

# **The Genetics of Body Weight Regulation. Ethical Considerations.**

Columbia University

19 May 2006

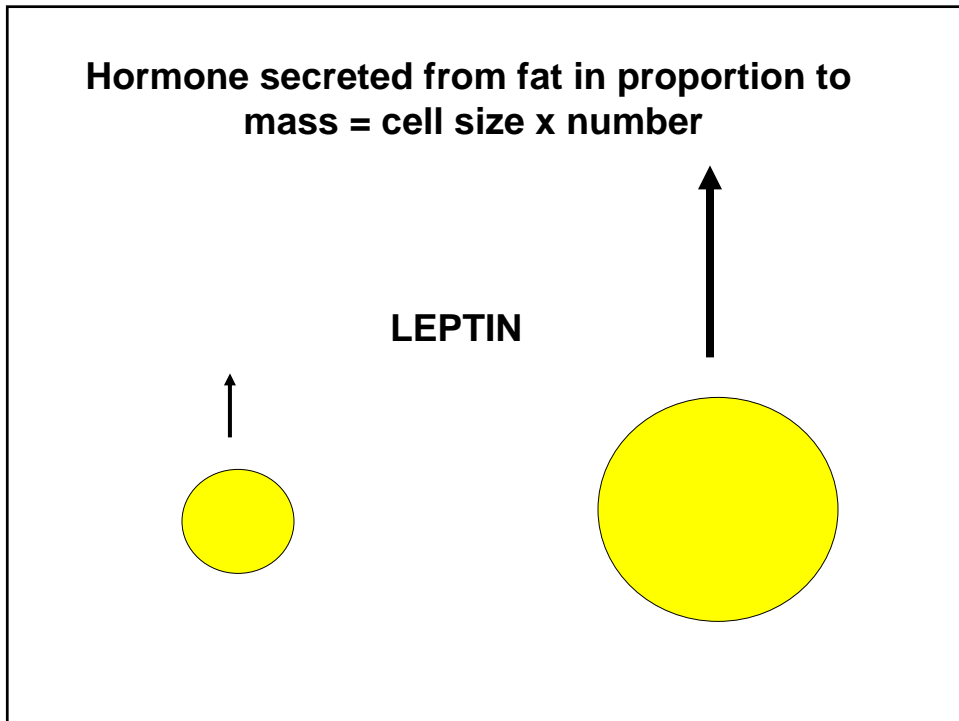
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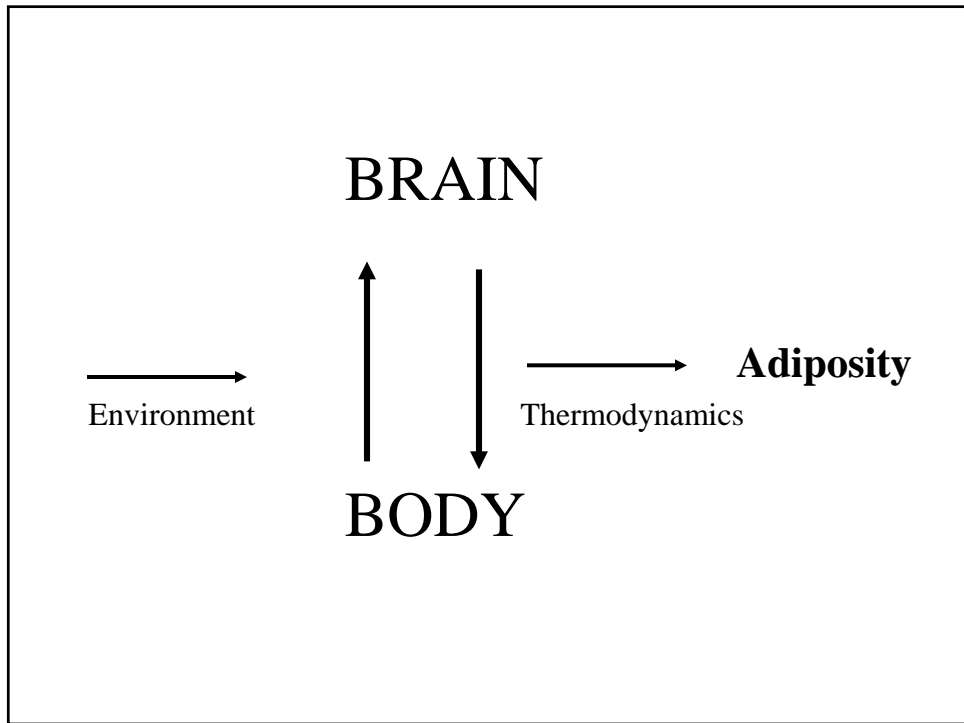
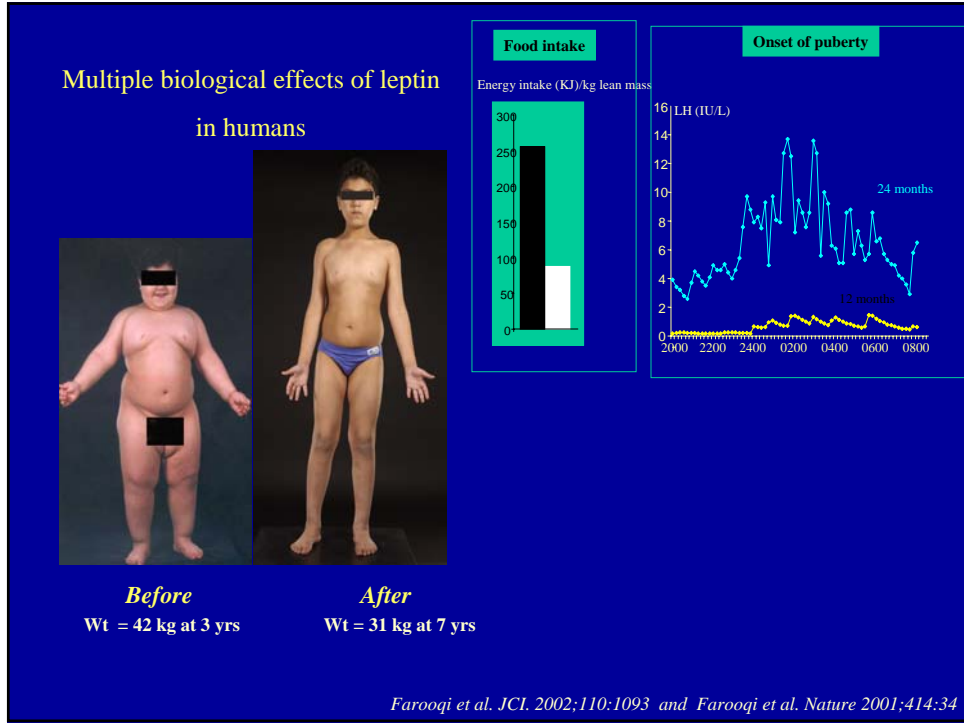
- Are there “blameworthy” medical phenotypes?**
- Is obesity an example? If so, who is to blame?**
- Complex traits: medical phenotypes at the interface of genes and environment**





