SINGLE NUCLEOTIDE POLYMORPHISMS AND OBESITY

By: Molly DePrenger & Kirstie Ducharme-Smith

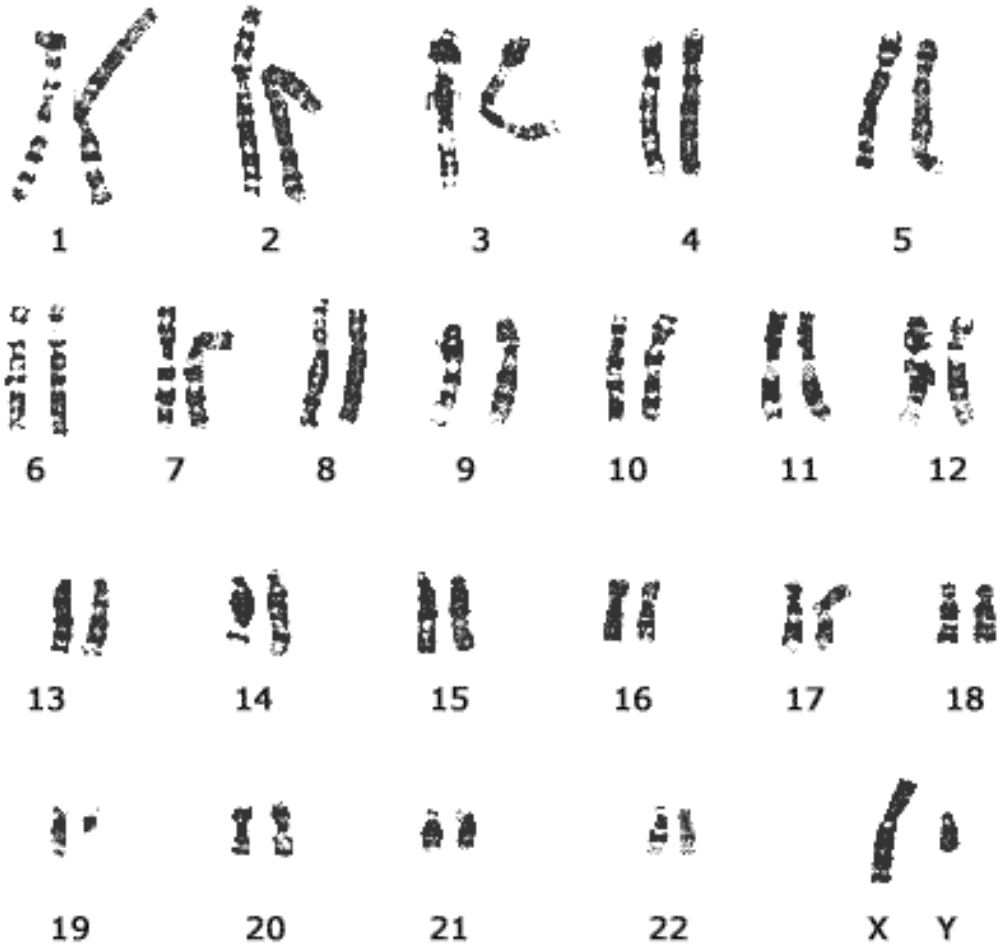
OUTLINE

- 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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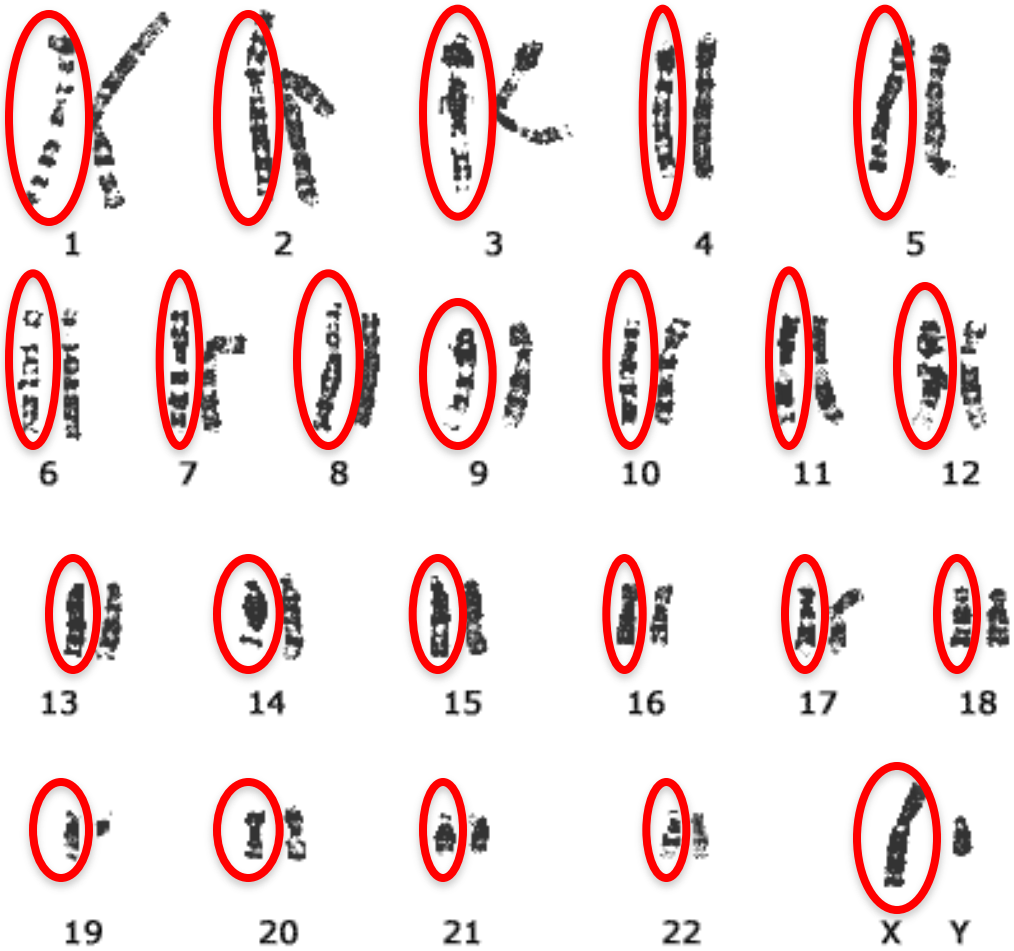

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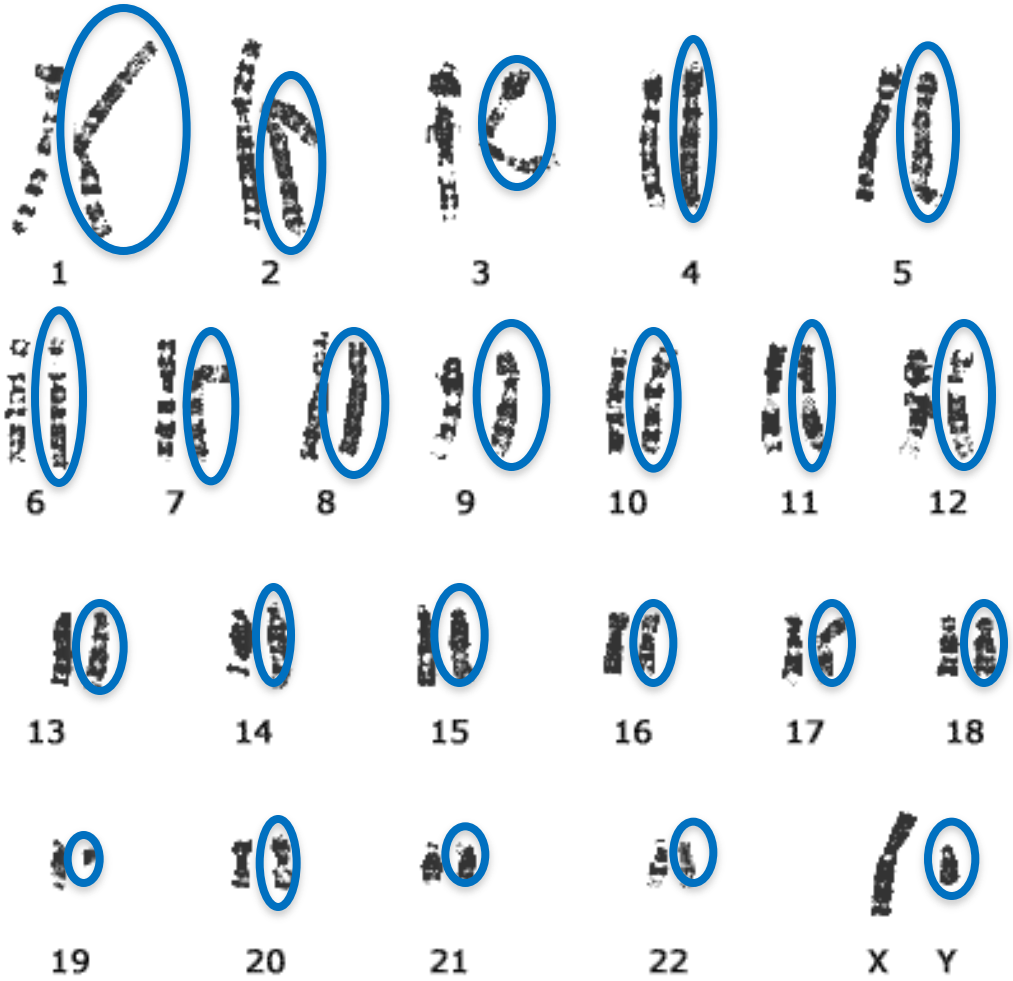

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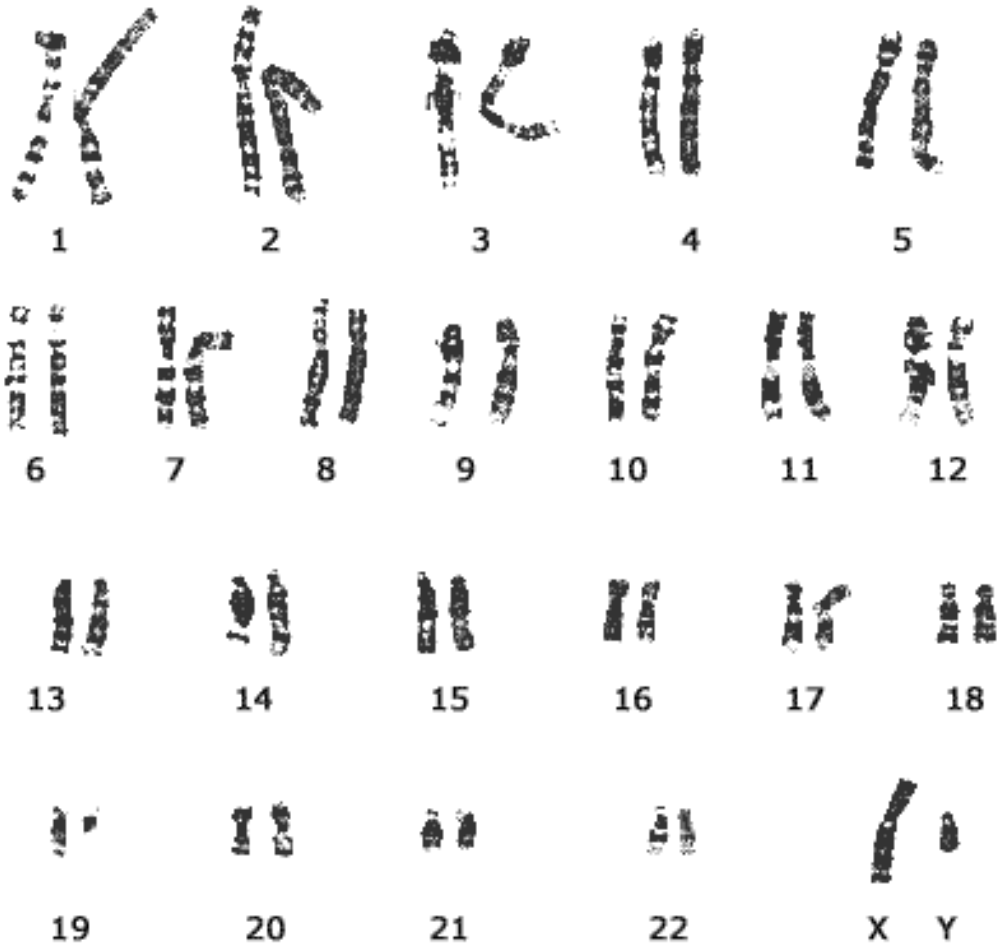

