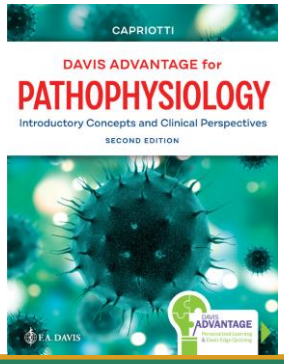
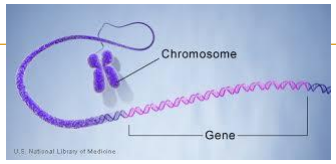


Chapter 3

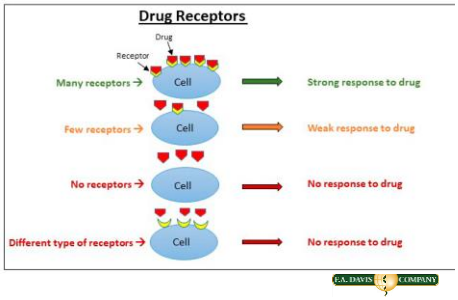
Genetic Basis of Disease

1

Basic Concepts



- Gene
  - Fundamental unit of DNA
  - Changes in DNA can be linked to diseases
- Epigenetic changes
  - Alterations in gene expression due to environmental stressors, behaviors, or lifestyle
- Pharmacogenomics
  - Gene function in health, disease, and responses to medications (study of how genes affect a person's response to drugs.)



2

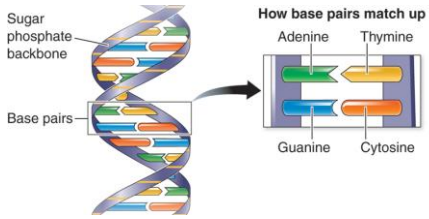
Basic Concepts (continued_1)

- Genetics
  - Study of inherited traits
- Genomics
  - Study of interaction of all genetic material (not only genes)

3

Deoxyribonucleic Acid (DNA)

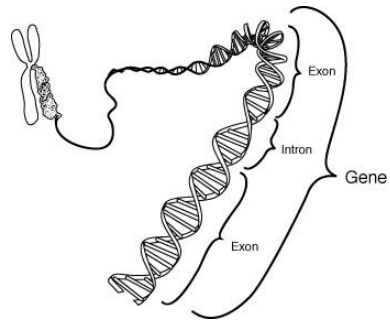
- **Double-helical structure of nucleotides**
- Nucleotide
  - Pentose sugar
  - Phosphate
  - Purine or pyrimidine nitrogen base
- Nitrogen bases
  - DNA: adenine, thymine, guanine, cytosine
  - A-T and C-G pairing
  - RNA: uracil replaces thymine



4

Basic Concepts (continued_2)

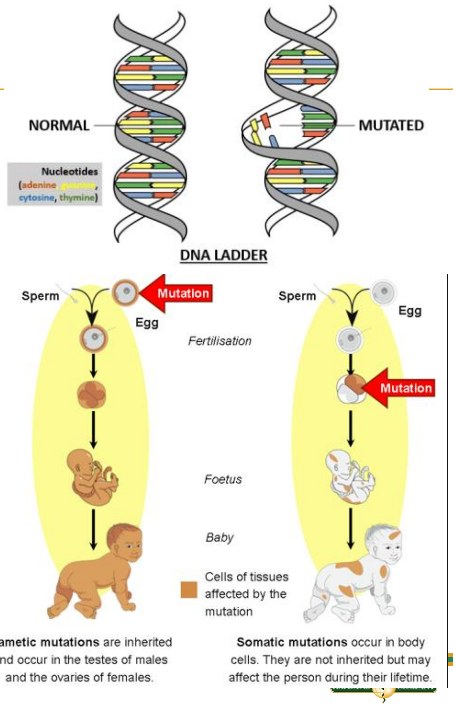
- **Gene**
  - Nucleotide sequence, basic unit of heredity
- Exons
  - Portion of genome that encodes proteins
- Introns
  - Portion of genome that does not code for protein
- Codon
  - Set of three nucleotides that signal a specific amino acid



