Genetic influences on weight loss – opportunities for personalisation?

John Mathers
Human Nutrition Research Centre
Institute of Cellular Medicine

Newcastle University
Human Nutrition Research Centre
UK
Obesity is 3\textsuperscript{rd} biggest societal burden

Impact on global GDP\textsuperscript{1}

- Smoking: $2.1$ trillion
- Armed violence, war, and terrorism: $2.1$ trillion
- Obesity: $2.0$ trillion
- Alcoholism: $1.4$ trillion

\textsuperscript{1}In 2014 dollars at purchasing-power parity.

Source: Literature review; World Health Organization global burden of disease (GBD) database; McKinsey Global Institute analysis.

http://www.mckinsey.com/insights/economic_studies/how_the_world_could_better_fight_obesity
Weight loss improves health and wellbeing
Sustained weight loss leads to Type 2 Diabetes remission

Effect of weight loss interventions

Mean 3.4kg after 12 months

Ma C et al. (2017) BMJ 359: j4849
The era of personalised (precision) medicine
Personalised nutrition and weight loss

Aspects of personalised nutrition:
- Dietary habits
- Genetics
- Microbiome
- Metabolism
- Environment/Social context
- Phenotype
- Exercise

Personalised approaches to lifestyle behaviour change
Hypothesis: Individualising advice, products, or services will be more effective than more generic approaches.

Personalisation can be based on:

1. Biological evidence of differential responses dependent on genotypic or phenotypic characteristics.

2. Analysis of current behaviour, preferences, barriers, and objectives and subsequent delivery of interventions that motivate and enable individuals to make appropriate behavioural changes.

Ordovas JM et al. (2018) BMJ 361: k2173
Genotype associated with weight loss


rs11185098 in amylase gene

Mechanism?
Rationale for personalised approaches to lifestyle behaviour change.

Personalised approaches may be more effective because:

• Such approaches are more relevant (biological basis)

• Such approaches feel more relevant (improve motivation…)
Hypothesis

Genetic susceptibility that makes it easier to gain weight will make it more difficult to lose weight.
Chromosomal locations of 127 genetic variants associated with obesity

Structure of $FTO$ gene on chr 16

AA genotype associated with ↑ weight and ↑ risk of obesity

Biological function of FTO protein

FTO is a $\text{m}^6\text{A}$ demethylase

Cao G et al. (2016) Open Biol. 6: 160003
Ghrelin is the "hunger" hormone

*FTO* genotype regulates ghrelin expression

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Does *FTO* genotype influence weight loss in intervention studies?

FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials

Katherine M Livingstone,1,2 Carlos Celis-Morales,1,3 George D Papandonatos,4 Bahar Erar,4 Jose C Florez,5,6 Kathleen A Jablonski,7 Cristina Razquin,8,9 Amelia Marti,9,10 Yoriko Heianza,11 Tao Huang,11,12 Frank M Sacks,13 Mathilde Svendstrup,14,15 Xuemei Sui,16 Timothy S Church,17 Tiina Jääskeläinen,18,19 Jaana Lindström,20 Jaakko Tuomilehto,21,22 Matti Uusitupa,18 Tuomo Rankinen,23 Wim H M Saris,24 Torben Hansen,14 Oluf Pedersen,14 Arne Astrup,25 Thorkild I A Sørensen,14,26 Lu Qi,11,13 George A Bray,17 Miguel A Martinez-Gonzalez,9,10 J Alfredo Martinez,9,10,27 Paul W Franks,13,28 Jeanne M McCaffery,29 Jose Lara,1,30 John C Mathers1
References identified (n=2833): Medline (OVID) (n=641) Embase (OVID) (n=1059) Scopus (n=1133)

Additional records identified through other sources (n=1)

Records screened after duplicates removed (n=2248)

Records excluded (n=2220)

Full text articles assessed for eligibility (n=28)

Full text articles excluded (n=17):
- Presented data from same study (n=5)
- Did not report results for FTO genotype (n=12)

Studies included in qualitative synthesis (n=11)

Full text article excluded due to no reply to request for access to data (n=3)

Studies included in quantitative synthesis (meta-analysis) (n=8)

