CHAPTER 2: CAUSES OF OBESITY

Part 1: Introduction and Genetic Basis of Obesity

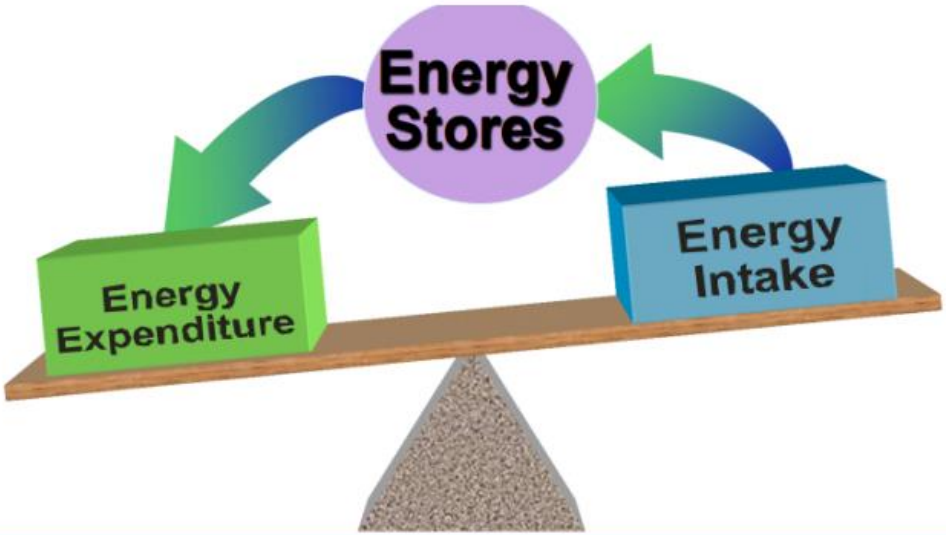
References:

1. Sharon Akabas, Sally Ann Lederman, Barbara J. Moore - Textbook of obesity_ Biological, psychological and cultural influences-Wiley-Blackwell (2012)
2. Peter G. Kopelman, Ian D. Caterson, William H. Dietz - Clinical Obesity in Adults and Children 4e-Wiley-Blackwell (2022)
3. Obesity: global epidemiology and pathogenesis. Matthias Blüher
4. Sharon Rady Rolfes_ Kathryn Pinna_ Ellie Whitney - Understanding Normal and Clinical Nutrition. 11-Cengage Learning (2017)
5. Michael S. Freemark. PediatricObesityEtiology, Pathogenesis and Treatment. Second Edition

CHAPTER 2 INTRODUCTION

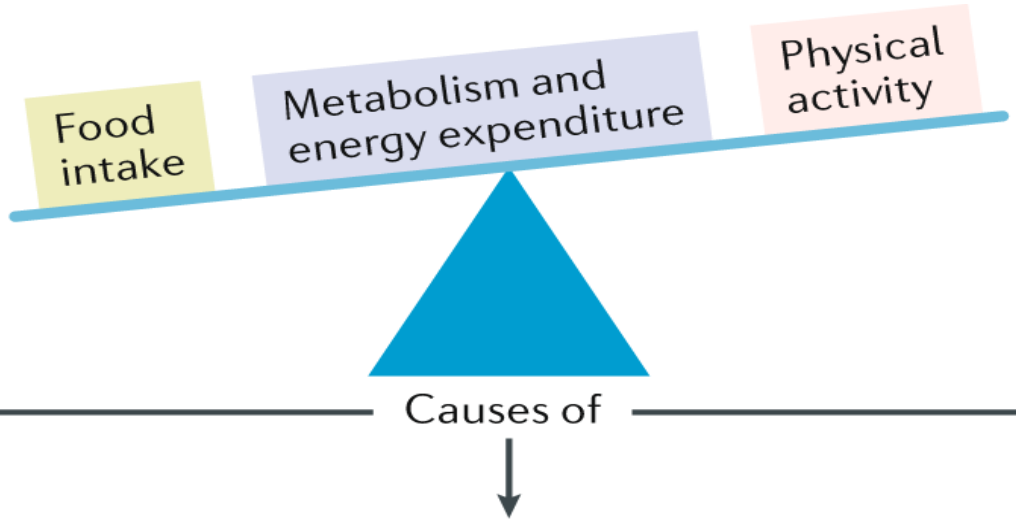
Introduction

It may seem odd to consider the etiology of obesity, when it may appear obvious:



Energy intake - Energy expenditure = Δ Energy stores

Pathogenesis



Overeating
- Socio-cultural
- Lack of knowledge
- Peer pressure
- Uncontrolled eating
- Hunger
- Emotional eating
- Snacking
- Lack of sleep
- Medications

Low energy expenditure
- Ageing
- Sex
- Genetics and epigenetics
- Neuroendocrine factors
- Prandial thermogenesis
- Brown fat
- Sarcopenia
- Microbiota
- Medications

Physical inactivity
- Socio-cultural
- Physical challenges
- Chronic fatigue
- Muscle pain
- Joint pain
- Low fitness level
- Emotional barriers
- Workplace
- Medications

Complex Condition

- The Foresight Obesity Project, ‘Tackling Obesities: Future Choices’, undertook a systems mapping exercise to visualize the causal factors of obesity to:
  - Help understand the complex systemic structure of obesity
  - Contribute to developing a tool that helps policy makers in responding to obesity.
- Let’s take a look:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/296290/obesity-map-full-hi-res.pdf

Then, there are these options:

Complex Condition

- Effective obesity management requires a systematic assessment of factors that can affect:

1. Energy Intake
2. Metabolism
3. Energy Expenditure

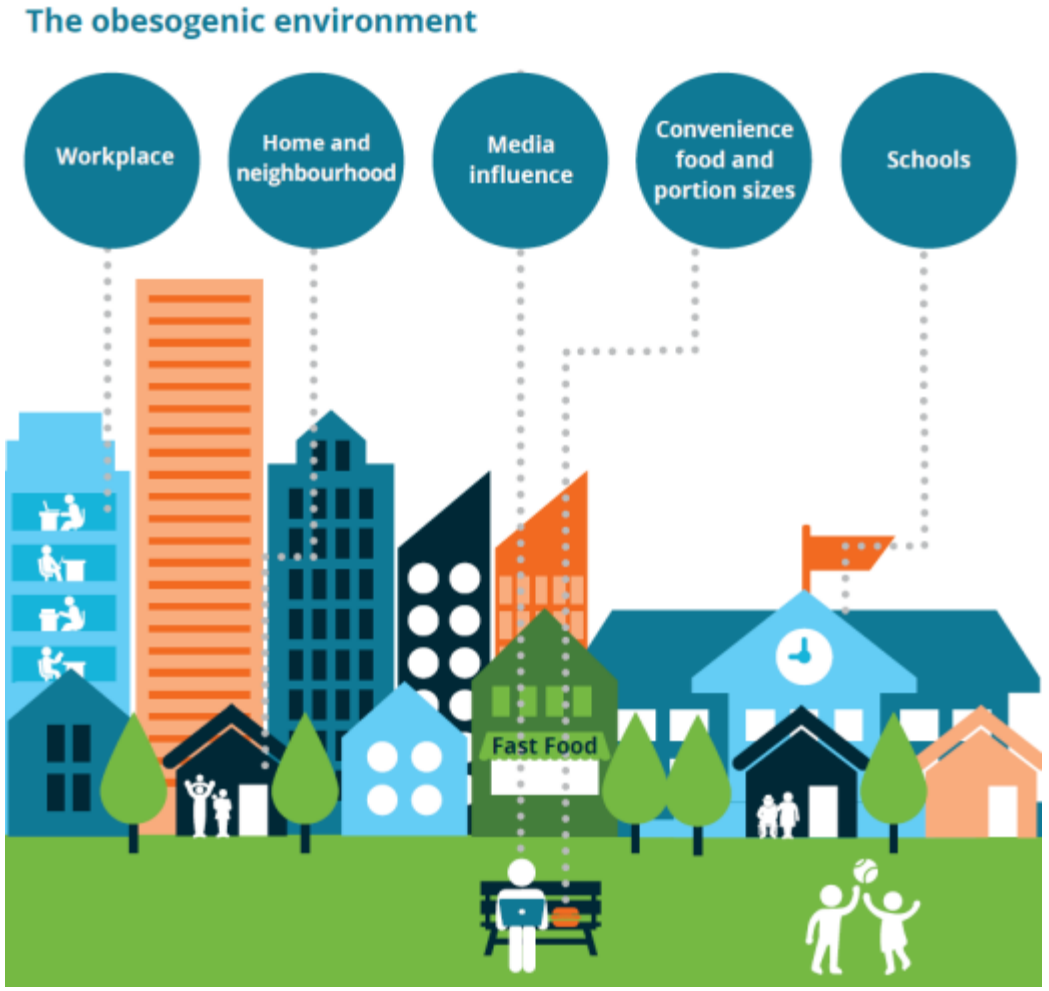
CHAPTER 2 PART 1: **GENETIC** BASIS OF OBESITY