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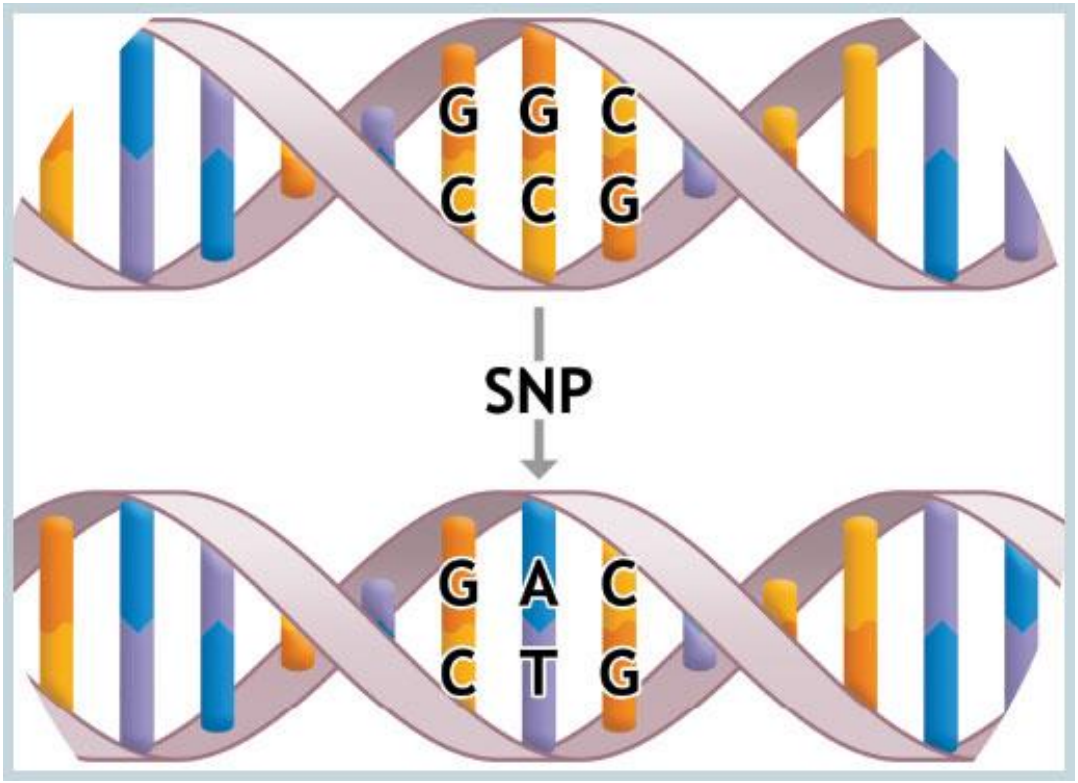
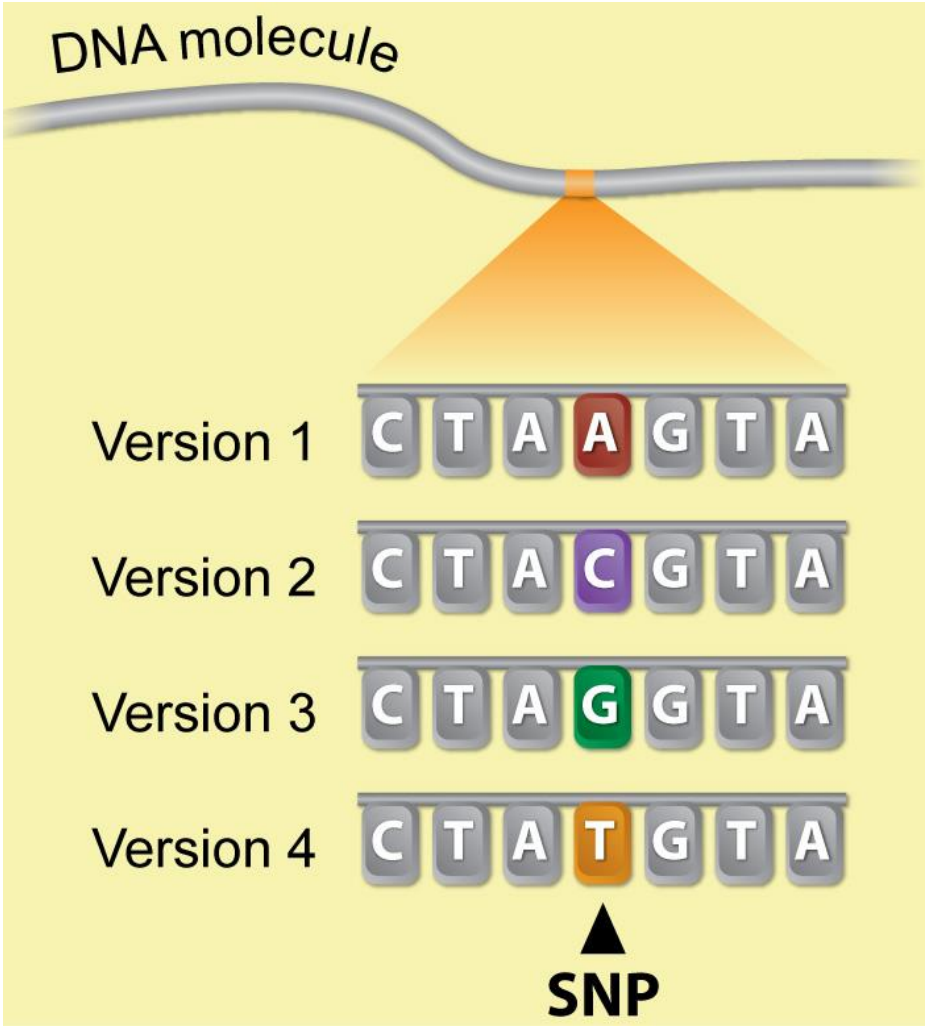
INTRODUCTION

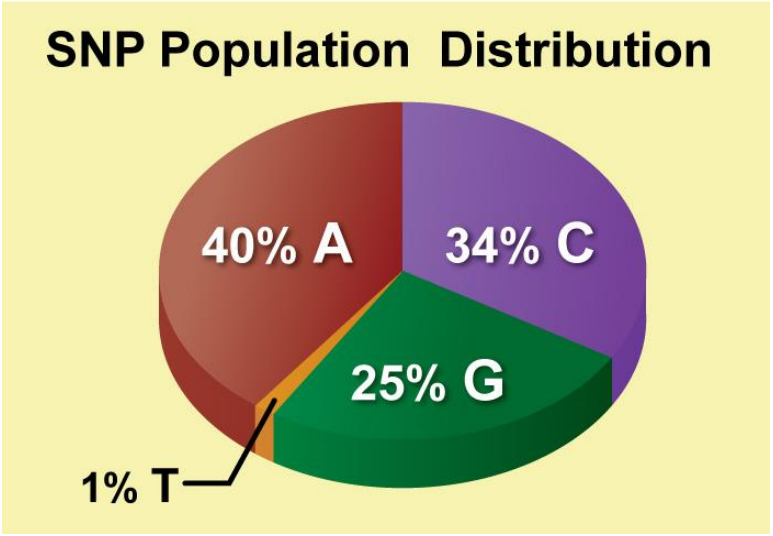
- Single nucleotide polymorphisms



Sherry,S.T., Ward,M. and Sirotkin,K. (1999) dbSNP—Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation. *Genome Res.*, **9**, 677-679.
23andme. What are SNPs? https://www.23andme.com/gen101/snps/. Accessed January 5, 2015. Web. 25 Feb. 2015

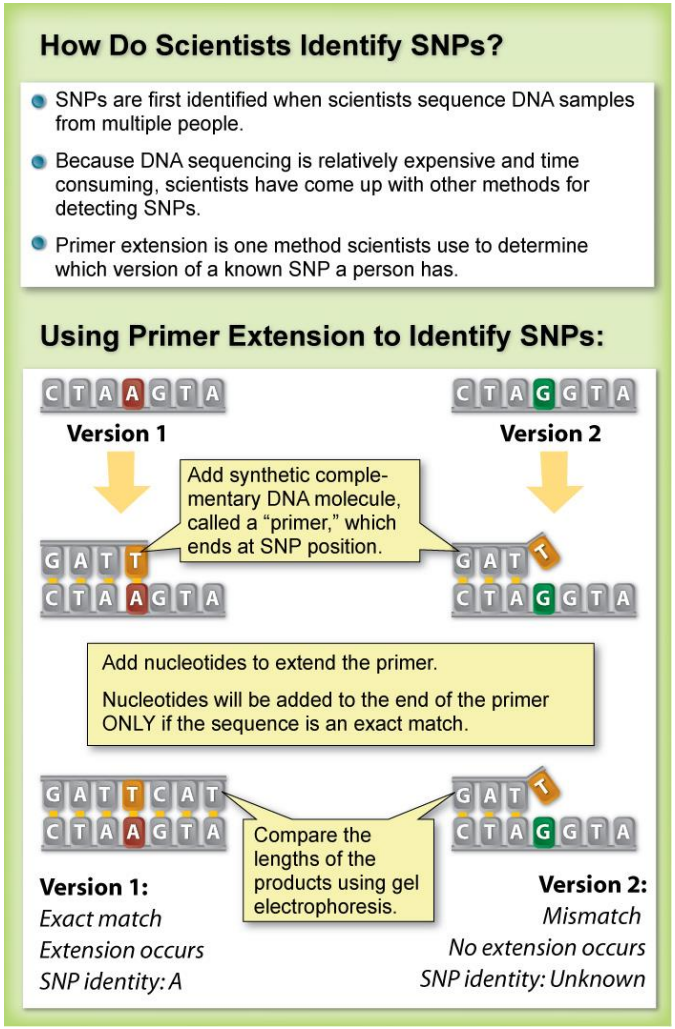
SINGLE NUCLEOTIDE POLYMORPHISMS





Genetic Science Learning Center. Making SNPs Make Sense. Learning. Genetics. http://learn.genetics.utah.edu/content/pharma/snips/. Accessed January 5, 2015.

LOCATING SNPS WITHIN THE GENOME



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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

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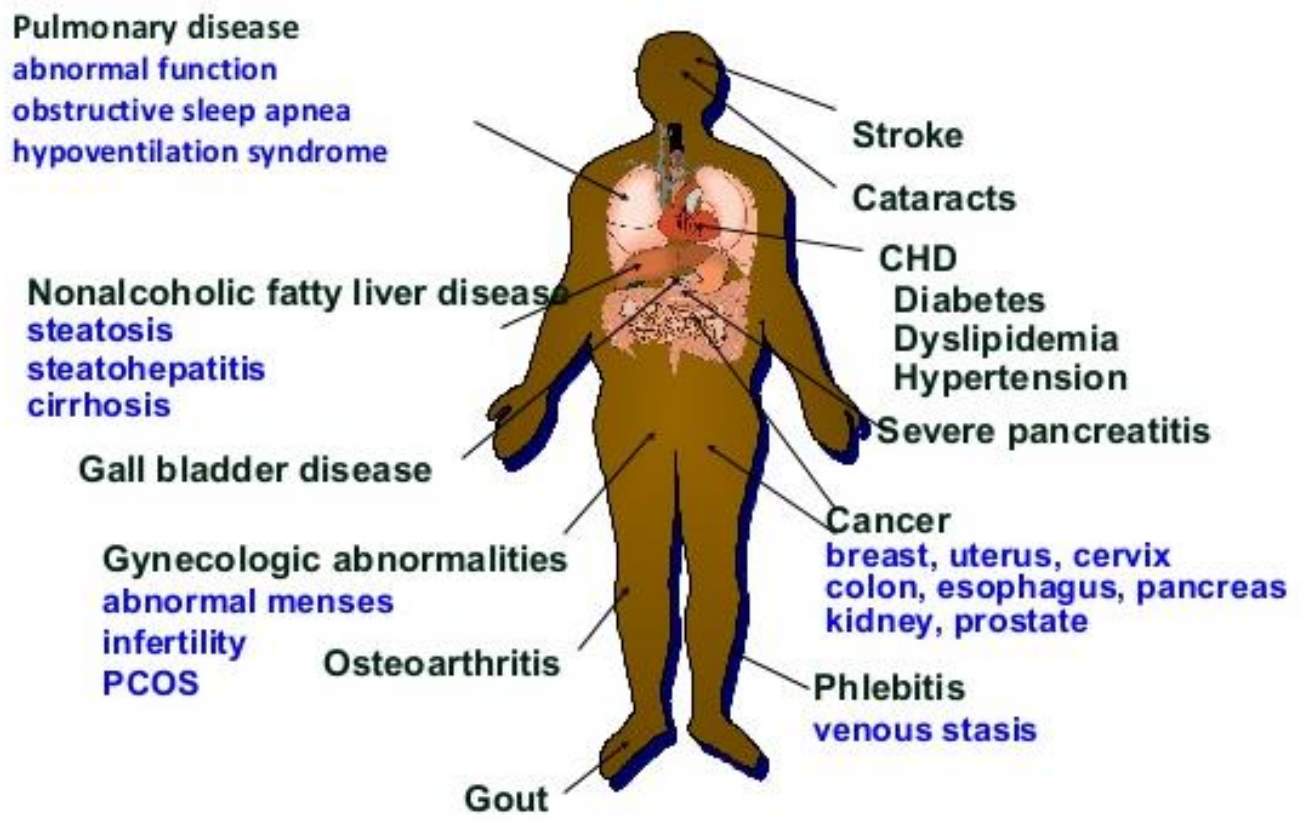
Trait of interest

- Obesity- disorder involving excessive body fat



Mayo Clinic. Diseases and Conditions: Obesity. http://www.mayoclinic.org/diseases-conditions/obesity/basics/definition/con-20014834. Accessed January 5, 2015.
Centers for Disease Control. Overweight and Obesity. http://www.cdc.gov/Obesity/. Accessed January 5, 2015.

