Pattern of Inheritance
Typical Mendelian inheritance

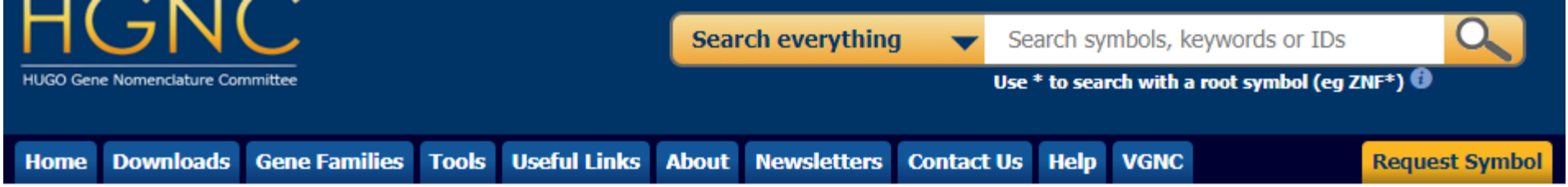
Lecture 7

Lecture Outline

- **Nomenclature of Human Genes**
- **Monogenic Versus Multifactorial Inheritance**
- **Mendelian Pedigree Patterns**
- **Pedigree drawing**

Nomenclature of Human Genes

- Human genes have upper-case italicized names; for example: *CFTR* gene
- ***CFTR* :cystic fibrosis transmembrane conductance regulator**
- **Synonym symbol(s):** ABCC7, MRP7, CFTR/MRP, TNR-CFTR, ABC35, dJ760C5.1
- The process of discovery often involves several competing research groups, so that the same gene may initially be referred to by several different names.
- Eventually an official name is assigned by the HUGO (Human Genome Organization) Nomenclature Committee, and this is the name that should be used henceforth.



New Beta Site!

Please view this page on our new HGNC beta site and let us know what you think via the feedback form.

Symbol Report: CFTR

APPROVED SYMBOL	CFTR
APPROVED NAME	cystic fibrosis transmembrane conductance regulator
HGNC ID	HGNC:1884
PREVIOUS SYMBOLS & NAMES	ABCC7, CF, "cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7)"
SYNONYMS	ABC35, "ATP-binding cassette sub-family C, member 7", CFTR/MRP, dJ760C5.1, MRP7, TNR-CFTR
LOCUS TYPE	gene with protein product
CHROMOSOMAL LOCATION	7q31.2
GENE FAMILY	Chloride channels, ATP-gated CFTR
	ATP binding cassette subfamily C
HCOP	Orthology Predictions for CFTR

Official names can be found on the nomenclature website (http:// www.genenames.org) or from entries in genome browser programs such as Ensembl, UCSC

Monogenic Versus Multifactorial Inheritance

- The simplest genetic characters are those whose presence or absence depends on the genotype at a single locus.
- That is not to say that the character itself is programmed by only one pair of genes: expression of any human character is likely to depend on the action of a large number of genes and environmental factors.
- However, sometimes a particular genotype at one locus is both necessary and sufficient for the character to be expressed, given the normal range of human genetic and environmental backgrounds (Mendelian characters)
  - Mendelian characters can be recognized by the characteristic pedigree patterns they give.

- The best starting point for acquiring information on any such character, whether pathological or non-pathological, is the Online Mendelian Inheritance in Man (OMIM) database.

BOX 3.2 DATABASES OF HUMAN GENETIC DISEASES AND MENDELIAN CHARACTERS

This is a short selective list of especially useful, reliable, and stable resources; many other useful databases may be found by searching.

OMIM (http://www.ncbi.nlm.nih.gov/omim). The Online Mendelian Inheritance in Man database is the most reliable single source of information on human Mendelian characters and the underlying genes. The index numbers quoted throughout this book (e.g. OMIM 193500) give direct access to the relevant entry. OMIM contains about 20,000 entries, which may be sequenced genes, characters or diseases associated with known sequenced genes, or characters that are inherited in a Mendelian way but for which no gene has yet been identified. Some entries describe characters that are not normally Mendelian. In those cases the OMIM entry will concentrate on any Mendelian or near-Mendelian subset and may therefore not give a balanced picture of the overall etiology. Each entry is a detailed historically ordered review of the genetics of the character, with subsidiary clinical and other information, and a very useful list of references. Entries have accumulated text over many years with only patchy rewrites, so that the early part of an entry may not reflect current understanding.

The **Genetic Association Database** (http://geneticassociationdb.nih.gov), maintained by the US National Institute on Aging, can be searched for a list of genes and publications reporting possible genetic susceptibility factors for multifactorial diseases. At the time of writing it is at an early stage of development, but it should become a valuable resource for accessing information that is otherwise dispersed over many individual publications.

Genecards (http://www.genecards.org), from the Weizmann Institute in Israel, contains about 50,000 automatically generated entries, mostly relating to specific human genes. It gives access to a large amount of biological information about each gene.

GeneTests (http://www.geneclinics.org) is a database of human genetic diseases, maintained by the US National Institutes of Health and aimed mainly at clinicians. It includes brief clinical and genetic reviews of about 500 of the most common Mendelian diseases. There is more clinical information than in OMIM.

