Workshop
The Omics of Eating Behaviors
December 9, 2010

The genetics of eating behaviors and dietary choices

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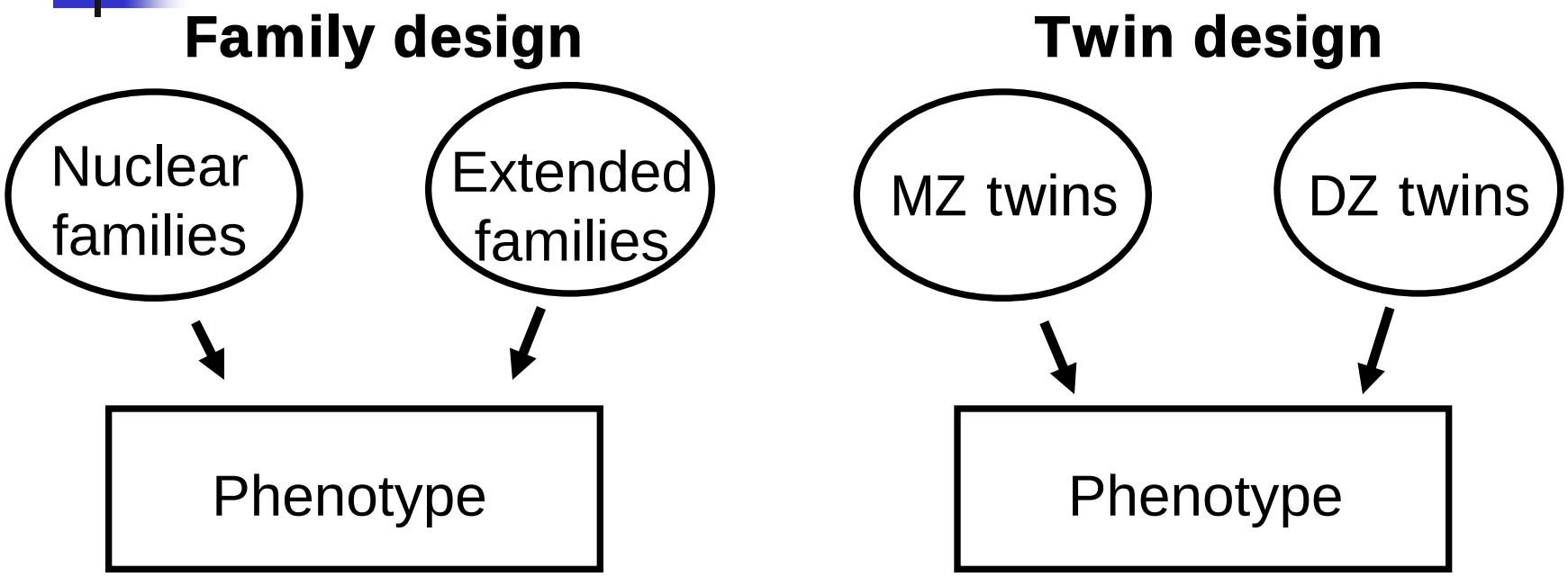
Outline of the presentation

- Phenotypes under review:
  - Energy and macronutrient intakes, food preferences, eating patterns
  - Normal eating behaviors: hunger, disinhibition, restriction, satiation, meal size, meal frequency.
- Familial aggregation and heritability
- Genetic determinants
  - Genes affecting dietary intakes and eating behaviors

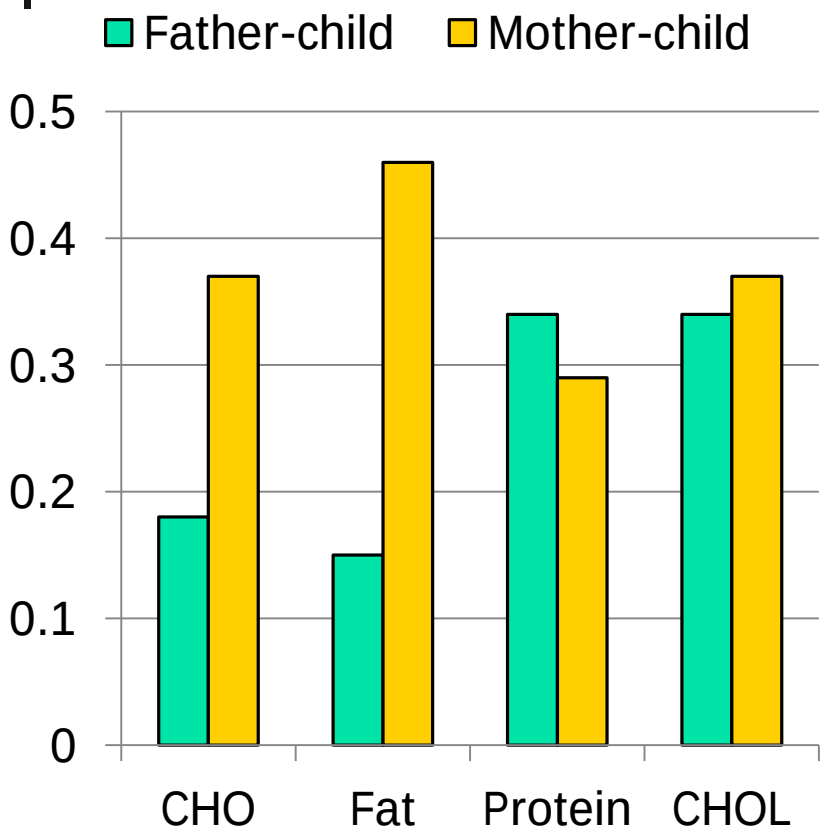
Testing genetic foundations of eating-related behaviours

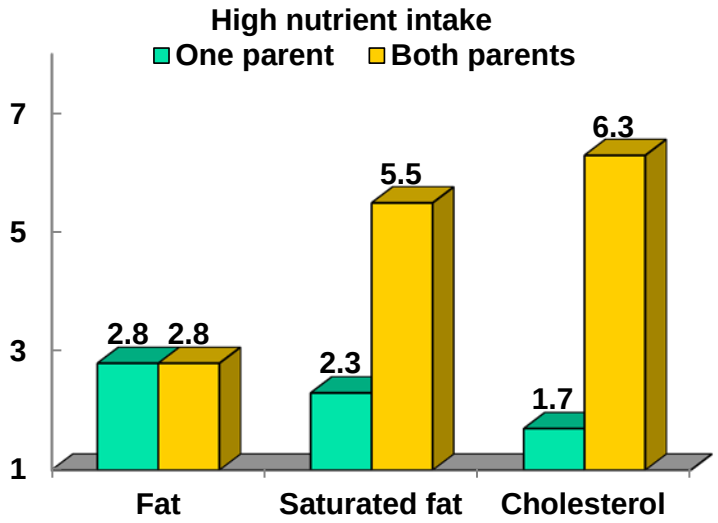


- Familial correlations
- Heritability (h^2)
- Transmission (t^2)

- $h^2 = 2 (r_{MZ} – r_{DZ})$
- Equal shared environment in MZ and DZ twins
- Upper estimate of h^2

Familial resemblance in nutrient intake: the Framingham children's study





- 9-day dietary record of parents and their children aged 3-5 yrs.
- Odds ratio estimates of effect of parents' nutrient intake on child's nutrient intake.
- High vs low nutrient intakes based on the median value of the distribution.

From Oliveria et al., Am. J. Clin.Nutr., 1992.

Parent–child dietary intake resemblance in the United States: Evidence from a large representative survey

May A. Beydoun [a,b], Youfa Wang [a,*]

	P-C (n=4244)	F-S (n = 982)	F-D (n = 978)	M-S (n=1156)	M-D (n=1128)
Energy (kcal/d)	0,22	0,29	0,14	0,23	0,26
Fat (g/d)	0,24	0,27	0,18	0,28	0,24
Saturated fat (g/d)	0,23	0,21	0,20	0,28	0,24
Cholesterol (mg/d)	0,30	0,32	0,20	0,47	0,31
Fiber (g/d)	0,26	0,31	0,18	0,33	0,25
Fruits & Veg (g/d)	0,29	0,29	0,21	0,31	0,37
HEIn	0,26	0,29	0,28	0,28	0,18

Data from 2,291 parents (aged 20-65 years) and 2,692 children (2-18 years) collected by the USDA.
Data adjusted for age, gender, child's BMI, physical activity, ethnicity, family income, education level, smoking status, self-rated health, geographical region, urbanization.
HEIn = 2005 Healthy Eating Index: sum of scores on 12 components covering dietary recommendations in terms of nutrient and food group intakes. Index of the overall quality of the diet .

