

Genetics and Developmental Disabilities

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Pediatric Genetics Team



Types of Disability

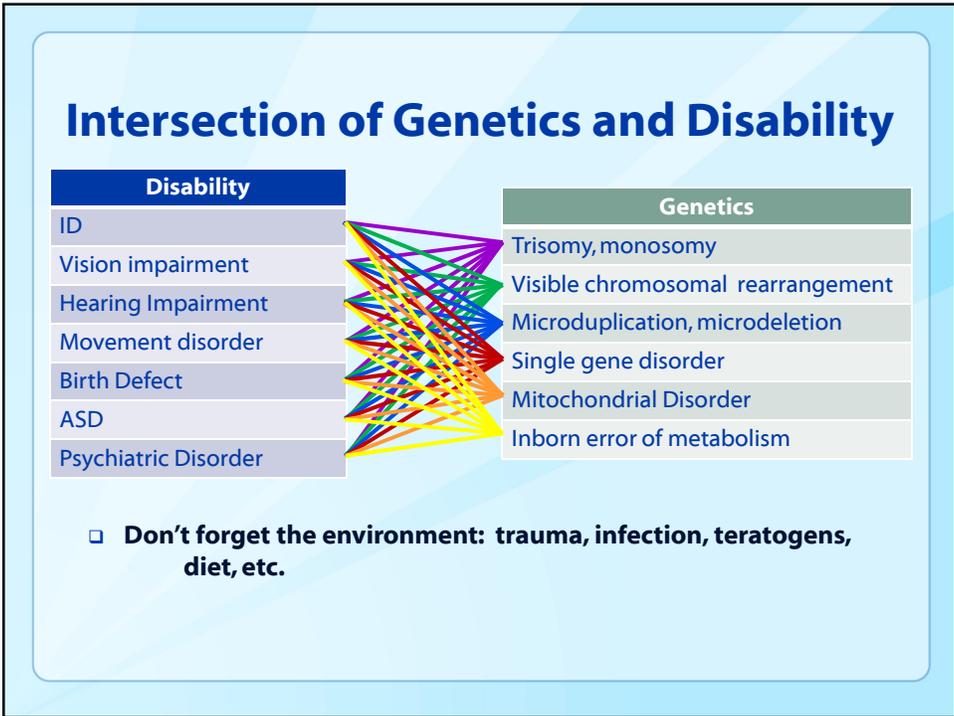
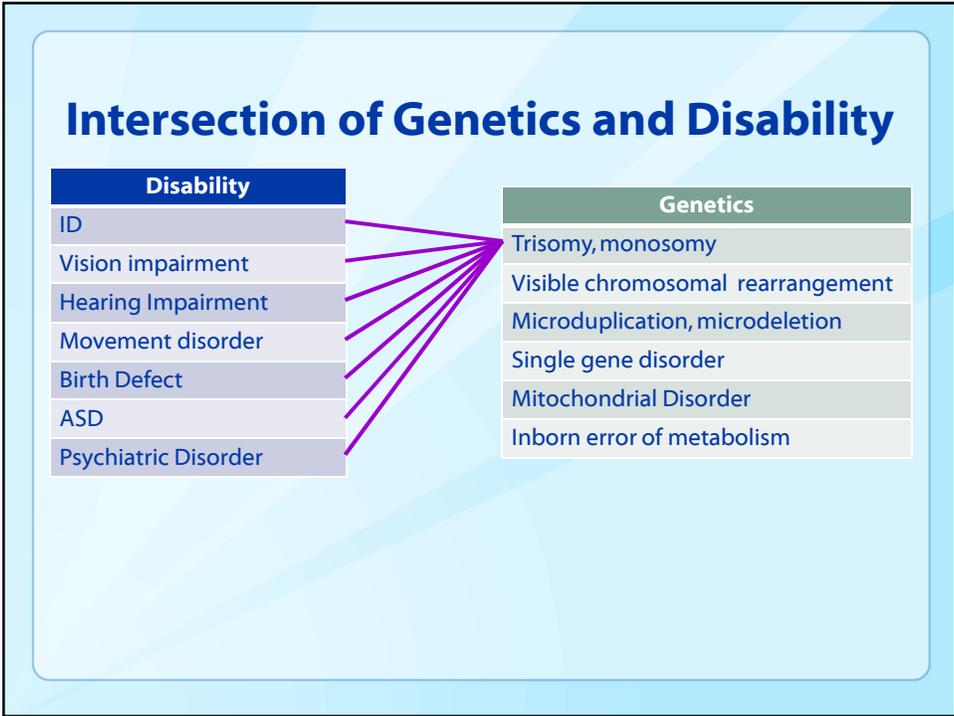
- Intellectual disability
- Vision impairment
- Hearing impairment
- Movement disorder
- Birth defect
- Autism spectrum disorders
- Psychiatric disorders