Types of Mendelian Pedigree Patterns

There are five basic Mendelian pedigree patterns:
They can be categorized based on the location of the gene and how many copies of the mutant allele are required to express the phenotype:

- Autosomal dominant
- Autosomal recessive
- X-linked dominant
- X-linked recessive
- Y-linked
- Mitochondrial inheritance
- Others

The Gene is the Unit of Inheritance

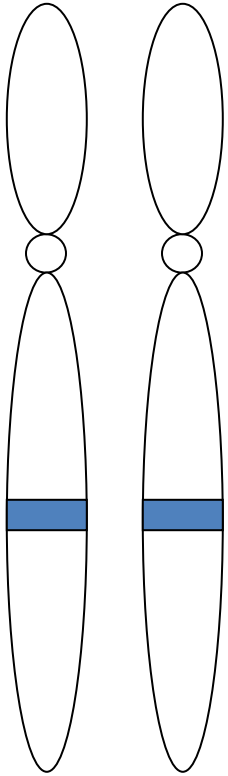
The location of a gene on a chromosome is its **locus**.

Alternative forms of a gene at a particular locus are referred to as **alleles**.

An individual's **genotype** (genetic composition) at a particular locus is defined by the nature of the alleles at that locus

If both alleles are identical, then the individual is **homozygous** at the locus. Homozygosity may refer to the presence of two normal or two mutant alleles.

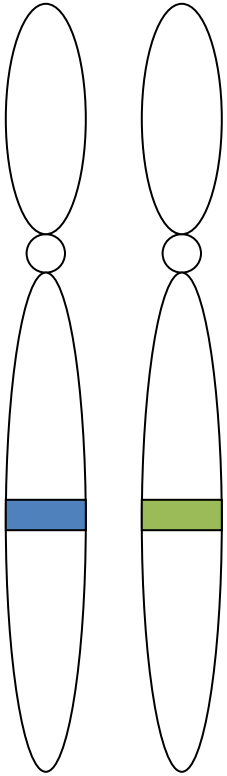
If the alleles differ, then the individual is **heterozygous** at the locus. If two different mutant alleles are present, then the individual is a **compound heterozygote**.



A A

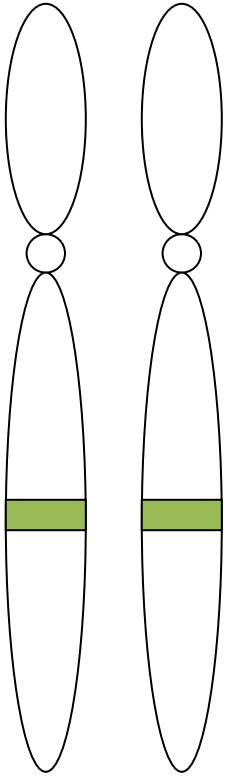
homozygote

A allele



A a

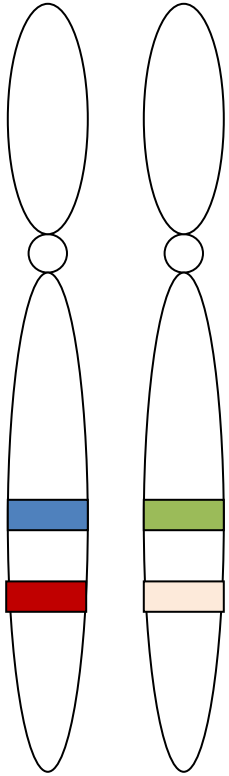
heterozygote



a a

homozygote

a allele



A a

B b

compound

heterozygote

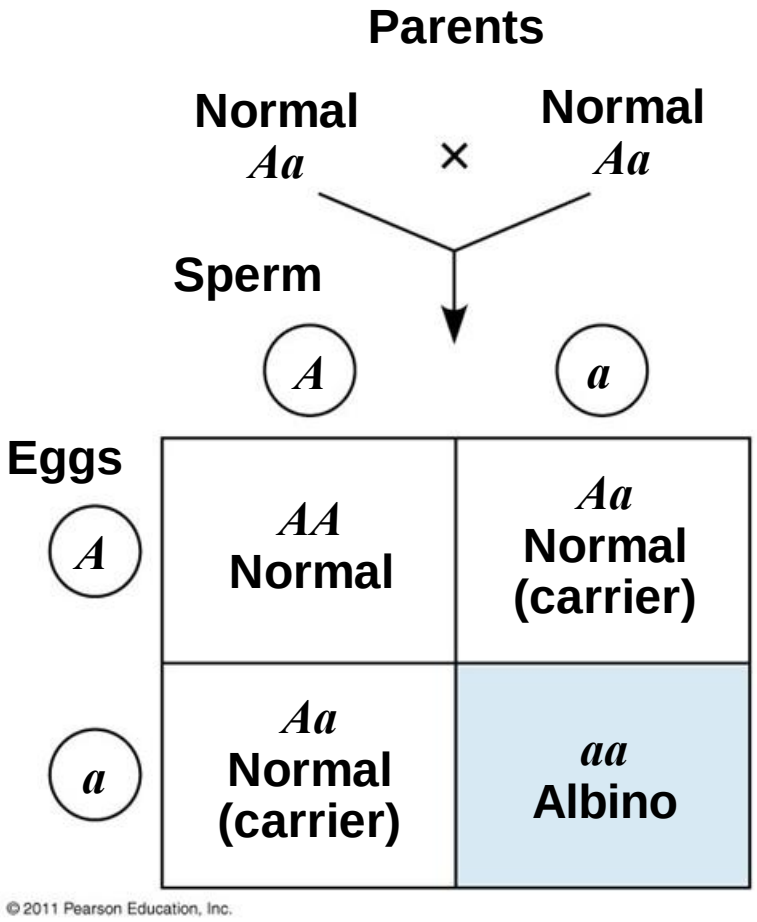
Traits that are determined by loci on one of the 22 autosomes are **autosomal**. Traits determined by loci on the X chromosome are **X-linked**, and those determined by loci on the Y chromosome are **Y-linked**.