Introduction

- There's not a lot of emphasis on the concept of an "**obesogenic**" environment
- This term refers to an environment that promotes obesity among individuals and populations, including **physical**, **economic**, **political**, and **sociocultural** factors

? Let's consider its effect on different individuals …

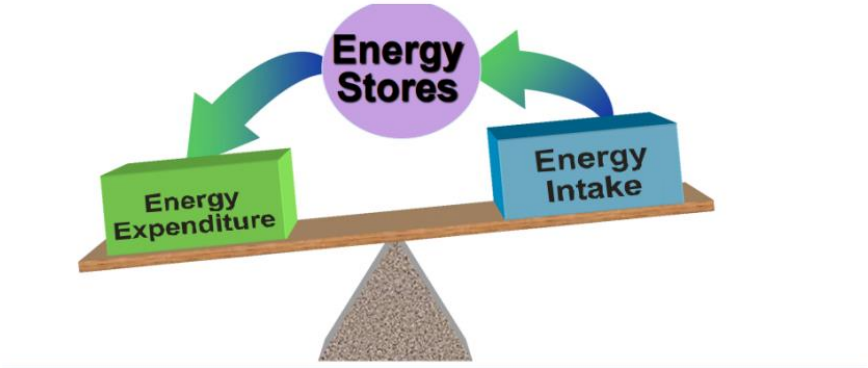
? Interaction between environment and genetic risk factors



https://www.aihw.gov.au/getmedia/25663b47-a9a6-418b-8677-a0af4627f1f8/aihw-phe-

Introduction

- “Obesity arises from the **interaction** between genetic, environmental, and behavioral factors acting through the physiologic mediators of energy intake and energy expenditure.”



- “Appreciating the importance of genetic variation as an underlying cause helps to dispel the notion that obesity represents an individual fault in behavior.”

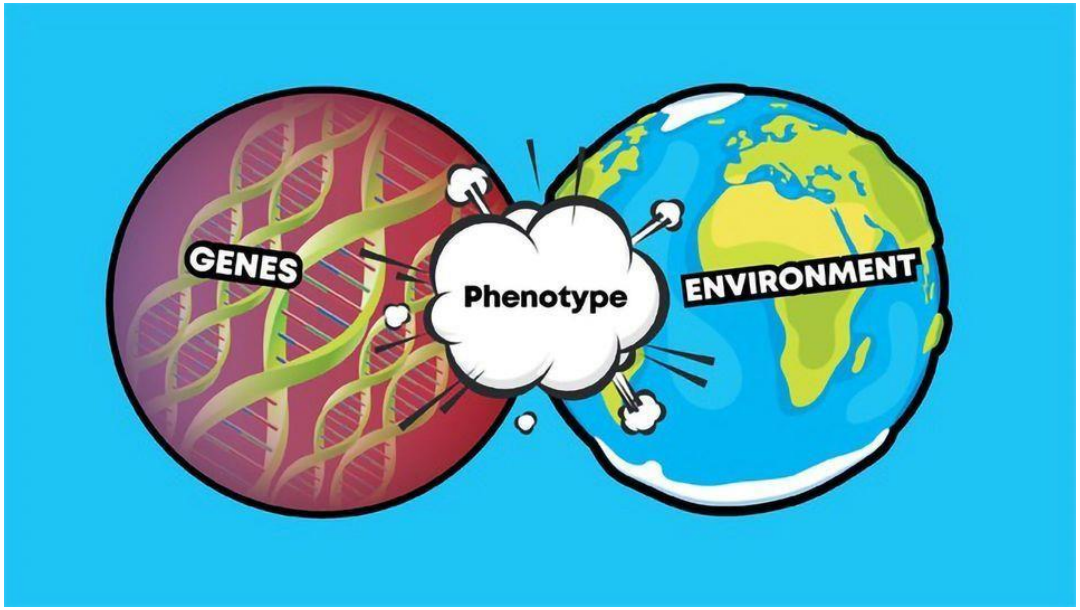
Throughout this section, we will discuss

1. The Heritability of Fat Mass
2. Specific Genes of Obesity
3. Gene-Environment Interaction

1. The Heritability of Fat Mass

- What do we mean by Heritability?

A measure of the extent to which the phenotypic variation in a trait such as obesity is genetically determined. Remaining phenotypic variation in this trait is attributed to environmental factors

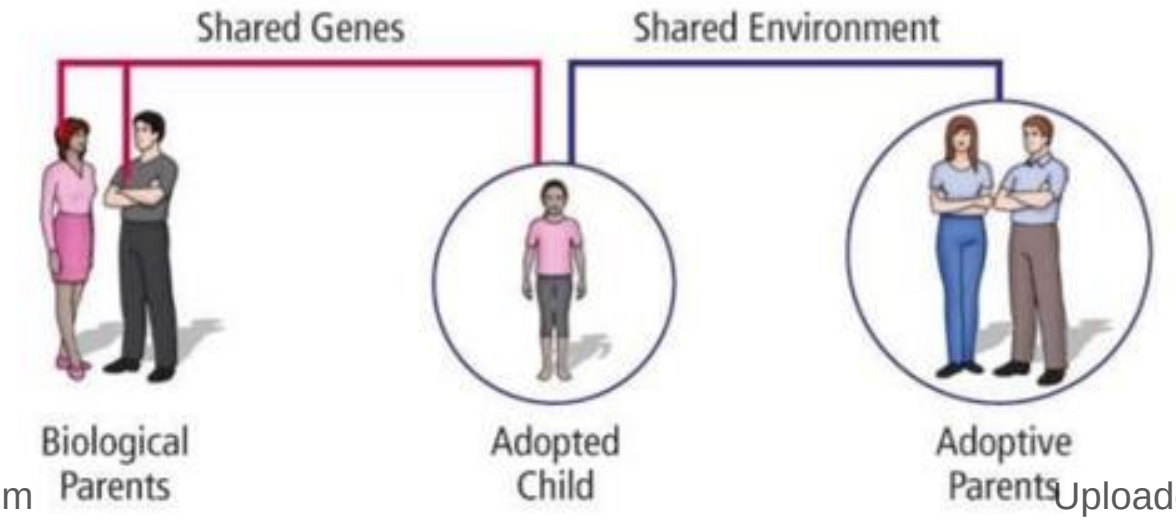


1. The Heritability of Fat Mass

- There is considerable evidence to suggest that weight is a **heritable trait**.
- Considering study designs for obesity heritability, in traditional nuclear families, family members generally share **both genes and environment** to some degree, so it is difficult to assess the contribution of each component
- Let's look at:
  1. Adoption studies
  2. Twin studies

Adoption studies

- Complete adoption studies are useful in separating the common environmental effects
- Adoptive parents and their Adoptive offspring share only **environmental** sources of variance
- Adoptees and their biologic parents share only **genetic** sources of variance.



