# Genetics of obesity and the Avon Longitudinal Study of Parents and Children

**Nic Timpson**

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Introduction to genetics in the post genomewide era

ALSPAC, what is it and what is is indicative of?

The role of environment in genetic studies:

- Removal of unwanted variation
- All genetic effects are subject to environment
- More formal gene/environment interactions

Limitations?

Discussion points

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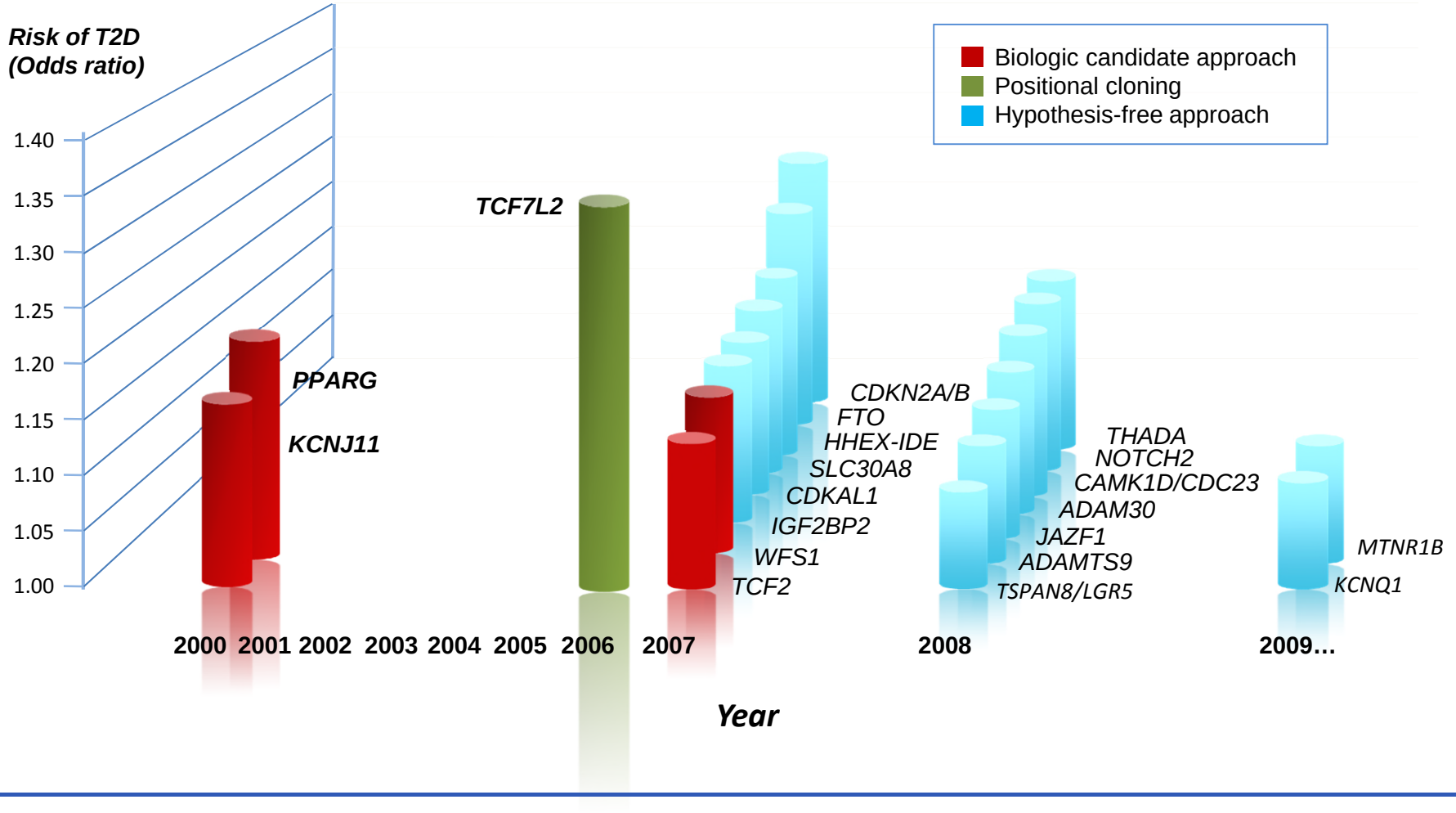
# “Step change?!”

# The Genome-Wide Association Study



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. Freath
Nigel W. Rayner
Christopher J. Gr
Debbie A. Lawlo
Amanda J. Benn
Nicholas J. Ware
Graham A. Hitm
George Davey-S
Mark I. McCarth

BRIEF COMMUNICATIONS

nature genetics

LETTERS

Variati
to chil
adult

Christian Di
Emmanuelle
Lena M S Ca
Cecile Lecoe
François Patt
Fritz Horber
Catherine Le
Michel Marr
Jean-Claude Chèvre[1] & Philip

nature

ARTICLES

nature genetics

Comi
mass,

Genome-wide
seven loci tha

Gudmar Thorleifsson[1,14],
Patrick Sulem[1], Anna Helg
Ingileif Jonsdottir[1,2], Thor
Thorvaldur Jonsson[2,4], Fro
Torben Jorgensen[7,8], Torst
Ellen Kampman[11], Lisa R
Diane M Becker[12], Jeffrey
Unnur Thorsteinsdottir[1,2] & Kari Stefansson[1,2]