Autosomal recessive inheritance

- **Autosomal recessive traits** are those traits in which the phenotype is expressed only if homozygous for the recessive allele, i.e., aa where a=recessive allele. Two copies of the recessive allele are necessary for expression.
- In general, **recessive** traits are associated with a reduced level of activity of a gene product in systems that have sufficient reserve function so that loss of half the activity in the **heterozygous** state **dose not** perturb the system.

Autosomal recessive inheritance

- The affected individual can be of either sex and either a homozygote or compound heterozygote for a single-gene defect.
- Autosomal recessive diseases are, for the most part, rare and often occur in the context of parental consanguinity.
- Affected persons are usually born to unaffected parents
- Parents would be described as asymptomatic carriers because they carry one mutant allele without being affected.
  - Heterozygous carriers of a defective allele are usually clinically normal, but they may display subtle differences in phenotype that become apparent only with more precise testing or in the context of certain environmental influences (i.e., sickle cell disease)
- It affects either sex



- Affected individuals carry two mutant alleles at the disease locus, one inherited from each parent.
- The chance that each future child born to these parents is also affected is normally 25 % (the risk that one parent transmits the mutant allele is 1/2, so the risk that they both transmit the mutant allele to a child is 1/2 × 1/2 = 1/4).

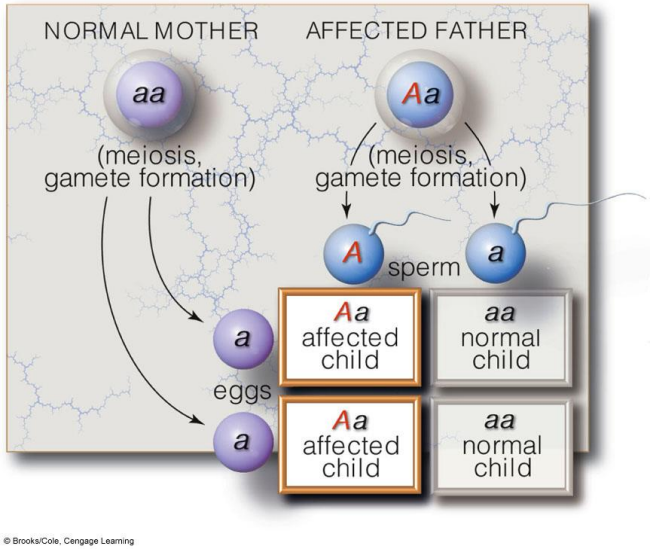
Autosomal recessive inheritance

- **Not** all recessive traits are due to ***enzyme*** deficiency.

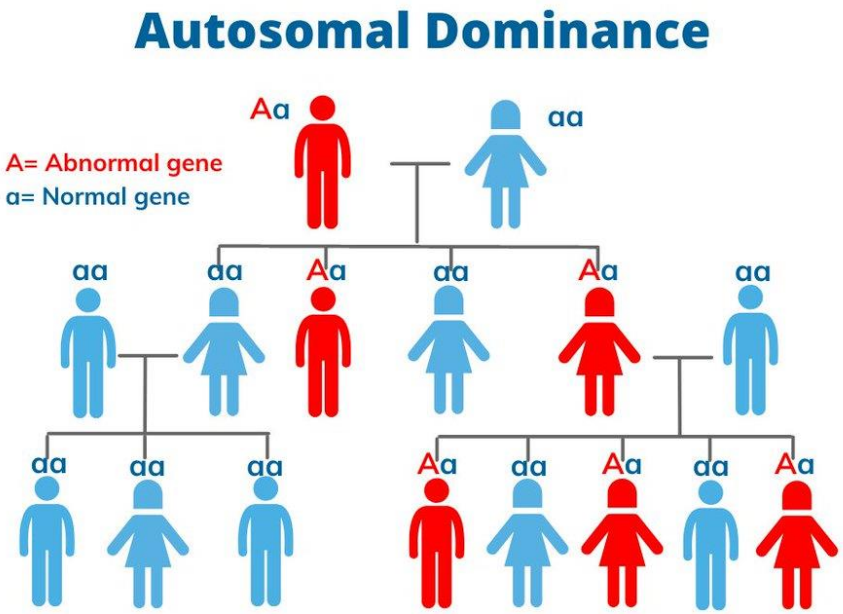
Disease	Effect	Incidence of Disease
Thallassemia (chromosome 16 or 11)	Reduced amounts of hemoglobin; anemia, bone, and spleen enlargement	1/10 in parts of Italy
Sickle-cell anemia (chromosome 11)	Abnormal hemoglobin; sickle-shaped red cells, anemia, blocked circulation; increased resistance to malaria	1/625 African-Americans
Cystic fibrosis (chromosome 7)	Defective cell membrane protein; excessive mucus production; digestive and respiratory failure	1/2000 Caucasians
Tay-Sachs disease (chromosome 15)	Missing enzyme; buildup of fatty deposit in brain; buildup disrupts mental development	1/3000 Eastern European Jews
Phenylketonuria (PKU) (chromosome 12)	Missing enzyme; mental deficiency	1/10,000 Caucasians