Classification of obesity

BMI classification	
Underweight	< 18.5
Normal range	18.5 - 24.9
Overweight	⩾ 25.0
Preobese	25.0 - 29.9
Obese	⩾ 30.0
Obese class I	30.0 - 34.9
Obese class II	35.0 - 39.9
Obese class III	⩾ 40.0

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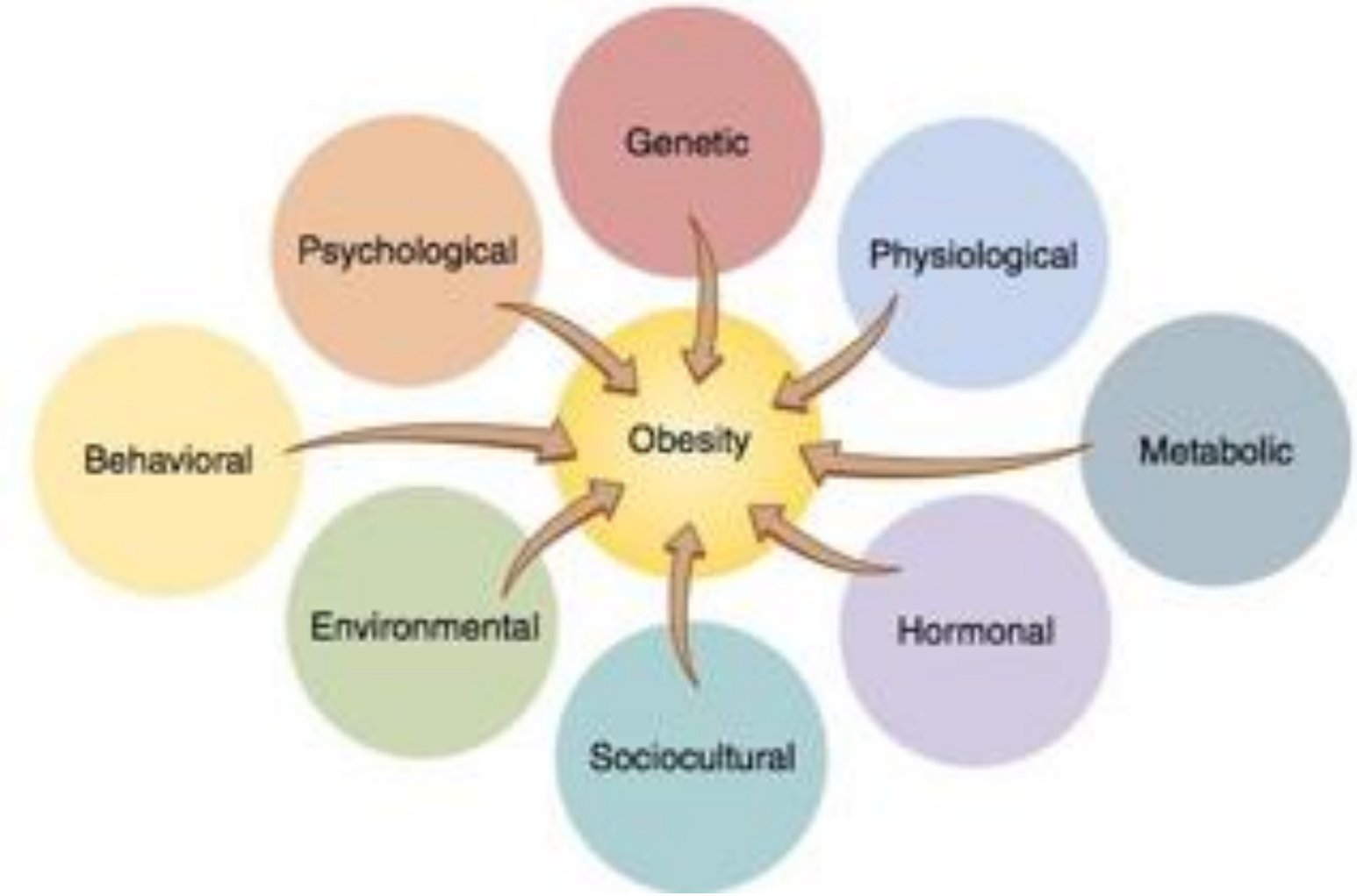
Causes of obesity



National Institutes of Health. National Heart, Lung, and Blood Institute. What Causes Overweight and Obesity? http://www.nhlbi.nih.gov/health/health-topics/topics/obe/causes. Accessed January 5, 2015.
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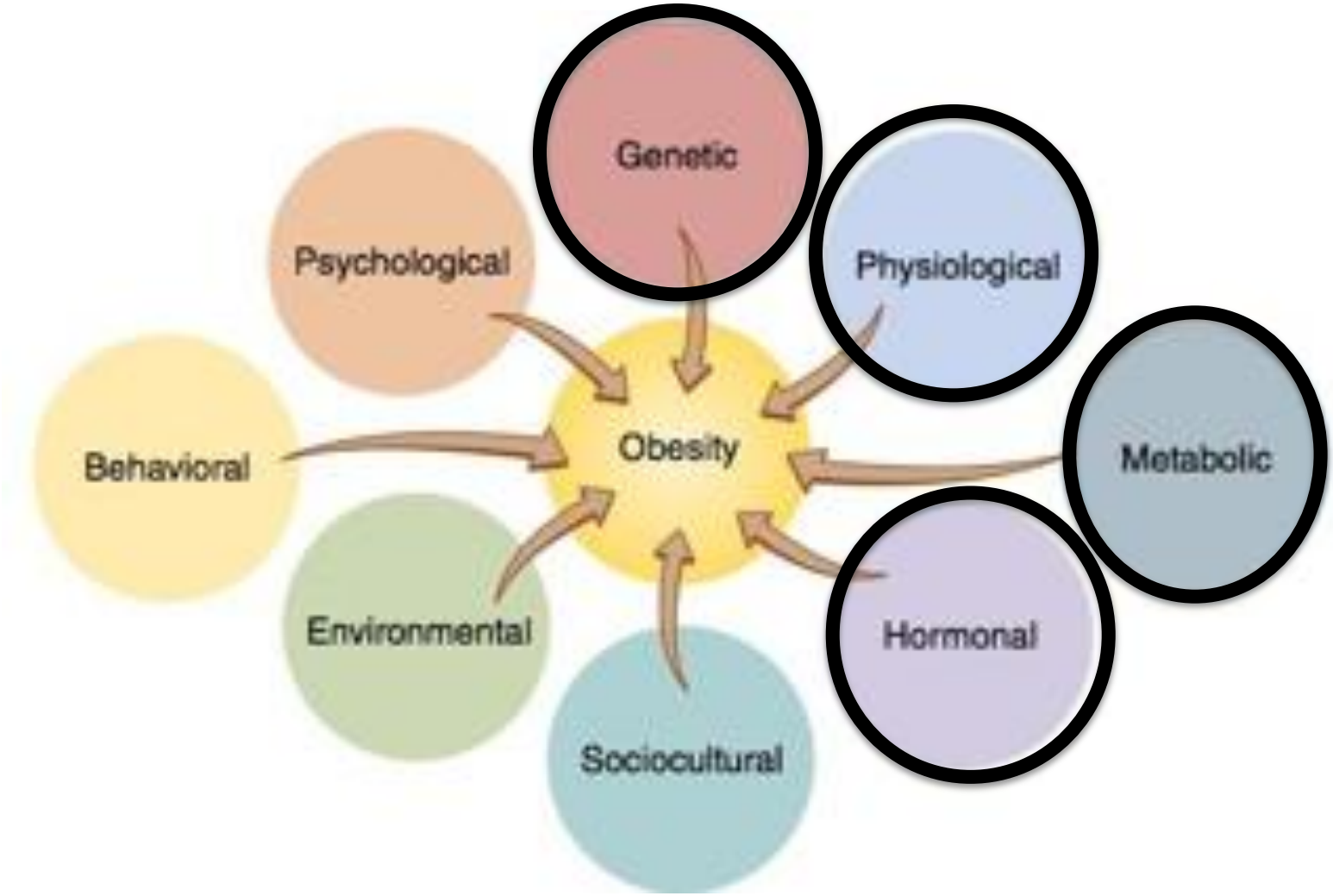

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Obesity in Children. Causes of Obesity in Children. http://obesityinchildren.net/causes-of-obesity-in-children/. Accessed January 5, 2015.

Energy Balance

- E_{in}-E_{out}= ΔBody Weight

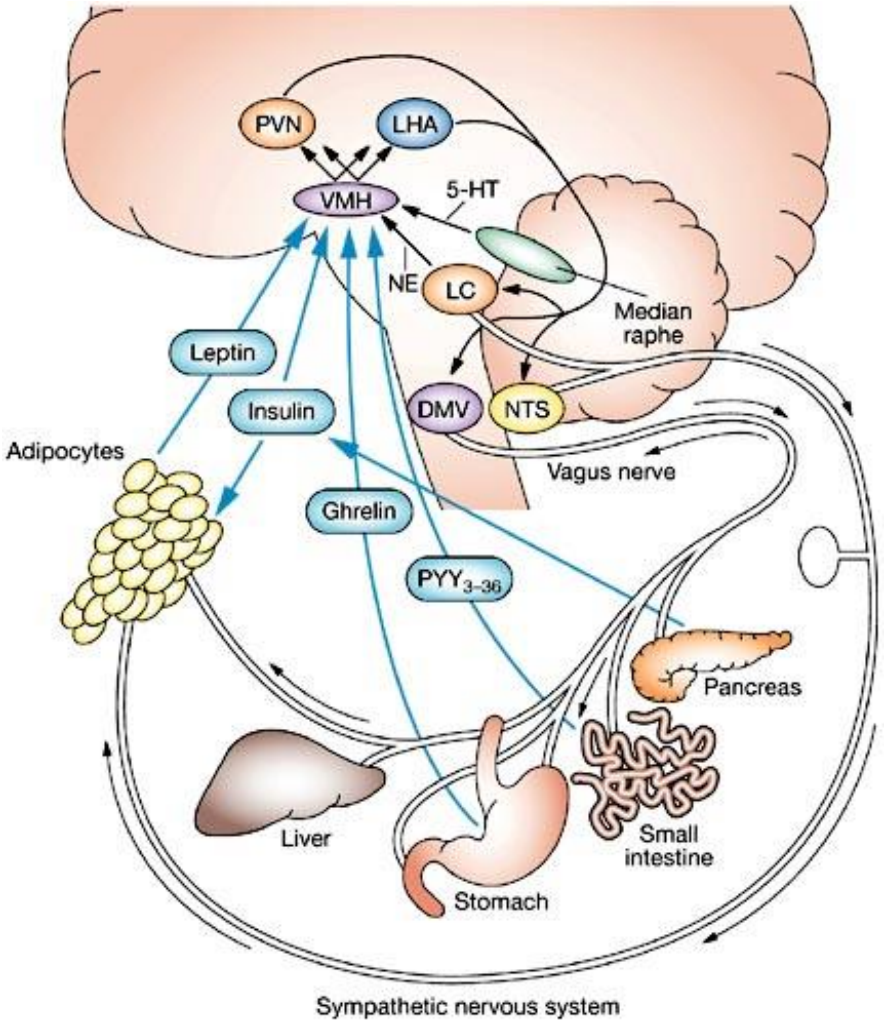
My Daily Intake. Daily Intake Guide. Healthy Eating Made Easy. http://www.mydailyintake.net/energy-in-energy-out/. Accessed January 5, 2015.
Body Recomposition. The Energy Balance Equation. http://www.bodyrecomposition.com/fat-loss/the-energy-balance-equation.html/. Accessed January 5, 2015.

Systems Regulating Energy Intake

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

Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. J Nutr 2009;139:629-32.
Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. Neuron 2002;36:199-211.

