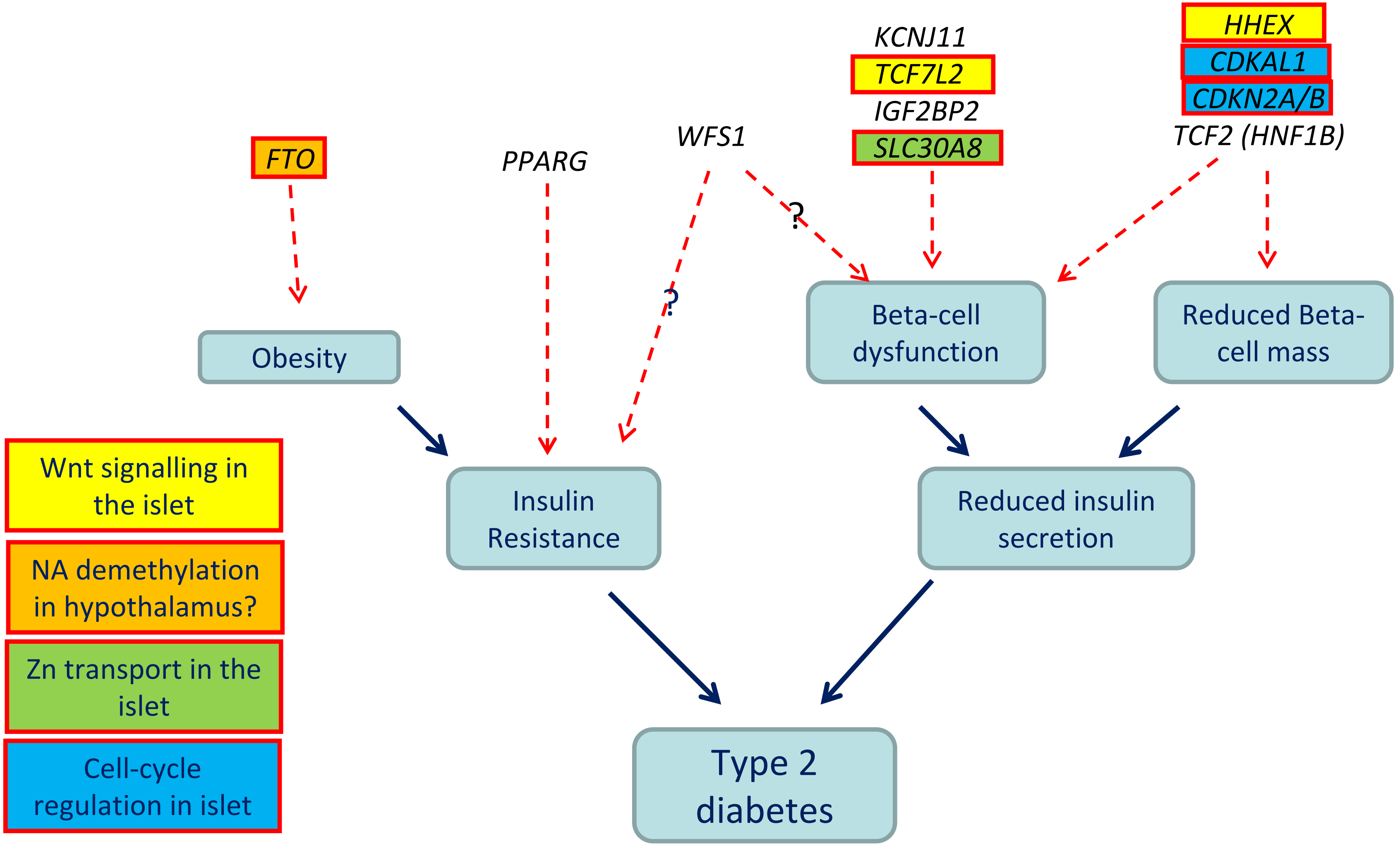
Type 2 diabetes

Wnt signalling in the islet

NA demethylation in hypothalamus?

Zn transport in the islet

What do they do?



FTO

PPARG

WFS1

KCNJ11
TCF7L2
IGF2BP2
SLC30A8

HHEX
CDKAL1
CDKN2A/B
TCF2 (HNF1B)

?

?

Obesity

Beta-cell dysfunction

Reduced Beta-cell mass

Insulin Resistance

Reduced insulin secretion

Type 2 diabetes

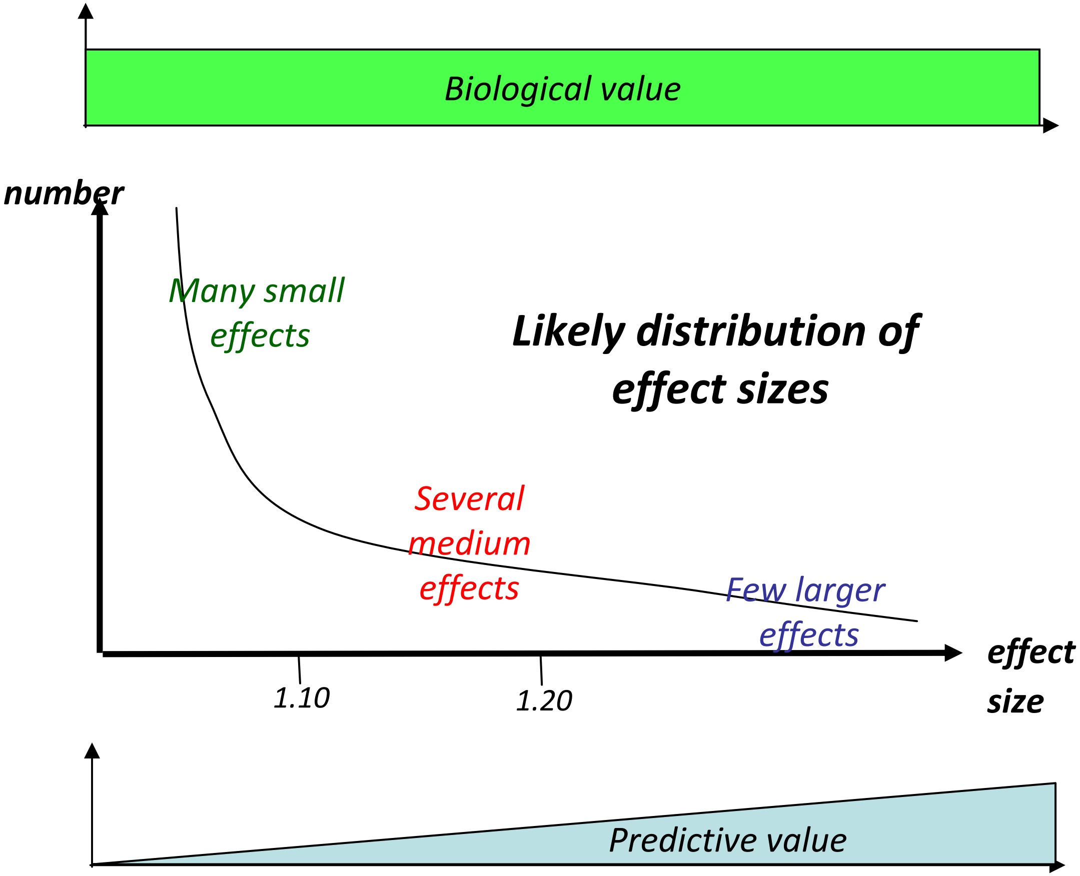
Wnt signalling in the islet

NA demethylation in hypothalamus?

Zn transport in the islet

Cell-cycle regulation in islet

It is worth finding more genes?



Small effects (if true) offer as much biological insight into mechanisms as large effects

More T2D genes….

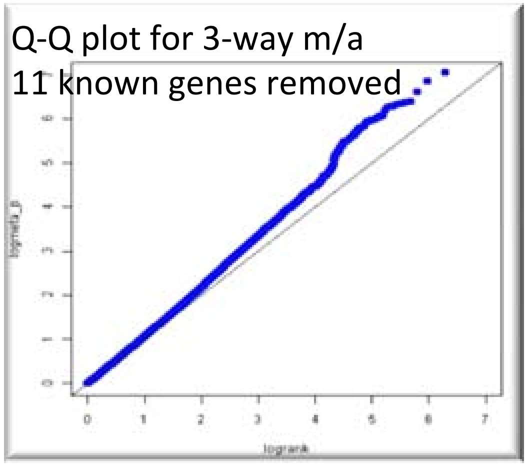
WTCCC: 2000 cases, 3000 controls Affymetrix 500k

DGI: 1500 cases, 1500 controls Affymetrix 500k

FUSION: 1200 cases, 1200 controls Illumina 317k

IMPUTE
MACH

~1.9M SNPs
10k+individuals



Q-Q plot for 3-way m/a
11 known genes removed

58 SNPs → 22442 individuals

11 SNPs → 5814 individuals (DECODE)

90,000+ individuals in all

11 SNPs → ~55k individuals (including KORA)

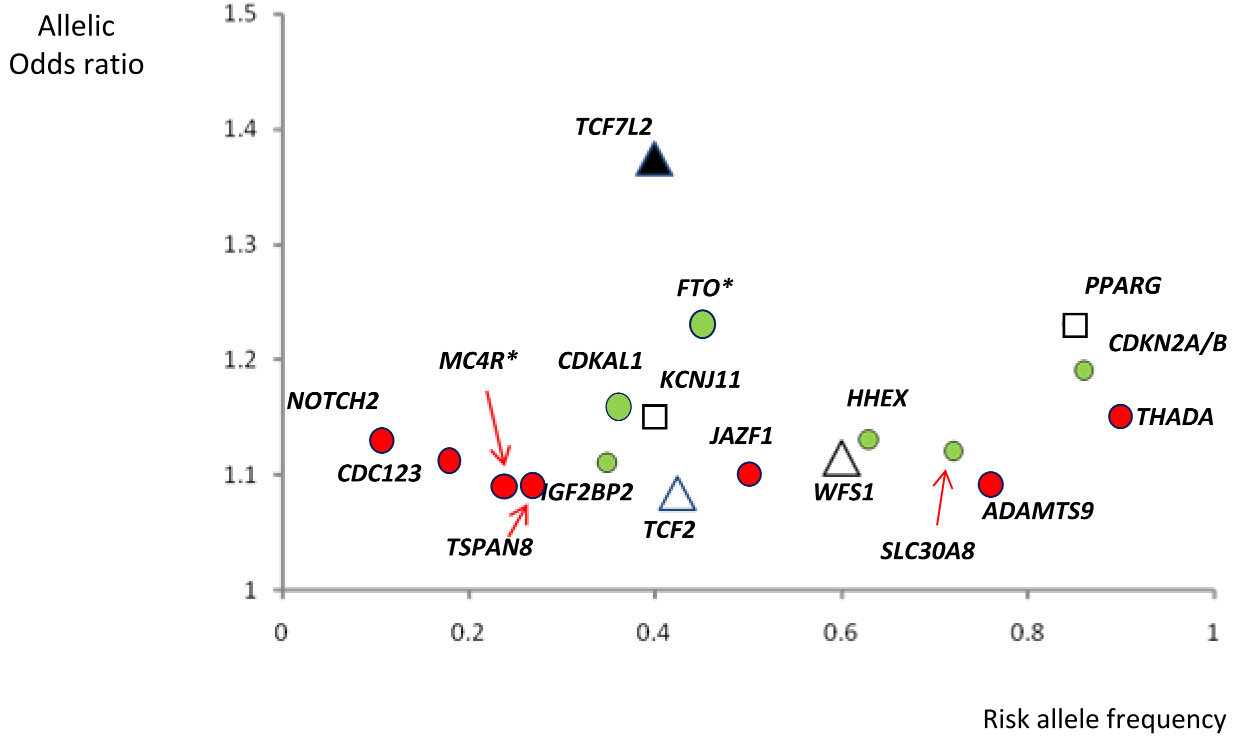
6 definite new genes ($p<5x10^{-8}$)
T2D genes #12 - 17

Zeggini et al, NG, in press

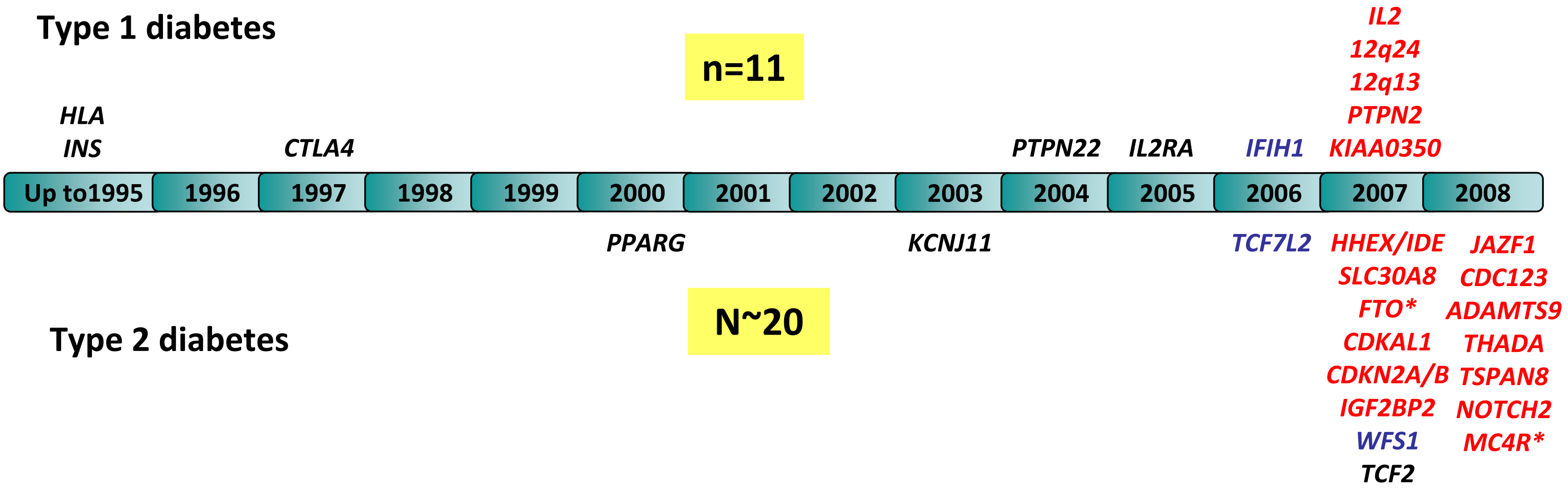
New T2D genes

			Stage 1 (DGI, FUSION, WTCCC)		All data		
Chr	**risk allele frequency**	**nearest gene(s)**	**OR (95%CI)**	***P* value**	**n_{eff}**	**OR (95%CI)**	***P* value**
7	**0.501**	***JAZF1***	**1.14 (1.07-1.20)**	**1.5E-04**	**59,617**	**1.10 (1.07-1.13)**	**5.0E-14**
10	**0.183**	***CDC123/CAMK1D***	**1.15 (1.06-1.24)**	**4.2E-04**	**62,366**	**1.11 (1.07-1.14)**	**1.2E-10**
12	**0.269**	***TSPAN8/LGR5***	**1.18 (1.10-1.26)**	**1.8E-05**	**62,301**	**1.09 (1.06-1.12)**	**1.1E-09**
2	**0.902**	***THADA***	**1.25 (1.12-1.40)**	**1.8E-04**	**60,832**	**1.15 (1.10-1.20)**	**1.1E-09**
3	**0.761**	***ADAMTS9***	**1.13 (1.06-1.22)**	**5.4E-04**	**62,387**	**1.09 (1.06-1.12)**	**1.2E-08**
1	**0.106**	***NOTCH2***	**1.30 (1.17-1.43)**	**1.1E-04**	**58,667**	**1.13 (1.08-1.17)**	**4.1E-08**