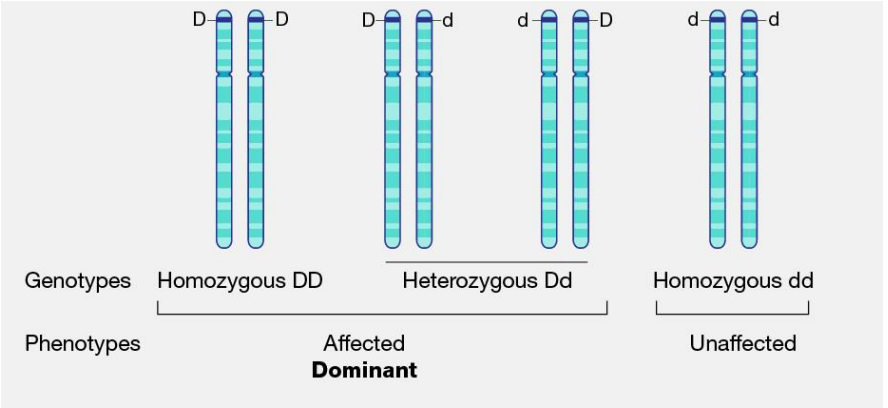
Autosomal dominant inheritance

- Every affected person has at least one affected parent
- Two affected parents can have unaffected children, if both are heterozygotes
- Two unaffected parents NEVER have affected offspring
- Affected individuals appear in every generation
- Transmission of the disease can be from both sexes
- Mutation in only one allele is enough to express the disease
- Heterozygotes much more common than homozygotes
- May see variable expressivity and variable age of onset
- May be due to new mutation



Actually, many human **dominant** disorders are **not** pure **dominant**, the **homozygote** may actually be more *severely* affected, and even may ***not*** *survive*, so clinically affected individuals will be **heterozygote**.

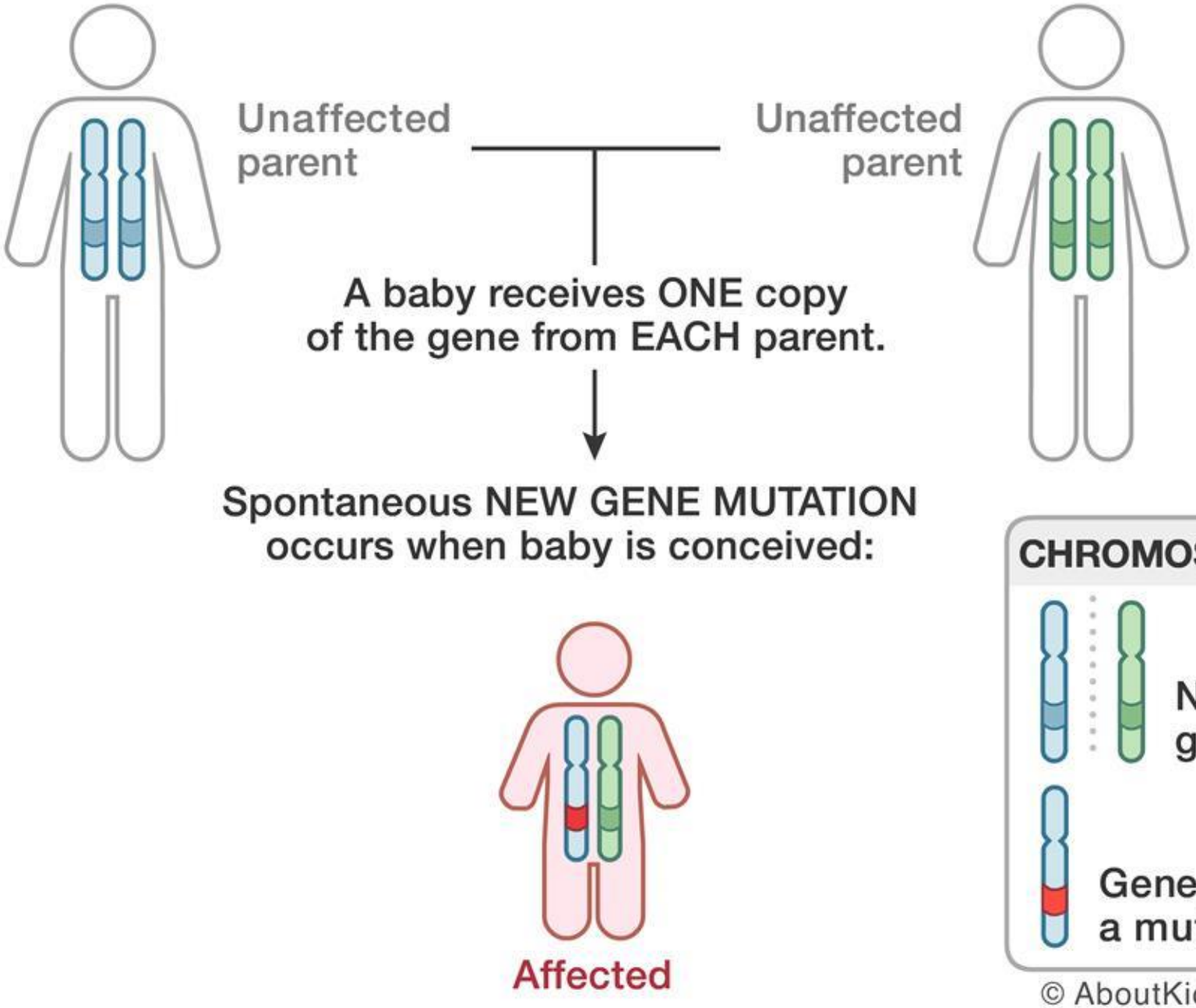




https://twitter.com/AllaboutAPDS/status/1597229418388541441

Figure
Example of autosomal dominant inheritance.

- If one parent has the disorder (assumed to be Aa) and the other does not (aa) then there is a 50% chance that the child will inherit the disorder and a 50% chance that they will not.
- If both parents have the disorder (assumed to be Aa x Aa) then there is a 75% chance that their children will inherit the disorder, and a 25% chance that they will not.