Types of Genetic Disorders

- ❑ **Chromosome abnormalities**
 - Extra or missing chromosomes (trisomy, monosomy)
 - Visible chromosomal rearrangements
 - Microdeletions, microduplications
- ❑ **Single gene disorders**
 - Dominant, recessive, X-linked
 - Mitochondrial disorders
- ❑ **Inborn errors of metabolism**

Intersection of Genetics and Disability

Disability	Genetics
ID	Trisomy, monosomy
Vision impairment	Visible chromosomal rearrangement
Hearing Impairment	Microduplication, microdeletion
Movement disorder	Single gene disorder
Birth Defect	Mitochondrial Disorder
ASD	Inborn error of metabolism
Psychiatric Disorder	



Primer in Genetics

- Now for a brief primer in genetics....



"You're the mother and those are your children? — I'd like to see a DNA test."

DNA (Deoxyribonucleic Acid)

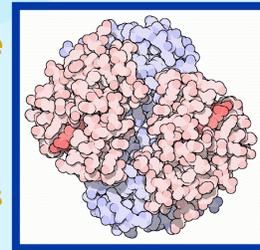
- DNA contains all of the genetic information that is needed for an organism to develop and for all the cells and the organs of the organism to function
- DNA is made up of two chemical strands that wind around each other; it looks like a twisting ladder.
- A DNA strand is made up of just four components (bases) arranged in different orders; these bases are T (thymine), A (adenine), C (cytosine), and G (guanine).
- The information in the DNA is "read" by the order or sequence of the bases, that is by the sequence of the Ts, Cs, Gs, and As (e.g. AATACCAGGATCCGAATAAAA).



Gene

- ❑ A gene is a segment or stretch of DNA that cells use to make a particular protein
- ❑ The sequence of the As, Ts, Cs, and Gs that make up the gene determines the final structure and function of the protein

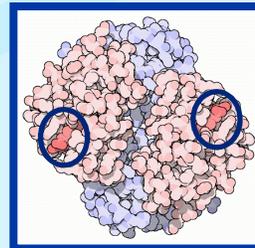
Example: The β -globin gene contains the information to make β -hemoglobin, which is one of the components of the hemoglobin complex, responsible for carrying oxygen in the blood to all cells of the body



Mutation

- ❑ A mutation is a change in the sequence of the Gs, As, Ts, and Cs within the gene which disrupts the structure and the function of the protein made by the gene

Example: The sickle cell mutation results from the change of a single T in the β -globin gene to an A; this mutation causes the β -globin gene to make abnormal β -hemoglobin, which is responsible for all of the medical problems related to the genetic condition known as sickle cell disease



Mutation

- ❑ A mutation can also result from the loss of most or all of the sequence of bases that make up the gene
- ❑ This type of mutation is known as a deletion and the result is that not enough of the protein is made for the cell to function normally

Example: If a β -globin gene is deleted there is not enough β -hemoglobin to make enough hemoglobin complex for carrying oxygen in the blood; the result is the genetic condition known as β -thalassemia