Zeggini et al, NG 2008

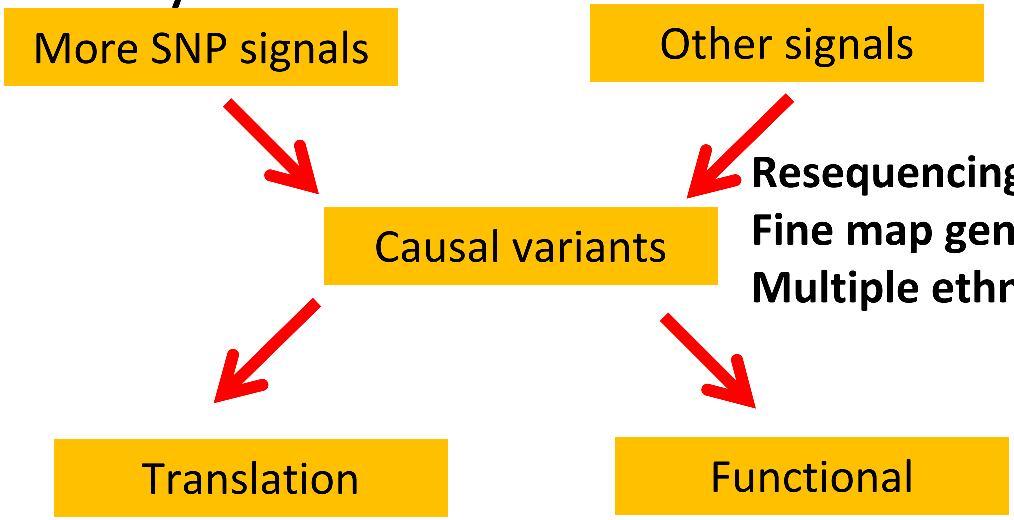

Allelic
Odds ratio
1.5
1.4
1.3
1.2
1.1
1
0
0.2
0.4
0.6
0.8
1
Risk allele frequency
TCF7L2
FTO*
PPARG
CDKN2A/B
MC4R*
CDKAL1
KCNJ11
NOTCH2
HHEX
THADA
JAZF1
CDC123
IGF2BP2
WFS1
TCF2
ADAMTS9
TSPAN8
SLC30A8

Keeping count...



Candidate gene approaches
High throughput LD mapping
Genome wide LD mapping
* Via primary effect on adiposity

Ongoing work



Larger metaanalyses
Other ethnic groups
Deeper replication
Functional “overlay”

More SNP signals

Global CNV screens
Resequencing
Rare-signal mining
Epi-SNPs

Other signals

Causal variants

Resequencing
Fine map genotyping
Multiple ethnic groups

Translation

Epidemiology – joint effects
Prediction
New biology
New drugs

Functional

Cellular studies
Animal models
Integrative physiology
Systems biology

Type 2 diabetes genes...

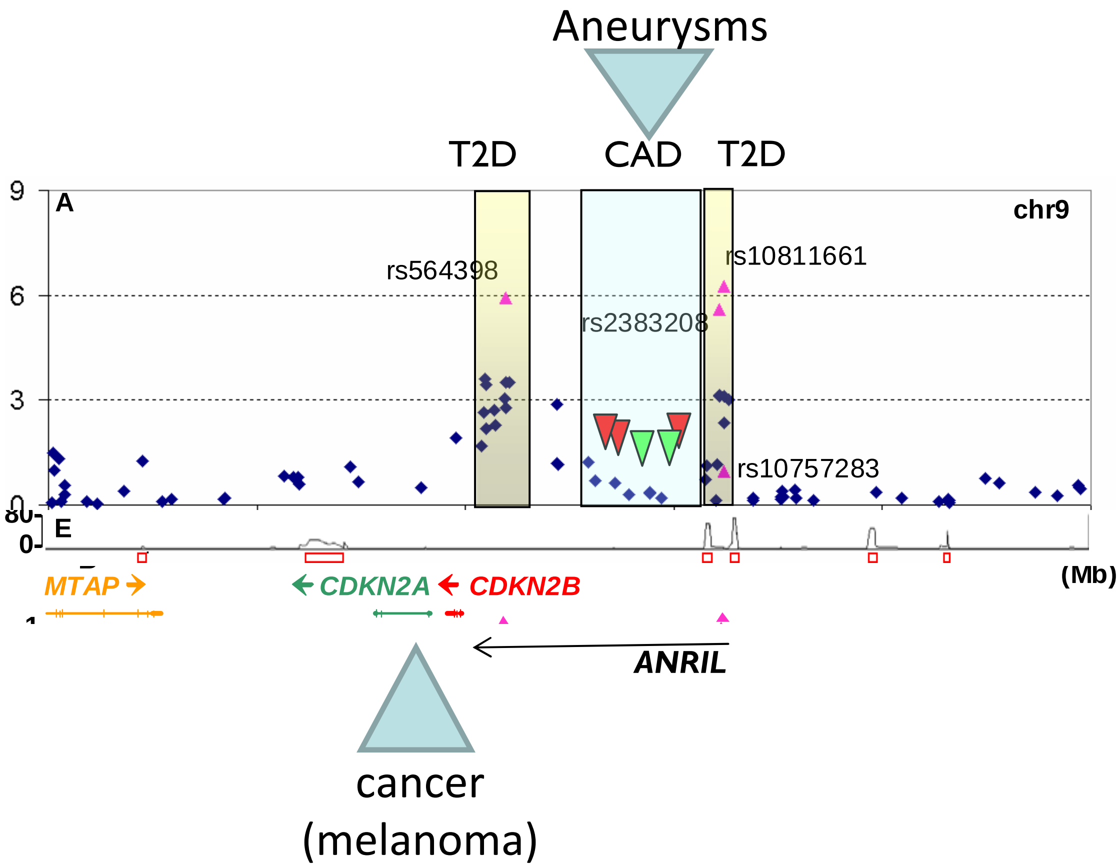
... and cancer

(PLEIOTROPY)

... and birthweight

(COMPLEXITY; NON-LINEARITY)

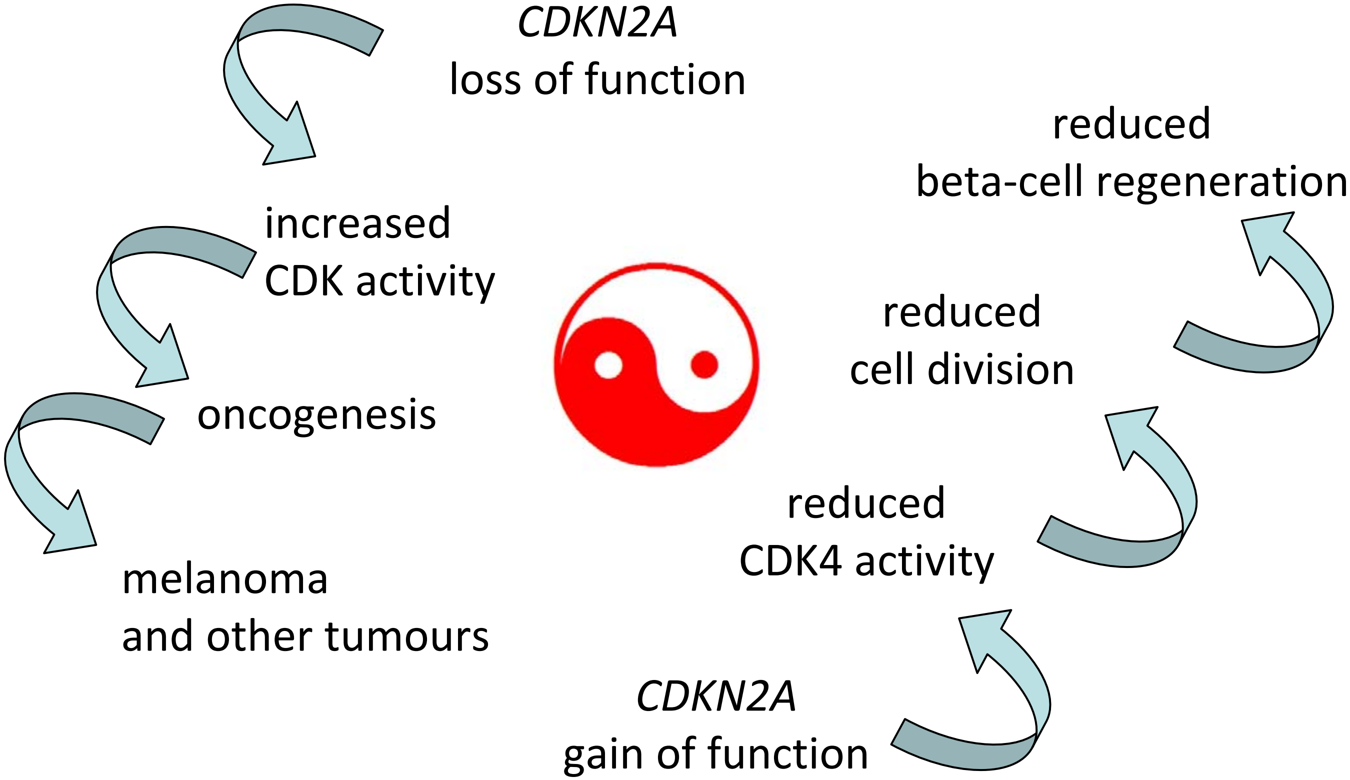
T2D and coronary artery disease signals..



Aneurysms

cancer
(melanoma)

The yin and yang of diabetes and cancer



CDKN2A
loss of function

increased
CDK activity

oncogenesis

melanoma
and other tumours

CDKN2A
gain of function

reduced
CDK4 activity

reduced
cell division

reduced
beta-cell regeneration

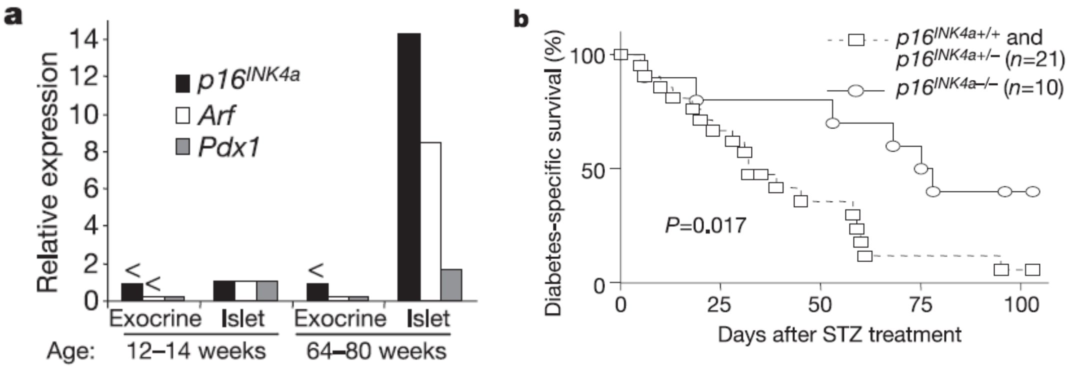
Cancer and diabetes

Vol 443|28 September 2006|doi:10.1038/nature05092 nature

LETTERS

p16^{INK4a} induces an age-dependent decline in islet regenerative potential

Janakiraman Krishnamurthy[1], Matthew R. Ramsey[1], Keith L. Ligon[2], Chad Torrice[1], Angela Koh[3], Susan Bonner-Weir[3] & Norman E. Sharpless[1]

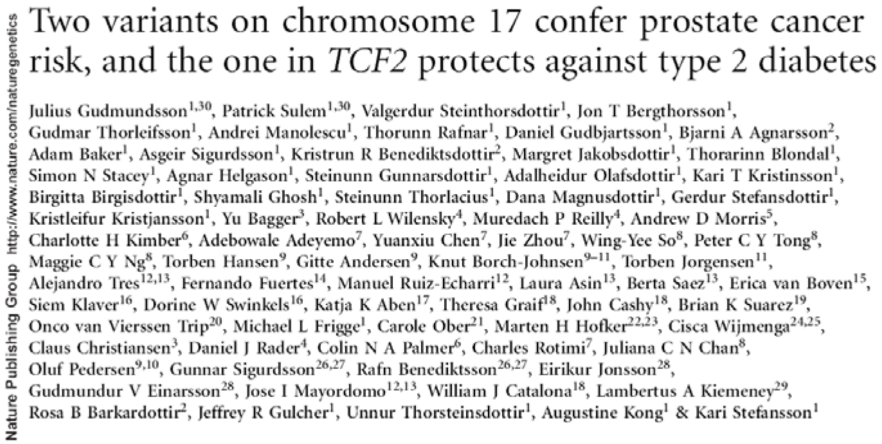


Cdkn2a expression in islet increases with age (effector of senescence)

Cdkn2a knockouts – enhanced islet survival

Cdkn2a overexpression/*Cdk4* knockouts → reduced islet regeneration, islet hypoplasia, T2D