From Beydoun and Wang, Social Sci. Med. 68:2137-44, 2009

Do children and their parents eat a similar diet? Resemblance in child and parental dietary intake: systematic review and meta-analysis

Y Wang,[1] M A Beydoun,[1,2] J Li,[1] Y Liu,[1] L A Moreno[3]

- PubMed search for studies:
  - Published between 01/01/1980 – 09/31/2009
  - Key words: family, parent, mother, father, child adolescent, diet, food.
- 24 studies met inclusion criteria, 15 used for analysis:
  - Most reported correlations for intakes of total energy and fat
  - The 15 studies provided a total of 117 data points.
- Weak to moderate correlations:
  - Total energy: 0.21 (95% CI 0.18 to 0.24)
  - Total fat: 0.25 (0.21 to 0.29)
  - Correlations varied by parent-child pairs, nutrient, dietary assessment method (lower for FFQ), age of children and country (weaker in the US).

From Wang et al, J Epidemiol Commun Health, ePub, November 4, 2010.

Familial correlations for energy and macronutrient intakes

Variable	Siblings by adoption (115)[a]	Foster parent–adopted child (314)	Spouses (339)	Parent–offspring (1212)	Siblings (361)	DZ twins (59)	MZ twins (59)
Energy intake (kcal/kg day)	0.21	0.29[b]	0.31[b]	0.26[b]	0.30[b]	0.58[b]	0.69[b]
Carbohydrate (% energy)	0.21[c]	0.08	0.50[b]	0.29[b]	0.37[b]	0.49[b]	0.70[b]
Fat (% energy)	0.04	0.18[b]	0.45[b]	0.31[b]	0.36[b]	0.59[b]	0.61[b]
Protein (% energy)	0.22[c]	0.22[b]	0.28[b]	0.27[b]	0.38[b]	0.55[b]	0.71[b]

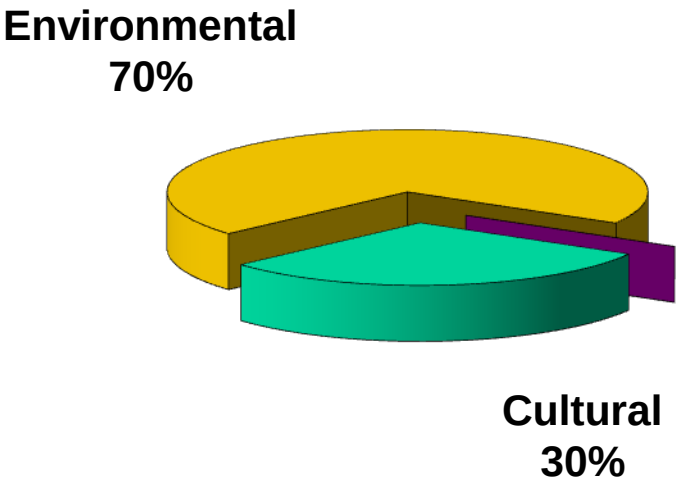
[a]Number of pairs in parentheses.

[b]$p < 0.01$.

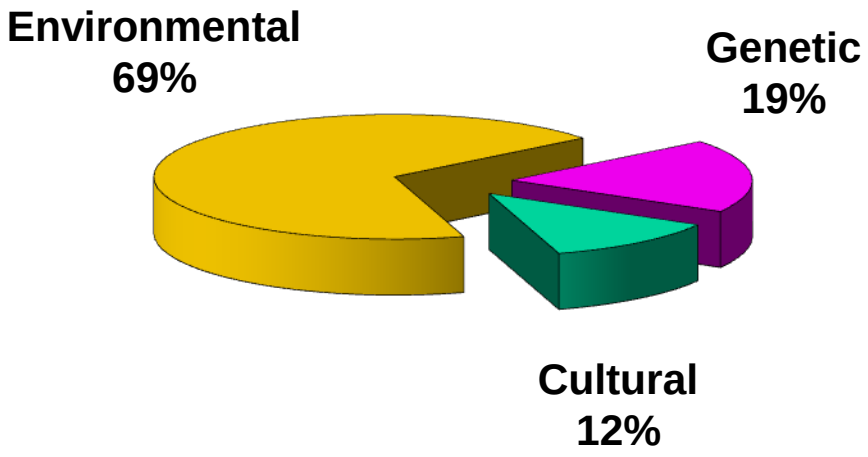
[c]$p < 0.05$.

From Pérusse et al., Am. J. Clin. Nutr. 47:629-635,1988

Genetic effects on energy intake and fat intake



Energy intake / kg



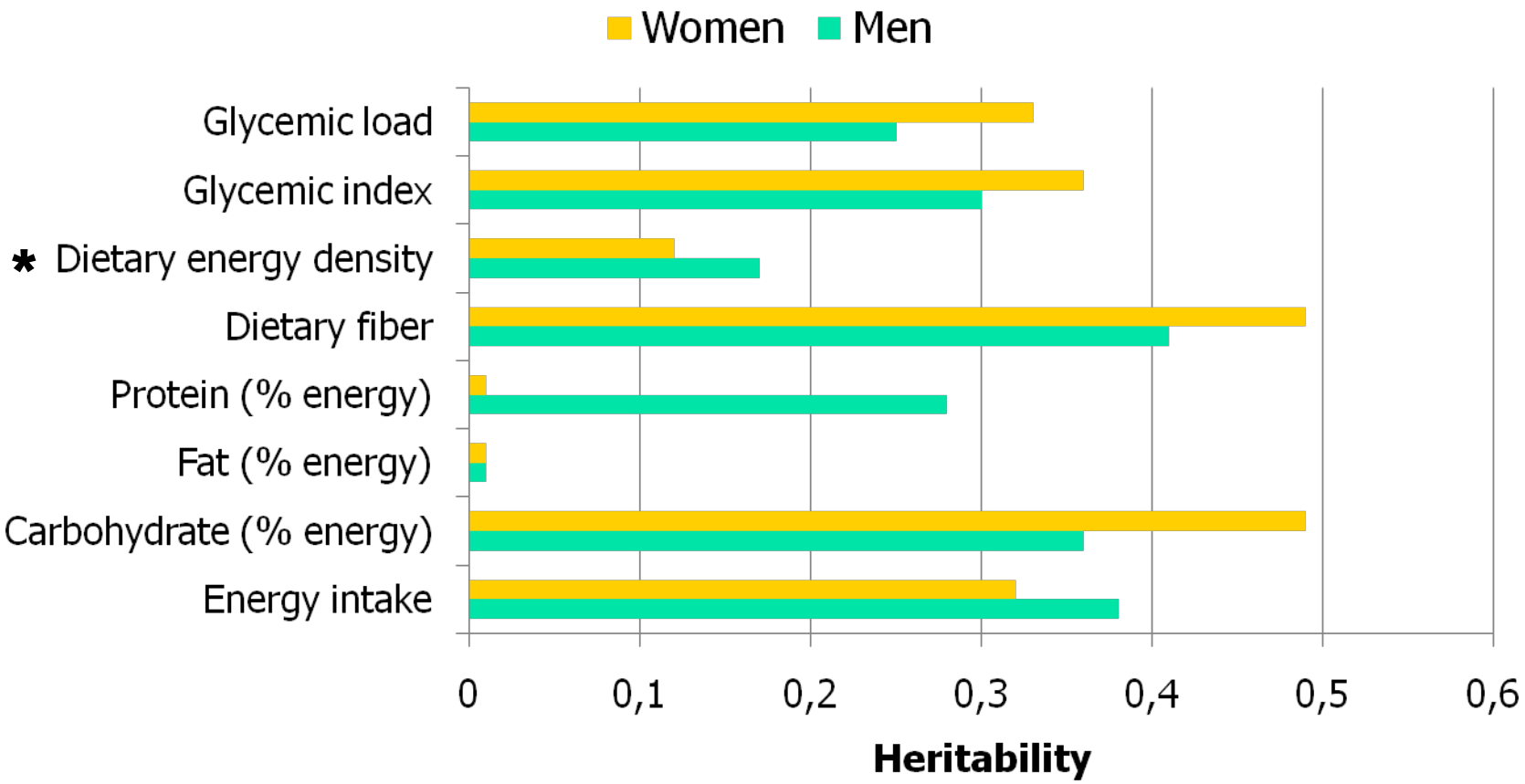
% Fat intake

Assessed from a 3-day dietary record in 1,597 subjects from 375 families using 9 types of relatives by descent or adoption

From Pérusse et al., Am. J. Clin. Nutr. 47:629-635,1988.

