Genes and type 2 diabetes: relevance to clinical practice?

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In the beginning……. MODY (Maturity Onset Diabetes of the Young)

- Early onset non-insulin dependent diabetes before the age 25 yrs
- autosomal dominant pattern of inheritance
- rare (1-3% of Type 2 diabetes)

MODY: Genetic heterogeneity

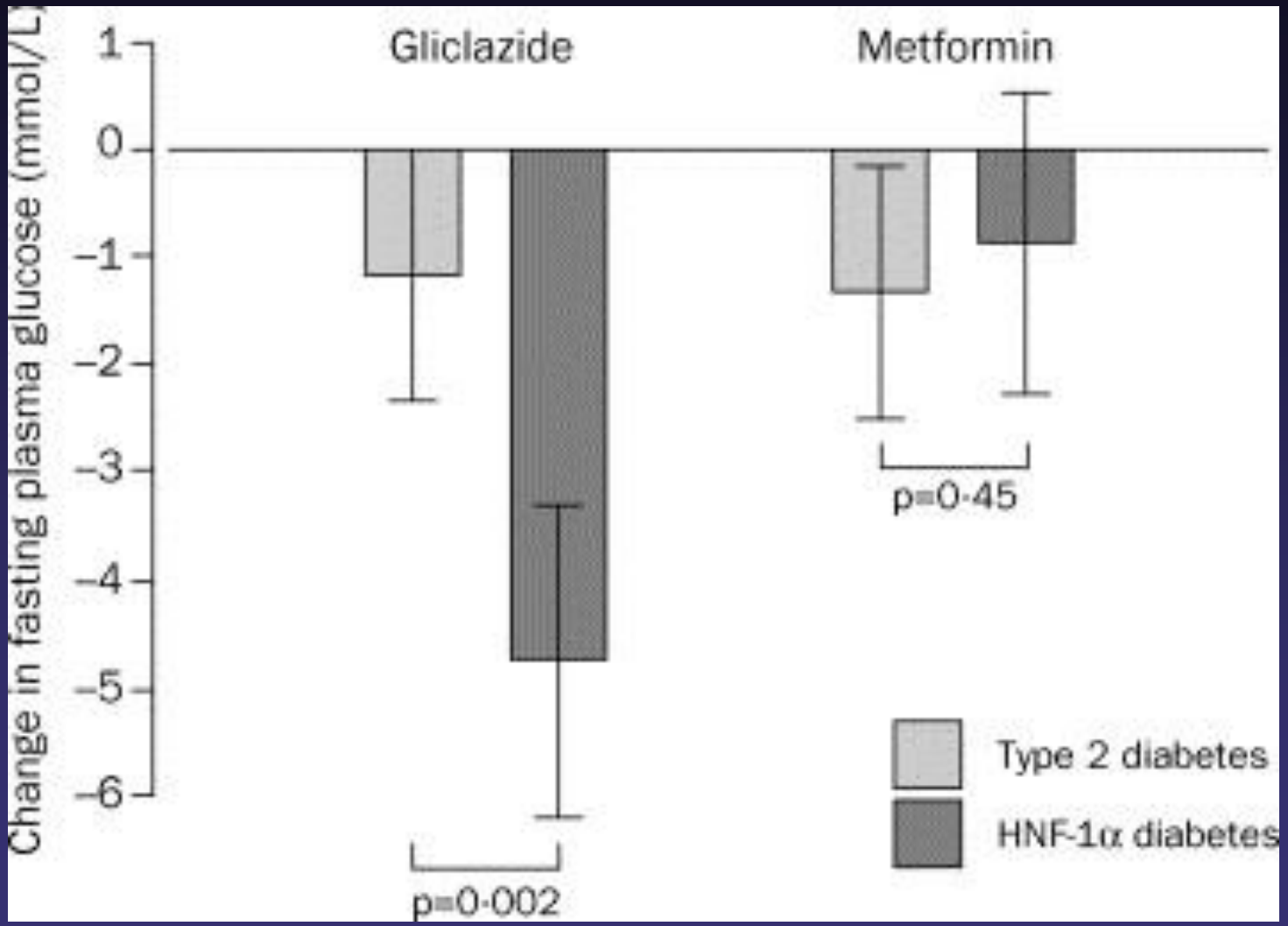
Type	Gene	Chr.	Frequency	Penetrance at 40yrs
MODY 1	HNF-4α	20q	5%	>80%
MODY 2	Glucokinase	7p	22%	95%
MODY 3	HNF-1α	12q	58%	>90%
MODY 4	IPF-1	13q	<1%	?
MODY 5	HNF-1β	17q	1%	?

MODY: Clinical heterogeneity

Feature	HNF1α (MODY 3)	Glucokinase (MODY 2)
Fasting hyperglycaemia	++	+
Diabetes progression	Yes	No
Small vessel complications	Common	Rare
Sulphonylurea sensitivity	Yes	No

RCT of gliclazide vs metformin in HNF1α MODY

HNF1α → Sulphonylurea Sensitivity (Hattersley)



