

The genetics of common obesity

What have we learned from genome-wide association studies?

Ruth Loos

Programme Leader – Genetics of Obesity
MRC Epidemiology Unit
Institute of Metabolic Science
Cambridge, UK
ruth.loos@mrc-epid.cam.ac.uk

Overview

- The genetics of common obesity before GWA
- Genome-wide association – the ‘discoveries’
- What have we learned so far?
- Future challenges

1960's - 1990's

Descriptive epidemiology

Familial aggregation

Heritability studies

Segregation analyses

1960's

1990's

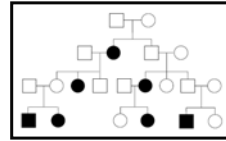
Ethnic variation in disease risk
Risk among immigrants



Estimates the recurrence risk of a disease/trait between family members relative to the risk in the population



Estimates the genetic model of a disease/trait by looking at multigenerational family data.



Estimate the genetic and environmental contribution to disease/trait



MRC | Medical Research Council

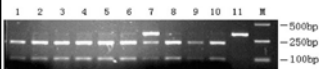
1990's - 2009

Candidate gene approach

1990's

2009

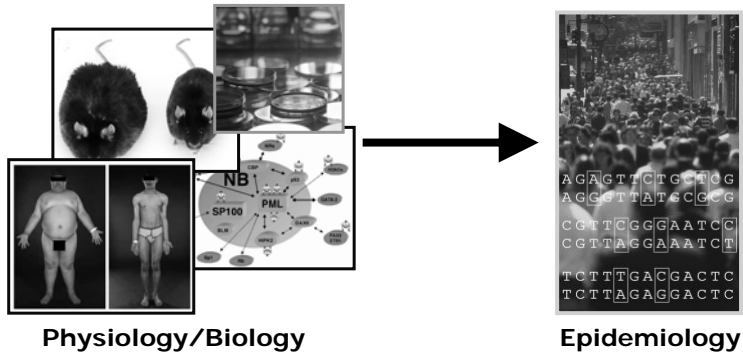
Association analyses between a genetic variant and a trait/disease



MRC | Medical Research Council

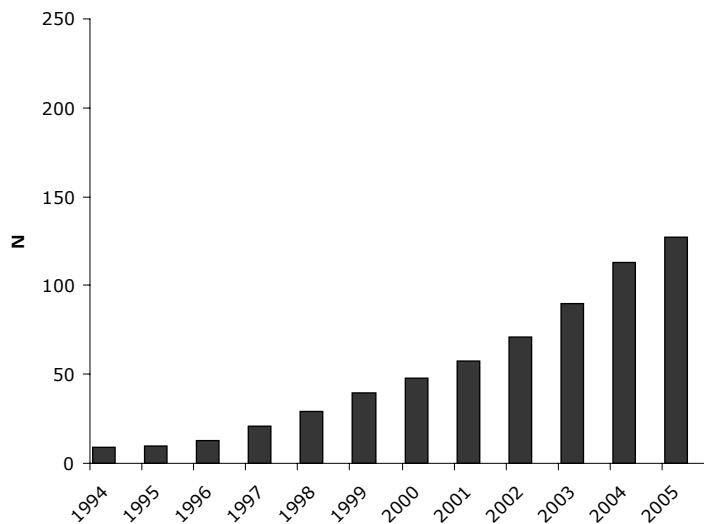
Candidate gene approach

= hypothesis-driven, based on the current understanding of the biology and pathophysiology of the trait/disease



MRC | Medical Research Council

Candidate genes for obesity



MRC | Medical Research Council

The Human Obesity Gene Map: The 2005 update: Rankinen et al. Obesity 2006

Candidate genes for obesity

- 22 genes with associations with obesity-related phenotypes in at least 5 studies
- Genes with more than 10 replications
PPARG, ADRB3, ADRB2, LEPR, GNB3, UCP3, ADIPOQ, LEP, UCP2, HTR2C, NR3C1, UCP1

→ **Meta-analyses**

→ **Studies with large(r) sample sizes**

1990's - 2009

Genome-wide analyses

1990's

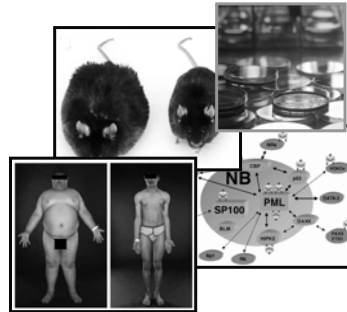
2009

Genome-wide scans

= hypothesis-free, to identify new, unanticipated, genes and thus expand the view of the biology and physiology of disease/trait



Epidemiology



Physiology/Biology

1990's - 2009

Genome-wide analyses

1990's

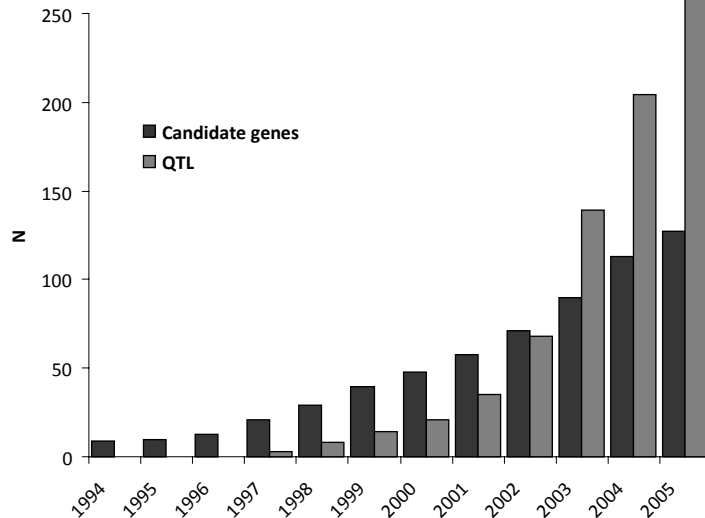
2009

Genome-wide linkage analyses

able to identify a crude chromosomal location of the gene or genes associated with a phenotype of interest