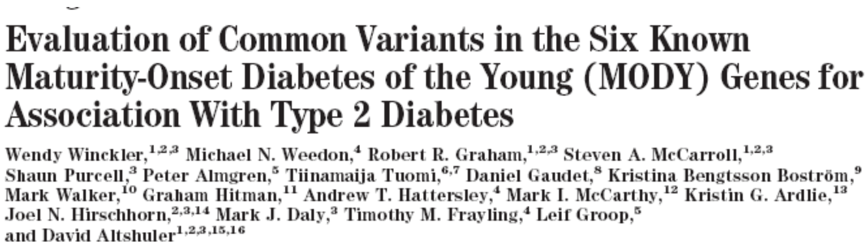
Pleiotropy



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

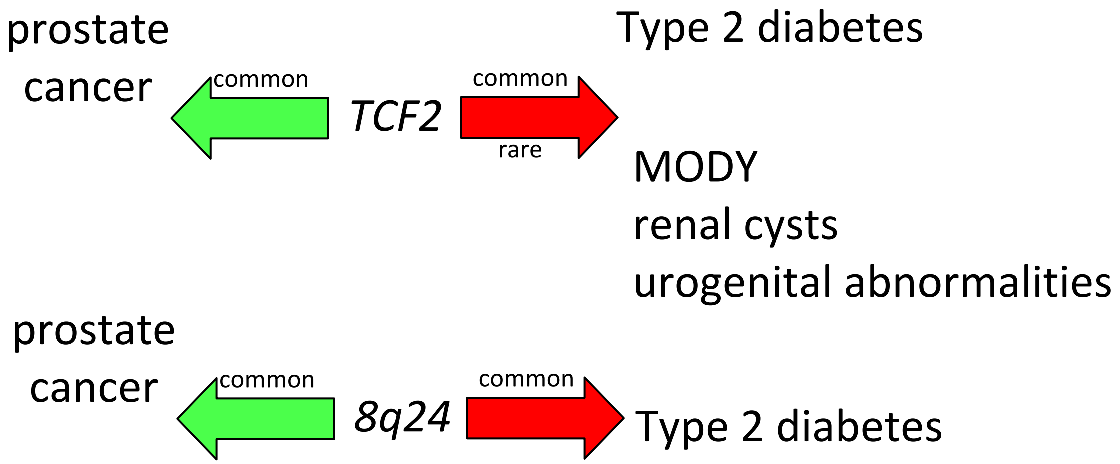
Julius Gudmundsson[1,30], Patrick Sulem[1,30], Valgerdur Steinthorsdottir[1], Jon T Bergthorsson[1], Gudmar Thorleifsson[1], Andrei Manolescu[1], Thorunn Rafnar[1], Daniel Gudbjartsson[1], Bjarni A Agnarsson[2], Adam Baker[1], Asgeir Sigurdsson[1], Kristrun R Benediktsdottir[2], Margret Jakobsdottir[1], Thorarinn Blondal[1], Simon N Stacey[1], Agnar Helgason[1], Steinunn Gunnarsdottir[1], Adalheidur Olafsdottir[1], Kari T Kristinsson[1], 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], Oluf 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]

Nature Publishing Group http://www.nature.com/naturegenetics



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 R. 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]



prostate cancer

common

TCF2

common

rare

Type 2 diabetes

MODY

renal cysts

urogenital abnormalities

prostate cancer

common

8q24

common

Type 2 diabetes

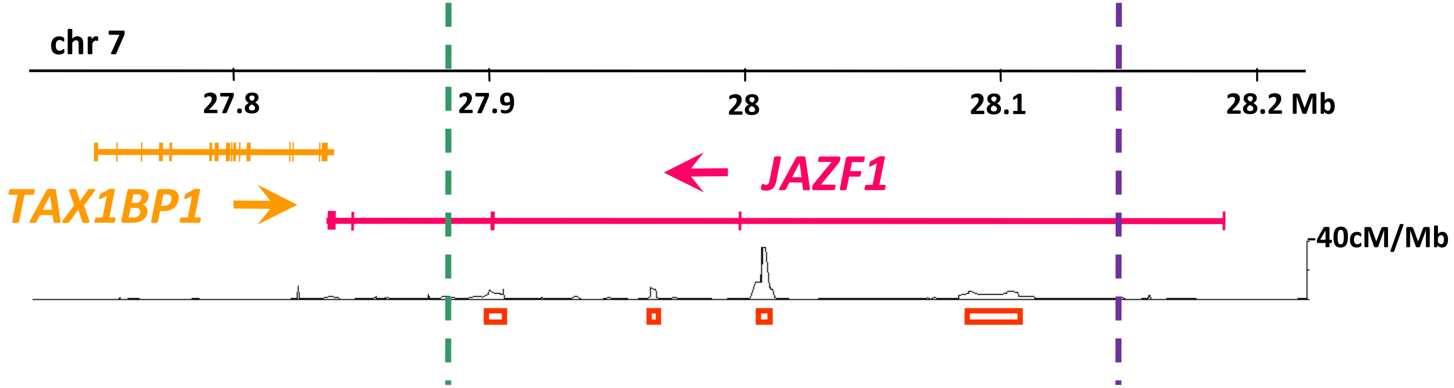
JAZF1

Zeggini *et al.*, Nat Gen 2008

T2D risk

OR = 1.26
(95%CI:1.17-1.34)
p = 2.14×10^{-6}

rs864745(T)



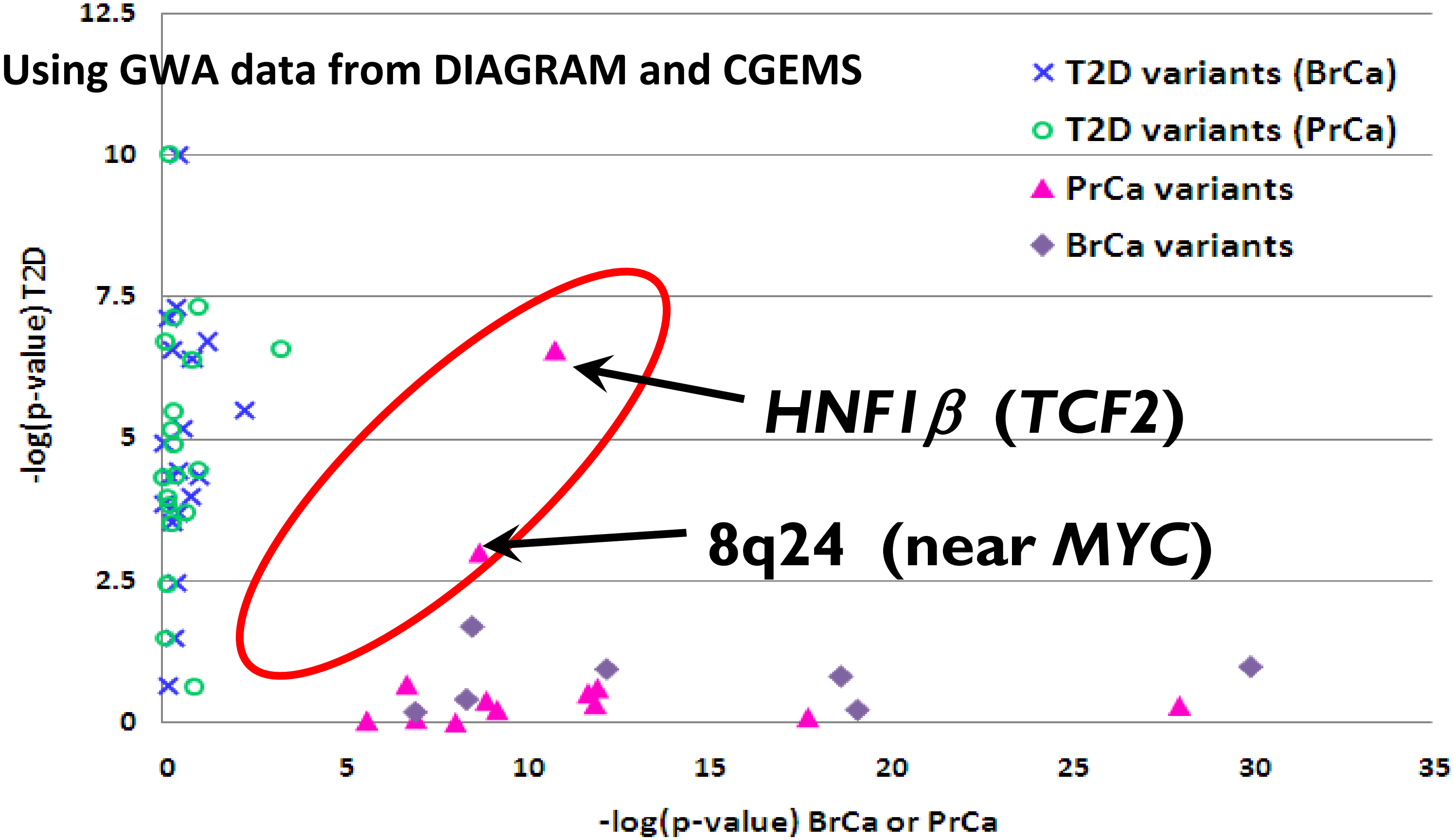
rs10486567(G)

PrCa risk

OR = 1.10
(95%CI:1.07-1.13)
p = 5×10^{-14}

Thomas *et al.*, Nat Gen 2008

T2D vs Ca associations at proven variants


Using GWA data from DIAGRAM and CGEMS

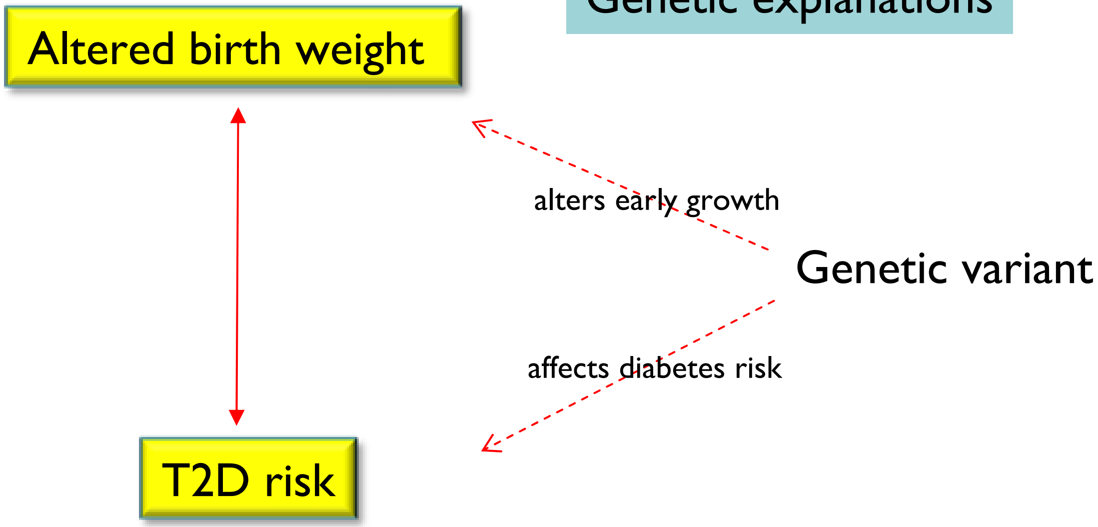
HNF1β (*TCF2*)

8q24 (near *MYC*)

Birthweight

Non-genetic explanations

Genetic explanations



Altered birth weight

T2D risk

Genetic variant

alters early growth

affects diabetes risk

Fetal origins hypothesis

Low BW – diabetes risk

Diabetic uterus effect

High BW – diabetes risk

Genes influencing insulin secretion are particularly good candidates for such a shared role

Glucokinase = proof of principle

Variable effect on birthweight

- *TCF7L2* diabetes risk allele → increased BW

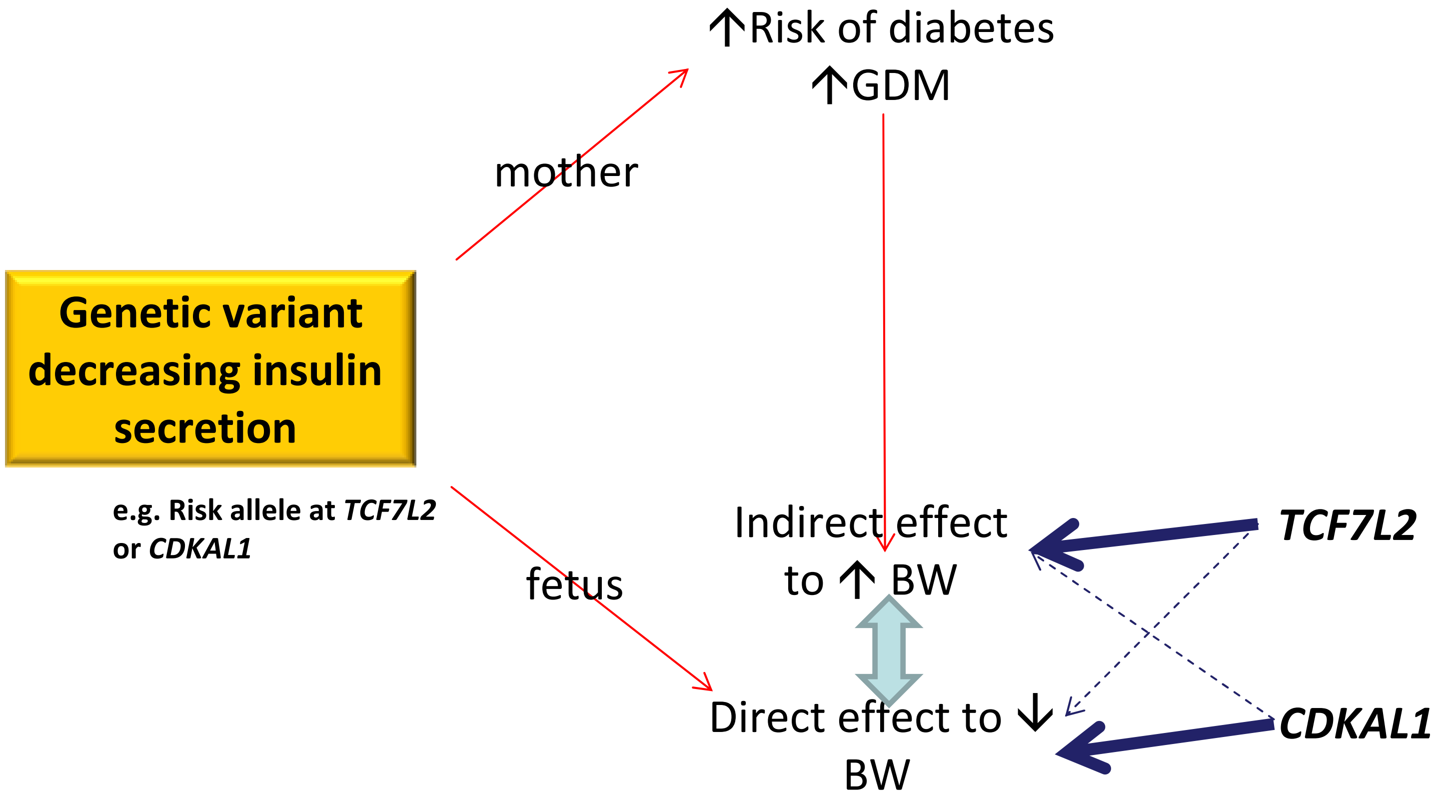
  (Freathy et al, AJHG 2007)

- *CDKAL1* diabetes risk allele → decreased BW

  (Freathy et al, submitted)

- Other diabetes risk alleles → no effect on BW

What’s going on?