ARTICLES

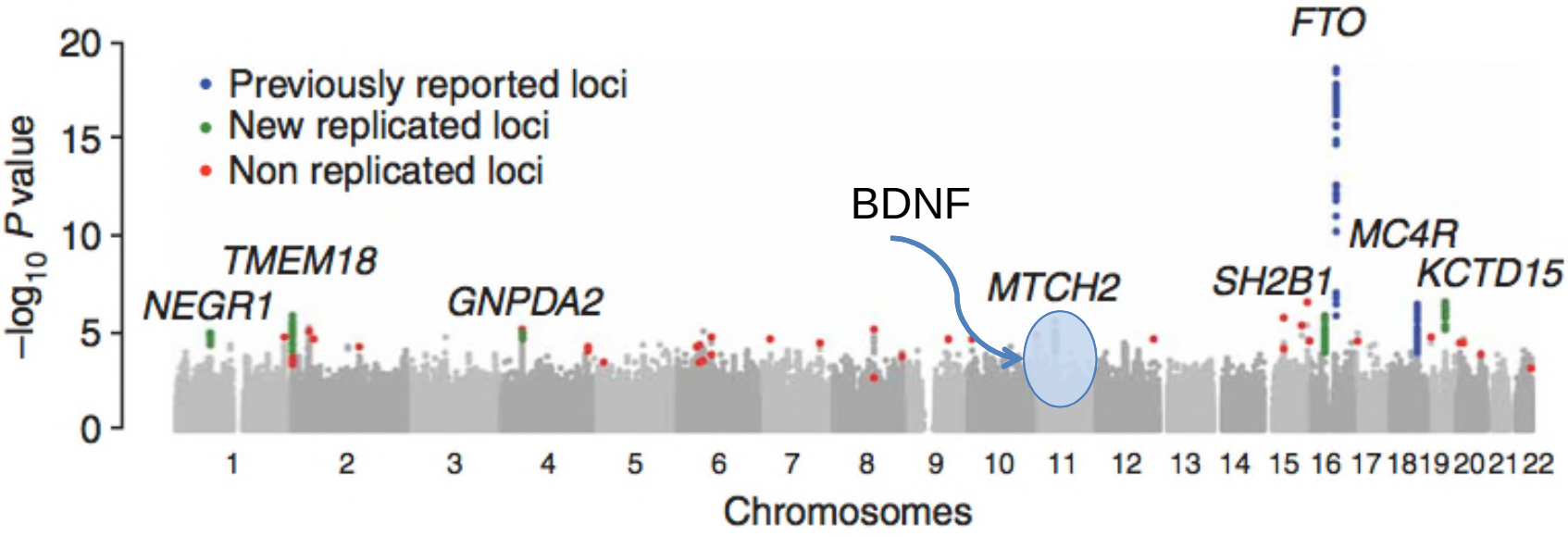
nature genetics

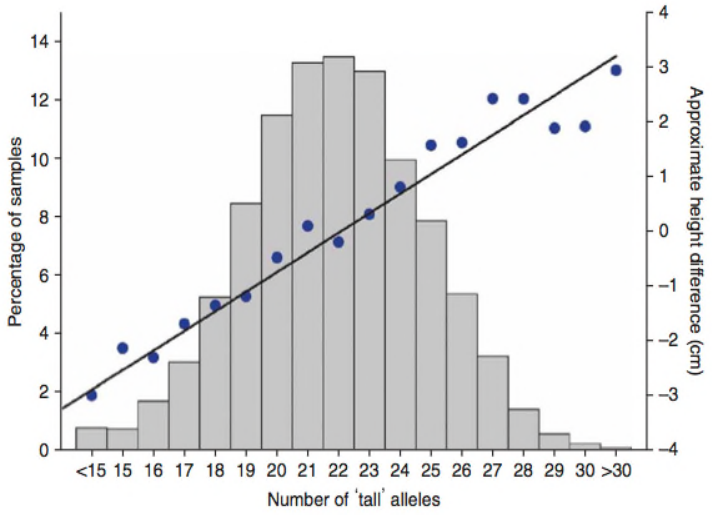
Six new loci associated with body mass index highlight a neuronal influence on body weight regulation

| Reference number | Gene | Discovery effort | Function |
|---|---|---|---|
| rs9939609 | FTO† | Frayling et al 2007 | Hypothalamic regulation of appetite? |
| rs17782313 | MC4R | Loos et al 2008 (GIANT_1) | Immediate function unknown – total size (really MC4R?) |
| rs6548238 | TMEM18* | Willer et al 2008 (GIANT_2) | Highly expressed in the brain – CNS function/weight regulation? |
| rs10938397 | GNPDA2 | Willer et al 2008 (GIANT_2) | Highly expressed in the brain – CNS function/weight regulation? |
| rs7498665 | SH2B1* | Willer et al 2008 (GIANT_2) | Highly expressed in the brain – CNS function/weight regulation? |
| rs10838753 | MTCH2* | Willer et al 2008 (GIANT_2) | Highly expressed in the brain – CNS function/weight regulation? |
| rs11084753 | KCTD15* | Willer et al 2008 (GIANT_2) | Highly expressed in the brain – CNS function/weight regulation? |
| rs2815752 | NEGR1* | Willer et al 2008 (GIANT_2) | Highly expressed in the brain – CNS function/weight regulation? |
| rs6265 | BDNF | Thorleifsson et al (DeCode) | Brain derived neurotrophic factor - mainly been associated with neurological and psychiatric disorders, although recent candidate gene studies have suggested its role in eating behavior |

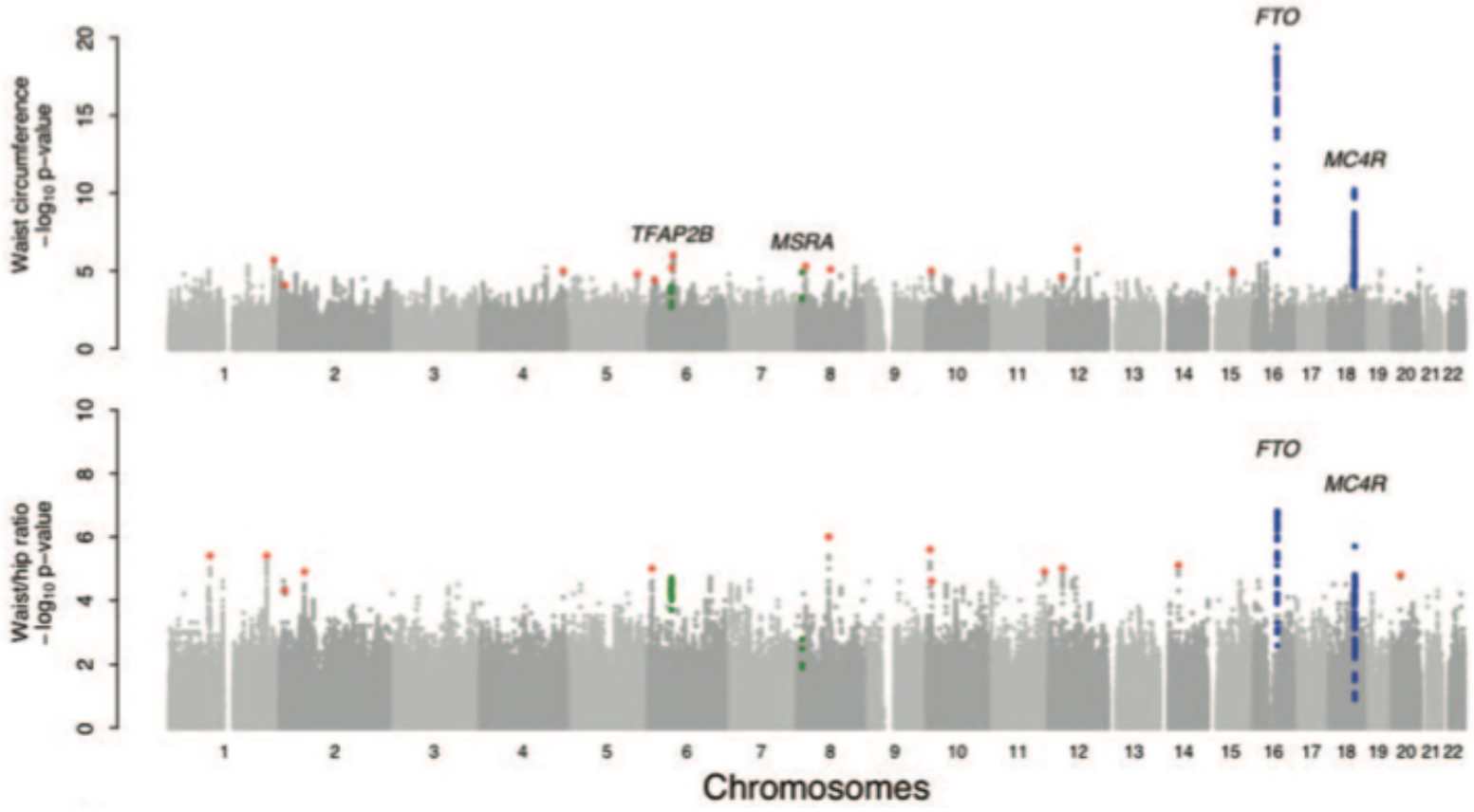
† Also reported by Dina et al NG 2007, * Reported simultaneously by Thorleifsson et al NG 2008

