"*Genetics, diabetes and obesity – where are we?*"

Winter School 2010-2011
Individual Health & Nutrition
9 november 2010

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Hagedorn Research Institute
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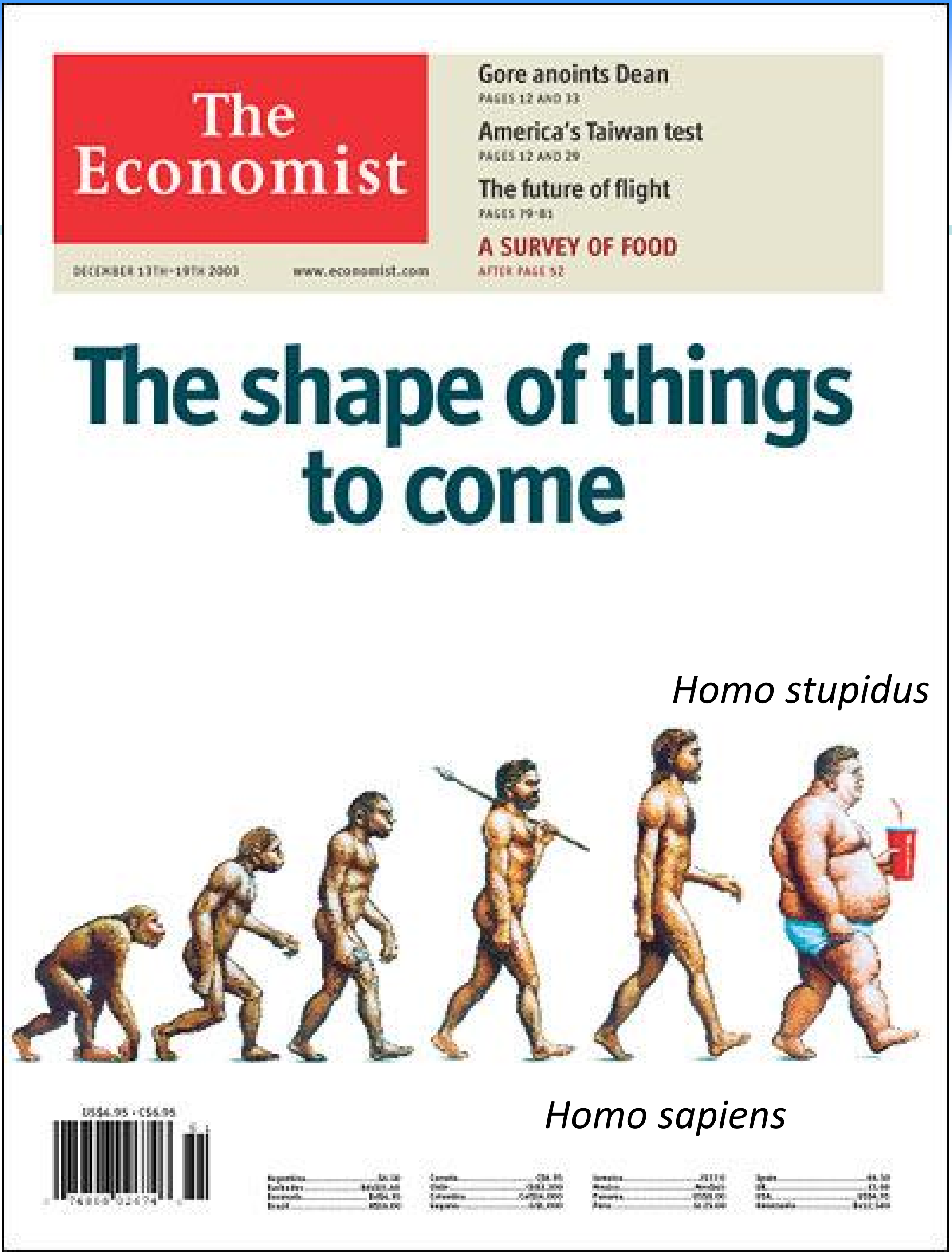
Steno

LuCamp
Lundbeck Foundation Centre for
Applied Medical Genomics in Personalised
Disease Prediction, Prevention and Care



The Economist

Gore anoints Dean
PAGES 12 AND 33

America's Taiwan test
PAGES 12 AND 29

The future of flight
PAGES 79-81

A SURVEY OF FOOD
AFTER PAGE 52

DECEMBER 13TH-19TH 2003

www.economist.com

The shape of things to come

Homo stupidus

Homo sapiens

US$4.95 · C$6.95

1. **Genetics of increased BMI/obesity and common forms of diabetes**
2. **Missing heritability**
3. **Our other genome**

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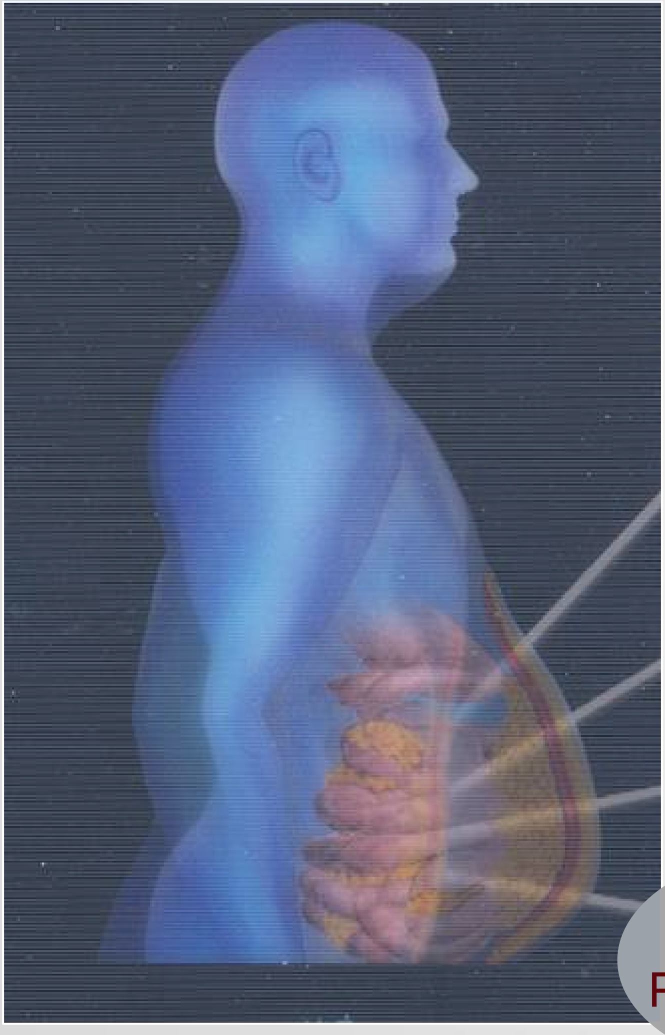
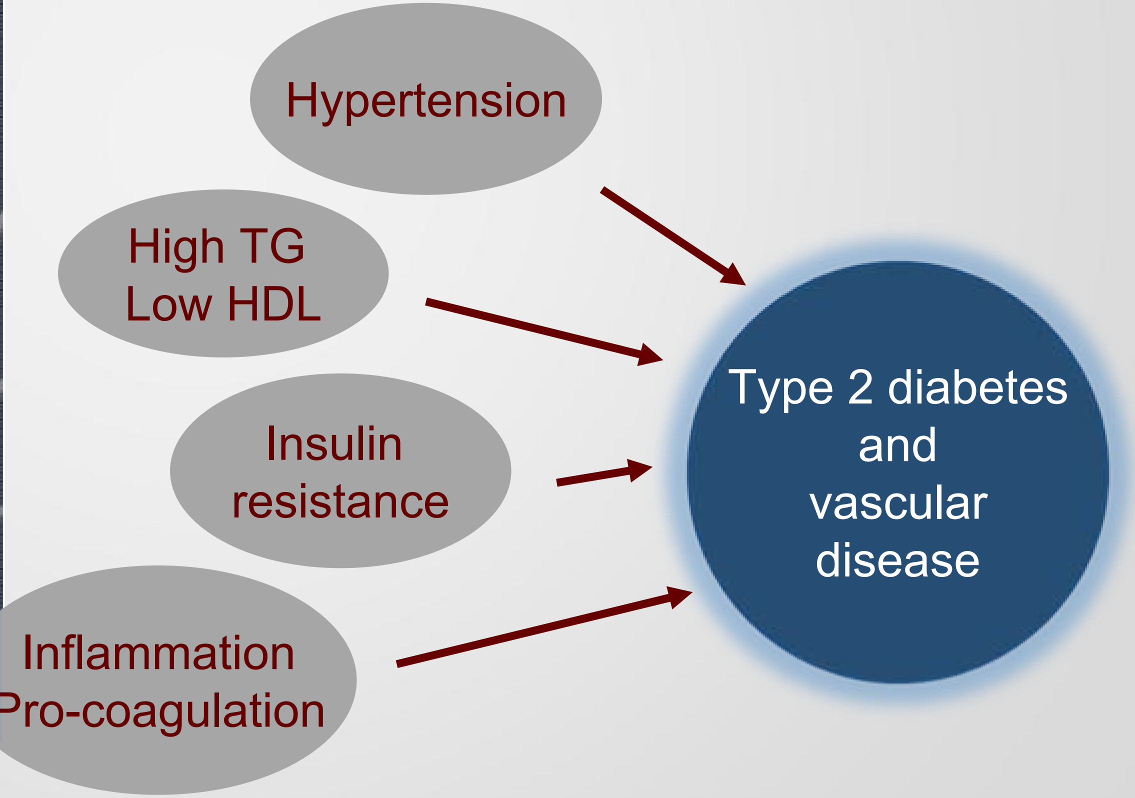
Features of obesity



Triggers:

- Overeating
- Physical inactivity



Hypertension

High TG
Low HDL

Insulin resistance

Inflammation
Pro-coagulation

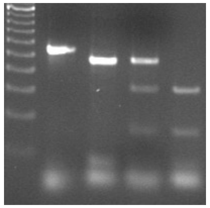
Type 2 diabetes and vascular disease

What about genetics of obesity?

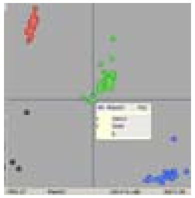
Photograph by Karen Kasmauski © National Geographic 2007

Studies of the genetics of complex disorders: the development of technology drives the progress

single variant
(10^0 SNPs; 10^3 genotypes)



detailed study of individual genes
(10^2 SNPs; 10^{5+} genotypes)



regional studies
(10^4 SNPs; 10^8 genotypes)

genome-wide association
(10^6 SNPs; 10^{10} genotypes)

Genome-wide association in 2007

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Studies of the genetics of complex disorders: the development of technology drives the progress

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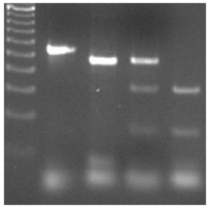
(10^0 SNPs; 10^3 genotypes)



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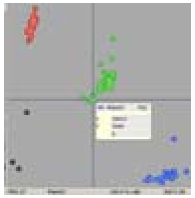
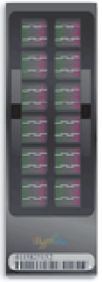


regional studies
(10^4 SNPs; 10^8 genotypes)

genome-wide association
(10^6 SNPs; 10^{10} genotypes)

Whole exome and whole
genome sequencing 2010

Genome-wide association (GWA) in short



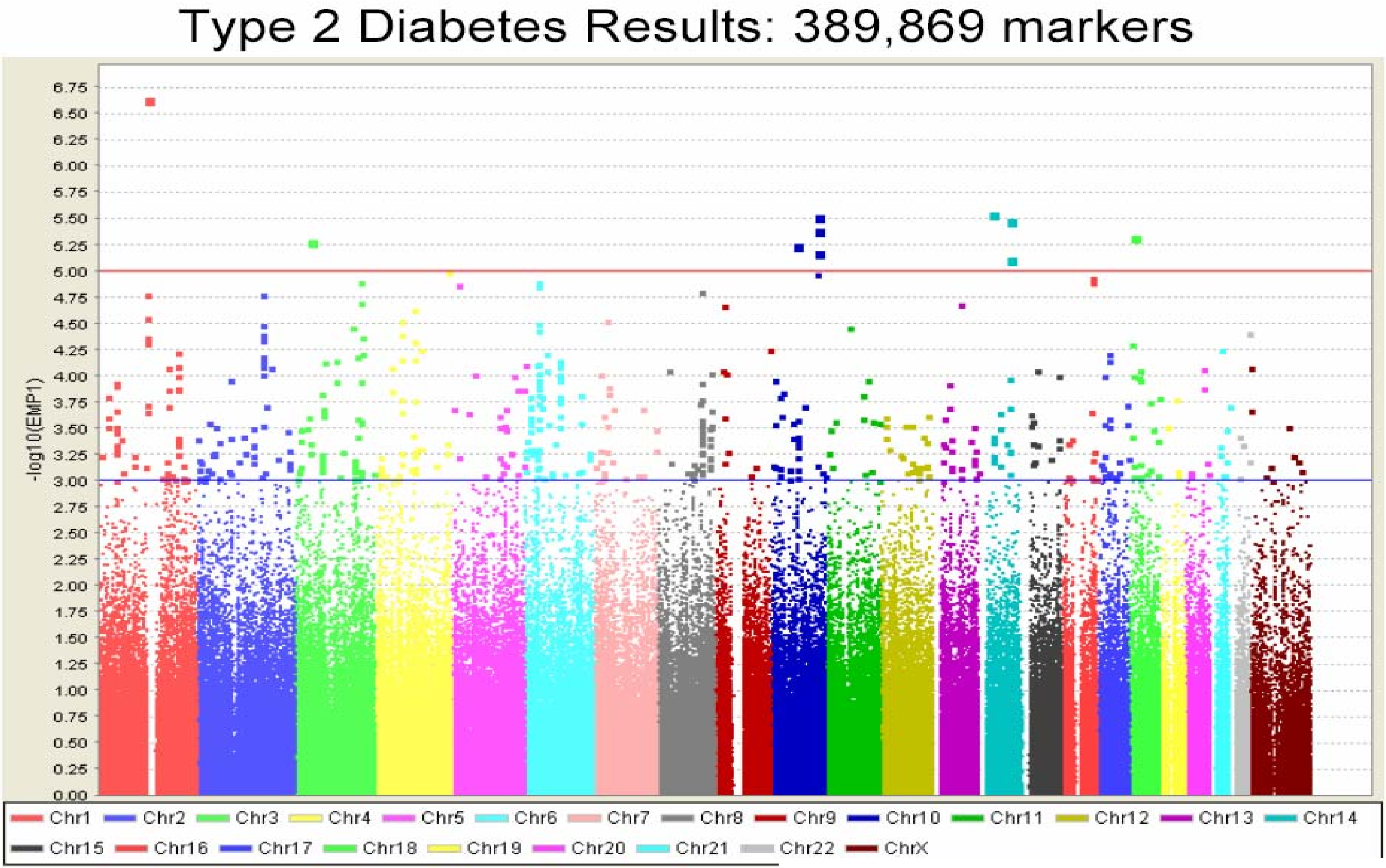
Type for ~/>500,000 SNPs

Obtain information about strength of association genome wide

(within limits of sample size, allele frequency, LD etc)

Validation in independent samples of what looks interesting
followed by combined analyses