Mutation

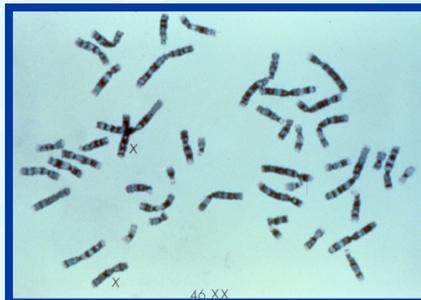
- ❑ Finally, a mutation can actually result from the gain of all of the sequence of bases that make up the gene
- ❑ This type of mutation is known as a duplication and the result is that too much of the protein is made for the cell to function normally

Example: The gene, *PMP22*, is responsible for making the protein, peripheral myelin protein-22; a duplication of the *PMP22* gene results in too much peripheral myelin protein-22 being made by nerve cells, and this causes the genetic condition known as Charcot-Marie-Tooth disease (CMT) type Ia



Chromosome

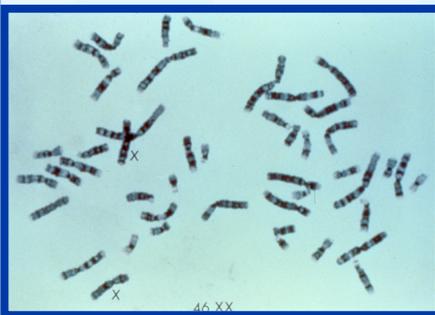
- ❑ A chromosome consists of a single, long piece of DNA made up of hundreds to thousands of specific genes
- ❑ The chromosome structures that can be seen under a microscope result from tightly packaging (condensing) the DNA before the cell divides



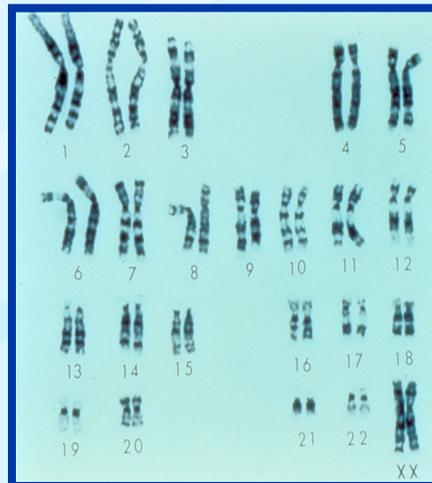
Chromosome

- ❑ In all human cells (except egg and sperm cells) there are 23 pairs of chromosomes
- ❑ The 23 pairs comprise 22 pairs of numbered chromosomes (1-22) called autosomes, and one pair of sex chromosomes (X and Y), which can be paired as either XX (girls) or XY (boys)
- ❑ Each pair consists of one chromosome inherited from the person's mother and the other from the person's father.

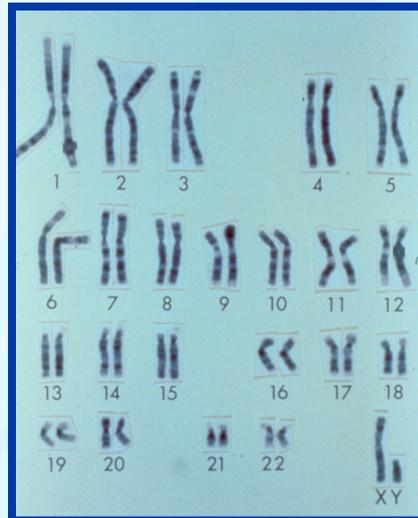
Normal Chromosome Pattern in Females



- ❑ Ordering the chromosomes from largest to smallest, with the sex chromosomes placed separately



Normal Chromosome Pattern in Males



Phenotype

- ❑ Physical traits that make up an individual
- ❑ Includes physical features, characteristics, symptoms, signs, and laboratory data
- ❑ **Example: The phenotype of Down syndrome....**

