Chapter 4-1. Patterns of single-gene inheritance
Outline

◆ Pedigree

◆ Inheritance pattern
  ◆ Autosomal dominant inheritance, AD
  ◆ Autosomal recessive inheritance, AR
  ◆ X-linked dominant inheritance, XD
  ◆ X-linked recessive inheritance, XR
  ◆ Y-linked inheritance
  ◆ Mitochondrial diseases
Pedigree

◆ **Pedigree:**

A diagram that describes family relationships, gender, disease status, and other attributes.

◆ **pedigree analysis**
Basic pedigree notation

- Normal male
- Normal female
- Affected male
- Affected female
- X-linked carrier
- Carrier
- Proband
- Dead
- Mating
- Consanguineous mating

- No offspring
- Abortion or stillborn
- Fraternal twins
- Identical twins
- Sex unspecific
How to draw a pedigree?

A proband is an individual being studied or reported on. A proband is usually the first affected individual in a family who brings a genetic disorder to the attention of the medical community.
Patterns of Single-Gene Inheritance

Autosomal dominant inheritance, AD

- The gene concerned to single-gene disorder was located on an autosome, and the phenotype is dominant.

Types
- complete dominance
- incomplete dominance
- irregular dominance
- Codominance
- delayed dominance
Complete dominance

Definition: A phenotype expressed in the same way in both homozygotes and heterozygote.

Genotype and Phenotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>affected</td>
<td>affected</td>
<td>normal</td>
</tr>
</tbody>
</table>
Characteristics of Complete Dominance
- Affecteds usually have at least one affected parent (vertical transmission). Exceptions: new mutations and reduced penetrance.
- A child of an affected and an unaffected individual usually has a 50% chance of being affected (If the disease is rare, almost all affecteds are heterozygotes)
- Affects both sexes, transmitted by either sex
- Normal children of an affected parent have only normal offspring (as well as further descendants). Exception: reduced penetrance.
- **Vertical transmission** of the disease phenotype, lack of skipped generation.
Example: Syndactyly type I

- Symptoms
  - Webbing between 3rd and 4th fingers
  - Fusion of the end bones in the 3rd and 4th fingers
  - Webbing between 2nd and 3rd toes
Example: Syndactyly type I
**incomplete dominance or semidominance**

**Definition:** The phenotype due to a heterozygous genotype is different from the phenotype seen in both homozygous genotypes and its severity is intermediate between them.

**Genotype and Phenotype**

A—mutant allele  
a— wildtype allele

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>Severely affected</td>
<td>Slightly affected</td>
<td>normal</td>
</tr>
</tbody>
</table>
Example: Achondroplasia ,ACH

- the problem is in converting cartilage to bone (a process called ossification), particularly in the long bones of the arms and legs.
- short stature (short-limbed dwarfism): short arms and legs; male 131 cm/ female 124 cm;
- enlarged head, a prominent forehead;
- limited range of motion at the elbows;
- short fingers a three-pronged (trident) hand due to the ring finger and middle finger diverge;
- bowed legs;
- normal intelligence.
Example: Achondroplasia, ACH
codominance

Definition: alleles that are both expressed when they occur together in the heterozygous state.

Genotype and Phenotype
Blood group MN: located on 4q

<table>
<thead>
<tr>
<th>Genotype</th>
<th>MM</th>
<th>MN</th>
<th>NN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>M</td>
<td>MN</td>
<td>N</td>
</tr>
</tbody>
</table>

![MM genotype](image1)

![NN genotype](image2)

![MN genotype](image3)
Blood group ABO:
Alleles $I^A$, $I^B$ and $i$ located on 9q.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>A</th>
<th>B</th>
<th>O</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I^A I^A$</td>
<td>$I^A$</td>
<td>$I^B$</td>
<td>$i$</td>
<td>$I^A I^B$</td>
<td></td>
</tr>
<tr>
<td>$I^A i$</td>
<td>$I^A$</td>
<td>$I^B$</td>
<td>$i$</td>
<td>$I^A I^B$</td>
<td></td>
</tr>
<tr>
<td>$I^B i$</td>
<td>$I^B$</td>
<td>$i$</td>
<td>$I^A I^B$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents’ blood type</td>
<td>Progeny’s blood type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A×A</td>
<td>A,O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A×O</td>
<td>A,O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A×B</td>
<td>A,B,O,AB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A×AB</td>
<td>A,B,AB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A×AB</td>
<td>A,B,AB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B×B</td>
<td>B,O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B×O</td>
<td>B,O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B×AB</td>
<td>A,B,AB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O×O</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O×AB</td>
<td>A,B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB×AB</td>
<td>AB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Irregular dominance**

**Definition**: The phenotypes of some of the heterozygotes, for some reason, **do not appear as affected**. It can be seen as a skipped generation.

