How Genetic, Extragenetic, and Epigenetic Factors Affect Body Weight

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ASBP Definition of Obesity

"Obesity is defined as a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences."

Fat Mass Disease

Cardiovascular

- Congestive heart failure and cor pulmonale
- Varicose veins
- Thromboembolic events (i.e., pulmonary embolus, stroke, etc.)
- Hypertension (i.e., compression of kidney)

Pulmonary

- Dyspnea
- Obstructive sleep apnea
- Hypoventilation syndrome
- Pickwickian syndrome
- Asthma

Neurologic

- Intracranial hypertension (pseudotumor cerebri) due to increased intra-abdominal pressure, sleep apnea, etc.
- Stroke (see “cardiovascular”)
- Nerve entrapment (i.e., meralgia paresthetica, carpal tunnel syndrome, etc.)

Fat Mass Disease

Musculoskeletal

- Immobility
- Osteoarthritis (e.g. knees, hips)
- Low back pain
- Myalgias
- Altered center of gravity
- Impaired balance

Gastrointestinal

- Gastrointestinal reflux
- Hernias

Integument

- Stria distensae (skin stretch marks)
- Stasis pigmentation
- Venous stasis ulcers
- Cellulitis
- Skin tags
- Intertrigo (i.e. bacterial, fungal skin fold infections)
- Carbuncles

Fat Mass Disease

Psycho-Social

- Depression
- Hopelessness
- Low self esteem
- Body image dissatisfaction
- Diminished sex drive
- Impaired intimacy and sexual relationships
- Decreased work productivity
- Increased work absenteeism
- Decreased work presenteeism

- **Biases**
  - Society
  - Family
  - Workplace
  - Harassment
  - Bullying
- **Negative self or external perceptions**
  - “Unmotivated”
  - “Weak-willed”
  - “Less intelligent”
  - “Less attractive”
  - “Unsuccessful”
  - “Overindulgent”
  - “Lazy”

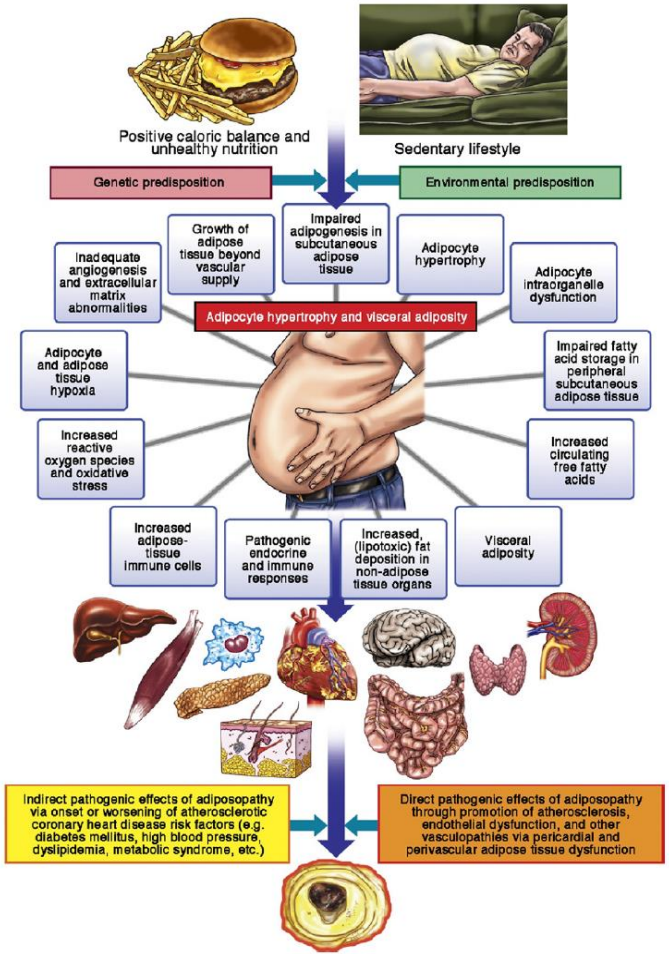


Figure 1 Adiposopathy: Simplified Relationship Between Pathogenic Adipose Tissue and Cardiovascular Disease

Bays. JACC 2011;57:2461-73

Adiposopathy (Sick Fat Disease)

- High blood glucose (prediabetes mellitus, type 2 diabetes mellitus)
- High blood pressure
- Metabolic syndrome
- Insulin resistance
- Hepatosteatosis (fatty liver)
- Hyperuricemia and gout
- Adiposopathic dyslipidemia
  - Increased triglyceride levels
  - Decreased high-density lipoprotein cholesterol levels
  - Increased atherogenic particle number (increased apolipoprotein B)
  - Increased proportion of small, dense, low-density lipoprotein particles
  - Increased triglyceride-rich lipoproteins
  - Increased lipoprotein-remnant lipoproteins
- Cholelithiasis
- Acanthosis nigricans
- Nephrolithiasis
- Glomerulopathy
- Pro-thrombotic predisposition
- Neuropsychiatric diseases (such as worsening depression due to adiposopathic immune and endocrine responses)
- Asthma (due to adiposopathic immune and endocrine responses)
- Worsening of other inflammatory diseases (osteoarthritis, atherosclerosis, etc.)