The New England
Journal of Medicine

Volume 314 JANUARY 23, 1986 Number 4

AN ADOPTION STUDY OF HUMAN OBESITY

ALBERT J. STUNKARD, M.D., THORKILD I.A. SØRENSEN, DR.MED., CRAIG HANIS, PH.D., THOMAS W. TEASDALE, M.A., RANAJIT CHAKRABORTY, PH.D., WILLIAM J. SCHULL, PH.D., AND FINI SCHULSINGER, DR.MED.

Study Summary

- We examined the contributions of genetic factors and the family environment to human fatness in a sample of 540 adult Danish adoptees.
- There was a strong relation between the weight class of the adoptees and the body-mass index of their biologic parents - for the mothers, $P<0.0001$; for the fathers, $P<0.02$.
- There was no relation between the weight class of the adoptees and the body-mass index of their adoptive parents.
- We conclude that **genetic influences have an important role in determining human fatness in adults**, whereas the family environment alone has no apparent effect.

Study Summary

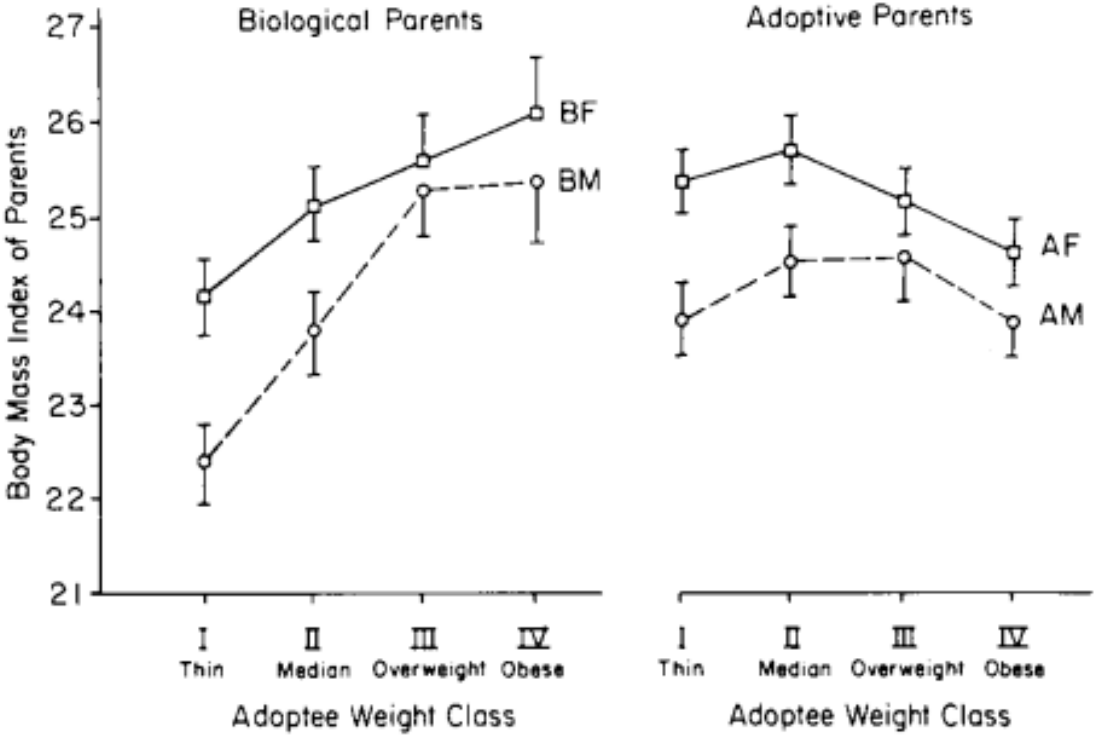
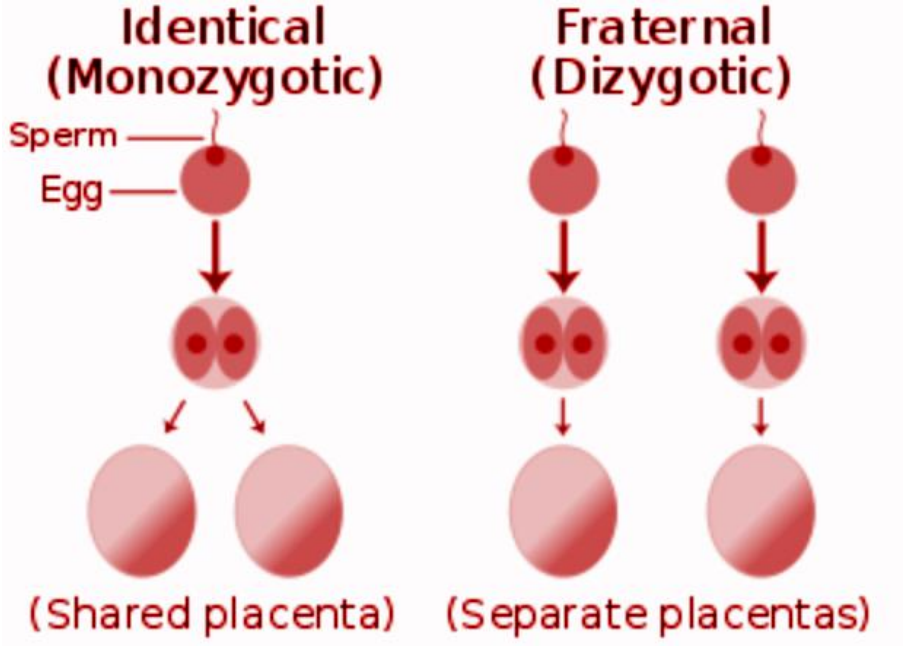


Figure 1. Mean Body-Mass Index of Parents of Four Weight Classes of Adoptees.

Note the increase in mean body-mass index of biologic parents with the increase in weight class of the adoptees. No such increase was found with adoptive parents. Bars represent 1 SEM. BF denotes biologic fathers, BM biologic mothers, AF adoptive fathers, and AM adoptive mothers.