5

Gene Mutation

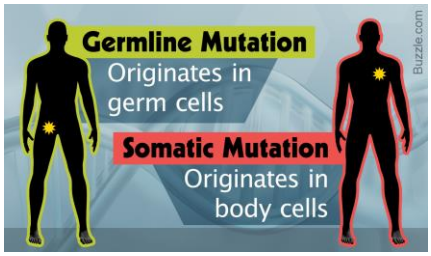
- Genetic mutations
  - *Damage* or *change* to a gene that alters genetic code
  - May be inherited or occur sporadically
- Germ cell mutation
  - Gametes affected: may be passed to offspring
- Somatic cell mutation
  - Body cells
  - Not passed to offspring



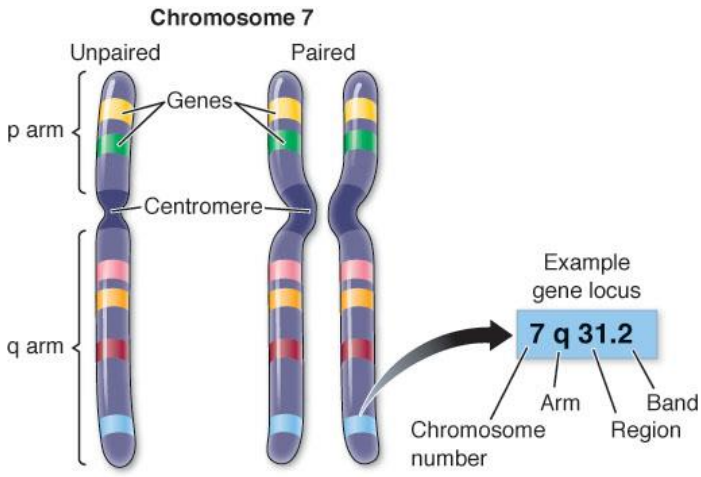
6

Gene Locus

- **Gene nomenclature**
  - Specific name: BRCA1 (breast cancer type 1)
  - Gene locus: Chromosome number, arm, and region
    - *Short arm: p*
    - *Long arm: q*
    - Further divided into regions, bands, and subbands
  - *Example:*
    - Cystic fibrosis: 7 q 31.2

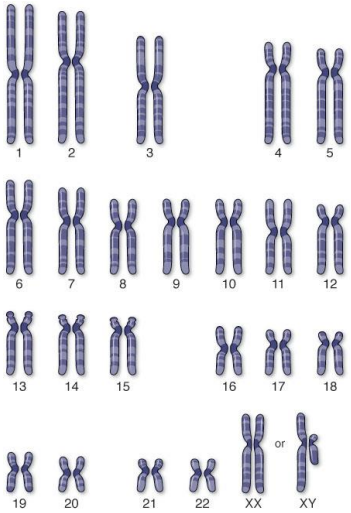


Gene Locus (continued)



Human Karyotype

- Picture of chromosome pairs (organized arrangement of all the chromosomes within a cell)
- **Humans: 23 pairs**
  - Autosomes: 1st 22 pairs
  - Sex: 23rd pair
    - XX: female
    - XY: male
- Can identify chromosomal abnormalities
  - i.e., Down syndrome (Trisomy 21: 3 copies)



9

Gene Expression

Transcription

- *DNA to mRNA (messenger RNA)*
- RNA polymerase uses DNA as template to form mRNA strand
- Splicesosomes
  - Excise introns
- mRNA leaves nucleus

Translation

- *mRNA to protein*
- Ribosome
  - mRNA transcript "read"
- tRNA (transfer RNA)
  - One end binds to 3-nucleotide sequence on mRNA
  - Other end contains corresponding amino acid for the nucleotide sequence
- Amino acids linked by peptide bonds