**Genotype and Phenotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>affected</td>
<td>normal or affected</td>
<td>normal</td>
</tr>
</tbody>
</table>
Penetrance (外显率): In a population, the proportion of individuals possessing a disease-causing genotype who express the disease phenotype.

- If the proportion is 100%, it is said complete penetrance;
- forme fruste: an atypical and usually incomplete manifestation of a disease

\[
\text{Penetrance} = \frac{\text{Affected heterozygotes}}{\text{Total heterozygotes}} \times 100\%
\]
Example: polydactyly postaxial I

Skipped generation
Expressivity (表现度): the variation of severity of the disease. It refers to the extent of expression of the disease phenotype.

Pleiotropy (基因多效性): the phenomenon in which a single gene contributes to multiple phenotypic traits.
**delayed dominance**

**Definition:** The individuals who carry mutant allele doesn’t onset until particular age.

**Genotype and Phenotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>affected</td>
<td>Onset at particular age</td>
<td>normal</td>
</tr>
</tbody>
</table>
Huntington’s chorea

- progressive chorea, rigidity, and dementia.
- the age of onset was between 30 and 40 years
- a damage of the nerve cells in the basal ganglia and cerebral cortex (caudate and putamen nucleus);
Pedigree of HD
◆ IT15 located on 4p16.3;(CAG)n in exon;
  ◆ n=9-34 normal
  ◆ n>36, even more than 120, affected
  ◆ Genomic imprinting

◆ **Anticipation**: A remarkable phenomenon in which a genetic disease appears earlier appearance and with increased from with each succeeding generation
 Huntington's Disease

Fragile X Syndrome SCA1, 2, 3, 6, 7
FRAXE Mental Retardation

(CGG)$_n$

DRPLA SBMA

(CAG)$_n$

Myotonic Dystrophy SCA8

(CTG)$_n$

5' UTR | ORF | 3' UTR

mRNA

protein

polyQ
Sex-influenced dominance

Definition: A dominant expression that depends on the sex of the individual although the traits is controlled by autosome.

Genotype and Phenotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>affected</td>
<td>Onset due to gender</td>
<td>normal</td>
</tr>
</tbody>
</table>
Example: baldness

- Symptom
- For Aa, Male is affected; Female is normal.
- An autosomal dominant trait is expressed in heterozygous males but not in heterozygous females. Heterozygous females are unaffected but pass this trait on to half of their sons.
- Autosomal alleles whose expression is modified by sex hormones
Autosomal recessive inheritance

**Definition:** The gene concerned to single-gene disorder was located on an autosome, and the phenotype is recessive.

**Genotype and Phenotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>A—wildtype allele</th>
<th>a—mutant allele</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>Aa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>normal</th>
<th>carrier</th>
<th>affected</th>
</tr>
</thead>
</table>
Characteristics of AR pedigree

- Affecteds within a single sibship (“horizontal” transmission)
- Affected individuals are usually born to unaffected (obligate carrier) parents – with a 1/4 probability of being affected, 2/3 of normal offspring is probable carrier.
- Increased probability of parental consanguinity
- Affects either sex.
Pedigree of AR
The chance that both parents are carriers of a mutant allele at the same locus is increased substantially if the parents are related and each could have inherited the mutant allele from a single common ancestor, a situation called **consanguinity**.

**Close relatives: 3 or 4 generation**
- Phenylketonuria type I
- Congenital deafness type I
- Infantile severe myopia
- Albinism type I

Albanism (recessive)
Definition: The gene concerned to single-gene disorder was located on the X chromosome, and the phenotype is recessive.

Genotype and Phenotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>X^aY</td>
<td>affected</td>
</tr>
<tr>
<td>X^A^aY</td>
<td>normal</td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>X^A^A</td>
<td>normal</td>
</tr>
<tr>
<td>X^A^a</td>
<td>carrier</td>
</tr>
<tr>
<td>X^aX^a</td>
<td>affected</td>
</tr>
<tr>
<td>X^aX^a</td>
<td>affected</td>
</tr>
</tbody>
</table>
Pedigree of XR
Characteristics of XR Pedigree

- Most affected individuals are male
- Affected males result from mothers who are affected or who are carriers (have affected brothers, fathers, or maternal uncles)
- Affected females have affected fathers and affected (or carrier) mothers
- The sons of affected females are affected
- Approximately half the sons of a carrier female should be affected
carrier girl 1 out of 4 chance 25%
normal girl 1 out of 4 chance 25%
affected boy 1 out of 4 chance 25%
normal boy 1 out of 4 chance 25%
carrier mother of mutant gene

\[ X^r = \text{recessive mutant gene} \]

\[ X \text{ or } Y = \text{wild-type gene} \]

eggs

\[ X' \]

sperms

\[ X^r \]

affected girl
1 out of 4 chance
25%

carrier girl
1 out of 4 chance
25%

affected boy
1 out of 4 chance
25%

normal boy
1 out of 4 chance
25%
Hemophilia A

- **Hemophilia**, hereditary blood disease, characterized by the inability of blood to clot, or coagulate, leading to hemorrhage, or excessive bleeding, even from minor injuries.