Genome-wide linkage for obesity-related traits



MRC | Medical Research Council

The Human Obesity Gene Map: The 2005 update: Rankinen et al. Obesity 2006

Meta-Analysis of Genome-wide Linkage Studies in BMI and Obesity

Catherine L. Saunders,*† Benedetta D. Chiodini,‡|| Pak Sham†§, Cathryn M. Lewis,‡ Victoria Abkevich,¶ Adebowale A. Adeyemo,# Mariza de Andrade,** Rector Arya,†† Gerald S. Berenson,‡‡ John Blangero,§§ Michael Boehnke,|||| Ingrid B. Borecki,||| Yvon C. Chagnon,¶¶ Wei Chen,‡‡ Anthony G. Comuzzie§§, Hong-Wen Deng,## Ravindranath Duggirala,§§ Mary F. Feitosa,||| Philippe Froguel,*** Robert L. Hanson,††† Johannes Hebebrand,‡‡‡ Patricia Huezo-Dias,§ Ahmed H. Kissebah,§§§ Weidong Li,||||| Amy Luke,¶¶¶ Lisa J. Martin,### Matthew Nash,§ Miina Öhman,****### Lyle J. Palmer,†††† Leena Peltonen,****‡‡‡‡ Markus Perola,**** R. Arlen Price,||||| Susan Redline,§§§§ Sathanur R. Srinivasan,‡‡ Michael P. Stern,†† Steven Stone,¶ Heather Stringham,||||| Stephen Turner,¶¶¶¶ Cisca Wijmenga#### and David A. Collier,†§

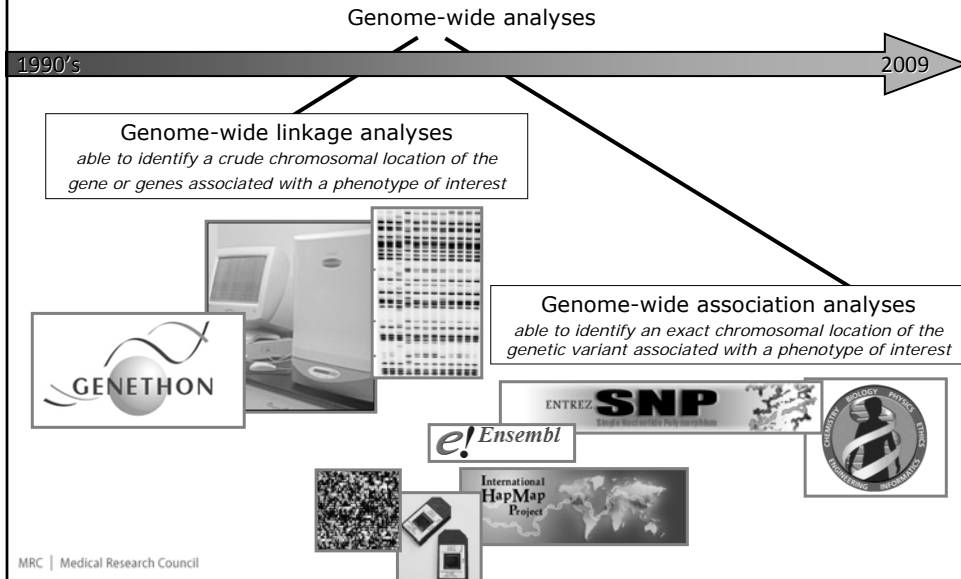
OBESITY Vol. 15 No. 9 September 2007

- 37 studies
- > 10.000 families
- > 31.000 individuals

No convincing evidence of linkage with BMI for any particular genomic region

MRC | Medical Research Council

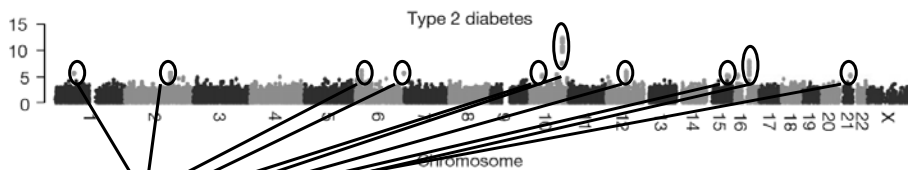
1990's - 2009



Genome-wide association study

STAGE 1 - Discovery stage

- 300,000 up to 1,000,000 genetic variants (SNPs)
- Case-control or cohort studies
- Large amount of tests → significance threshold $p < 0.0000001$



STAGE 2 - Replication/ Follow-up stage

- 1-100 SNPs that represent top loci
- Case-control or cohort studies – at least equal size of discovery panel
- Meta-analysis of stage 1 & 2 results

Overview

- The genetics of common obesity before GWA
- Genome-wide association – the 'discoveries'
 - 3 'waves' so far
- What have we learned so far?
- Future challenges