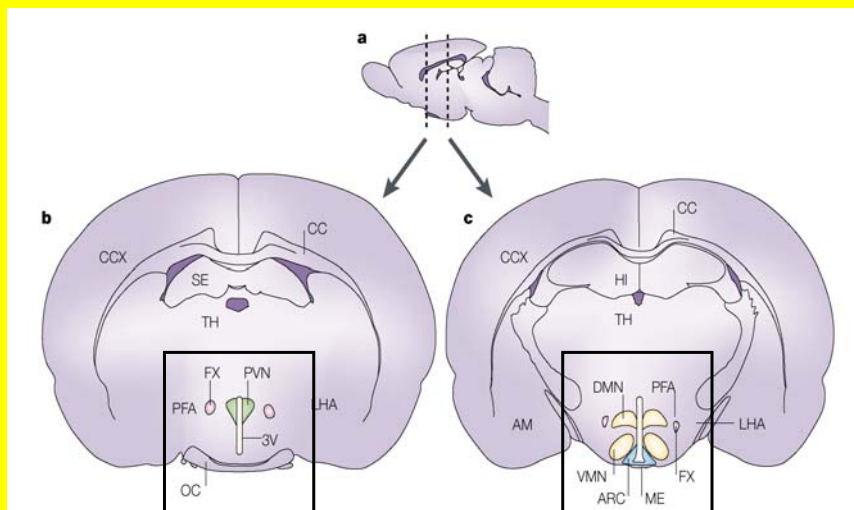
**“The will is by its nature so free that  
it can never be constrained”**