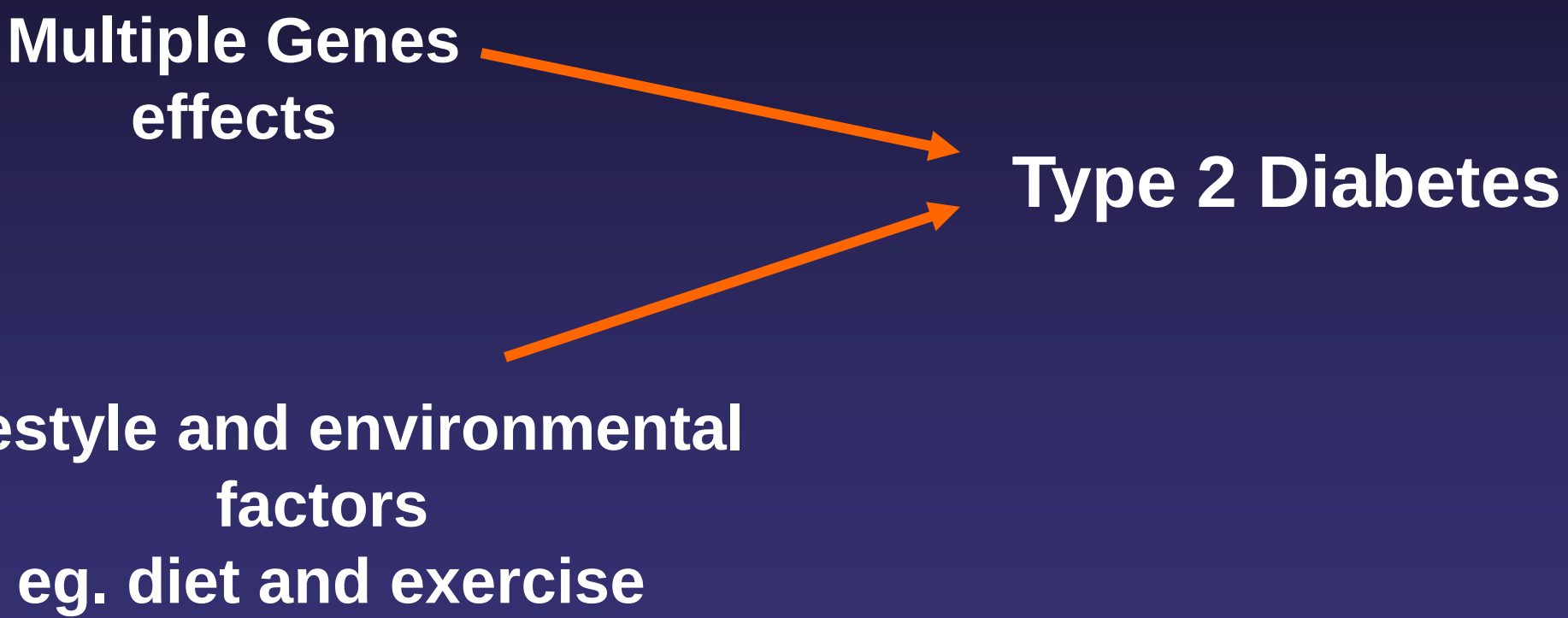
MODY: summary

- Gene mutations cause diabetes
- Genetic heterogeneity explains clinical heterogeneity
- Gene identification informs clinical management (pharmacogenetics)

Genes and type 2 diabetes: outline of talk

- Discovery of new type 2 diabetes (T2DM) genes
- How do the new genes increase T2DM risk?
- How can this new information be used in clinical practice?

Type 2 Diabetes: a Complex Trait



Gene scientists bring hope of cure for seven major diseases

By Roger Highfield and Stephen Adams

A GENETIC breakthrough today paves the way for potential new treatments of seven common diseases that could help more than 20 million people.

The largest study of its kind has found 10 new genes linked to seven of the most common ailments: heart disease, rheumatoid arthritis, high blood pressure, type 1 and type 2 diabetes, bipolar disorder and Crohn's disease.

Some 200 British scientists from 50 research groups collaborated in the discovery of the genes after screening DNA from 17,000 people. In two years, the £9 million investigation analysed 10 billion pieces of genetic information.

Together the seven diseases affect more than 20 million people across the UK. Coronary heart disease alone claims the lives of 105,000 people every year, making it the country's biggest killer.

The study has identified some of the genes that can significantly raise the risk of contracting these diseases.

Prof Peter Weissberg, medical director of the British Heart Foundation, said the research held out the hope of a new understanding of heart disease and high blood pressure that could ultimately lead to new treatments. The two-year Wellcome Trust Case Control Consortium investigation is the biggest study of the genetics behind common diseases ever undertaken.

INSIDE

Stem cell breakthrough
P8

ONLINE

Listen: How gene research went mainstream
telegraph.co.uk/news

The scientists analysed DNA samples from 2,000 patients per disease comparing them with 3,000 "control" samples from healthy volunteers.

One of the most exciting finds was a link between type 1 diabetes and Crohn's disease, a type of inflammatory bowel disorder that affects up to 60,000 people in the UK.

A gene called PTPN2 was found to be common to both auto-immune diseases, suggesting that they share similar biological pathways

Prof Peter Donnelly from Oxford University, chairman of the consortium, last night said the new approach – published today in the journal *Nature* – would open a new chapter in the study of how genetics influences the development of diseases.

"Our study heralds a new dawn in genetics," he said. "It is absolutely clear now that this approach works. The findings are reliable and the whole field is changing. So our understanding of human genetics will be quite different in a year or so.

"By identifying the genes underlying these conditions, our study should enable scientists to understand better how disease occurs, which people are most at risk and, in time, to produce more effective, more personalised treatments."

However, the study has also raised the question of whether people could face higher health and life insurance premiums if they are identified as being at risk of disease.

Dr Mark Walport, director of the Wellcome Trust, the UK's largest medical research charity, was optimistic about the study's potential.

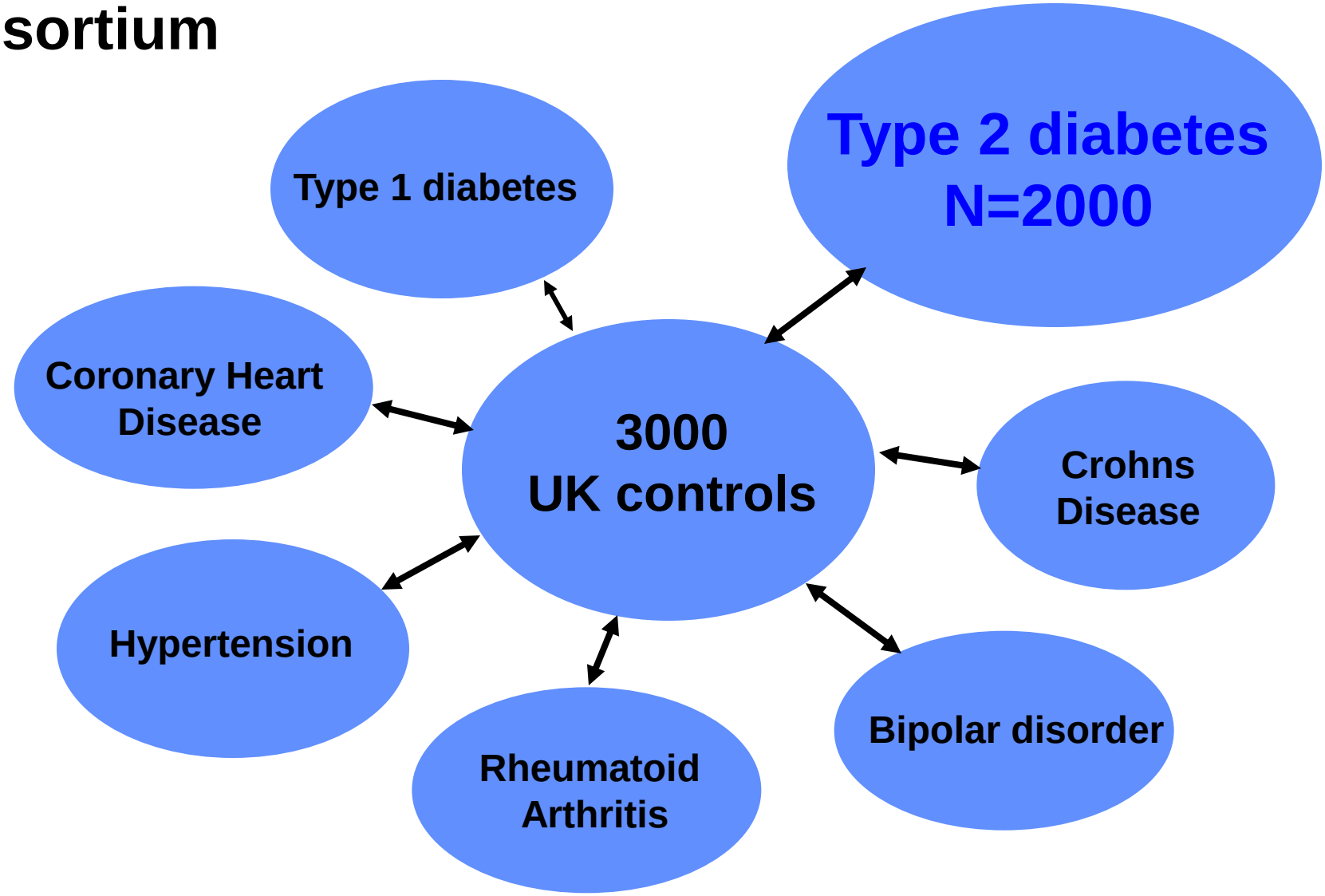
"Just a few years ago it would have been thought wildly optimistic that it would be possible in the near future to study a thousand genetic variants in each of a thousand people," he said.