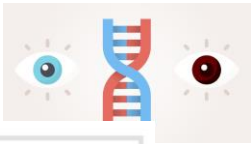
10

Regulating Gene Expression

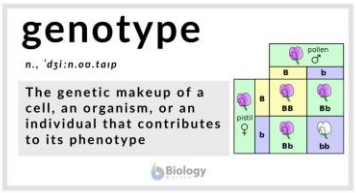
- All cells contain the same genes
- Expression and rate of expression varies between cells
- Enhancers and silencers
  - Transcription factor binding sites on DNA that affect DNA transcription rates

Inheritance Patterns

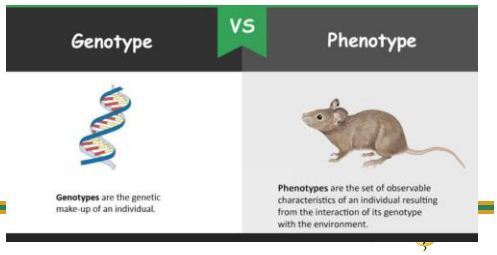
- Allele
  - Gene inherited from one parent



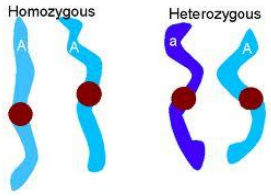
- Genotype
  - Genetic code



- Phenotype
  - Physical expression of the genes

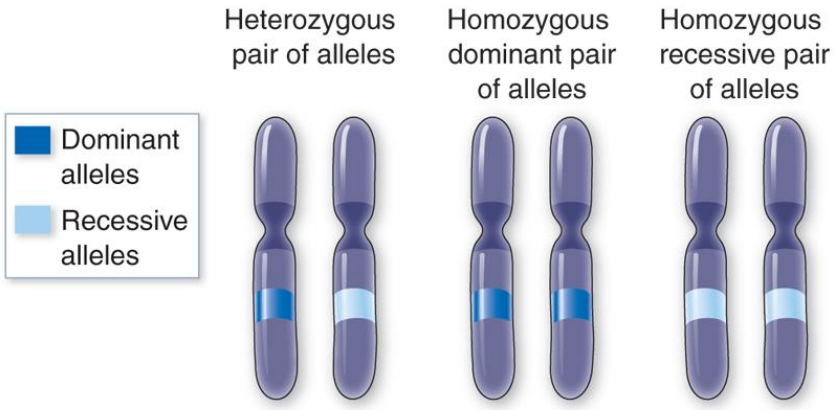


Inheritance Patterns: Allele



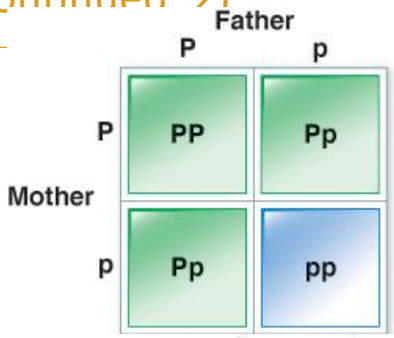
- Heterozygous
  - Alleles carry different traits
- Homozygous
  - Alleles have identical traits
- Dominant trait
  - 1 allele needed for expression
  - Indicated by capital letter
- Recessive trait
  - Both identical alleles needed
  - Indicated by lower case letter
- Carrier
  - Heterozygous for recessive trait

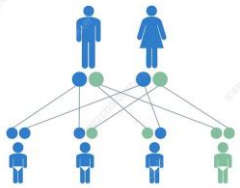
Inheritance Patterns (continued_1)



Inheritance Patterns (continued 2)

- Mendelian Inheritance
  - 1 copy of a gene is inherited from each parent
  - Punnett square
- Autosomal Traits
  - 1 copy of dominant allele needed for expression
  - 2 copies of recessive allele needed for expression