(Passions of the Soul, I, art.41).  
R. Descartes





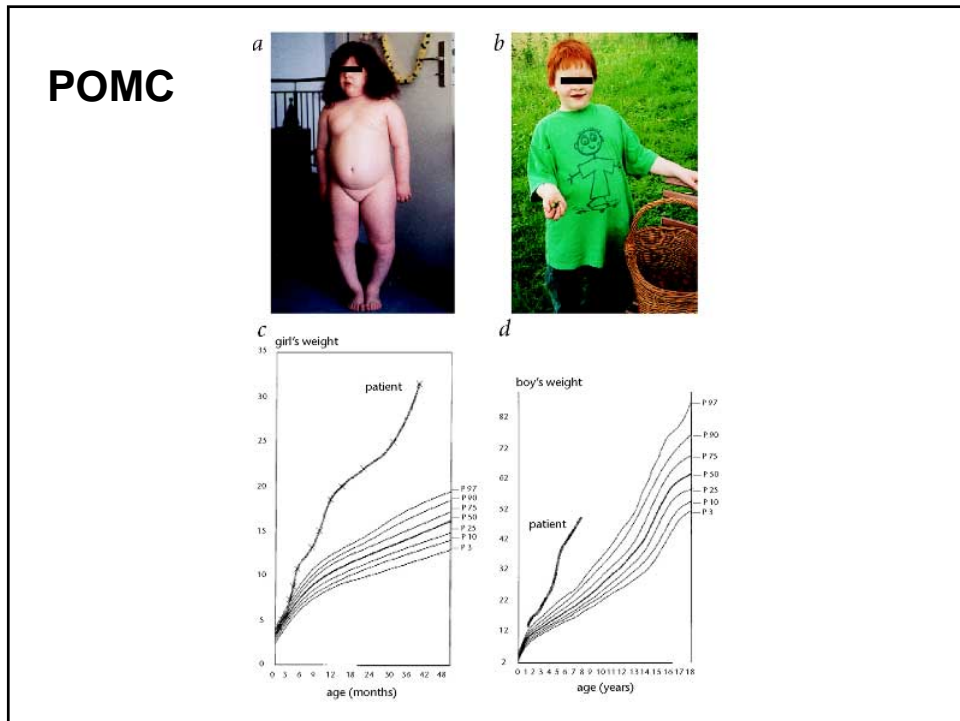
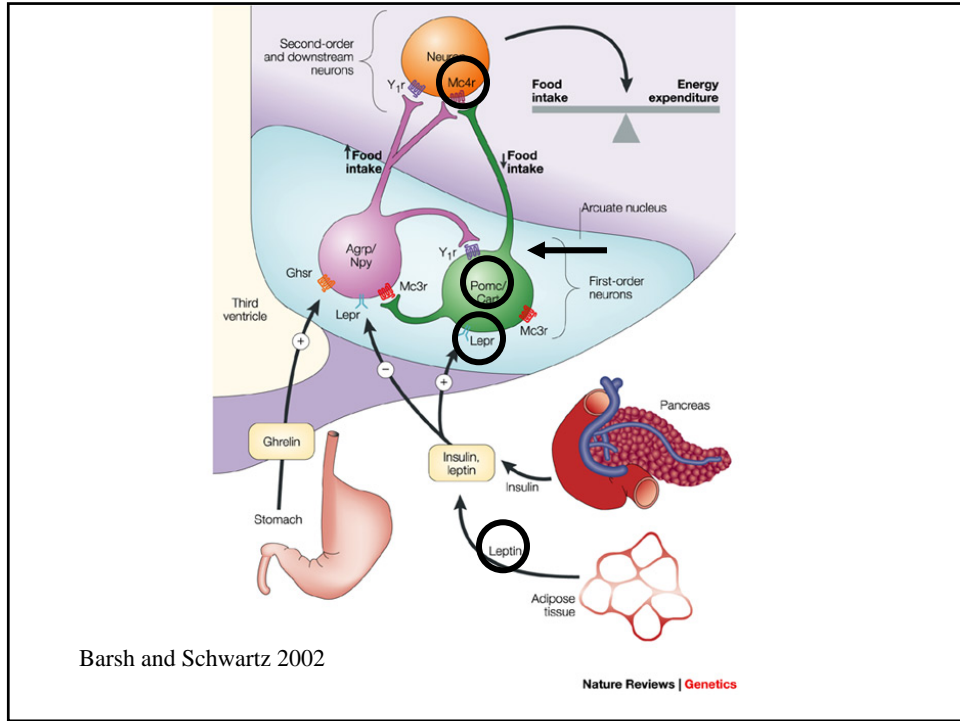
**Prader Willi Syndrome**