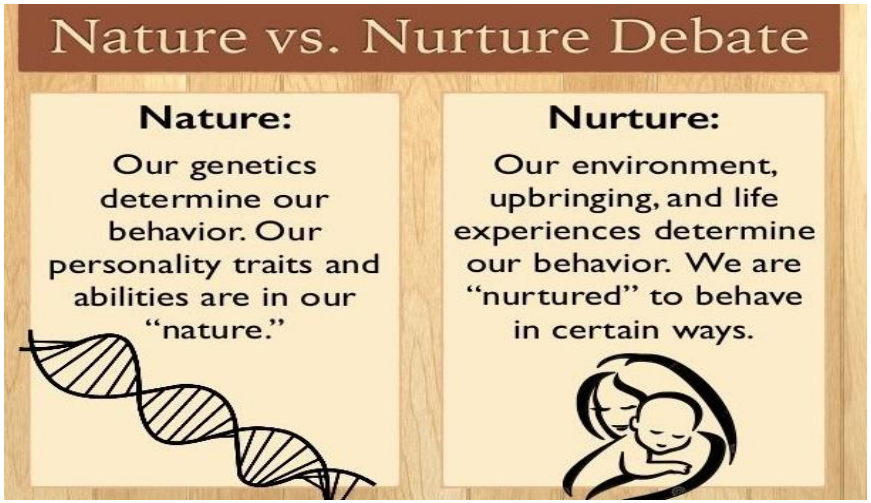
Twin Studies

- Traditionally the most favored model for separation of the genetic component of variance is based on studies of twins
  - Monozygotic twins share 100% of their genes
  - Dizygotic twins share 50% on average.



Twin Studies

- Genetic contribution to the BMI has been estimated to be 64–84%. The limitation here might be that the twins **share environmental factors**.
- A powerful tool for estimating genetic influence is the study of **monozygotic twins reared apart →**
  - it is virtually a direct estimate of the heritability
  - does not rely on the equal environmental exposure assumption



THE BODY-MASS INDEX OF TWINS WHO HAVE BEEN REARED APART

ALBERT J. STUNKARD, M.D., JENNIFER R. HARRIS, PH.D., NANCY L. PEDERSEN, PH.D., AND GERALD E. MCCLEARN, PH.D.

Study Summary

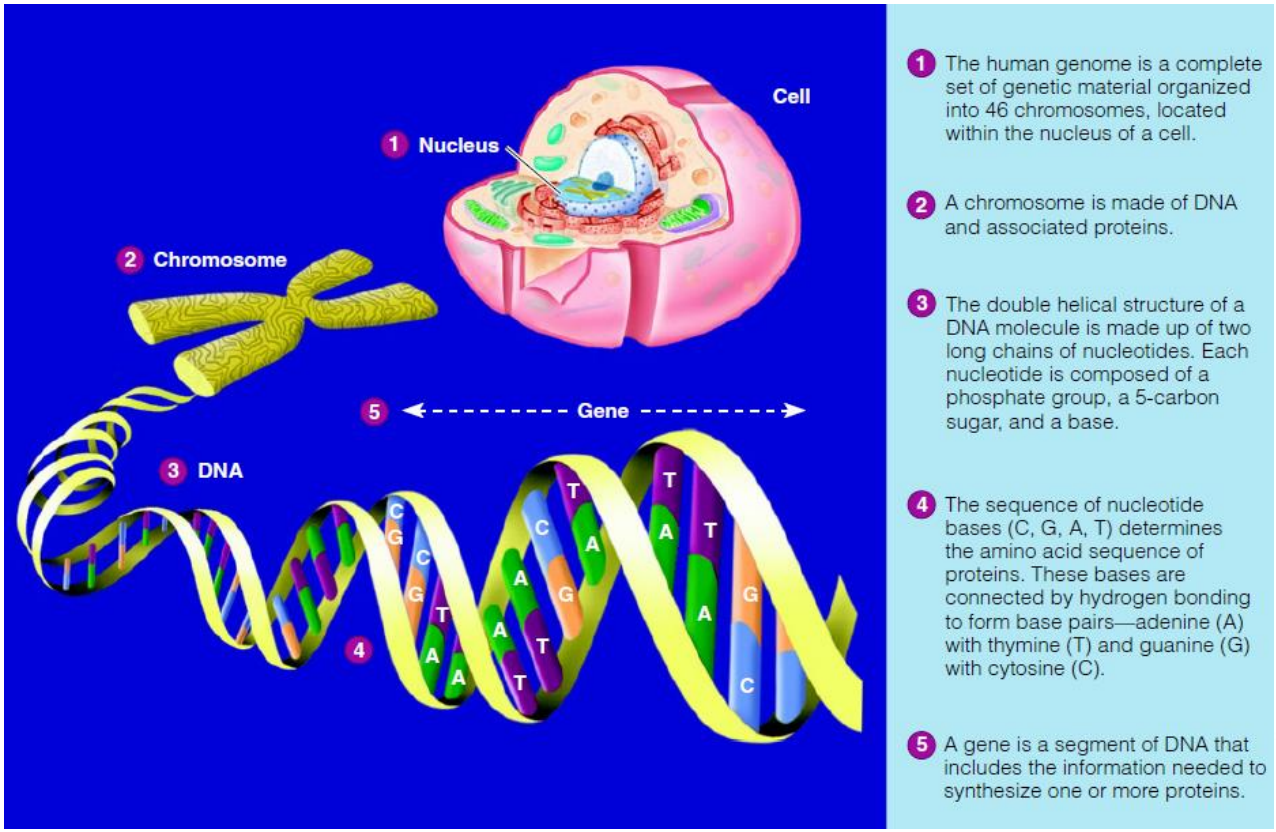
- The samples consisted of:
  - **Identical**: 93 reared apart and 154 reared together
  - **Fraternal**: 218 reared apart and 208 reared together
- These were participants in the Swedish Adoption/Twin Study of Aging
- The results showed strong evidence that heredity (genetics) plays a significant role in determining BMI. These values suggest that genetics account for about **70% of the variation in BMI for men** and **66% for women**, even when the twins were raised in **different environments**.

2. Specific Genes of Obesity

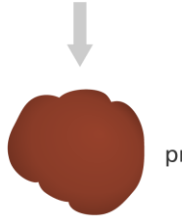
- Hereditary factors involved in obesity are associated with three types of biochemical processes:

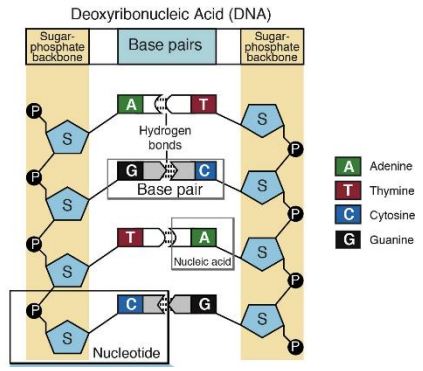
1) **Food intake** biochemical pathway (Satiety, hunger, and amount of food eaten)
2) Energy **metabolism** process (Energy from food is used or stored)
3) **Adipogenesis** process (Creating adipocytes).

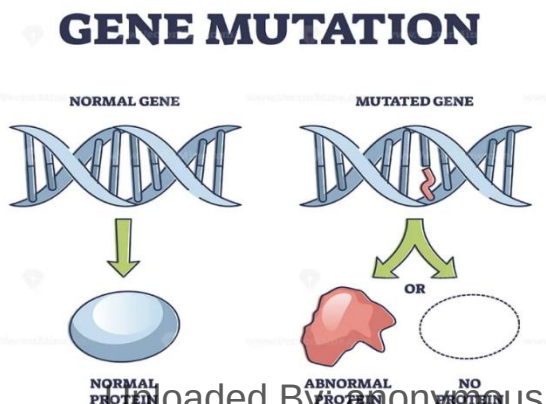
Basic Genetic Terms



1. The human genome is a complete set of genetic material organized into 46 chromosomes, located within the nucleus of a cell.
2. A chromosome is made of DNA and associated proteins.
3. The double helical structure of a DNA molecule is made up of two long chains of nucleotides. Each nucleotide is composed of a phosphate group, a 5-carbon sugar, and a base.
4. The sequence of nucleotide bases (C, G, A, T) determines the amino acid sequence of proteins. These bases are connected by hydrogen bonding to form base pairs—adenine (A) with thymine (T) and guanine (G) with cytosine (C).
5. A gene is a segment of DNA that includes the information needed to synthesize one or more proteins.