Livingstone KM et al. (2016) BMJ 354: i4707
No effect of *FTO* genotype on BMI response to weight loss intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Mean</th>
<th>Treatment SD</th>
<th>Treatment Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean difference IV, random (95% CI)</th>
<th>Weight (%)</th>
<th>Mean difference IV, random (95% CI)</th>
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<tbody>
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<td>Body mass index</td>
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<td>DPP^{20}</td>
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<td>-0.13 (-0.34 to 0.08)</td>
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<td>-0.09</td>
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<td>-0.18 (-0.88 to 0.52)</td>
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<td>Finnish DPS^{21}</td>
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<td>23</td>
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<td>-0.72</td>
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<td>0.05 (-0.72 to 0.82)</td>
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<td>0.05 (-0.72 to 0.82)</td>
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<tr>
<td>Food4Me^{36}</td>
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<td>0.15 (-0.44 to 0.14)</td>
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<td>0.14 (-0.29 to 0.29)</td>
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<tr>
<td>POUNDS LOST^{16}</td>
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<td>0.15 (-0.44 to 0.14)</td>
<td>0.15</td>
<td>0.15 (-0.44 to 0.14)</td>
</tr>
</tbody>
</table>

Data were adjusted for age, sex, outcome variable at baseline, ethnicity, country/centre, socioeconomic status, physical activity and smoking.

Similar findings for body mass and for waist circumference.

Livingstone KM *et al.* (2016) *BMJ* 354: i4707
Lack of effect of *FTO* genotype on weight loss is robust

Findings unaffected by:

**Intervention characteristics**
- Modality (diet or diet + exercise)
- Duration

**Participant characteristics**
- Age
- Sex
- Initial BMI
- Race/ethnicity

Livingstone KM *et al.* (2016) *BMJ* **354**: i4707
Genetic susceptibility that makes it easier to gain weight will make it more difficult to lose weight

At least for FTO...
The DIETFITS study

- Compared effects of healthy “low fat” and “low carbohydrate” diets on weight loss over 12 months
- No differences between treatments

Gardner CD et al. (2018) JAMA 319, 667-679
Individual variation in weight loss in DIETFITS study

Gardner CD et al. (2018) JAMA 319, 667-679
Key questions

• What is the biological (genetic) basis for this inter-individual variation?

• Could knowledge of the (genetic) basis of inter-individual variation in weight loss be used to develop more effective, personalised, weight-loss interventions?
Does genotype influence response to weight loss intervention in DIETFITS study?

Genotypes investigated:

- **PPARG** (rs1801282) – encodes transcription factor for which fatty acids are ligands
- **ADRB2** (rs1042714) – encodes beta-2 adrenergic receptor
- **FABP2** (rs1799883) – encodes fatty acid binding protein

**Genotype groups**

<table>
<thead>
<tr>
<th>Pattern</th>
<th>FABP2 Genotype</th>
<th>PPARα Genotype</th>
<th>ADRB2 Genotype</th>
<th>Frequency³</th>
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<td>CC</td>
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<td>CC</td>
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<td>CG</td>
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<td>9</td>
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<td>CC</td>
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<td>14</td>
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<tr>
<td>15</td>
<td>GG</td>
<td>CC</td>
<td>CC</td>
<td>0.167</td>
</tr>
</tbody>
</table>

- More sensitive to “Low Fat” diet
- More sensitive to “Low Carb” diet
- Not sensitive
Similar weight trajectories for all treatment groups

Gardner CD et al. (2018) JAMA 319, 667-679
No interactions between genotype and dietary intervention on weight loss over 12 months

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Diet</th>
<th>Participants</th>
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</thead>
<tbody>
<tr>
<td>Low-fat genotype</td>
<td>Healthy low-fat diet</td>
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<tr>
<td></td>
<td>Healthy low-carbohydrate diet</td>
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<tr>
<td>Low-carbohydrate genotype</td>
<td>Healthy low-fat diet</td>
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<td>Neither genotype</td>
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<tr>
<td></td>
<td>Healthy low-carbohydrate diet</td>
<td>60</td>
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</tbody>
</table>

12-mo Weight Change, kg

Rationale: Individualising advice, products, or services will be more effective than more generic approaches.

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Ordovas JM et al. (2018) BMJ 361: k2173
Genetic basis of behaviour change?

Genetic basis for:

- Attention
- Memory
- Reward
- Motivation…

Behavioural genetics
Rationale for personalised approaches to lifestyle behaviour change

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Ordovas JM et al. (2018) BMJ 361: k2173
Potential for personalised interventions to improve weight loss

Participant characteristics

Barriers & facilitators

Aspirations etc.

Personalised intervention

Self-monitoring

↑ Weight loss
Summary

• Genotype contributes to obesity risk

• Genetic variants that increase susceptibility to obesity are **NOT** impediments to weight loss

• Lack of knowledge of genetic determinants of behaviour change

• Personalisation of interventions may improve behaviour change
Human Nutrition Research Centre

- Understanding Molecular Nutrition
- Tackling Childhood Obesity
- Innovating for Global Nutritional Health

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Human Nutrition Research Centre

Investigating worldwide nutritional issues linked with:

- Obesity
- Ageing

From Newcastle. For a healthier world.