Genetic variant decreasing insulin secretion

e.g. Risk allele at *TCF7L2* or *CDKAL1*

mother

↑Risk of diabetes

↑GDM

fetus

Indirect effect to ↑ BW

Direct effect to ↓ BW

TCF7L2

CDKAL1

Direction of effect on BW is a “bioassay” of the timing of the beta-cell defect

Continuous glycemic traits

MAGIC consortium

GWA based discovery in ~50,000

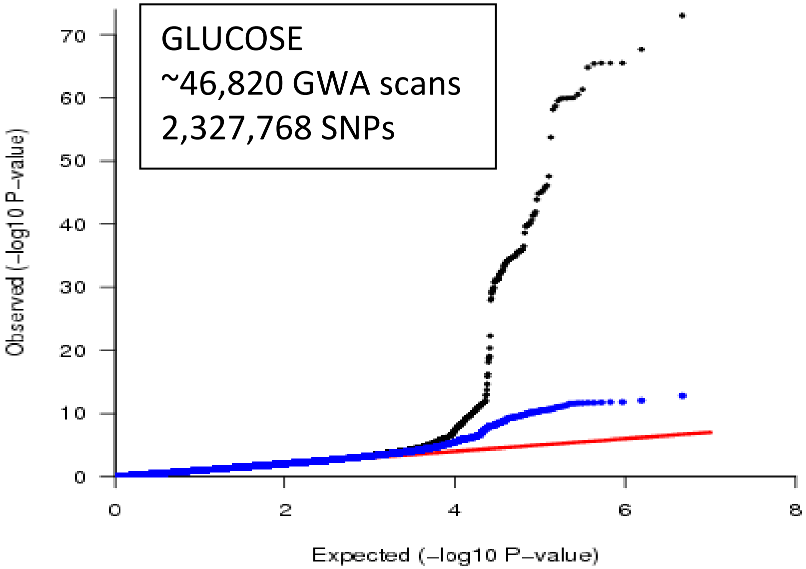
DeCODE genetics
Northern Finland Birth Cohort 1966
Netherlands Twin Resource/NESDA
Rotterdam cohort
KORA
EUROSPAN, Sorbs
CoLaus
Twins UK
Framingham Heart Study
Diabetes Genetics Initiative
FUSION
SardiNIA
Baltimore Study of Ageing (BLSA)
CHS
Inchianti
Procardis
GEMS

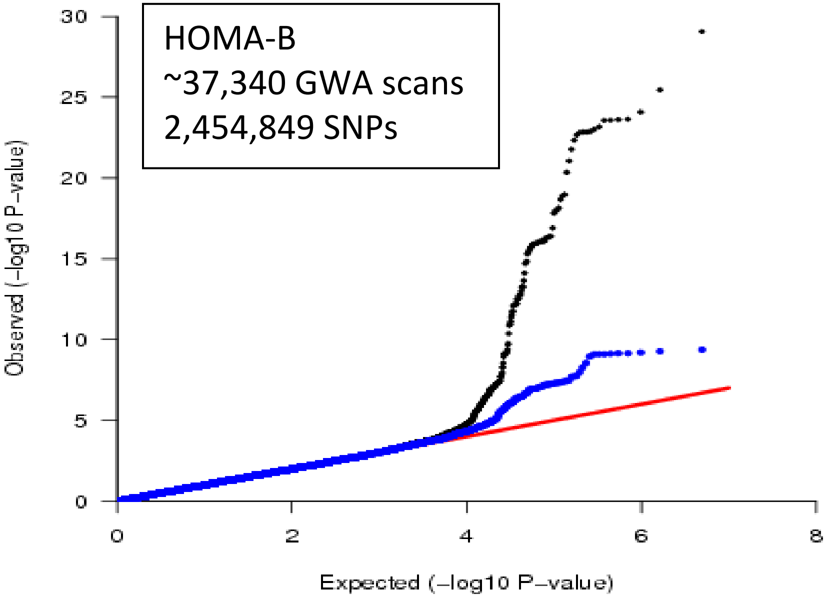
Finrisk 2007
Health 2000
BWHHS
Segovia
Caerphilly
Twins UK
Oxford Biobank
Neth Twin Resource
GHRAS
GENDAI

Ely
Fenland
EYHS
FUSION
METSIM
DIAGEN
PIVUS
ULSAM
DARTS
NFBC86
DESIR

Replication studies in ~70,000

More MAGIC


GLUCOSE
~46,820 GWA scans
2,327,768 SNPs
Observed (–log10 P–value)
0
10
20
30
40
50
60
70
0
2
4
6
8
Expected (–log10 P–value)


HOMA-B
~37,340 GWA scans
2,454,849 SNPs
Observed (–log10 P–value)
0
5
10
15
20
25
30
0
2
4
6
8
Expected (–log10 P–value)

Physiology and pathology

PHYSIOLOGICAL
VARIATION IN THE
FASTING GLUCOSE SETPOINT

vs

PATHOLOGICAL
VARIATION IN THE
BETA-CELL RESPONSE
TO INSULIN RESISTANCE

GCK
GKRP
G6PC2

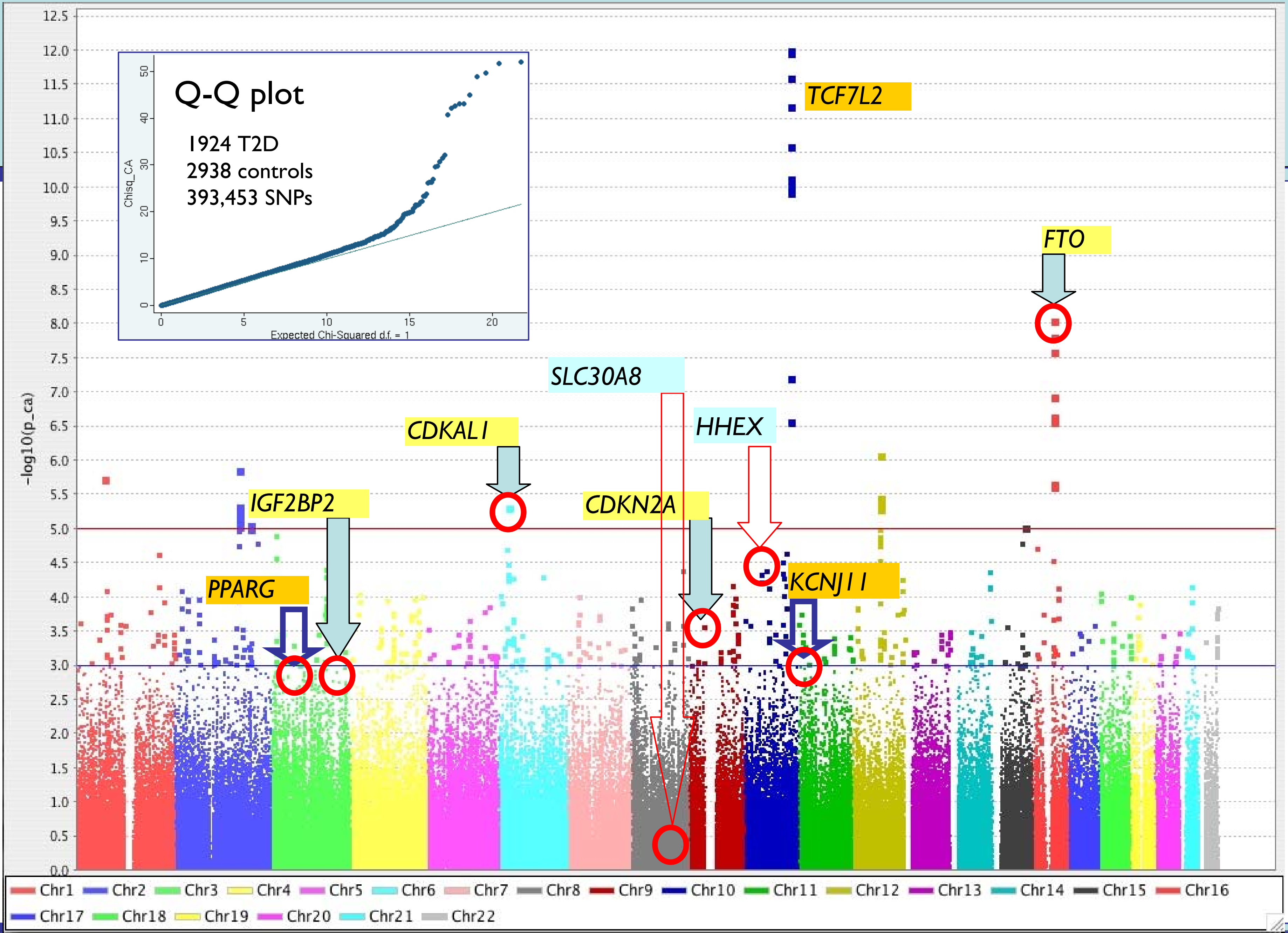
CDKN2A
CDKAL1
HHEX
JAZF1
THADA
....

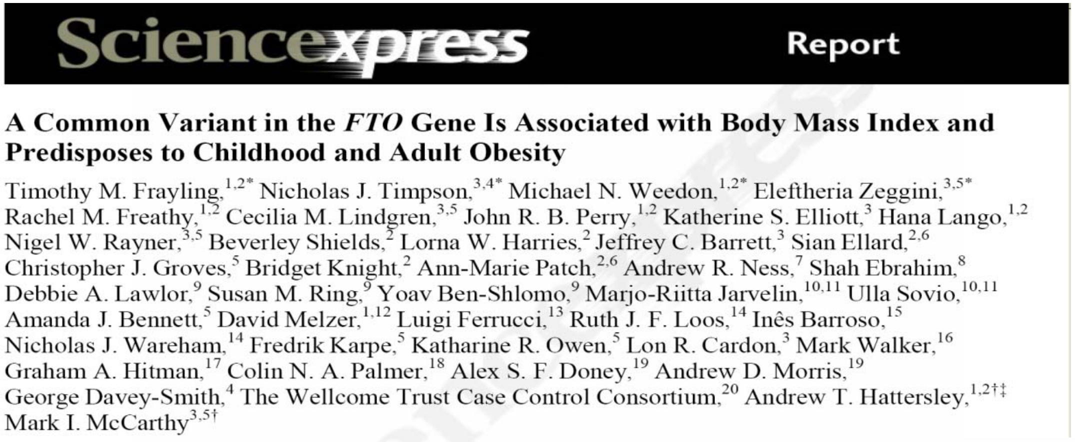
Little or no effect on T2D risk

Little or no effect on fasting glucose levels (provided subclinical T2D excluded)

Except *MTNR1B*

Weight, adiposity and obesity


Q-Q plot
1924 T2D
2938 controls
393,453 SNPs
Chisq_CA
Expected Chi-Squared d.f. = 1
0
5
10
15
20
10
20
30
40
50
-log10(p_ca)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
11.5
12.0
12.5
TCF7L2
FTO
SLC30A8
CDKAL1
HHEX
IGF2BP2
CDKN2A
KCNJ11
PPARG
Chr1
Chr2
Chr3
Chr4
Chr5
Chr6
Chr7
Chr8
Chr9
Chr10
Chr11
Chr12
Chr13
Chr14
Chr15
Chr16
Chr17
Chr18
Chr19
Chr20
Chr21
Chr22



Sciencexpress Report

A Common Variant in the *FTO* Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity

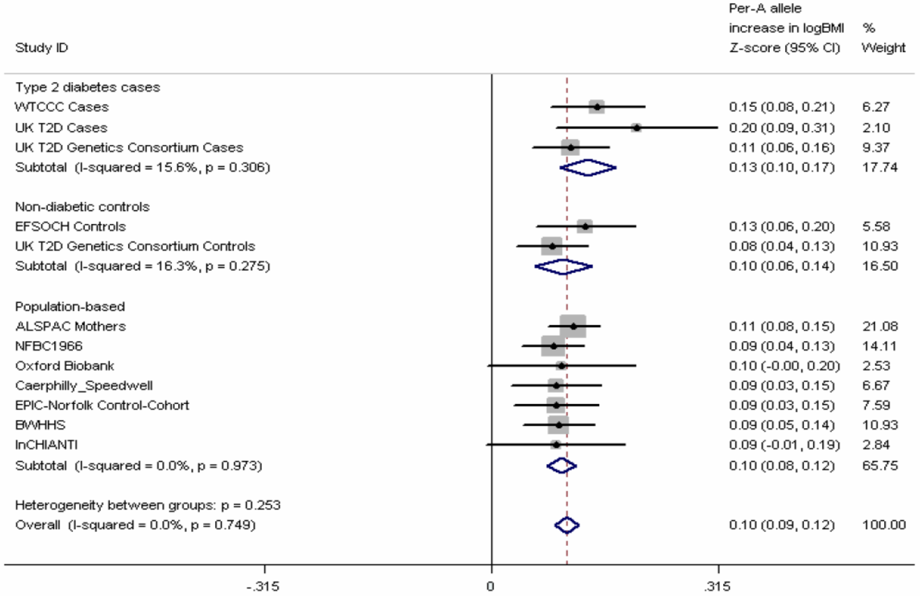
Timothy M. Frayling,[1,2*] Nicholas J. Timpson,[3,4*] Michael N. Weedon,[1,2*] Eleftheria Zeggini,[3,5*] Rachel M. Freathy,[1,2] Cecilia M. Lindgren,[3,5] John R. B. Perry,[1,2] Katherine S. Elliott,[3] Hana Lango,[1,2] Nigel W. Rayner,[3,5] Beverley Shields,[2] Lorna W. Harries,[2] Jeffrey C. Barrett,[3] Sian Ellard,[2,6] Christopher J. Groves,[5] Bridget Knight,[2] Ann-Marie Patch,[2,6] Andrew R. Ness,[7] Shah Ebrahim,[8] Debbie A. Lawlor,[9] Susan M. Ring,[9] Yoav Ben-Shlomo,[9] Marjo-Riitta Jarvelin,[10,11] Ulla Sovio,[10,11] Amanda J. Bennett,[5] David Melzer,[1,12] Luigi Ferrucci,[13] Ruth J. F. Loos,[14] Inês Barroso,[15] Nicholas J. Wareham,[14] Fredrik Karpe,[5] Katharine R. Owen,[5] Lon R. Cardon,[3] Mark Walker,[16] Graham A. Hitman,[17] Colin N. A. Palmer,[18] Alex S. F. Doney,[19] Andrew D. Morris,[19] George Davey-Smith,[4] The Wellcome Trust Case Control Consortium,[20] Andrew T. Hattersley,[1,2†‡] Mark I. McCarthy[3,5†]