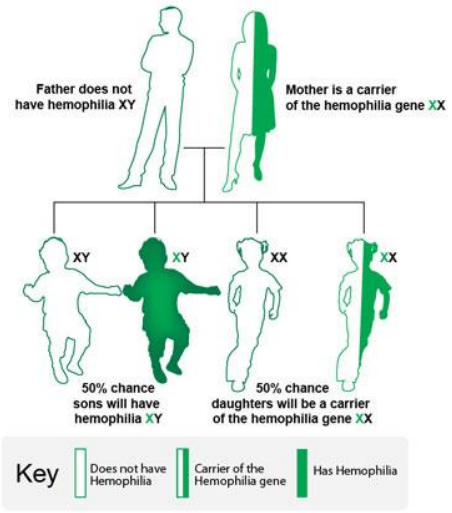




15

Sex-Linked Inheritance (AKA X-linked)

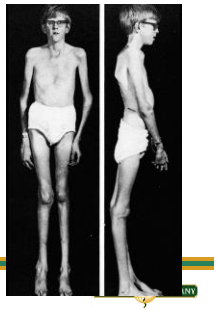
- Males: 46 XY
- X chromosome larger than Y chromosome and carries more genes
  - Some genes do not have a corresponding allele on the Y chromosome
- Allele on the X chromosome is expressed, regardless whether it is dominant or recessive
  - *Example:* hemophilia



16

Penetrance and Expressivity

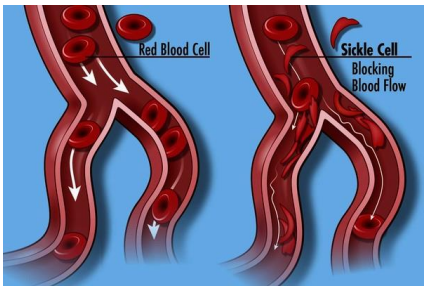
- Genetic penetrance
  - Ratio of people with phenotype compared to genotype
  - *High penetrance* indicates almost all individuals with the gene express phenotype
  - *Example:* BRCA1 has 85% penetrance
- Genetic expressivity
  - Related to severity of genetic disorder
  - May vary for a given condition
    - *Example:* Marfan's syndrome ---------->



17

Complex (Multifactorial) Inheritance

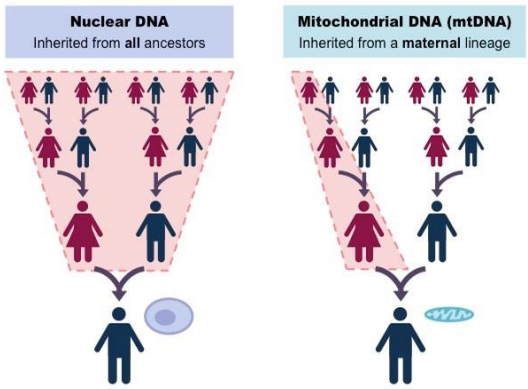
- Combination of 1 or more genes plus environmental triggers
  - *Majority of diseases* have this pattern
  - *Examples:* hypertension, diabetes mellitus, cancer
- Single-nucleotide polymorphisms (SNP's)
  - Changes in one nucleotide of a gene sequence
    - *Example:* AACGT vs ATCGT
  - Can have profound effects if improper amino acid coded
    - *Example:* sickle cell anemia --->



18

Mitochondrial DNA

- Inherited from the mother (maternity testing)
- Can be damaged by free radicals
  - Lacks the repair process of DNA found in nucleus
- Damage implicated in diseases such as diabetes, cancer, and heart failure
- Disorders can be inherited: neurodegenerative disorders, hypertrophic cardiomyopathy
  - Defective mitochondrial DNA can be replaced with normal mitochondrial DNA



19

CRISPR

- **C**lustered **R**egulatory **I**nterspaced **S**hort **P**alindromic **R**epeats
- Gene "editing" in embryonic development
- **Highly controversial**

20

Pharmacogenomics

- Interaction between a person's genetics and medications
- *Examples:*
  - Slow acetylator phenotype
    - Some individuals have less of an enzyme necessary to metabolize certain medications
  - Warfarin (Coumadin)
    - Two genes cause variability in response to this drug
    - Requires monitoring and dosage modification

Oncogenes

- Proto-oncogene
  - Normal genes the control cell proliferation
  - Mutation leads to activate oncogene
  - A **proto-oncogene** is a gene whose protein product has the capacity to induce cellular transformation given it sustains some genetic insult.
- Oncogene
  - Enables uncontrolled cell proliferation
  - Direct synthesis of oncoproteins
  - Viral insertion of an oncogene may also occur
    - *Example:* human papillomavirus leading to cancer
  - An **oncogene** is a gene that has sustained some genetic damage and, therefore, produces a protein capable of cellular transformation.

