Are your genes to blame when you jeans don’t fit?

Dr Giles Yeo
gshy2@cam.ac.uk
## Presentation Overview

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Some numbers to mull over...

- **730,000 Kcal** consumed a year (2000 Kcal diet)

- While aging from **20 years to 50 years**, the average person will gain **15 kgs** of weight

- Assuming **5000 Kcal/kg of body weight**, 15 kg of excess weight = **75,000 Kcal**

- Over 30 years, that is an intake – output imbalance of **2500 Kcal/year**, or a discrepancy of **0.34%**

- In other words, an excess of **7 Kcal a day for 30 years** is all that is needed to gain the **15kgs of weight.....!!**
Energy balance

<table>
<thead>
<tr>
<th>Energy Intake</th>
<th></th>
<th>Energy Expenditure</th>
</tr>
</thead>
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<tr>
<td>• Food Intake</td>
<td></td>
<td>• Basal Metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Physical Activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Adaptive Thermogenesis</td>
</tr>
</tbody>
</table>
Set point hypothesis

- Decreased food intake leads to decreased energy expenditure
- Increased food intake leads to increased energy expenditure
Obesity Trends* Among U.S. Adults
BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

No Data  <10%  10%-14%

Source: CDC behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 1987

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: CDC behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 1989

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: CDC behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 1991

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: CDC behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 1993

(*BMI ≥ 30, or ~ 30 lbs. overweight for 5' 4" person)

No Data  <10%  10%-14%  15%-19%

Source: CDC behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 1995

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

No Data  <10%  10%–14%  15%–19%

Source: CDC behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 1997

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

![Map showing obesity trends across the U.S. with different states shaded in varying shades of blue to indicate percentages of obesity.

Source: CDC behavioral risk factor surveillance system]
Obesity Trends* Among U.S. Adults
BRFSS, 1999

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: CDC behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 2001

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: CDC behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 2003

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: CDC behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: Behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 2007

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: Behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 2009

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: Behavioral risk factor surveillance system
Obesity Trends* Among U.S. Adults
BRFSS, 2010

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

Source: Behavioral risk factor surveillance system
Changing pattern of bodyweight

Frequency (%)

BMI (kg/m²)

1985
2010
## Genetic control of body weight

- Variable response to same environment
- Some ethnic groups are more likely to develop obesity
- There have always been some people predisposed to weight gain
- Data from twin and adoption studies
- Heritability of fat mass is equivalent to that of height
"thrifty gene" theory, James Neel 1962

50% of adult Pima Indians here have diabetes, 95% of those with diabetes are overweight.

10% of adult Pima Indians here have diabetes, population not overweight.

Genetically identical.
What are the factors governing body size?

- Genetic
- Physiological
- Psychological
- Social
- Environmental
The discovery of leptin

Mouse weighed down by genetics

Disruption of melanocortin signalling causes severe obesity
## Human congenital leptin deficiency

### Detailed phenotype of 5 leptin deficient subjects

- Normal birthweight
- Hyperphagia after weaning
- No macronutrient preference

- Normal basal temperature
- No defect in BMR or free-living energy
- Expenditure

- Increased fat mass (57%)
- Normal bone density and mineralisation

- Hyperinsulinaemia consistent with obesity
- Normal linear growth
- No thyroid or adrenal dysfunction
- Hypogonadotrophic hypogonadism

- Impaired T cell mediated immunity
Treatment of leptin deficiency

A 3yr old weighing 42kg

B 7yr old weighing 32kg
Brain as a target organ of peripheral feedback signals that regulate energy homeostasis
Targeted disruption of the Melanocortin-4 Receptor results in obesity in Mice

Dennis Huszar,* Catherine A. Lynch,* Victoria Fairchild-Huntress,* Judy H. Dunmore,* Qing Fang,* Lucy R. Berkemeier,* Wei Gu,* Robert A. Kesterson,† Bruce A. Boston,‡ Roger D. Cone,† Francoise J. Smith,§ L. Arthur Campfield,§ Paul Burn,§ and Frank Lee*

*Millennium Pharmaceuticals, Inc.
640 Memorial Drive Cambridge, Massachusetts 02139, US


- Hyperphagic
- Severely Obese
- Hyperinsulinaemic
- Increased Linear Growth
- Heterozygotes show intermediate weight-gain
These new genes make me look fat

FAT people may be unable to control the desire to eat because of a newly-discovered gene defect, research shows. Scientists say the fault upsets the natural mechanism in the brain which tells the body when it is full.

