SINGLE NUCLEOTIDE POLYMORPHISMS AND OBESITY

By: Molly DePrenger & Kirstie Ducharme-Smith
OUTLINE

- Objectives
- Introduction
- Trait of Interest
- Obesity related genes
- FTO, ghrelin, impaired brain food-cue responsivity
- Dietary manipulation
  - POUNDS LOST trial
OBJECTIVES

1. To understand the meaning of single nucleotide polymorphism (SNP)
2. To recognize major pathways involved in energy intake (homeostatic, hedonic, frontal executive)
3. To recognize common obesity related genes (FTO)
4. To understand the interaction between FTO and major pathways involved in energy intake
5. To explore effect of food choice (protein) on FTO
INTRODUCTION

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- Single nucleotide polymorphisms


LOCATING SNPS WITHIN THE GENOME

How Do Scientists Identify SNPs?

- SNPs are first identified when scientists sequence DNA samples from multiple people.
- Because DNA sequencing is relatively expensive and time consuming, scientists have come up with other methods for detecting SNPs.
- Primer extension is one method scientists use to determine which version of a known SNP a person has.

Using Primer Extension to Identify SNPs:

<table>
<thead>
<tr>
<th>Version 1</th>
<th>Version 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTAAGTA</td>
<td>CTAAGTA</td>
</tr>
<tr>
<td>Add synthetic complementary DNA molecule, called a “primer,” which ends at SNP position.</td>
<td></td>
</tr>
<tr>
<td>GATTCAT</td>
<td>GATTCAT</td>
</tr>
<tr>
<td>Add nucleotides to extend the primer. Nucleotides will be added to the end of the primer ONLY if the sequence is an exact match.</td>
<td></td>
</tr>
<tr>
<td>GATTGTA</td>
<td>GATTGTA</td>
</tr>
<tr>
<td>Compare the lengths of the products using gel electrophoresis.</td>
<td></td>
</tr>
<tr>
<td>Version 1: Exact match Extension occurs SNP identity: A</td>
<td></td>
</tr>
<tr>
<td>Version 2: Mismatch No extension occurs SNP identity: Unknown</td>
<td></td>
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IMPLICATIONS

- Variations in the DNA sequences can affect how humans develop diseases and respond to pathogens, drugs, vaccines, and other agents.

- **GWAS (Genome Wide Association Studies)**
  - Examine genetic variants in individuals and associations with traits.
    - Typically traits as major diseases.
  - If one type of the variant (allele) is more frequent in people with the disease, the SNP is thought to be associated with the disease.
TRAIT OF INTEREST

- Obesity - disorder involving excessive body fat
# Classification of Obesity

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<td><strong>Obese class I</strong></td>
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Causes of Obesity


CAUSES OF OBESITY


ENERGY BALANCE

- $E_{\text{in}} - E_{\text{out}} = \Delta\text{Body Weight}$
**Systems Regulating Energy Intake**

- Homeostatic (energy-based) system
- Hedonic (reward-based) circuit
- Frontal executive system

Homeostatic “Energy-Based” System

ARCUATE NUCLEUS

Hedonic “Reward” System

**Frontal Executive System**

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“Obesity - A Lack of Willpower”

- Do you agree?
OBESITY RELATED GENES

- Genes
  - Vary in size from a few hundred DNA bases to more than 2 million bases
## Obesity Related Genes - Prevalence

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FTO GENE

FTO Gene

- Contributes to the regulation of the global metabolic rate, energy expenditure and energy homeostasis

FTO Gene- mTOR Pathway

FTO Gene

- Alphaglutamate-dependent dioxygenase

FTO GENE-rs9939609

- **SNP**
  - A allele=high risk
  - T allele=low risk

- **Heterozygous**
  - AT

- **Homozygous**
  - TT, AA

Each A allele associated with mean BMI increase of 0.36 kg/m²

AA weigh ~3 kg more, AT weigh ~1.5 kg more than TT individuals

LINK BETWEEN FTO, GHRELIN, AND IMPAIRED BRAIN FOOD-CUE RESPONSIVITY

Karra et al.
**STUDY PURPOSE**

- Determine the mechanisms responsible for increased energy intake in those with an *FTO* genotype associated with obesity (rs9939609-AA)
  - AA=“High Risk”
  - TT=“Low Risk”
OBJECTIVES

- Assess appetite and circulating acyl-ghrelin levels in AA vs. TT FTO genotypes
- Determine the appetite response and hedonic food susceptibility in AA vs. TT FTO genotypes and assess impact of dysregulated circulating acyl-ghrelin on these neural circuits
Ghrelin and Acyl Ghrelin

- Ghrelin is orexigenic hormone
- Acyl ghrelin is “active” form of ghrelin and has the greatest orexigenic effects of all forms of ghrelin.