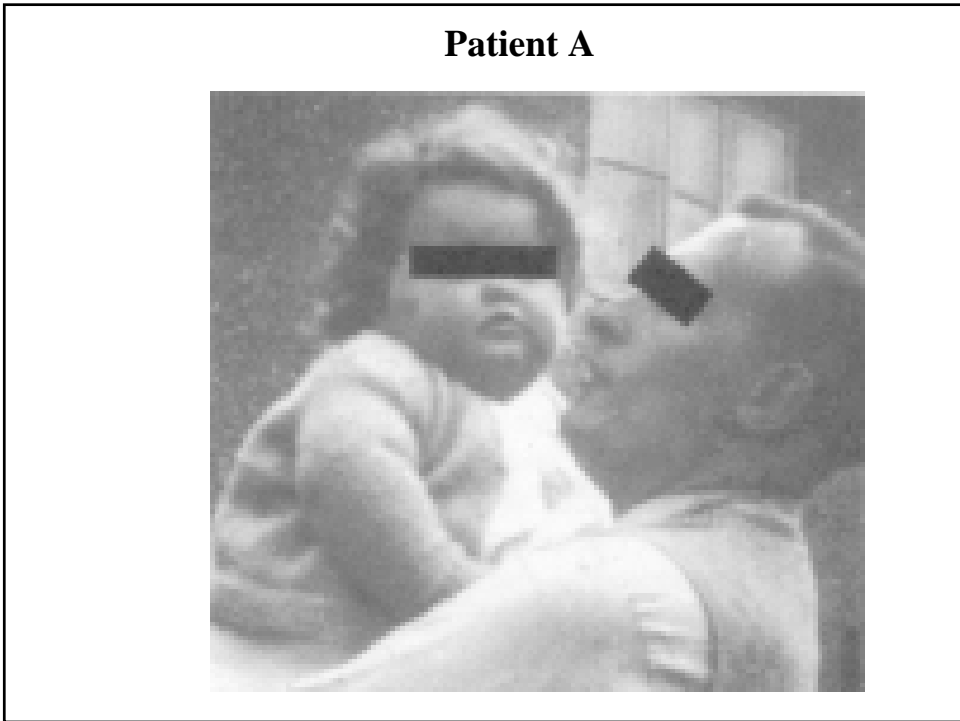
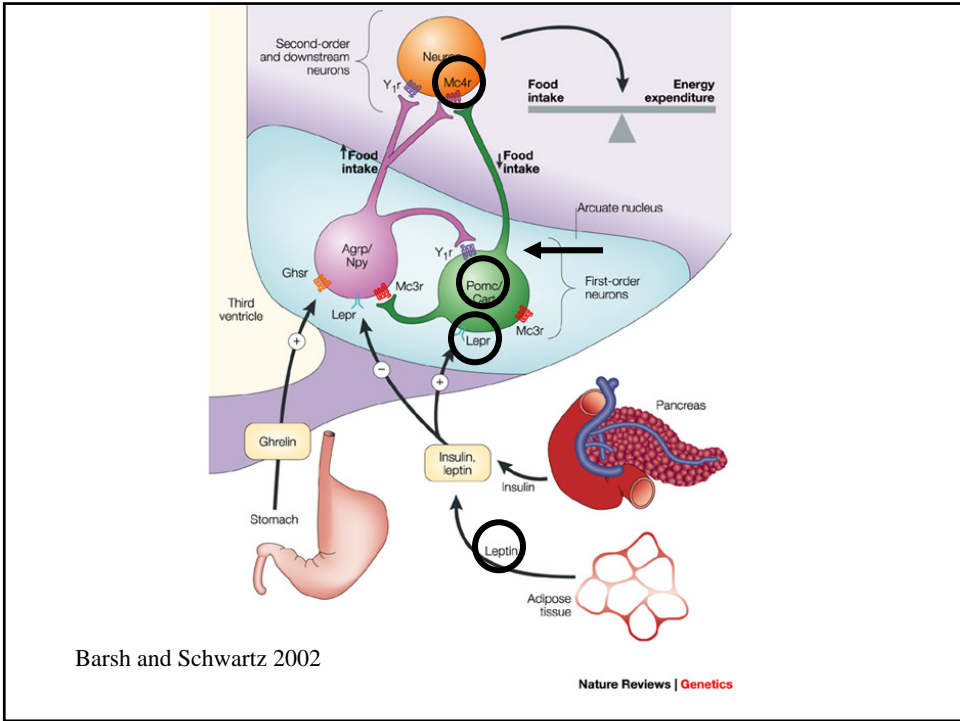


X LHA: anorexia, weight loss

X VMN: profound obesity

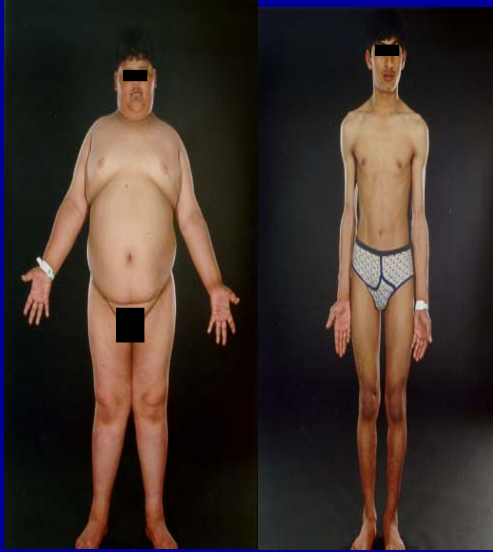
Barsh and Schwartz, Nature Rev Genetics, 3:589, 2002