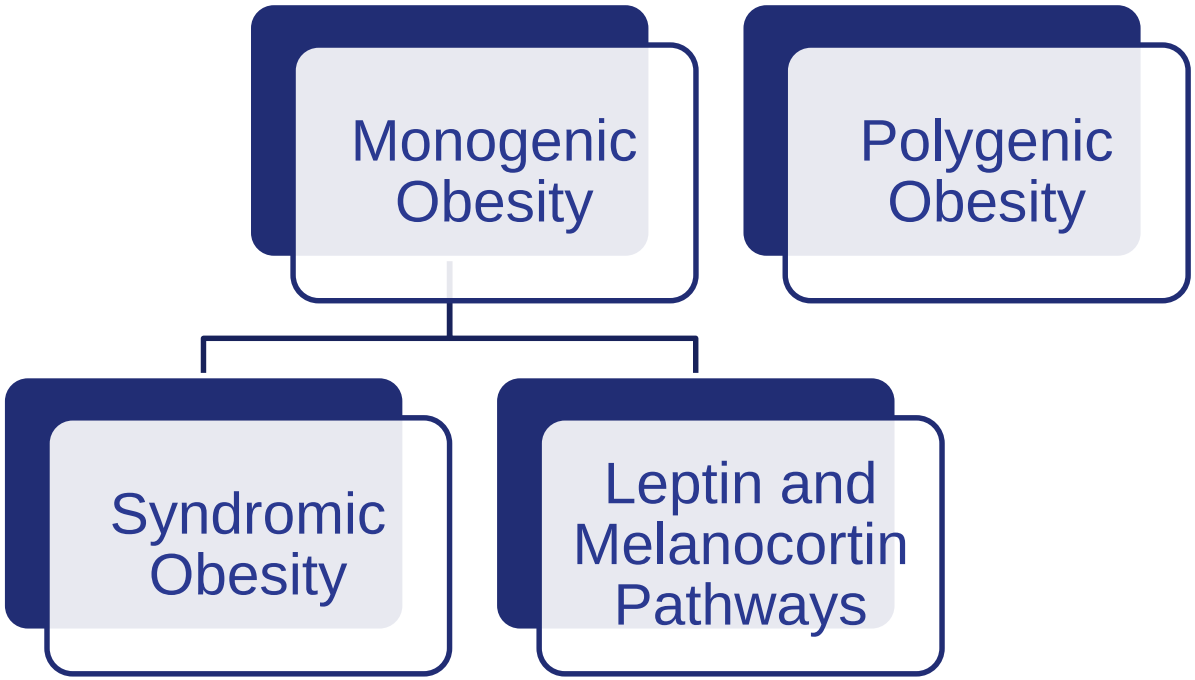






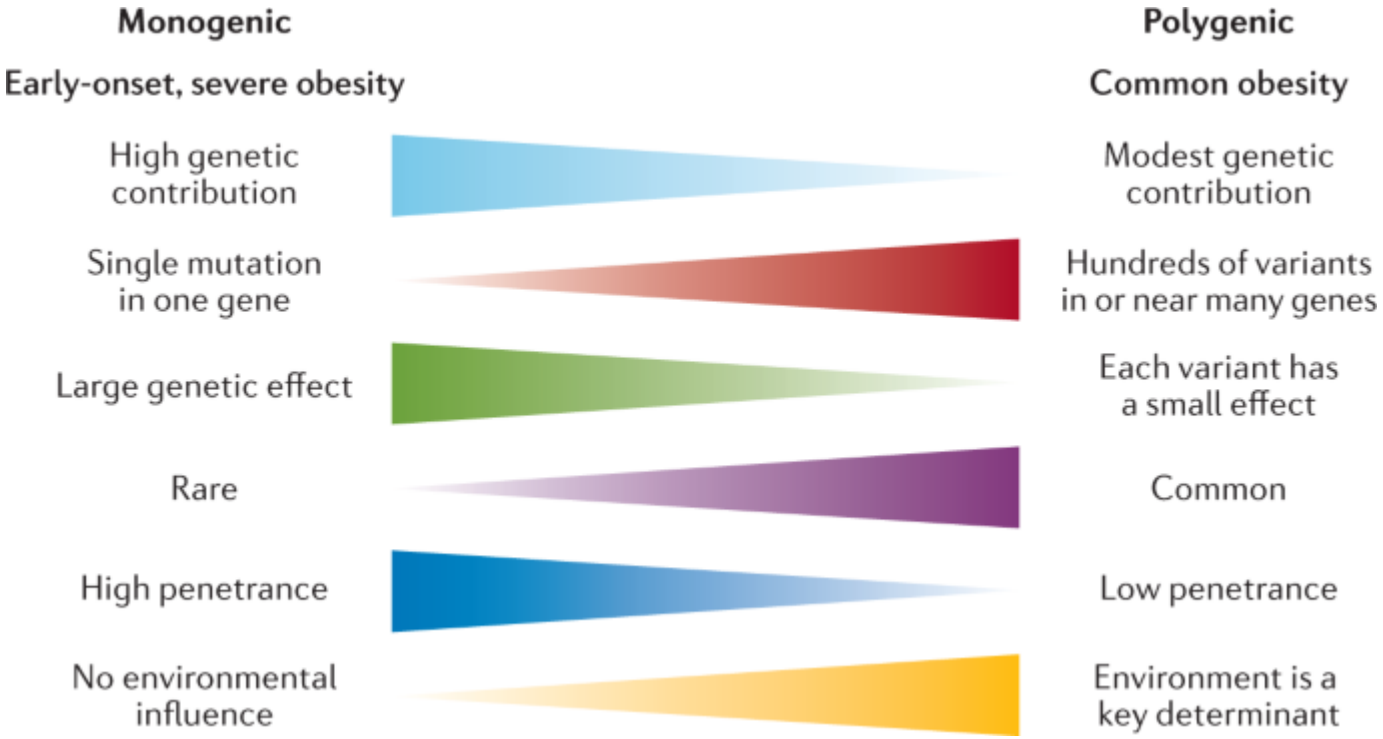
Specific Genes

Obesity can be categorized into monogenic obesity and polygenic obesity, based on the **number of genes** believed to be involved



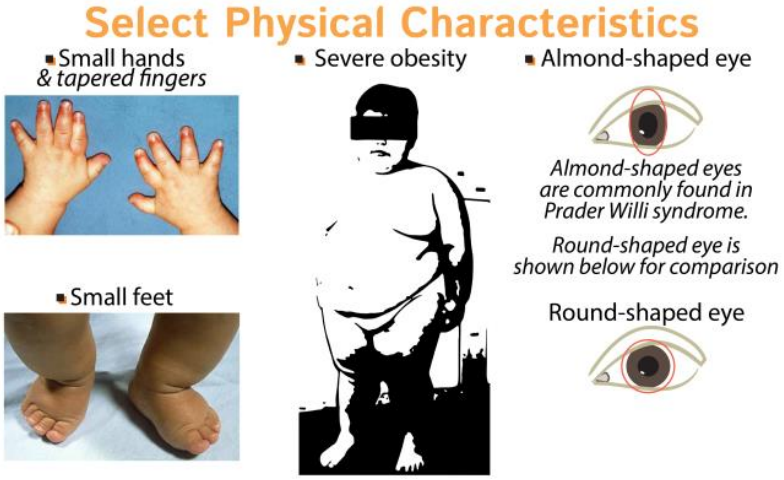
Monogenic Obesity

- Monogenic forms of obesity are rare, severe, and start in childhood. These single-gene disorders include cases in which obesity is one of many clinical symptoms



The genetics of obesity: from discovery to biology. Ruth J. F. Loos & Giles S.H. Yeo

Monogenic Obesity



1. **Syndromic Obesity**

The obesity occurs as part of a **syndrome. Example:**

Prader-Willi Syndrome (PWS)

PWS is perhaps the most common of the obesity syndromes (prevalence 1/25,000 births).