Adiposopathy (Sick Fat Disease)

Sex-specific Manifestations

Women

- Hyperandrogenemia
- Hirsutism
- Acne
- Polycystic ovarian syndrome
- Menstrual disorders
- Infertility
- Gestational diabetes mellitus
- Preeclampsia
- Thrombosis

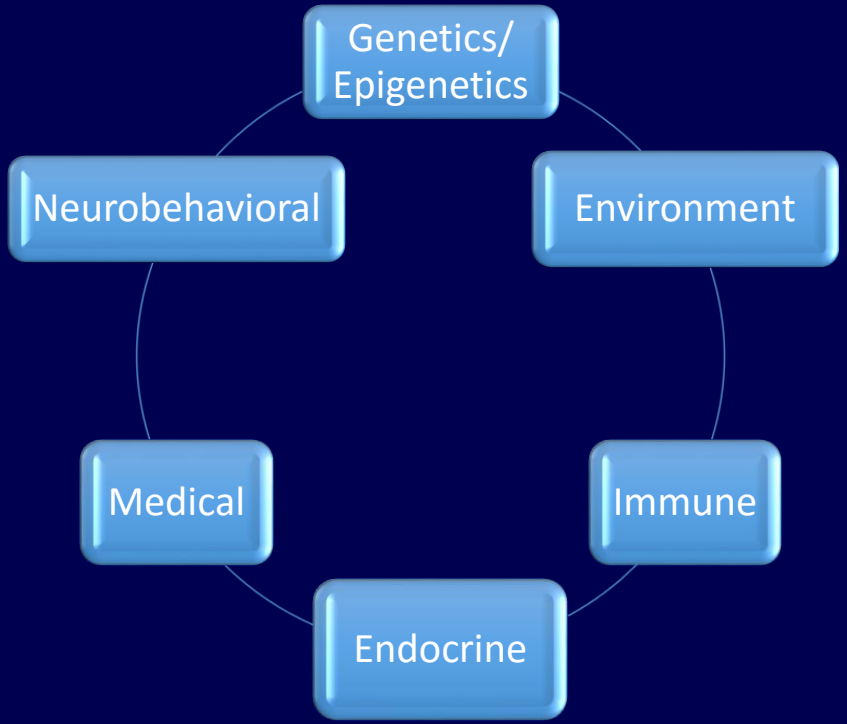
Men

- Hypoandrogenemia
- Hyperestrogenemia
- Erectile dysfunction
- Low sperm count
- Infertility

Cancer Manifestations

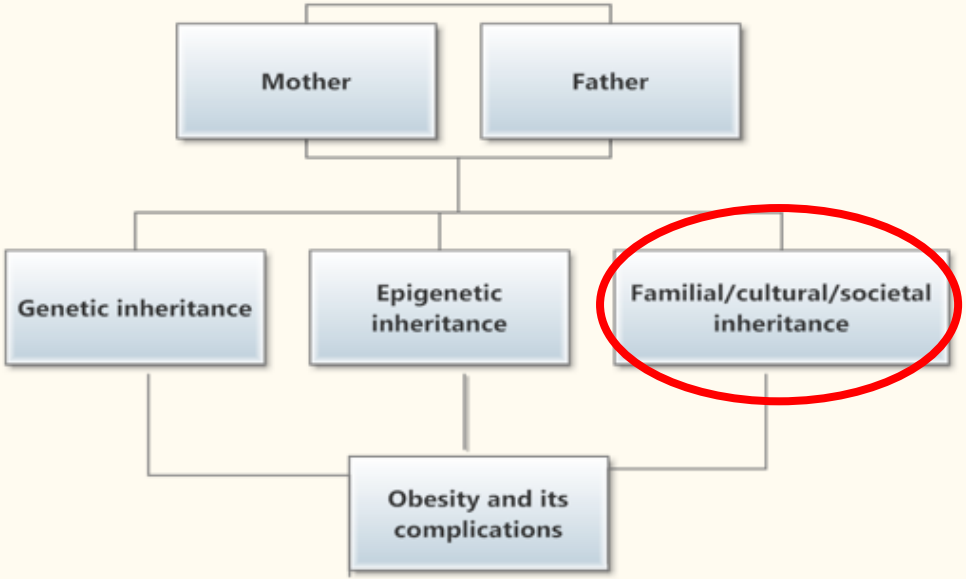
- Postmenopausal breast cancer
- Colon cancer
- Endometrial/uterine cancer
- Esophageal cancer
- Stomach cancer
- Pancreatic cancer
- Renal cell/kidney cancer
- Gallbladder cancer
- Brain cancer
- Leukemia
- Non-Hodgkin's lymphoma
- Multiple myeloma
- Liver cancer
- Cervical cancer
- Ovarian cancer
- Prostate cancer (prognosis not necessarily increased risk)
- Bladder cancer
- Thyroid cancer