Studies of Twins Indicate That Genetics Influence Dietary Intake[1,2]

Ann Louise Hasselbalch,[3]* Berit L. Heitmann,[4] Kirsten O. Kyvik,[5] and Thorkild I. A. Sørensen[3]



Based on 600 male and female twin pairs aged 18 to 67 years.
* Evidence of shared family environment

Hasselbaclch et al., J. Nutr. 138:2406-12, 2008

Studies of Twins Indicate That Genetics Influence Dietary Intake[1,2]

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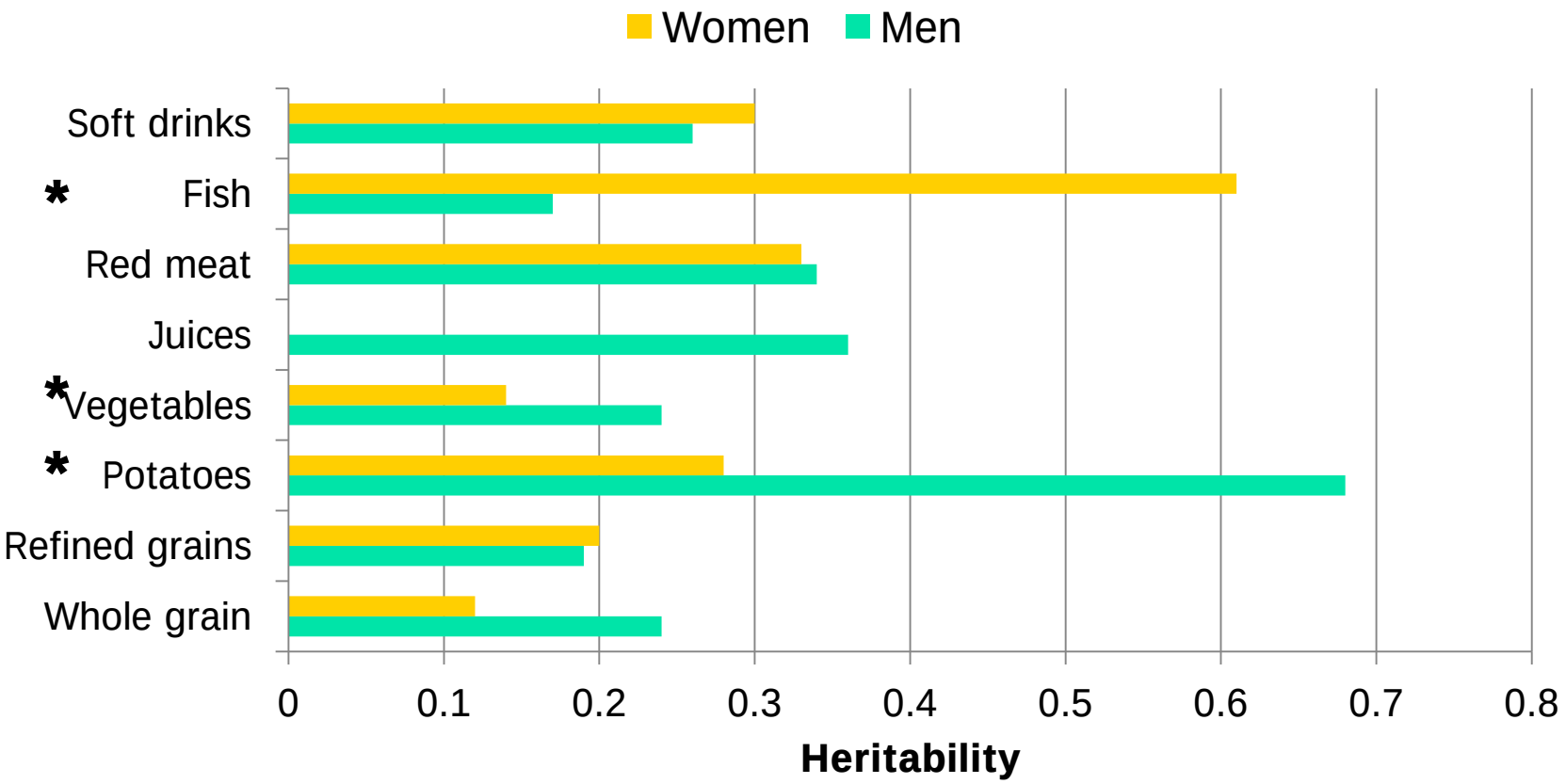
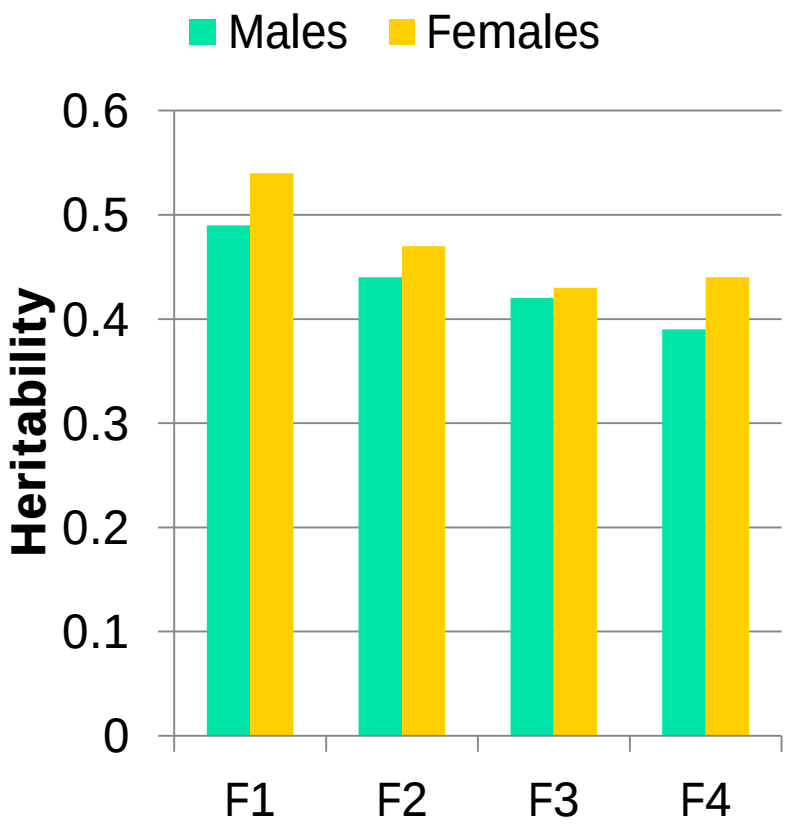


Food groups are adjusted for total energy intake

* Food groups influenced by shared familial environment

Hasselbaclch et al., J. Nutr. 138:2406-12, 2008

Genetic and environmental contributions to food use patterns of young adult twins



- Population-based cohort of young (22-27 yrs) male and female twins:
  - 663 MZ twin pairs
  - 1346 DZ twin pairs
- Evaluation of use-frequencies of 24 food items by postal questionnaire:
  - 1 (never) to 5 (several times/day)
  - h^2 = 0,22 to 0,54
- Factor analysis of food items:
  - F1 = Healthy foods
  - F2 = High-fat foods
  - F3 = Sweet foods
  - F4 = Meat
- No shared familial environment

From Keskitalo et al., Physiol. Behav. 93:235-42, 2008

Eating behaviours in humans

- Three-Factor Eating Questionnaire: 51-items questionnaire.
- Cognitive dietary restraint (21 items):
  - Tendency to conciously restrict food intake control body weight.
  - Q; I conciously hold back at meals in order to not gain weight.
- Disinhibition (16 items):
  - tendency to overeat in response to a variety of disinhibiting stimuli such as social events or emotional stress
  - Q: I usually eat to much at social occasions, like parties or picnics.
- Susceptibility to hunger (14 items):
  - refers to the desire to eat in response to the feelings of hunger percieved by the body.
  - Q: At certain times of the day, I get hungry because I have gotten used to eating then.

Three-Factors Eating Questionnaire, **Stunkard and Messick,** J Psychosom Res, 1985 29:71-83.

Familial Resemblance in Eating Behaviors in Men and Women from the Quebec Family Study

Véronique Provencher, Louis Pérusse,† Luigi Bouchard,† Vicky Drapeau,† Claude Bouchard,§ Treva Rice,¶ D.C. Rao,¶‖ Angelo Tremblay,† Jean-Pierre Després,†‡ and Simone Lemieux**

Parameter	Dietary restraint	Disinhibition	Hunger
F-M	0.17 ± 0.09	0.13 ± 0.09	0.13 ± 0.09
F-S	0.05 ± 0.11	0.07 ± 0.10	0.17 ± 0.12
M-S	0.12 ± 0.09	0.03 ± 0.10	0.03 ± 0.10
F-D	-0.14 ± 0.10	0.10 ± 0.09	0.09 ± 0.09
M-D	0.03 ±0.09	0.23 ± 0.07	0.31 ± 0.07
S-D	-0.04 ± 0.07	0.05 ± 0.08	0.15 ± 0.09
S-S	-0.02 ± 0.12	0.13 ± 0.12	0.24 ± 0.16
D-D	0.13 ± 0.09	-0.06 ± 0.09	0.08 ± 0.08
H^2	5.5%	17.5%	28.4%

Values adjusted for age, sex and BMI. F = Father; M = Mother; S = Son; D = Daughter

From Provencher et al., Obes Res. 13:1624-29, 2005.