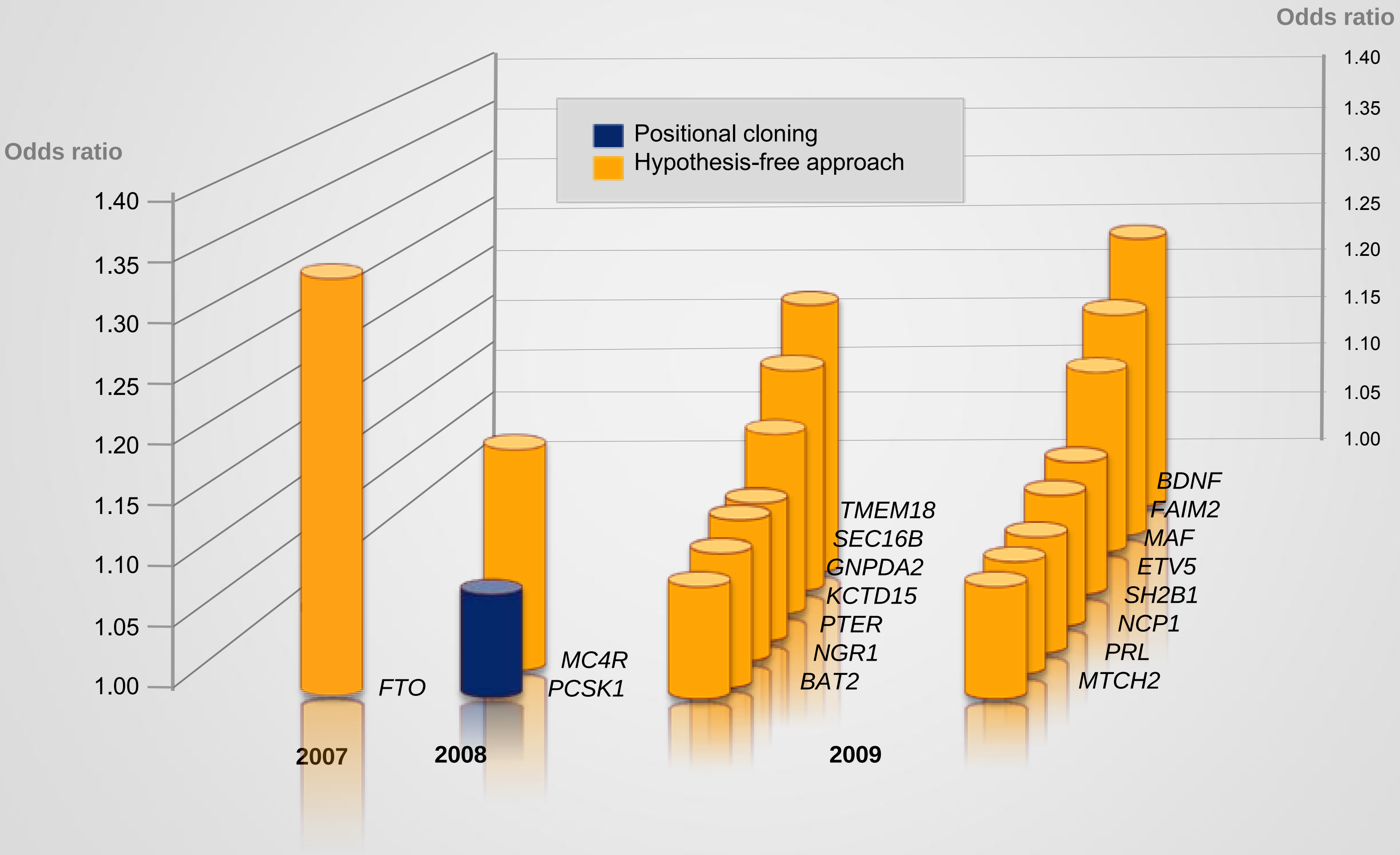
Example of a GWA with 389,000 SNPs successfully genotyped



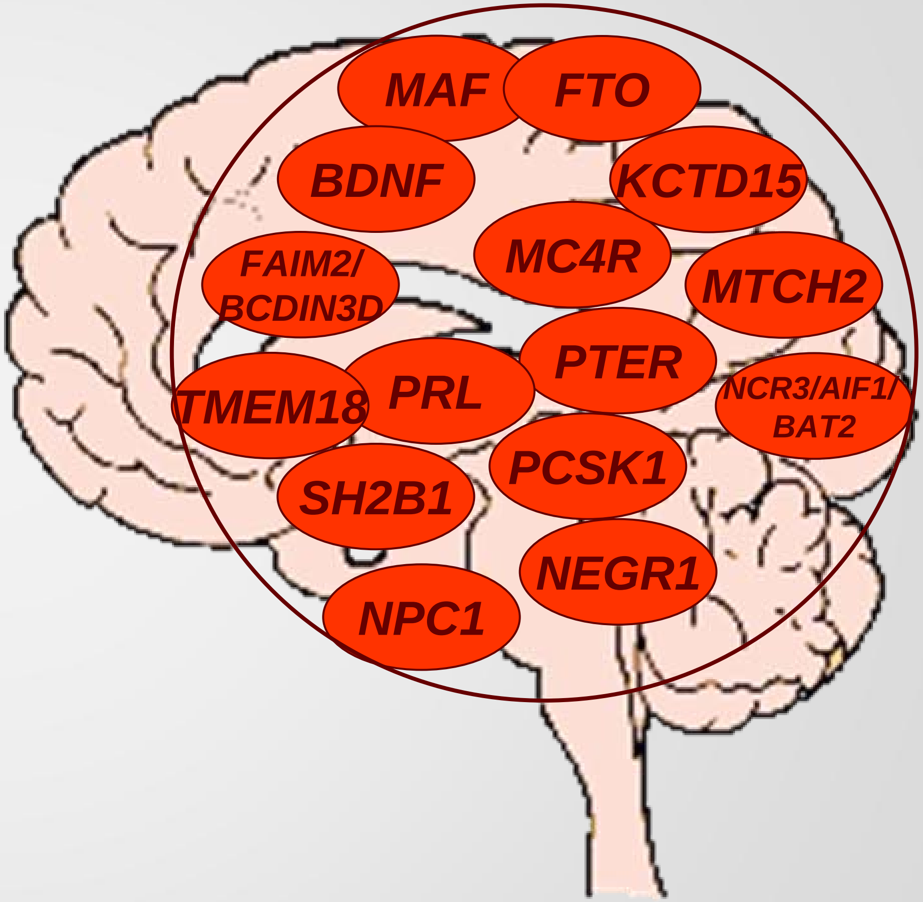
By courtesy of http://www.broad.mit.edu/diabetes/

Eighteen risk loci associate with obesity/increased BMI with genome-wide significance

Each of them are common but only increase risk of obesity with 8-33%

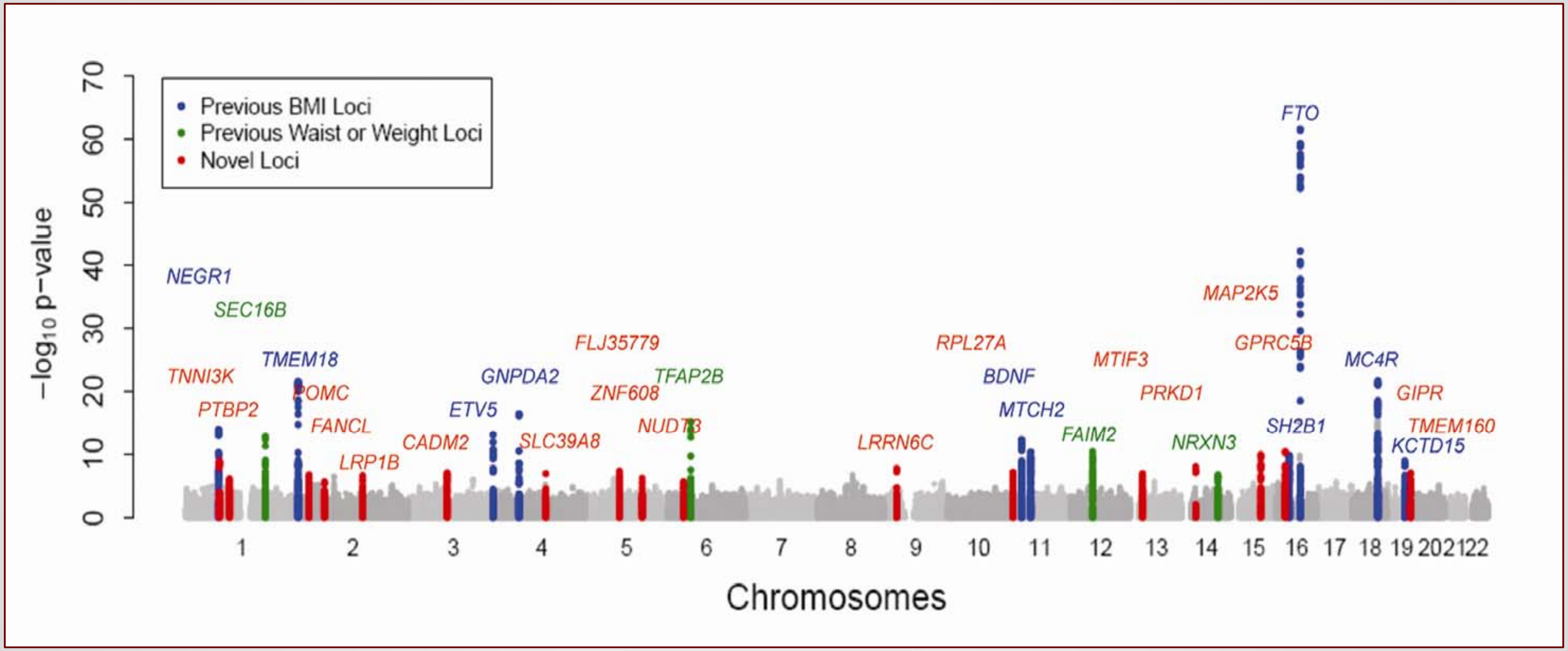


Most of obesity risk loci are related to genes in the hypothalamus -> disturbed appetite regulation



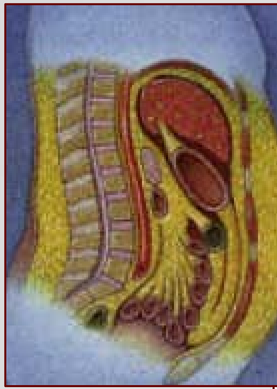
Explain collectively about 1 % of the genetic component of obesity

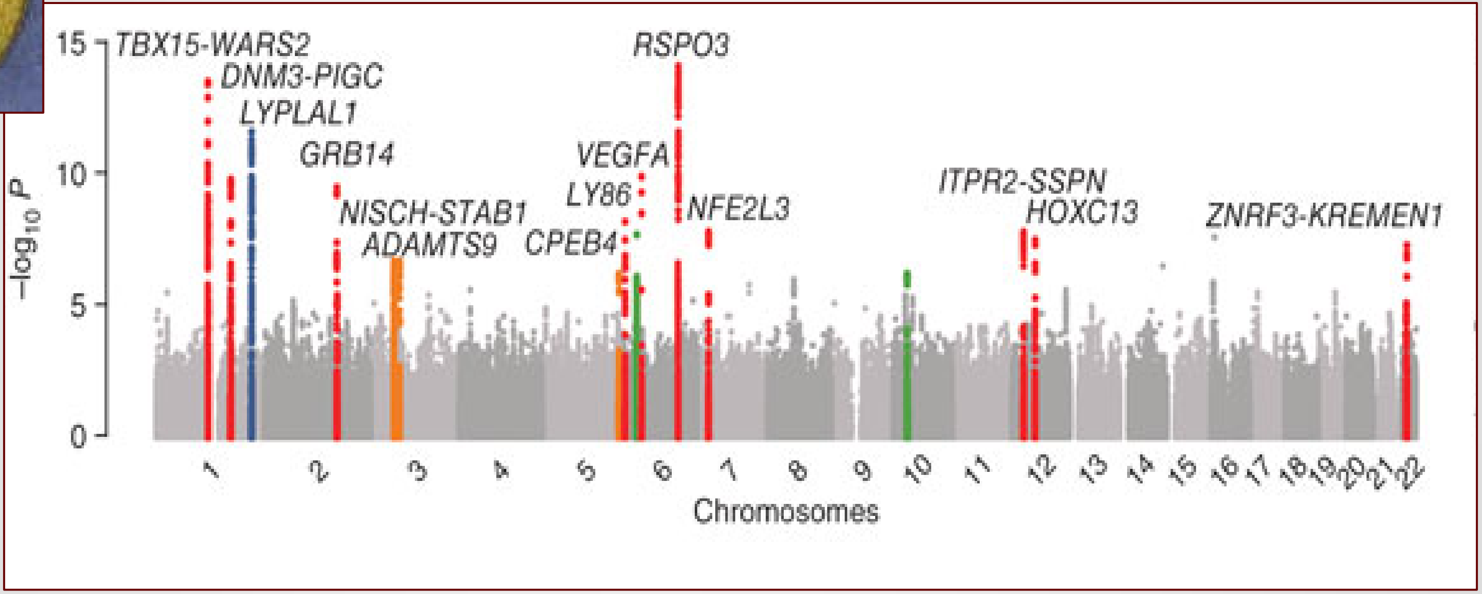
Combined association analyses of 249,796 individuals show additional eighteen new loci associated with body mass index



Speliotes-EK et al.
Nature Genetics. Online Oct. 10, 2010

Meta-analysis of GWAS identifies 13 new loci associated with waist-hip ratio



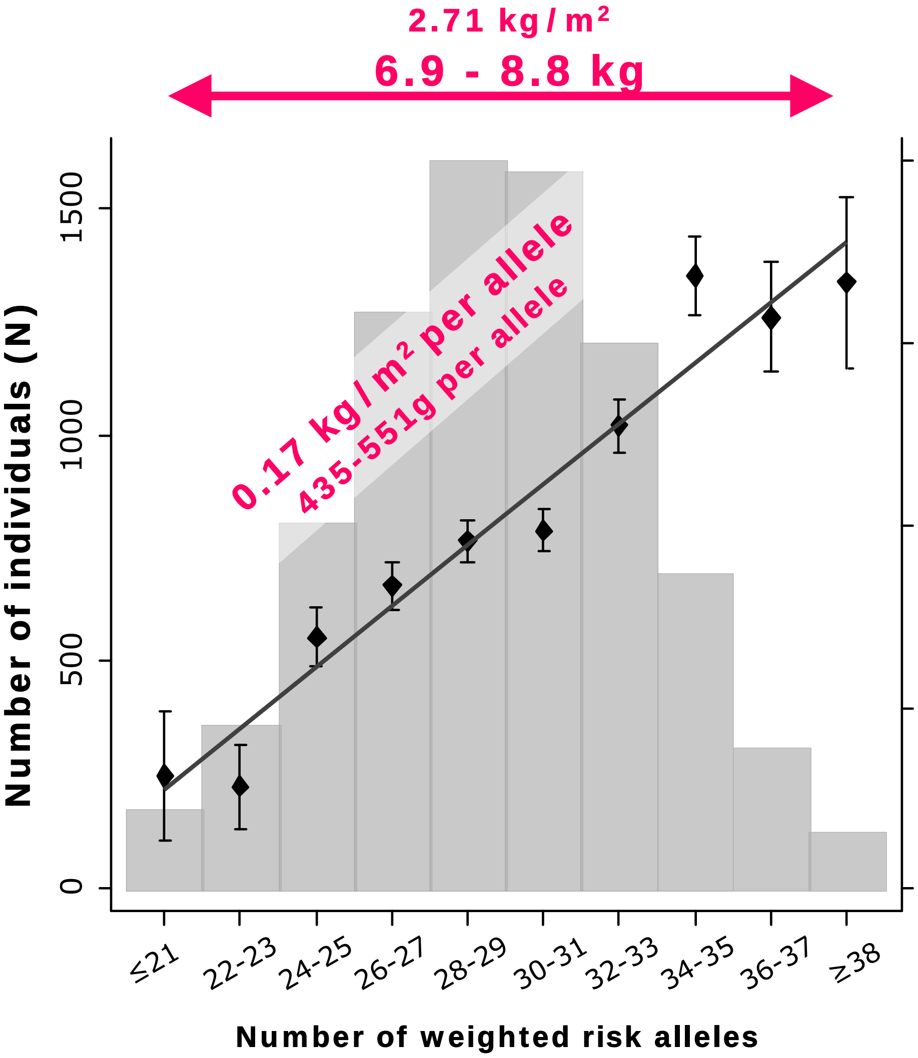


Nature Genetics
Online
October 10, 2010

The clinician’s view!