2007

2008

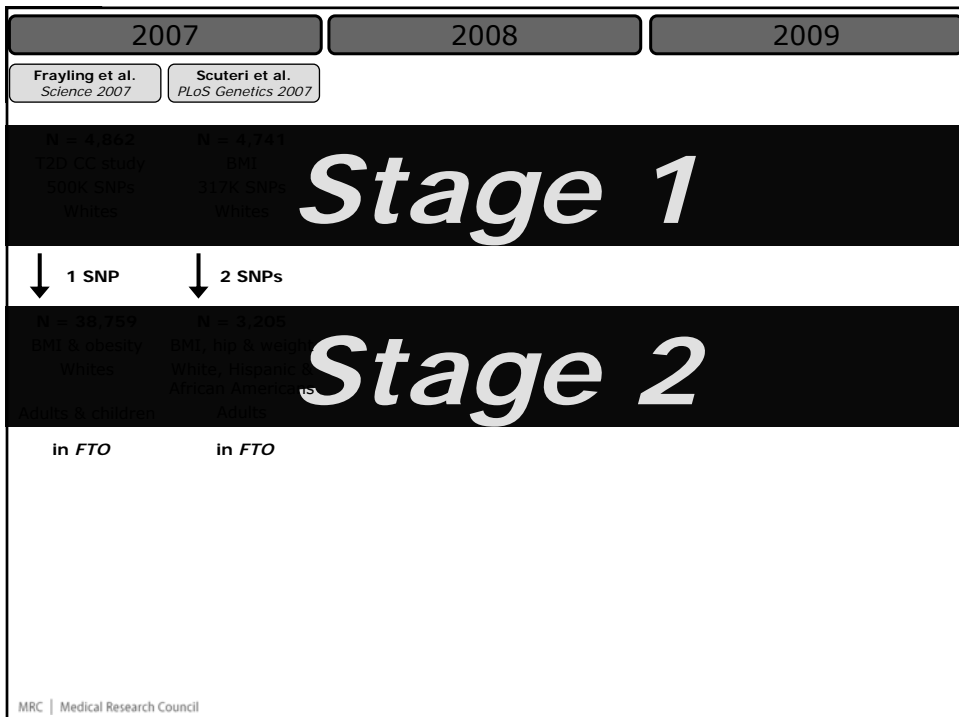
2009

Stage 1

Stage 2

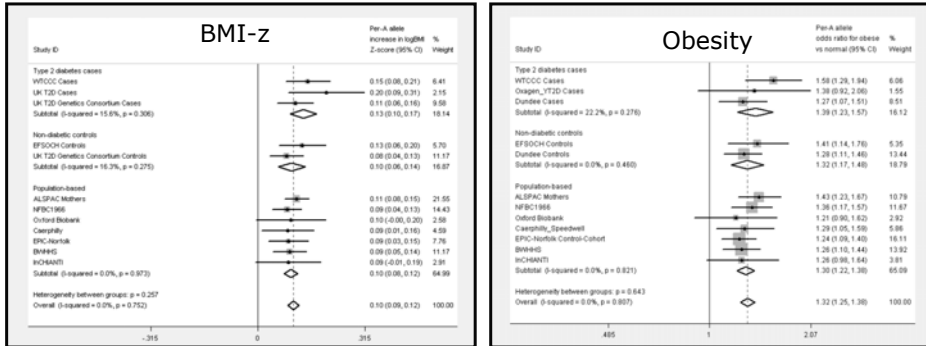
Wave 1

MRC | Medical Research Council



MRC | Medical Research Council

FTO is consistently associated with obesity and BMI in 38,759 individuals

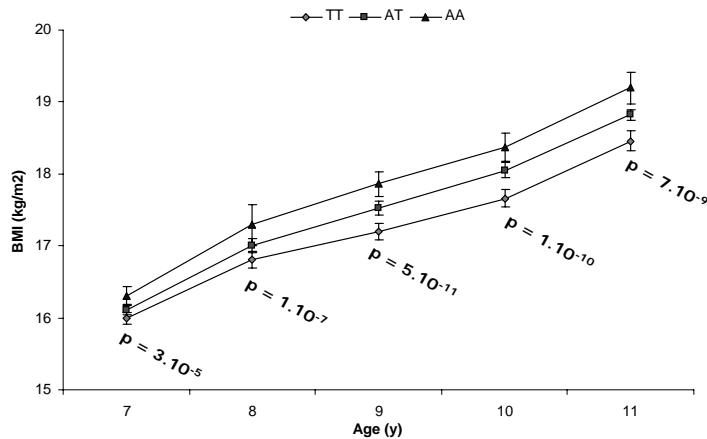


per risk allele:
1-1.5kg increase in weight

per risk allele:
30% increased risk for obesity

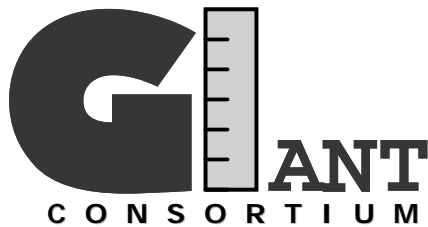
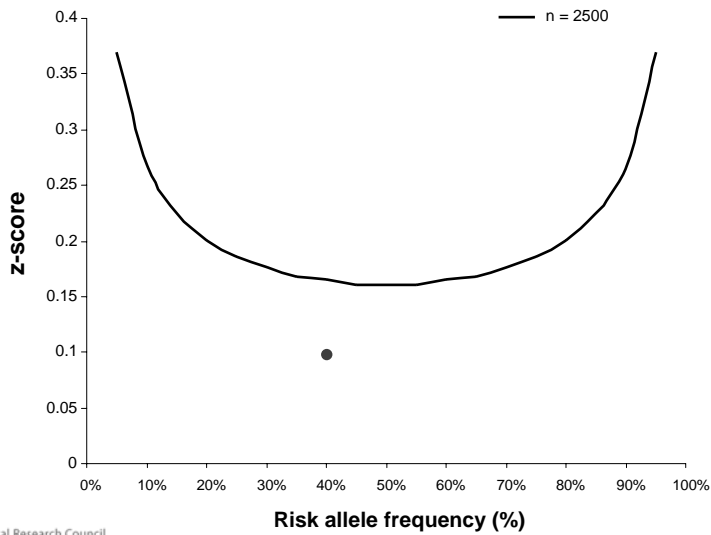


FTO is associated with BMI in children (from ALSPAC)