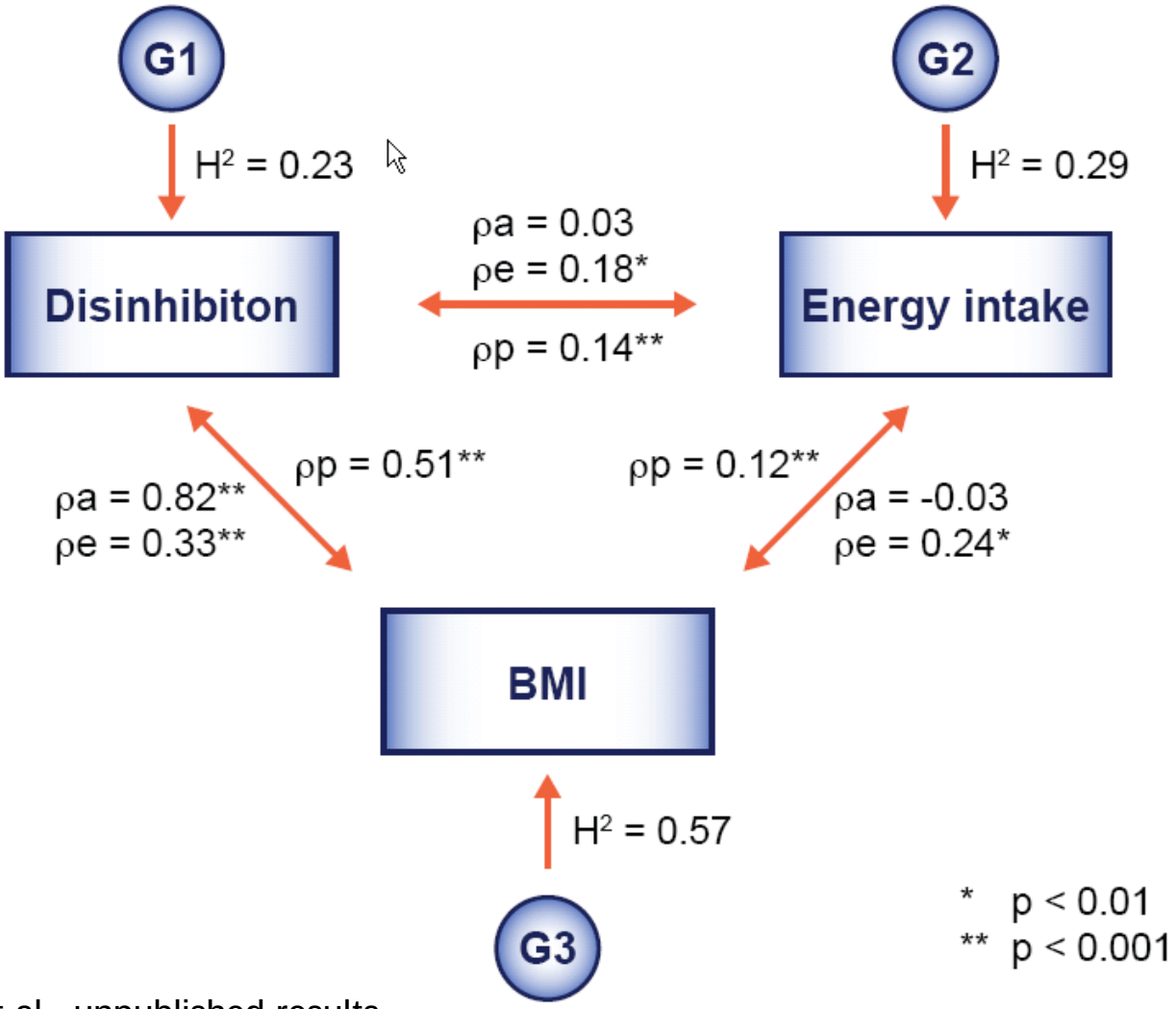
Heritability of eating behaviors from various family and twin studies

Description	Restraint	Disinhibition Emotional eating	Hunger Uncontroled eating	Reference
624 subjects from 28 Amish families	28%	40%	23%	Steinle et al, 2002
210 female twin pairs 25-64 years	0	45%	8%	Neale et al., 2003
326 DZ; 456 MZ 23-39 years	59%	60%	45%	Tholin et al., 2005
110 DZ; 39 MZ 28-68 years	44%	0	24%	de Castro et al., 2005
327 DZ; 314 MZ 17-82 years	26-63%	9-45%	45-69%	Keskitalo et al., 2008
124 DZ; 443 MZ 20-65 years	30%	32%	21%	Sung et al., 2010

Heredity affects several aspects of eating

- Energy intake and macronutrient intakes (Keller et al. 2003):
  - From twin studies: h^2 from 11% to 65%
- Eating patterns: factor analysis of 99 food items (van den Bree 1999):
  - Healthy eating pattern: 33% (frequency) to 40% (food use).
  - High-fat, salt, sugar: 15% (serving size) to 33% (frequency).
- Relationship between food eaten during a meal and (deCastro, 2002):
  - Time of the meal: 14%.
  - Number of people attending the meal: 27%.
  - Before meal self-rating of hunger: 14%.
- Eating in the absence of hunger (Fisher et al. 2007):
  - h^2 = 51% (44% after adjustment for BMI)
- Fast food eating and breakfast (Nelson et al. 2006):
  - Fast food eating (times/week): h^2 = 24% (adults) 34% (adolescents)
  - Breakfast (d/week): h^2 = 27% (adults) 33% (adolescents)

Evidence of a shared genetic basis between eating behaviors and obesity



From Pérusse et al., unpublished results

Chasing behavior genes: two basic approaches

- Candidate gene studies:
  - Test for association between a candidate gene and the phenotype in unrelated subjects
    - Case-control studies
    - Test for differences between genotypes
  - Two types of candidate genes:
    - Functional candidates
    - Positional candidates (e.g. Prader-Willi syndrome).
- Genome-wide screening:
  - Scan the whole genome with several genetic markers
  - Genome-wide linkage studies
  - Genome-wide association studies

Genome-wide linkage analyses for energy and macronutrient intakes

Quantitative trait locus determining dietary macronutrient intakes is located on human chromosome 2p22[1–3]

Guowen Cai, Shelley A Cole, Raul A Bastarrachea-Sosa, Jean W MacCluer, John Blangero, and Anthony G Comuzzie

A genome-wide linkage scan for dietary energy and nutrient intakes: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study[1–3]

Agron Collaku, Tuomo Rankinen, Treva Rice, Arthur S Leon, DC Rao, James S Skinner, Jack H Wilmore, and Claude Bouchard

Evidence of a quantitative trait locus for energy and macronutrient intakes on chromosome 3q27.3: the Québec Family Study[1–3]

Anne C Choquette, Simone Lemieux, Angelo Tremblay, Yvon C Chagnon, Claude Bouchard, Marie-Claude Vohl, and Louis Pérusse

Evidence of a quantitative trait locus for energy and macronutrient intakes on chromosome 3q27.3: the Québec Family Study[1–3]