The Cambridge University team believe it could affect entire families after studying a 21st man whose four-year-old son already weighs 5st.
Mutations & sequence variants in MC4R

Source: Farooqi et al, NEJM, 2003
Genotype – Phenotype correlation

**Mean ad libitum energy intake**
(kcal/kg lean mass)

<table>
<thead>
<tr>
<th>Inactive</th>
<th>Partial</th>
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<tbody>
<tr>
<td>BMI sds</td>
<td>3.9</td>
</tr>
<tr>
<td>Height sds</td>
<td>1.9</td>
</tr>
<tr>
<td>BMD z score</td>
<td>1.9</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>27</td>
</tr>
</tbody>
</table>

**Fold induction of Luciferase activity**

**MC4R mutations**

***
Disruption of the leptin melanocortin pathway results in severe obesity in humans and mice.
Monogenic vs Polygenic

Obesity
A Common Variant in the FTO gene is associated with Body Mass Index & Predisposes to Childhood & Adult Obesity

Log(fat mass) Z score

P = 6 x 10^{-10}

Adults homozygous for risk allele (AA) 3 kg heavier (16% of population)

Heterozygotes intermediate

FTO expression

Fasting → Food intake
High-fat diet → Food intake

Hypothalamic
Arcuate nucleus
Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index

"We strongly confirm FTO and MC4R and identify six additional loci: TMEM18, KCTD15, GNPDA2, SH2B1, MTCH2 and NEGR1... Several of the likely causal genes are highly expressed or known to act in the central nervous system (CNS), emphasizing, as in rare monogenic forms of obesity, the role of the CNS in predisposition to obesity."

Obesity, whether monogenic or polygenic, is a brain disease!

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Primary antibodies

- Rabbit polyclonal antibody to Leptin (ab3583)
  - Tested applications: ICC/IF, ICC, IHC-Fr, WB
  - Reacts with: Mouse, Rat, Sheep, Human, Pig

- Rabbit monoclonal antibody to FTO [EPR6894] (ab126605)
  - Tested applications: WB, IHC-P, Flow Cyt, ICC/IF
  - Reacts with: Human

- Chicken polyclonal antibody to Leptin Receptor (ab92615)
  - Tested applications: IHC-FoFr, ICC/IF
  - Reacts with: Rat
Primary antibodies

- Rabbit polyclonal to Ghrelin Receptor (ab95250)
  - Applications: WB, IHC-FoFr
  - Reacts: with Mouse, Human

- Rabbit polyclonal to Tmem (ab100954)
  - Applications: WB
  - Reacts: with Mouse, Rat, Human

- Rabbit monoclonal [E175] to S6K (ab32359)
  - Applications: WB, IHC-P, IP
  - Reacts: with Mouse, Rat, Human
| Antibody                  | Description                                                                 |
The|--------------------------|-----------------------------------------------------------------------------|
| Rabbit polyclonal to UCP1 (ab23841) | Tested applications: WB, IHC-P, IHC-FoFr Reacts with: Mouse, Rat, Dog          |
| Rabbit polyclonal to ACTH (ab75683) | Tested applications: WB, IHC-P Reacts with: Human                             |
| Rabbit polyclonal to AGRP (ab92615)  | Tested applications: IHC-P Reacts with: Human                                |
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**ELISA kits**

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- DCFDA - Cellular Reactive Oxygen Species Detection Assay Kit
- Mitochondrial Viability Stain
- Mitochondrial Biogenesis Assays
- Extracellular Oxygen Probes
- Oxidative Stress Assays