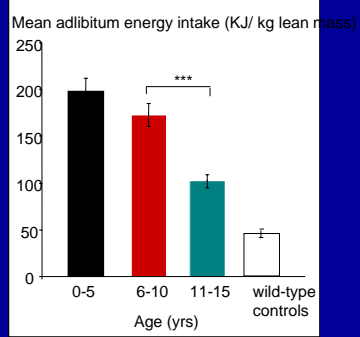


## MC4R Mutations Result In A Dominantly Inherited Obesity Syndrome

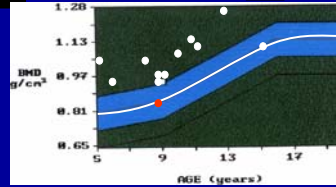
INCREASED LINEAR GROWTH  
9 YR OLD PROBAND      16 YR OLD WILD-TYPE BROTHER



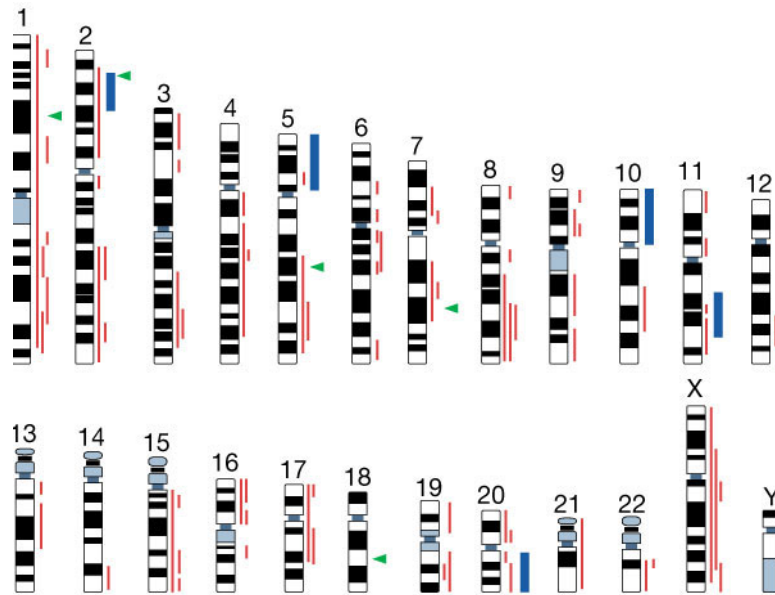
HYPERPHAGIA



INCREASED BONE MINERAL DENSITY



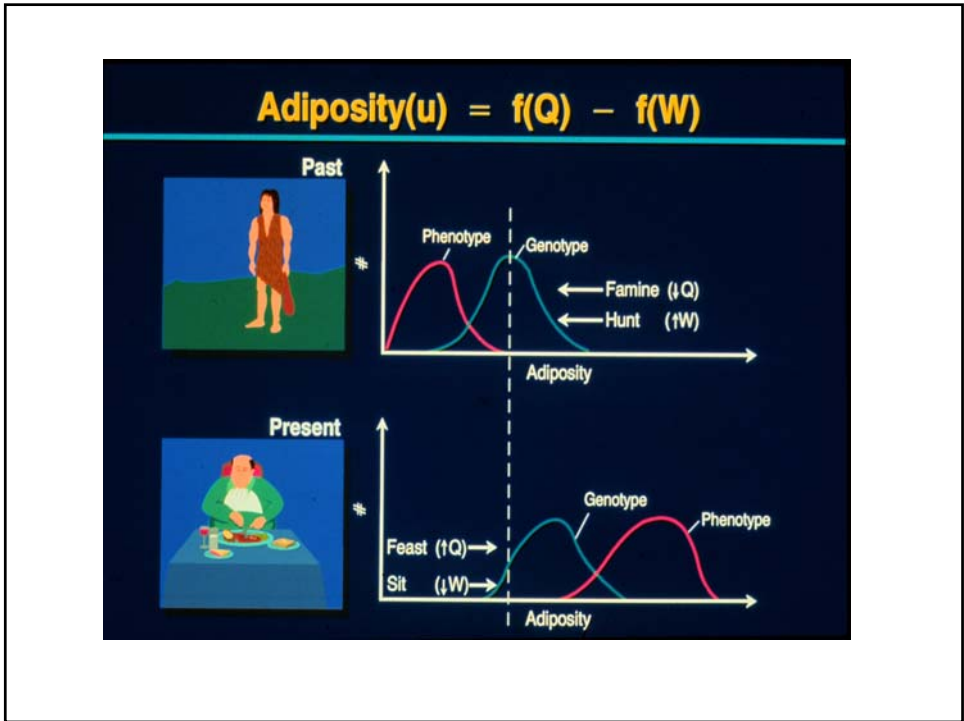
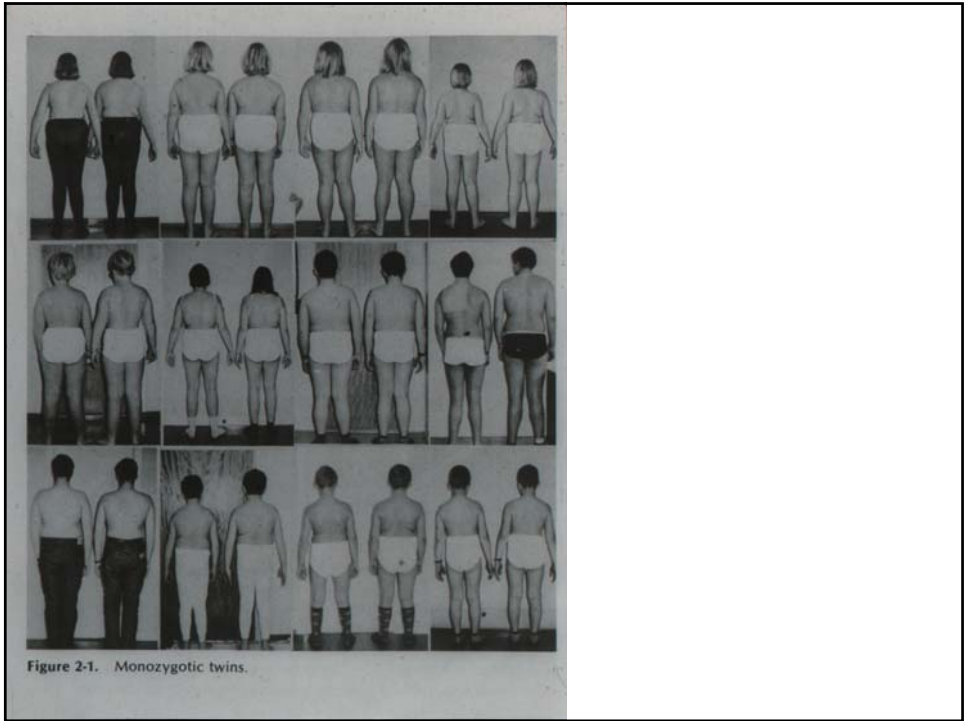
Farooqi et al. NEJM 2003;348:1085-10