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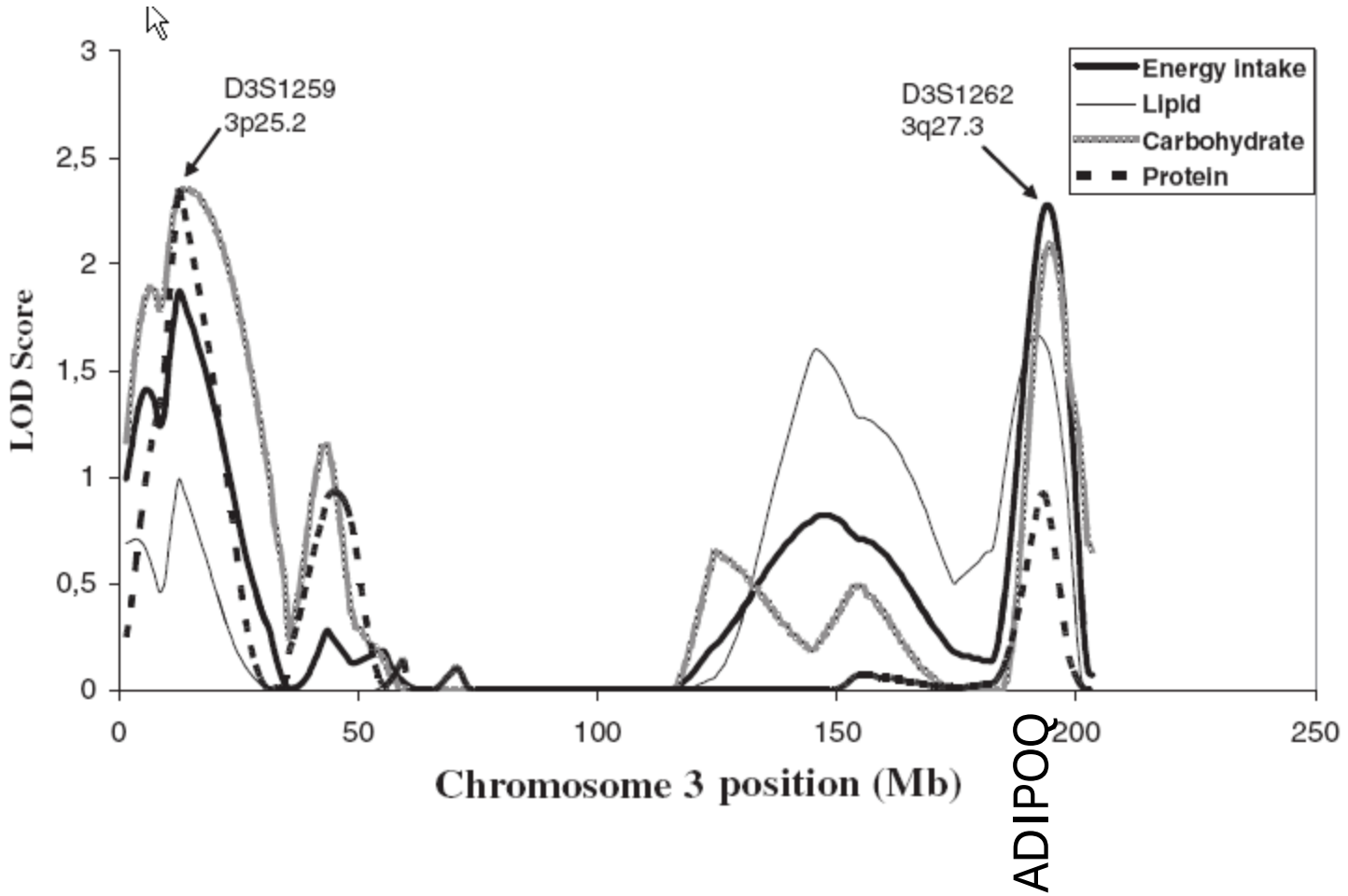
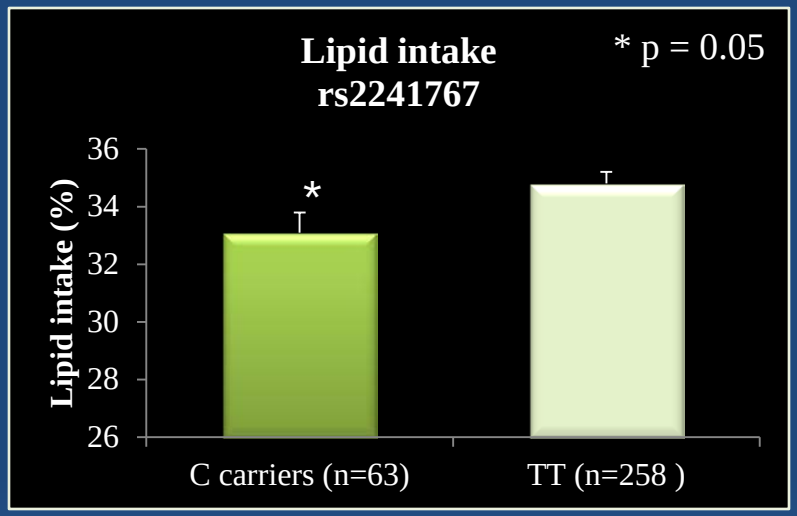
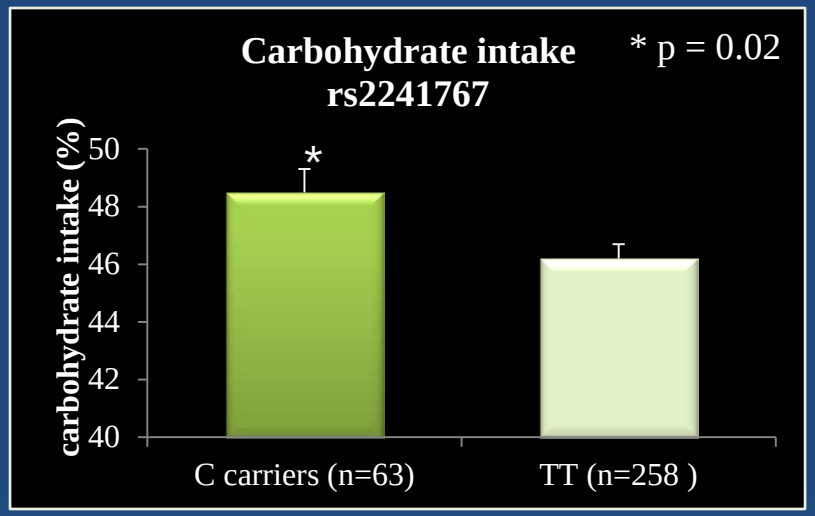
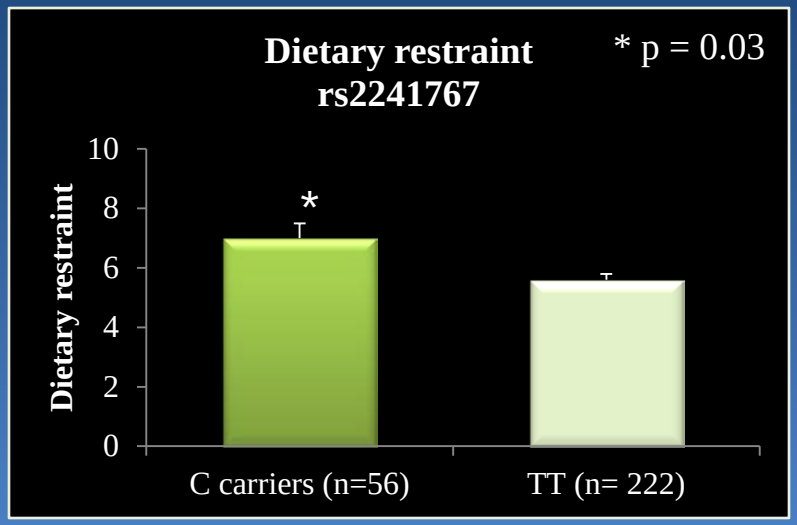


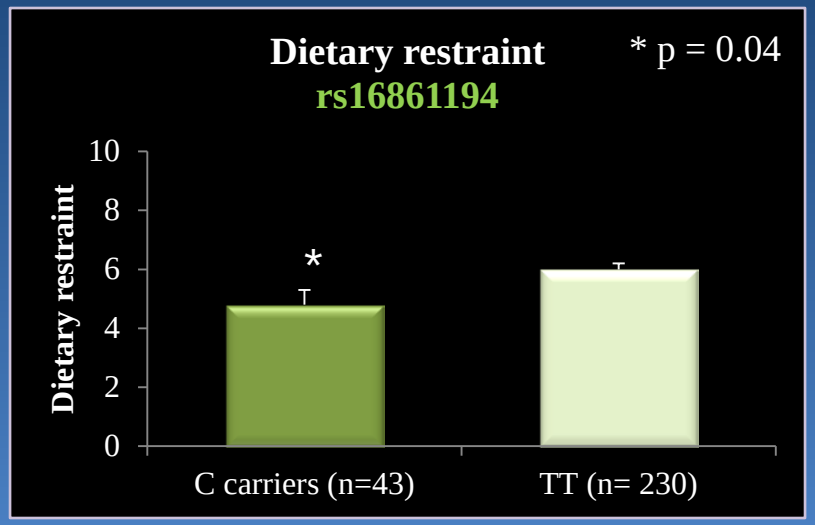
Choquette et al., AJCN, 88:1142-48, 2008