Examples and Features of Autosomal Dominant Inheritance

- More than half of Mendelian phenotypes are autosomal dominant
- Examples:
- Familial hypercholesterolemia
- Myotonic dystrophy
- Huntington disease
- Neurofibromatosis
- Polycystic kidney disease
- Achondroplasia

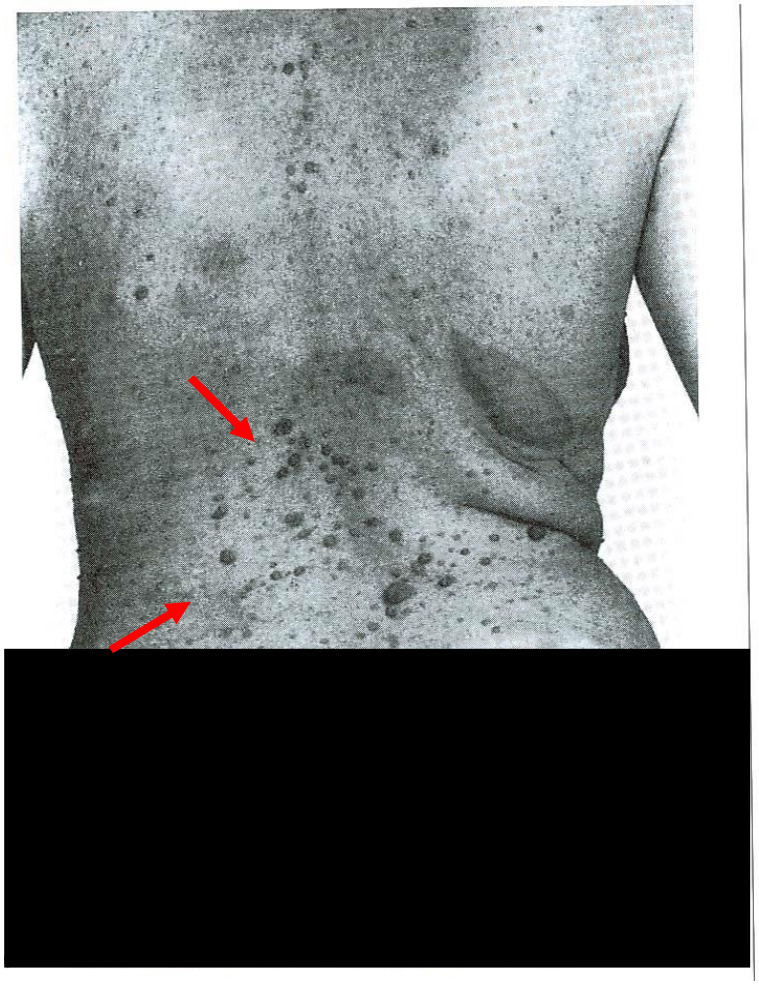
Autosomal Dominant disorders frequently have differences in expression of mutant genes

1. **Penetrance:** probability of any phenotype all or none concept
2. **Expressivity:** severity of the phenotype in individuals with the same genotype
3. **Pleiotropy:** a genetic defect results in diverse phenotypic effects

Example: Neurofibromatosis

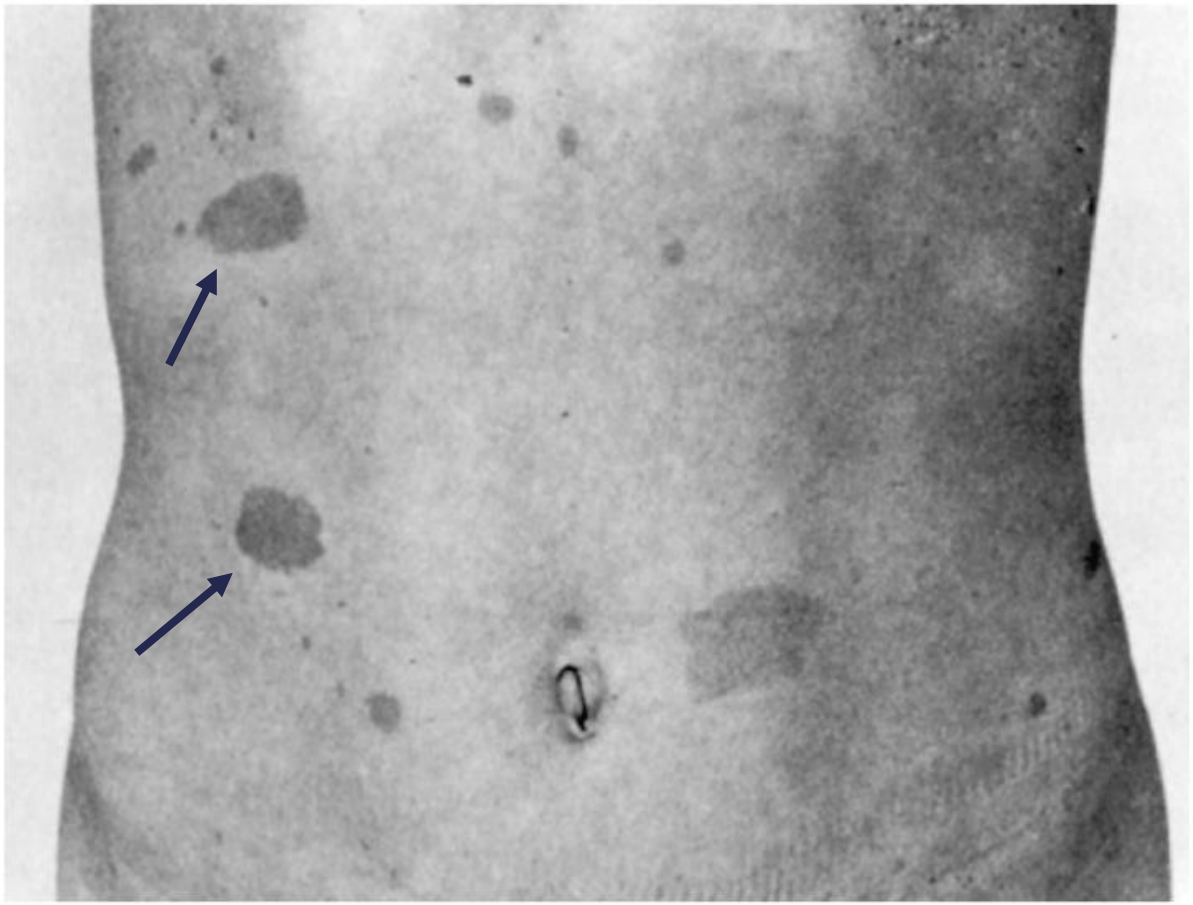
Neurofibromatosis (NF1)-common disorder of the nervous system