"This research shows that it is possible to analyse human variation in health and disease on an enormous scale."

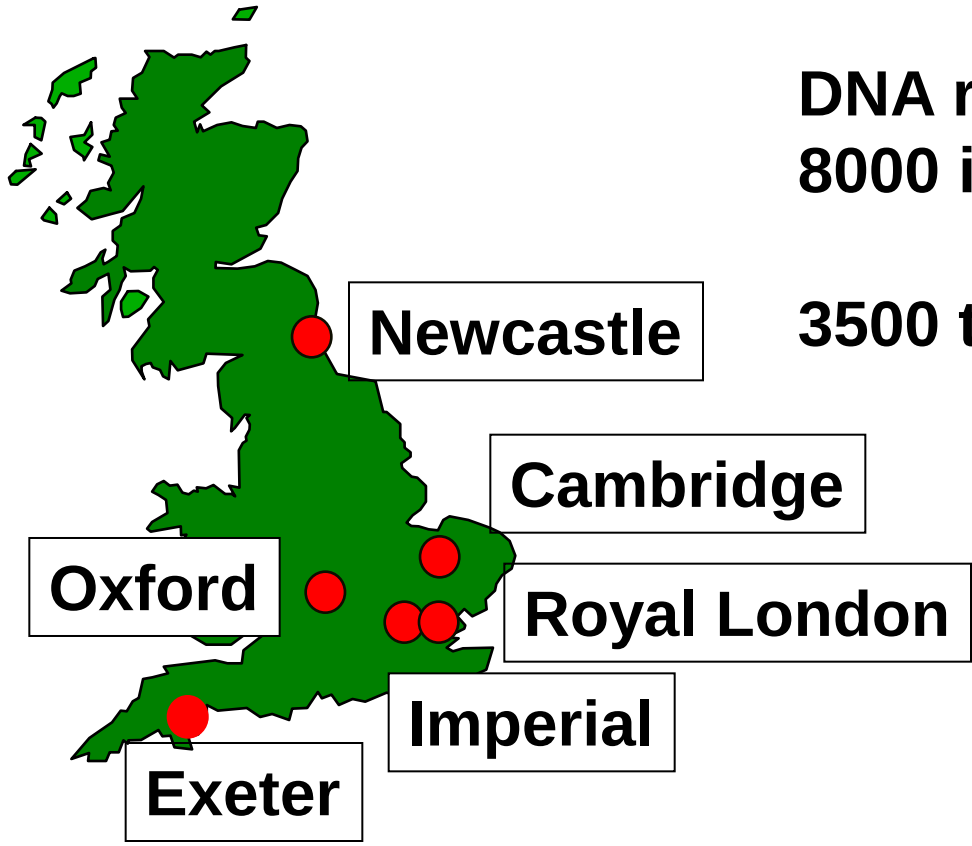
Karen Addington, chief executive officer of the Juvenile Diabetes Research Foundation in the UK, said the "landmark" study could help

Continued on Page 2

Wellcome Trust Case Control Consortium



The Diabetes UK Warren 2 resource: 1995-2003



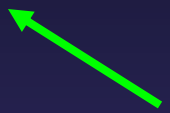
DNA resource established from 8000 individuals:

3500 type 2 diabetic cases

SNP: single nucleotide polymorphism

Allele 1: A A C T A A A C C G G T A T T G G

Allele 2: A A C T T A A C C G G T A T T G G



SNP

Allele 1: 20% population

Allele 2: 80% population

Type 2 diabetes vs Non-diabetic controls

Allele 1 freq: 32% vs 20%

SNP: single nucleotide polymorphism

Allele 1: A A C T A A A C C G G T A T T G G C

Allele 2: A A C T T A A C C G G T A T T G G G

SNP

Functional change predisposing to Type 2 diabetes

GWA involves typing around 500,000 SNPs in each individual

For 5000 cases and controls = 2,500,000,000 genotypes

Replicated T2DM gene loci

SUSCEPTIBILITY GENE LOCUS	GENE FUNCTION	RISK VARIANT	ODDs RATIO (per allele)
TCF7L2	Cell signalling	rs7901695	1.37
KCNJ11	K+ channel component	E23K	1.14
PPARG	Transcriptional regulator	Pro12Ala	1.14
FTO	unknown	rs8050136	1.17
HHEX/IDE	Transcription factor	rs1111875	1.15
CDKAL1	Cyclin dependent kinase	rs10946398	1.14
CDKN2A/2B	Tumour suppressor	rs10811661	1.20
IGF2BP2	Binding protein	rs4402960	1.14
SLC30A8	Zinc transporter	rs13266634	1.15