Association of ADIPOQ with dietary intakes and eating behaviors in men



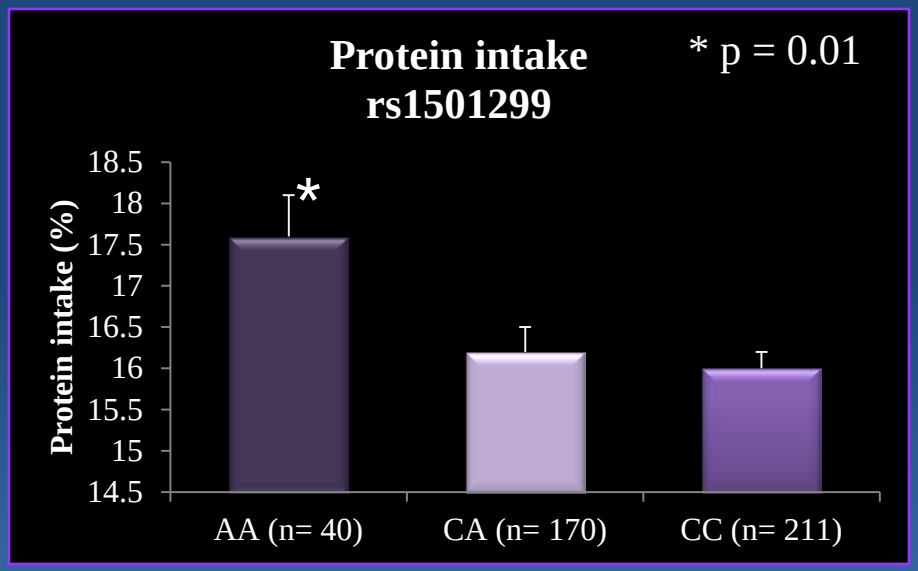


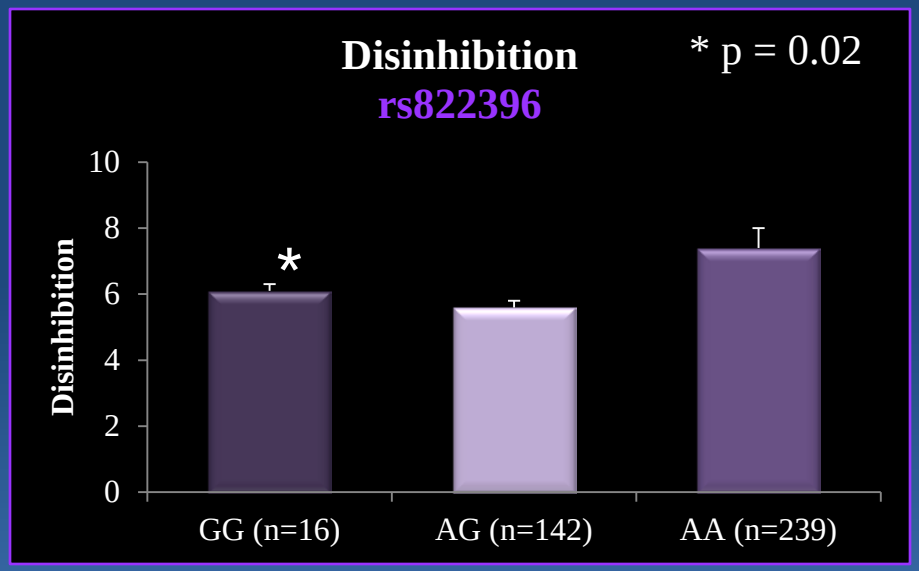




Values are LS Means (adjusted for age and BMI) ± SEM

Association of ADIPOQ with dietary intakes and eating behaviors in women

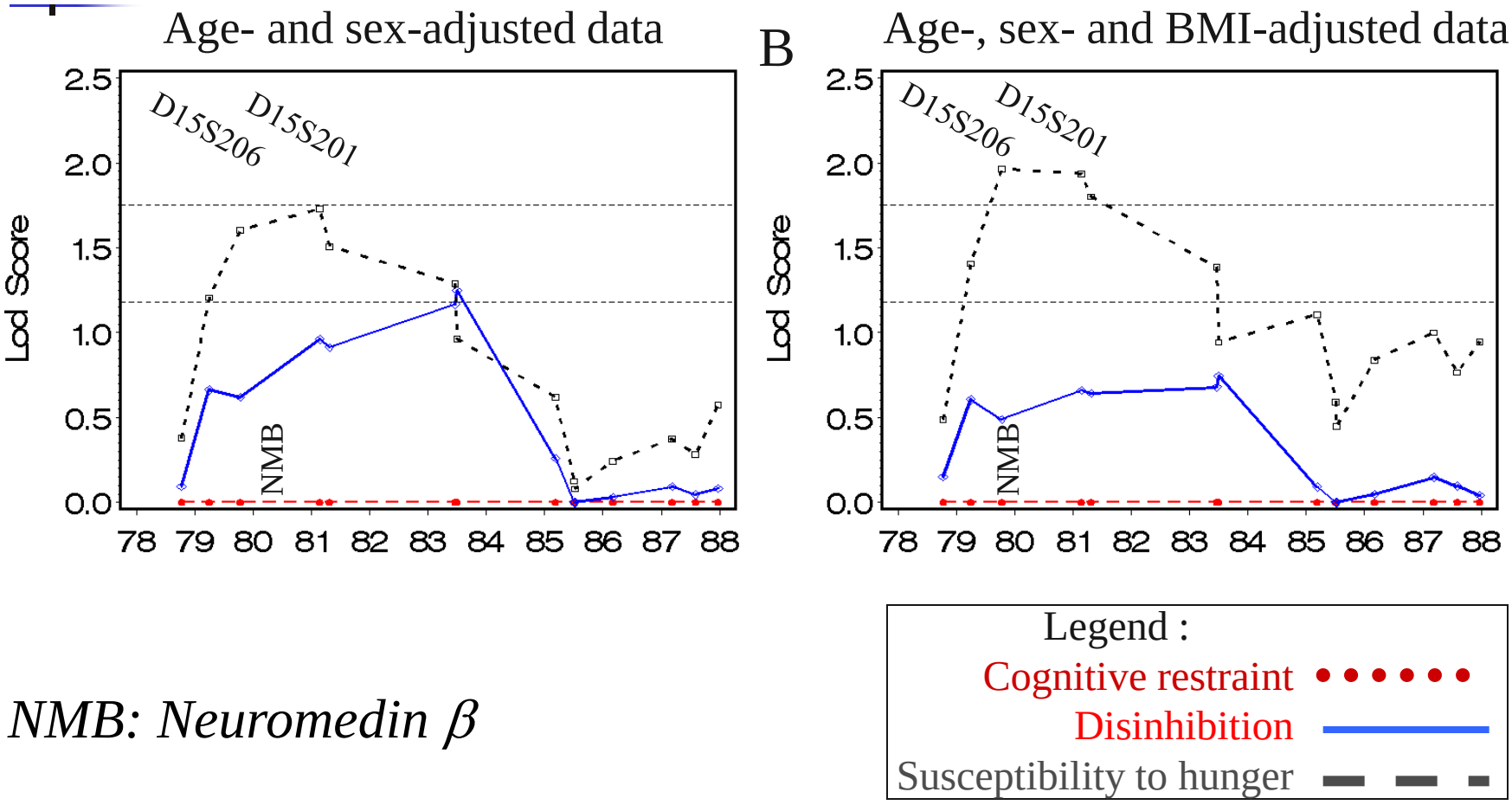




Values are LS Means (adjusted for age and BMI) ± SEM

Neuromedin β: a strong candidate gene linking eating behaviors and susceptibility to obesity[1–3]

Luigi Bouchard, Vicky Drapeau, Véronique Provencher, Simone Lemieux, Yvon Chagnon, Treva Rice, DC Rao, Marie-Claude Vohl, Angelo Tremblay, Claude Bouchard, and Louis Pérusse



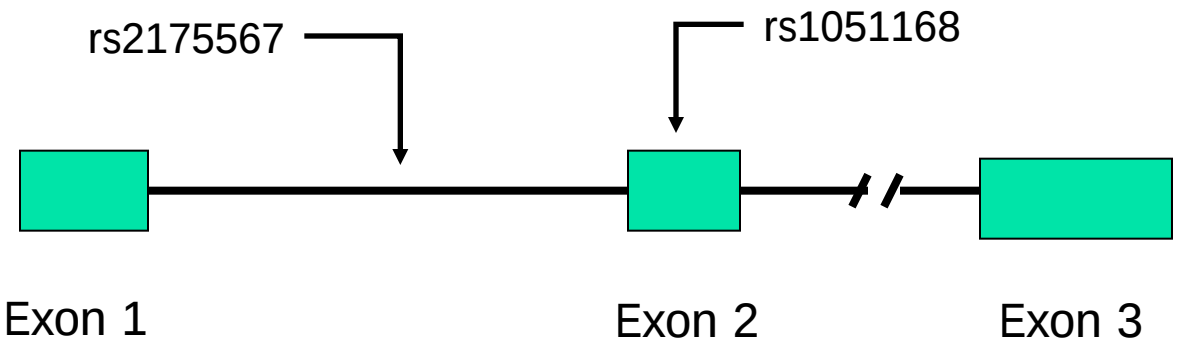
NMB: Neuromedin β

From L. Bouchard et al., Am. J. Clin. Nutr, 80:1478-86, 2004.