GIANT_2 (n~32,000 & 59,000)

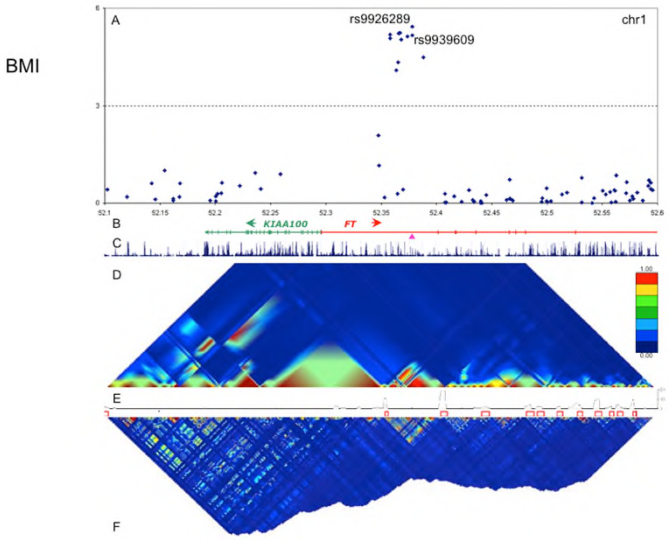


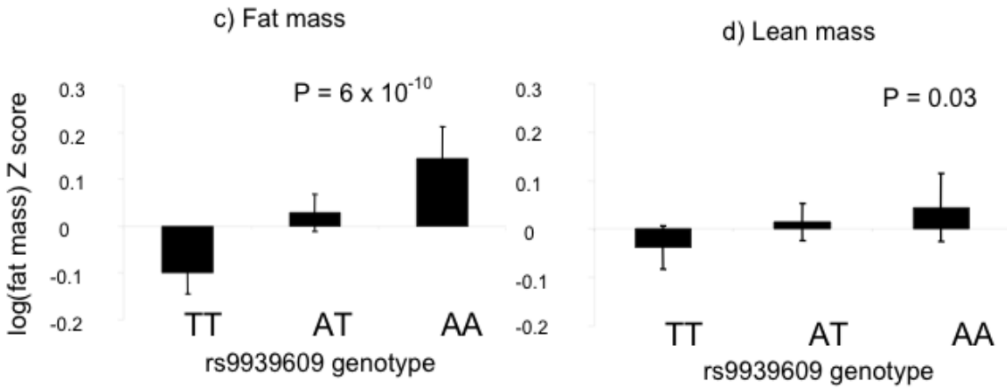



# Power in consortia versus other strategies

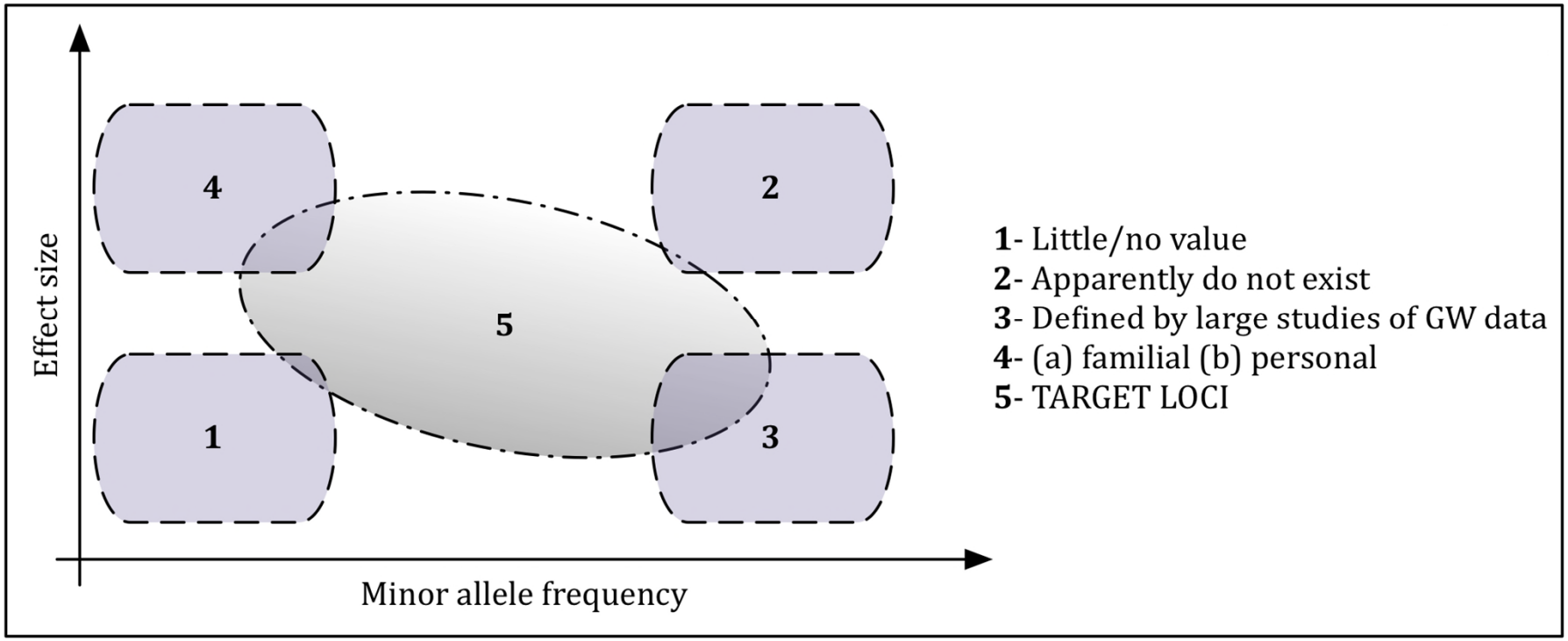


# BUT, are these “genes for obesity”?



# Genetic architecture and syndromic obesity




Monogenic obesity exists – rare, familial, mutations in POMC/Leptin/brain derived Neurotrophic factor/*MC4R*

However critically different in architecture to that interrogated by recent studies

University of BRISTOL | Avon Longitudinal Study of Parents and Children | CHILDREN OF THE 90s

ALSPAC home | Contacts

## Working towards a better life for future generations

### Welcome

The Avon Longitudinal Study of Parents and Children (ALSPAC) - which is also known as Children of the 90s - is a long-term health research project.

Participants | Scientific Community | Media | General Public

http://www.bristol.ac.uk/alspac/

Introduction to genetics in the post genomewide era

ALSPAC, what is it and what is is indicative of?

The role of environment in genetic studies: *epidemiology*

- Removal of unwanted variation
- All genetic effects are subject to environment
- More formal gene/environment interactions

Limitations?