Large samples needed to identify small effect sizes

$\alpha = 10^{-6}$ power = 80%



Genetic Investigation of ANthropometric Traits

Consortium co-ordinator: **Joel Hirschhorn**

WTCCC

GEM-Cambridge

16,876 individuals

PLCO

NHS

FUSION

KORA

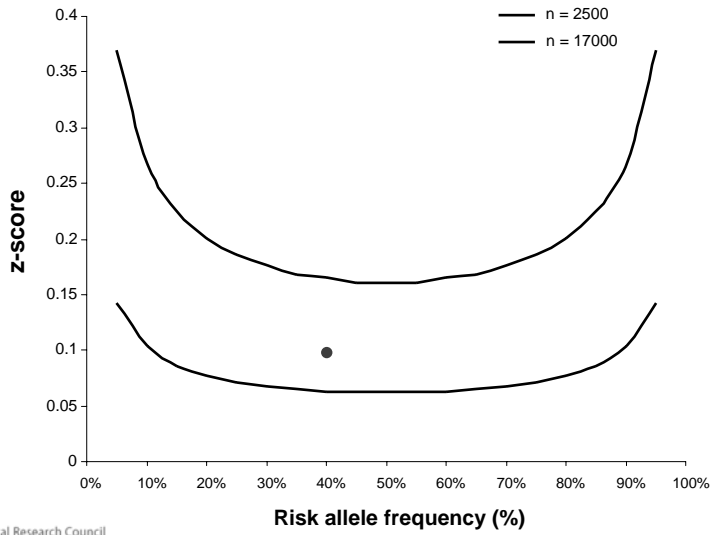
DGI

SardiNIA

15 genome-wide association scans
> 32,000 individuals

Large samples needed to identify small effect sizes

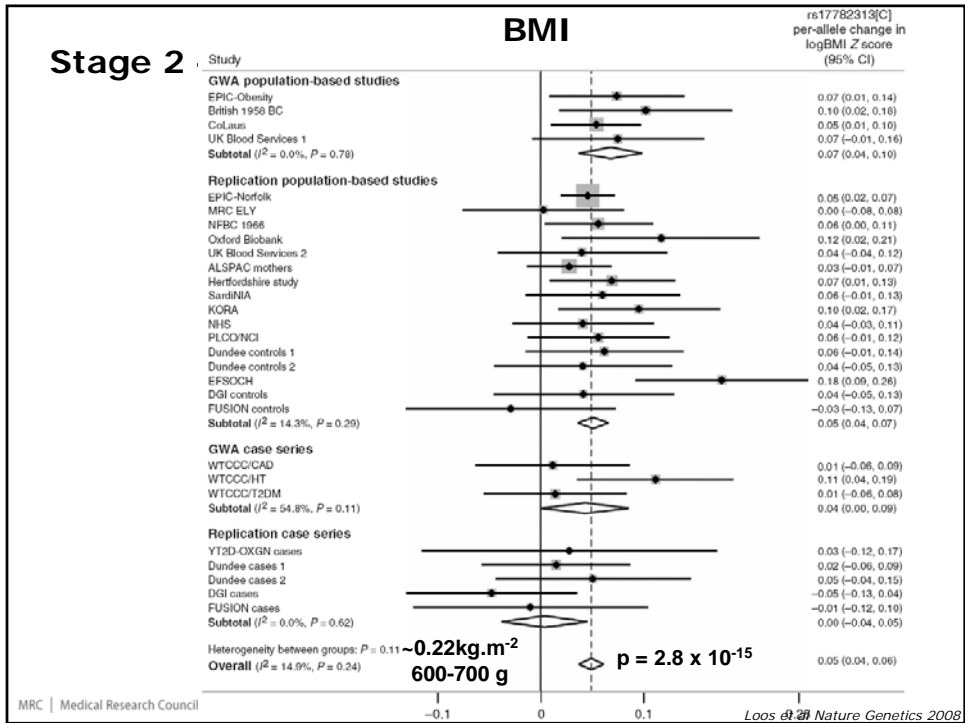
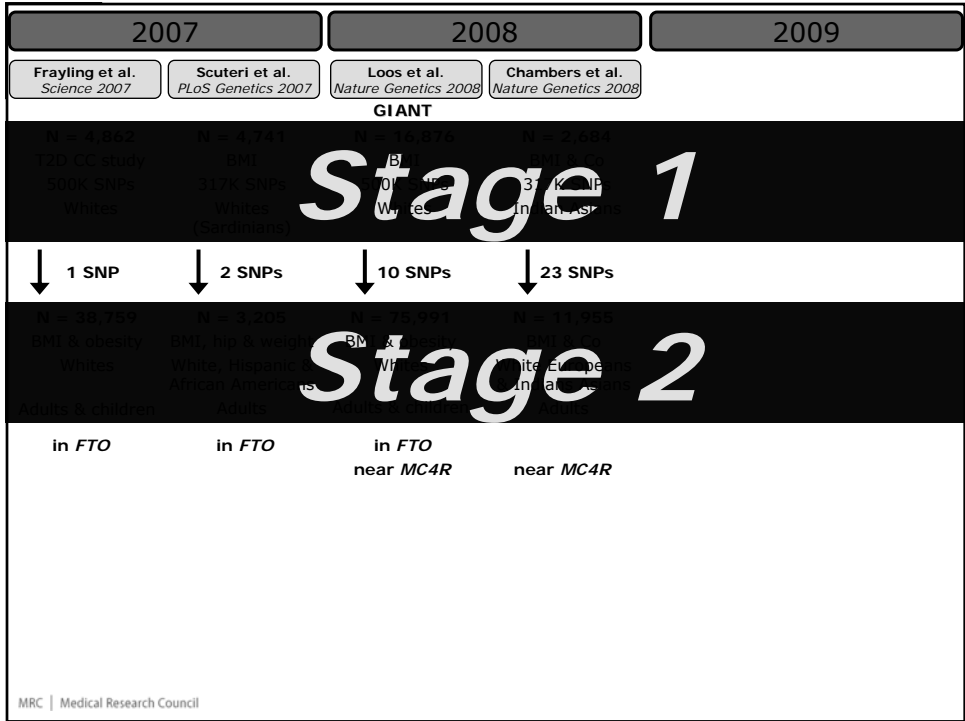
$\alpha = 10^{-6}$ power = 80%