Cumulative effect and predictive value of 32 loci

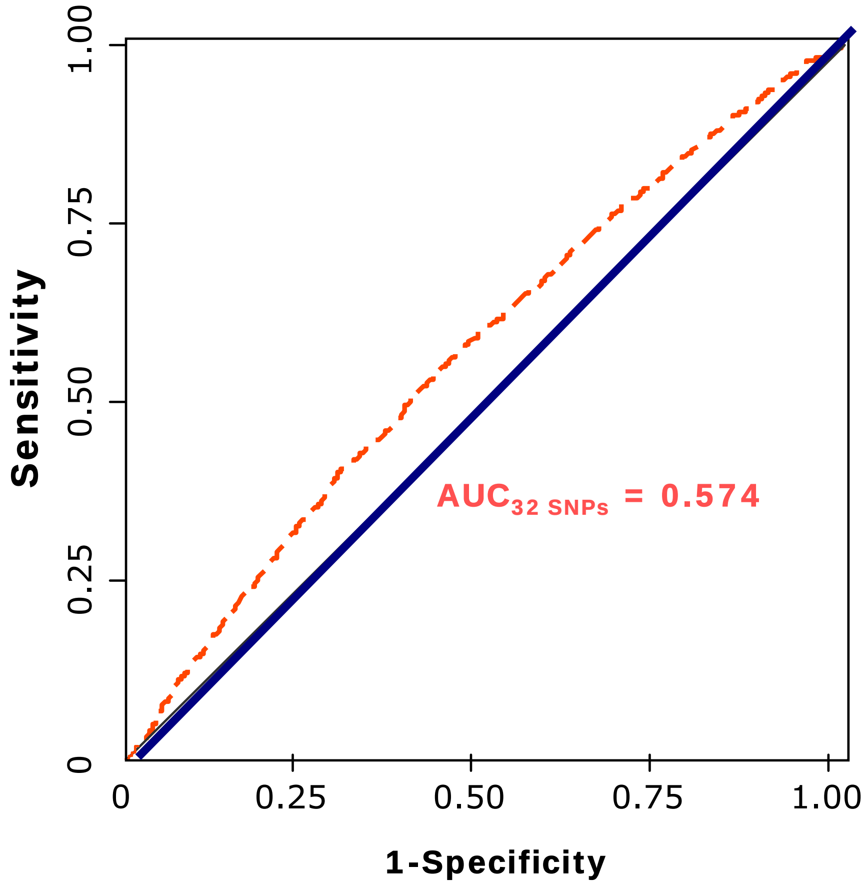
- ARIC study, 8,120 individuals, population-based, whites


2.71 kg / m^2

6.9 - 8.8 kg

0.17 kg / m^2 per allele

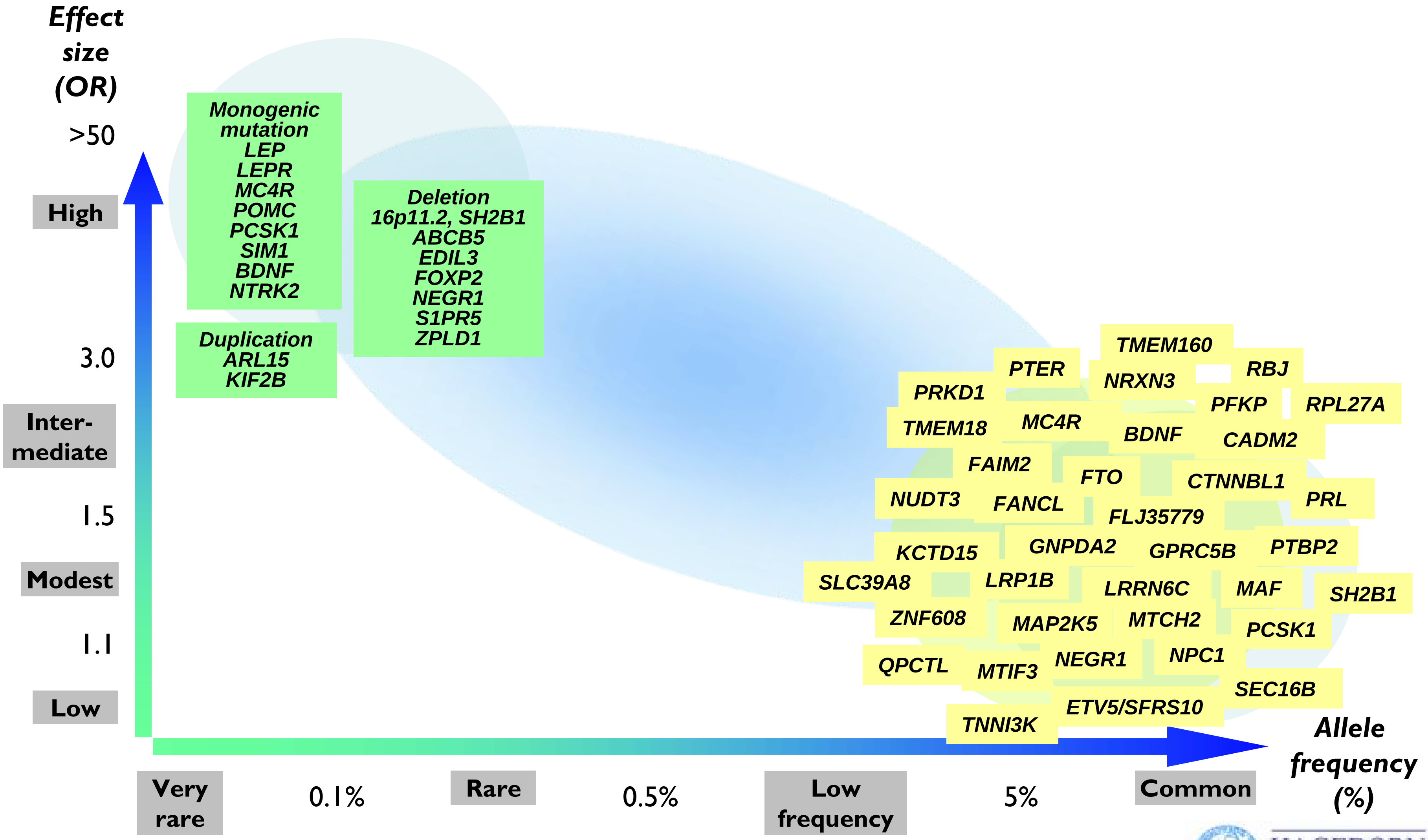
435-551g per allele


AUC$_{32\ SNPs}$ = 0.574

By courtesy of Dr. Ruth Loos

Speliotes et al., Nature Genetics. Online 10 October, 2010

Genetics of obesity



Effect size (OR)

>50

High

3.0

Inter-mediate

1.5

Modest

1.1

Low

Monogenic mutation
LEP
LEPR
MC4R
POMC
PCSK1
SIM1
BDNF
NTRK2

Duplication
ARL15
KIF2B

Deletion
16p11.2, SH2B1
ABCB5
EDIL3
FOXP2
NEGR1
S1PR5
ZPLD1

TMEM160
PTER
RBJ
NRXN3
PRKD1
PFKP
RPL27A
TMEM18
MC4R
BDNF
CADM2
FAIM2
FTO
CTNNBL1
NUDT3
FANCL
PRL
FLJ35779
KCTD15
GNPDA2
GPRC5B
PTBP2
SLC39A8
LRP1B
LRRN6C
MAF
SH2B1
ZNF608
MAP2K5
MTCH2
PCSK1
QPCTL
MTIF3
NEGR1
NPC1
SEC16B
ETV5/SFRS10
TNNI3K

Very rare

0.1%

Rare

0.5%

Low frequency

5%

Common

Allele frequency (%)

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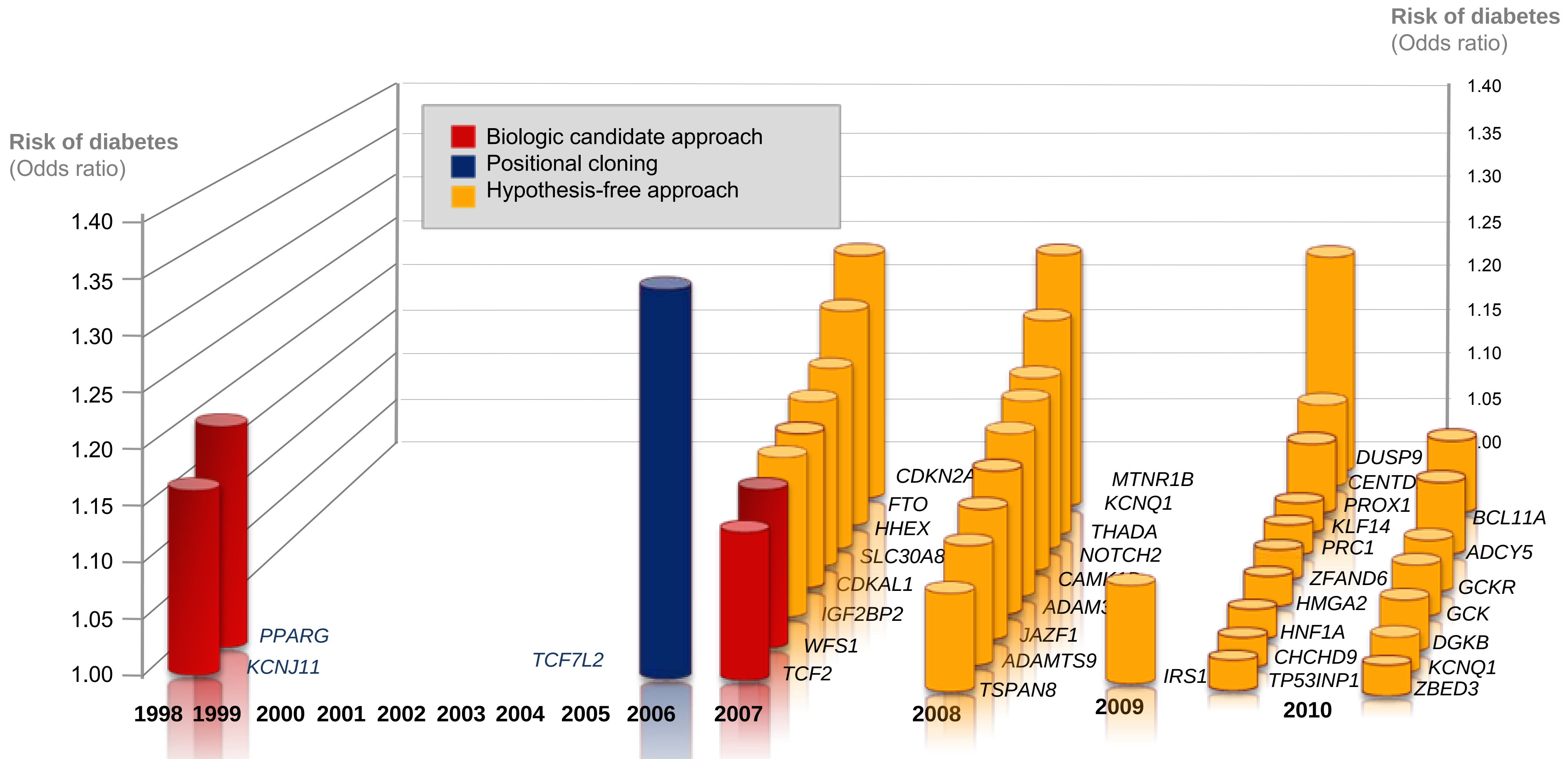
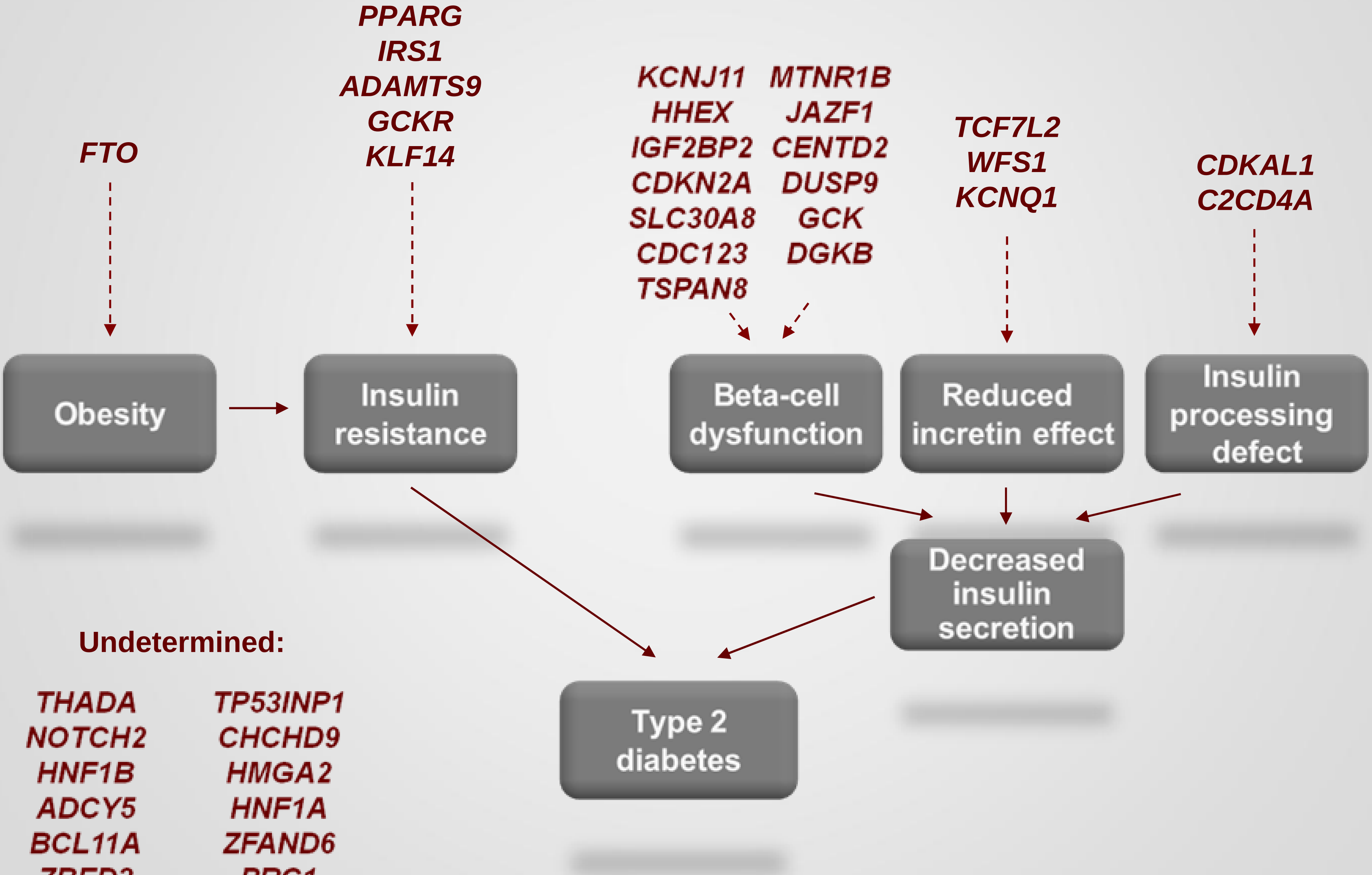
37 risk loci associate with T2D with genome-wide significance