1. Multiple benign fleshy tumors (neurofibromas) in the skin



Neurofibromatosis (NF1)-common disorder of the nervous system

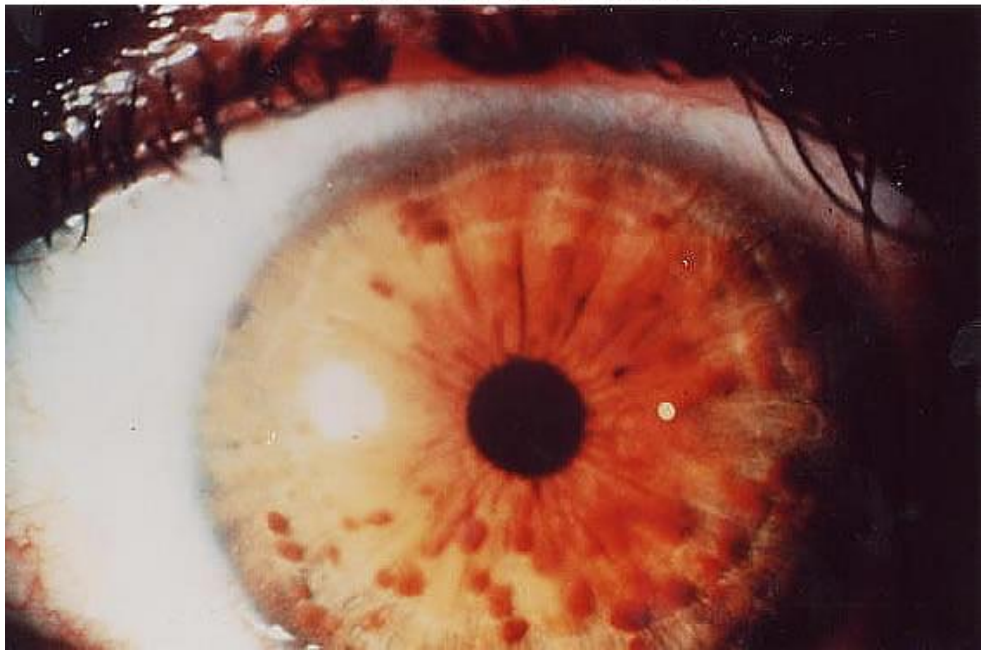
2. Multiple flat, irregular pigmented skin lesions known as café au lait spots



Neurofibromatosis (NF1)-common disorder of the nervous system

3. Small benign tumors (hamartomas) on the iris of the eye

Lisch Nodules



Neurofibromatosis (NF1)-common disorder of the nervous system

4. Less frequently, mental retardation, CNS tumors, diffuse plexiform neurofibormas and the development of cancer of the NS or muscle

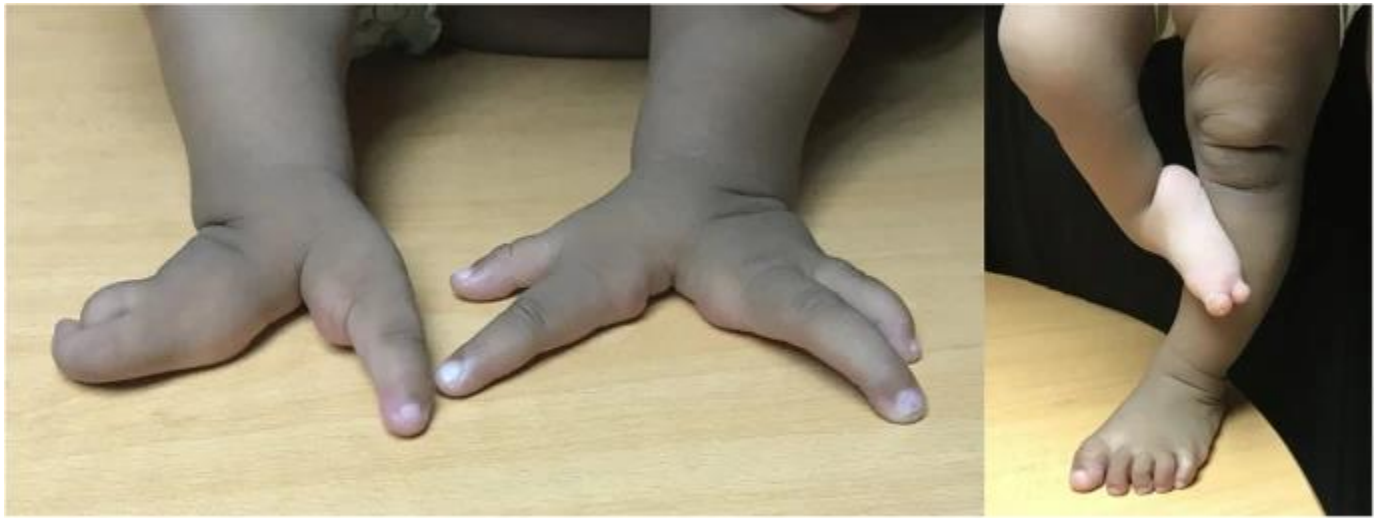
Adult heterozygotes almost always demonstrate some sign of the disease → Penetrance is 100% but age-dependent