Barsh et al. Nature 404:644, 2000







		Hanis				Loyola	
		obese	lean			obese	lean
<b>CPE</b>	CPE4	Red	Red	<b>EnkephalinB</b>	ENK1	Blue	Blue
	CPE8	Blue	Blue		ENK2	Blue	Blue
<b>Ghrelin</b>	-604 G/A	Red	Red	ENK4-1	Blue	Blue	
	G1939A	Grey		ENK4-2	Blue	Blue	
	Arg51Gln			ENK4-3	Red	Red	
	Leu72Met	Grey					
<b>PPAR gamma</b>	PPAR1	Red	Red	<b>NPY</b>	NPY1	Blue	Blue
	PPAR1A	Blue	Blue	NPY3	Red	Red	
	PPAR6	Blue	Blue	<b>Orexin Receptor</b>	OXR1-1	Blue	Blue
			OXR1-2		Red	Red	
			OXR3-1		Blue	Blue	
			OXR3-1b				
			OXR3-2		Blue	Blue	
			OXR5		Grey		
			OXR7		Blue	Blue	

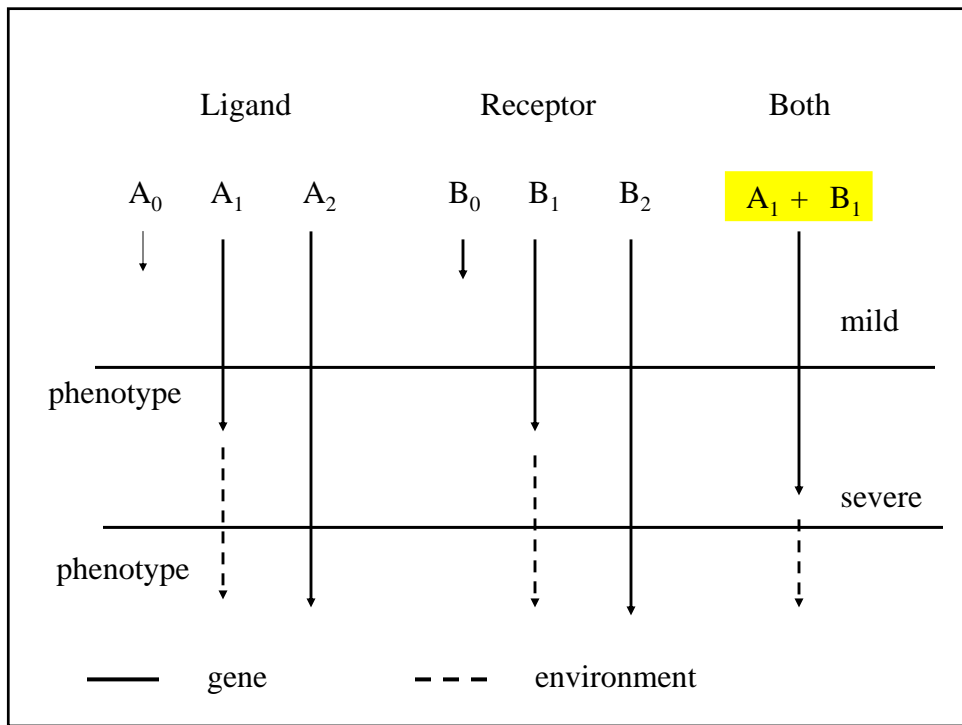
**Mexican American**

**African American**

		IOWA			
		Adult		Child	
		obese	control	obese	control
<b>CPE</b>	CPE4	Blue	Blue	Blue	Blue
	CPE8	Blue	Blue	Red	Red
<b>LEPR</b>	<b>Gln223Arg</b>	Red	Red	Blue	Blue
	Lys656Asn	Blue	Blue	Blue	Blue
<b>MC3R</b>	-769	Blue	Blue	Blue	Blue
	-762	Blue	Blue	Blue	Blue
	-201	Blue	Blue	Blue	Blue
	Val81Ile	Blue	Blue	Blue	Blue
<b>MC4R</b>	MC4R3	Red	Red	Blue	Blue
	PPAR1	Blue	Blue	Blue	Blue
<b>PPAR gamma</b>	PPAR1A	Red	Red	Blue	Blue
	PPAR6	Blue	Blue	Blue	Blue