Each of them are common but only increase risk of type 2 diabetes with 5-35%



Estimated functions of variants at type 2 diabetes risk loci



FTO

Obesity

PPARG
IRS1
ADAMTS9
GCKR
KLF14

Insulin resistance

KCNJ11
HHEX
IGF2BP2
CDKN2A
SLC30A8
CDC123
TSPAN8

MTNR1B
JAZF1
CENTD2
DUSP9
GCK
DGKB

Beta-cell dysfunction

TCF7L2
WFS1
KCNQ1

Reduced incretin effect

CDKAL1
C2CD4A

Insulin processing defect

Decreased insulin secretion

Type 2 diabetes

Undetermined:

THADA
NOTCH2
HNF1B
ADCY5
BCL11A
ZBED3

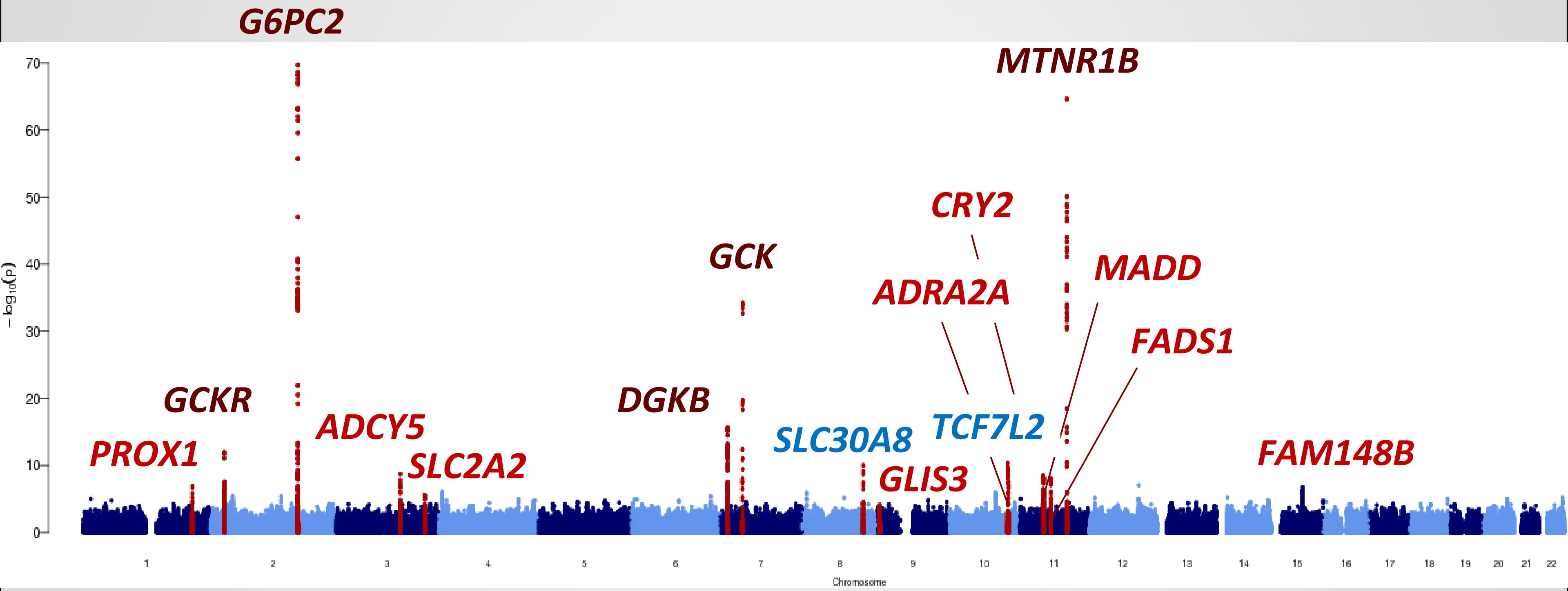
TP53INP1
CHCHD9
HMGA2
HNF1A
ZFAND6
PRC1

Fasting glucose meta-analysis discovers

Five known FGP loci

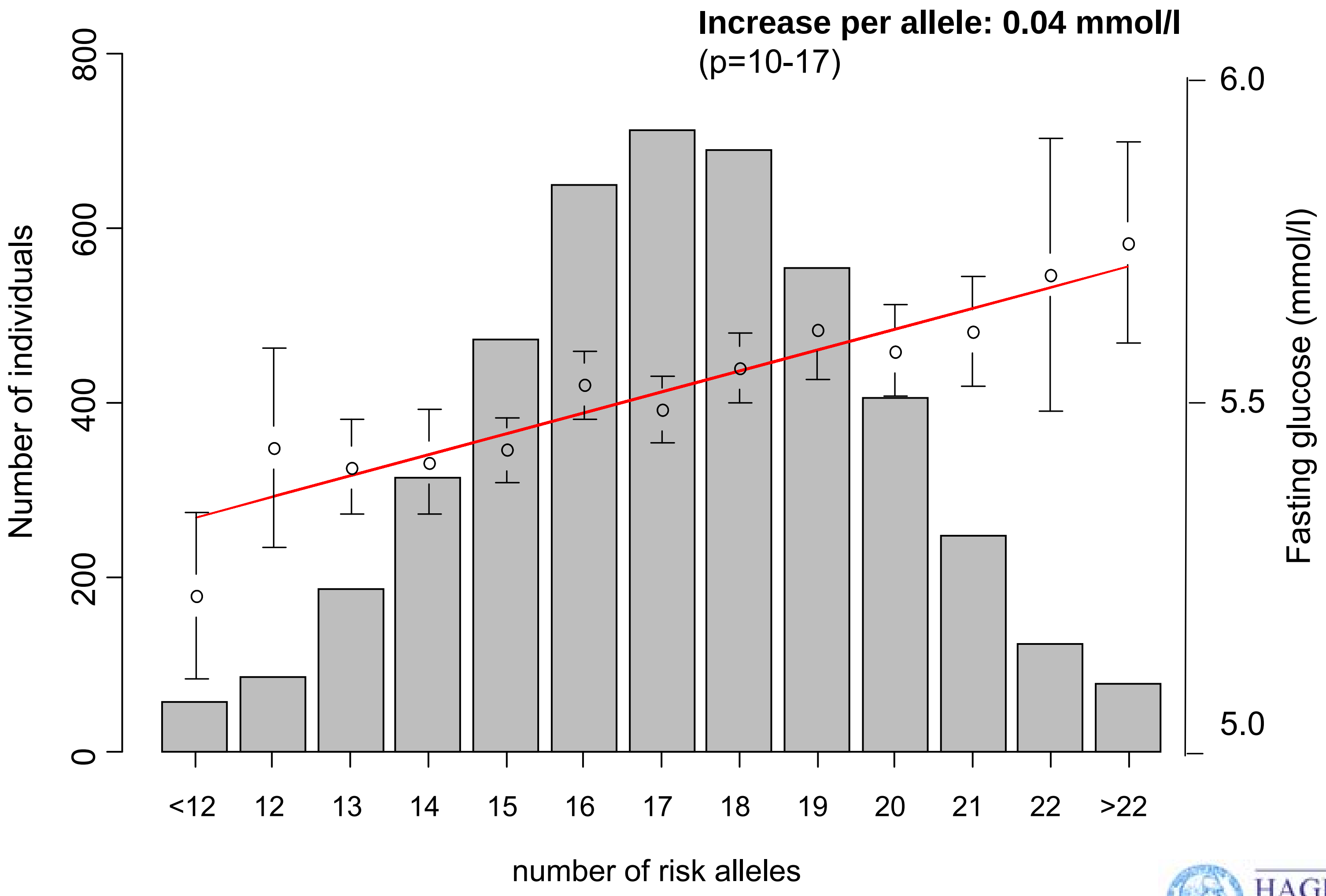
Two established T2D loci

Nine novel loci



Dupuis et al, *Nat Genet* online Jan 17th 2010

The combined impact of 16 risk variants on fasting glucose in a non-diabetic population



Common variants *explain a minor fraction of the variance* in metabolic phenotypes in the general population

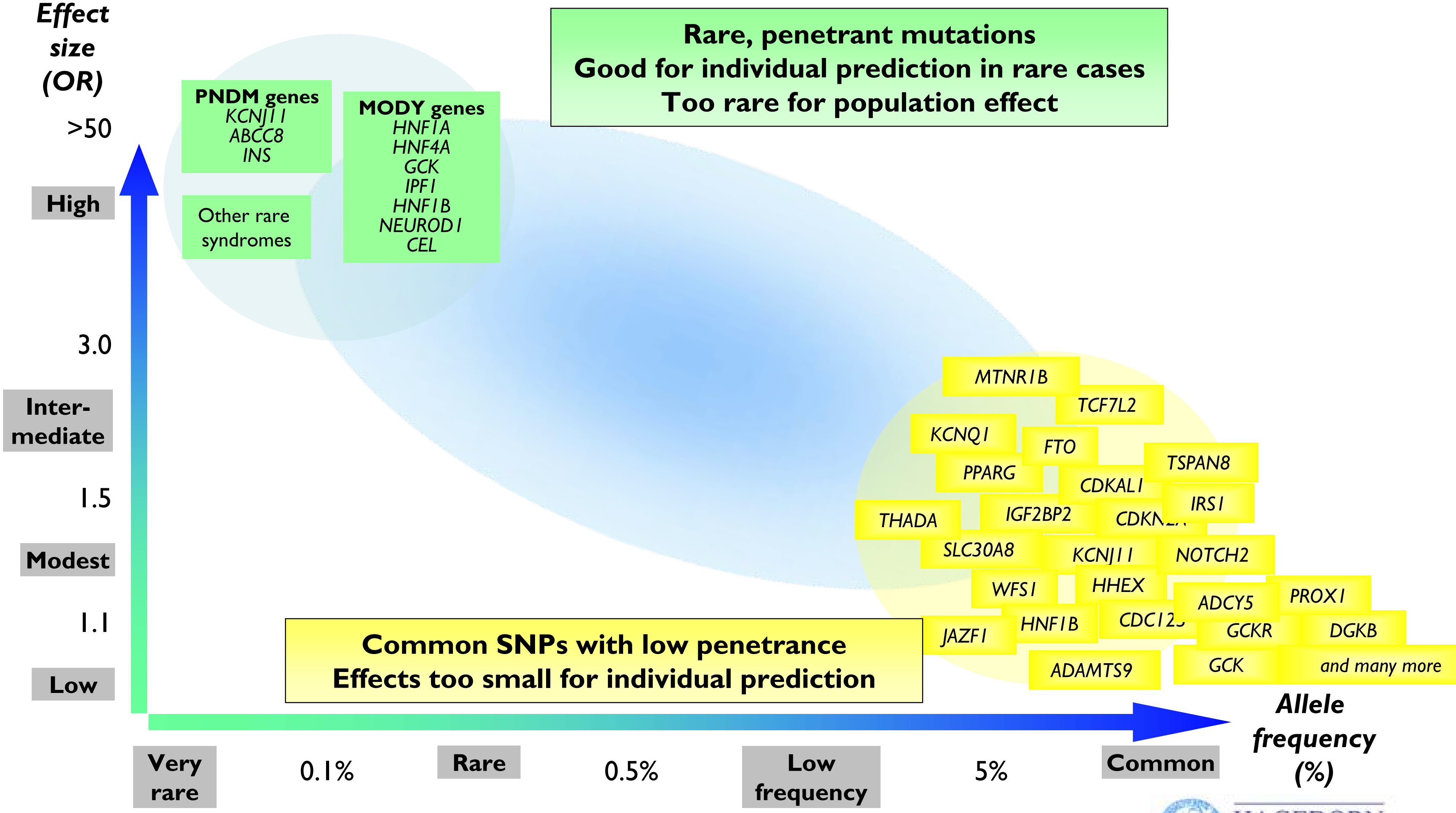
Fasting plasma glucose

Heritability 30-40%

Of total:
4-6%

Of genetic:
8-12%

Genetics of non-autoimmune diabetes



Effect size (OR)

>50

High

3.0

Inter-mediate

1.5

Modest

1.1

Low

PNDM genes
KCNJ11
ABCC8
INS

Other rare syndromes

MODY genes
HNF1A
HNF4A
GCK
IPF1
HNF1B
NEUROD1
CEL

Rare, penetrant mutations
Good for individual prediction in rare cases
Too rare for population effect

MTNR1B
TCF7L2
KCNQ1
FTO
TSPAN8
PPARG
CDKAL1
IRS1
THADA
IGF2BP2
CDKN2
SLC30A8
KCNJ11
NOTCH2
WFS1
HHEX
ADCY5
PROX1
JAZF1
HNF1B
CDC12
GCKR
DGKB
ADAMTS9
GCK
and many more

Common SNPs with low penetrance
Effects too small for individual prediction

Allele frequency (%)

Very rare

0.1%

Rare

0.5%

Low frequency

5%

Common

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Explosion in the number of validated common variants for all diabetes-related metabolic traits

Type 2 diab — 37+ loci

Common variants with low individual impact

Fasting plasma glucose — ~16 loci

Circula lipid levels

Unknown causal mutation and gene

BMI obes

Identified variants explain 5-10 % of the genetic contribution

Hypertension or — ~14 loci

Cardiova disease

Collectively the variants have no clinical utility for disease discrimination or prediction

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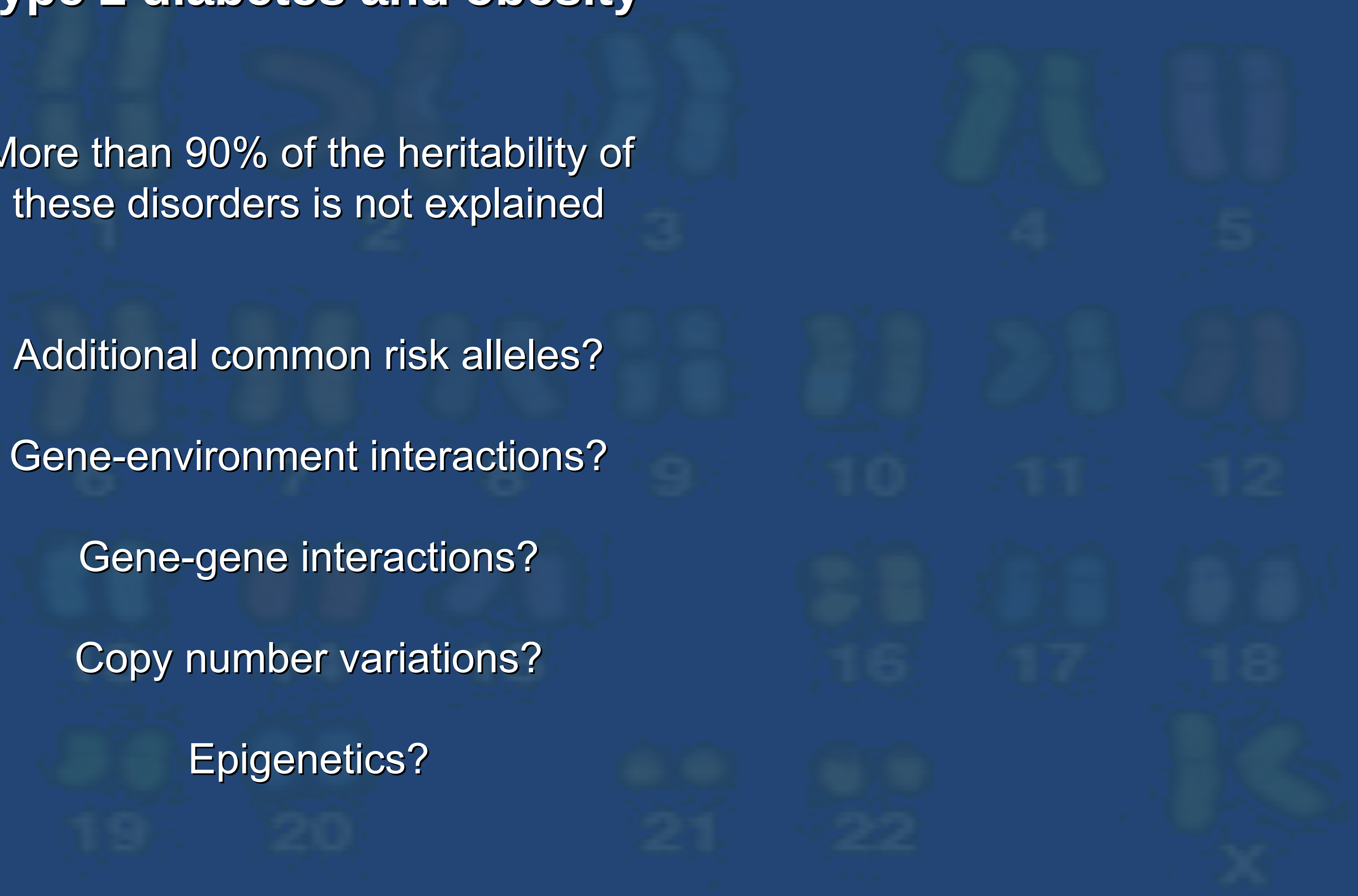
The ‘missing heritability’ of type 2 diabetes and obesity



More than 90% of the heritability of these disorders is not explained

Additional common risk alleles?