THERE IS AN OBESITY GENE

We've found obesity gene, say scientists

Weighty matters

Genetic link to obesity does not remove need for exercise

THE FAT GENE

By EMILY COOK
Health Correspondent

Experts discover trigger to obesity for 1 in 6 Brits

Obese are born to put on weight, geneticists claim

Researchers uncover genetic link to obesity

It's in the genes: breakthrough confirms DNA link with obesity

Scientists find the gene that makes you fat

Does my bum look big in these genes? Absolutely, say scientists

DOCTORS FIND THE FAT GENE

SCIENTIFIC RESEARCH

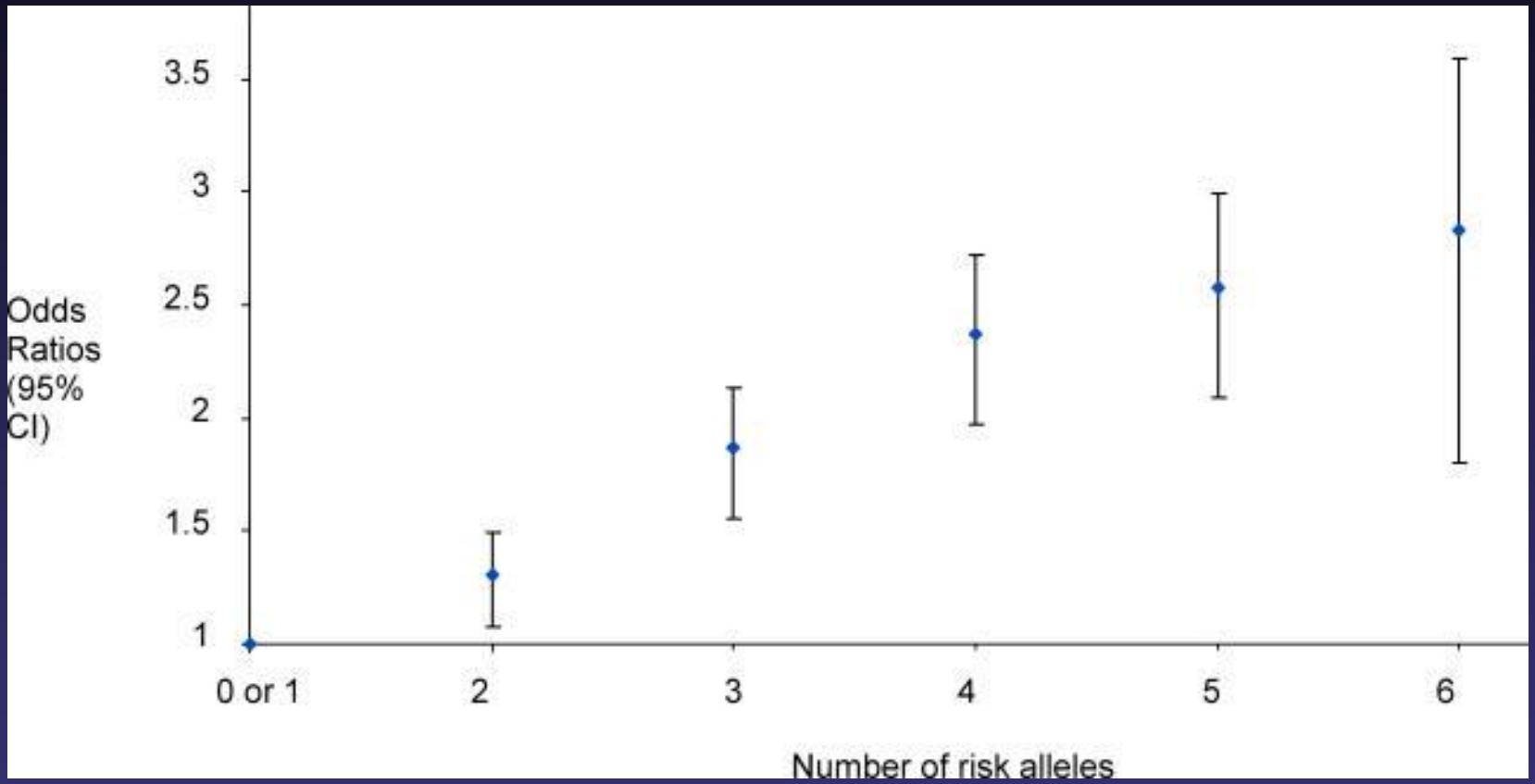
Common gene causes obesity, says study

2nd Wave: meta-analysis of 3 GWAs

- Meta-analysis based on 10,128 individuals
- Identified 6 further T2DM risk loci
- *JAZF1, CDC123-CAMK1D, TSPAN8-LGR5, THADA, ADAMTS9*, and *NOTCH2*
- 0Rs 1.09 – 1.13

Zeggini et al, 2008

Effect of multiple common susceptibility variants on diabetes risk



Risk variants in *TCF7L2, PPARG* and *KCNJ11* typed in over 6000 individuals

Weedon et al, 2006

Part 1 Summary:

- Common variants of weak functional effect
- Risk alleles combine in an additive manner to increase overall diabetes susceptibility

Genes and type 2 diabetes: outline of talk

- Discovery of new type 2 diabetes (T2DM) genes
- How do the new genes increase T2DM risk?

RISC: Relationship between Insulin Sensitivity and CVD

Pisa
London
Amsterdam
Newcastle
Lyon
Odense
Dublin
Perugia
Geneva
Frankfurt

Malmö
Rome
Glasgow
Vienna
Madrid
Athens
Milan
Belgrade
Kuopio

Paris
Padova

RISC: novel T2DM genes and metabolic phenotypes

Aim:

Do the T2DM susceptibility genes increase diabetes risk through altered insulin sensitivity?

Methods:

- **1276 healthy non-diabetic individuals (701 women)**
- **Insulin sensitivity measured by hyperinsulinaemic clamp.**
- **Linear trend analysis for additive model, followed by GLM analysis for other inheritance patterns.**

Susceptibility loci and insulin sensitivity (M/I)

Locus/variant	Genotype 1/2	Trait	11	12	22	P value
FTO rs9939609	A/T	M/I BMI	123 25.5	127 25.1	134 24.6	0.023 0.022
CDKAL1 rs10946398	A/C	M/I	126	129	117	0.11
HHEX/IDE rs1111875	G/A	M/I	127	128	132	0.14
SLC30A8 rs13266634	C/T	M/I	128	126	153	0.33
IGF2BP2 rs4402960	G/T	M/I	131	126	126	0.20
CDKN2B rs10757283	C/T	M/I	133	127	124	0.08
Pro12Ala rs1801282	Pro/Ala	M/I	127	125	168	0.21 0.02*