Homeostatic “Energy-Based” System
APPETITE AND CIRCULATING GHRELIN

- 10 AA and 10 TT fasted subjects consumed a standard test meal and completed blood samples and appetite analysis for 3 hours post-prandially.
APPETITE AND CIRCULATING GHRELIN

- Appetite measured pre- and post-prandially using 100 mm visual analogue scale (VAS) measuring hunger

Blood work measured circulating PYY3-36 and leptin (satiety hormones) and acyl-ghrelin (orexigenic hormone)
**Figure 1. AUC Hunger Reduction**

- Hunger reduced less in AA than TT subjects
- ($TT = 9671 \pm 566$, $AA = 6957 \pm 641$, $P = 0.003$)
**Figure 2. AUC acyl ghrelin reduction (pg/L x min)**

- No difference in fasting acyl-ghrelin concentrations between AA and TT
- Less post-prandial suppression of acyl-ghrelin in AA subjects
- (TT = 15298 ± 1408, AA = 9439 ± 1291, P=0.002)
CONCLUSION: HOMEOSTATIC SYSTEM

- Subjects with AA genotype had weaker appetite suppression than TT genotype when fed the same meal.
- Subjects with AA genotype also had weaker suppression of circulating acyl-ghrelin than TT genotype following consumption of the same meal.
Hedonic “Reward” System
NEURAL RESPONSE TO FOOD
Hedonic “Reward” System

VS.

OFC/ Ant. insula
Putamen

z = -11

z = -8

z = 1
High calorie foods significantly more appealing to AA than TT (p<0.05)
Figure 4. High calorie vs. low calorie image BOLD response
Figure 5: BOLD response in hedonic system vs. post-prandial acyl-ghrelin suppression.
CONCLUSIONS

- High calorie food more appealing to high risk subjects
- Attenuated suppression of hunger and acyl-ghrelin in high risk subjects
- Differing neural responses to hedonic food cues, circulating acyl-ghrelin
Discussion questions

- Does this information entice you to get your genomes mapped?
  - Would you recommend a patient to map their genes?
- Would you utilize a different approach in weight loss counseling for patients with the AA genotype?
DIETARY INTERVENTION IN OBESITY RELATED SNPs
POUNDS LOST TRIAL

- 742 overweight or obese participants assigned to one of four hypocaloric diets for 2 years
- Subjects genotyped for FTO variant rs1558902
  - AA=high risk
  - TT=low risk

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<th>Low Fat (20%)</th>
<th>High Fat (40%)</th>
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<td>Low Protein (15%)</td>
<td>Fat: 20%</td>
<td>Fat: 40%</td>
</tr>
<tr>
<td></td>
<td>Protein: 15%</td>
<td>Protein: 15%</td>
</tr>
<tr>
<td></td>
<td>CHO: 65%</td>
<td>CHO: 45%</td>
</tr>
<tr>
<td>High Protein (25%)</td>
<td>Fat: 20%</td>
<td>Fat: 40%</td>
</tr>
<tr>
<td></td>
<td>Protein: 25%</td>
<td>Protein: 25%</td>
</tr>
<tr>
<td></td>
<td>CHO: 55%</td>
<td>CHO: 35%</td>
</tr>
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POUNDS LOST RESULTS

• High protein diet associated with -1.51 kg weight loss per A allele (p=0.010) at 2 years
• Low protein diet associated with increase in total adipose tissue mass (+2.11 kg, p=0.001), increased superficial adipose tissue mass (+1.46 kg, p=0.0004) per A allele at 2 years

**Decrease in Fat Mass Percentage (n=224)**

- Significant decrease in fat mass percentage in high protein group

CONCLUSION: POUNDS LOST

- High protein diet associated with weight loss, decrease in fat mass % in AA (high risk) allele at 2 years in POUNDS LOST trial
- Mixed results of association between FTO SNPs and type of diet on change in body weight in other dietary intervention trials

CONCLUSIONS

- FTO SNP rs9939609 genotype AA associated with increased prevalence of obesity
- Several possible mechanisms:
  - Attenuated suppression of acyl-ghrelin, hunger
  - Differing neural responses to hedonic food cues, acyl-ghrelin suppression
- High protein diet associated with weight loss in AA subjects
  - Increased satiety in patients with blunted hunger satiation
DISCUSSION QUESTION

- Does this information change your approach to preventing or treating obesity?
- What role do RDs play in preventing and treating obesity when genetics play a more significant component than previously believed?
Sources