Phenotype of Down Syndrome

Relatively flattened face

Upslanting eyes

Epicanthal folds

Prominent tongue

Small ears

Redundant neck skin

Congenital heart defects

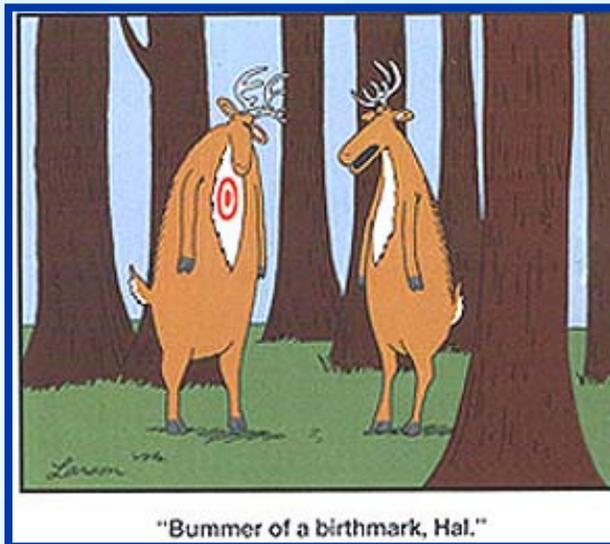
Gastrointestinal abnormalities

Wide spacing between the first and second toes

Single transverse palmar creases

Decreased muscle
tone (hypotonia)

Intellectual disability



Genes and Chromosomes

- ❑ There are 20,000 to 25,000 genes in humans
- ❑ The average-sized chromosome will contain about 1400 genes
- ❑ For many, but not all genes, the cell needs 2 normal copies (one on each of the pair of chromosomes) in order for the function of the gene to occur normally.
- ❑ Missing copies of genes (from either DNA mutation or deletion) or extra copies (from duplication) can cause the function of the gene to be abnormal

Chromosome Abnormalities

- ❑ Chromosome abnormalities result from mistakes in cellular processes when cells divide
- ❑ Since an average chromosome contains approximately 1400 genes, **aneuploidy** (additional or missing chromosomes) would result in large imbalances
 - Trisomy: 3 copies of a particular chromosome
 - Monosomy: 1 copy of a particular chromosome

Trisomy 21 (Down Syndrome)

- ❑ The most common chromosome abnormality in live born infants
- ❑ Occurs approximately 1 in every 600 live births
- ❑ Approximately 95% of cases are due to typical trisomy for chromosome 21 and 4% are due to an attachment of an extra copy of chromosome 21 to another chromosome



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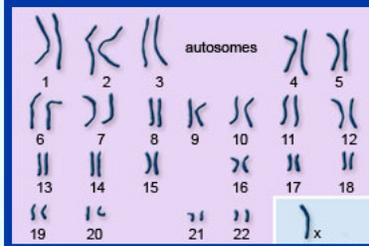
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Trisomy 21 (Down Syndrome)



Turner Syndrome (Monosomy X)

- ❑ Occurs approximately 1 in every 2500 female live births
- ❑ Approximately 65% of girls with Turner syndrome have the typical monosomy X (45,X) chromosome pattern, while 35% have other X chromosome abnormalities

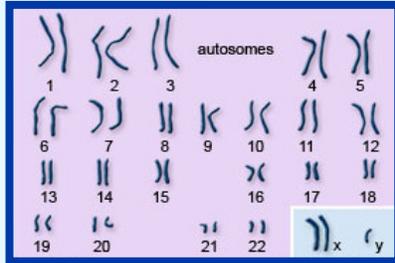


Turner Syndrome (Monosomy X)

- ❑ Phenotype: short stature, low posterior hairline, webbed neck, shield chest, wide-spaced nipples, cubitus valgus (wide carrying angle of the arms), lymphedema (puffiness of the hands and feet), congenital heart defects, urinary tract abnormalities, visual-spatial learning disabilities, but overall normal intelligence