Neuromedin Beta

- Member of the bombesin-like peptides family
  - Bombesin is a peptide first purified in the skin *Bombina bombina* frog
  - Two mammalian homologues: gastrin-relasing peptide (GRP) and NMB.
- Mainly expressed in the hypothalamus and GI tract (stomach and colon).
- Injection of NMB peptide:
  - Affects behaviours: grooming and locomotor activity.
  - Smooth muscle contraction.
  - Decreases food intake.
- NMB receptor: expressed in thalamic and olfactory regions of the brain and in the GI tract.

The NMB gene



	Allélique		Génotypique		
	A	C	A/A	A/C	C/C
rs1051168	0.29	0.71	0.10	0.38	0.52

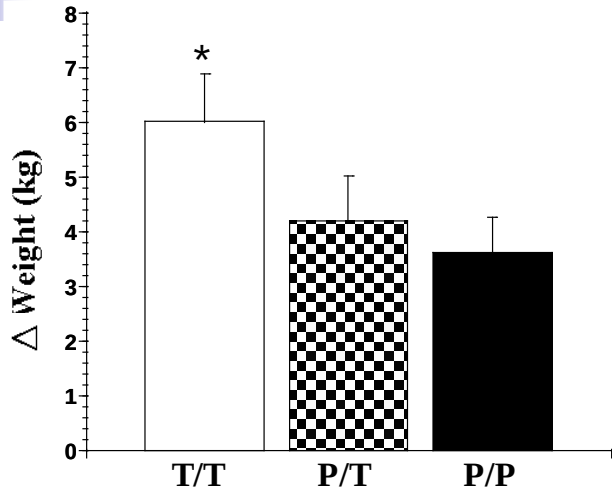
Associations between NMB P73T polymorphism and eating behaviours

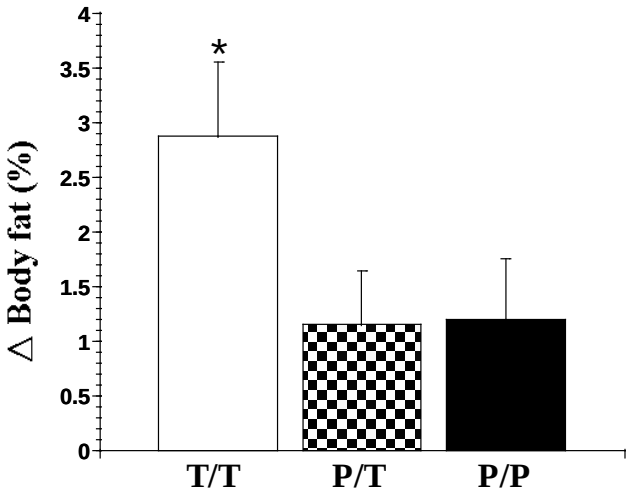
TABLE 4
Genotypic frequencies of the *p.P73T* neuromedin β polymorphism in subjects with low and high levels of disinhibition and susceptibility to hunger

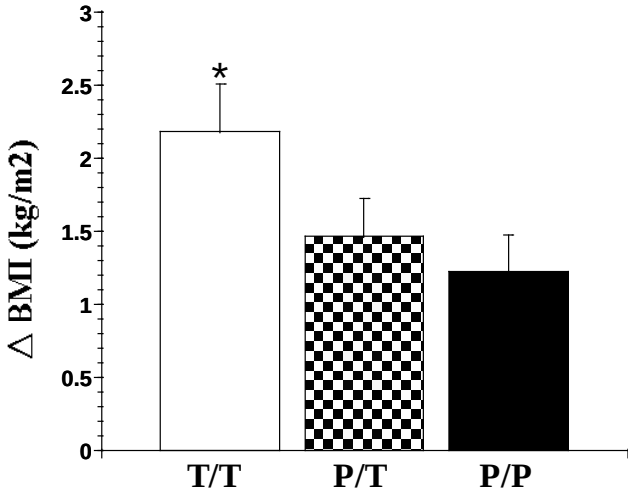
	Disinhibition[1]					Susceptibility to hunger[2]				
Genotype	Low (n = 266)	Middle (n = 257)	High (n = 102)	Odds ratio (95% CI)	P	Low (n = 258)	Middle (n = 229)	High (n = 145)	Odds ratio (95% CI)	P
P/P	0.51	0.48	0.55	—	—	0.53	0.49	0.53	—	—
P/T	0.41	0.42	0.28	0.9 (0.64, 1.19)	0.396[3]	0.41	0.39	0.32	0.9 (0.66, 1.21)	0.446[3]
T/T	0.08	0.11	0.17	1.8 (1.07, 2.89)	0.026[4]	0.07	0.11	0.15	1.9 (1.15, 3.06)	0.012[4]

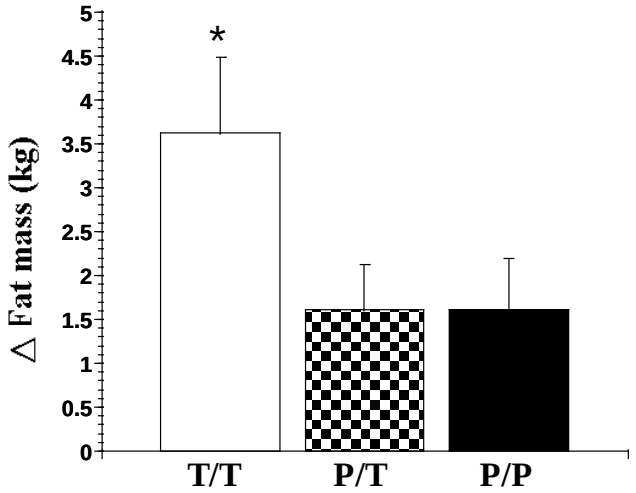
[1] $\chi^2 = 10.6$, $P = 0.032$. Cutoffs were 3 and 8 (0–3, 4–7, and 8–16) in men and 4 and 10 (0–4, 5–9, and 10–16) in women.
[2] $\chi^2 = 9.5$, $P = 0.050$. Cutoffs were 2 and 7 for men and women (0–2, 3–6, and 7–14), respectively.
[3] For comparison with *P/P* homozygotes.
[4] For comparison with *P* carriers.

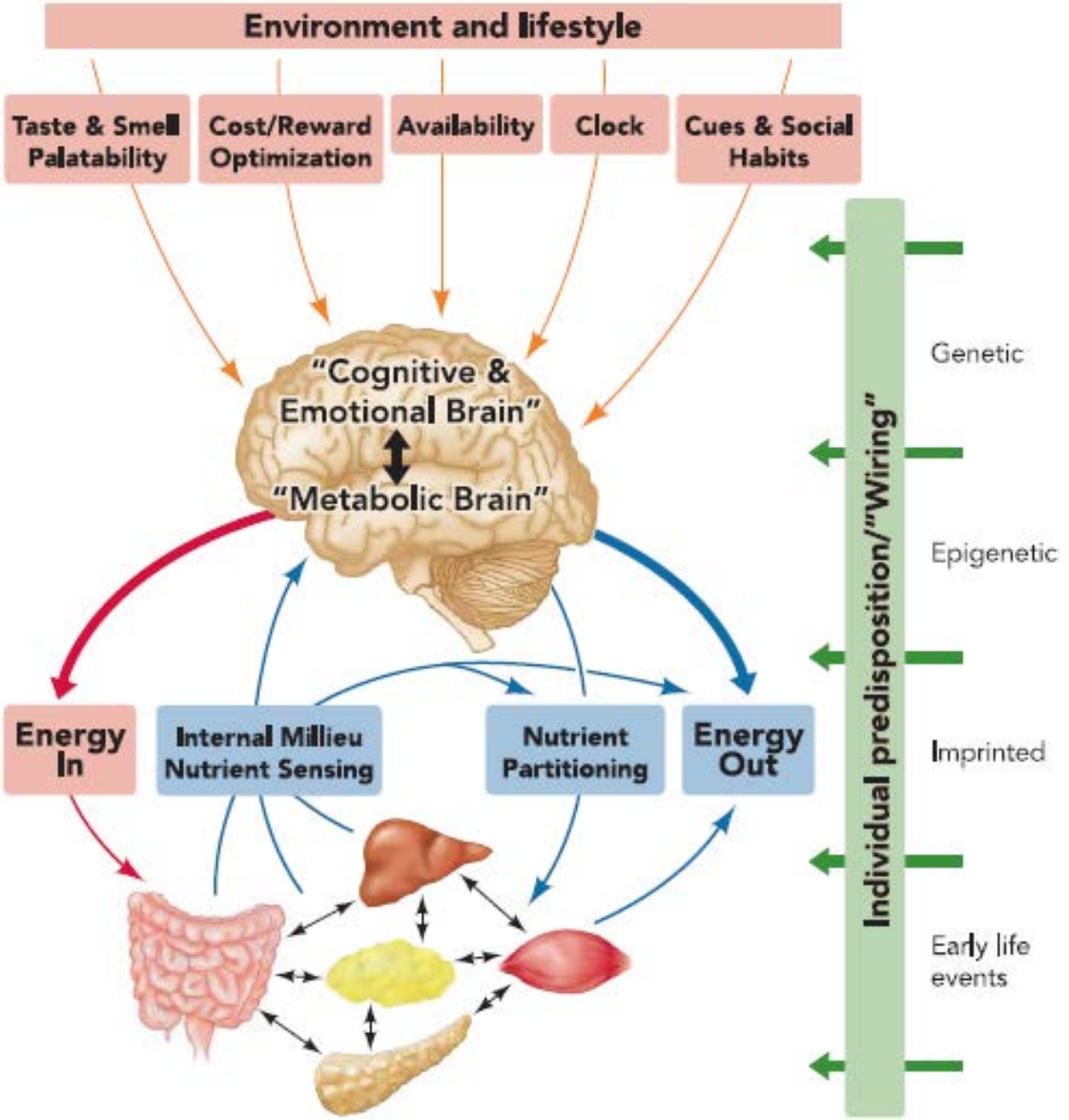
Effect of the Phe73Thr mutation in the NMB gene on body weight gain