Obesity as a Multifactorial Disease



Obesity and Inheritance

Figure 1. Multifactorial inheritance factors that may contribute to obesity and its complications



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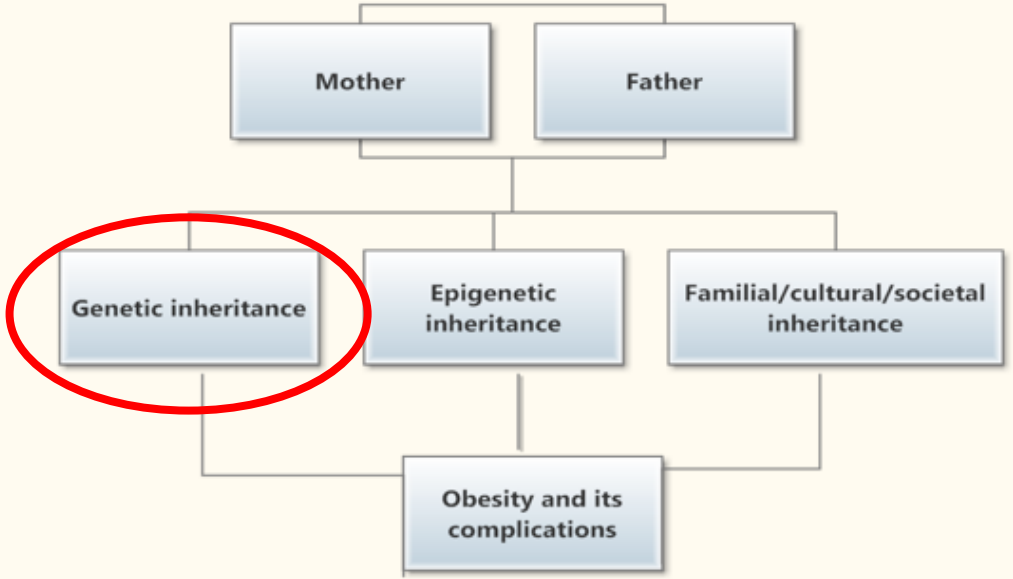

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Obesity and Genetics

Genetic syndrome	Clinical presentation	Gene abnormality
Melanocortin 4 receptor deficiency	• Obesity, especially in families • Hyperphagia in early childhood • Increase in bone mineral density – "big boned" • Accelerated linear growth • Reduced sympathetic nervous activity	• Autosomal dominant or recessive, but also co-dominant • Most common known genetic defect predisposing to obesity • Polygenetic, with no single gene abnormality yet identified
Albright's hereditary osteodystrophy	• Obesity • Short stature • Rounded face • Skeletal defects: Shortened fourth metacarpals and other bones of the hands and feet • Dental hypoplasia • Soft-tissue calcifications/ossifications • Pseudohypoparathyroidism (hypocalcemia, hyperphosphatemia)	• Possibly autosomal dominant • Associated with molecular defect in the gene (GNAS1) which encodes for the alpha subunit of the stimulatory G protein
Prader-Willi syndrome	• Obesity, often hyperphagic • Short stature • Weak muscle tone • Poor growth • Small hands/feet • Delayed development • Underdeveloped genitals (often with infertility) • Behavioral/emotional challenges • Mild to moderate intellectual impairment • Insatiable appetite • Narrow forehead • Almond-shaped eyes • Triangular mouth • Often with fair skin and light colored hair	• Most common human genetic obesity syndrome • Not inherited • Most cases involve loss of function of a portion of chromosome 15