Gene-environment interactions?

Gene-gene interactions?

Copy number variations?

Epigenetics?

The ‘missing heritability’ of type 2 diabetes and obesity

More than 90% of the heritability of these disorders is not explained

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Gene-gene interactions?

Copy number variations?

Epigenetics?

We’ve found obesit

gene, say scientists

BY SUZY AUSTIN

THE first proof that a gene can affect

responsible for Britain’s rapidly rising

obesity ra

Althou

accounts

as much exercise as my friend ne

Scientists find one in six Britons is progra mmed to be o

THE FA

By EMILY COOK
Health Correspondent

Experts discover trigger to obesity for 1 in 6 Brits

UP to one in six people carry a gene which makes them much more likely to get fat, scientists found.

They discovered those with a variation of a gene known as FTO – almost 50 per cent of the population – have a 30 per cent increased risk of obesity.

And the 16 per cent of people with two copies, or one in six, are 70 per cent more likely to

ask, “I eat the same and do as much exercise as my friend next door, so why am I fatter?’ There is clearly a component to obesity that is genetic.”

The study looked at the white population of the UK which makes up 88 per cent of the whole.

Scientists discovered a person with one copy of the gene variation will be an average two and a half lbs heavier or 1cm fatter

THERE IS AN OBESITY GENE

By Fiona MacRae

The findings may also help expla why some people find it harder to lose weight th others.

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

LYNDSA OSS
HEALTH CORRES

and Oxford Universit then tested a furth 00 genetic to look for the varia-

DOCTORS F THE FAT GENE

Why son
re like
overw

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

FINANCIAL TIMES

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New York, NY 10019
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Fax: +1 212 641 6515

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FRIDAY APRIL 13 2007

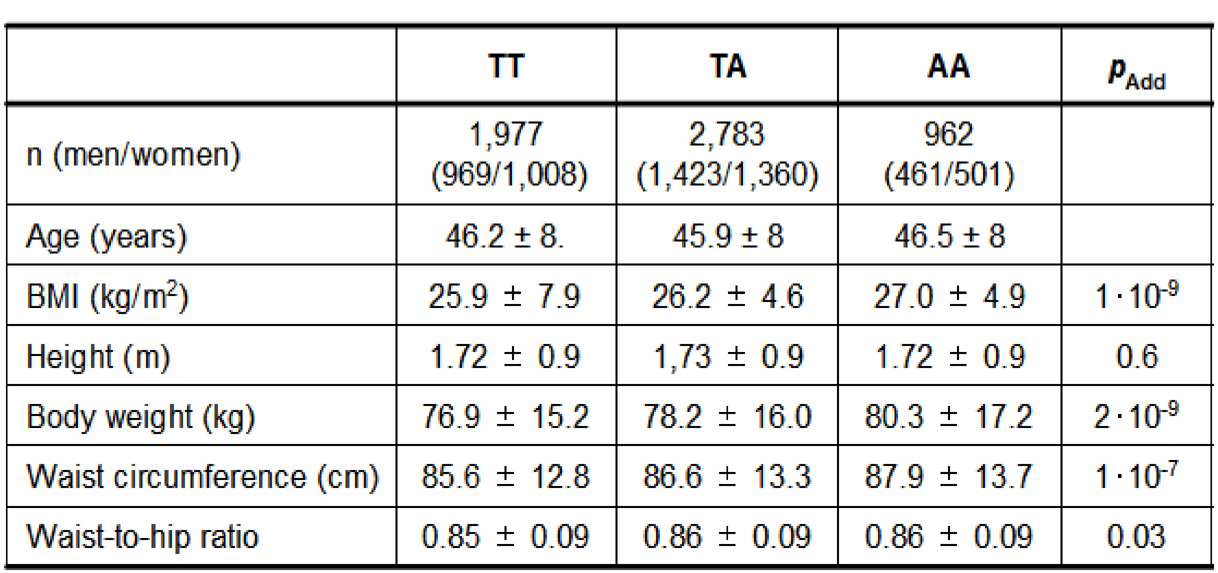
Weighty matters

Genetic link to obesity does not remove need for exercise

By courtesy of Dr. Mark McCarthy

The association of FTO with obesity-related quantitative traits in Inter99

- FTO associates with increased BMI, body weight and waist circumference
- No association with serum lipids



	TT	TA	AA	p_{Add}
n (men/women)	1,977 (969/1,008)	2,783 (1,423/1,360)	962 (461/501)	
Age (years)	46.2 ± 8.	45.9 ± 8	46.5 ± 8	
BMI (kg/m²)	25.9 ± 7.9	26.2 ± 4.6	27.0 ± 4.9	$1 \cdot 10^{-9}$
Height (m)	1.72 ± 0.9	1,73 ± 0.9	1.72 ± 0.9	0.6
Body weight (kg)	76.9 ± 15.2	78.2 ± 16.0	80.3 ± 17.2	$2 \cdot 10^{-9}$
Waist circumference (cm)	85.6 ± 12.8	86.6 ± 13.3	87.9 ± 13.7	$1 \cdot 10^{-7}$
Waist-to-hip ratio	0.85 ± 0.09	0.86 ± 0.09	0.86 ± 0.09	0.03

Andreasen CH, *Diabetes* 2008;57:95-101

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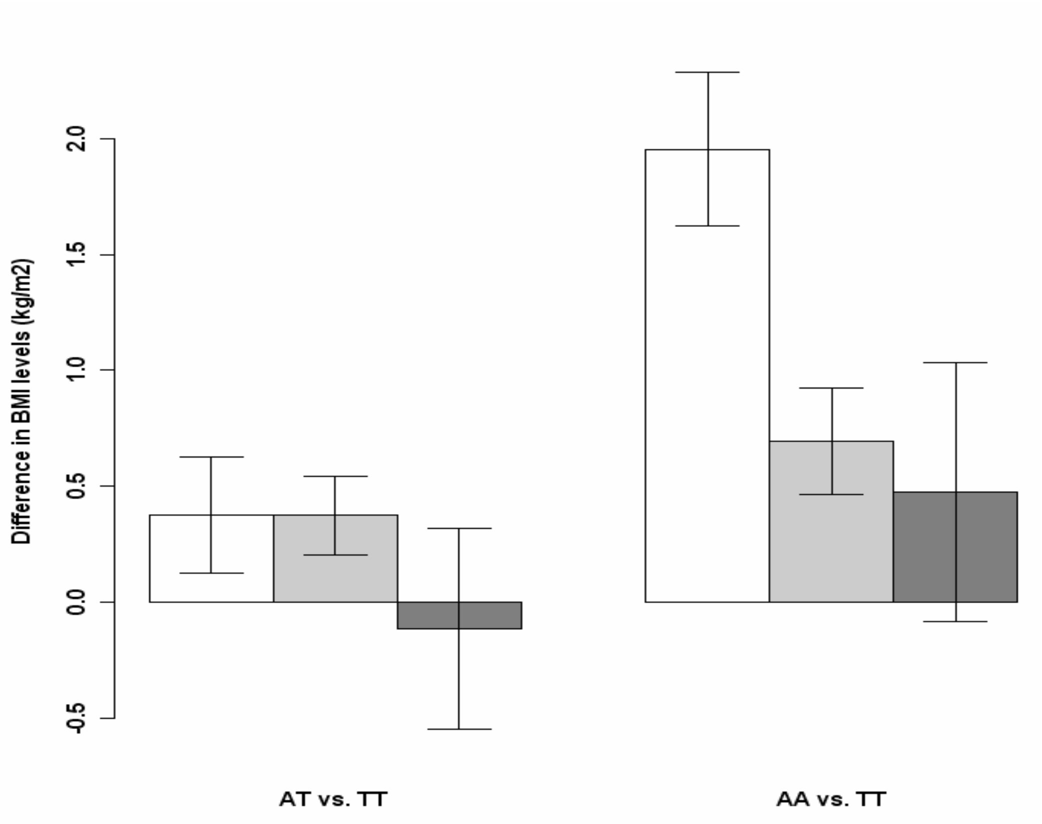
The impact of the *FTO* rs9939609 genotype on BMI-levels is highly influenced by habitual physicial activity: Physical inactivity was associated with an increase of 1.95 BMI units in AA-allele carriers

A population-based study of 5,722 middle-aged Danes



Number of subjects (TT/TA/AA)

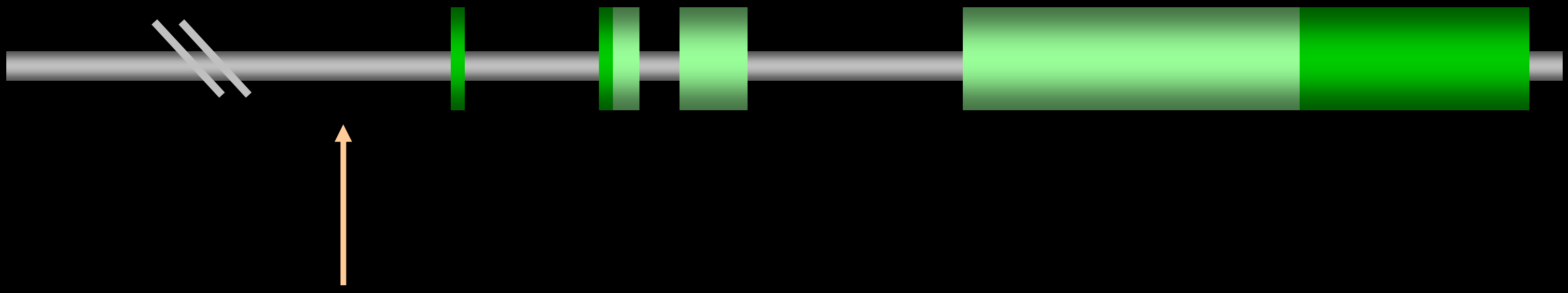
- ☐ Physically passive (633/943/338)
- ▨ Light or medium physically active (1,131/1,572/521)
- ■ Hard or very hard physically active (152/189/75)

$P_{\text{int}} = 0.007$

Physical activity was self-reported by questionnaire

Andreasen CH, *Diabetes* 2008;57:95-101

APOLIPOPROTEIN A-V; APOA5



-1131T>C

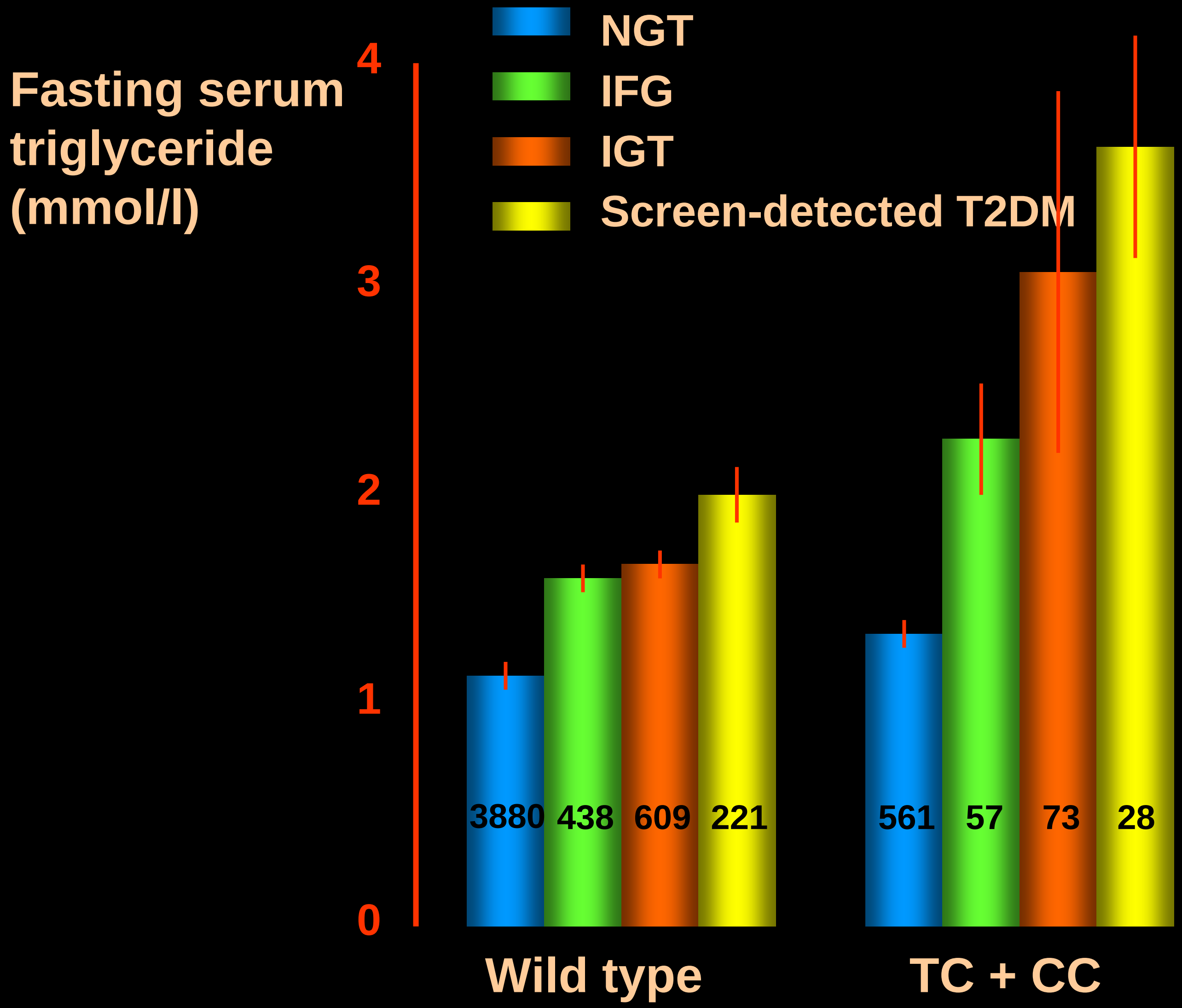
- Carrier frequency ~ 11 % among Caucasians

Association with fasting serum triglycerides in the general population of 5,873 middle-aged Danes

	T/T	T/C	C/C	*p*
n(men/women)	5,152(2,563/2,589)	698(356/342)	23(10/13)	
Age (years)	46 ± 8	46 ± 8	44 ± 7	
BMI (kg/m^2)	26.2 ± 4.5	26.4 ± 4.8	24.3 ± 4.6	0.7
Waist-to-hip ratio	0.86 ± 0.09	0.86 ± 0.09	0.84 ± 0.08	0.9
Fasting serum lipids (mmol/l)				
Triglyceride	1.3 ± 1.1	1.7 ± 2.7	1.8 ± 0.9	$1 \cdot 10^{-15}$