Visit: www.abcam.com/MitoTox
## Assay kits

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<tr>
<th>Category</th>
<th>Product name</th>
<th>Product ID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid formation</strong></td>
<td>Adipogenesis detection kit</td>
<td>ab102513</td>
</tr>
<tr>
<td></td>
<td>Adipogenesis Assay Kit (cell-based)</td>
<td>ab133102</td>
</tr>
<tr>
<td></td>
<td>Adipolysis Assay Kit</td>
<td>ab133115</td>
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<tr>
<td></td>
<td>Cholesterol Assay Kit (cell-based)</td>
<td>ab133116</td>
</tr>
<tr>
<td></td>
<td>Cholesterol/Cholesteryl Ester Detection Kit</td>
<td>ab102515</td>
</tr>
<tr>
<td></td>
<td>Free Fatty Acid Quantification Kit</td>
<td>ab65341</td>
</tr>
<tr>
<td></td>
<td>Free Glycerol Assay Kit</td>
<td>ab65337</td>
</tr>
<tr>
<td><strong>Insulin signaling pathway</strong></td>
<td>Glucose Detection kit</td>
<td>ab102517</td>
</tr>
<tr>
<td></td>
<td>Glucose Uptake Assay Kit (colorimetric)</td>
<td>ab136955</td>
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<tr>
<td></td>
<td>Glucose Uptake Assay Kit (fluorometric)</td>
<td>ab136956</td>
</tr>
<tr>
<td></td>
<td>Glycogen Assay Kit</td>
<td>ab65620</td>
</tr>
<tr>
<td></td>
<td>Lipase Detection Kit (colorimetric)</td>
<td>ab102524</td>
</tr>
<tr>
<td></td>
<td>Lipase Detection Kit II (colorimetric)</td>
<td>ab102525</td>
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<tr>
<td></td>
<td>Lipase Detection Kit III (fluorometric)</td>
<td>ab118969</td>
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<tr>
<td><strong>Lipid metabolism</strong></td>
<td>Triglyceride Quantification kit</td>
<td>ab65336</td>
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<tr>
<td></td>
<td>HDL and LDL/VLDL Cholesterol Assay Kit</td>
<td>ab65390</td>
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## ELISA kits

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<tr>
<th>Product ID</th>
<th>Product name</th>
<th>Tests</th>
<th>Sensitivity</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ab100581</td>
<td>Leptin Human ELISA</td>
<td>1 x 96</td>
<td>&lt; 2 pg/ml</td>
<td>1.64 pg/ml - 400 pg/ml</td>
</tr>
<tr>
<td>ab100718</td>
<td>Leptin Mouse ELISA</td>
<td>1 x 96</td>
<td>&lt; 4 pg/ml</td>
<td>4.1 pg/ml - 1000 pg/ml</td>
</tr>
<tr>
<td>ab100773</td>
<td>Leptin Rat ELISA</td>
<td>1 x 96</td>
<td>&lt; 30 pg/ml</td>
<td>10.97 pg/ml - 8000 pg/ml</td>
</tr>
<tr>
<td>ab119574</td>
<td>LeptinR Human ELISA</td>
<td>1 x 96</td>
<td>&lt; 8 pg/ml</td>
<td>156 pg/ml - 10000 pg/ml</td>
</tr>
<tr>
<td>ab100578</td>
<td>Insulin Human ELISA</td>
<td>1 x 96</td>
<td>&lt; 4 μlU/ml</td>
<td>4.69 μlU/ml - 300 μlU/ml</td>
</tr>
</tbody>
</table>
# Abcam cell imaging products

<table>
<thead>
<tr>
<th>Cyto-Painter cellular staining</th>
<th>Fluorescent dyes</th>
</tr>
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<tr>
<td>• Ideal tool for staining subcellular structures in combination with antibodies and nuclear dyes</td>
<td><strong>Nuclear dyes</strong></td>
</tr>
<tr>
<td>• Staining of:</td>
<td>• Nuclear staining in only 5 minutes</td>
</tr>
<tr>
<td>• Actin filaments: fixed cells</td>
<td>• Far-red dyes: ideal for combining with other labels</td>
</tr>
<tr>
<td>• Mitochondria &amp; Lysosomes: live cells</td>
<td>• DRAQ5™ (ab108410): staining on live and fixed cells</td>
</tr>
<tr>
<td></td>
<td>• DRAQ7™ (ab109202): staining of fixed and dead cells</td>
</tr>
<tr>
<td></td>
<td>• Red, yellow and green dyes for multicolour staining</td>
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</tbody>
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Discover more at abcam.com
# Abcam cell imaging products