Oncogenes and Tumor Suppressor Genes

- Oncoproteins
  - Regulate cell cycle, produced from oncogenes
  - Direct cell to undergo uncontrolled proliferation
  - Defects leading to oncogene and oncoprotein formation increase cancer risk
- Tumor suppressor genes
  - Inhibit uncontrolled cell proliferation
  - p53 tumor suppressor gene stops mitosis
  - p53 mutation may lead to uncontrolled cell growth

Knudson's "Two Hit" Hypothesis

- Alfred Knudson proposed "two hit" hypothesis for cancer development
  - Both alleles must be damaged
  - "First hit"
    - Initial hereditary allele mutation
  - "Second hit"
    - Mutation or damage to other allele
- Holds primarily true unless a disease is autosomal dominant

Chromosomal Alterations

- Aneuploidy
  - Different number of chromosomes than 46
    - *Examples:* Trisomy 21; Turner syndrome (45, XO)
- Translocation
  - One piece of a chromosome breaking off and joining another
- Deletion
  - Piece of chromosome is broken off and lost

Genetic Assessment

- Pedigree (genogram)
  - Multigeneration history
- Karyotyping
- Polymerase chain reaction (PCR)
- Fluorescence in Situ Hybridization (FISH)
- Southern blotting

Prenatal Screening

- Women 35 years or older
- Abnormal ultrasound findings
- Couples who are close blood relatives
- Women who have a condition associated with increased risk of fetal problems
- Unexplained or multiple miscarriages
- Family history of an inherited condition, intellectual disability, or birth defects

Prenatal Diagnosis of Genetic Disorders

- Can be used to identify
  - Neural tube defects
  - Down syndrome
  - Chromosome abnormalities
  - Spina bifida
  - Cleft palate
  - Cystic fibrosis, and more

Prenatal Diagnosis of Genetic Disorders (continued_1)

- Genetic testing offered to couples or individuals identified as being at risk for a genetic problem
- Screenings include amniocentesis, percutaneous umbilical cord blood screening

29

Prenatal Diagnosis of Genetic Disorders (continued_2)

- Maternal serum screening
  - Proteins from the placenta and fetus enter maternal circulation
  - Elevation of certain proteins indicate further testing
- Chorionic villus sampling
  - Usually for women age 35 years or older
  - Performed between 10 and 12 weeks of pregnancy
  - Sample of placenta obtained to screen for chromosomal abnormalities

30

Prenatal Diagnosis of Genetic Disorders (continued_3)

- Amniocentesis
  - Diagnose fetal chromosome problems
  - Performed on amniotic fluid between 16 and 18 weeks of pregnancy
- Percutaneous umbilical cord blood sampling
  - Also called cordocentesis
  - Examines fetal umbilical cord
  - Significant risk of complications

Gene Therapy and Ethical Concerns

- Gene therapy
  - Use of genes to prevent or treat diseases
  - A “normal” gene is used to replace an “abnormal” gene
  - A vector (carrier) is used to insert the gene, most commonly a virus
- Ethical concerns
  - Health-care professionals need to be able to counsel patients about the results of genetic testing
  - New area of health care, health-care professionals are exploring the best options

Familial Hypercholesterolemia

- Autosomal dominant
  - Short arm of chromosome 19
- Lack of LDL receptors (results in elevated LDL levels in the blood)
- Homozygous and heterozygous forms
  - Homozygous forms more severe (serum LDL levels may be higher than 600 mg/dL)
- Widespread atherosclerosis may develop

Familial Adenomatous Polyposis

- Autosomal dominant
  - Mutated gene at 5q21, called “APC” gene
  - Normally, APC gene is tumor suppressor
- Early onset of adenomatous polyps in colon and increased colon cancer risk
- Symptoms may include rectal bleeding, diarrhea, abdominal pain
- Recommended colonoscopy every 1 to 2 years, beginning at age 10 to 12 years