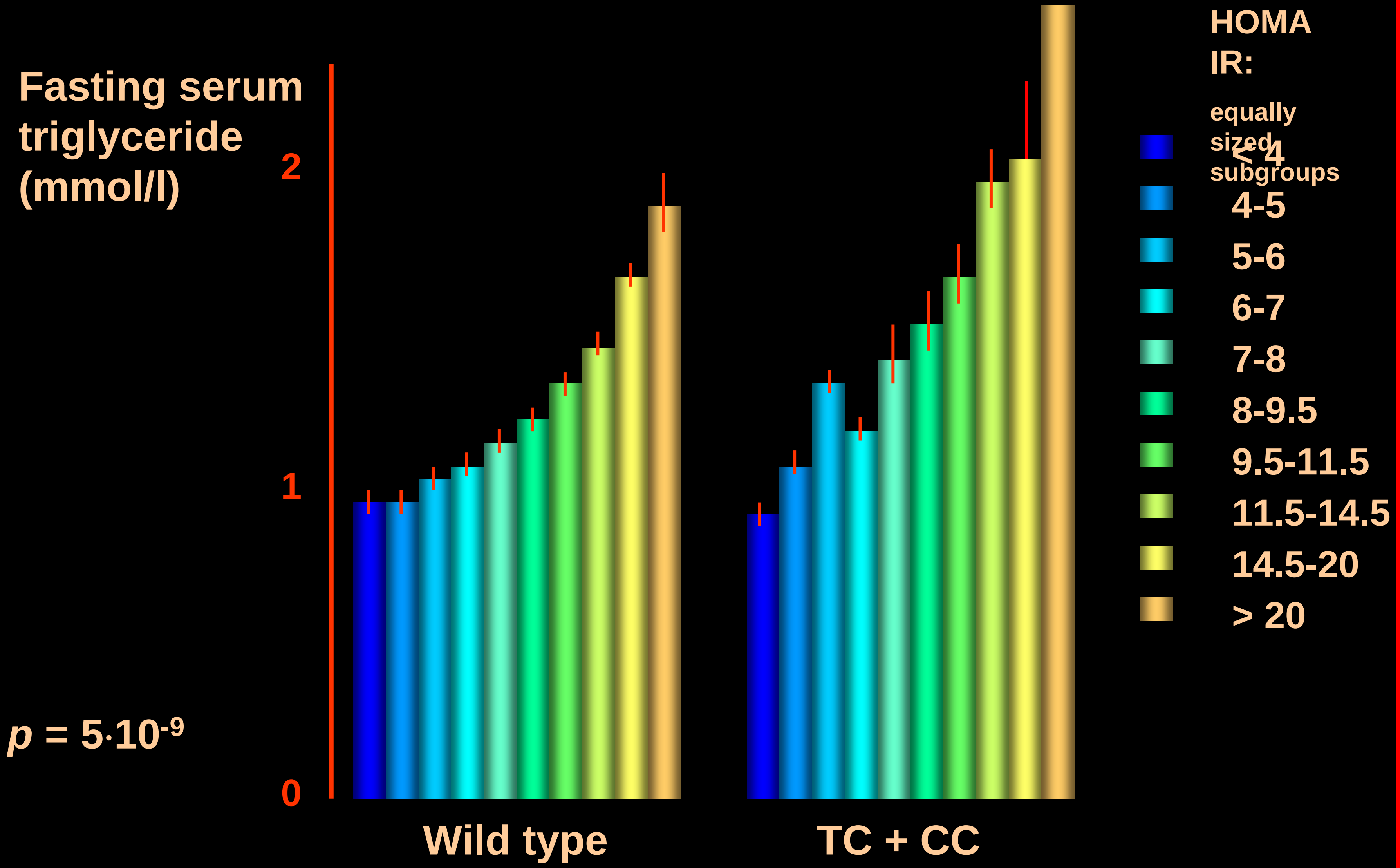
Mean ± SD. Adjustment for age, sex, and BMI (where appropriate). Calculated by GLM assuming additivity.

The effect of *APOA5* -1131T>C on fasting serum triglycerides is modulated by the level of hyperglycaemia in studies of 5,873 middle-aged Danes

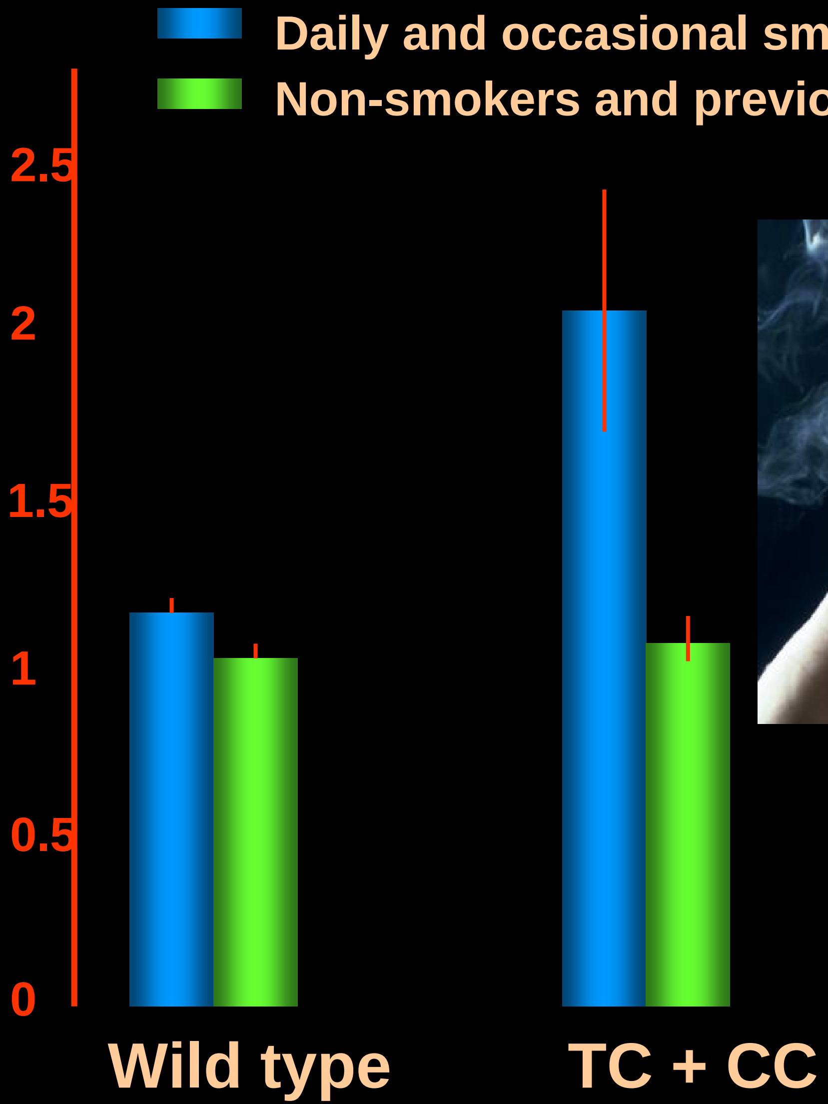


$p = 5 \cdot 10^{-9}$

The impact of *APOA5* -1131T>C on fasting serum triglycerides is modulated by the degree of insulin resistance (Homa-IR) in studies of 5,873 middle-aged Danes

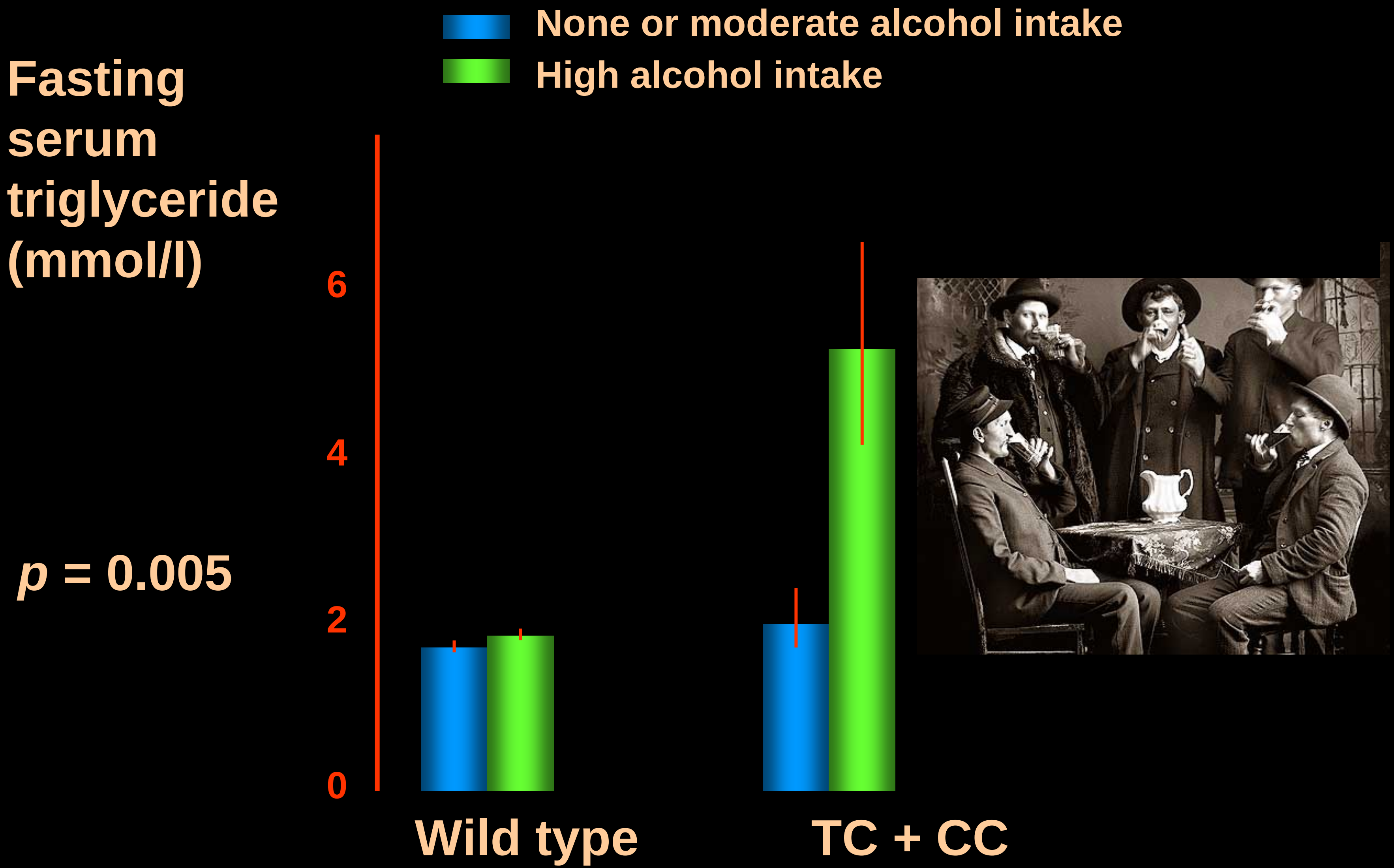


The impact of *APOA5* -1131T>C on fasting serum triglyceride is modulated by smoking



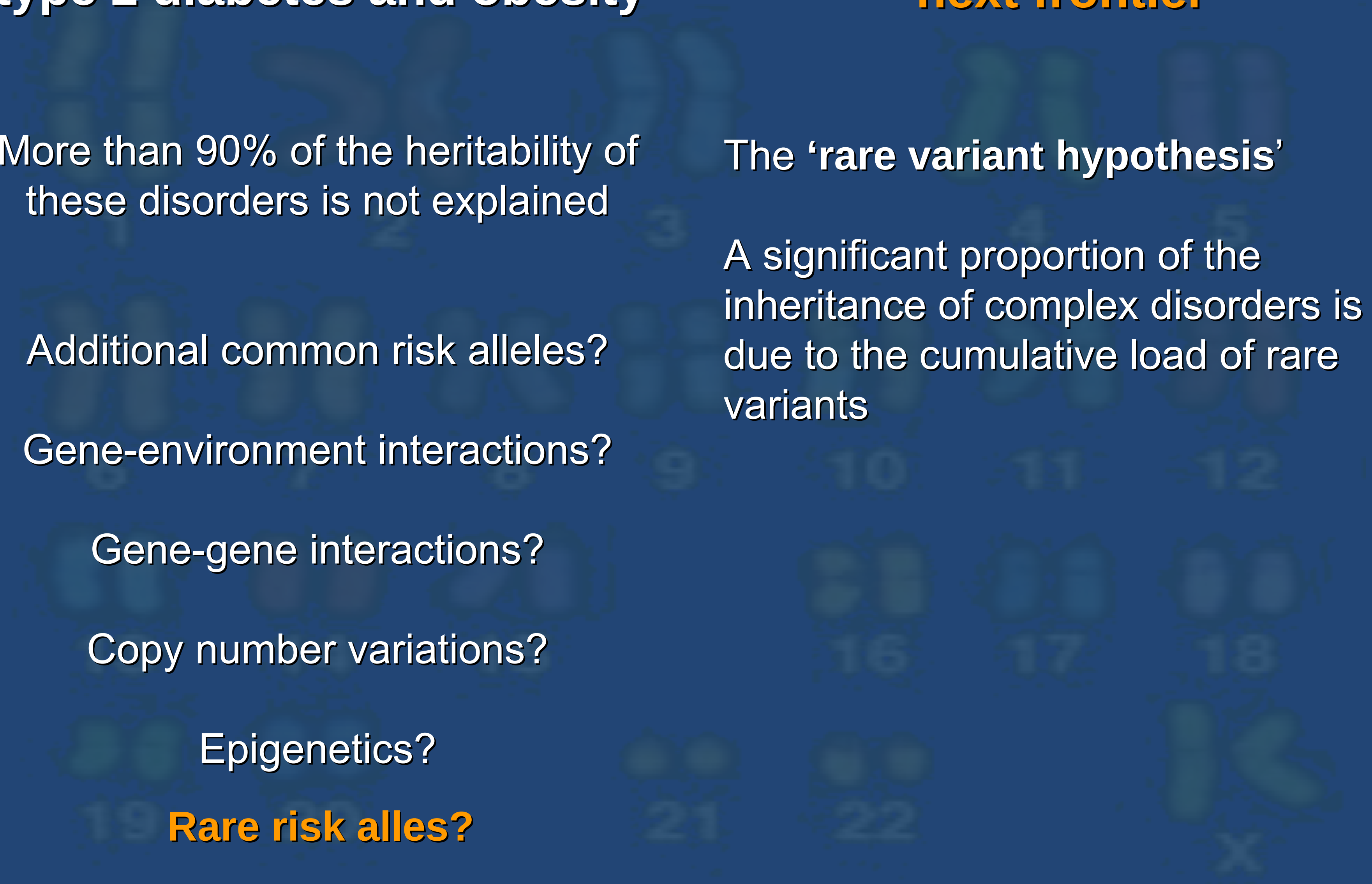
$p = 0.0003$

The impact of *APOA5* -1131T>C on fasting serum triglyceride is modulated by alcohol intake



Public health implications: Gene-Lifestyle and Gene-Metabolism Interactions

Specific health behaviour recommendations seem appropriate based upon knowledge of the *FTO*, *LIPC* and *APOA5* genotypes



The ‘missing heritability’ of type 2 diabetes and obesity

More than 90% of the heritability of these disorders is not explained

Additional common risk alleles?

Gene-environment interactions?

Gene-gene interactions?

Copy number variations?

Epigenetics?