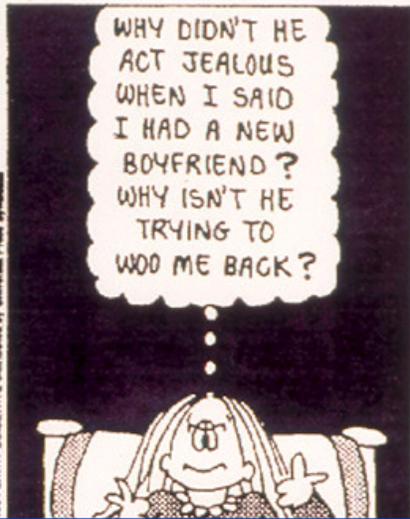
Klinefelter Syndrome (47,XXY)

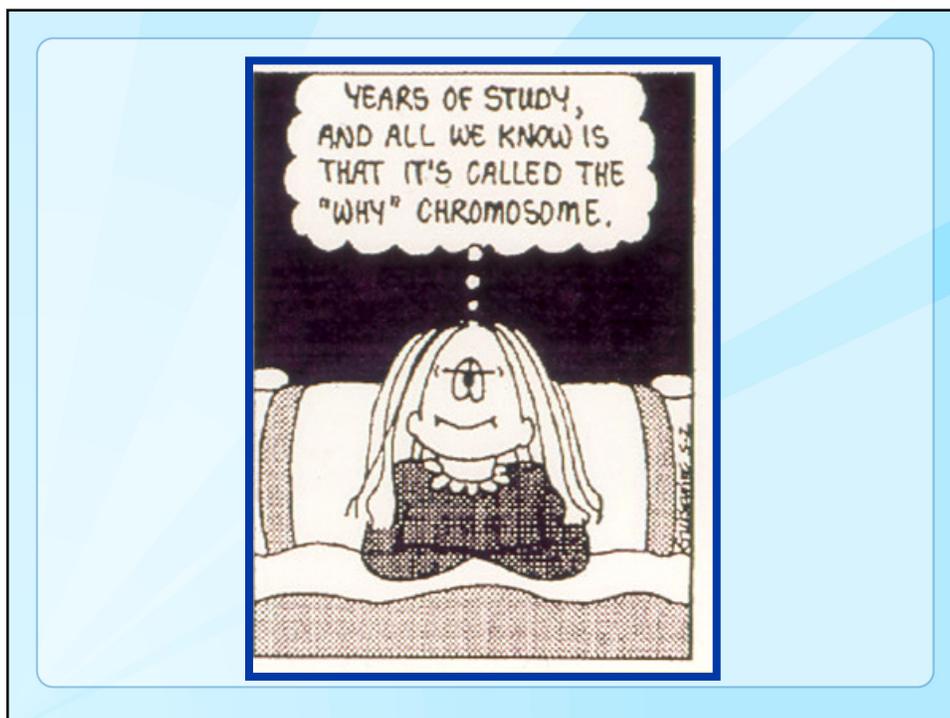
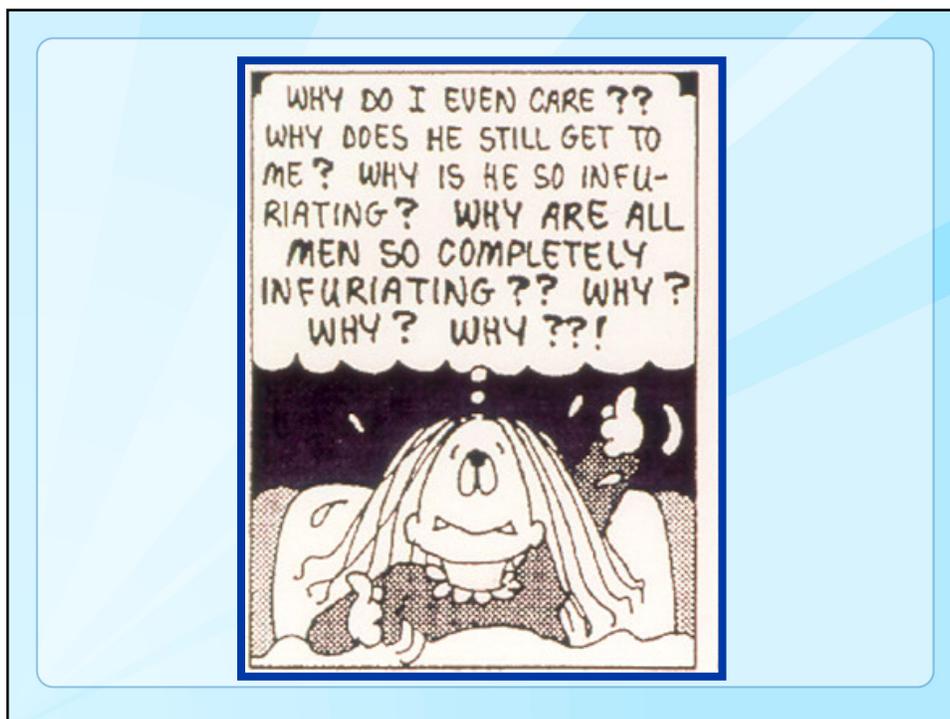