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Obesity and Genetics

Bardet-Biedl syndrome	• Obesity • Metabolic abnormalities (e.g., type 2 diabetes mellitus, high blood pressure, dyslipidemia) • Blindness (retinal dystrophy and pigmentary retinopathy) • Anosmia • Hearing loss • Dysmorphic extremities: Polydactyly and short or fused fingers and toes • Poor Coordination • Dental abnormalities • Intellectual disability • Behavioral/emotional challenges • Hypogonadism (with infertility) • Renal cystic disease; renal insufficiency, which may lead to end-stage renal disease	• Autosomal recessive • Mutations of at least 16 genes (BBS genes) applicable to cilia involved in cell movement, chemical signaling, and sensory input (sight, hearing, and smell)
Cohen syndrome	• Obesity • Developmental delay • Intellectual disability • Small head size • Narrow hands and feet with slender fingers • Weak muscle tone • Retinal dystrophy • Joint hypermobility • Thick hair and eyebrows • Thick eyelashes • "Open mouth" expression with incisoral prominence • Low white blood cell count • Overly friendly behavior	• Typically auto recessive • Mutation of the VPS13B gene (COH1 gene)

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Obesity and Genetics

Börjeson-Forssman-Lehmann syndrome	• Obesity • Mainly in males • Intellectual disability • Seizure disorders • Large earlobes • Shortened toes • Small genitalia • Gynecomastia	• X-linked disorder • Mutation of the zinc finger gene PHF6 (located on the X chromosome)

Examples of other genetic conditions associated with obesity include:

- leptin deficiency
- leptin receptor deficiency
- src homology 2 B adapter protein (SH2B1) mutations
- carboxypeptidase E mutations
- prohormone convertase-1 deficiency
- proopiomelanocortin deficiency
- **proprotein convertase subtilisin kexin 1/3 deficiency**
- brain derived neurotrophic factor (BDNF) deficiency
- TrkB deficiency
- Sim1 deficiency
- maternal uniparental disomy of chromosome 14
- trisomy 21
- fragile X syndrome
- Turner's syndrome
- Alstrom syndrome
- Carpenter syndrome
- Rubinstein-Taybi syndrome
- Rapid-onset Obesity with Hypothalamic dysfunction, Hypoventilation and Autonomic Dysregulation (ROHHAD syndrome)
- deletions/mutations of various other gene loci and polymorphisms of fat mass and obesity associated (FTO) gene located on chromosome 16

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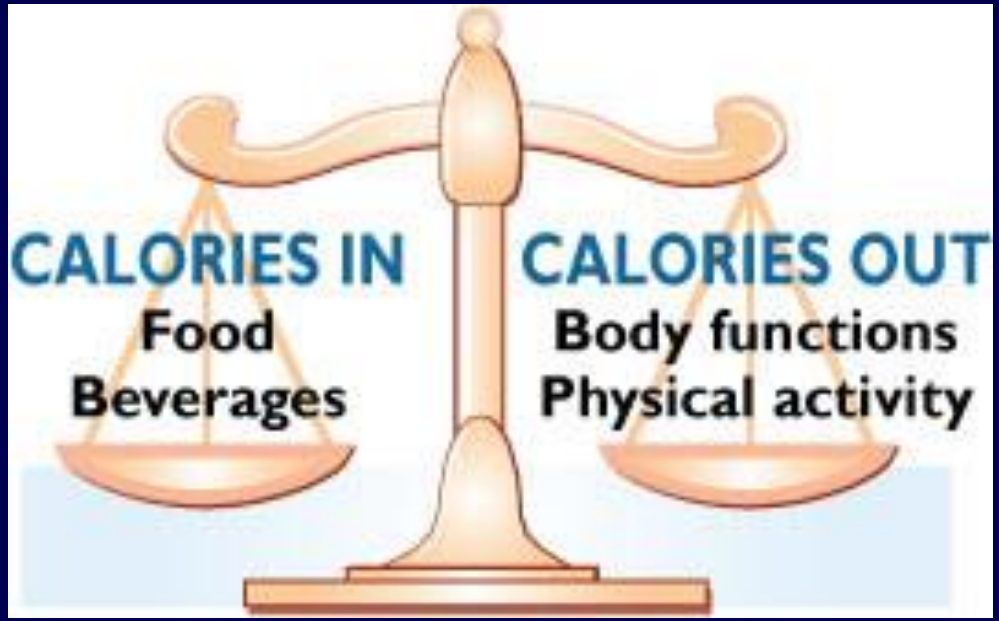
Table 1 Official and alternative protein name of the nine PCSK members

Member type	Official name	Alternative name
Typical	PCSK1	PCSK1
	PCSK2	PCSK2
	FURIN	PCSK3
	PCSK4	PCSK4
	PCSK5	PCSK5
	PCSK6	PCSK6
	PCSK7	PCSK7
Atypical	MBTPS1*	PCSK8
	PCSK9	PCSK9

-MBTPS1: membrane-bound transcription factor peptidase, site 1.

Choi, Korstanje. Biomark Res. 2013 Sep 18;1(1):27.