## Secondary antibody portfolio
Extensively validated products for cell imaging, including:
- DyLight® conjugated secondaries
- Chromeo™ conjugated secondaries
- Pre-adsorbed secondaries
- F(ab’)2 fragment secondaries
- AbGold conjugated secondaries

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- **Receptor agonists & antagonists**
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- **Ion channel modulators**

- **Enzymes modulators**

- **Signaling tools**
  - Apoptosis & cell cycle, Ca\(^{2+}\) signaling, NO signaling

Rapidly expanding range 40 new products/month
<table>
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<tr>
<th>ab ID</th>
<th>Product name</th>
<th>Biological description</th>
<th>Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ab141010</td>
<td>Apelin 13</td>
<td>Selective endogenous apelin receptor (APJ) ligand</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab141011</td>
<td>Apelin 17</td>
<td>Endogenous apelin receptor (APJ) agonist</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab141009</td>
<td>Apelin 36 (human)</td>
<td>Endogenous apelin receptor (APJ) agonist</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab120209</td>
<td>CCK Octapeptide sulfated</td>
<td>C-terminal octapeptide of CCK</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab120743</td>
<td>Dexamethasone</td>
<td>Anti-inflammatory glucocorticoid</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>ab120230</td>
<td>Ghrelin (human)</td>
<td>Endogenous GHS agonist</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab120231</td>
<td>Ghrelin (rat)</td>
<td>Endogenous GHS agonist</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab120181</td>
<td>Kisspeptin-13 (4-13) (human) (KiSS-1 (112-121))</td>
<td>AXOR12 agonist</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab120208</td>
<td>Neuropeptide Y (NPY) (human, rat)</td>
<td>Endogenous neuropeptide</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab120171</td>
<td>Neuropeptide Y 13-36 (porcine)</td>
<td>NPY Y2 agonist</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab120071</td>
<td>Obestatin</td>
<td>Endogenous peptide involved in feeding</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>ab120212</td>
<td>Orexin A (bovine, human, mouse, rat)</td>
<td>Neuropeptide involved in feeding and sleep</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>ab141012</td>
<td>Pyr1-Apelin 13</td>
<td>Highly potent, selective endogenous APJ receptor agonist</td>
<td>&gt; 95%</td>
</tr>
</tbody>
</table>

**Coming soon!**

<table>
<thead>
<tr>
<th>ab ID</th>
<th>Product name</th>
<th>Biological description</th>
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</thead>
<tbody>
<tr>
<td>ab141175</td>
<td>GIP (1-39) (human)</td>
<td>Truncated endogenous gastric inhibitory peptide (GIP)</td>
</tr>
<tr>
<td>ab141176</td>
<td>GIP (human)</td>
<td>Endogenous gastric inhibitory peptide (GIP)</td>
</tr>
</tbody>
</table>

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# Programming Obesity: Central and Peripheral Contributors

**Date:** April 14-16, 2013  
**Venue:** University of Cambridge, UK

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<th>Conference Topics</th>
<th>Confirmed speakers</th>
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| • Evolutionary origins and fetal programming of obesity  
  • Genetic determinants of obesity  
  • Role of adipose tissue in metabolic health  
  • Brain circuitry underlying energy balance  
  • Gastrointestinal peptides influencing hunger and satiety  
  • Metabolic disease treatment: 2013 and beyond | • Steve O'Rahilly, Steve Bloom, Michael Cowley, John Speakman, Tamas Horvath, Kevin Grove and many more.... |

**Meeting website:** [http://www.abcam.com/obesity2013](http://www.abcam.com/obesity2013)

**Oral Abstract Deadline:** January 18, 2013
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Optimizing IHC/ICC results through careful experimental design
• December 11, 2012
  15:00 GMT, 10:00 EDT, 07:00 PDT

Fluorescent Western Blot
• February 28, 2013
  15:00 GMT, 10:00 EDT, 07:00 PDT

To interact or not to interact? Immunoprecipitate to answer this question
• March 21, 2013
  15:00 GMT, 10:00 EDT, 07:00 PDT

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