Phenotype ranges from café au lait spots to tumors of the spinal cord → Variable expressivity

Pleiotropic → affects skin, iris, brain, muscle

Reduced Penetrance

- Ectrodactyly or split hand/foot malformation (SHFM) is a group of genetic skeletal disorders with variable phenotypes.
- SHFM is clinically heterogeneous, varying from slight shortening of a single central digit to monodactyly in extreme cases.
- Ectrodactyly may occur as an isolated anomaly affecting only one or more limbs, or in syndromic forms with extra-limb manifestations

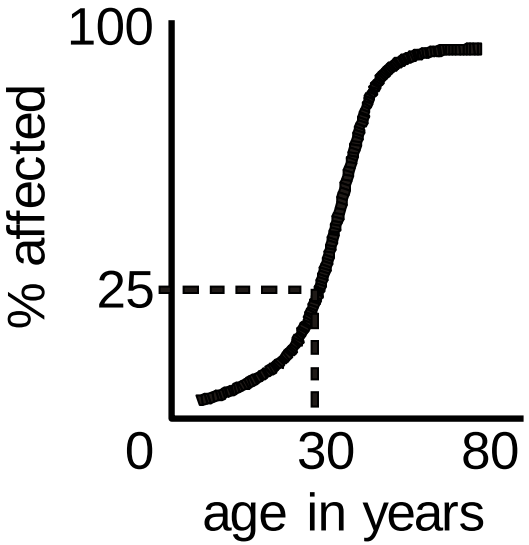


https://bmcmedgenet.biomedcentral.com/articles/10.1186/s12881-019-0839-2

Age of Onset
(age-dependent penetrance)

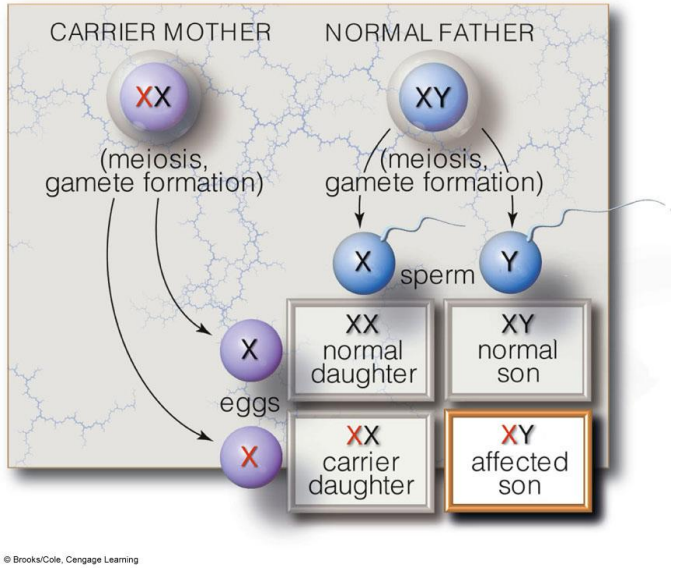
Example: Huntington Disease

- HD is a neurodegenerative disease characterized by progressive dementia and abnormal movements
- HD is an exception in that severity of the disorder (clinical expression) is the same in heterozygotes and homozygotes (onset age?)



X-linked recessive inheritance

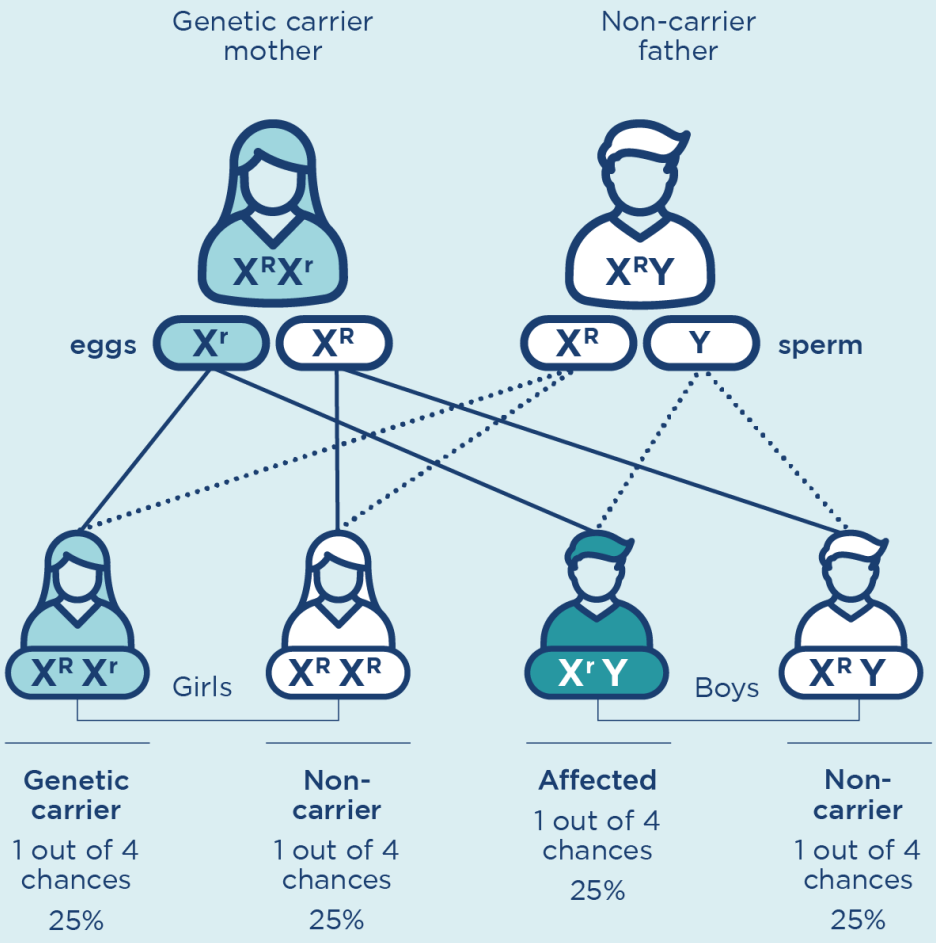
- More males than females have X-linked recessive genetic disorders
  - Males have only one X-chromosome and can express a single recessive allele **hemizygous**
  - A female heterozygote has two X chromosomes and may not show symptoms
- Males transmit an X- linked trait only to their daughters
- Males NEVER transmit an X- linked trait to their sons.