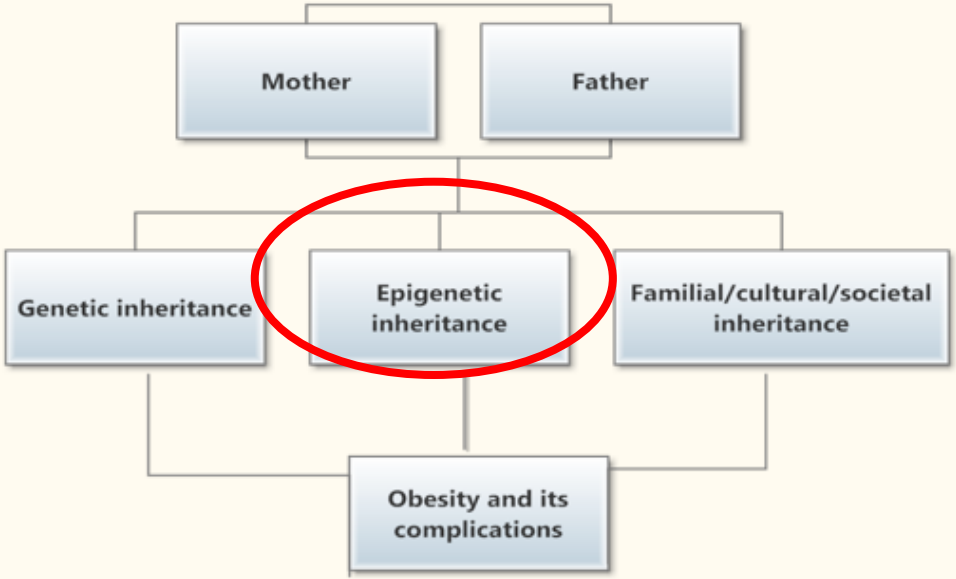
Obesity and Extragenetics



Centers for Disease Control: Division of Nutrition, Physical Activity, and Obesity http://www.cdc.gov/healthyweight/calories/ Accessed September 2015

Obesity and Inheritance

Figure 1. Multifactorial inheritance factors that may contribute to obesity and its complications



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Obesity and Inheritance

- Extragenetic and genetic factors promote obesity and its adiposopathic consequences.

- Epigenetic factors may also contribute to obesity and its adiposopathic consequences, not only in the offspring, but for future generations.

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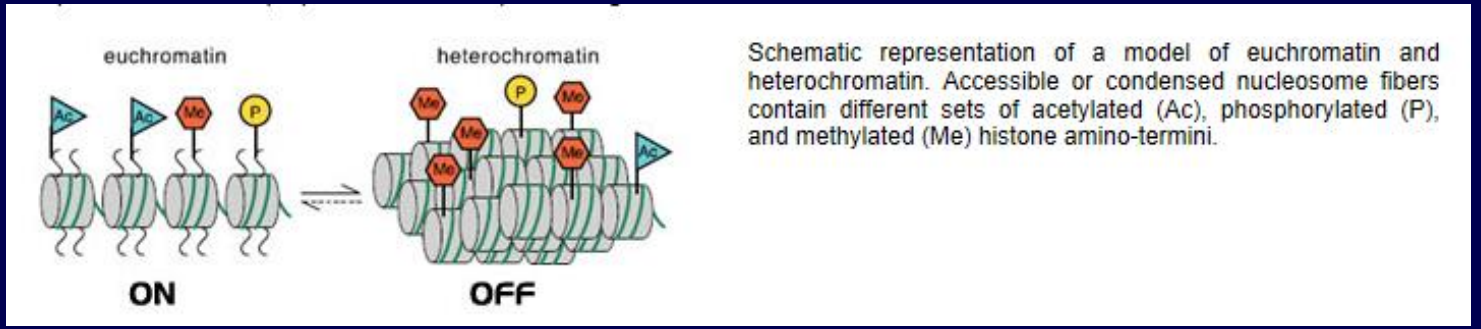
Epigenetics: What is it?

- Alterations in gene expression, without alteration in the genetic code
- Non-pathological: inactivation (heterochromatin formation) of one of two copies of x chromosome (Barr body) throughout lifetime of a woman



Schematic representation of a model of euchromatin and heterochromatin. Accessible or condensed nucleosome fibers contain different sets of acetylated (Ac), phosphorylated (P), and methylated (Me) histone amino-termini.