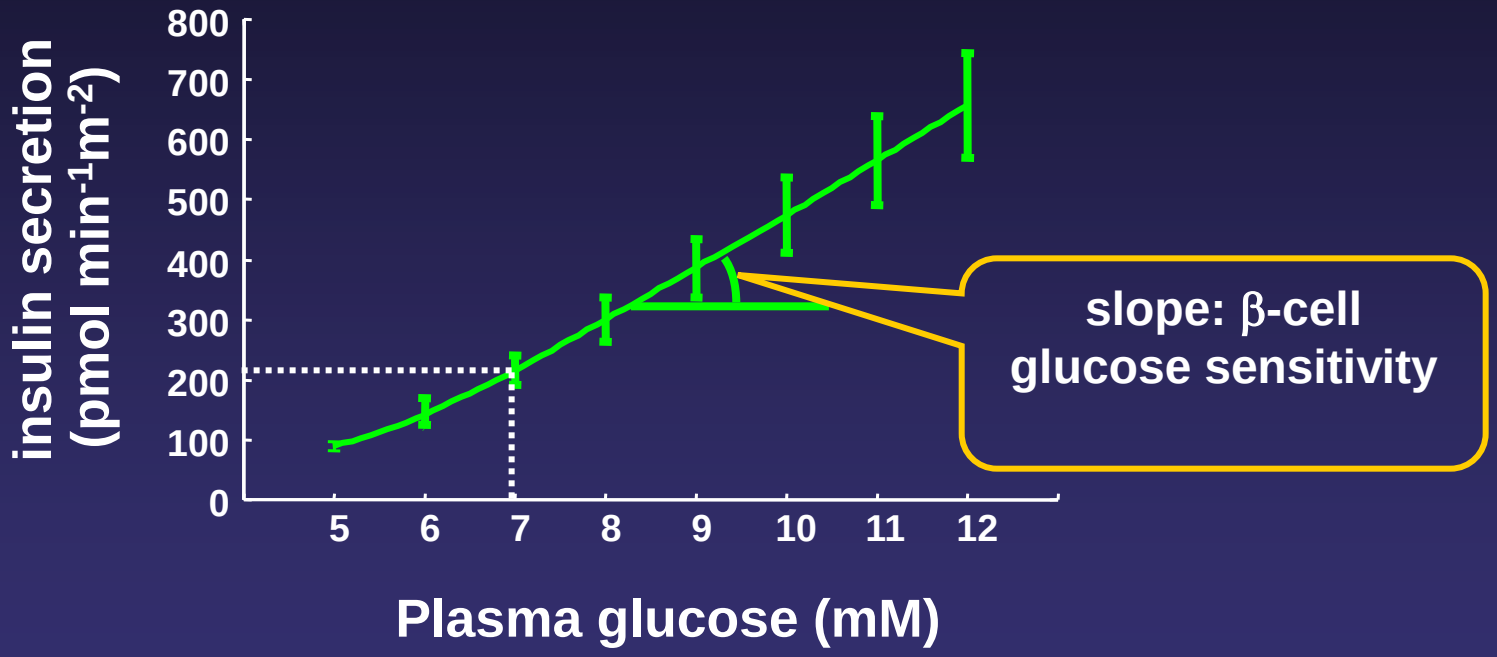
M/I: μmol/min/kgFFM/nM & * GLM analysis

Susceptibility loci and pancreatic Beta-cell function

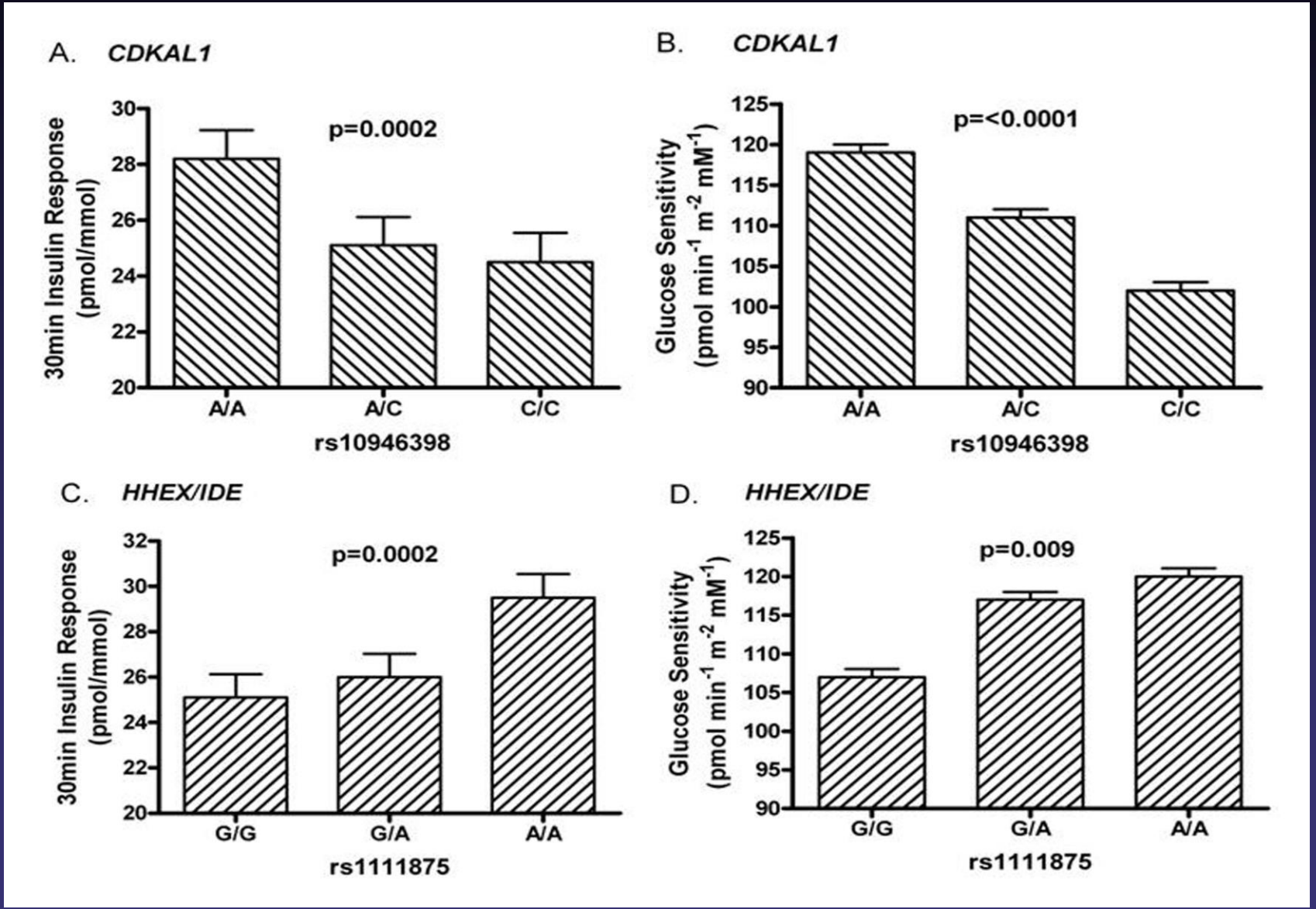
OGTT derived measures of beta-cell function:

- **30min insulin response**
  (30 – 0 min insulin /30 min glucose)
- **Beta-cell sensitivity based on C-peptide derived insulin secretion rates from the OGTT**