X-linked recessive inheritance

- Males who inherit the trait will be affected.
- Affected males are usually born to unaffected parents; the mother is normally an asymptomatic carrier but may have affected male relatives.
- ALL of daughters of affected male are carriers (heterozygotes)
- Females will express the trait **ONLY** if both her mother and her father have the allele
- Females who inherit the trait will be **carrier**
- Females may be affected if the father is affected and the mother is a carrier,
  - Female carriers with a single mutant allele can occasionally be quite severely affected and are known as manifesting heterozygotes.
- A female carrier for an X-linked recessive trait faces a 50% risk of transmission of the trait to any offspring.

Figure 9.3:
X-linked recessive inheritance where the mother is a carrier of the non-working copy of the X-linked gene. The X-linked recessive non-working gene copy is represented by ‘r’; the working copy by ‘R’.



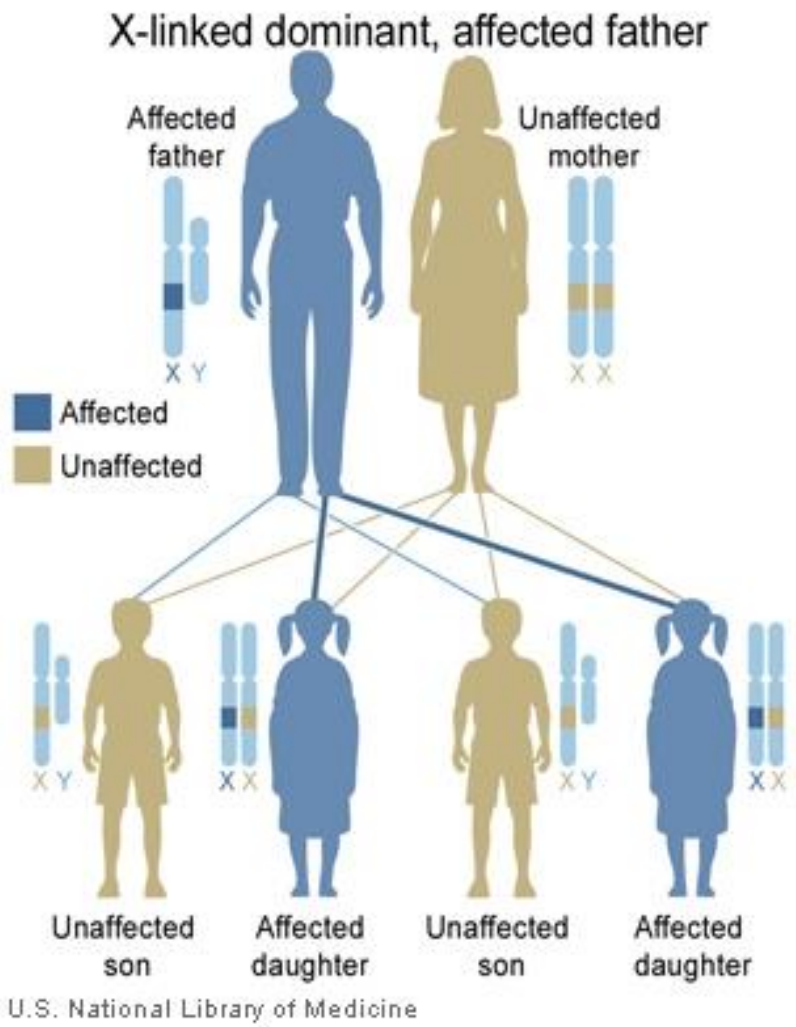
X-linked recessive inheritance

Examples of common X-linked recessive disorders are:

- Hemophilia A
  - Bleeding caused by lack of blood-clotting protein
- Duchenne muscular dystrophy
  - Degeneration of muscles caused by lack of the structural protein dystrophin

X-linked dominant inheritance

- Males and females are equally likely to be affected
- An affected **female** has a **50%** chance of passing the trait to any offspring,
- Whereas **males** transmit the trait to all of their ***daughter*** but **NON** of their **son**.
- For an affected male, all his daughters but none of his sons are affected.



The pattern of inheritance of mitochondria

- Mutations in mitochondrial genes are also the cause of several single gene disorders.
- It affects both sexes.
- It is usually inherited from an affected mother (but is often caused by *de novo* mutations, with the mother unaffected).
- It is not transmitted by a father to any of his children.
- Clinical manifestations are often highly variable.