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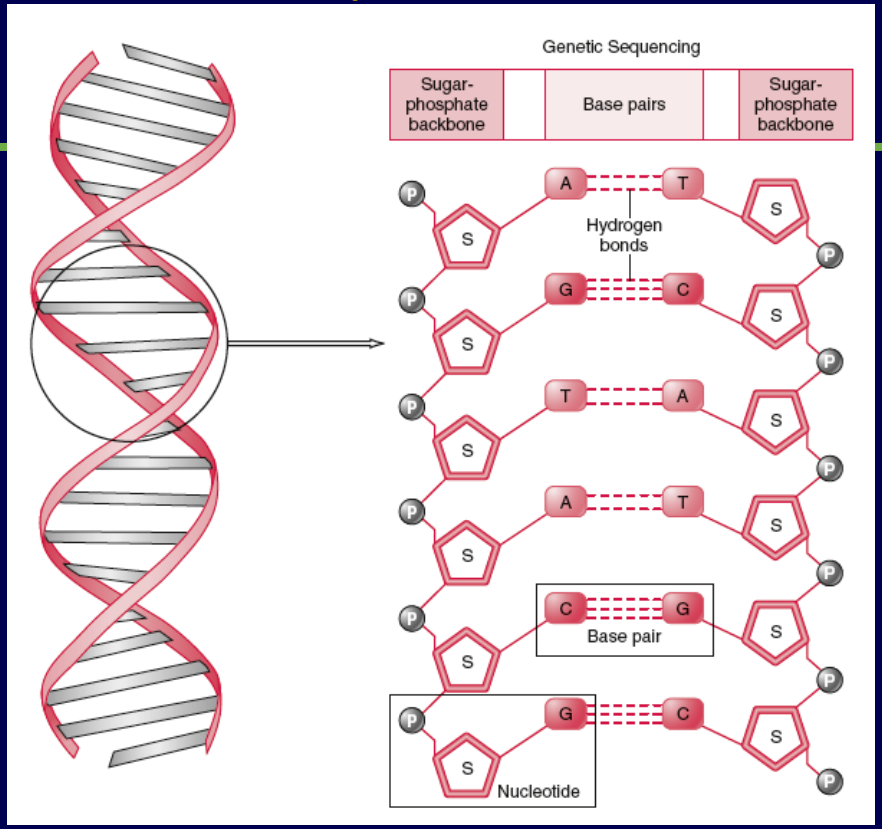
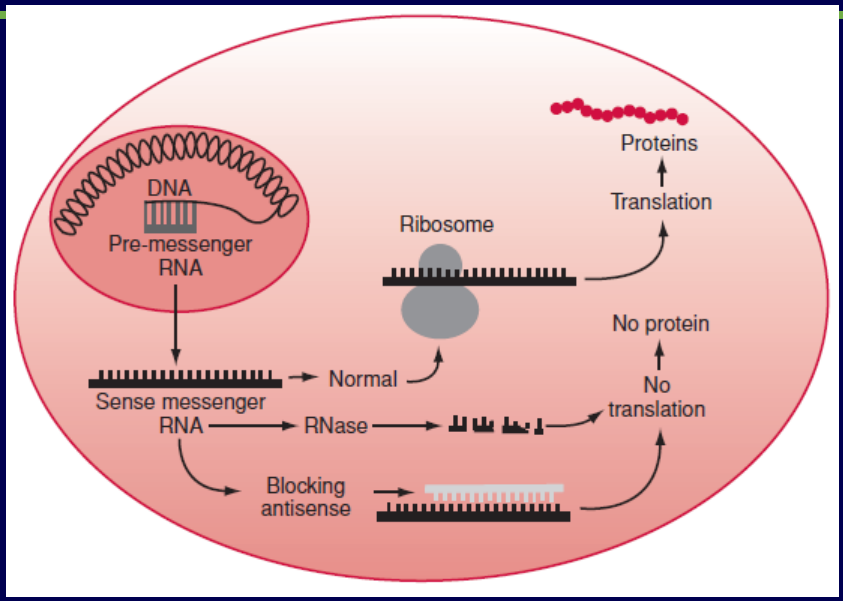
Deoxynucleic Acid (DNA) and Protein Translation