From Zheng et al., Physiology 23:75-83, 2008

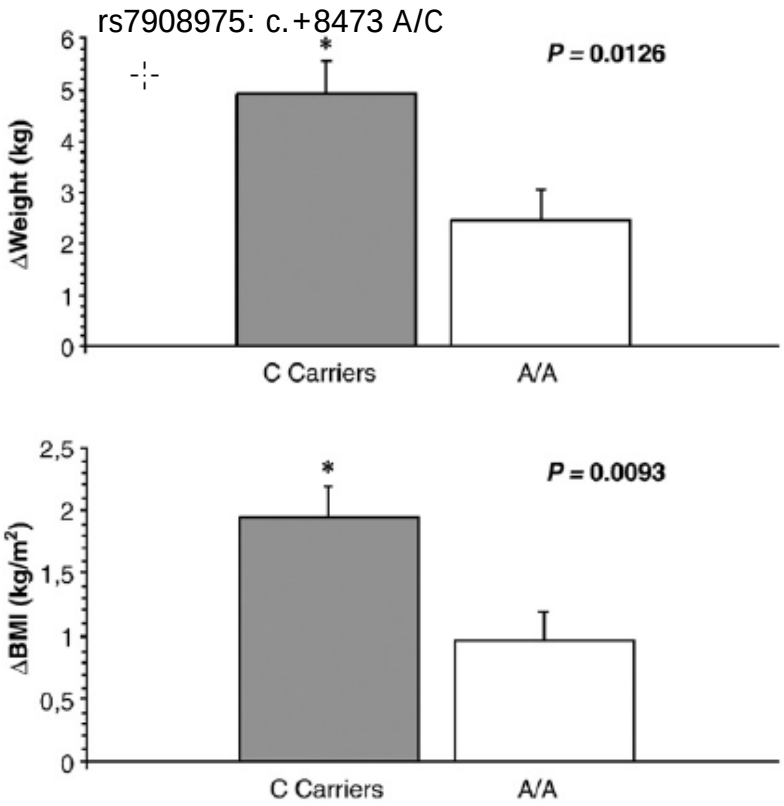
Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

GAD2 gene sequence variations are associated with eating behaviors and weight gain in women from the Quebec family study

Anne C. Choquette [a,b], Simone Lemieux [c,d], Angelo Tremblay [a,d], Vicky Drapeau [e], Claude Bouchard [f], Marie-Claude Vohl [b,c,d], Louis Pérusse [a,b,d,*]



- Glutamate decarboxylase 2: gene coding for the enzyme responsible for the production of the GABA neurotransmitter involved in the regulation of food intake.
- 6 GAD2 variants genotyped in 873 sujets and tested for association with eating beahviors and weight gain.
- In women, associations were found with eating behaviors (rs992990), CHO and lipid intakes and weight gain (see Figure)

Choquette et al., 2009

Genes associated with food intake and eating behaviors

Gene	SNP	Associated traits	Reference
FTO	rs9939609	Satiety in children	Wardle et al., 2008
		Energy intake in children	Cecil et al., 2008
		Loss of control over eating	Tanofsky-Kraff et al., 2009
	rs8050136	Energy intake	Haupt et al., 2008
		Disinhibition	Choquette et al., unpubl.
MC4R	rs17782313	Energy, fat and protein intakes	Qi et al., 2008
		Enjoyment of food, satiety responsiveness	Valladares et al., 2010
		Snacking in children; Hunger in adults	Stutzmann et al., 2009
CCK	4 SNPs	Extreme meal size	de Krom et al., 2007
LEPR	rs2025804	Extreme snack behavior	de Krom et al., 2007
LEP	2 SNPs	Extreme snack behavior	de Krom et al., 2007

Genes associated with food intake and eating behaviors

Gene	SNP	Associated traits	Reference
HRT2A	-1438 G/A	Energy and fat intake	Herbert et al, 2005
UCP3	2 SNPs	Energy and fat intake	Damcott et al., 2004
AGRP	Ala67Thr	Fat and carbohydrate intakes	Loss et al, 2005
TUB	rs2272382	Fat and carbohydrate intakes	Vliet-Ostaptchouk et al, 2008
GAD2	rs992990	Disinhibition and susceptibility to hunger	Choquette et al., 2009
TAS2R38	rs1726866	Disinhibition	Dotson et al. 2010
TAS1R2	rs35874116	Sugar consumption	Eny et al., 2010

There is more to eating than just a response to metabolic signals !!!

« *Although humans have the ability to make conscious, voluntary decisions and choices, most of our actions have a subconscious component that escapes voluntary control* »

From Zheng et al., Physiology 23:75-83, 2008

The rewarding properties of food: Dopamine as physiological mediator of eating behaviors

- Evidence from both human and animal studies show that dopamine (DA) plays a crucial role in feeding behaviors.
- Brain neuroimaging studies in humans have shown that DA release in the brain influences the regulation of feeding (Small et al., 2003) and eating behaviors (Volkow et al., 2003).
- Variations in the dopamine genes have been associated with eating behaviors, eating disorders and addictive behaviors.
- The DRD2 Taq1A polymorphism has been associated with:
  - Lower density of D2 receptors in the brain (Pohjalainen et al., 1998) and reduced DA binding (Thompson et al., 2002)
  - Food reinforcement and energy intake (Esptein et al., 2007)
  - Greater intake of fat and saturated fat (Barnard et al., 2009).
  - Brain activation in response to food cues and food intake (Stice et al., 2008)

Maternal High-Fat Diet Alters Methylation and Gene Expression of Dopamine and Opioid-Related Genes

- Maternal consumption of palatable foods can lead to an increase preference for that type of foods in the offspring (Teegarden et al., 2009; Brion et al., 2010).
- As dopamine and opioid neural pathways are associated with the rewarding properties of food, the authors hypothesized that dopamine- and opioid-related gene expression within the brain may be altered in the offspring of HF-fed dams.
- Mice were maintained on a HF diet from 3 months before breeding through lactation and weaning, and all offspring were maintained on the control diet.
  - A 3- to 10-fold up-regulation of the DAT gene and decreased expression of D1 and D2 receptors (hypo-dopaminergic state)
  - Increased expression of MOR and PENK genes
  - Global and gene-specific DNA hypomethylation
- HF diet can change the offspring's epigenetic marks along with alterations in gene expression and behaviors.

From Vucetic et al., Endocrinology 151:4756-64. 2010

Summary and conclusion

- Strong evidence of familial aggregation for total energy, macronutrient intakes, food choices and eating behaviors.
  - Stronger correlations between mothers and their children
- Several aspects of eating appears to be influenced by genetic factors
  - Heritability estimates are very heterogenous across studies and tend to be higher when derived from twin studies compared to family studies
  - Sex-differences: generally higher estimates for women
- Environmental factors are more important than genetic factors
  - Shared familial environment more important for children than adults
- Although specific genes have been associated with dietary intake and eating behaviors, relatively little is known about the genes influencing these traits.
  - Eating is a complex behavior, difficult to assess and under the influence of several systems/pathways.