Characteristics: Obesity, reduced fetal activity, muscular hypotonia at birth, short stature, small hands and feet, intellectual disability, hypogonadism, and hyperphagia.

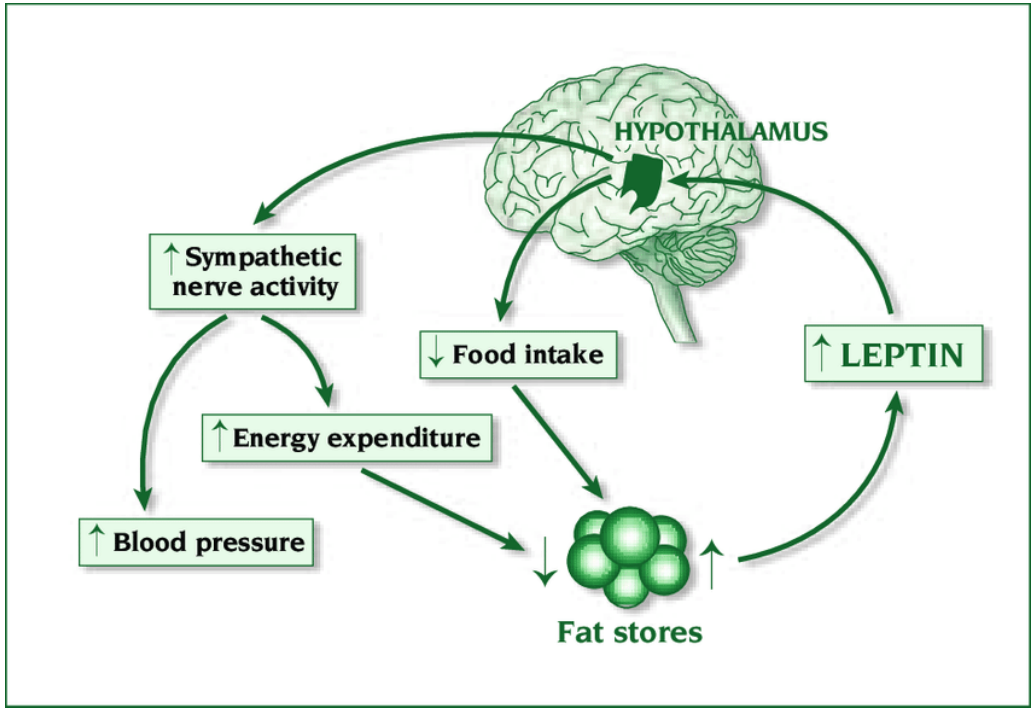
Monogenic Obesity

2. **Alteration of the Leptin and Melanocortin Pathways**

Some disorders specifically affect key factors of body **weight regulation** linked to the **leptin** and **melanocortin** pathways

Monogenic Obesity

1. Leptin and Leptin Receptors:



Case 1: Some humans with severe forms of hyperphagia and obesity have been shown to have **congenital leptin deficiency**

Case 2: Mutations affecting the **leptin receptor**, rather than leptin levels, are responsible for obesity and hyperphagia in humans.

Monogenic Obesity

- Congenital leptin deficiency

LEP gene mutations that cause congenital leptin deficiency lead to an absence of leptin

– Severe early-onset obesity (first few months of life)

– Intense hyperphagia with food-seeking behavior

– inability to discriminate between appetizing and bland foods.

– Hyperinsulinemia

– Respond well to therapy (daily subcutaneous injections of recombinant human leptin)

Monogenic Obesity

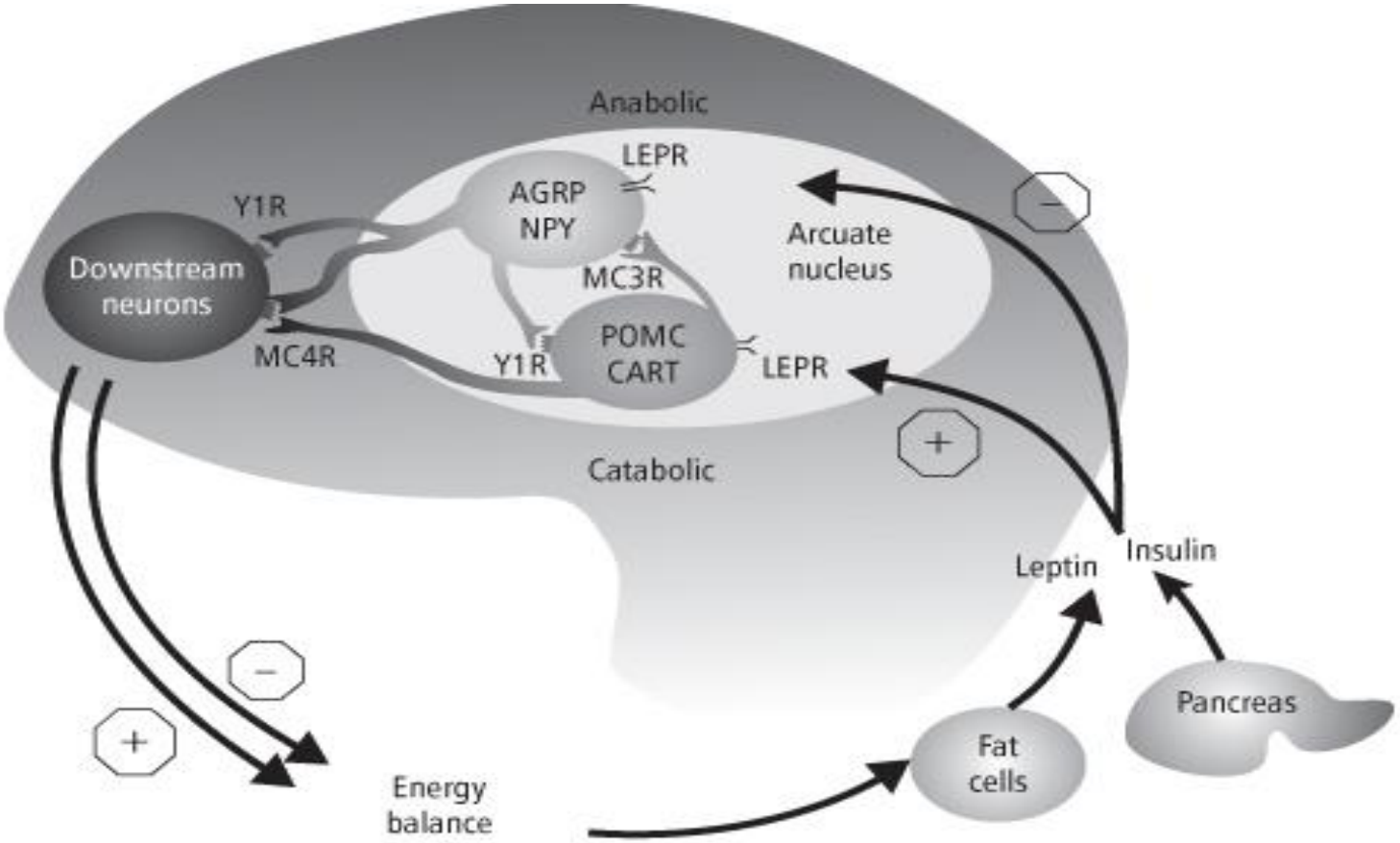
2. **Proopiomelanocortin (POMC) and Melanocortin-4 Receptor (MC4R)**

The POMC protein plays a role in the transmission of the leptin signal from the periphery to the brain.