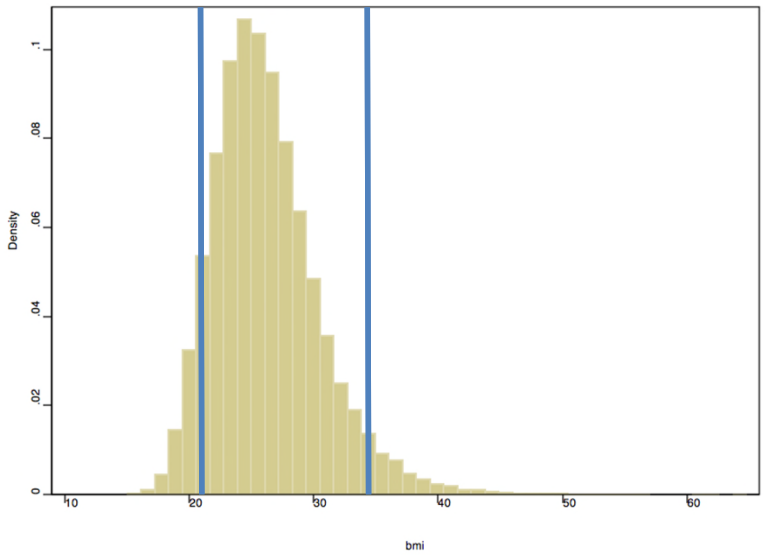
Discussion points

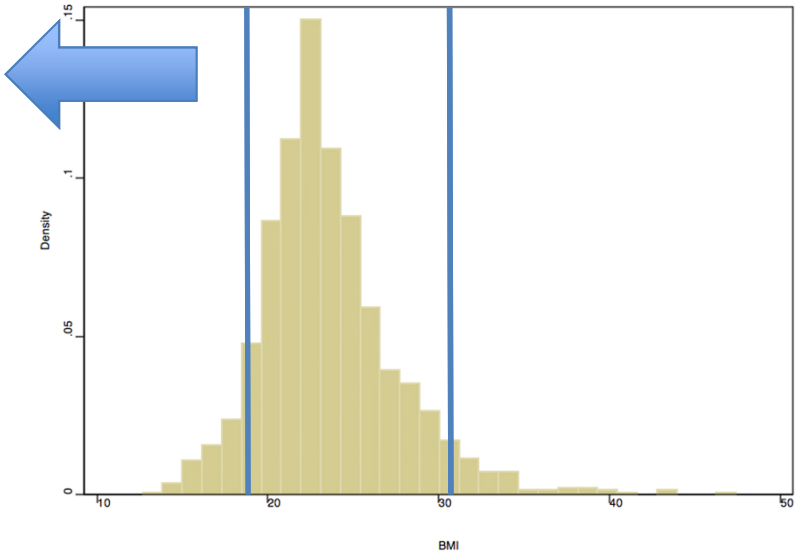
# Role of environment in genetic studies of obesity

Environment in genetic studies and the impact of “obesogenic environments”?

# Anthropometric data

## Comparative BMI




**Copenhagen**

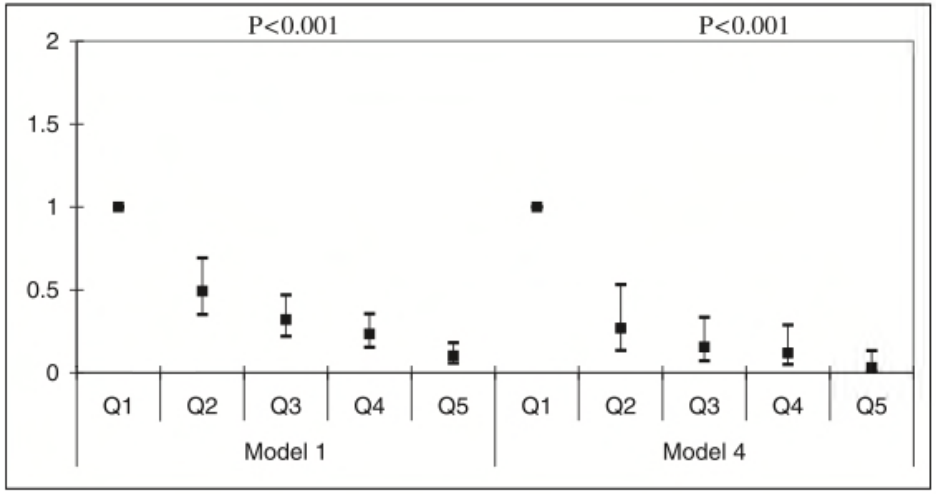
Mean BMI ~26kg/m$^2$
5$^{th}$/95$^{th}$ percentiles:
~20kg/m$^2$ & ~34kg/m$^2$

**The Solomons**

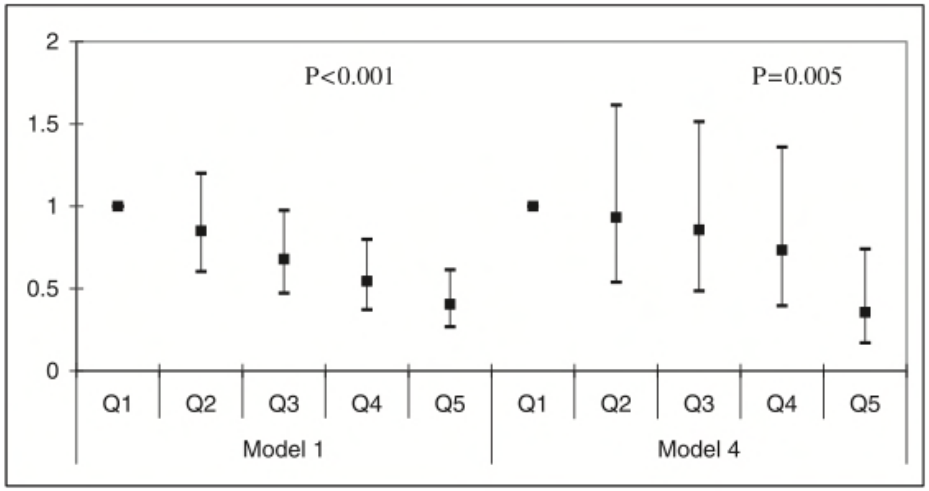
Mean BMI ~23.5kg/m$^2$
5$^{th}$/95$^{th}$ percentiles:
~18kg/m$^2$ & ~31kg/m$^2$

# ALSPAC - activity & BMI

Odds of age specific "obesity" boys




Odds of age specific "obesity" girls




Activity objectively assessed from records of actigraph wearing.