FTO variants
influence adult weight

30,081 adults
from 13 studies

P=3x10^{-35}

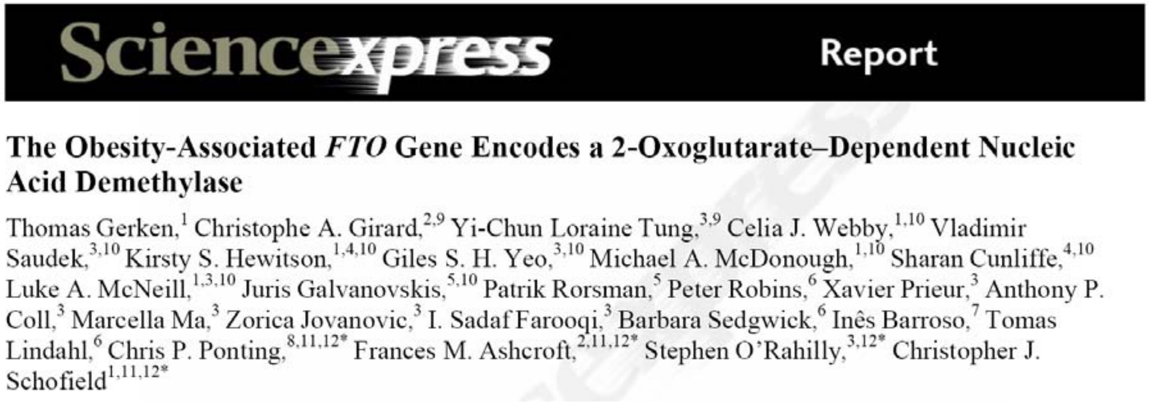
Frayling et al, Science 2007



16% of the population who are homozygous for risk allele ~2-3kg heavier

Independent discoveries subsequently reported by French and US groups

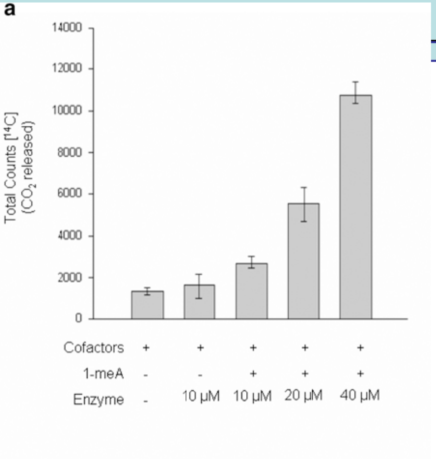
Clues to what *FTO* does

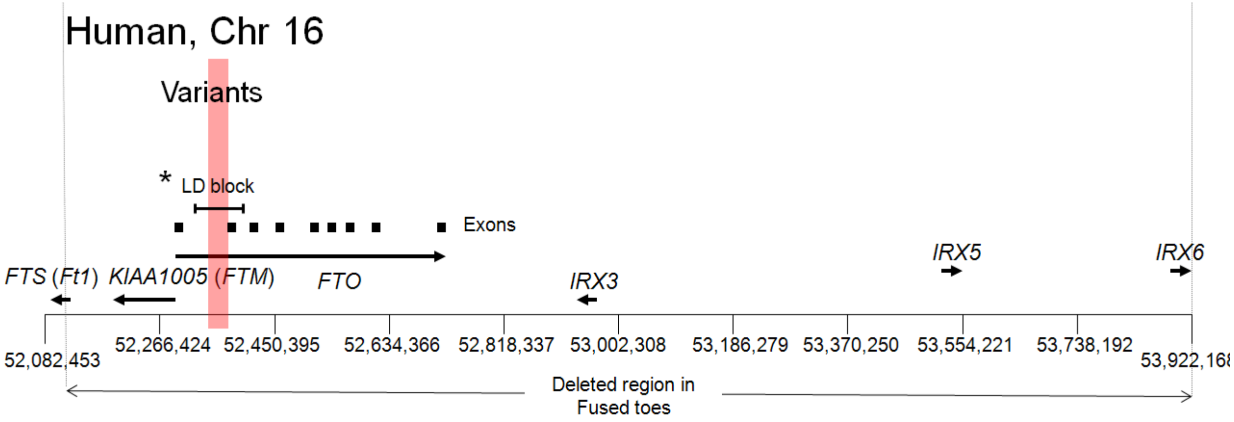


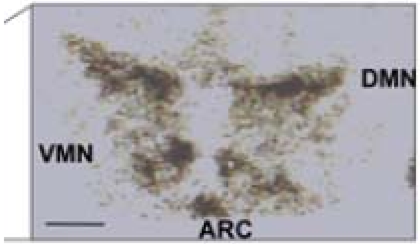
Sciencexpress Report

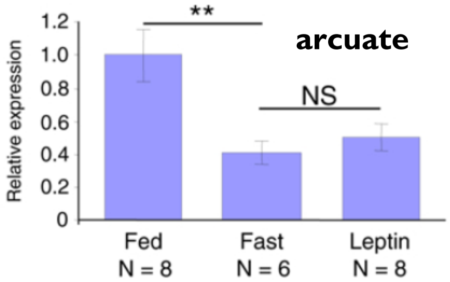
The Obesity-Associated *FTO* Gene Encodes a 2-Oxoglutarate–Dependent Nucleic Acid Demethylase

Thomas Gerken,[1] Christophe A. Girard,[2,9] Yi-Chun Loraine Tung,[3,9] Celia J. Webby,[1,10] Vladimir Saudek,[3,10] Kirsty S. Hewitson,[1,4,10] Giles S. H. Yeo,[3,10] Michael A. McDonough,[1,10] Sharan Cunliffe,[4,10] Luke A. McNeill,[1,3,10] Juris Galvanovskis,[5,10] Patrik Rorsman,[5] Peter Robins,[6] Xavier Prieur,[3] Anthony P. Coll,[3] Marcella Ma,[3] Zorica Jovanovic,[3] I. Sadaf Farooqi,[3] Barbara Sedgwick,[6] Inês Barroso,[7] Tomas Lindahl,[6] Chris P. Ponting,[8,11,12*] Frances M. Ashcroft,[2,11,12*] Stephen O'Rahilly,[3,12*] Christopher J. Schofield[1,11,12*]