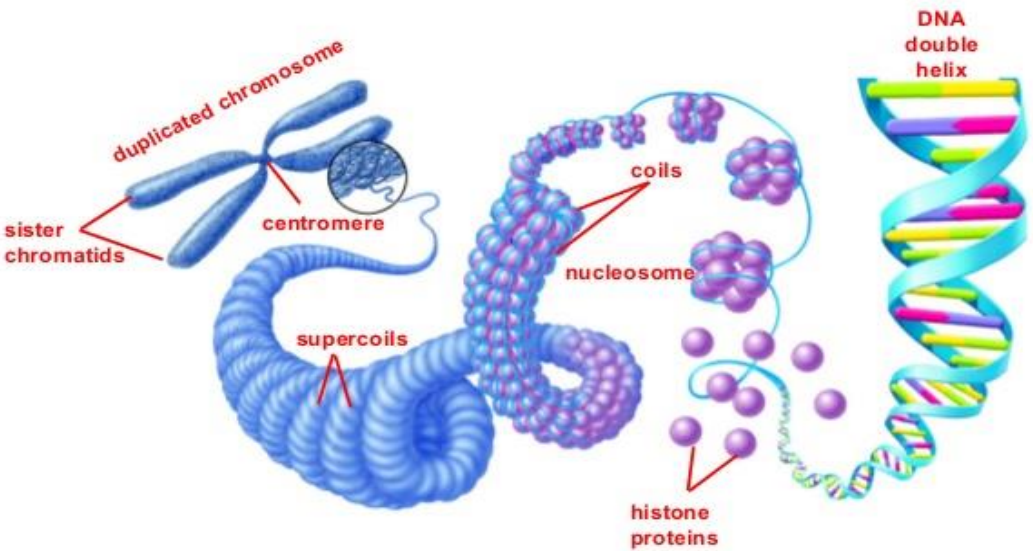


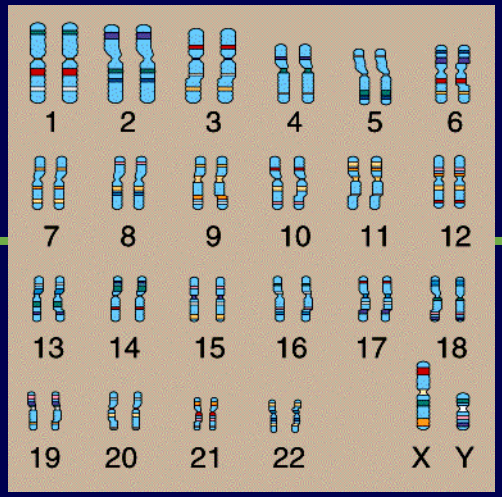


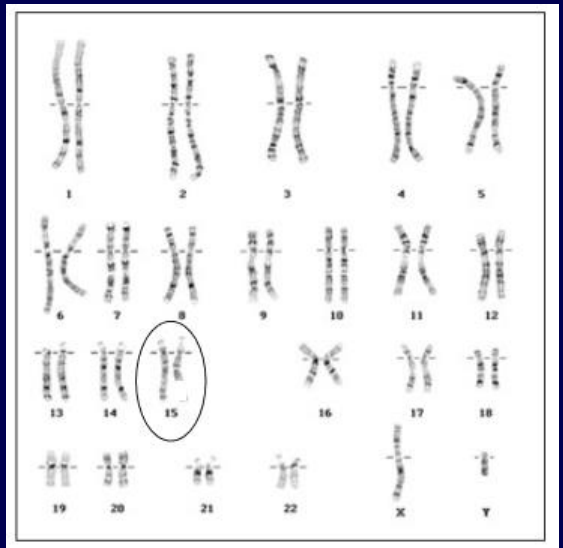
Bays. Chapter 44: Investigational Agents Affecting Atherogenic Lipoproteins. Clinical Lipidology: A Companion to Braunwald's Heart Disease, by Christie Ballantyne MD. ISBN-13: 978-1-4160-5469-6 ISBN-10: 1-4160-5469-3 Saunders. Dec 2008; 530-543.

Chromosomes

In eukaryotic cells, DNA is packaged into multiple chromosomes.







Prader Willi Syndrome

- Multisystemic genetic disorder caused by a maternally imprinted section of chromosome 15 paired with a lack of expression of a paternal section of chromosome 15
  - 70% due to paternal 15q11-q13 gene deletion
  - 25% maternal uniparental disomy: two copies from the mother; none from the father
  - <5% imprinting defects: Paternal section of chromosome is present, but imprinted due to a failure to erase the maternal imprint during spermatogenesis

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Epigenetic Regulation: How Does it Happen?

- DNA methylation: suppressive
- Histone modification
  - Methylation: suppressive
  - Acetylation: promotive
  - Other: ubiquitylation, phosphorylation, sumoylation, ribosylation, and citrullination

- Epigenetic-regulated cellular processes:
  - Cell differentiation: Guidance of stem cells to desired lineage fate
  - Dosage compensation: Lyonization (inactivation of one of two X chromosomes in women)
  - Genome structure maintenance: DNA damage repair
  - Genomic/parental imprinting: Small number of traits from one parent only, due to silencing of the imprinted gene
  - Repetitive element repression: Deactivation of repetitive genes via DNA methylation and histone modification (heterochromatin)

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Epigenetic Dysregulation: What Causes It?

Pathological:

- Obesogens: toxins such as tributyltin, brominated diphenyl ether 47, polycyclic aromatic hydrocarbons, as well as endocrine disrupting chemicals such as excessive estrogens or cortisol exposure in the womb or early life
- Lack of physical activity
- Infection
- Medications
- Endocrine disruptors: environmental pesticides, exogenous hormones, estrogenic agents (dichlordiphenyltrichloroethane or DDT), high-dose phytoestrogens, polychlorinated biphenyls, dioxins, bisphenol A), androgenic agents (testosterone), anti-estrogenic agents (low-dose phytoestrogens), anti-androgen agents (DDT)]

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Epigenetic Dysregulation: What About Caloric Balance?