Data summarised in quintile of counts per minute

Findings consistent across fat mass (DXA)

N>2500, age 12yrs

Ness et al PLoS Med 2007

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# Eat to beat the big C

There may not be a cure for cancer yet, but research shows how even small changes in diet can dramatically reduce your risk of getting it

**BREAST**
Three glasses of milk a day can cut the risk by 50 per cent

**OVARIAN**
Five carrots a week can cut the risk by 50 per cent

**COLON**
Eating fish twice a week can cut the risk by 50 per cent

**STOMACH**
A few radishes a week can cut the risk by 35 per cent

**MOUTH**
Six sweet potatoes a week can reverse cancer of the mouth


**LUNG**
Eating tomato ketchup every day can cut the risk by 25 per cent

**LIP**
Wearing lipstick can cut the risk by 50 per cent

**SKIN**
Lemon tea can cut the risk by 70 per cent

Pictures: PSC

OPEN ACCESS Freely available online PLOS MEDICINE

# Clustered Environments and Randomized Genes: A Fundamental Distinction between Conventional and Genetic Epidemiology

George Davey Smith[1,2*], Debbie A. Lawlor[1,2], Roger Harbord[1], Nic Timpson[1,2], Ian Day[1,2], Shah Ebrahim[3]

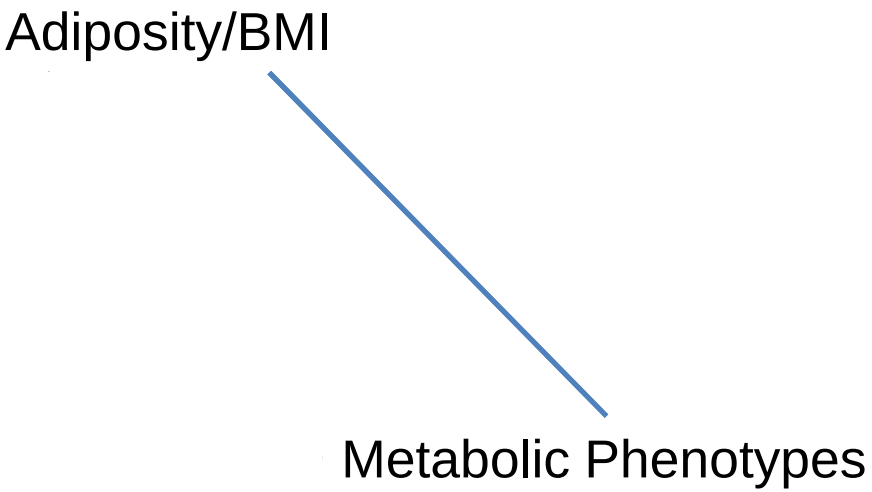
"…large excess of observed over expected associations among the nongenetic variables indicates that many nongenetic modifiable factors occur in clusters"

"Researchers doing observational studies always try to adjust for confounding but this result suggests that this adjustment will be hard to do, in part because it will not always be clear which factors are confounders"

"…the lack of a large excess of observed over expected associations among the genetic variables (and also among genetic variables paired with nongenetic variables) indicates that little confounding is likely to occur"

## Mendelian Randomisation

Davey Smith & Ebrahim BMJ (2005)


Adiposity/BMI
Metabolic Phenotypes

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# *FTO* – An effect through appetite?

## The fat mass– and obesity-associated locus and dietary intake in children[1–3]

*Nicholas J Timpson, Pauline M Emmett, Timothy M Frayling, Imogen Rogers, Andrew T Hattersley, Mark I McCarthy, and George Davey Smith*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## An Obesity-Associated *FTO* Gene Variant and Increased Energy Intake in Children

Joanne E. Cecil, Ph.D., Roger Tavendale, Ph.D., Peter Watt, Ph.D., Marion M. Hetherington, Ph.D., and Colin N.A. Palmer, Ph.D.

ABSTRACT

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*]

*Am J Physiol Regul Integr Comp Physiol* 294: R1185–R1196, 2008.
First published February 6, 2008; doi:10.1152/ajpregu.00839.2007.

## Regulation of *Fto/Ftm* gene expression in mice and humans

**George Stratigopoulos,[1] Stephanie L. Padilla,[1] Charles A. LeDuc,[1] Elizabeth Watson,[1] Andrew T. Hattersley,[4] Mark I. McCarthy,[2,3] Lori M. Zeltser,[1] Wendy K. Chung,[1] and Rudolph L. Leibel[1]**

*[1]Division of Molecular Genetics, Naomi Berrie Diabetes Center, Columbia University, New York, New York; [2]Oxford Centre for Diabetes Endocrinology and Metabolism, University of Oxford, UK; [3]Wellcome Trust Centre for Human Genetics, University of Oxford, UK; and [4]Institute of Biomedical and Clinical Science, Peninsula Medical School, Exeter, UK*

Submitted 20 November 2007; accepted in final form 31 January 2008

## The fat mass– and obesity-associated locus and dietary intake in children[1–3]

*Nicholas J Timpson, Pauline M Emmett, Timothy M Frayling, Imogen Rogers, Andrew T Hattersley, Mark I McCarthy, and George Davey Smith*

Dietary record data (3-4 day records)
*Corrected for mis-reporting
*Adjusted for BMI

Energy intake

| TT | AT | AA |
|---|---|---|
| 1732.12 (1730.15, 1734.08) | 1750.21 (1748.25, 1752.18) | 1785.31 (1783.34, 1787.29) |

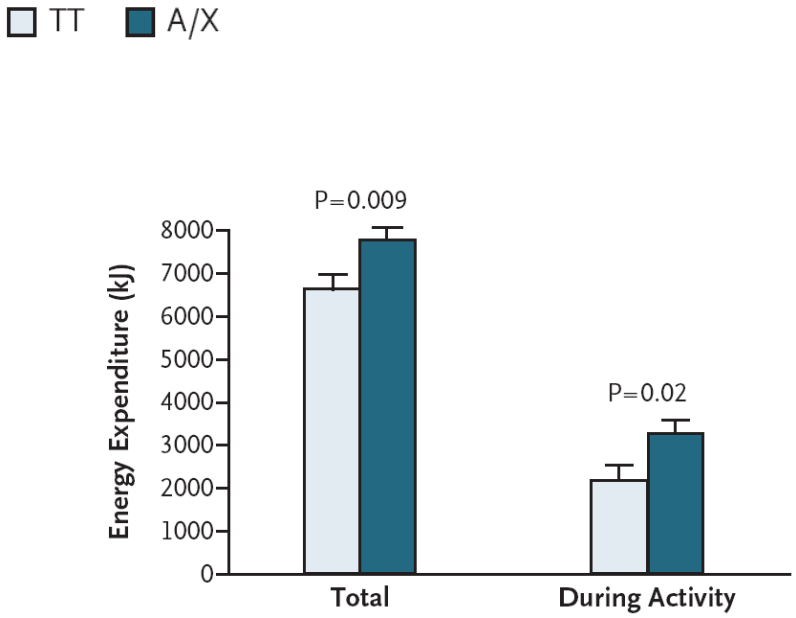
Kcal/dat
p<0.05

Persons carrying minor variants at rs9939609 were consuming more ***fat and total energy*** than were those not carrying such variants

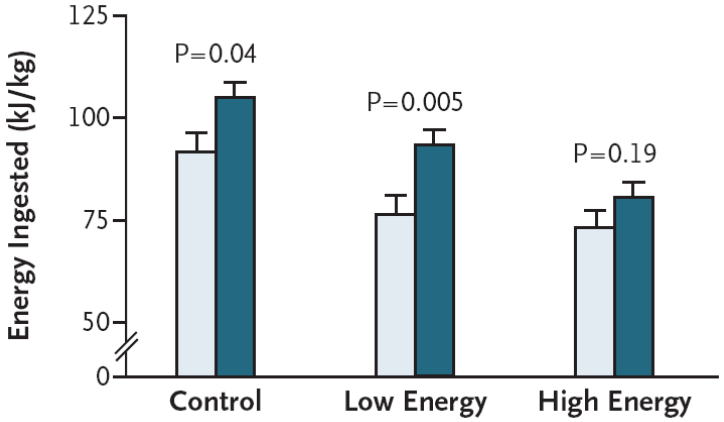
This difference was not simply dependent on having higher average BMIs

# Association between the A allele at the *FTO* rs9939609 variant and energy balance

Scottish school children (N=76; age 4-10 yrs)




Indirect calorimetry & INDEPENDENT of BMI or lean mass




Energy ingested after different energy intake pre-meal loads & INDEPENDENT of fat or lean mass

Cecil et al. NEJM (2008)

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# What do we mean by gene/environment interaction?