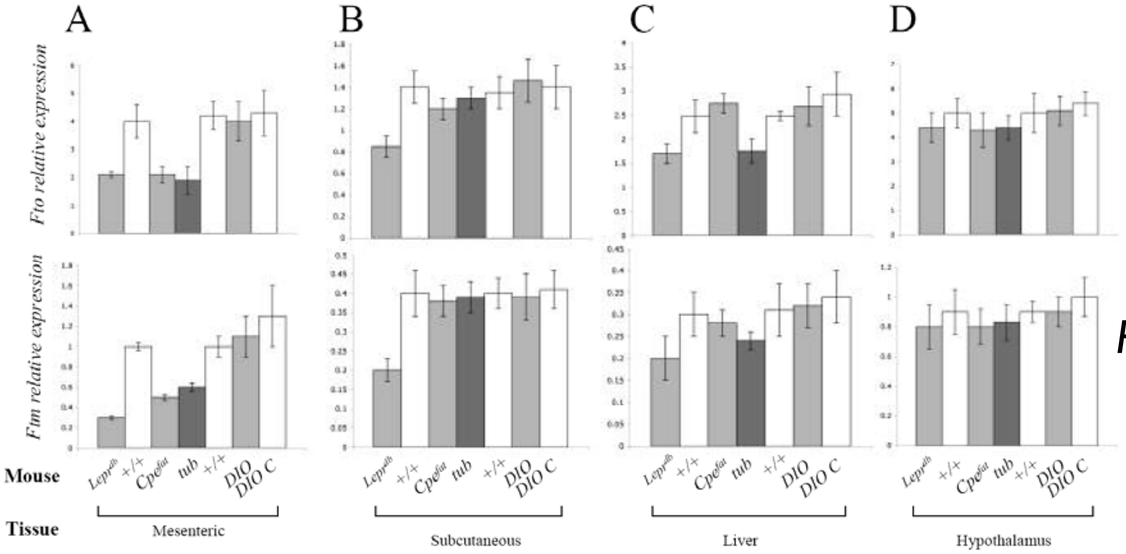






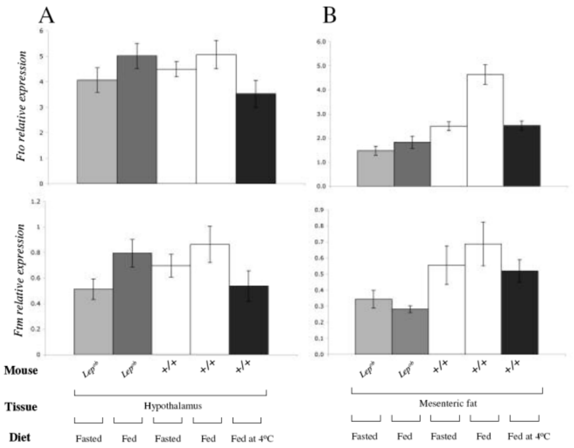


Fto and *Ftm* are coordinately regulated



Fto

Ftm



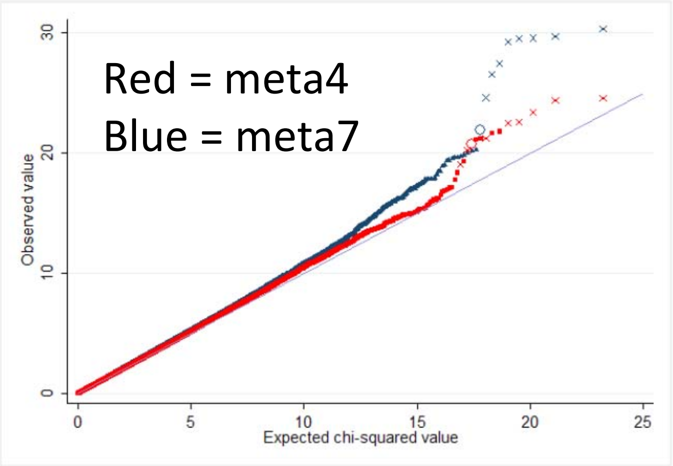
Stratigopolous et al, Am J Physiol 2008

More obesity genes

4 population based
N=11,012
359,062 SNPs

+

3 case series
N=5,864
344,883 SNPs



10 population based
N=40,701

3 case series
N=3,757

+

6 population based
N=13,244

2 case-series
N=2,638

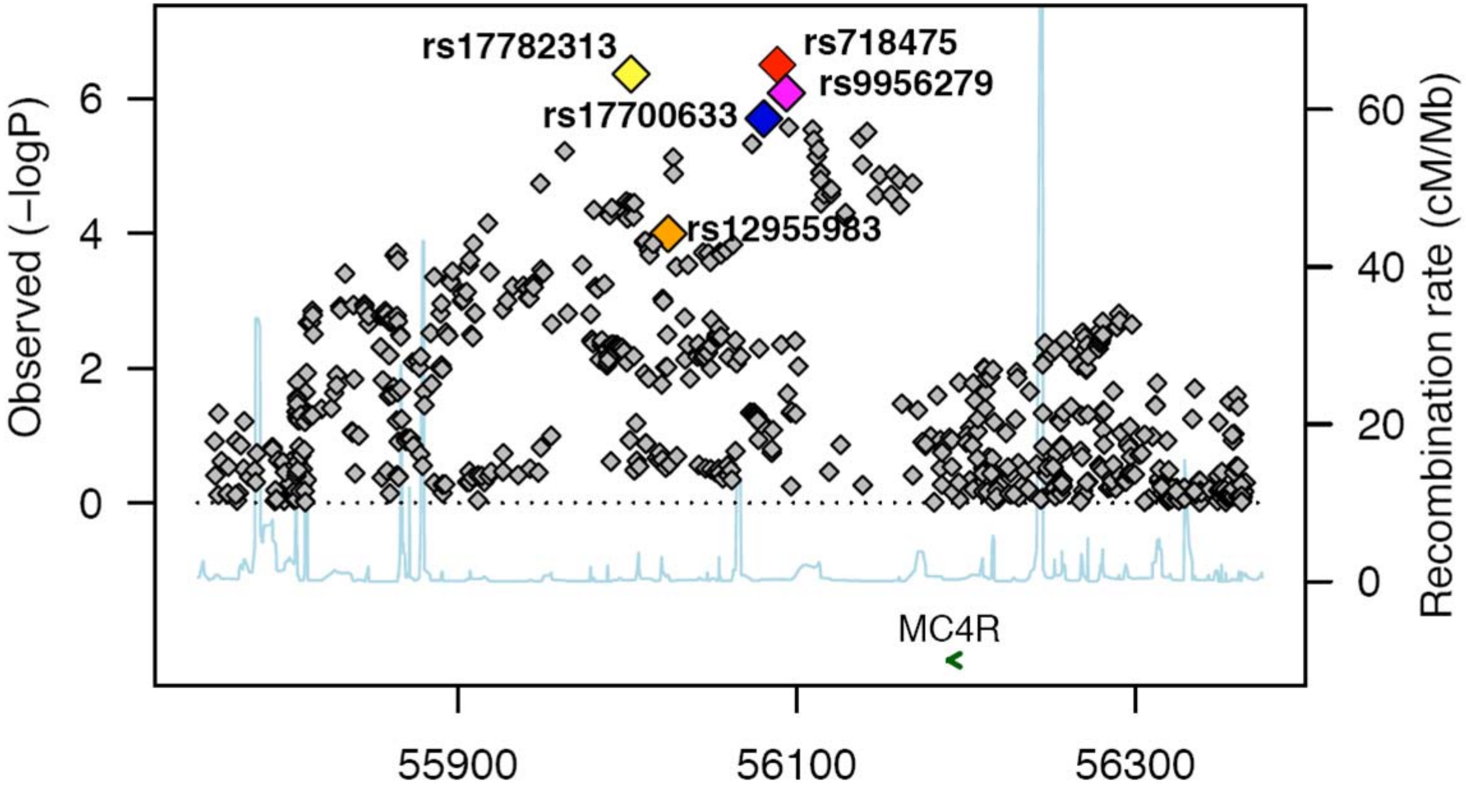
1 childhood cohort
N=5,988

+

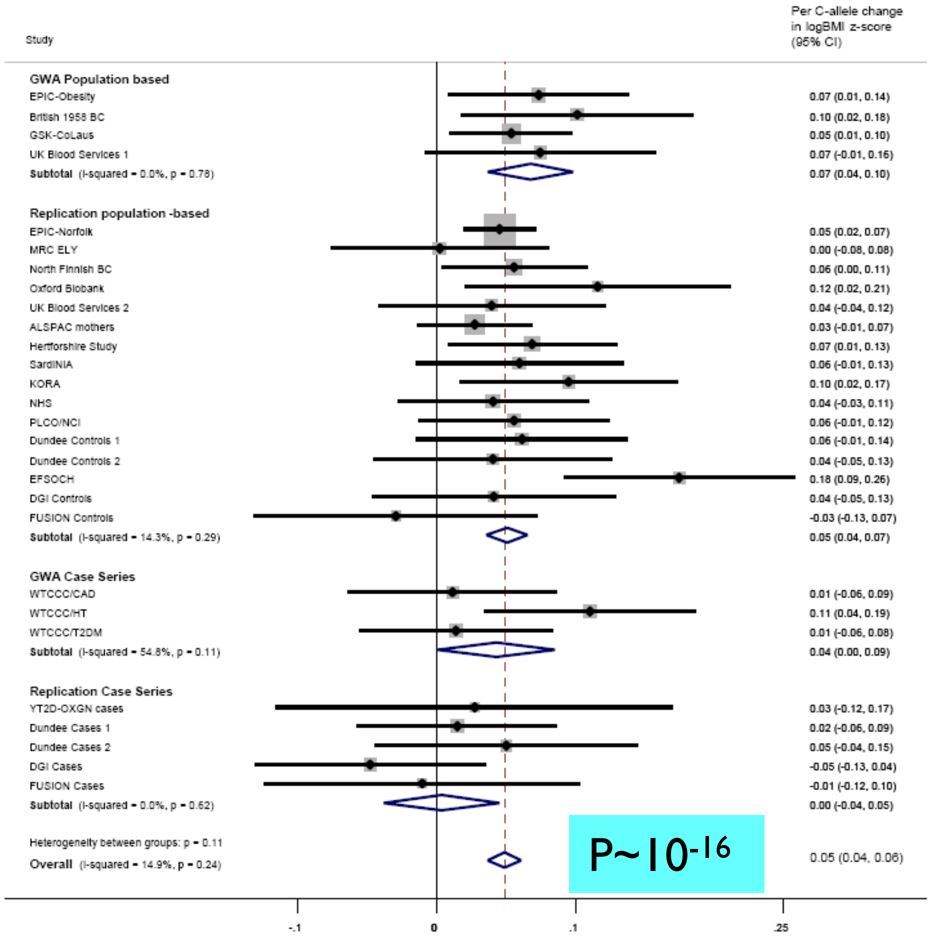
3 childhood case-control
N~7,000

Loos et al, NG, 2008

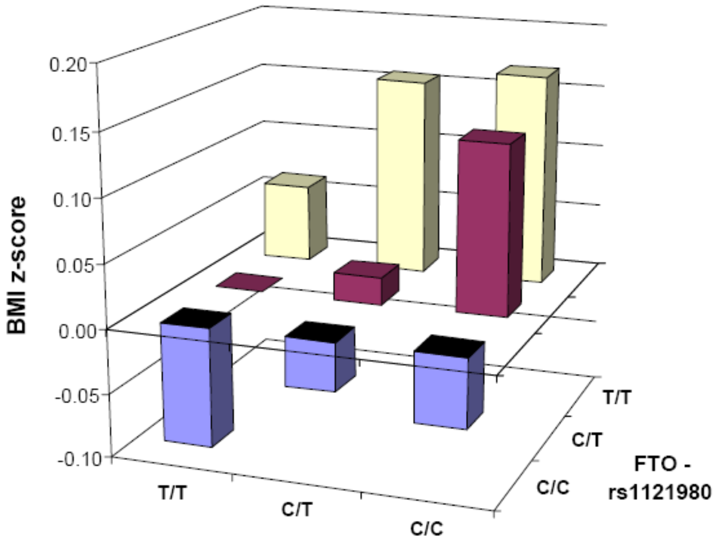
Data from 32,000 GWA scans...



70,000 adults.....



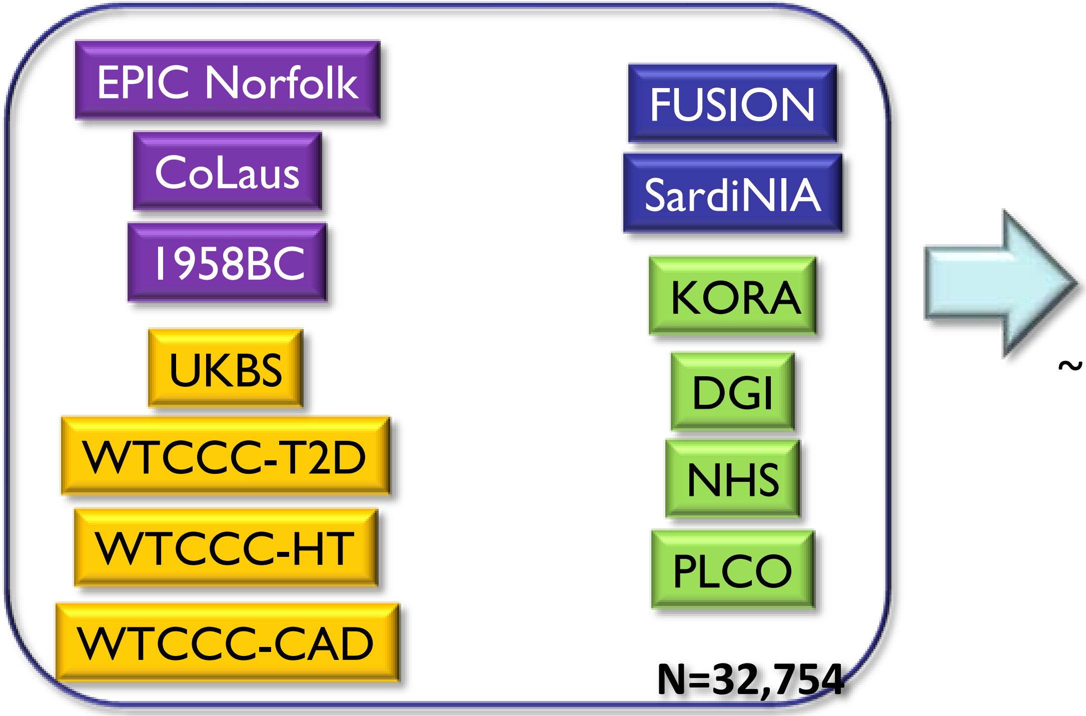
$P \sim 10^{-16}$



Half the effect of FTO
Approx 0.3% variance
5% of a SD

GIANT consortium

- **G**enetic **I**nvestigation of **ANT**hropometric Traits
- Joel Hirschhorn + 11 groups (Oxford, Cambridge, Exeter)



EPIC Norfolk

CoLaus

1958BC

UKBS

WTCCC-T2D

WTCCC-HT

WTCCC-CAD

FUSION

SardiNIA

KORA

DGI

NHS

PLCO

N=32,754

8 more BMI signals
~50 more height signals
~5 signals for central adiposity

More genes....

GIANT
CONSORTIUM

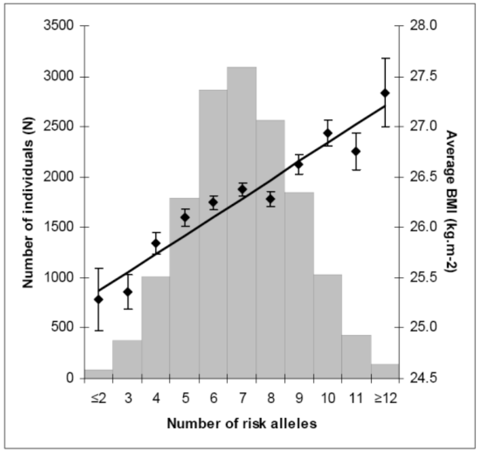
Combine
GWAs from
32000 individuals

+

Check top hits in
GWAs from
44,000 individuals

+

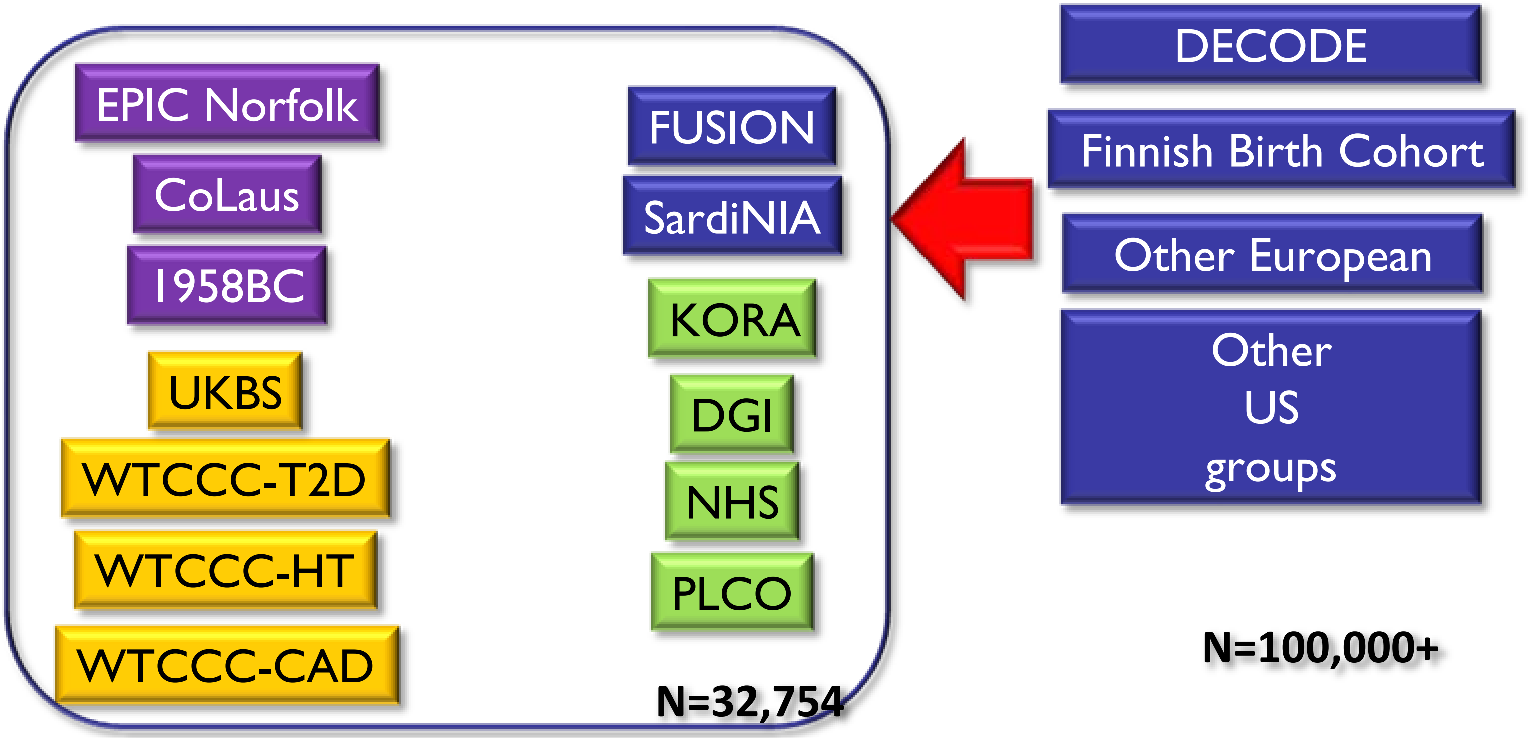
Do more genotyping
in 40,000 samples



Willer et al, NG in revision

GIANT consortium

- **G**enetic **I**nvestigation of **ANT**hropometric Traits
- Joel Hirschhorn + 11 groups (Oxford, Cambridge, Exeter)