OGTT model derived Beta-cell sensitivity to glucose

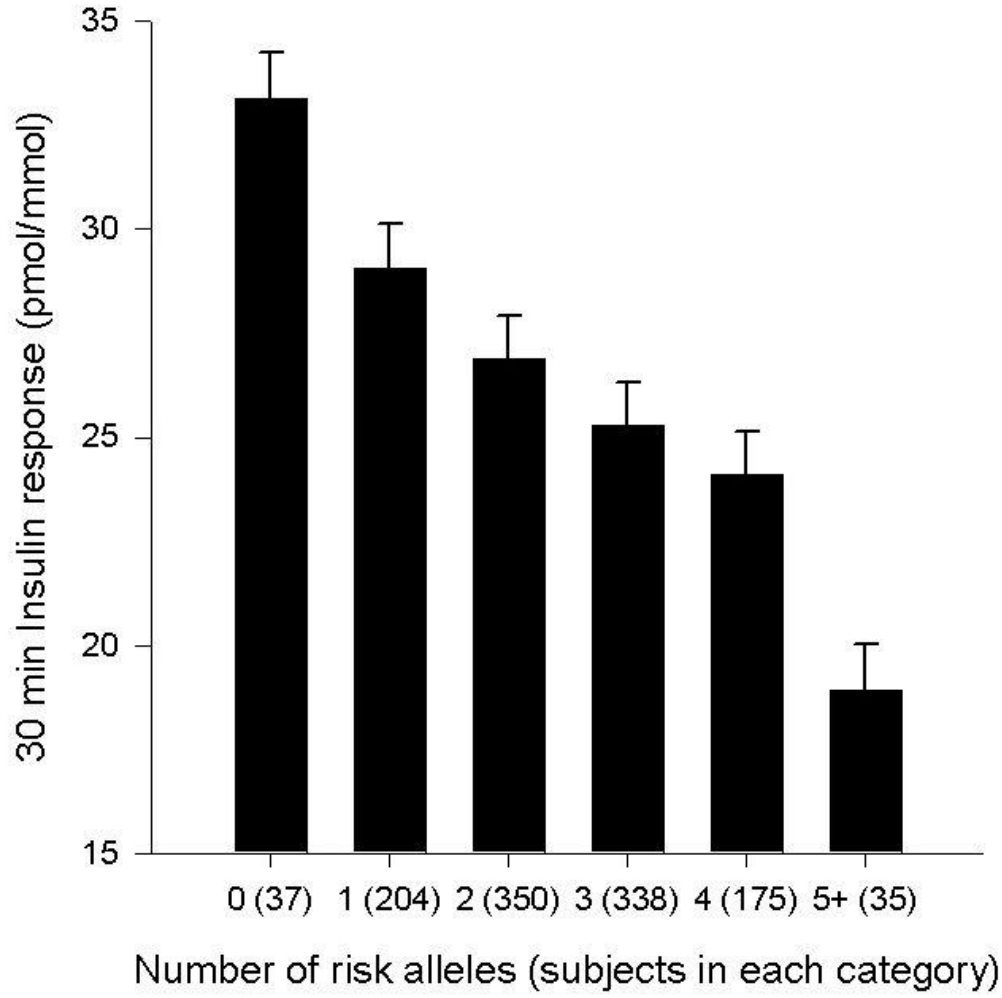


Susceptibility loci and pancreatic Beta-cell function



Pascoe et al, 2007

Additive effect of *TCF7L2, HHEX/IDE* and *CDKAL1* risk alleles on beta-cell function



Pascoe et al, 2008

Part 2 Summary:

- Only *FTO* associated with decreased insulin sensitivity-this was mediated via increased adiposity
- *CDKAL1* and *HHEX/IDE* susceptibility alleles associated with impaired pancreatic beta-cell function
- Other new genes appear to primarily increase T2DM risk through impaired beta-cell function

Genes and type 2 diabetes: outline of talk

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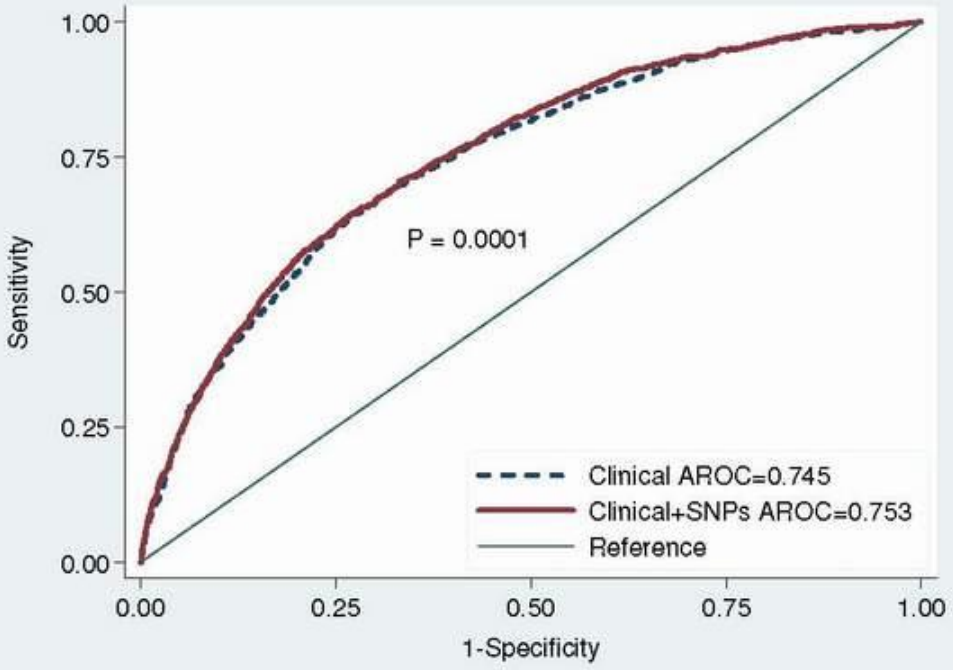
- How do the new genes increase T2DM risk?
- How can this new information be used in clinical practice?