Homeostatic "Energy-Based" System



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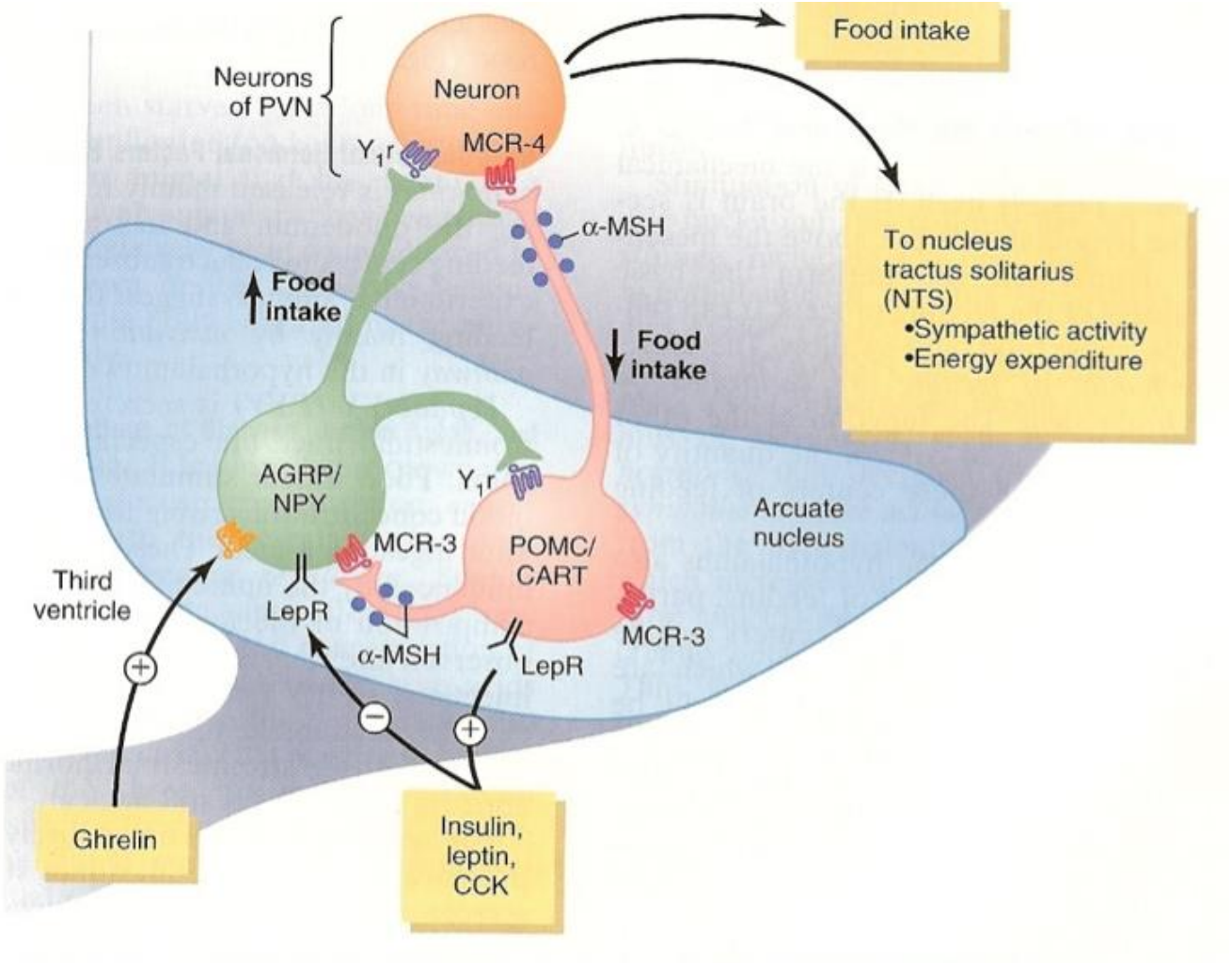
Arcuate Nucleus



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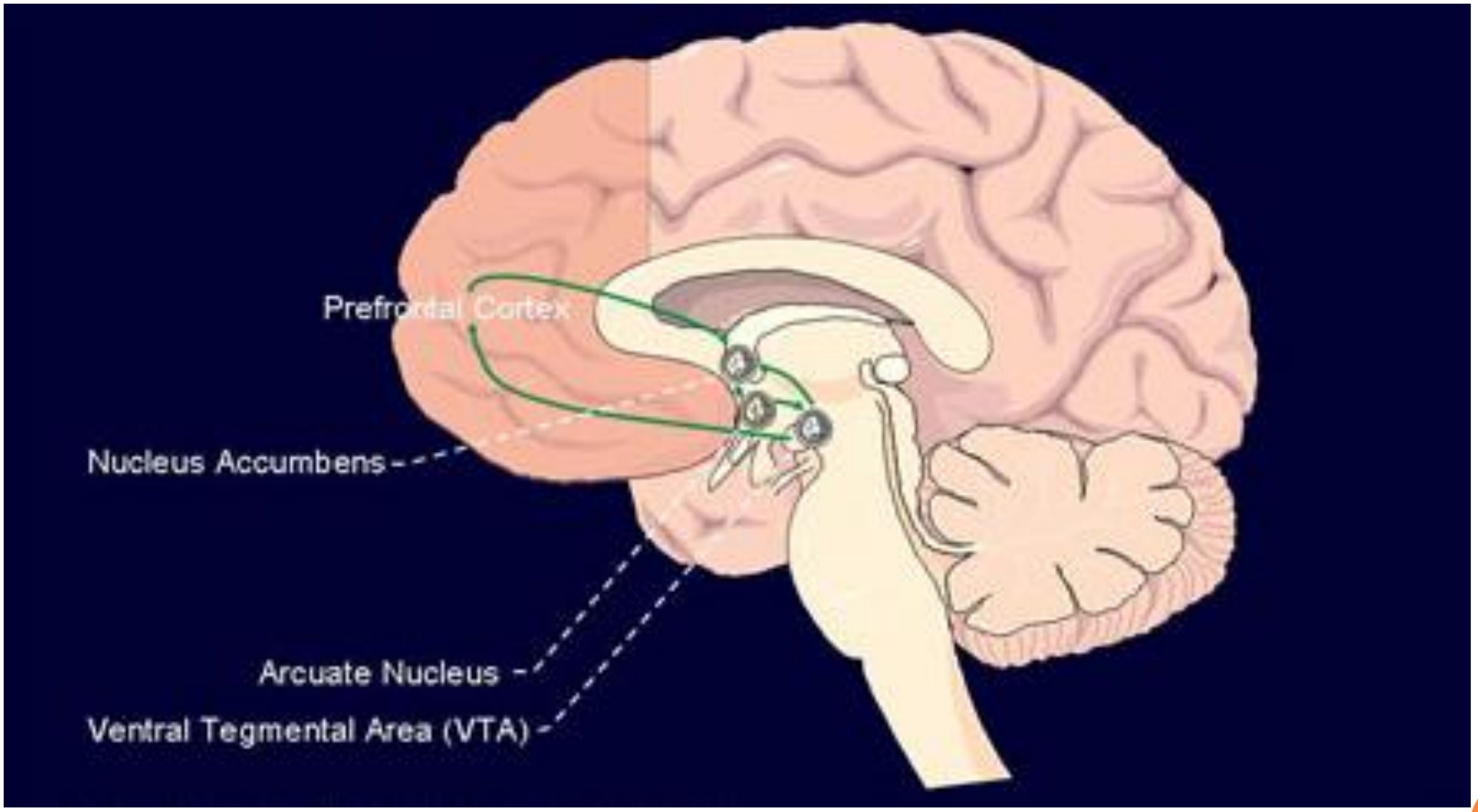
Hedonic “Reward” System



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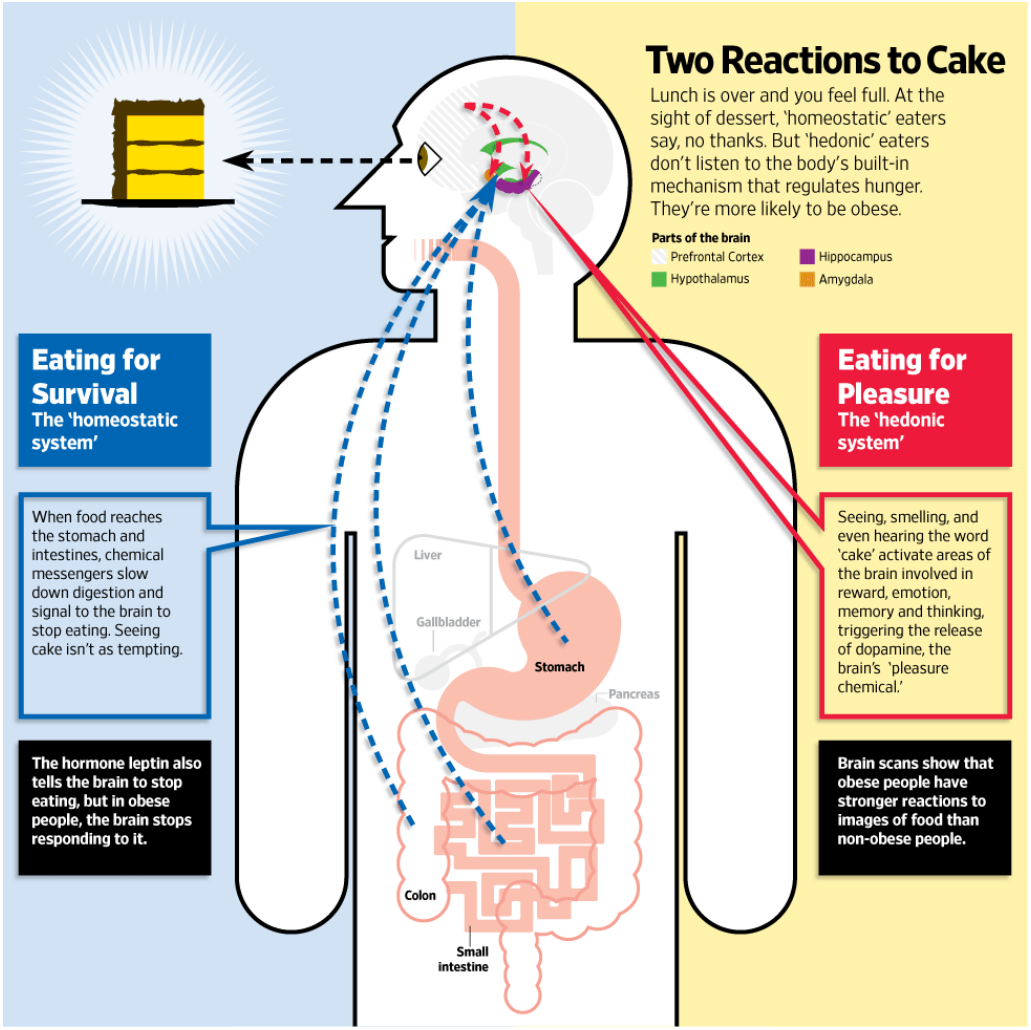
Frontal Executive System



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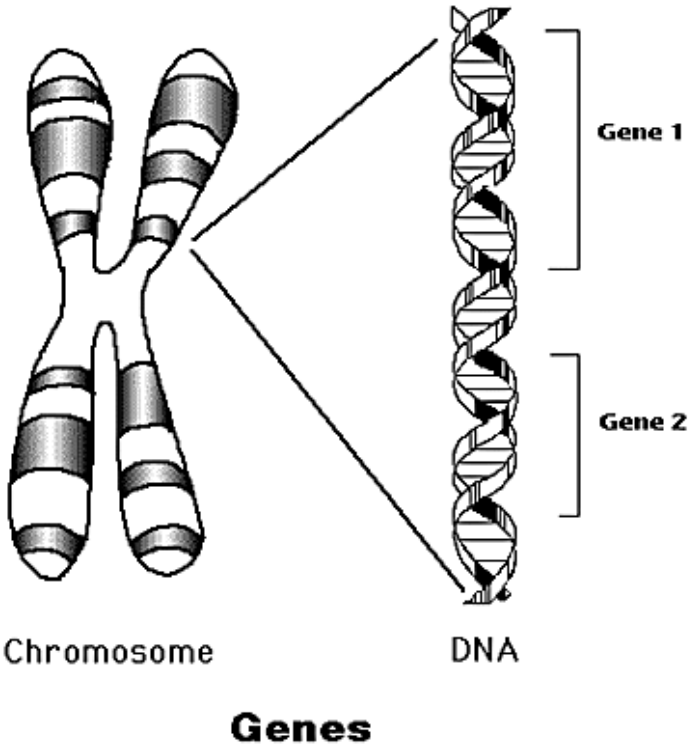
Beck, M. (2010, July 13). Eating to Live or Living to Eat? *Wall Street Journal*. http://www.wsj.com/articles/SB10001424052748704288204575363072381955744. Accessed January 5, 2015.

“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



The National Health Museum. Genes. http://www.accessexcellence.org/RC/VL/GG/genes.php. Accessed January 5, 2015.
Genetics Home Reference. What is a gene? http://ghr.nlm.nih.gov/handbook/basics/gene. Accessed January 5, 2015.