EPIC Norfolk

CoLaus

1958BC

UKBS

WTCCC-T2D

WTCCC-HT

WTCCC-CAD

FUSION

SardiNIA

KORA

DGI

NHS

PLCO

N=32,754

DECODE

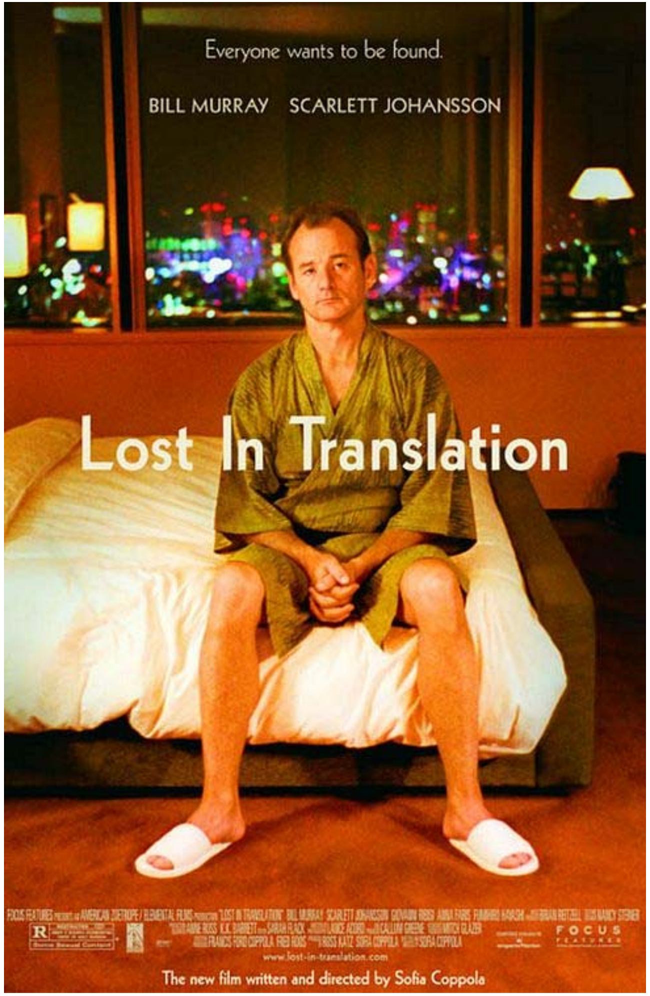
Finnish Birth Cohort

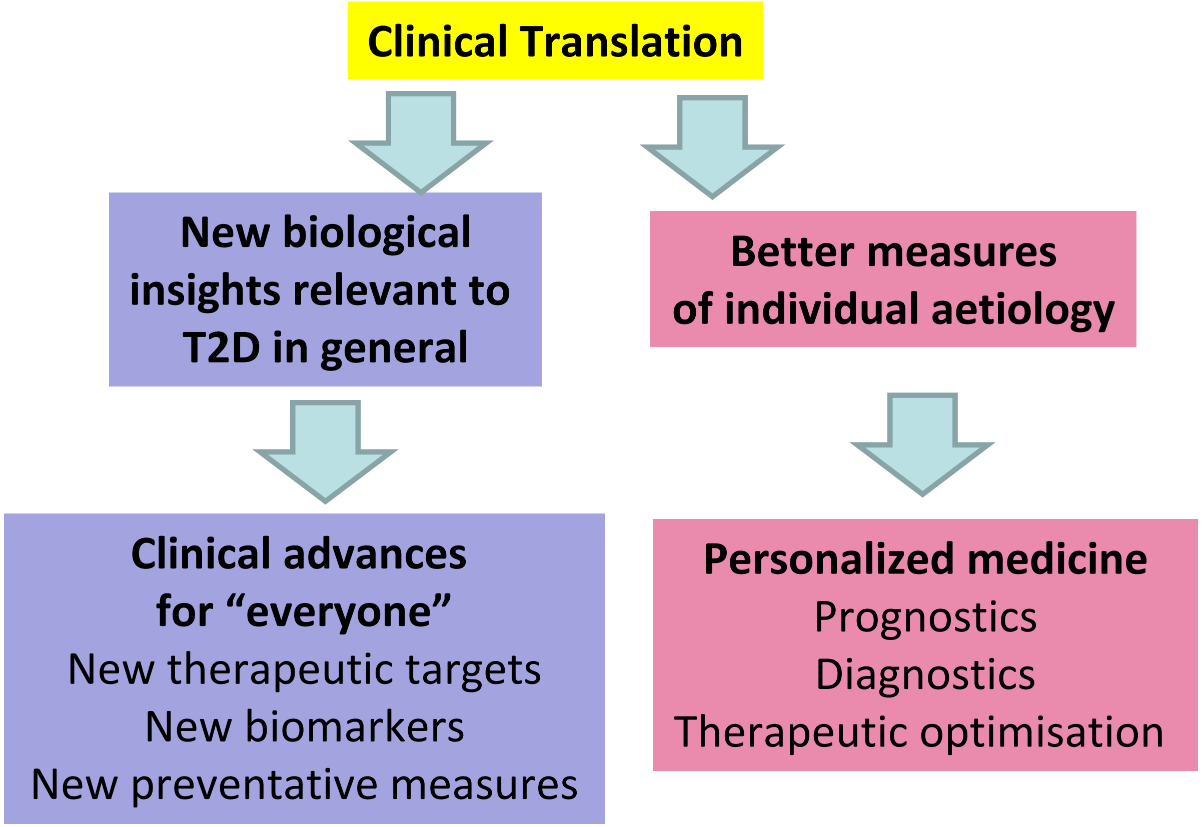
Other European

Other
US
groups

N=100,000+

Translation





Clinical Translation

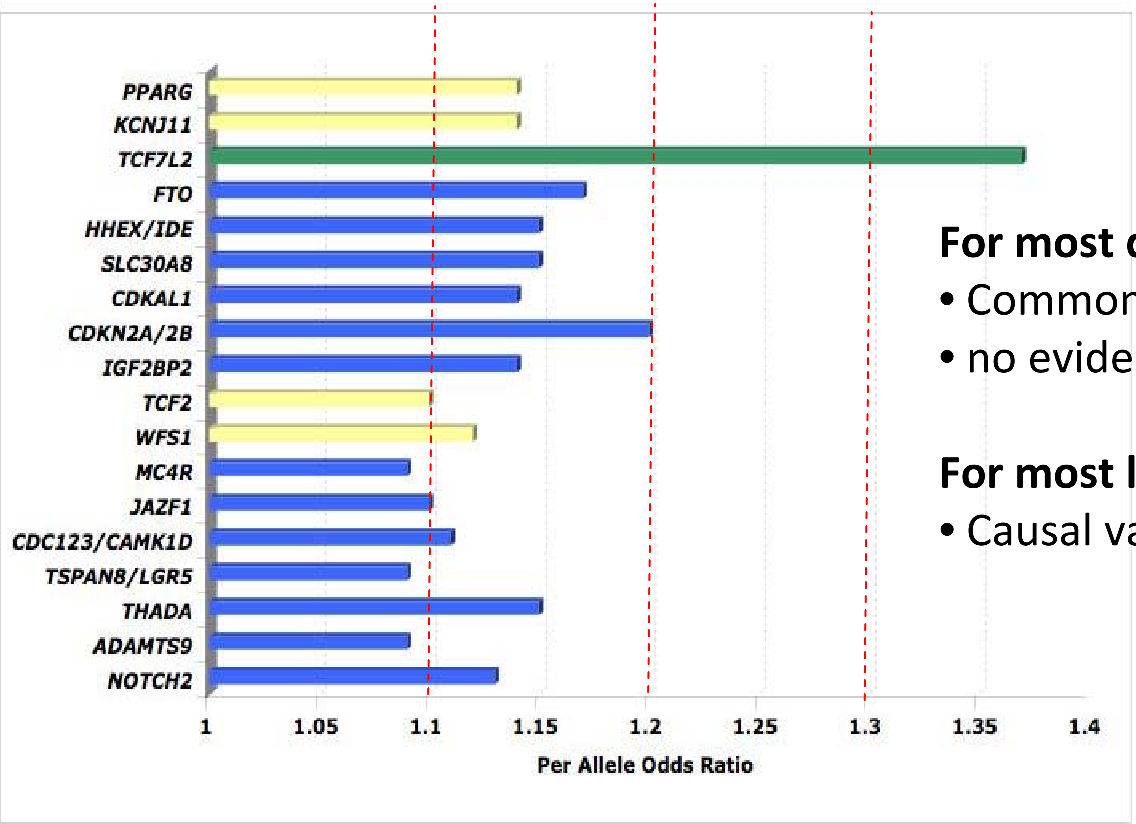
New biological insights relevant to T2D in general

Clinical advances for "everyone"
New therapeutic targets
New biomarkers
New preventative measures

Better measures of individual aetiology

Personalized medicine
Prognostics
Diagnostics
Therapeutic optimisation

Number and size



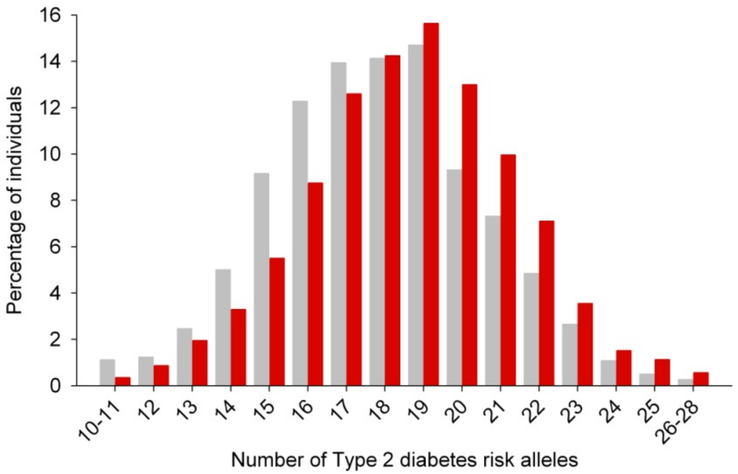
For most diseases

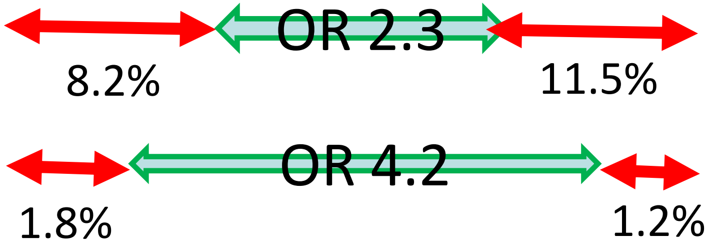
- Common variants of modest effect
- no evidence of departure from additivity

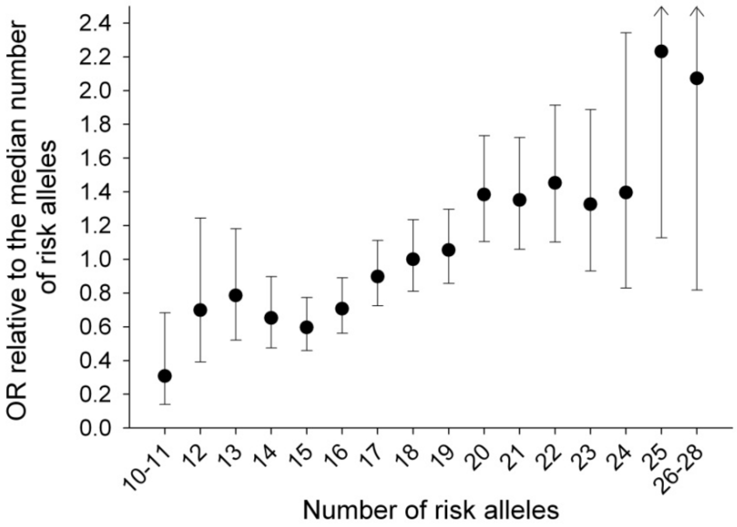
For most loci

- Causal variants not yet known

Individualised “prediction”





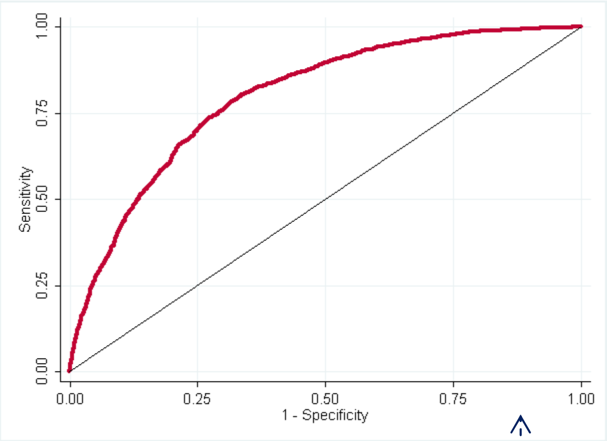


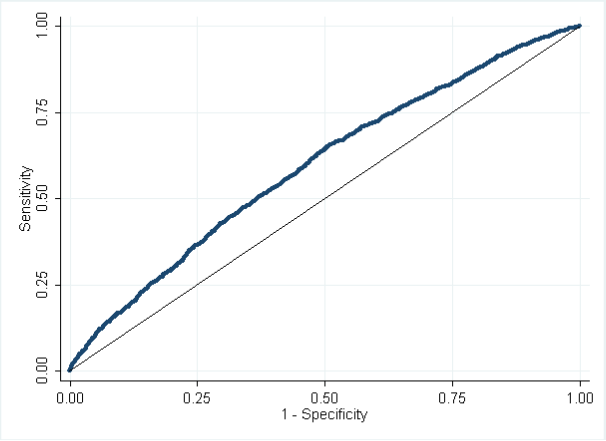
Big effects of “possible” clinical value restricted to just a small proportion

Limited empirical evidence that this information would translate into better outcomes…

Weedon et al, PLOS, 2007
Lango et al, Diabetes 2008

Individualised "prediction"

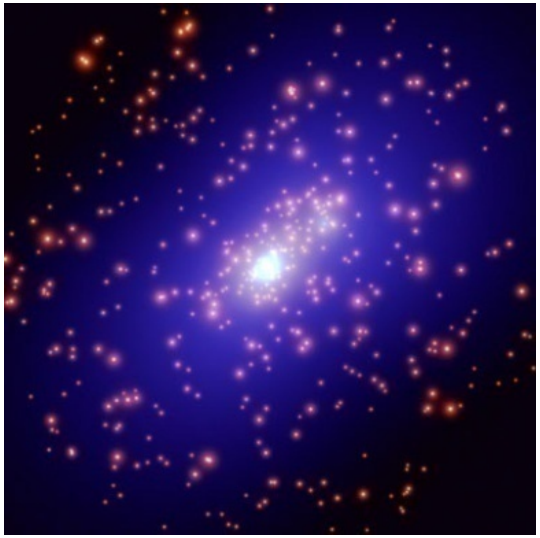




11 variants (-FTO), BMI, age	**AUC = 80%**
BMI and age	**AUC = 78%**
12 variants	**AUC = 59%**

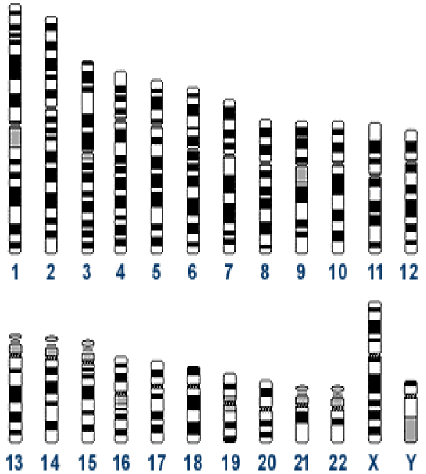
Sibling relative risk (overall)	3.0
Sibling relative risk (18 genes)	1.07

So where's the "dark matter"?

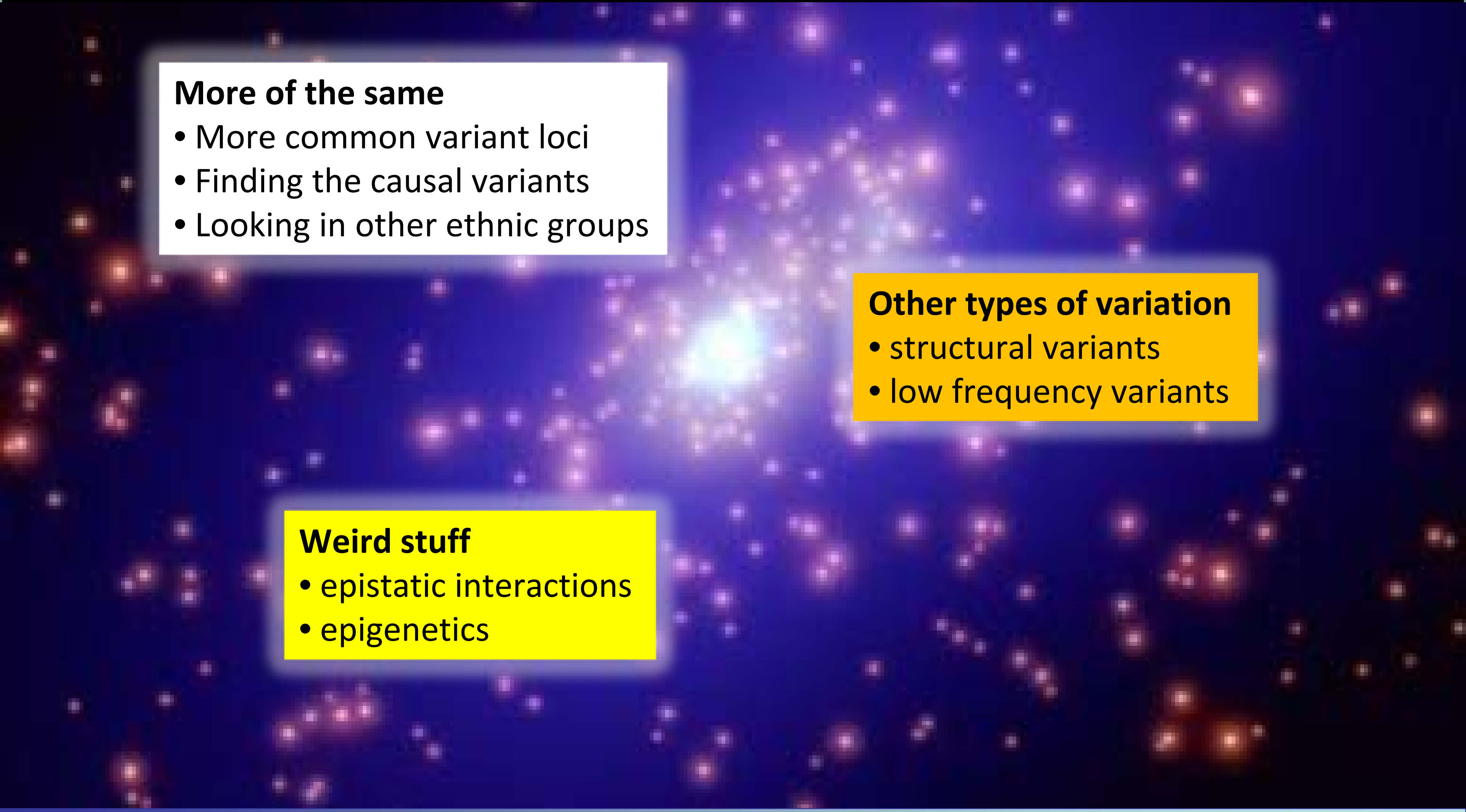


Mismatch between visible mass of the universe &
that inferred from gravitational effects on visible matter
➔ **"dark matter"**

Mismatch between genes found &
that inferred from measures of heritability
➔ **"dark heritability"**



So where’s the “dark matter”?