POMC-derived neuropeptides act on the melanocortin-4 receptor (MC4R), increasing the receptor's activity when it is activated.

POMC deficiency in humans has been reported in several patients and results in hyperphagia and early-onset obesity due to loss of melanocortin signaling.

Monogenic Obesity

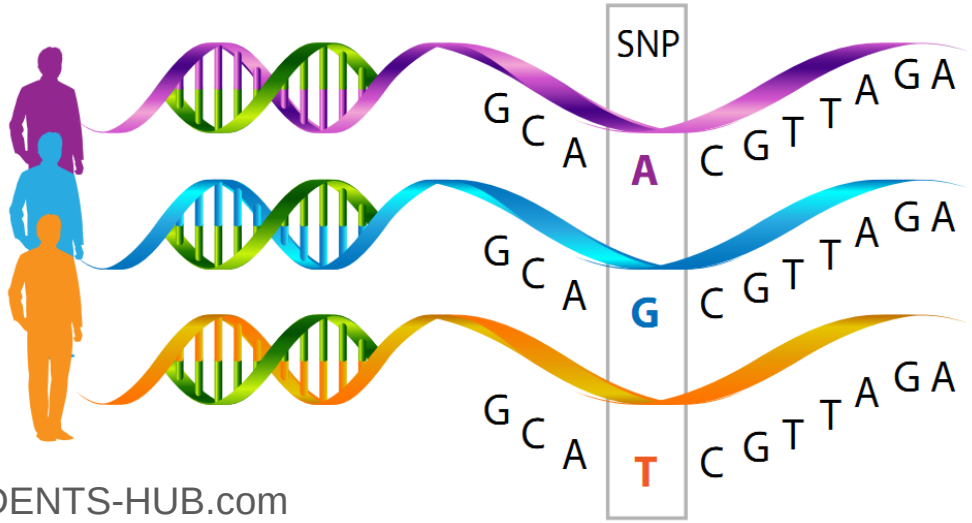


Polygenic Obesity

- The most common types of obesity result from **interactions among multiple genes**, **environmental** factors, **behavioral** habits, and **lifestyles**.
- Many genes have been studied by a variety of genetic approaches and are thought to be associated with body mass, body fat, and fat distribution, or their potential to affect food intake, energy expenditure, nutrient partitioning, or adipogenesis.
- **They do not necessarily indicate causal relationships between genes and traits**.

Polygenic Obesity

- More than 100 polygenes/polygenic loci that play a role in body weight regulation are identified.
- Genes considered “candidates” for BMI variance due to their roles in central or peripheral pathways controlling energy intake and expenditure.



Example: FTO gene SNPs (Single nucleotide polymorphisms)
One of the most studied genetic variants associated with obesity is **FTO rs9939609**
The SNP involves a change from adenine (A) to thymine (T) at a specific position in the FTO gene (alleles are different versions of that gene)

Table 2. Association of the rs9939609 Variant of the *FTO* Gene with Height, Weight, and Body-Mass Index in the Total Study Group.*

Characteristic	No. of Participants	TT	AT	AA	P Value
Height	2423	1.25±0.002	1.25±0.002	1.26±0.003	0.17
Weight	2422	26.99±0.168	27.16±0.148	28.07±0.270	0.003
BMI†	2422	17.09±0.075	17.17±0.066	17.58±0.121	0.003

* Plus–minus values are means ±SE, with adjustment for age and sex (i.e., age and sex were included as covariates) after univariate analysis of variance. AA denotes homozygous carriers of the A allele, AT heterozygous carriers, and TT non-carriers.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

The A allele of the rs9939609 (SNP; T>A)

An Obesity-Associated *FTO* Gene Variant and Increased Energy Intake in Children

Authors: Joanne Cecil, Ph.D., Roger Tavendale, Ph.D., Peter W att, Ph.D., Marion M. Hetherington, Ph.D., and Colin N.A. Palmer. **Published December 11, 2008**

What about managing weight?

- https://pubmed.ncbi.nlm.nih.gov/22310469/

- Key message: Individual differences in genetic makeup can significantly influence responses to treatment!

Abstract

Objective: The A-allele of the fat mass and obesity-associated (FTO) gene variant rs9939609 has been associated with increased body weight, whereas no effect on weight loss during weight reduction programs has been observed. We questioned whether the AA-genotype interferes with weight stabilization after weight loss.

Design: We conducted a monocentric, longitudinal study involving obese individuals. The FTO gene variant rs9939609 was genotyped in participants attending a weight reduction program that was divided into two phases: a weight reduction period with formula diet (12 weeks) and a weight maintenance phase (40 weeks). Body weight, body mass index (BMI), blood pressure and concentrations of blood glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides were determined in week 0 (T(0)), after 12 weeks (T(1)) and at the end in week 52 (T(2)).

Subjects: A total of 193 obese subjects aged between 18 and 72 years (129 female, 64 male; initial body weight: 122.4±22.3 kg, initial BMI: 41.8±6.7 kg m(-2)) were included.

Results: Genotyping revealed 32.1% TT-, 39.4% AT- and 28.5% AA-genotype carriers. At T (0), carriers of the AA-genotype had significantly higher body weight (P=0.04) and BMI (P=0.005) than carriers of the TT-genotype. Of the 193 participants, 68 discontinued and 125 completed the program. Dropout rate was not influenced by genotype (P=0.33). Completers with AA-genotype showed significantly lower additional weight loss during the weight maintenance phase than TT-genotype carriers (P=0.02). Furthermore, among participants facing weight regain during weight maintenance (n=52), more subjects were carrying the AA-genotype (P=0.006). No influence of genotype on weight reduction under formula diet was observed (P=0.32).

Conclusion: In this program, the AA-genotype of rs9939609 was associated with a higher initial body weight and did influence success of weight stabilization. Thus, emphasizing the maintenance phase during a weight reduction program might result in better success for AA-genotype carriers.

Polygenic Obesity

Table 10.1 List of GWAS-derived SNPs and corresponding genes associated with body mass index (BMI) or (extreme) obesity