- The disease is caused by an insufficiency or absence of **factor VIII**, that participate in blood clotting.
  - It is caused by a recessive allele on the X chromosome.
Hemophilia A
Color-blindness

Can not recognize correctly red color and green color
**X—linked dominant inheritance, XD**

- **Definition:** The gene concerned to single-gene disorder was located on the X chromosome, and the phenotype is dominant.

- **Genotype and Phenotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
</tr>
<tr>
<td>X&lt;sup&gt;a&lt;/sup&gt;Y</td>
<td>normal</td>
</tr>
<tr>
<td>X&lt;sup&gt;A&lt;/sup&gt;Y</td>
<td>affected</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
</tr>
<tr>
<td>X&lt;sup&gt;A&lt;/sup&gt;X&lt;sup&gt;A&lt;/sup&gt;</td>
<td>affected</td>
</tr>
<tr>
<td>X&lt;sup&gt;A&lt;/sup&gt;X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>affected</td>
</tr>
<tr>
<td>X&lt;sup&gt;a&lt;/sup&gt;X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>normal</td>
</tr>
</tbody>
</table>
Pedigree of XD
Characteristics of XD Pedigree

- Affects females preferentially, but also affects males
- Females often more mildly and more variably affected
- If mother is affected, recurrence risk is 50%; if father, 100% of daughters will be affected
- No male to male transmission
- Does not skip generations
non carrier
mother

LEGEND: $X^D$ =
dominant faulty gene
on X chromosome

$X$ or $Y$ =
correct gene

father

eggs $X$ $X$

sperm $X^D$ $Y$

$XX^D$

$XX^D$

$XY$

$XY$

□ All girls affected □

□ No boys affected □
LEGEND: $X^D =$ dominant faulty gene on X chromosome

$X$ or $Y =$ correct gene

affected mother $X^D X$

non carrier father $XY$

eggs $X^D$ $X$

sperm $X$ $Y$

affected $X^D X$

non carrier $XX$

affected $X^D Y$

non carrier $XY$

---

GIRLS 1 OUT OF 2 CHANCE 50%

BOYS 1 OUT OF 2 CHANCE 50%
Vitamin D resistant Rickets

- this is the most frequently encountered form of rickets
- Hypophosphatemia
- decreased reabsorption of phosphate by the renal proximal tubule
- administration of high doses of vitamin D have no beneficial effect
Vitamin D resistant Rickets

- Widening of epiphyseal plates
- Bowing of the leg
Y-linked inheritance

- Disease genes are on Y chromosome
- Affects males only
- All sons of affected father are affected
- TDF or SRY
- AZF (azoospernia factor)
Pedigree of Y-linked inheritance
Mitochondrial diseases

- Disease genes are on mitochondria
- Maternal inheritance

![Family Tree](image)
heterogeneity

- Same diseases caused by different genetic factors;
- **Locus heterogeneity** —— A single disorder, trait, or pattern of traits caused by mutations in genes at different chromosomal loci.
- **Allelic heterogeneity** —— A single disorder, trait, or pattern of traits caused by different mutations within a gene.
Example of heterogeneity

- **Congenital deafness:**
  - AD
  - AR (more than 100 loci)
  - XR

- **Retinitis pigmentosa**
  - 12 autosomal dominant forms
  - 5 autosomal recessive forms
  - 3 X-linked forms
phenocopy

- A mimic of a phenotype that is usually determined by a specific genotype, produced instead by the interaction of some environmental factor with a normal genotype.
- Phenotype (generally referring to a single trait), under a particular environmental condition, is identical to phenotype determined by the genotype.

Chocolate-colored male Himalayan Rabbi
Pedigree Analysis

- Dominant or recessive?
- Sex difference?
- Genotype analysis
AD: Irregular dominance

I

II

III

IV

Aa

aa

Aa

Aa

aa

aa

Aa

aa

Aa

a

Aa
Normal male is AB blood type; normal female is B blood type, and her father is O blood type with color blind. What are the phenotype and genotype of their offspring when the man and female married?

\[
P: I^A I^B X^B Y \times I^B i X^B X^b \\
\text{gamete: } I^A X^B, I^A Y, I^B X^B, I^B Y \downarrow I^B X^B, I^B X^b, i X^B, i X^b \\
\]
Thank you