- Approximately 1 in every 1000 male live births
- Phenotype: tall stature, long legs, gynecomastia (breast enlargement), decreased masculinization, small testes, infertility, language delay, but overall average intelligence



CATHY





Structural Chromosome Abnormalities

- ❑ DNA or chromosomes are frequently damaged or broken
- ❑ DNA damage is quickly repaired
- ❑ Chromosome damage improperly repaired produces a variety of structural rearrangements of chromosomes
- ❑ Alternatively, when chromosomes are replicated (copied) prior to cell division, imprecise copying can lead to structural chromosome rearrangements
 - Terminal deletions or duplications (involves the end of the chromosome)
 - Interstitial deletions or duplications (within a chromosome)

Wolf-Hirschhorn Syndrome (4p Deletion)

- ❑ A well-recognized chromosomal deletion syndrome
- ❑ Phenotype includes cutis aplasia, cataracts, ear anomalies, "Greek helmet" appearance, cleft lip/palate, growth retardation, seizures, and moderate to severe intellectual disability



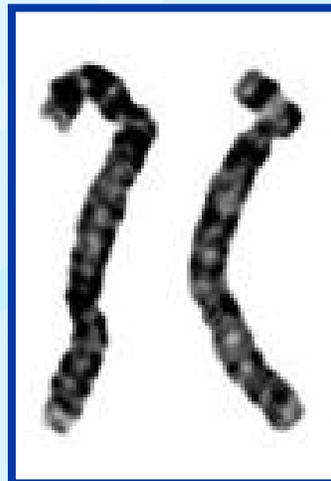
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Wolf-Hirschhorn Syndrome (4p Deletion)

- Most deletions are visible by standard chromosome testing, although some deletions in patients with Wolf-Hirschhorn syndrome are quite small



Velocardiofacial/DiGeorge Syndrome (22q11.2 Deletion)

- ❑ **Presence and severity of the clinical features vary considerably from person to person, even within the same family**
- ❑ **Classic triad of features in DiGeorge syndrome are**
 - Congenital heart disease
 - Hypocalcemia (low blood calcium) from parathyroid gland hypoplasia (underdevelopment)
 - Thymus gland hypoplasia (T-cell deficiency)
- ❑ **Clinical features in Velocardiofacial syndrome (VCFS) are similar to DiGeorge syndrome, but are often milder**