Marfan's Syndrome

- Autosomal dominant, can result from sporadic mutation
- Connective tissue disorder
- Fibrillin-1 (FBN1) gene mutation on chromosome 15
- Damage to fibrillin affects microfibrils which are structural components of aorta, heart valves, lungs, dura mater

Marfan's Syndrome (continued)

- Cardiovascular disease, mainly aortic dilatation and dissection, are a major cause of morbidity
  - If untreated, average of death is between 30–40 years
- Prevention procedures for cardiac issues are necessary
- Signs and symptoms
  - Tall stature
  - Kyphoscoliosis
  - Ligament hypermobility
  - Heart murmur
  - Dysrhythmia

Neurofibromatosis (NF)

- Autosomal dominant, some forms sporadic mutation
- Two forms:
  - NF1 (chromosome 17)
  - NF2 (chromosome 22)
- NF1 and NF2 genes code for tumor suppressors
- Tumors of central and peripheral nervous system

Neurofibromatosis (NF) (continued)

- Typical age of onset of symptoms is late teenage years
- Signs and symptoms
  - Café-au-lait spots (dark, flat macules)
  - Optic nerve tumor
  - Tumors in iris
- Diagnosis requires genetic testing, CT, MRI, neurological examinations

Ehlers-Danlos Syndrome

- Abnormalities in collagen synthesis
- Classic form is a mutation in 9q34.2 and 9q34.3 genes
- Diminished strength and integrity of skin, joints, and other connective tissues
  - Hypermobility of joints, easy bruising, mitral valve prolapse, arterial aneurysms are clinical manifestations
- Patient should not place undue stress on joints

39

Cystic Fibrosis (CF)

- Autosomal recessive
- Most common lethal inherited disease in Caucasians
- Defect in cystic fibrosis transmembrane conductance regulator gene (CFTR), 7q31
- Disrupts lung function (excess mucus) and pancreatic secretions (malabsorption of nutrients)

40

Cystic Fibrosis (CF) (continued)

- Newborns screened in U.S.
- Treatment includes pancreatic enzyme supplements, bronchodilators, mucolytics, nutritional supplements
- End-stage lung disease is the principal cause of death

Lysosomal Storage Disease

- Failure of lysosomes enables accumulation of harmful substances
- More than 50 lysosomal storage diseases have been discovered
- Tay-Sachs Disease
  - Abnormal hexosaminidase A enzyme (chromosome 15) leading to ganglioside accumulation in CNS
  - Death normally occurs by age 3

Lysosomal Storage Disease (continued)

- Niemann-Pick Disease
  - Deficiency in sphingomyelinase
  - Type A is more severe, with death by age 3 years
  - Lipids accumulate in brain, spleen, liver, and lymph nodes
- Gaucher Disease
  - Most common lysosomal storage disease
  - Accumulation of glucocerebrosides in macrophages and CNS
  - 150 gene mutations can result in this condition, thus can not be identified with single test

43

Wilson Disease and G6PD Deficiency

Wilson Disease

- Autosomal recessive
- Copper excretion is impaired
- Copper accumulates in liver and other organs
- Kayser-Fleisher rings in the eyes may be present
- Diagnosis based on measuring ceruloplasmin levels
- Chelating agents to clear copper

G6PD Deficiency

- X-linked, most common enzyme disorder
- Lack of glucose-6-phosphate dehydrogenase disrupts RBC functioning, hemolysis results
- Diagnosis with CBC and RBC smear
- Prevention of hemolysis is key

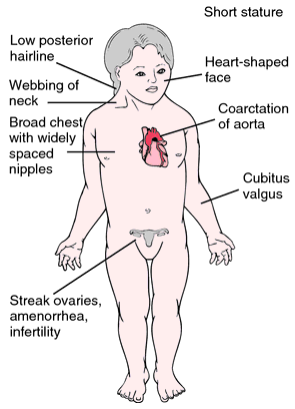
44

Chromosomal Abnormalities

- Klinefelter Syndrome: 47, XXY karyotype
  - Lack of development of testes, gynecomastia, skeletal and cardiovascular abnormalities
  - Decreased cognitive development
  - Testosterone replacement needed