Obesity Related Genes-Prevalence

Obesity Related Genes	Codes for	Site of SNP
FTO	Alpha-ketoglutarate-dependent dioxygenase	rs17817964 rs9939609
PCSK1	Prohormone convertase 1/3 hormone	rs6232 rs6235
MC4R	Melacortin 4 receptor	rs4450508 rs502933
CTNNBL1	Beta-catenin-like protein 1	rs6013029 rs4811196
POMC	Pro-opiomelanocortin	rs6713532 rs1047521 rs3754860
BDNF	Brain derived neurotrophic factor	rs6265

Sherry,S.T., Ward,M. and Sirotkin,K. (1999) dbSNP—Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation. *Genome Res.,* **9**, 677-679.
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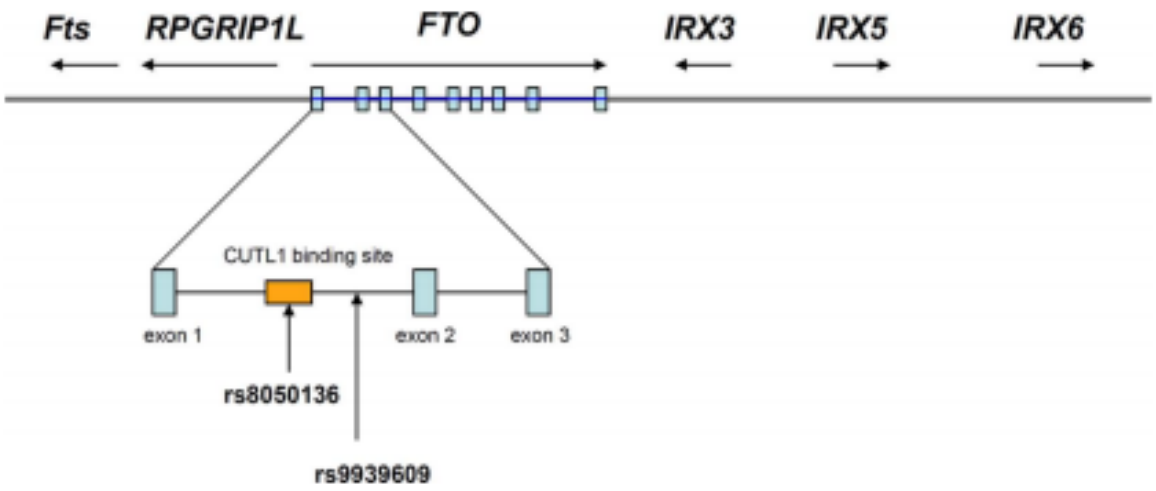
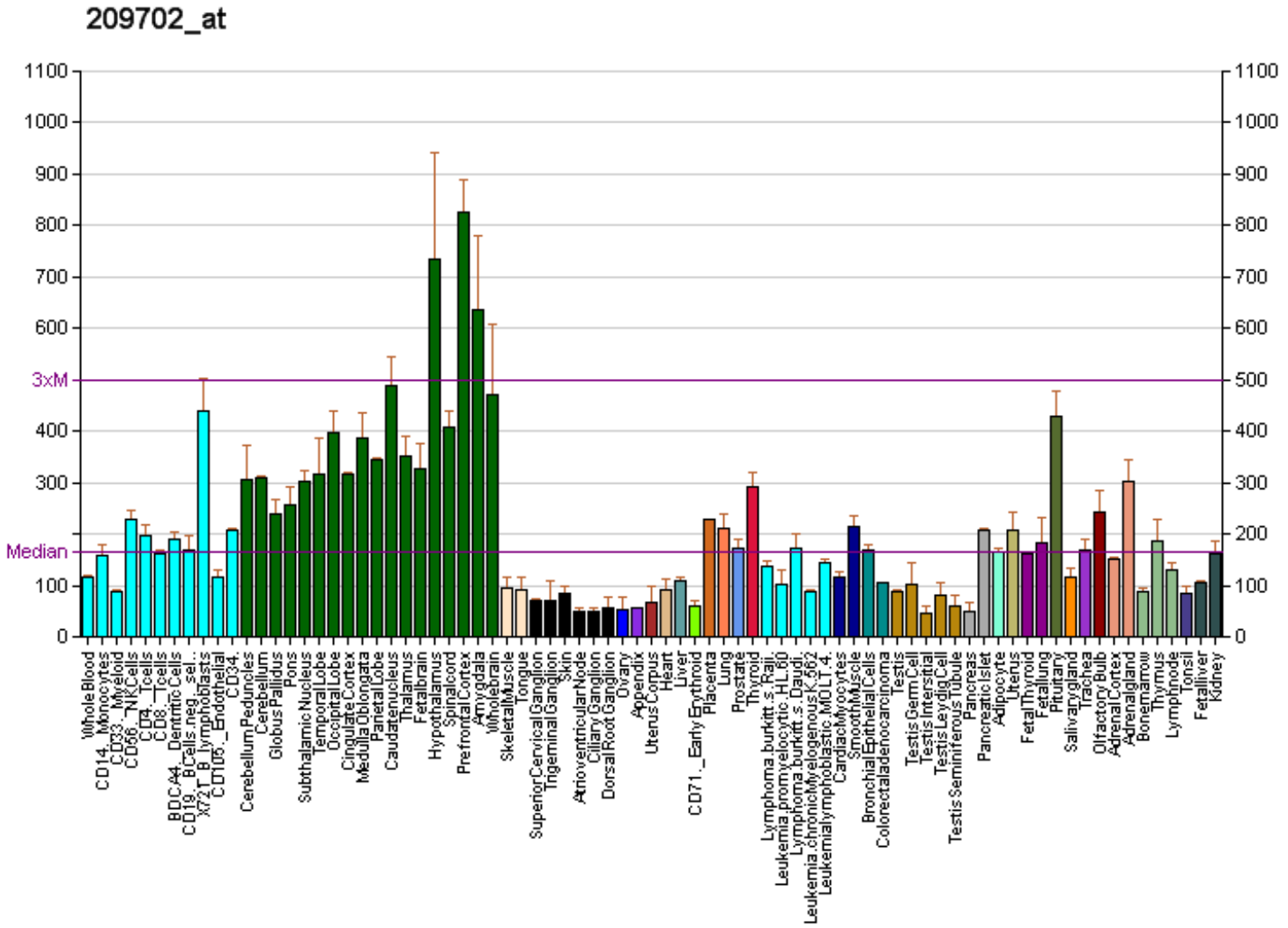
FTO Gene



Cheung MK, Yeo GS. FTO Biology and Obesity: Why Do a Billion of Us Weigh 3 kg More? Front Endocrinol (Lausanne) 2011;2:4.

FTO Gene- Expression



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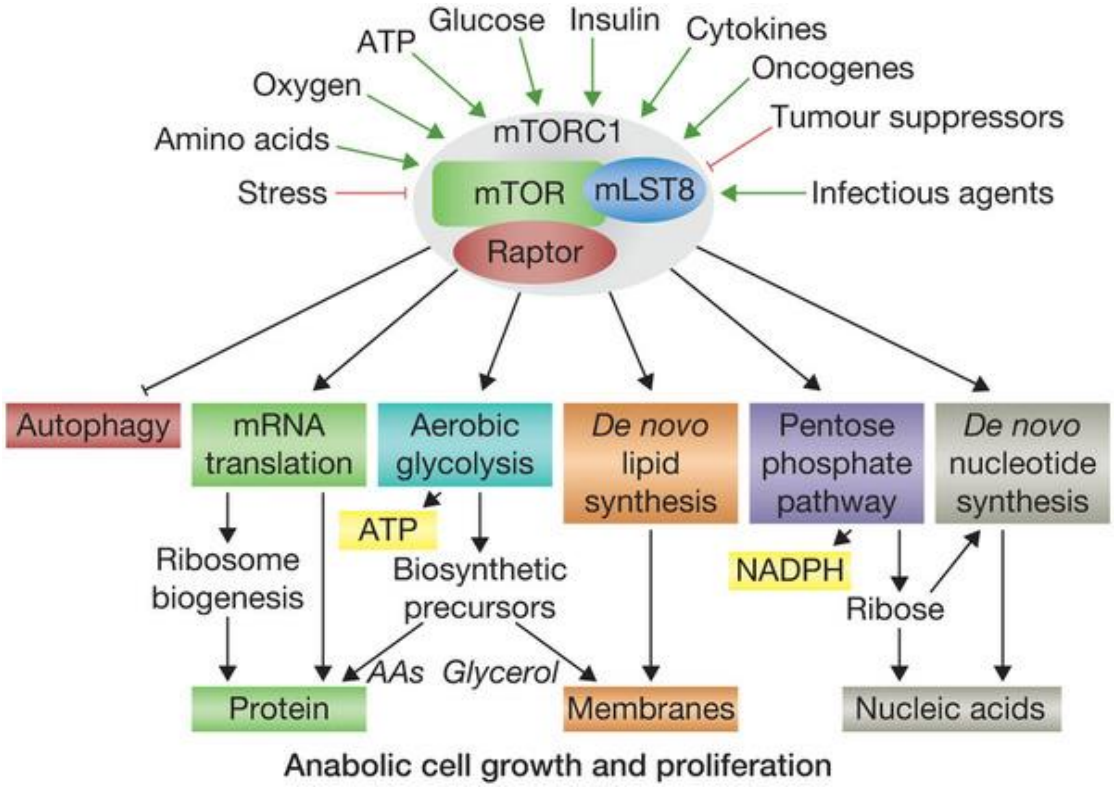
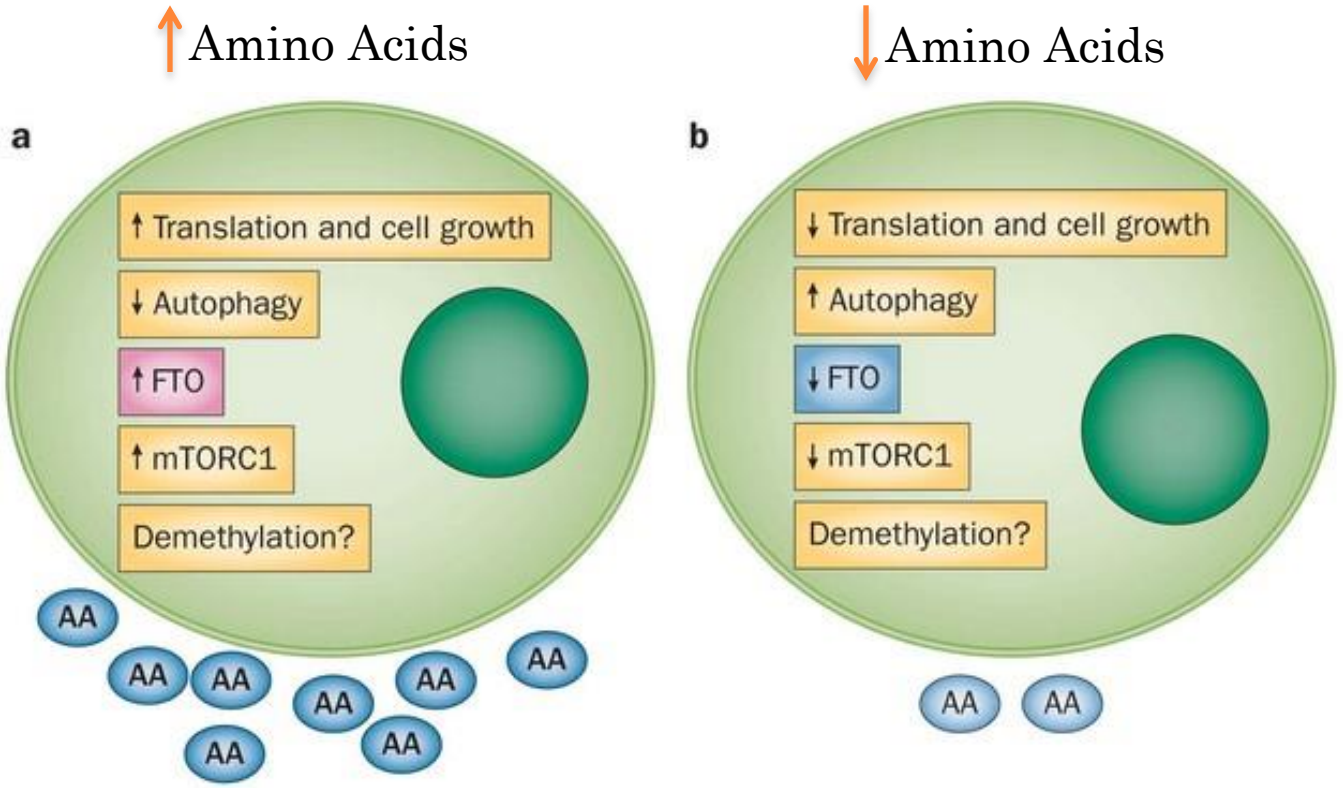
FTO Gene

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



Dibble CC, Manning BD. Signal integration by mTORC1 coordinates nutrient input with biosynthetic output. Nat Cell Biol 2013;15:555-64.
Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. Nat Rev Endocrinol 2014;10:51-61.

FTO Gene- mTOR Pathway



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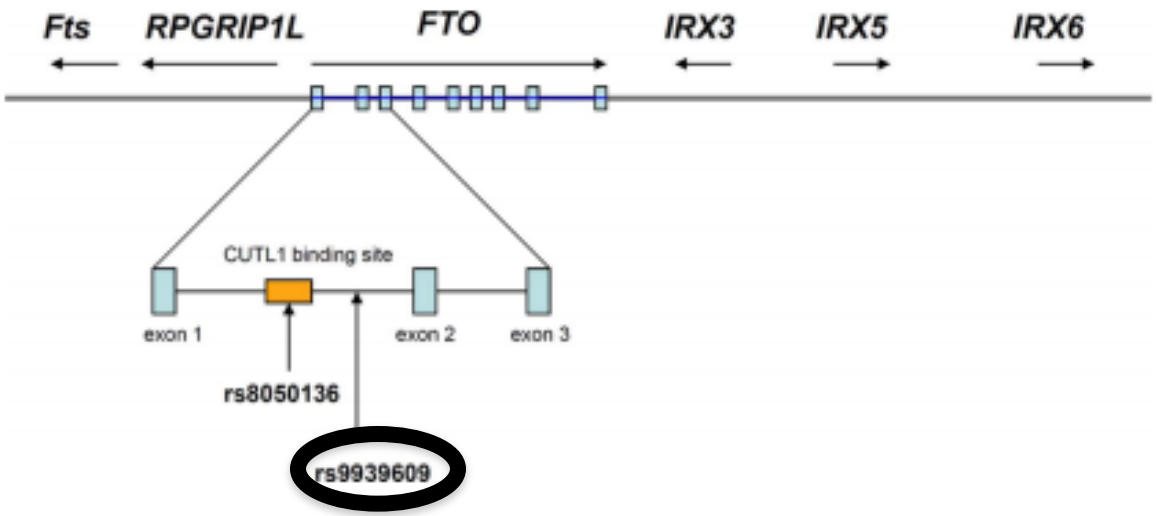
Fischer, Julia. "Inactivation of the FTO Gene Protects from Obesity." *International Weekly Journal of Science*. Nature, 22 Feb. 2002. Web. 25 Feb. 2015.