Classic example:

**Phenylketonuria**

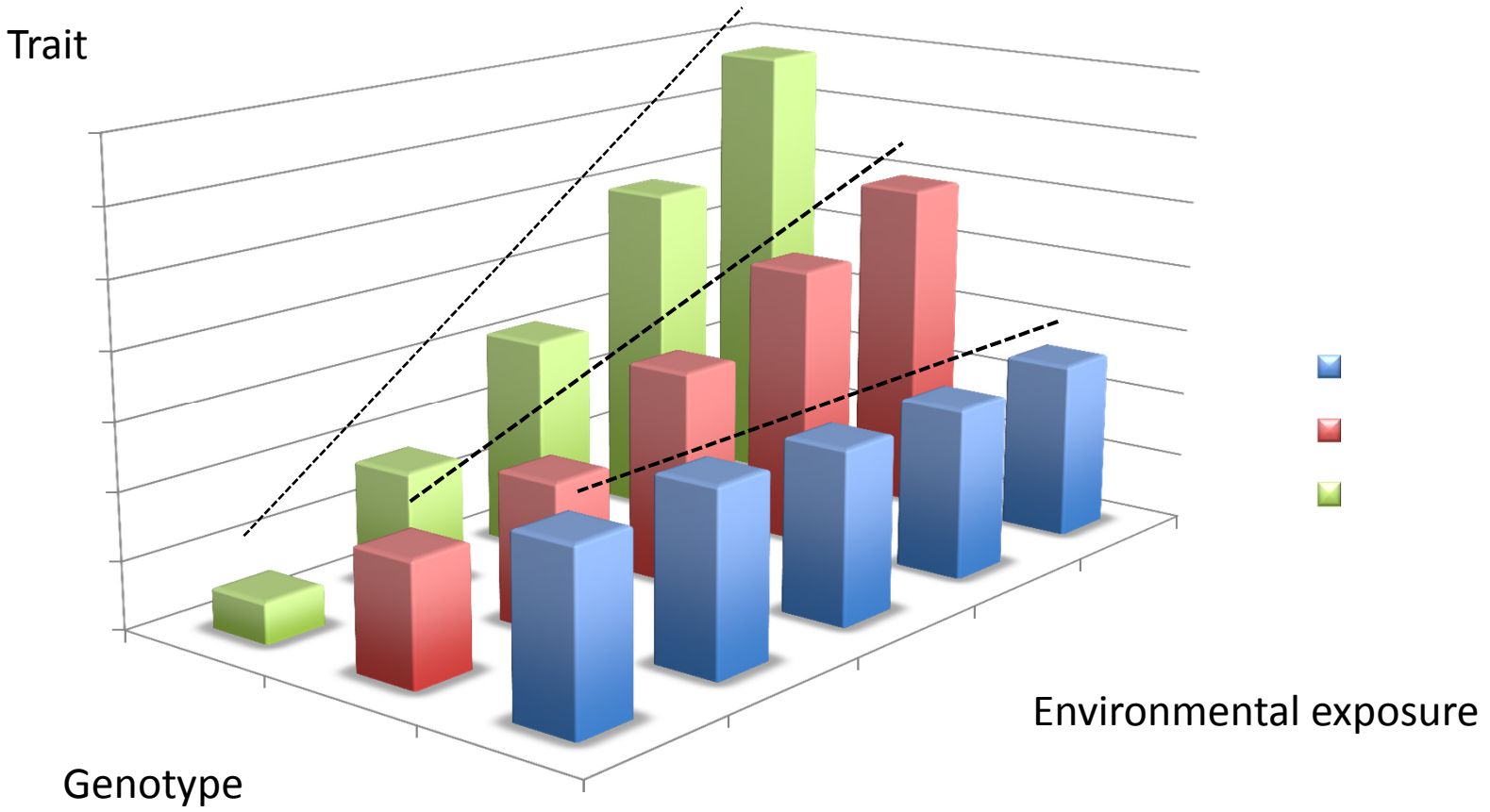
Autosomal recessive disorder characterised by a deficiency in the hepatic enzyme phenylalanine hydroxylase.

Phenylalanine → Tyrosine

Phenylalanine → Phenylpyruvate → Brain development
Mental retardation
Seizures

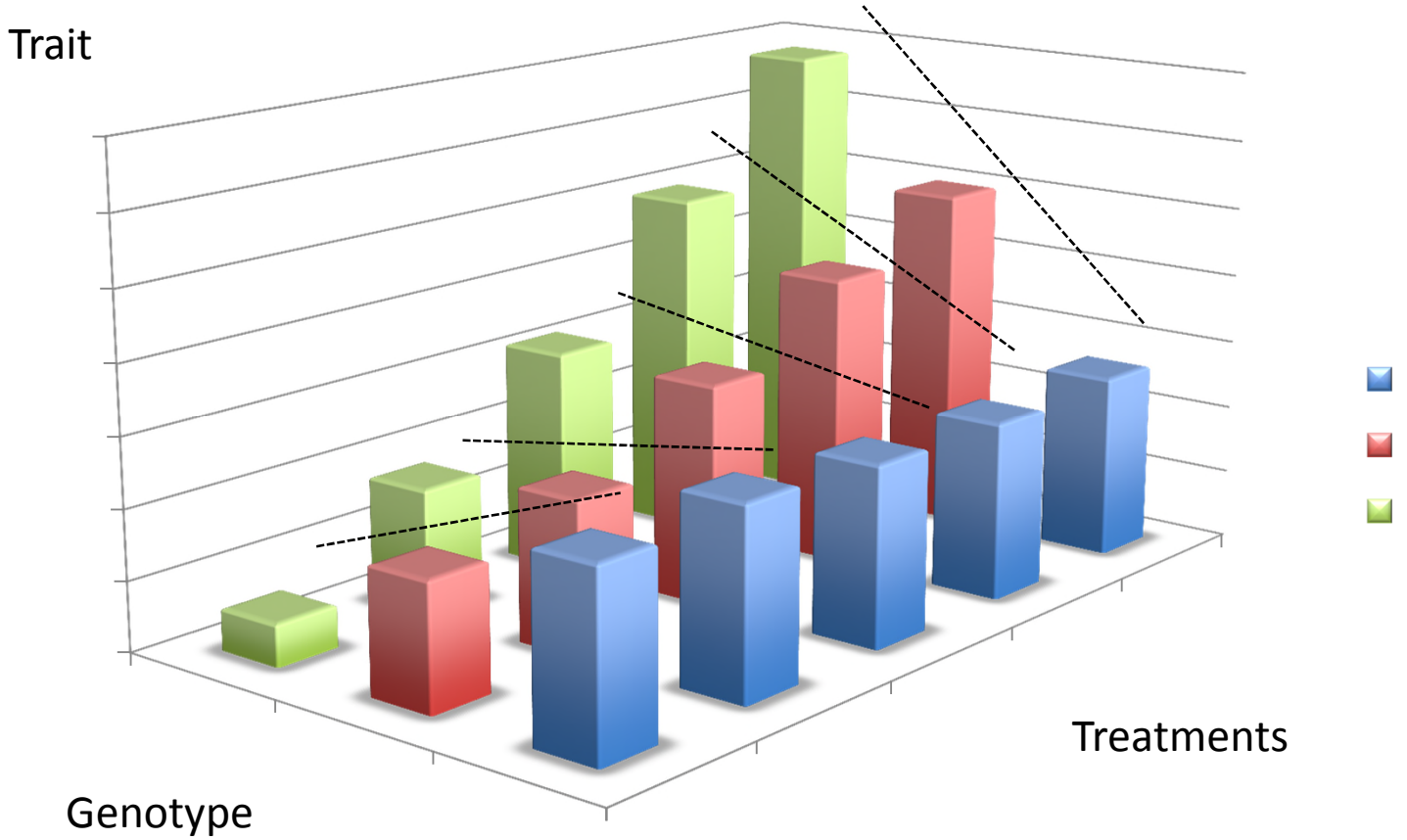
Effective intervention post screening - low phenlyalanine diet