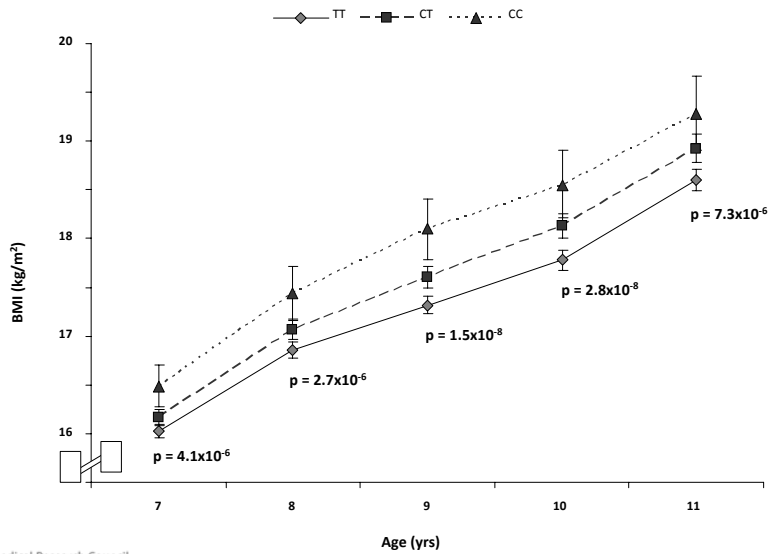
MRC | Medical Research Council

Wave 2

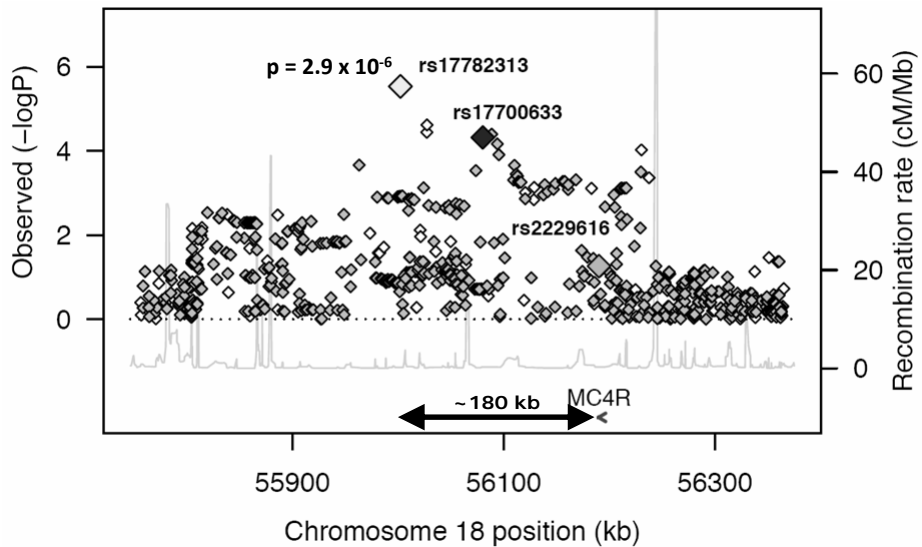
MRC | Medical Research Council

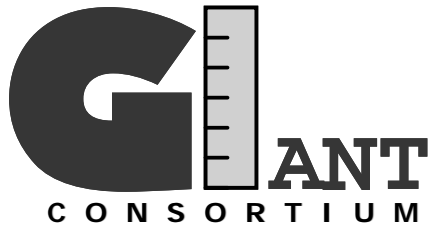


Near *MC4R* SNP – ALSPAC children



SNP locates near *MC4R*





Genetic Investigation of ANthropometric Traits

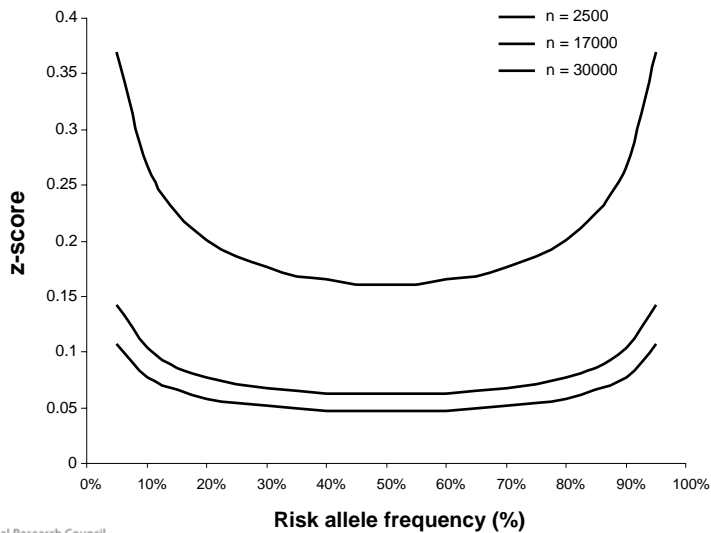
Consortium co-ordinator: **Joel Hirschhorn**

WTCCC	GEM-Cambridge
PLCO	NHS
FUSION	KORA
DGI	SardiNIA

15 genome-wide association scans
> 32,000 individuals

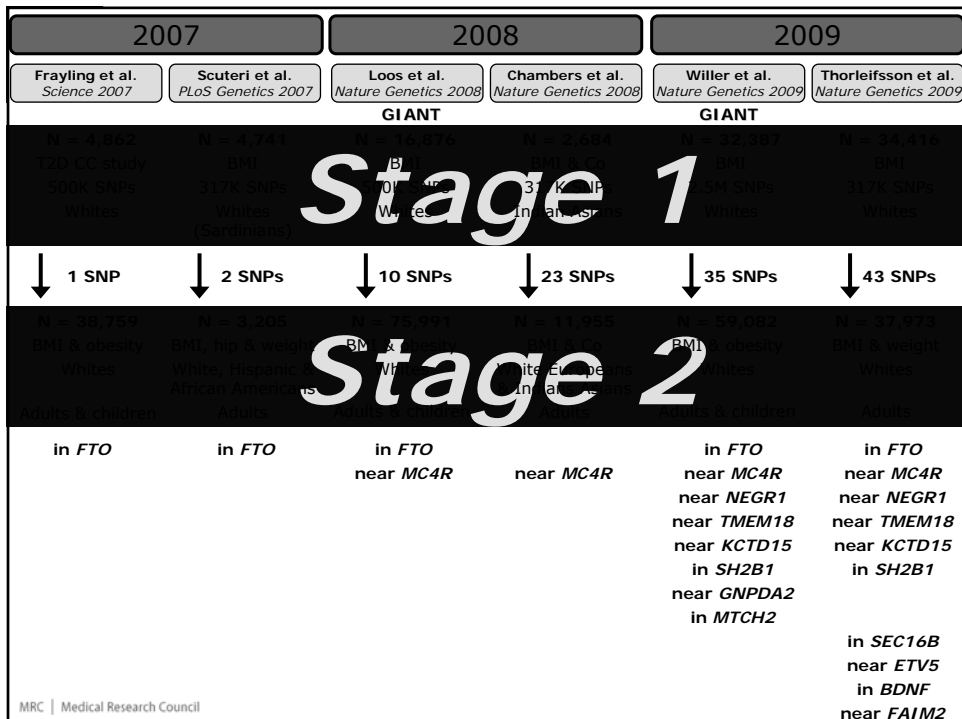
Large samples needed to identify small effect sizes