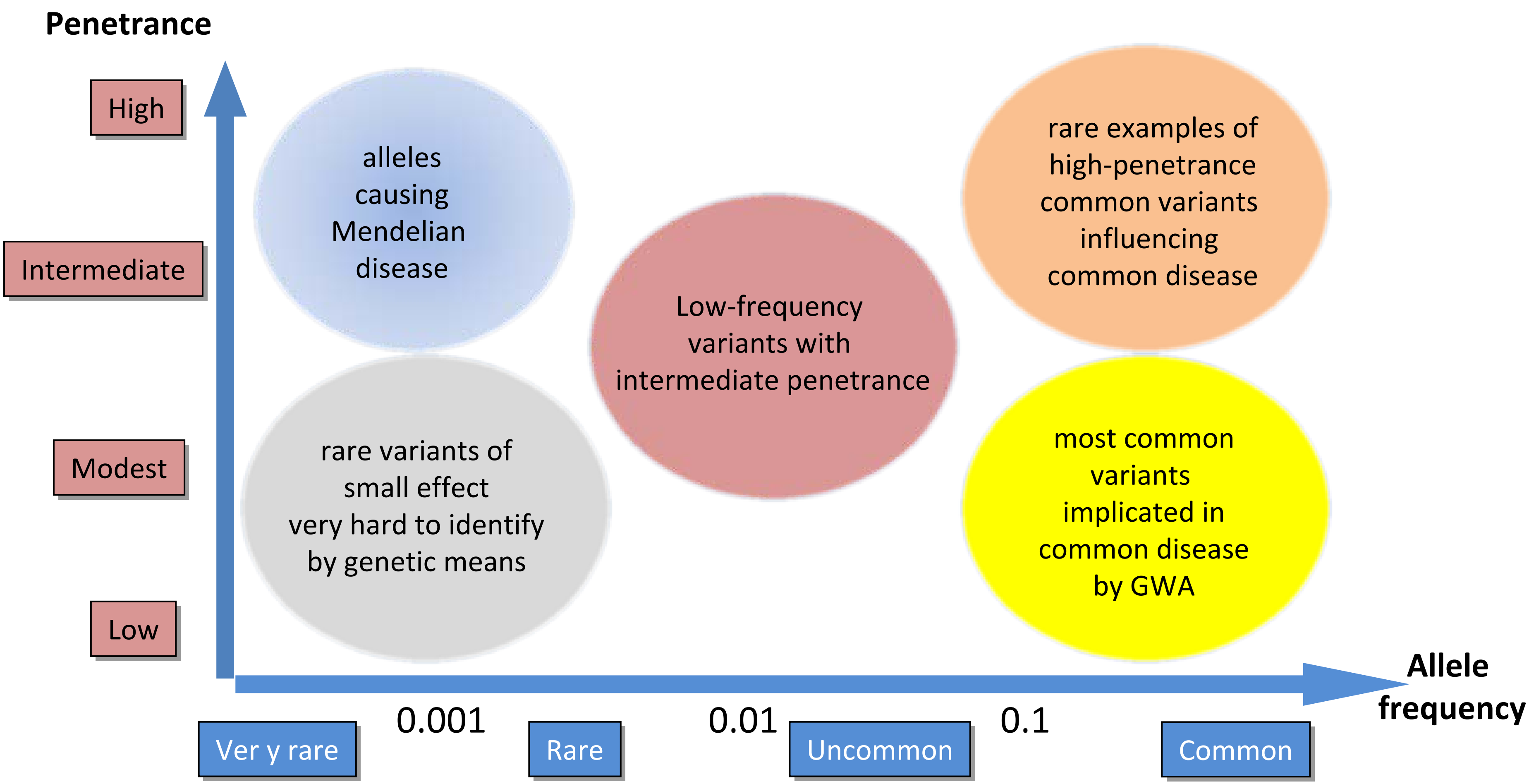


More of the same
- More common variant loci
- Finding the causal variants
- Looking in other ethnic groups

Other types of variation
- structural variants
- low frequency variants

Weird stuff
- epistatic interactions
- epigenetics

Atlas of susceptibility



Penetrance

High

Intermediate

Modest

Low

alleles causing Mendelian disease

rare variants of small effect very hard to identify by genetic means

Low-frequency variants with intermediate penetrance

rare examples of high-penetrance common variants influencing common disease

most common variants implicated in common disease by GWA

Allele frequency

Ver y rare

0.001

Rare

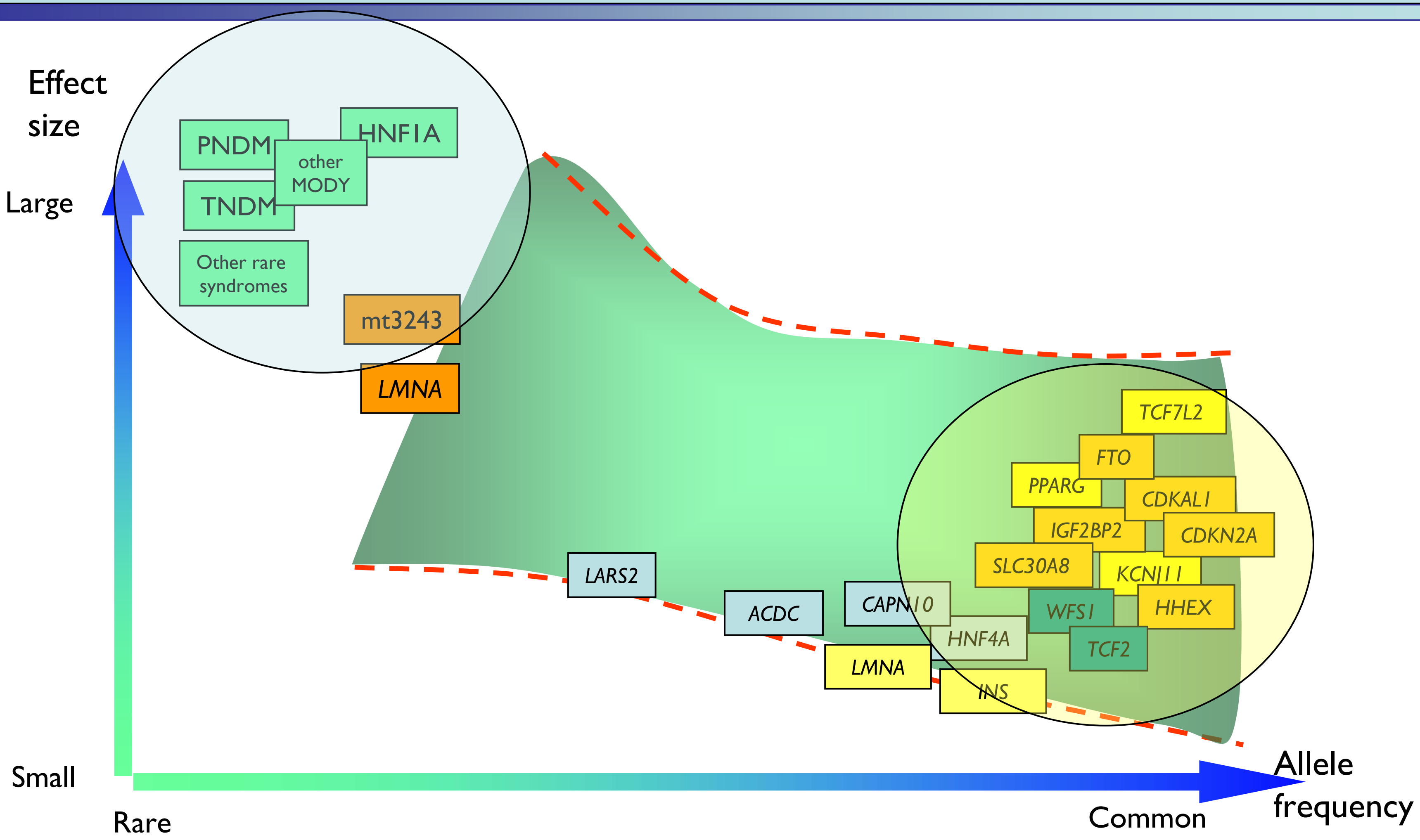
0.01

Uncommon

0.1

Common

Atlas of diabetes susceptibility



Consider the following variant….

MAF of 1%
GRR of 3

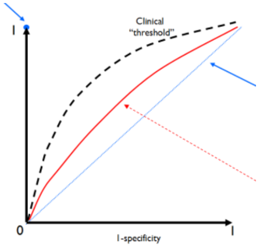
For disease prevalence of 5%
Penetrance of het = 0.14
Penetrance of homoz = 0.43

Too rare for GWA studies
Penetrance too low for linkage

Find by:
Resequencing
- Previously implicated genes
- Exons/promoters etc

Lambda(s) 1.038

20 such loci would give lambda(s) > 2.0
3-5 such variants in a single locus would → linkage signal

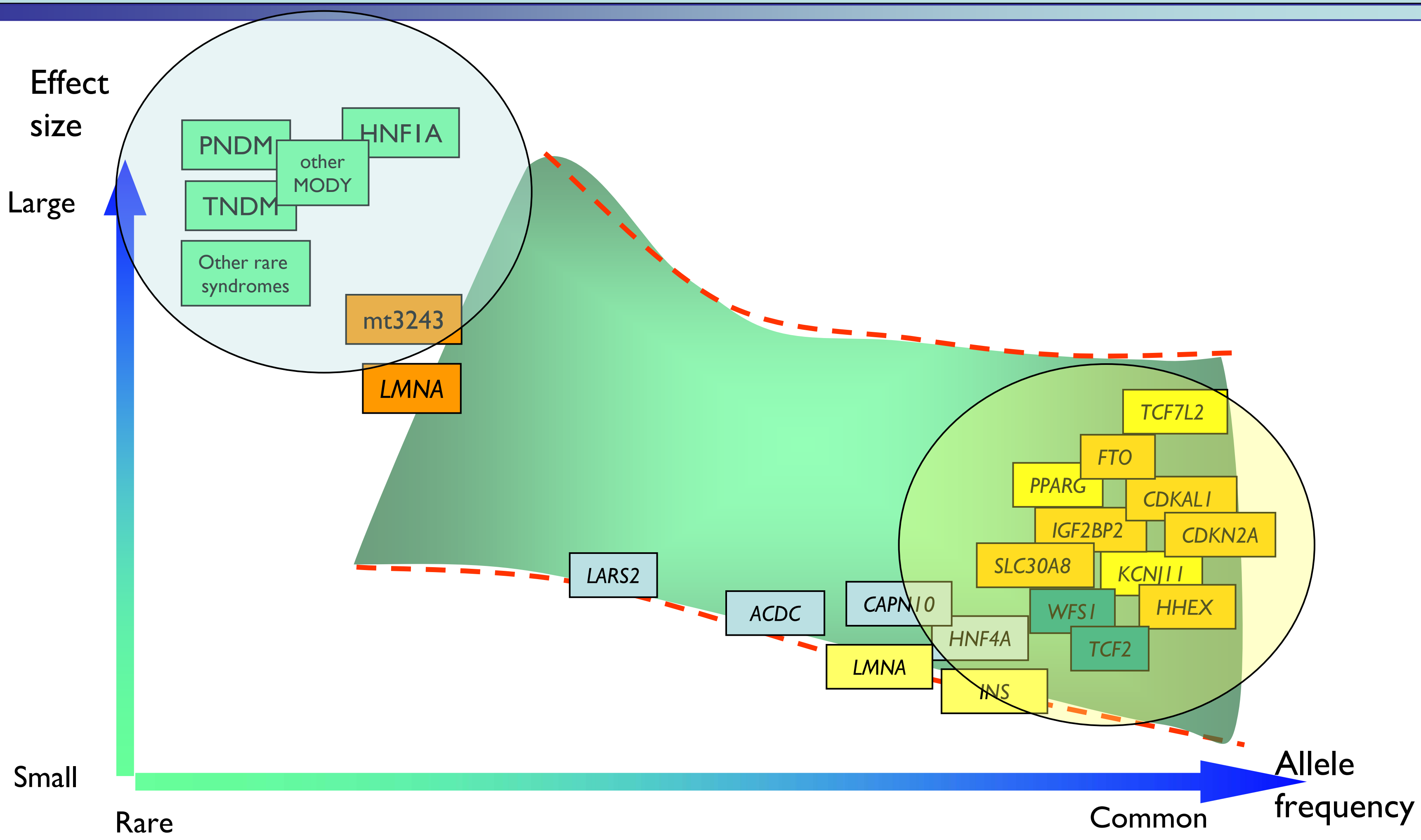


ROC curve
20 variants → AUC 0.72
30 variants → AUC 0.77

Association testing
Power 90%, alpha = 10^{-6}

1953 unselected case-control pairs
559 pairs if cases are selected from sibpairs

Atlas of diabetes susceptibility



Summary…

- GWA studies demonstrate the contribution of the common disease/common variant concept
- Significant differences in tractability of different phenotypes
- Common variants so far explain only a small proportion of the variance in these traits
- CNVs, low frequency variants, epistasis to be measured
- Other major ethnic groups almost completely unexplored
- Challenges: resequencing, fine-mapping, functional studies, epidemiology, translation……..
- Many novel insights into disease biology
- Opportunities for translation

Acknowledgements

Too numerous to mention......

DIAGRAM consortium

GIANT CONSORTIUM

Meta-Analyses of Glucose and Insulin-related traits Consortium

MAGIC

International T2D 1q Consortium

Diabetes UK

wellcome trust Case Control Consortium

MolPAGE

ENGAGE

Acknowledgements


Ele Zeggini


John Perry


Cecilia Lindgren


Tim Frayling


Rachel Freathy


Will Rayner


Nic Timpson

Inga Prokopenko
Amanda Bennett
Andy Usher


Kate Elliott


Chris Groves


Hana Lango


Mike Weedon

Thanks for the invitation, and your attention