Prediction of T2DM: Malmo and Botnia Study

- 16,061 Swedish non-diabetic subjects
- 2063 new cases of T2DM over 25 yrs
- Genotyped 16 SNPs in 16 novel T2DM genes
- Clinical and anthropometric predictors
- ROC analyses

Lyssenko et al, 2008

A



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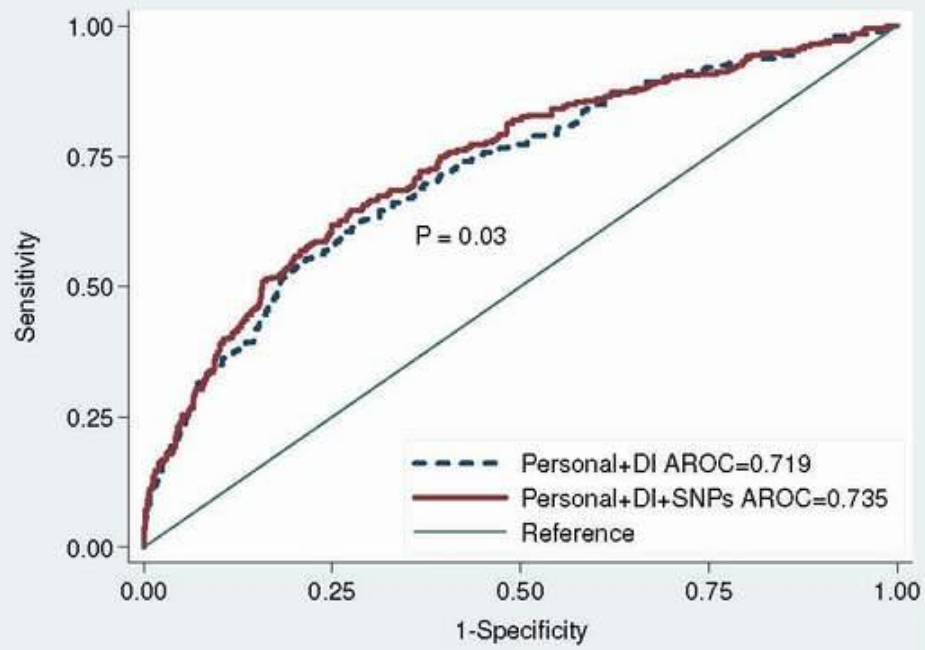
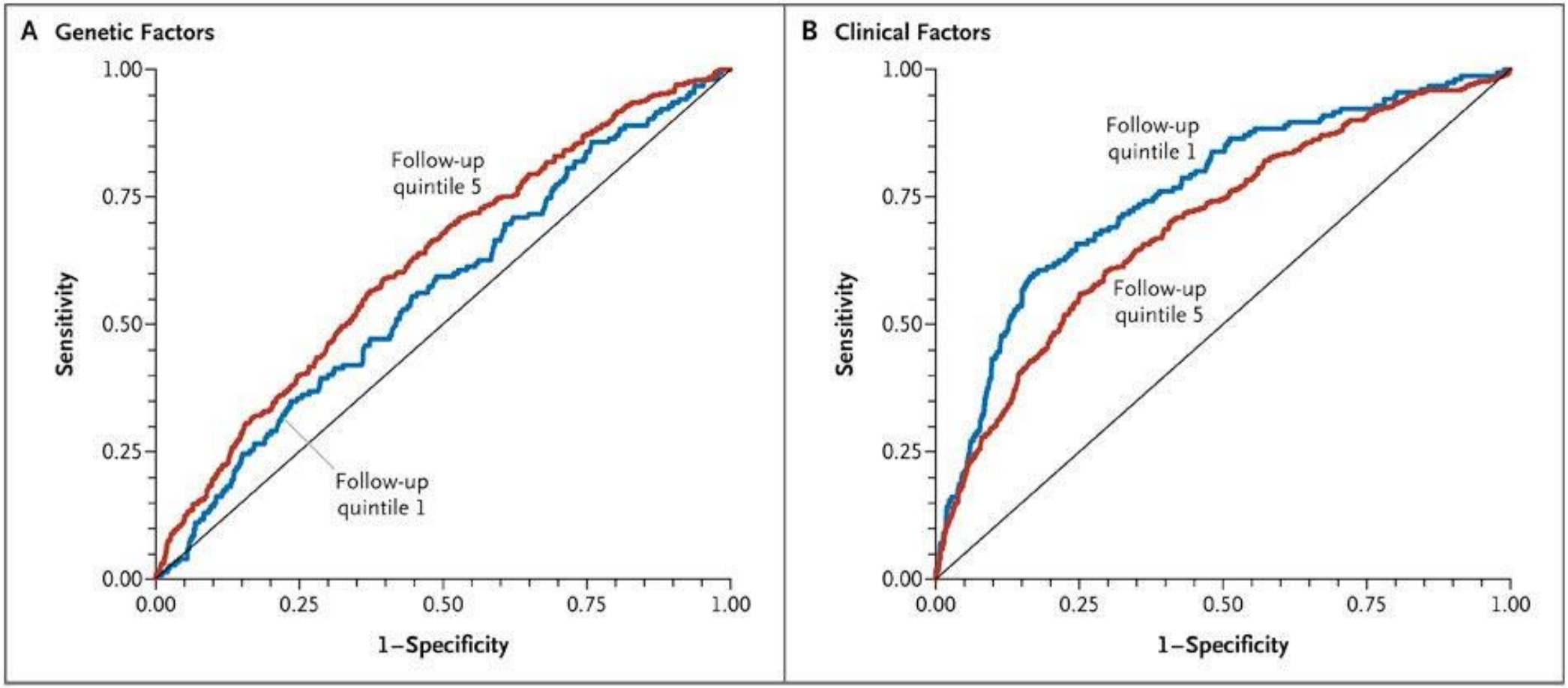


Panel A:	**AUC**
Clinical predictors alone (age, sex, FHx, BMI, Trigs, Fasting P. Glucose)	**0.745**
Clinical predictors + genotype data	**0.753**



Duration of follow-up:

Longest duration (red line) vs shortest duration (blue line)

Prediction of T2DM: Framingham Offspring Study

- 2377 non-diabetic relatives of T2DM patients
- 255 new cases of T2DM over 28 yrs FU
- Genotyped 18 SNPs in 18 T2DM genes
- Genotype score based on number of risk alleles (max 36)
- Clinical score (age, sex, FHx, BMI, FPG, SBP, HDL-chol and Trigs)