**Caucasian**

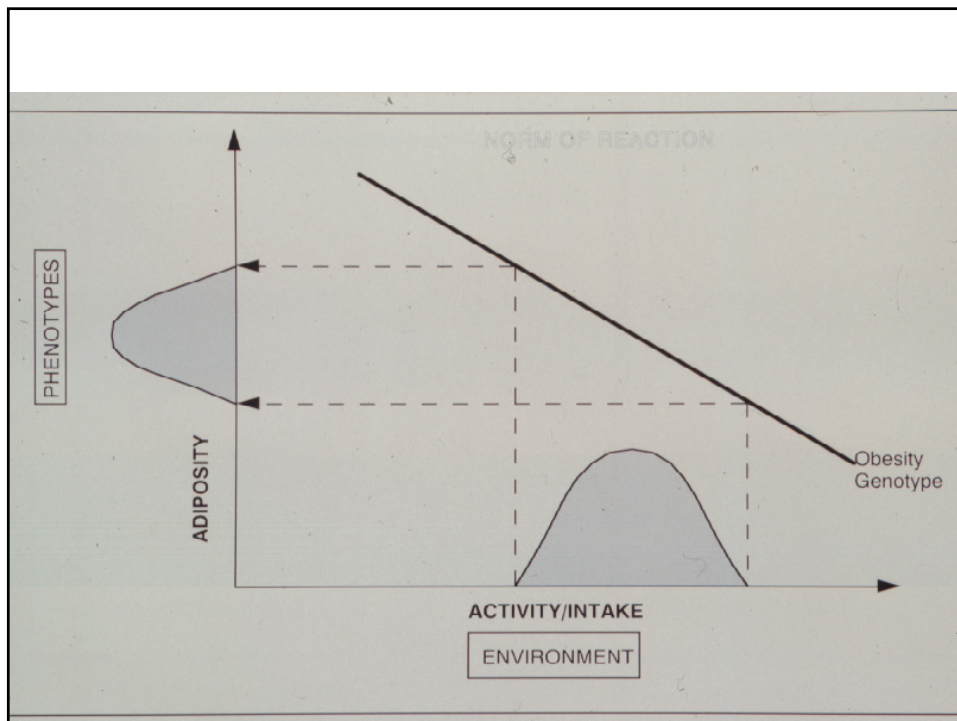
Gene	WT	OB	Famusta		Neibrand		Boyer		TOPS		Liyella		Alan Shulman			Amden						GWA			
			obese	lean	obese	lean	obese	lean	obese	lean	obese	lean	ob	ob	lean	M	white	black	Chinese	Hispanic	ADP	Child			
Adiponectin	E-2-1585T>	E-3-7-17873A>T																							
CART	CAS12																								
CPE	CPE4																								
Ekapahin	ENK1																								
	ENK2																								
	ENK4-2																								
	ENK4-2																								
OATAD	OATAD-1-2																								
	OATAD-2B-1																								
	OATAD-2B-2																								
	OATAD-3-2																								
Oxelin	OXE1																								
	OXE2																								
Lipin-1	LIP1																								
	LIP2																								
MC2R	MC2R																								
	MC2R-2																								
	MC2R-3																								
	MC2R-4																								
NPY	NPY1																								
	NPY2																								
	NPY3																								
	NPY4																								
OxR	OXR1																								
	OXR2																								
	OXR3-1																								
	OXR3-2																								
	OXR3-3																								
	OXR3-4																								
PPAR	PPAR1																								
	PPAR2																								
	PPAR3																								
	PPAR4																								