FTO Gene

- Alphaglutarate-dependent dioxygenase



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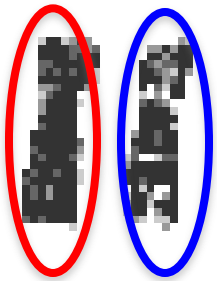
FTO Gene-rs9939609

- SNP
  - A allele=high risk
  - T allele=low risk
- Heterozygous
  - AT
- Homozygous
  - TT, AA



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FTO-Associated with Body Weight

Study	Age, years (mean, SD)	Males (%)	*N*	Mean BMI (95% CI) by genotype			*P*
				TT	AT	AA	
Population-based studies							
Adult							
ALSPAC (mothers)	28.4 (4.7)	0	6376	22.42 (22.28, 22.56)	22.73 (22.61, 22.85)	23.27 (23.03, 23.51)	3×10^{-10}
NFBC1966 (age 31)	31	48	4435	24.12 (23.94, 24.31)	24.43 (24.26, 24.60)	24.82 (24.53, 25.12)	5×10^{-5}
Oxford Biobank	40.6 (6.1)	55	765	25.48 (25.02, 25.94)	25.36 (24.95, 25.78)	26.43 (25.70, 27.17)	0.09
Older adult							
Caerphilly	56.7 (4.5)	100	1328	26.10 (25.80, 26.40)	26.48 (26.20, 26.76)	26.69 (26.11, 27.28)	0.03
EPIC-Norfolk	59.7 (9.0)	47	2425	25.87 (25.63, 26.11)	26.20 (25.99, 26.42)	26.61 (26.22, 27.01)	0.001
BWHHS	68.8 (5.5)	0	3244	26.77 (26.51, 27.02)	27.33 (27.09, 27.56)	27.58 (27.17, 28.00)	0.0002
InCHIANTI	74.3 (6.9)	45	851	26.99 (26.53, 27.47)	26.99 (26.61, 27.37)	27.84 (27.23, 28.46)	0.06
Combined population studies (I^2)							2×10^{-20} (0%)
Combined population and control studies (I^2)							1×10^{-25} (0%)
All studies (I^2)							3×10^{-35} (0%)

- Each A allele associated with mean BMI increase of 0.36 kg/m^2
- AA weigh ~3 kg more, AT weigh ~1.5 kg more than TT individuals

Frayling TM. Timpson NJ. A Common Variant in the FTO Gene is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. Science. (2007)

Link between FTO, ghrelin, and impaired brain food-cue responsivity

Karra et al.

Karra E, O'Daly OG, Choudhury AI, Yousseif A, Millership S, Neary MT, Scott WR, Chandarana K, Manning S, Hess ME, et al. A link between FTO, ghrelin, and impaired brain food-cue responsivity. J Clin Invest 2013;123:3539-51.

Study Purpose

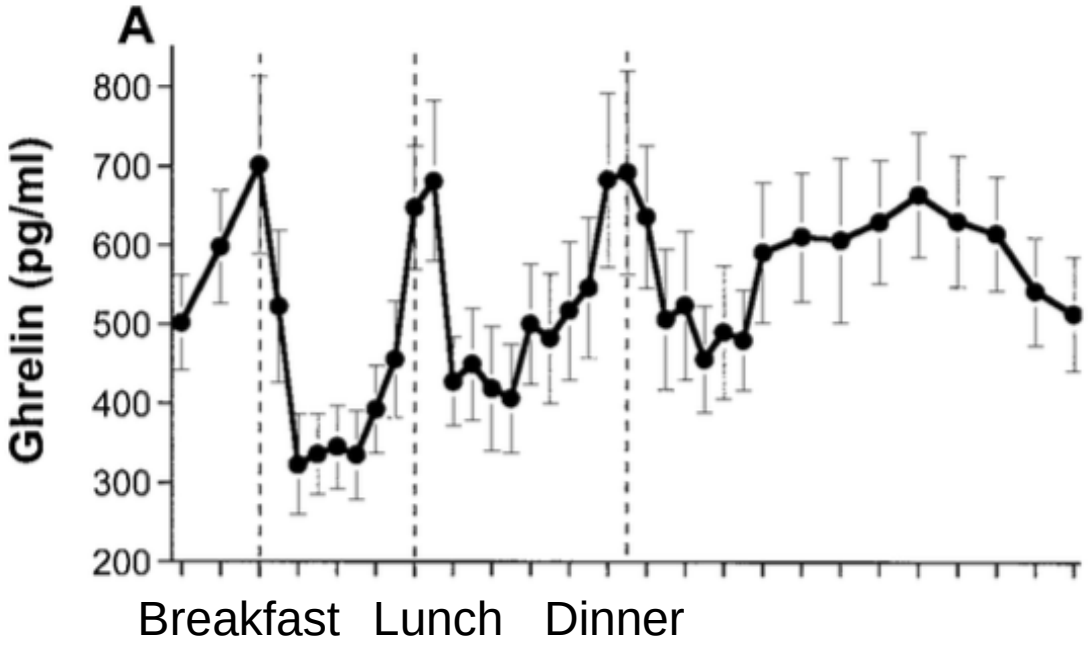
- Determine the mechanisms responsible for increased energy intake in those with an *FTO* genotype associated with obesity (rs9939609-AA)
  - AA="High Risk"
  - TT="Low Risk"

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

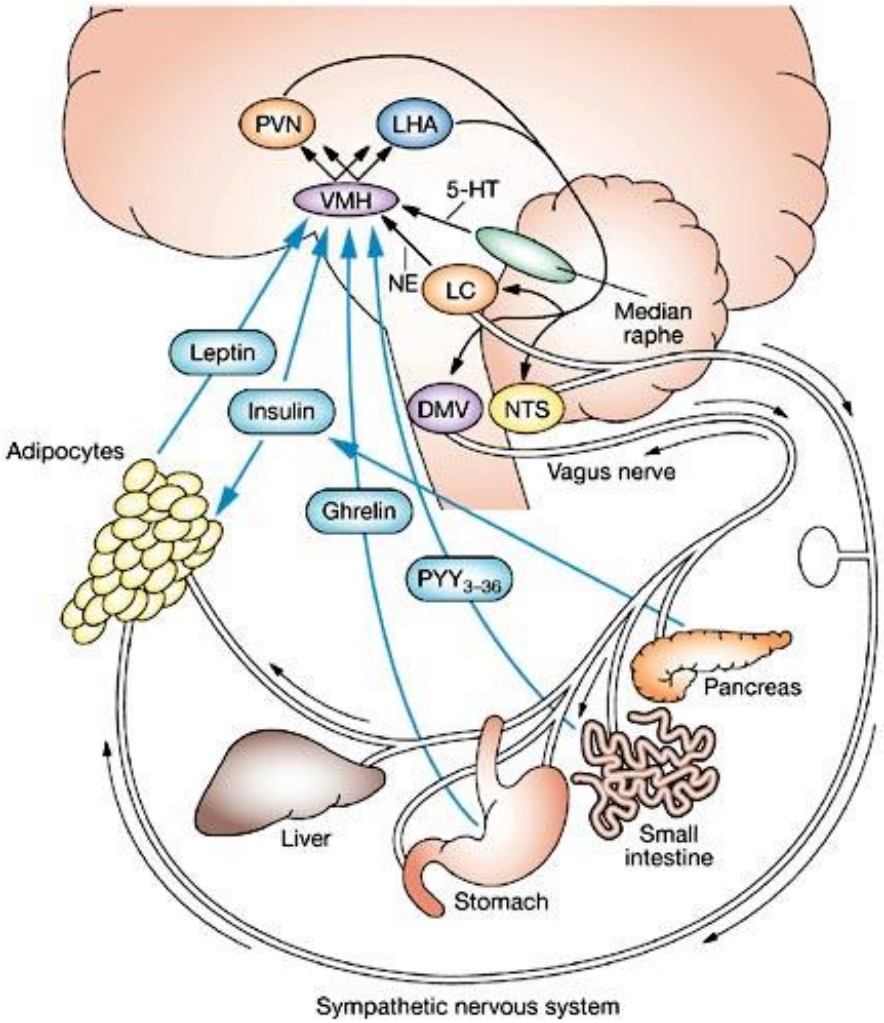
Ghrelin and Acyl Ghrelin

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



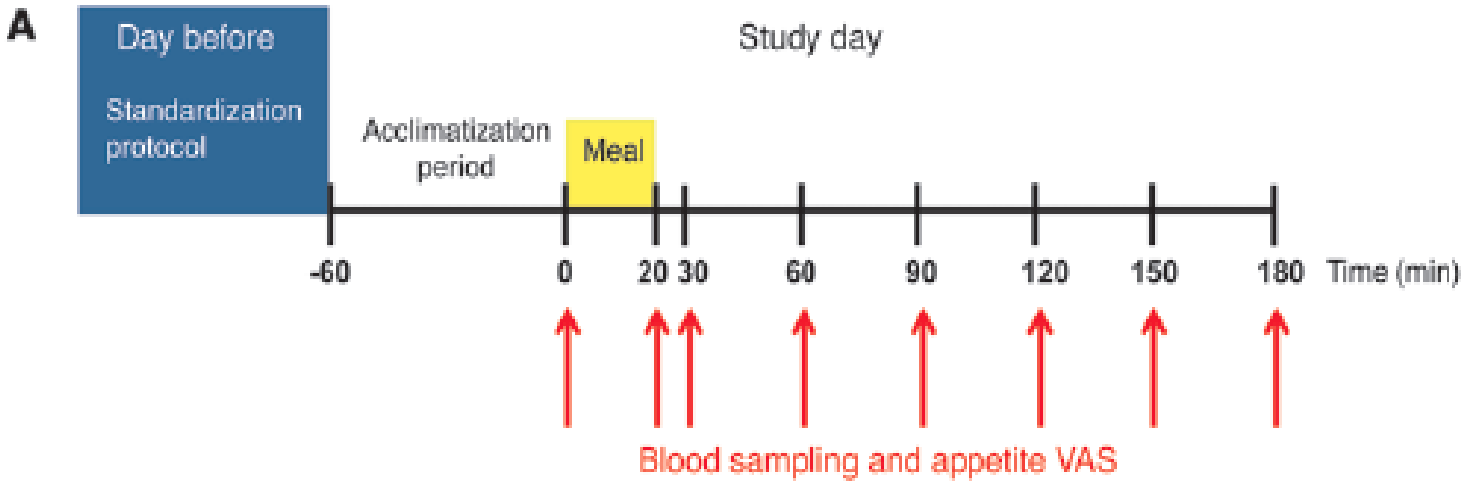
Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. Diabetes 2001;50:1714-9.
Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JQ.. N Engl J Med 2002;346:1623-30.
Sharifi F, Yamini M, Esmaeilzadeh A, Mousavinasab N, Shajari Z. J Diabetes Metab Disord 2013;12:51,6581-12-51.