Nutritional abnormalities:

- Adiposopathic disease development in an adult may be influenced by his/her perinatal environment
- Maternal nutrition affects epigenetic mechanisms during development in utero, resulting in pathogenic biologic changes maintained through subsequent cell division into adult, as well as generations

Overnutrition and gestational diabetes mellitus and increased offspring risk of obesity, overweight, and diabetes mellitus

- Increased transport of glucose, lipids, fatty acids, and amino acids to the fetus
- Increased delivery of nutrients to the fetus resulting in:
  - Modification of DNA and chromatin
  - Alterations in stem cell fate
  - Alterations in postnatal biologic processes involved in substrate metabolism

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Epigenetic Dysregulation: What About Caloric Balance?

Undernutrition and increased offspring risk of obesity, overweight, diabetes mellitus, and cardiovascular disease

- Alteration in metabolic programming resulting in adipose tissue abnormalities of structure and function (adiposopathy)
- Alterations of appetite regulators in offspring
- Mobilization of free fatty acid and ketone formation which may be transported from the mother to the fetus

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Epigenetics: Who Is to "Blame"?

- Increasing data support paternal epigenetic effects contributing to adverse effects in offspring:
  - Epigenetic transgenerational inheritance of sperm epimutations
  - Toxin and nutritional exposures may result in programming transmissions or epigenetic inheritance, via either maternal or paternal origin
- Both parents may share responsibilities with regard to offspring and generational predisposition to obesity and metabolic disease via:
  - Genetics
  - Extragenetics
  - Epigenetics

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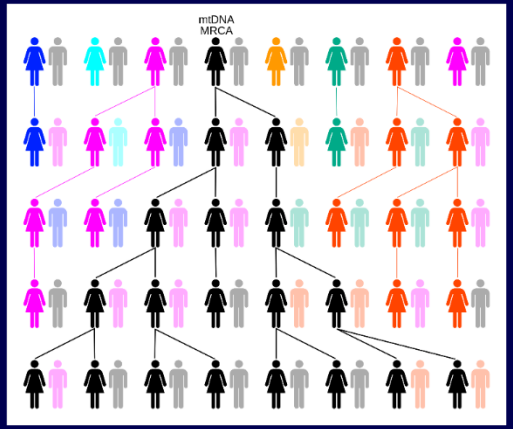
Epigenetics: Who Is Affected?

Epigenetic dysregulation may have generational transmission of increased predisposition to metabolic disease affecting offspring and future generations to metabolic disease (e.g., obesity, diabetes mellitus, heart disease, etc.)



Epigenetics: How to Treat?

- Optimal weight and nutritional management before conception (including potential bariatric surgery)
- No “crash diet” at time of conception discovery

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Epigenetics: How Does it Integrate with Individual Patient Care?

*"**With the possible exception of bariatric surgery, weight management interventions** (e.g., behavior and lifestyle recommendations) alone among patients with advanced metabolic disease **may not reduce CVD risk**. **Some metabolic disease guidelines suggest the most aggressive treatments of metabolic disorders are reserved for those with the most advanced disease.** For example, lipid guidelines suggest patients with CVD should receive the most aggressive lipid therapies."*

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Epigenetics: How Does it Integrate with Individual Patient Care?

"However, for adiposopathy, the greatest CVD benefit of weight management via behavior and lifestyle interventions may be to prevent metabolic diseases and avoid CVD risk factors in the first place. That is because ***those who never develop metabolic disease and CVD risk factors would be expected to reduce their risk of CVD."***

Bays. Curr Atheroscler Rep. 2014 May;16(5):409. doi: 10.1007/s11883-014-0409-1

Epigenetics: How Does it Integrate with Individual Patient Care?

*"Conversely, **if therapy is delayed until patients with overweight and/or obesity develop metabolic diseases and CVD risk factors and experience CVD events**, then this would increase their CVD risk, which at that stage, **may not be as responsive to nutritional and physical activity interventions**."*

Bays. Curr Atheroscler Rep. 2014 May;16(5):409. doi: 10.1007/s11883-014-0409-1

Epigenetics: How Does it Integrate with Individual Patient Care?

"To some, placing a higher priority on obesity prevention relative to obesity treatment may seem paradoxical. But Benjamin Franklin (1706–1790) once said: 'An ounce of prevention is worth a pound of cure.' ***That prevention might be considered paradoxical is perhaps the greatest obesity paradox of all****."*

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