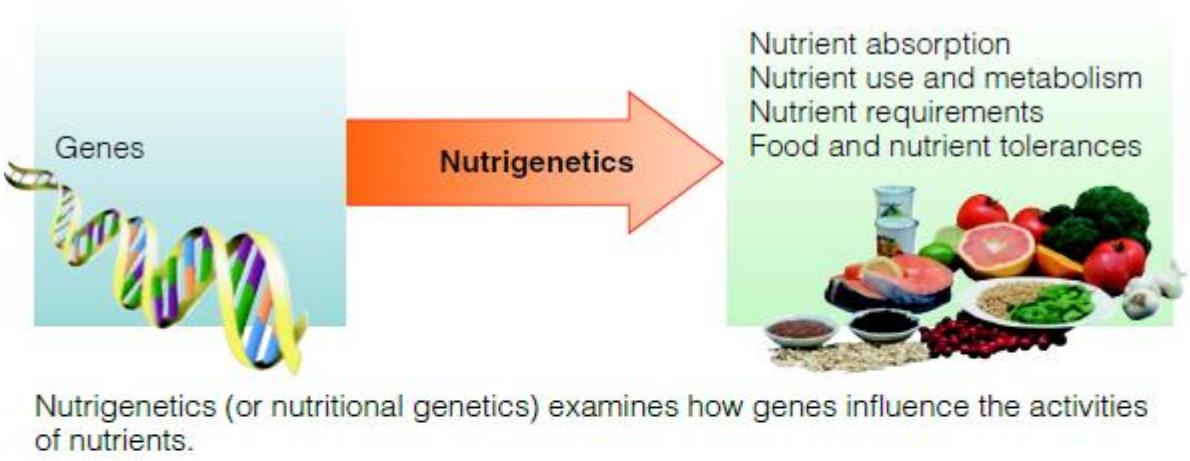
Chrom.	SNPs	Nearest gene	Phenotype	References
1	rs657452	*AGBL4*	BMI	[1]
1	rs11583200	*ELAVL4*	BMI	[1]
1	rs17024258	*GNAT2*	Obesity	[20]
1	rs11208659	*LEPR*	Childhood obesity	[64]
1	rs2820292	*NAV1*	BMI	[1]
1	rs2815752, rs2568958, rs1993709	*NEGR1*	BMI, obesity, overweight	[17, 18, 64]
1	rs1555543	*PTBP2*	BMI	[16]
1	rs12145833	*SDCCAG8*	Childhood obesity	[22]
1	rs10913469, rs543874, rs574367, rs516636, rs591120	*SEC16B*	BMI, obesity, overweight	[18, 20, 23, 65, 68, 70]
1	rs977747	*TAL1*	BMI	[1]
1	rs1514175, rs12142020, rs1040070, rs1514174	*TNNI3K*	BMI, obesity	[16, 20, 23, 65]
1	rs17381664	*ZZZ3*	Obesity	[20]
2	rs116612809	*BRE*	BMI	[66]
2	rs17203016	*CREB1, KLF7*	BMI	[1]
2	rs11688816	*EHBP1*	BMI	[1]
2	rs7599312	*ERBB4*	BMI	[1]
2	rs887912	*FANCL*	BMI, obesity, overweight	[16]
2	rs12617233	*FANCL, FLJ30838*	BMI	[67]
2	rs1460676	*FIGN*	BMI	[1]
2	rs11126666	*KCNK3*	BMI	[1]
2	rs2890652	*LRP1B*	BMI	[16]
2	rs492400	*PLCD4, CYP27A1, USP37, TTLL4, STK36, ZNF142, RQCD1*	BMI	[1]
2	rs713586, rs6545814, rs1561288, rs6752378, rs10182181	*POMC*	BMI, obesity, overweight	[16, 20, 23, 65, 68]
2	rs6548238, rs7561317, rs2867125, rs12463617, rs4854344	*TMEM18*	BMI, obesity, overweight	[16–18, 20, 23, 64, 65, 67]

3. Gene–Environment Interactions

- The genetic and environmental aspects of obesity cannot be considered in isolation
- Responses to dietary restrictions may vary depending on an **individual's genetic make-up**
- Although certain genes may increase one's chances of becoming obese, changes in behavior or the environment may reduce the chances of developing this condition.
- So → → changing the current environment to one less conducive to obesity development may be critical to preventing the expression of genetic risk for obesity.

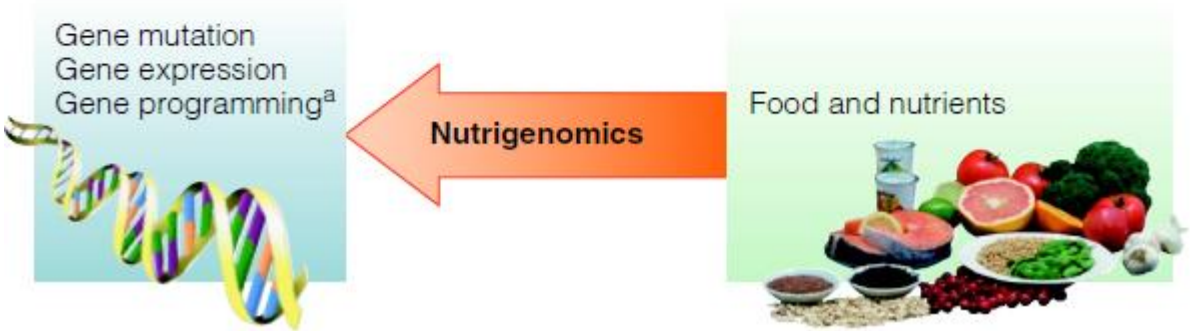
Let’s discuss examples:

- FTO gene variants on responses to dietary fat intake



Nutrigenetics (or nutritional genetics) examines how genes influence the activities of nutrients.

- The effect of omega-3 on gene expression related to fat metabolism in obesity



Gene–Environment Interactions

- The increase in the prevalence of obesity in the last 30 years demonstrates the importance of changing environmental factors.
- Further evidence for the critical role of environmental factors in the development of obesity comes from migrant studies:

→ Let's take a look

ENDOCRINE SOCIETY JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

J Clin Endocrinol Metab. 2010 Nov; 95(11): E358–E362.
Published online 2010 Jul 28. doi: 10.1210/jc.2010-0297

PMCID: PMC2968731
PMID: 20668044

Differences in Insulin Resistance in Mexican and U.S. Pima Indians with Normal Glucose Tolerance

Julian Esparza-Romero, Mauro E. Valencia, Maria Elena Martinez, Eric Ravussin, Leslie O. Schulz, and Peter H. Bennett

Study Summary

- Mexican Pima Indians have **lower insulin resistance** in comparison with their genetically related U.S. counterparts, even after controlling for differences in obesity, age, and sex.
- This finding underscores the importance of lifestyle factors as **protecting factors**

Physical and biochemical characteristics by population group with normal glucose tolerance

Variable	Mexican Pima	U.S. Pima	*P* value
n	194	449	
Age (yr)	36.8 ± 14.7	32.5 ± 10.0	<0.0001
BMI (kg/m^2)	24.6 ± 4.2	34.1 ± 8.0	<0.0001
Body fat (%)	26.9 ± 11.0	39.6 ± 9.5	<0.0001
Waist circumference (cm)	83.1 ± 11.0	107.5 ± 19.4	<0.0001
Fasting glucose (mg/dl)	89.0 ± 8.8	92.9 ± 8.8	<0.0001
2-h glucose (mg/dl)	94.6 ± 21.4	104.0 ± 20.3	<0.0001
2-h insulin (μU/ml)[a]	21.8 (18.8, 25.4)	64.1 (57.6, 71.4)	<0.0001
HDL cholesterol (mg/dl)	39.1 ± 9.4	44.7 ± 12.5[b]	<0.0001
Total cholesterol (mg/dl)	170.6 ± 37.1	173.0 ± 32.6	0.4234
Triglycerides (mg/dl)[a]	104.4 (96.8, 112.7)	101.0 (93.4, 109.3)[c]	0.5588
SBP (mm Hg)	115.7 ± 13.7	118.0 ± 15.3	0.0729
DBP (mm Hg)	71.3 ± 10.6	70.5 ± 11.1	0.3869
PA (METs, h/wk)[a]	131.7 (121.5, 142.8)	32.7 (27.9, 38.8)	<0.0001

Summary: Key Points

1. The heritability of adiposity has been shown to be substantial, complex, and non-additive;
2. Several regions of the human genome appear to harbor genes increasing the risk of obesity
3. The interactions between environmental and genetic factors are likely to play an important role in the development of obesity