Homeostatic "Energy-Based" System



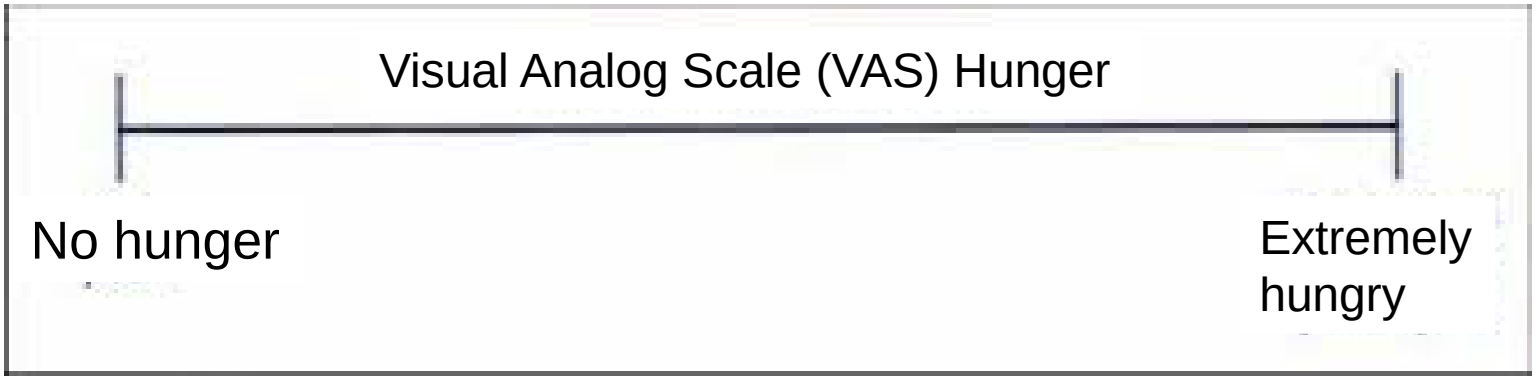
Appetite and Circulating ghrelin

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



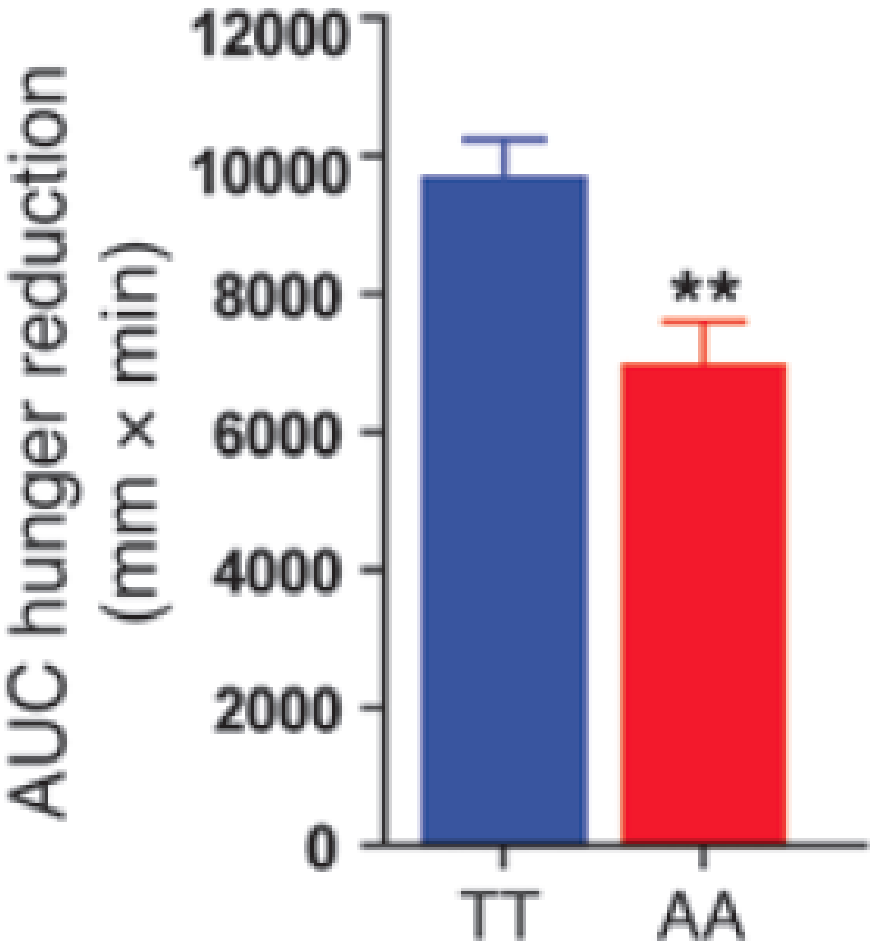
Appetite and Circulating ghrelin

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



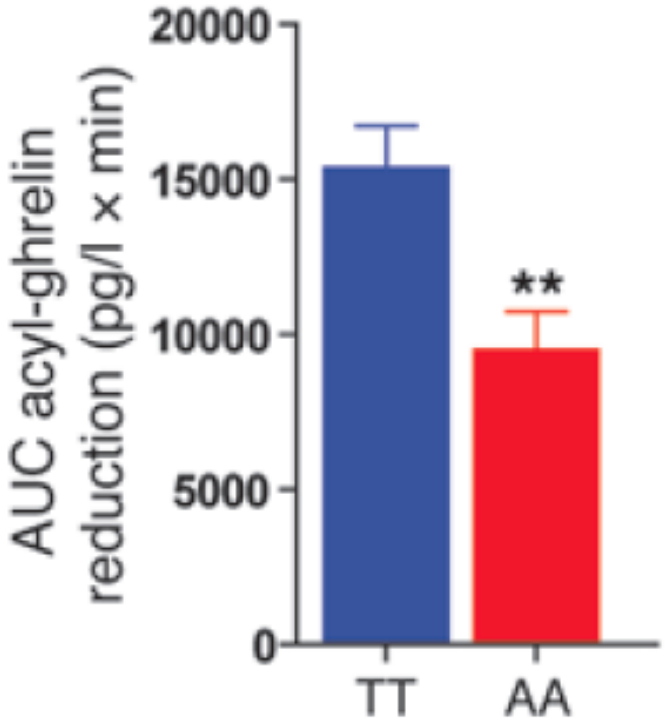
- Blood work measured circulating PYY3-36 and leptin (satiety hormones) and acyl-ghrelin (orexigenic hormone)

Figure 1. AUC Hunger Reduction



- Hunger reduced less in AA than TT subjects
- (TT = 9671 ± 566, AA = 6957 ± 641, P = 0.003)

Figure 2. AUC acyl ghrelin reduction (pg/L x min)

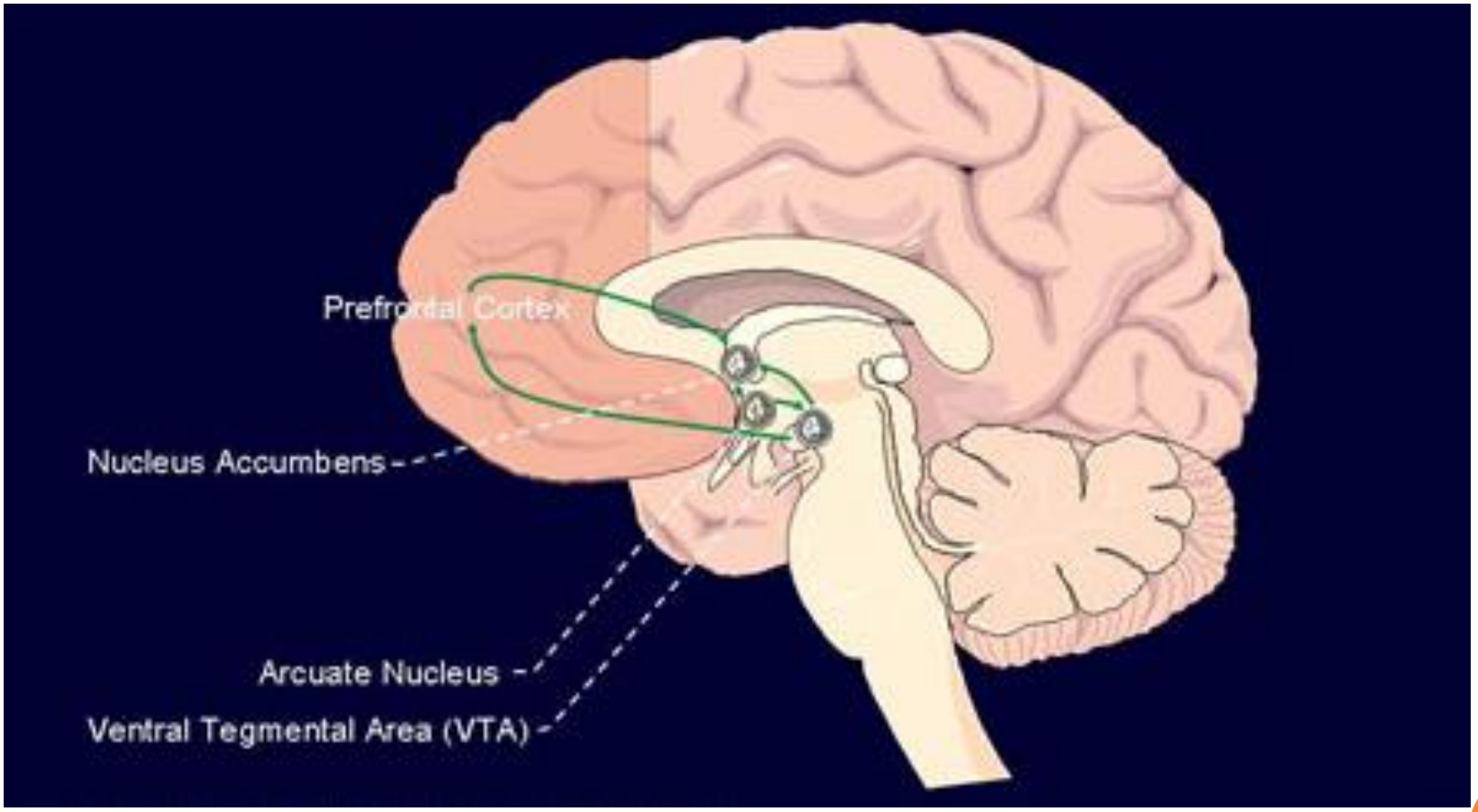


- No difference in fasting acyl-ghrelin concentrations between AA and TT
- Less post-prandial suppression of acyl-ghrelin in AA subjects
- (TT = 15298 ± 1408, AA = 9439 ± 1291, P=0.002)

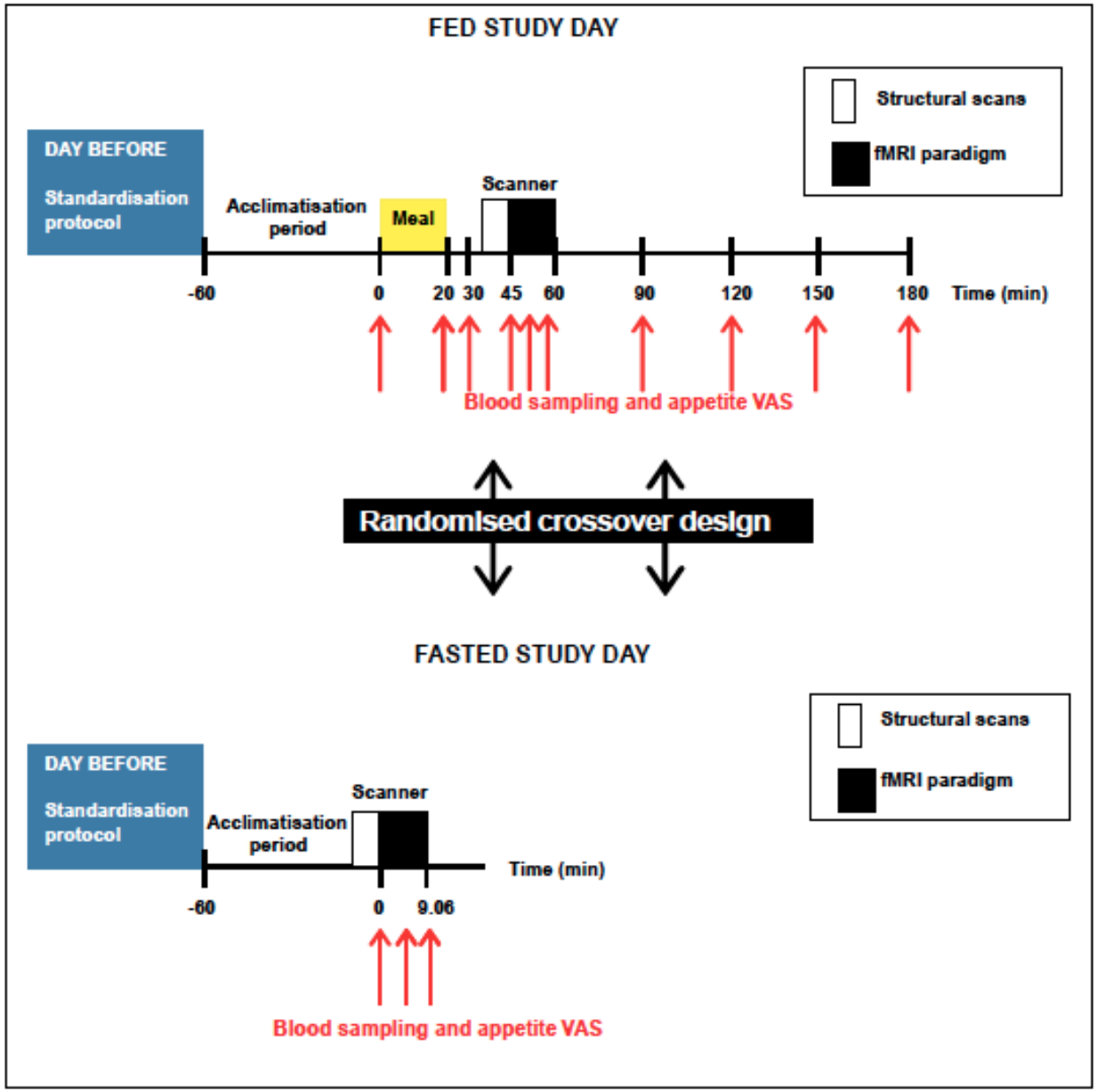
Conclusion: Homeostatic system

- 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.