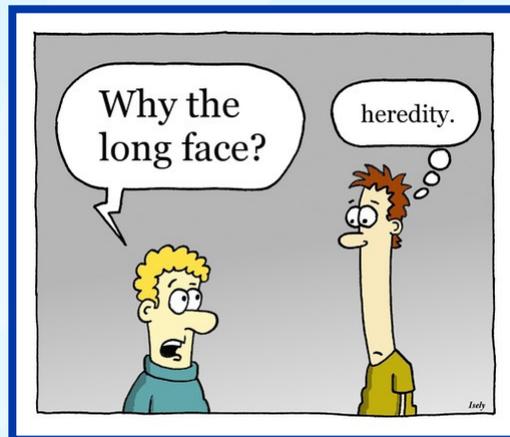
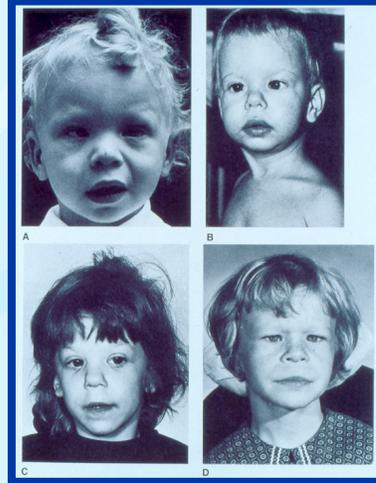
Velocardiofacial/DiGeorge Syndrome (22q11.2 Deletion)

- ❑ **Phenotype in VCFS patients also includes distinctive facial features (bulbous nose with hypoplasia of the alae nasi and prominent or protuberant ears), milder congenital heart defects, cleft palate or pharyngeal insufficiency (velopharyngeal incompetence), learning disabilities, and often developmental delay**



Williams Syndrome (Submicroscopic Deletion in 7q11.23)

- Phenotype includes characteristic heart defects (supravalvular aortic stenosis), hypercalcemia (elevated blood calcium), distinctive facial features, intellectual disability, hoarse voice, and "Cocktail party" personality



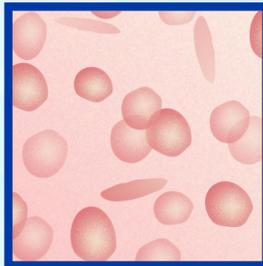
Single Gene Disorders

- ❑ Caused by mutations in the sequence of the Gs, As, Ts, and Cs within the gene which disrupts the structure and the function of the protein made by the gene
- ❑ For some single gene disorders, only one of the pair of genes needs to have a mutation in order for there to be a phenotype
 - Autosomal dominant disorders
 - E.g. Achondroplasia, deLange syndrome, Apert syndrome



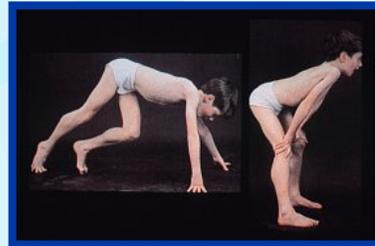
Single Gene Disorders

- ❑ For some single gene disorders, both of the pair of genes need to have a mutation in order for there to be a phenotype
 - Autosomal recessive disorders
 - E.g. Albinism, Sickle Cell disease, Hurler syndrome



Single Gene Disorders

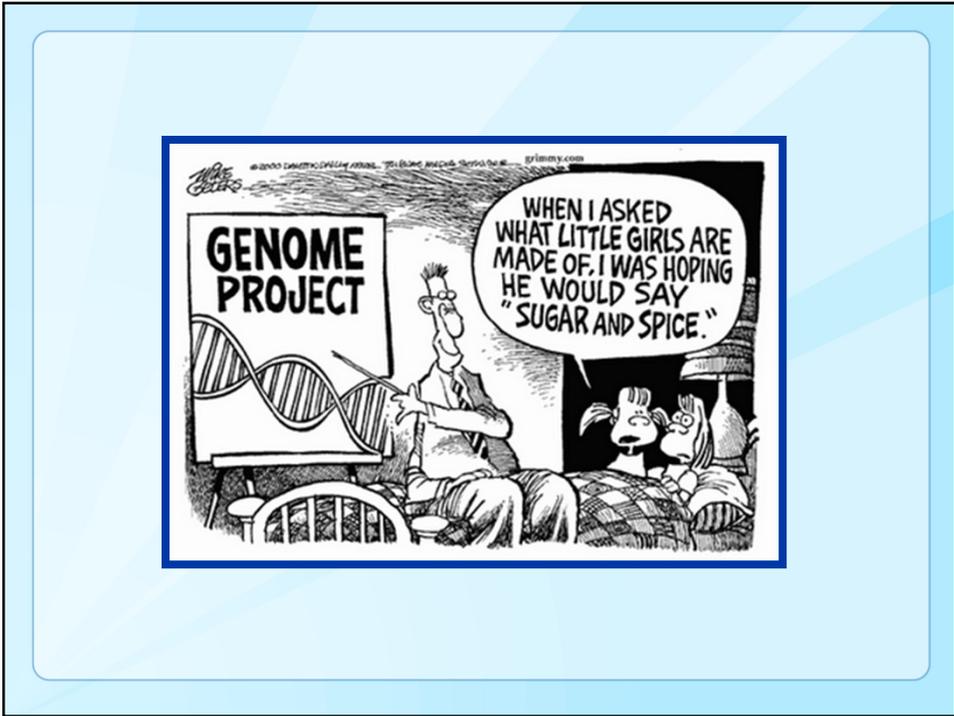
- ❑ For some single gene disorders, the gene is part of the X chromosome
- ❑ If the gene has a mutation, boys will be affected because they have only one X chromosome (XY) while girls are either more mildly affected or have no features (carriers) because they have the normal gene on the other X chromosome (XX)
 - X-linked disorders
 - E.g. Fragile X syndrome, Duchenne muscular dystrophy