Meigs et al, 2008

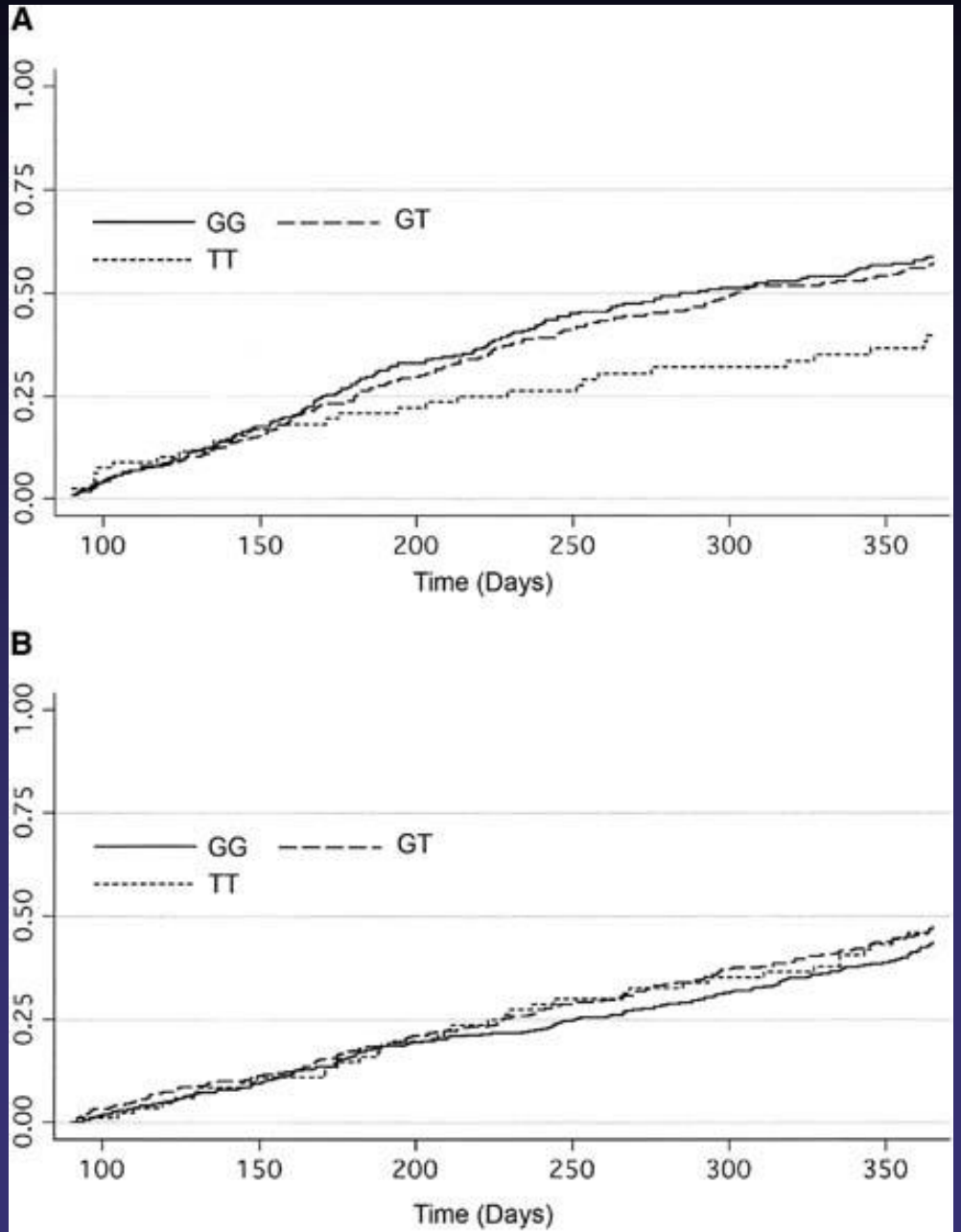
ROC data:

Predictor	AUC
Clinical model	0.901
Clinical model + genotype data	0.904

Genotype data provided significant improvement in T2DM prediction in subjects < 50 yrs

Family history and genotype data were independent predictors of T2DM

Variation in *TCF7L2* affects SU response



- K-M plot of patients by rs12225372 genotype achieving HbA1c < 7% after (A) sulfonylurea and (B) metformin

(T allele = the diabetes risk allele)

Pearson et al, 2007

Part 3 Summary:

- Genotype data do not appreciably improve the predictive value of existing clinical scores
- Genotype data perform better in younger subjects
- Emerging evidence that genotype may influence response to therapy

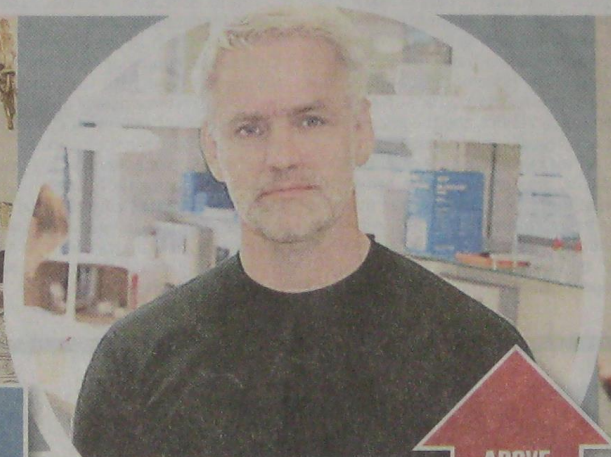
Rival genetic tests leave buyers confused

Health Firms that offer to predict your risk of disease give worryingly varied results, discovers **Nic Fleming**

JULIAN ANDREWS/ FRED PROUSER

Dr Paul Jenkins of GeneticHealth
The firm rated the reporter's risk of cardiovascular disease as 'low to moderate'

LOW TO MODERATE



Kari Stefansson of deCODEme
The company assessed the reporter's risk of heart attack, angina and sudden cardiac death as above average

ABOVE AVERAGE

Anna Wojcicki of 23andMe
The firm described the reporter's risk of heart attack between the ages of 45 and 84 as below average

BELOW AVERAGE

> **"THE SCIENCE ON THIS IS STILL REALLY WORK IN PROGRESS**

LEADING genetic testing companies are providing clients with widely divergent and inaccurate predictions of their chances of developing serious diseases. That is the finding from tests conducted by different firms on the same person.

Using my own DNA, I approached three firms who between them provide the majority of genetic tests for common diseases in the UK. They gave contradictory assessments of the risk I faced of developing illnesses, including Alzheimer's and glaucoma, and a confused verdict on my risk of suffering heart problems.

The findings reveal that those paying up to £825 for the tests and Stefansson said: "My prediction is within five years every reasonably educated person in western society will have had a genetic profile."

Helen Wallace, of the campaign group GeneWatch, said: "At present there is a regulatory black hole that allows companies to mislead people about their health. Handing over your genetic information [also] increases the likelihood that insurers will discriminate against you in the future."

were associated with "a four-fold increased risk of developing Alzheimer's disease by your late 80s".

According to deCODEme, my risk of a heart attack, angina or sudden cardiac death is 54.8%, which is 6% above average. By

Co-founded by Anna Wojcicki, wife of the Google co-founder Sergey Brin, 23andMe asks customers to sign a legal waiver stating they understand their service is for "research and educational use only".

The firms point to their successes, saying some clients have been given an early diagnosis of their condition.

Lauralee Nygaard, a dentist, in Spokane, Washington state, had a stroke three years ago and doctors could not find the cause. A deCODEme test identified a susceptibility to atrial fibrillation, and she now takes blood-thinning drugs.

Testing for single gene diseases has been available on the NHS for more than a decade. Women with a family history of breast or ovarian cancer receive a test for BRCA gene mutations. Multi-gene disorders are more complex.

So far an estimated 2,000 Britons have taken private gene

Acknowledgements:

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- **Patients and volunteers**