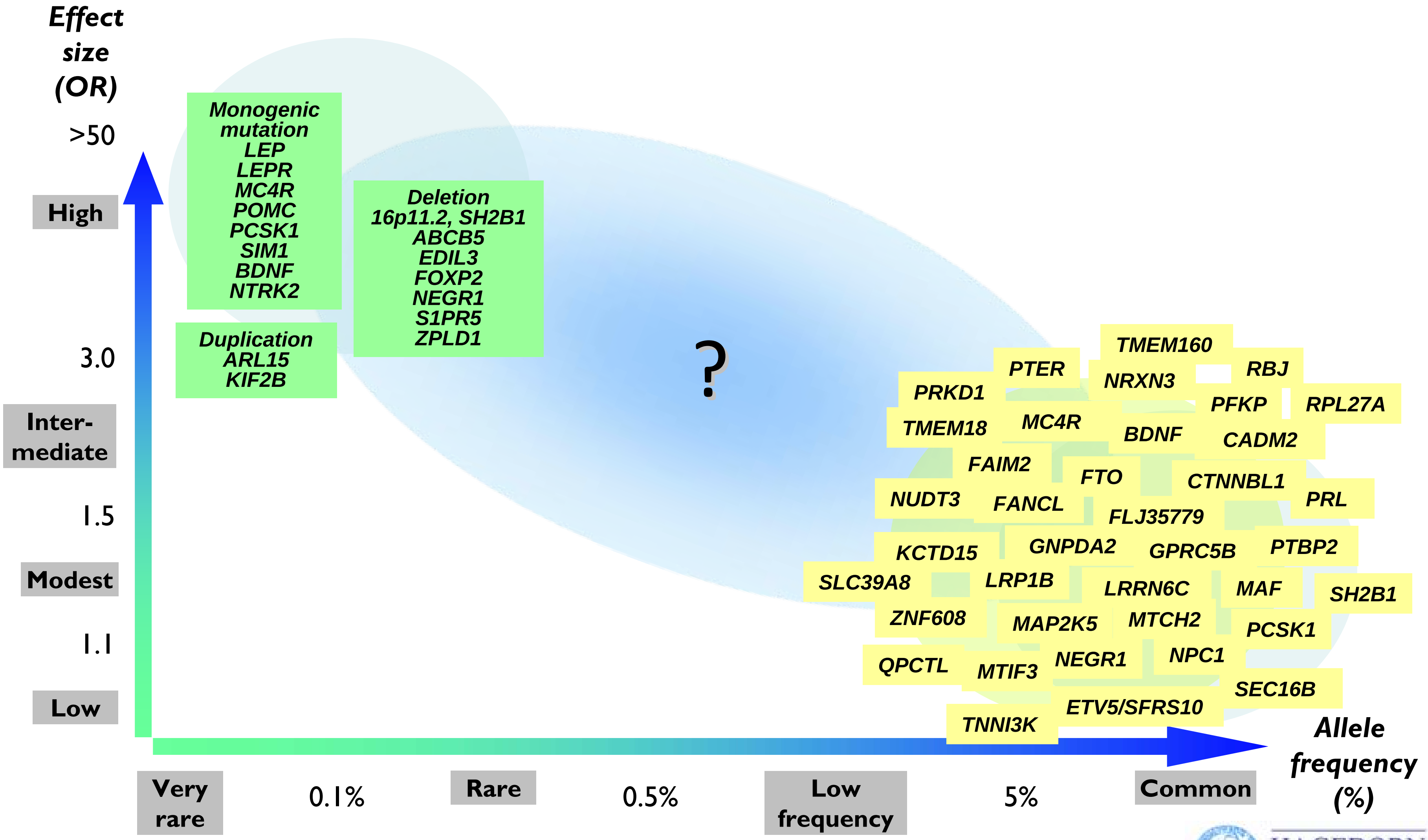
Rare risk alles?

Rare risk alleles – next frontier

The **‘rare variant hypothesis**’

A significant proportion of the inheritance of complex disorders is due to the cumulative load of rare variants

Where is the missing heretability?



Effect size (OR)

>50

High

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Monogenic mutation
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POMC
PCSK1
SIM1
BDNF
NTRK2

Duplication
ARL15
KIF2B

Deletion
16p11.2, SH2B1
ABCB5
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?

TMEM160
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MC4R
BDNF
CADM2
FAIM2
FTO
CTNNBL1
NUDT3
FANCL
PRL
FLJ35779
KCTD15
GNPDA2
GPRC5B
PTBP2
SLC39A8
LRP1B
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ZNF608
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MTIF3
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NPC1
SEC16B
ETV5/SFRS10
TNNI3K

Allele frequency (%)

Very rare

0.1%

Rare

0.5%

Low frequency

5%

Common

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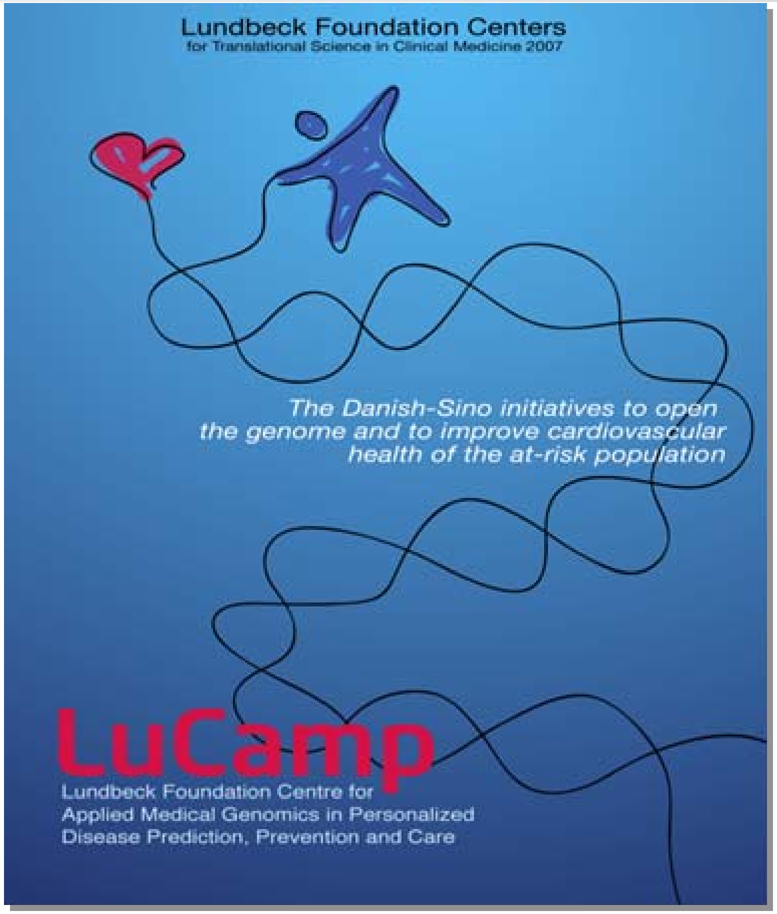
The Lundbeck Foundation Initiative in genomics of type 2 diabetes and obesity

- Sequencing of the coding part of the human genome in 2,000 Danes

- Gene-wise comparisons of ~ 20,000 likely deleterious gene variants in 17,000 Danes



Lundbeck Foundation Centers
for Translational Science in Clinical Medicine 2007

The Danish-Sino initiatives to open the genome and to improve cardiovascular health of the at-risk population

LuCamp

Lundbeck Foundation Centre for
Applied Medical Genomics in Personalized
Disease Prediction, Prevention and Care

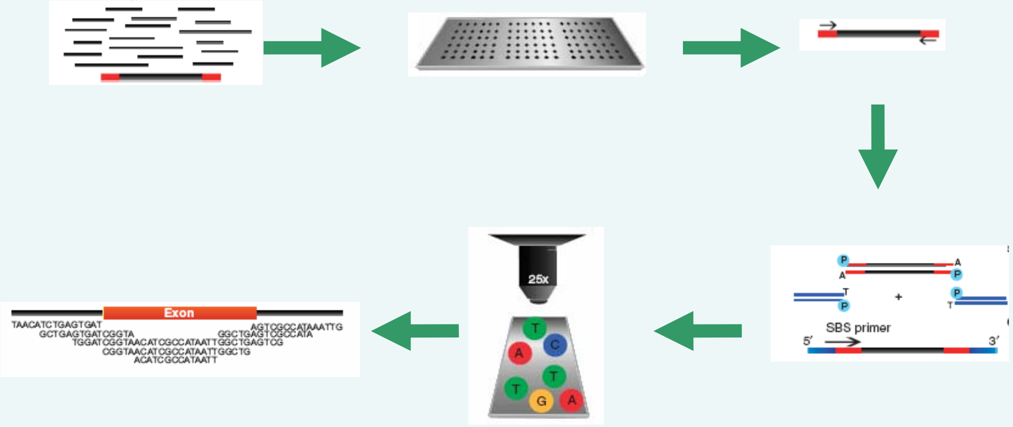
www.lucamp.org

Exome capturing

- The “exome” is defined to be the designed target region which would be hybridized with the NimbleGen 2.1M-probe sequence-capturing array.

- 18,654 genes, ~34Mbp length in total

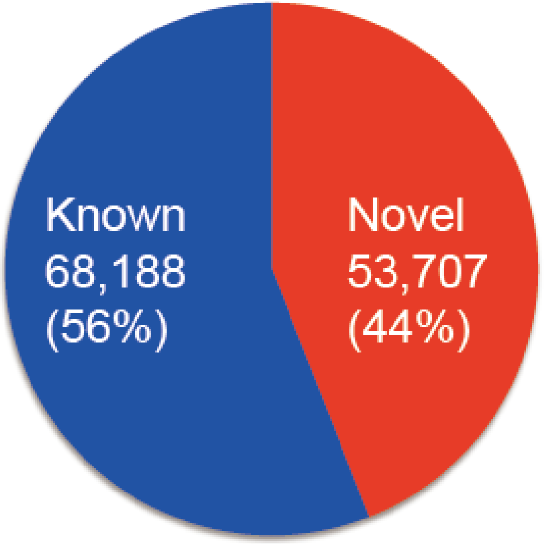
Genome elements	# Of elements	Total length
Promoter	1,917	490,995
5-UTR	17,046	672,142
CDS-exons	209,095	32,584,741
3-UTR	6,524	401,002
Intron	55,372	4,349,839

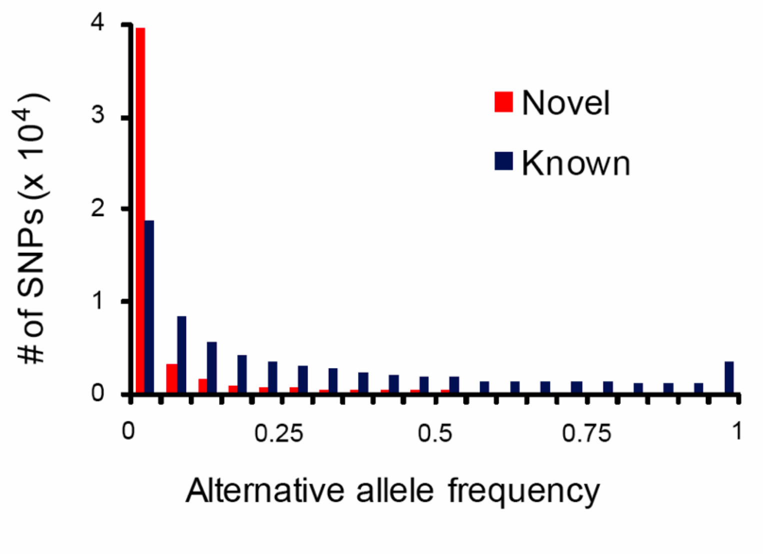


Production of huge amounts of data through high-throughput DNA sequencing in China

HAGEDORN
RESEARCH INSTITUTE

Individual sequencing of the coding region of 200 initial Danish human genomes covering ~20,000 genes discovered ~53,000 novel variants (= not in available databases)





Li et al., Nat Genet, online 3 October 2010

LuCamp

Lundbeck Foundation Centre for Applied Medical Genomics in Personalised Disease Prediction, Prevention and Care

The bacteria in our distal intestines function as **a metabolic organ**

Is an imbalance in gut bacteria in part to blame for metabolic complications

Nature 444, 21 December 2006

Human colon bacteria

≈ 1.5 kg microbes

Bacteriodetes and *Firmicutes* account for > 90%

Functions:

Trophic

Control of epithelial cell proliferation and differentiation

Protective

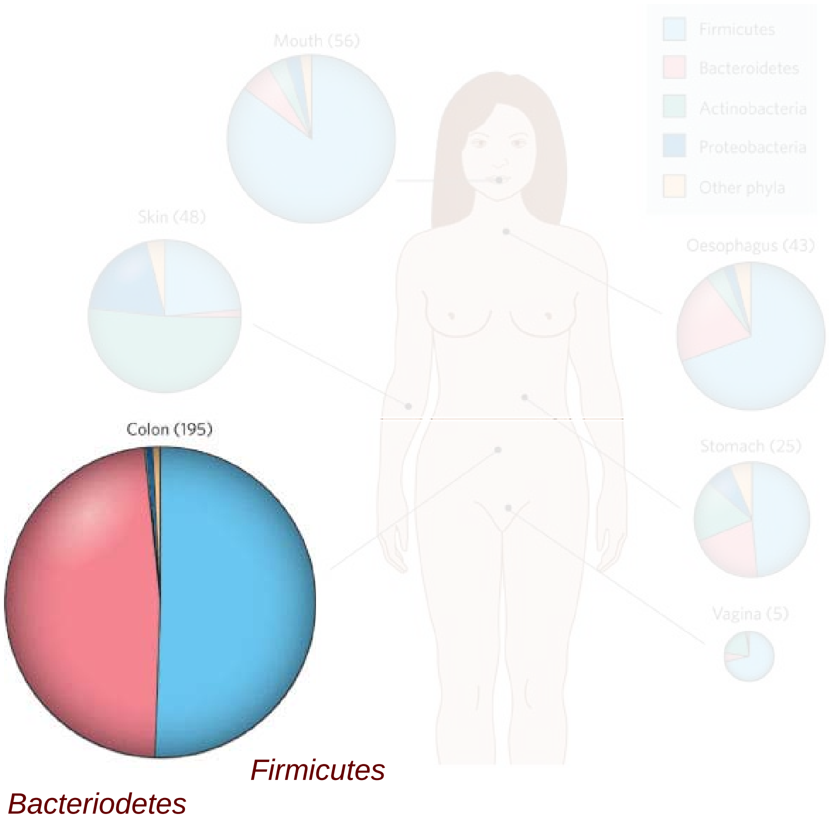
Protection against pathogens

Metabolic

Fermentation of non-digestible polysaccharides and storage of the extracted energy in host fat depots. Contributes with about 10% of total daily energy infusion

Who is who?