$\alpha = 10^{-6}$ power = 80%

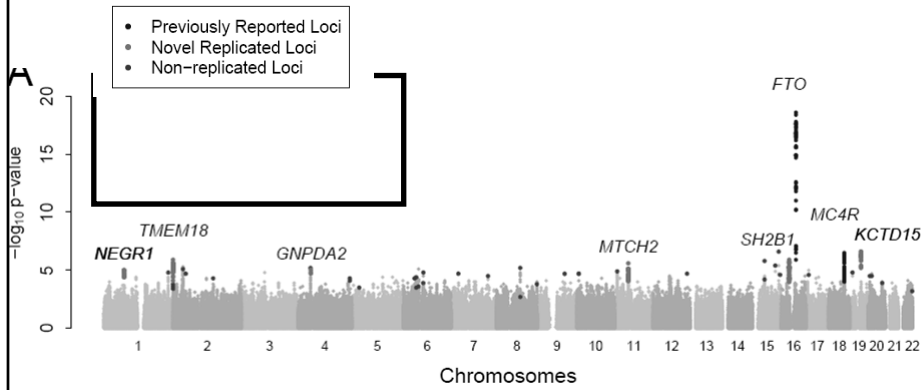


Wave 3

MRC | Medical Research Council



6 new variants associated with BMI



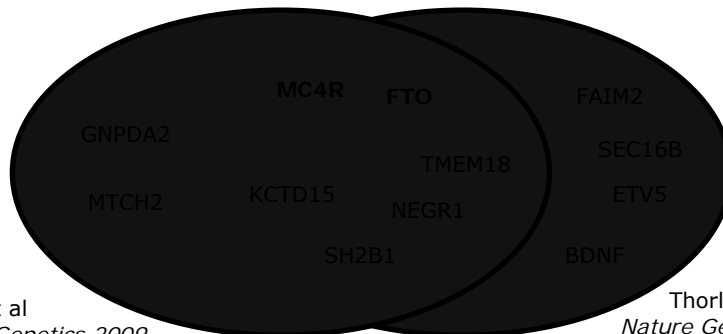
MRC | Medical Research Council

Willer et al *Nature Genetics* 2009

Genetic loci for BMI identified with GWAs

Loos et al *Nature Genetics* 2008
Chambers et al *Nature Genetics* 2008

Frayling et al *Science* 2007
Scuteri et al *PLoS Genetics* 2007



Willer et al
Nature Genetics 2009

Thorleifsson et al
Nature Genetics 2009

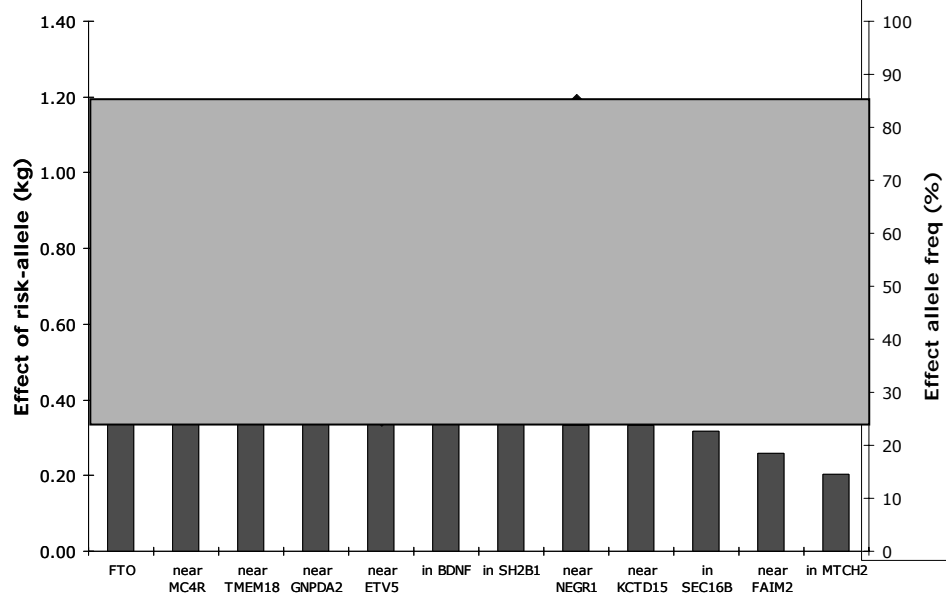
**12 new obesity-susceptibility loci
in the last 3 years !**

MRC | Medical Research Council

Overview

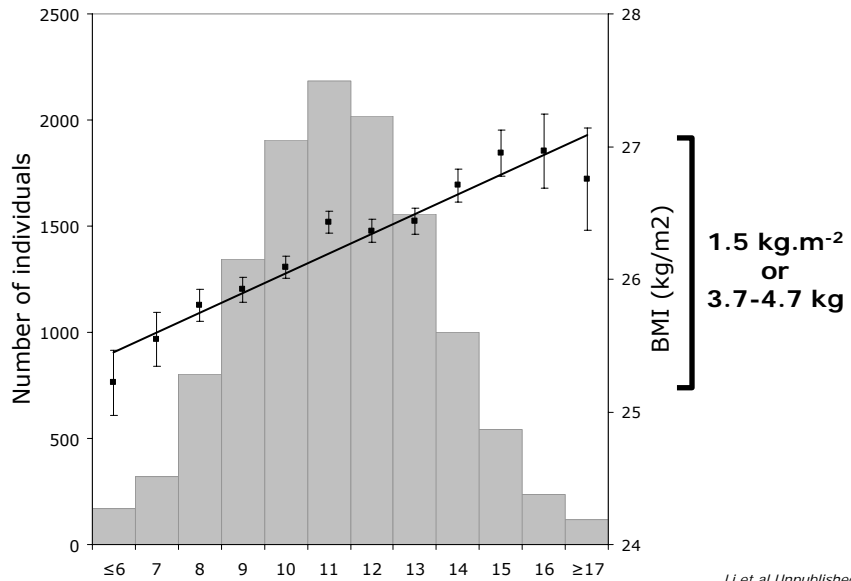
- The genetics of common obesity before GWA
- Genome-wide association – the ‘discoveries’
- What have we learned so far ?
 - Implication for public health
 - New biology
- Future challenges