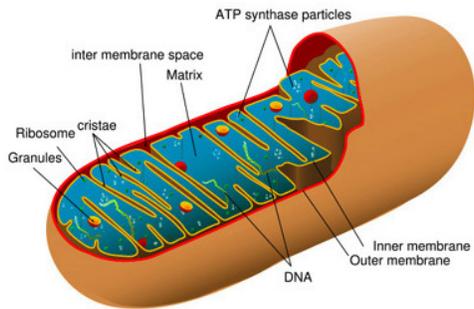
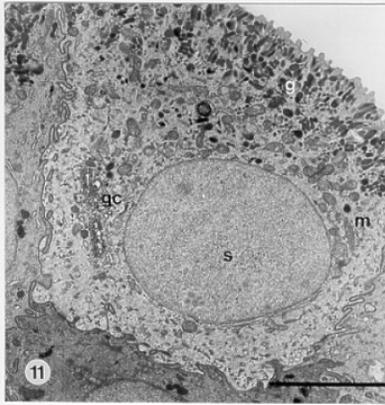
Waardenburg Syndrome

- ❑ Autosomal dominant disorder due to mutations in the *PAX3* gene
- ❑ Affects 1/40,000 to 1/50,000 people
- ❑ Phenotype: sensorineural hearing loss (deafness), iris pigmentary abnormalities, white forelock, widely-spaced eyes, other distinctive facial features, white skin patches



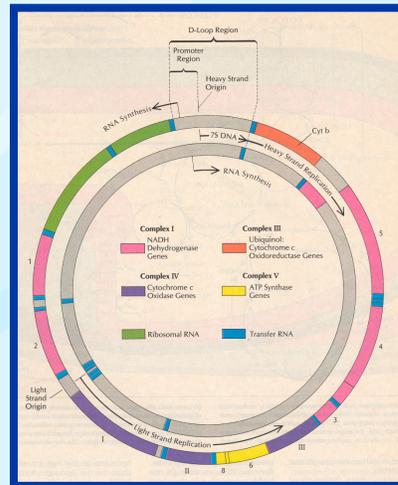


Mitochondria



The Mitochondrial Chromosome

- ❑ A double-stranded circular DNA molecule that contains 16,569 base pairs
- ❑ It is called mitochondrial DNA (mtDNA)
- ❑ The chromosome produces
 - 13 proteins involved in making energy (oxidative phosphorylation)



Mitochondrial Genetics

- ❑ Each mitochondria contains 50-100 copies of the mitochondrial chromosome
- ❑ Each cell contains hundreds to thousands of mitochondria
- ❑ Mitochondrial disorders usually involve the central nervous system (brain and cranial nerves), eyes, and muscles (skeletal, cardiac, and smooth), since these are sites of high energy requirements