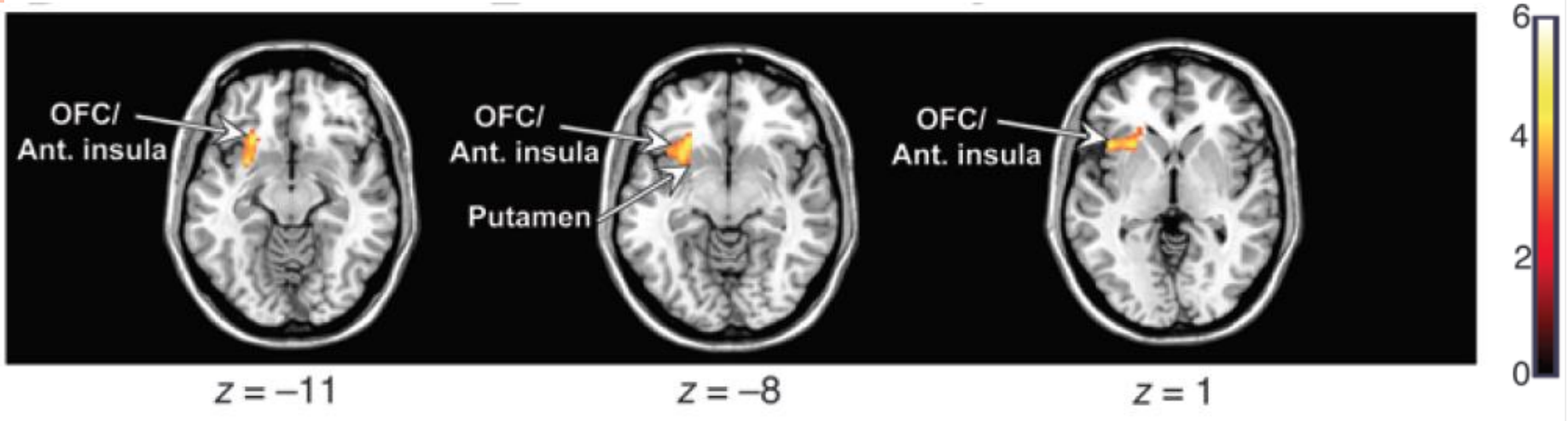
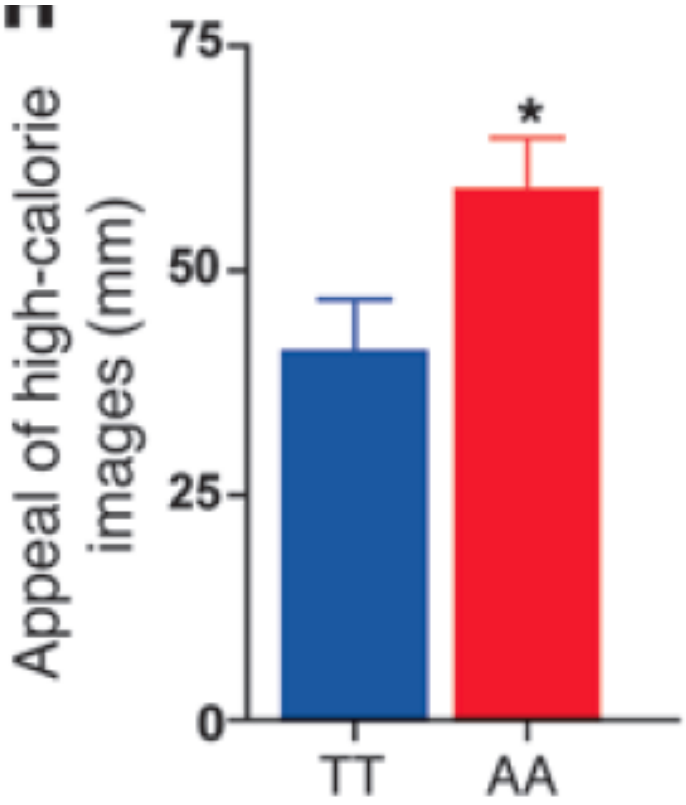


Figure 3. Appeal of high calorie images)



- High calorie foods significantly more appealing to AA than TT ($p<0.05$)

Figure 4. High calorie vs. low calorie image BOLD response

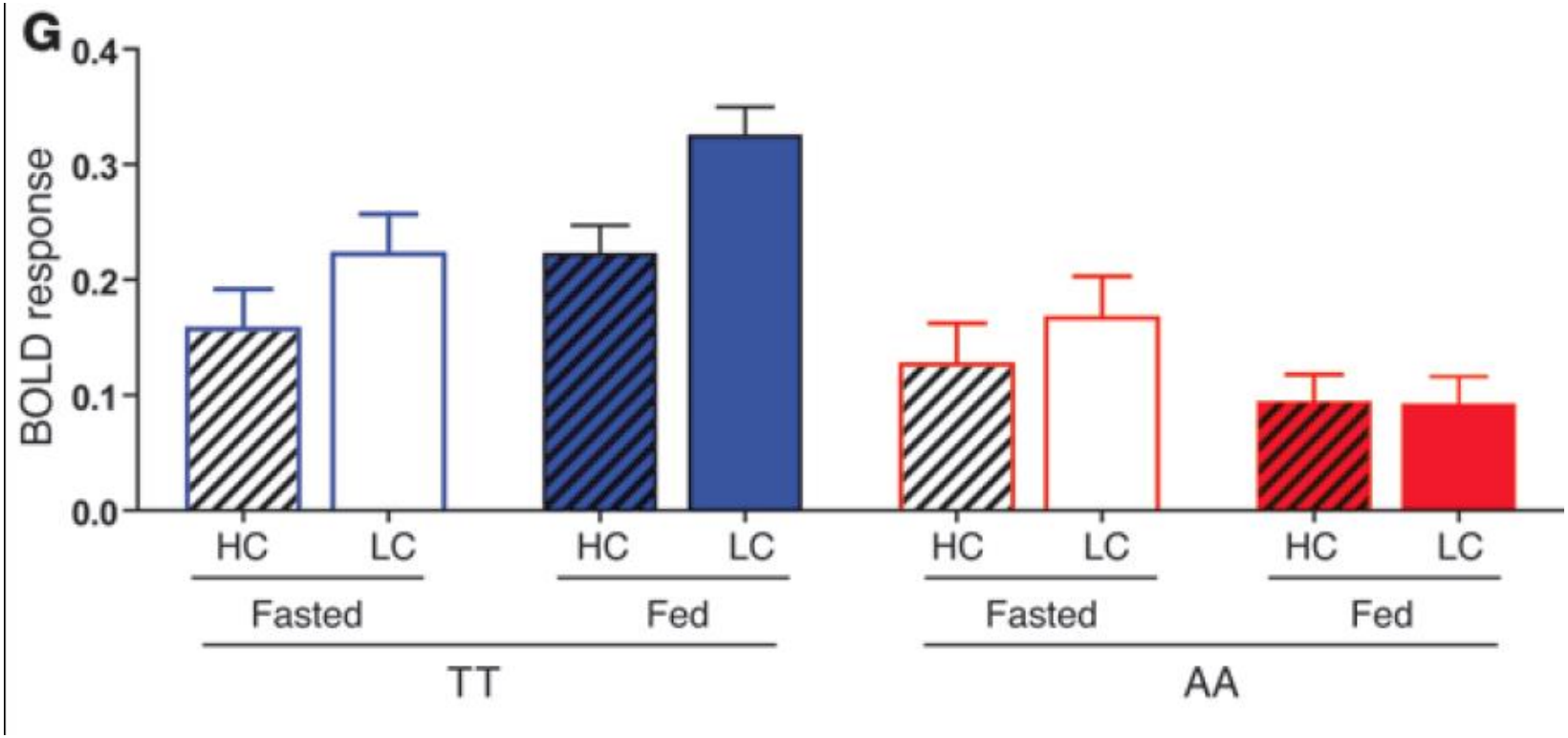
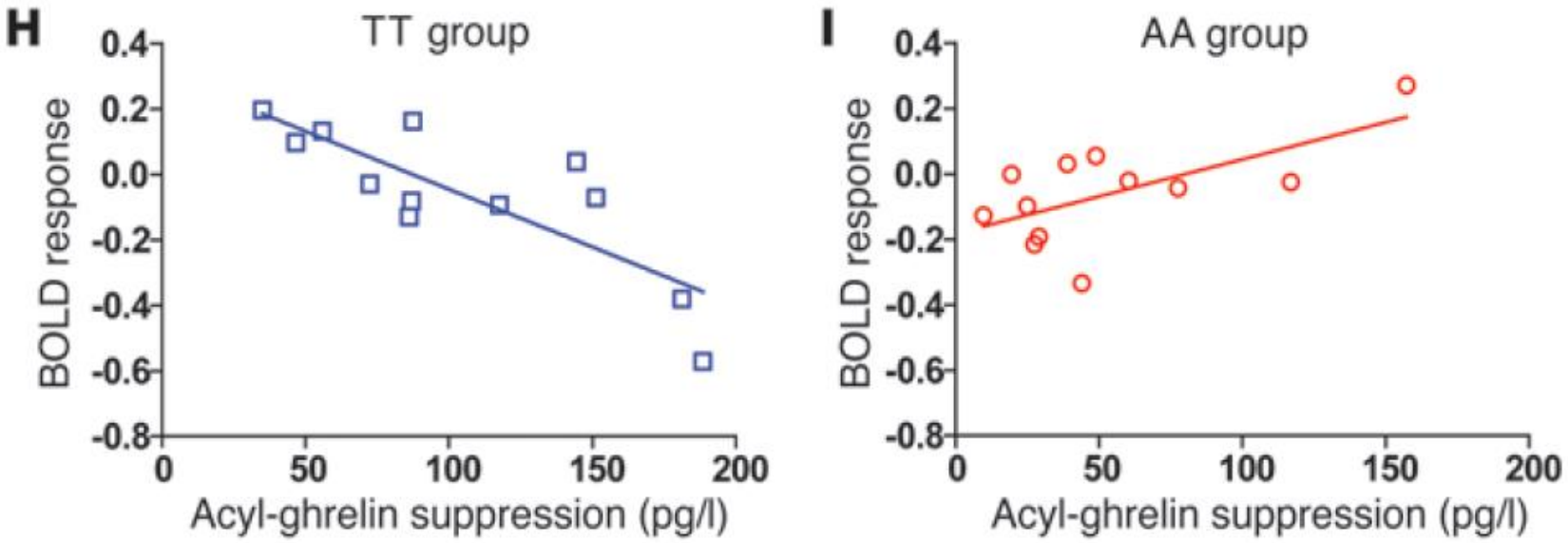


Figure 5: BOLD response in hedonic system vs. post-prandial acyl-ghrelin suppression



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

	Low Fat (20%)	High Fat (40%)
Low Protein (15%)	Fat: 20% Protein: 15% CHO: 65%	Fat: 40% Protein: 15% CHO: 45%
High Protein (25%)	Fat: 20% Protein: 25% CHO: 55%	Fat: 40% Protein: 25% CHO: 35%

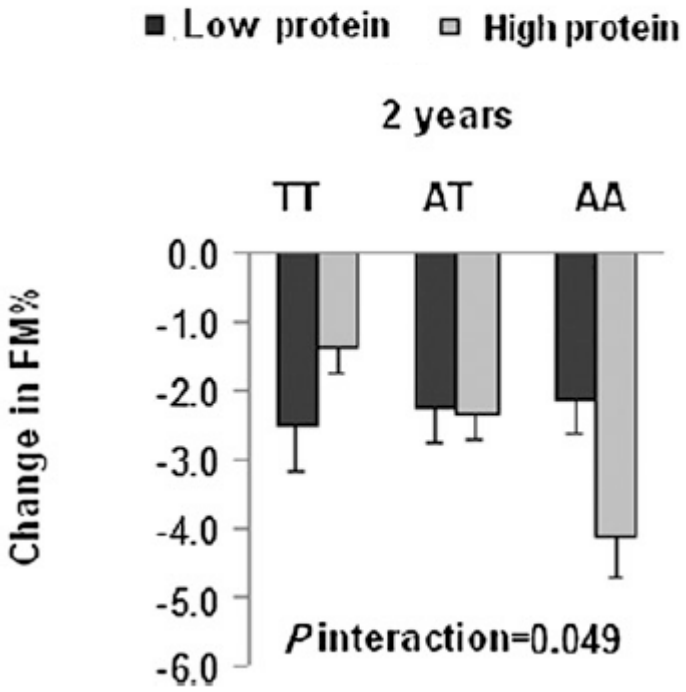
Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859-73.
Zhang X, Qi Q, Zhang C, Smith SR, Hu FB, Sacks FM, Bray GA, Qi L. FTO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST Trial. Diabetes 2012;61:3005-11.

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

Zhang X, Qi Q, Zhang C, Smith SR, Hu FB, Sacks FM, Bray GA, Qi L. FTO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST Trial. Diabetes 2012;61:3005-11.

Decrease in Fat Mass Percentage (n=224)



- Significant decrease in fat mass percentage in high protein group

Zhang X, Qi Q, Zhang C, Smith SR, Hu FB, Sacks FM, Bray GA, Qi L. FTO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST Trial. Diabetes 2012;61:3005-11.

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

Zhang X, Qi Q, Zhang C, Smith SR, Hu FB, Sacks FM, Bray GA, Qi L. Diabetes 2012;61:3005-11.
Muller TD, Hinney A, Scherag A, Nguyen TT, Schreiner F, Schafer H, Hebebrand J, Roth CL, Reinehr T. BMC Med Genet 2008;9:85,2350-9-85.
Razquin C, Martinez JA, Martinez-Gonzalez MA, Bes-Rastrollo M, Fernandez-Crehuet J, Marti A.. Int J Obes (Lond) 2010;34:266-72.

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?

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