Chromosomal Abnormalities (continued_1)

- Turner Syndrome
  - 45, X0 karyotype
  - May result in spontaneous abortion
  - Variations in disease severity
    - Short stature and infertility
    - Lack of breast development and amenorrhea at puberty
    - Estrogen therapy and hormone replacement



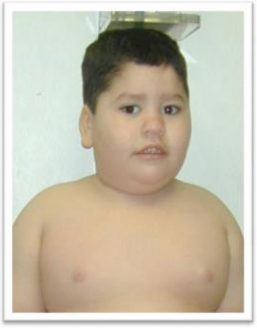
Chromosomal Abnormalities (continued_2)

- Fragile X Syndrome
  - Disorder of X chromosome at Xq27.3
  - Characterized by long repeating sequences of CGG
  - Cognitive impairment
    - Familial mental retardation (FMR)
  - Mild-to-moderate autistic-like behaviors

Chromosomal Abnormalities (continued_3)

- Down Syndrome
  - Most common chromosomal disorder
  - Trisomy 21
  - Wide variation of severity
  - Flat facial profile, epicanthic folds around the eyes
  - 80% have IQ of 25 to 50

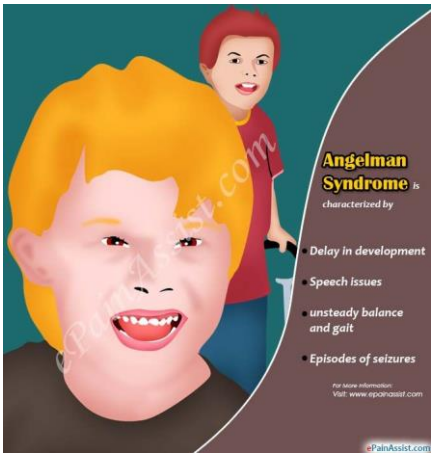
Prader-Willi Syndrome



- Disruption or deletion of genes on chromosome 15
  - Usually paternal chromosome
- Usually due to sporadic genetic mutation
- Associated with hypothalamic dysfunction
- Persons often overeat, leading to risk of obesity
- Hypotonia, low IQ, short stature, and hypogonadism

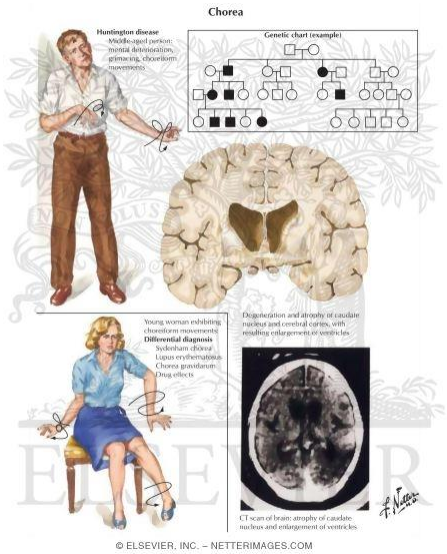
Angelman's Syndrome

- Similar defect in same gene that causes Prader-Willi Syndrome
- Gene defect inherited from mother
- Rare
- Children present with neurological problems



Huntington's Disease

- Two forms of Huntington's Disease, most common is the adult-onset
  - Autosomal dominant
  - Huntingtin protein (HTT) disrupted by trinucleotide repeats (CAG)
- No specific diagnostic imaging study
- No cure



Huntington's Disease (continued)

- Clinical presentation includes a movement disorder, a cognitive disorder, and a behavior disorder
  - Chorea is the most common movement disorder
    - Dance-like movement progressing to flailing
- Persons with adult onset HD usually develop symptoms between 35 and 44 years old
- Antidepressants, antipsychotic medications, and anticonvulsants are common management strategies