# Genetic effects on traits that differ across environmental contexts




Thanks to Paul Franks

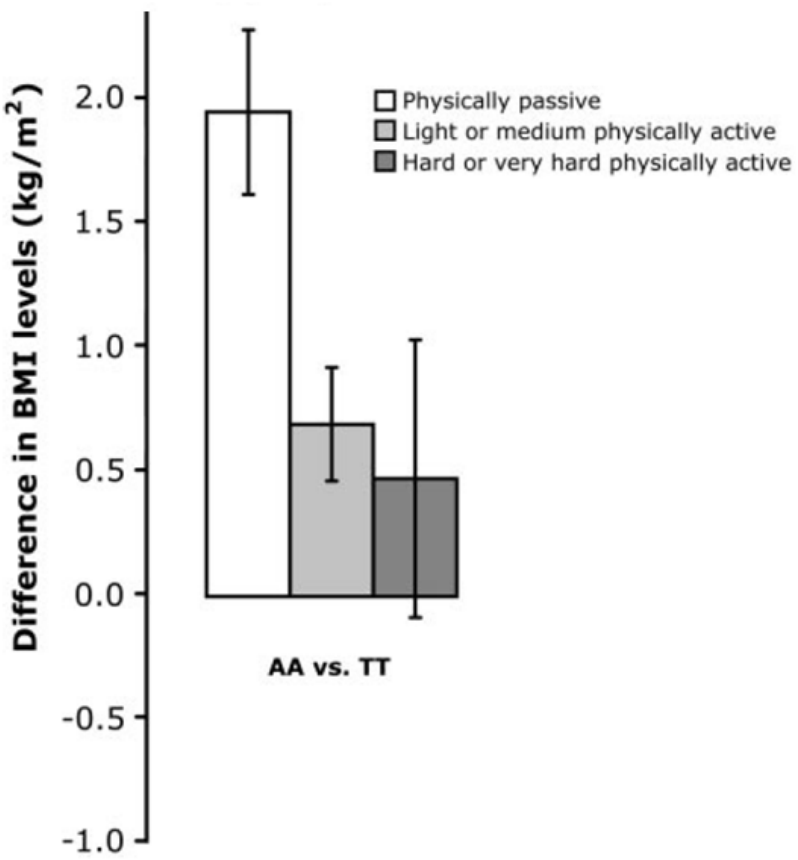
# Treatment effects that across genotypes at a given locus



BRIEF REPORT

# Low Physical Activity Accentuates the Effect of the *FTO* rs9939609 Polymorphism on Body Fat Accumulation

Camilla H. Andreasen,[1] Kirstine L. Stender-Petersen,[1] Mette S. Mogensen,[1] Signe S. Torekov,[1] Lise Wegner,[1] Gitte Andersen,[1] Arne L. Nielsen,[1] Anders Albrechtsen,[2] Knut Borch-Johnsen,[1,3,4] Signe S. Rasmussen,[1] Jesper O. Clausen,[1] Annelli Sandbæk,[5] Torsten Lauritzen,[5] Lars Hansen,[6] Torben Jørgensen,[3] Oluf Pedersen,[1,4] and Torben Hansen[1]

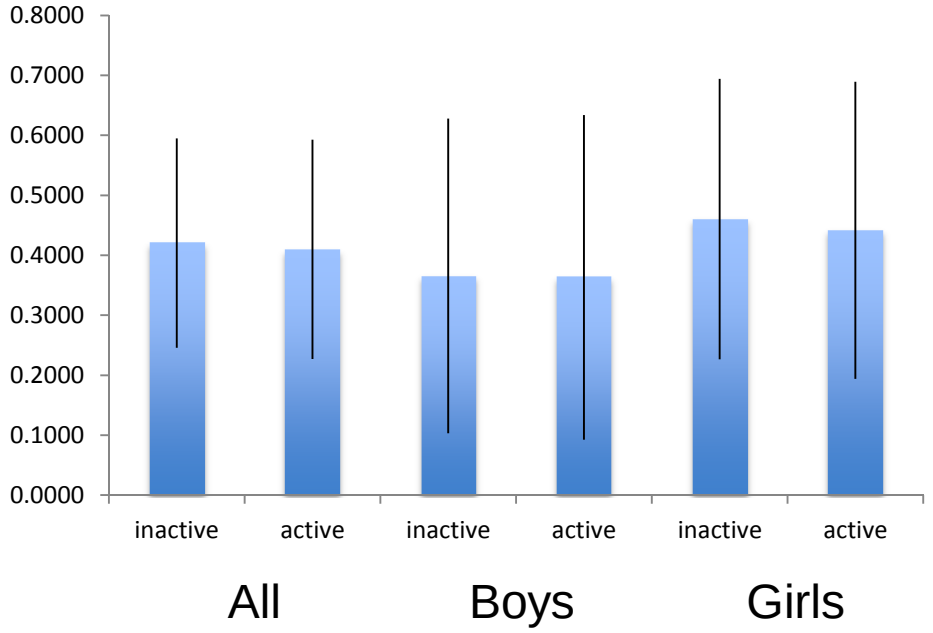


# Current efforts:

Large consortium based approach concerned with the interaction betwee ACTIVITY and the effects of variation at *FTO*.

Led by the MRC Cambridge (Tuomas Kilpelainen) who will extend this to genomewide analyses considering the mediating effects of activity on BMI associations.