Effect sizes are small & allele frequencies common



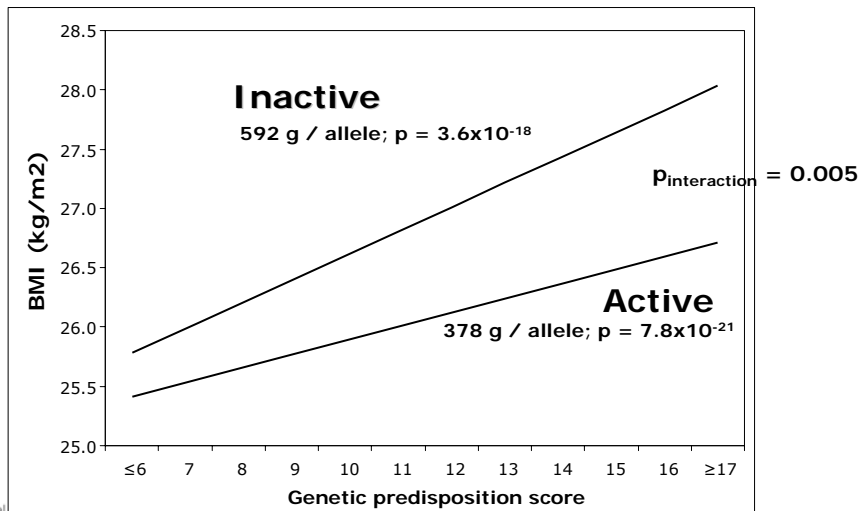
Loci have a cumulative effect on BMI

Combined effect of 12 susceptibility loci on BMI in 20,000 individuals of the EPIC-Norfolk study



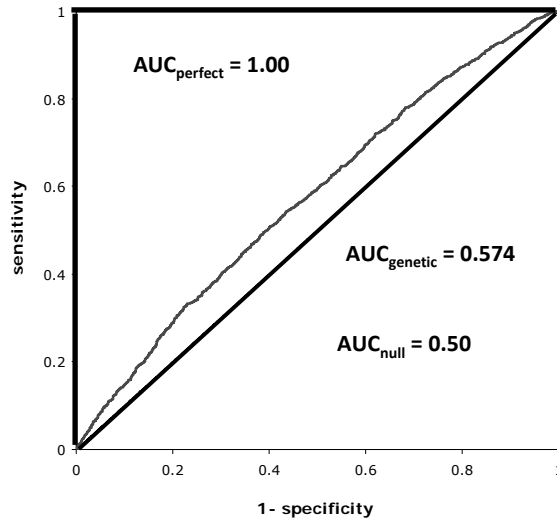
Implication for public health

Can physical activity attenuate the genetic susceptibility ?
Interaction between physical activity and genetic risk score on BMI in 20,000 individuals of the EPIC-Norfolk study



Implication for public health

Predictive value of obesity by 12 genetic variants in 20,000 individuals of the EPIC-Norfolk study



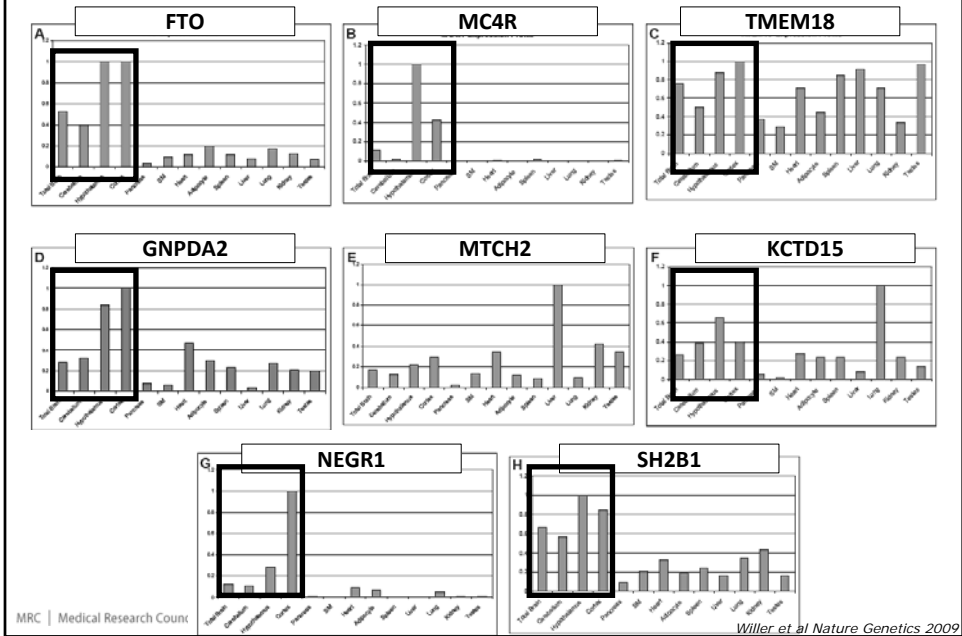
MRC | Medical Research Council

New biology

Locus	Chr	Function
• NEGR1	1p31	Neural development / central regulation of feeding ?
• SEC16B	1q25	Protein/lipid transport from the ER to the Golgi complex
• TMEM18	2p25	Regulating general cell motility
• GNPDA2	4p13	Addiction ?
• ETV5	3q27	Transcription factor that plays a role in development and cancer
• NCR3	6p21	NK cell activating receptor involved in the destruction of tumor cells and immature dendritic cells
• MTCH2	11p11	Putative mitochondrial carrier protein, may function in cellular apoptosis
• BDNF	11p14	Neural development, feeding and weight regulation
• FAIM2	12q13	Protects against Fas mediated apoptosis
• SH2B1	16p11	Neural signalling, feeding regulation
• FTO	16q12	Fatty acid metabolism, DNA repair and posttranslational modifications
• MC4R	18q21	Neural signalling / appetite / feeding regulation
• KCTD15	19q13	A voltage gated potassium channel

MRC | Medical Research Council

New biology - Expression of nearest genes

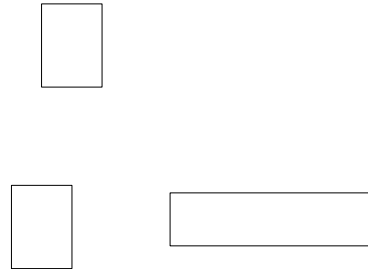


Overview

- The genetics of common obesity before GWA
- Genome-wide association – the 'discoveries'
- What have we learned ?
- Future challenges