The microflora of human body cavities



Dethlefsen L. et al. Nature 449: 811-818,2007

Obese mice have more *Firmicutes*

Obese mice have 50 % higher representation of gut *Firmicutes* division and proportionally less of the *Bacteroidetes* division than lean mice

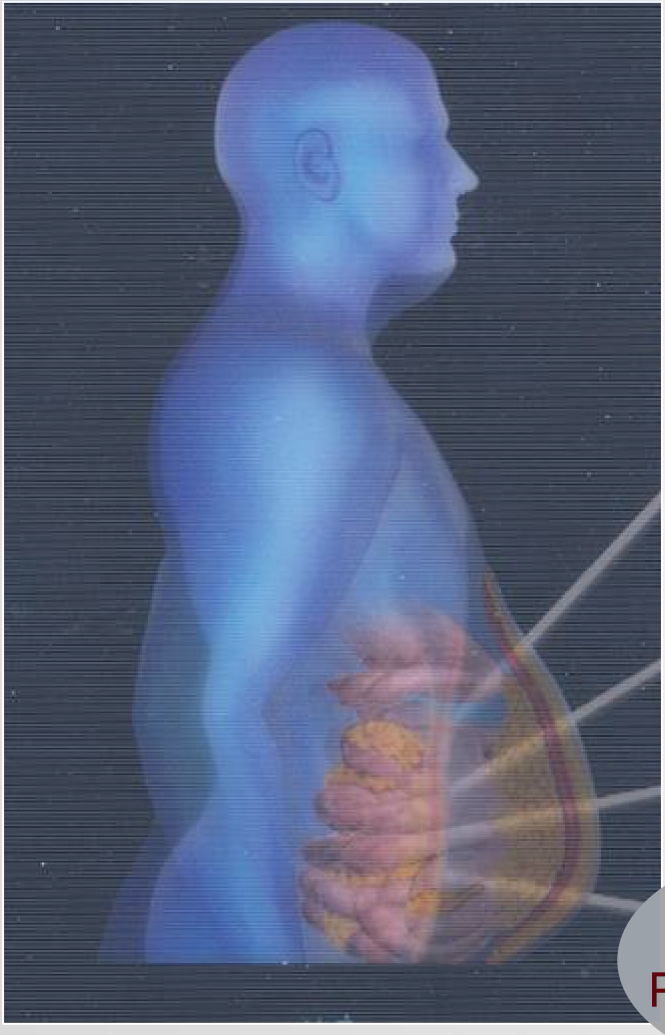
This trait was transmissible:

When germ-free mice were given an 'obese gut microflora' it resulted in an increase in total body fat compared with colonization with a 'lean gut microflora’

The *Firmicutes* have a higher capacity for fermentation of non-digestible polysaccharides than *Bacteriodetes*

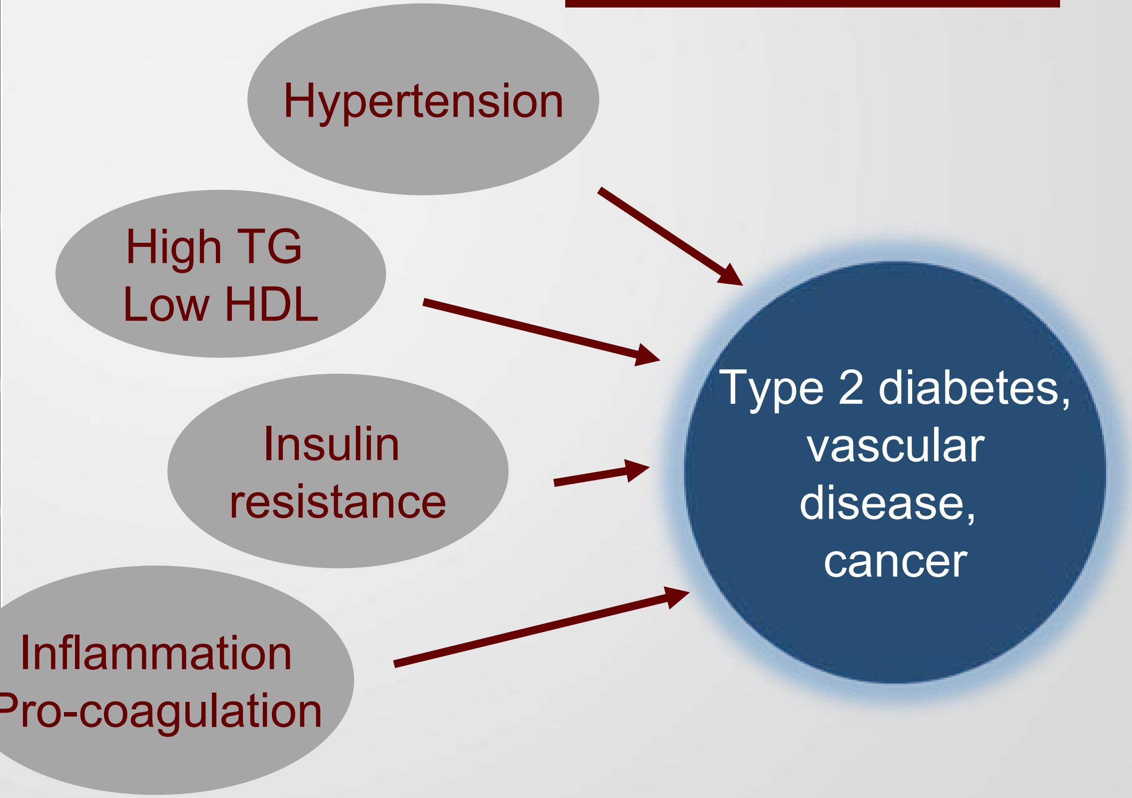
Ley RE et al. PNAS 102:11070-5,2005
Turnbaugh PJ et al., Nature 444:1027-31,2006

Features of obesity



Triggers:

- Genetic risk factors
- Overeating
- Physical inactivity
- **The gut microbiome?**



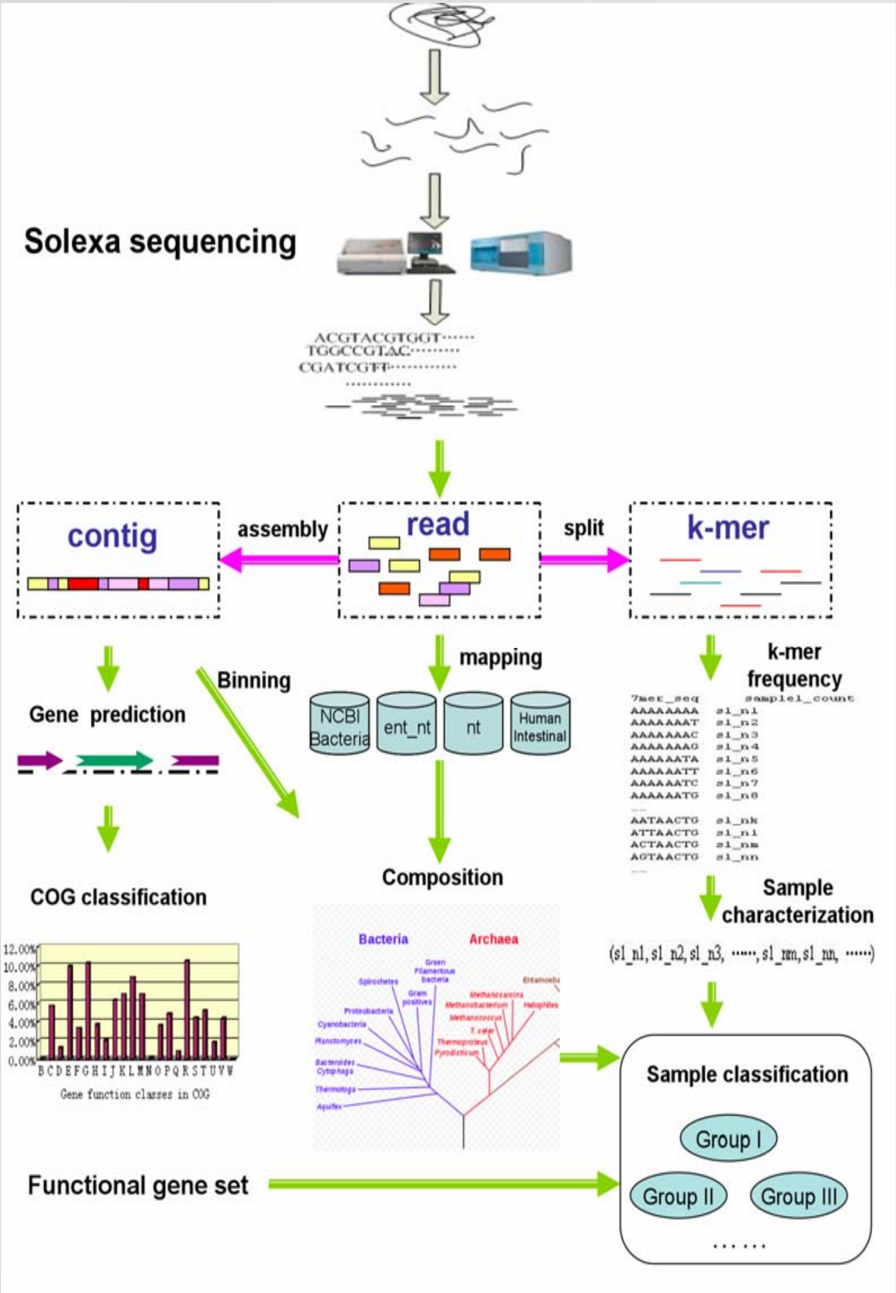
Hypertension

High TG
Low HDL

Insulin resistance

Inflammation
Pro-coagulation

Type 2 diabetes, vascular disease, cancer

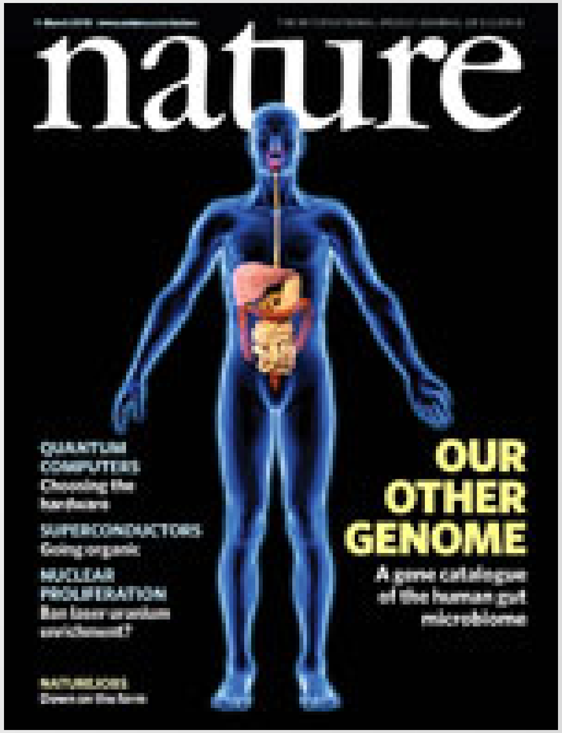


Massively parallel shotgun sequencing of genes from distal gut bacteria of 86 Danes and 38 from Spain

a culture-independent approach
to identify the gut bacterial genes

Identification of 3.3 million genes from distal gut of 86 Danes and 38 from Spain

- Human gut gene set is at least 150 times larger than the gene set of the human genome
- \> 99% of gut genes are bacterial
- Each individual harbors ~ 160 gut bacterial *species* with ~ 530,000 bacterial *genes*
- 64 out of 160 gut bacterial species are shared by >90% of individuals
- *Bacteriodetes* and *Firmicutes* are the most abundant



Nature 464:59-65, 2010

Which molecular mediators are involved in the metabolic dysfunctions?

……bacterial lipopolysaccharides?
……bacterial short chain fatty acids?
…....bacterial amino acids?
……other mediators

What are the primary drivers?

….host genomics?

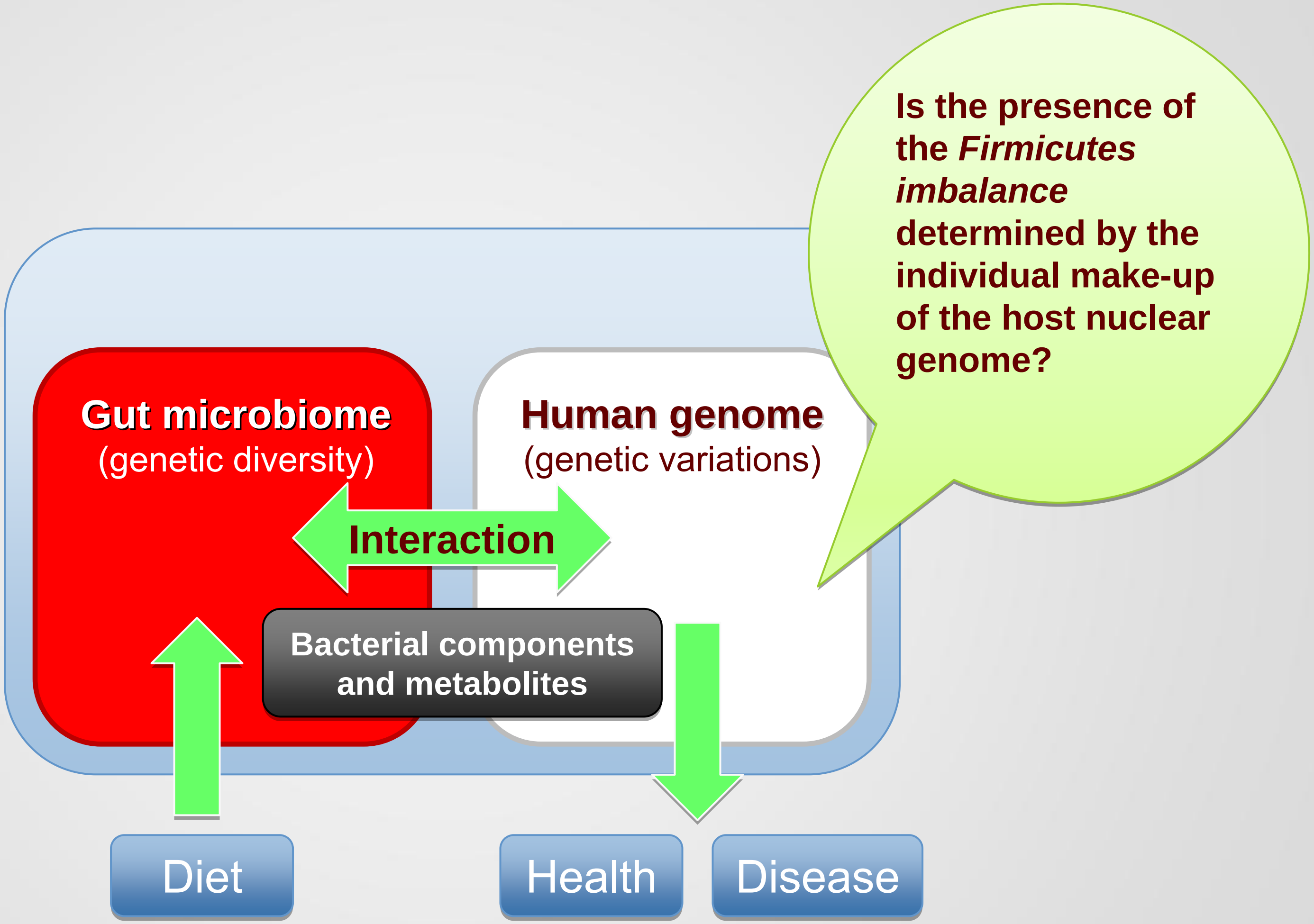
…..unhealthy dietary habits with preference of fat food?

Gut microbiome based interventions: perspectives

- Coloscopic replacement with a mixture of cultured or fresh ’healthy’ bacteria species?
- Oral prebiotics?
- Oral probiotics?
- Irradications?

Individualizing the gut treatment
dependent on host genotype profiles?

Next steps



Is the presence of the *Firmicutes imbalance* determined by the individual make-up of the host nuclear genome?

Gut microbiome
(genetic diversity)

Human genome
(genetic variations)

Interaction

Bacterial components and metabolites

Diet

Health

Disease

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Niels Grarup
Thomas Sparsø
Michel Kristensen
Grete Lademann
Arne Lykke Nielsen
Toby Brunt
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Mette Andersen
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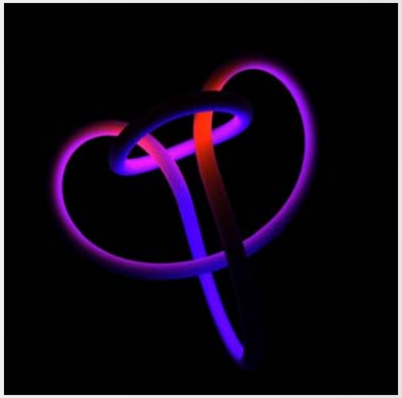

Metagenomics of the Human Intestinal Tract

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