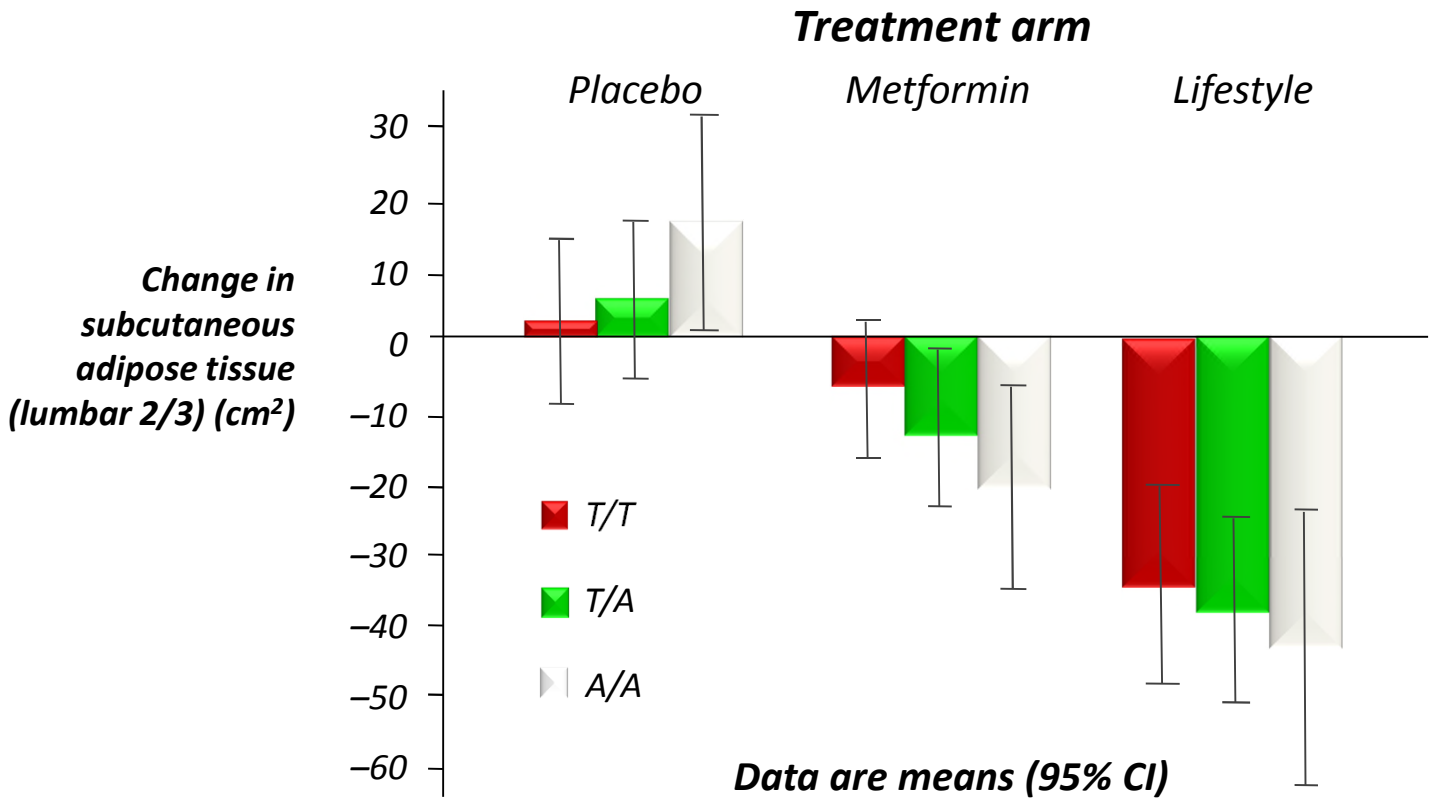
Per minor allele effect rs9939609 BMI




n~3000

# Diabetes Prevention Program

FTO gene x treatment interaction on adiposity




Franks PW, et al. (Diabetologia, 2008)

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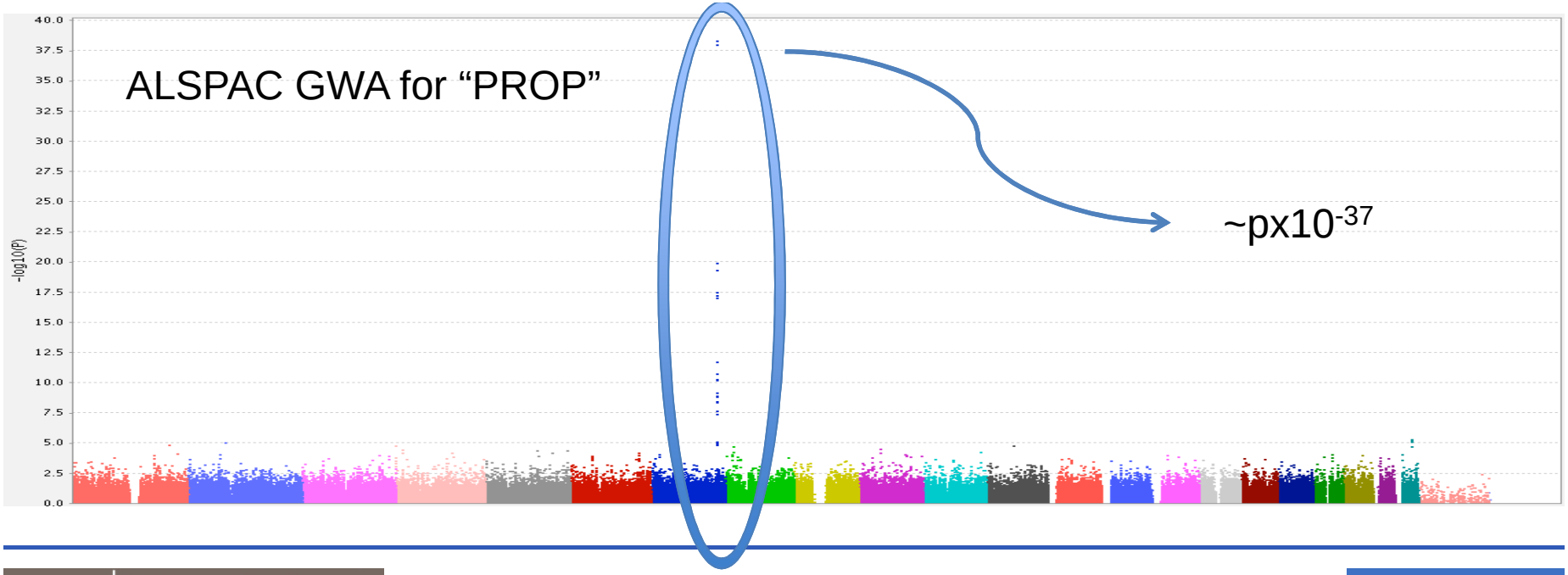
# Dependence on measurement

How equipped are we to assess genotypic variation reliably?

Era of outsourcing/DNA chip technology and high throughput technologies.
*(cost/accuracy/reliability/rapidity*)



# Discussion points

What can be done with associations of common genetic variation with obesity/BMI?

How can we better incorporate an appreciation of environmental context into genetic studies of obesity/adiposity?

Epigenetics

Do population specific patterns exist and what are their (i) clinical implications and
(ii) genetic/environmental underpinnings?

What are the next steps in the analysis of genetic data and the implications of these? “Next Generation Sequencing”

How can rare and common genetic variants associated with BMI/obesity/adiposity (or risk of these features) be used to unpick the so called “obesogenic” environment?