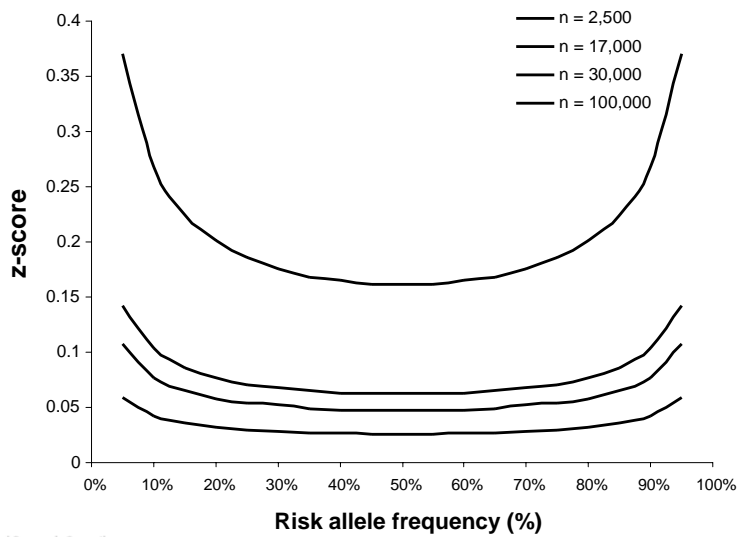
Future ahead

- Epidemiologist to find more genetic variants
 - Extended meta-analysis → 4th wave



4th wave of GWA for BMI

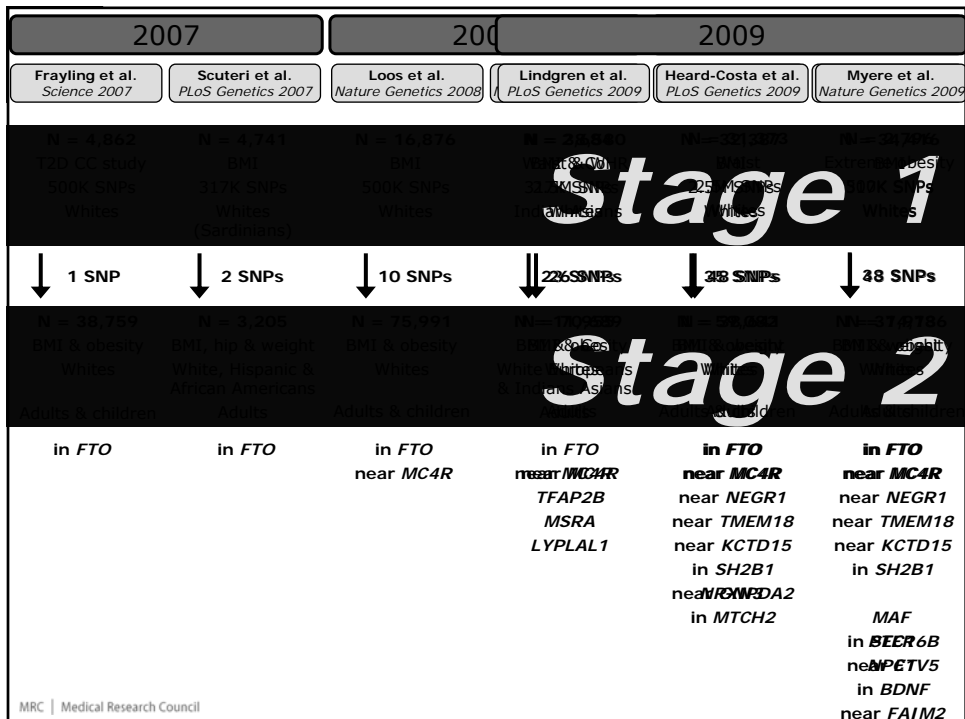
$\alpha = 10^{-6}$ power = 80%



Future ahead

- **Epidemiologist to find more genetic variants**

- Extended meta-analysis
- GWAs of other sources of genetic variation (CNVs, epigenome, rare variants, ...)
- GWAs in other ethnicities
- Metabochip (= follow up of sub-significant loci)
- Other obesity-related outcomes (waist, extreme obesity, fat%, physical activity, food intake)

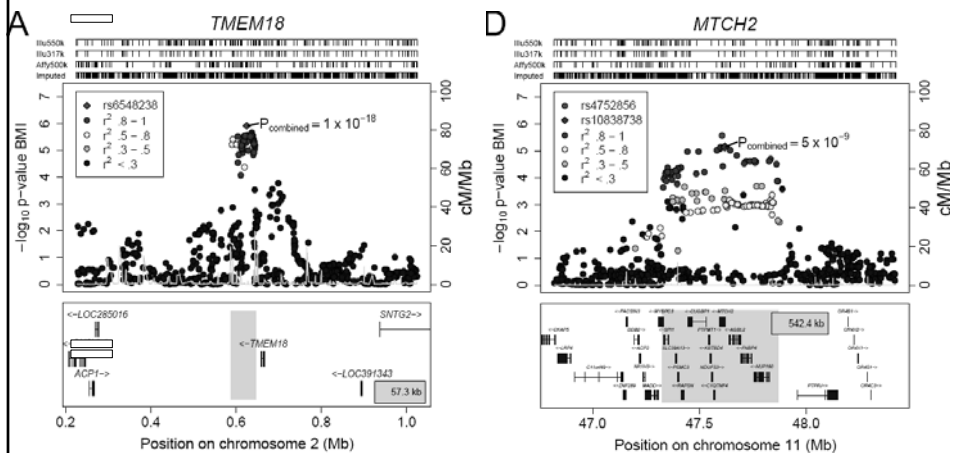


Future ahead

- **Epidemiologist to find more genetic variants**
 - Extended meta-analysis
 - GWAs of other sources of genetic variation (CNVs, epigenome, rare variants, ...)
 - GWAs in other ethnicities
 - Metabochip (= follow up of sub-significant loci)
 - Other obesity-related outcomes (waist, extreme obesity, fat%, physical activity, food intake)
 - Identify GxE and GxG interactions
- **Physiologist/biologist**
 - Find the underlying physiological pathways
 - Translate physiology into preventive healthcare or treatment

MRC | Medical Research Council

Future ahead



MRC | Medical Research Council

Witter et al Nature Genetics 2009