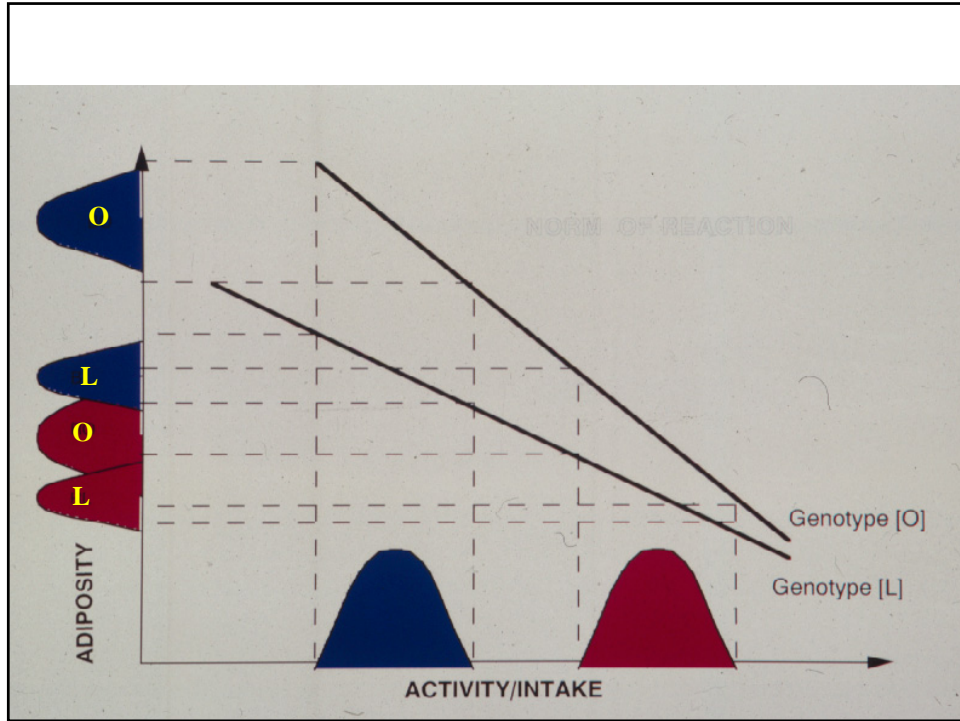


# THANKS

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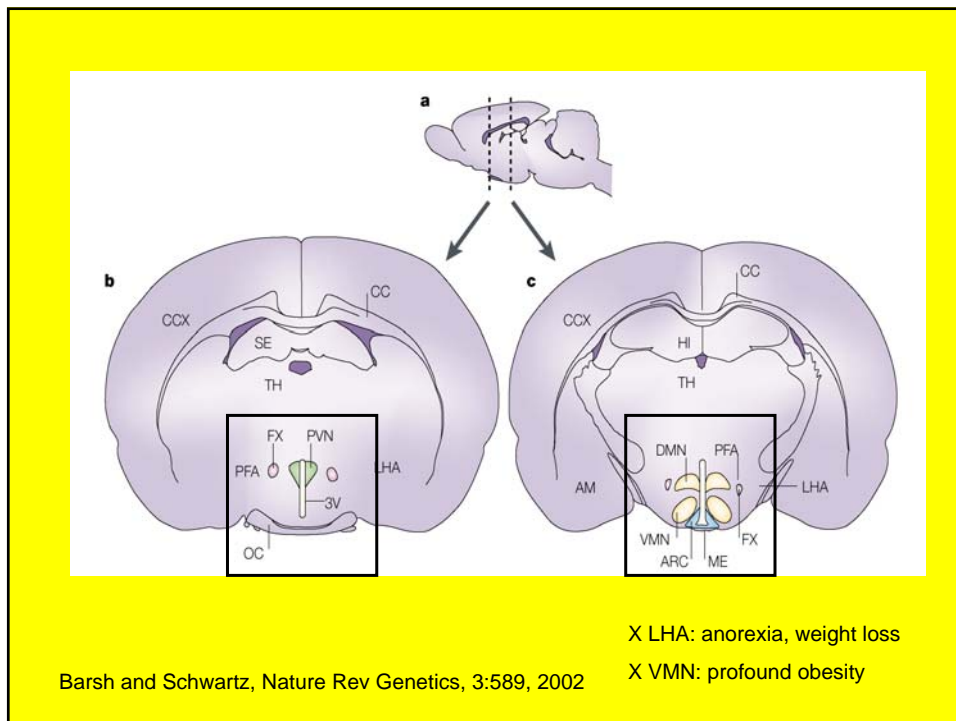
Extreme and/or familial obesity  
Obesity with short stature or developmental delay

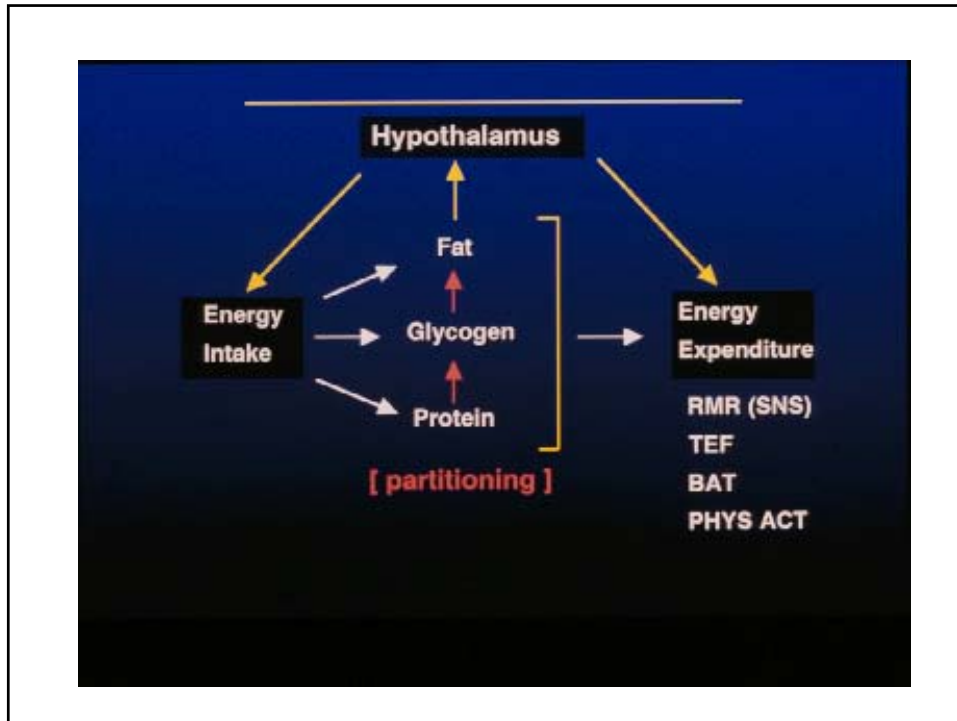




THANKS

**I.**  
**The vegetative brain (hypothalamus)**  
**participates in**  
**energy homeostasis**





#### IV.

### Free Will and Body Weight



## Cartesian Issues Relating to Control of Body Energy Stores

- Explicit signals emanating from the soma communicate with the brain
  - Endocrine (**leptin, insulin, ghrelin, ppy, cck**)
  - Neural (**vagus**)
- The brain uses biochemical pathways parallel to those in the soma gauge systemic fuel status (**AMP kinase; fatty acids; glucose**)
- The brain contains a physical analog of peripheral fuel storage cell(s) ("**homunculus**")

