In the previous part we saw that Mendel principles were built on presence of 2 alleles, one of them is completely dominant over the other, controlling each character. These two alleles segregate during gamete formation and are rejoined at random, one from each parent, during fertilization. In addition, alleles of each character assort independently. However, these conditions are not always present that leads to modifications and extensions from Mendelian ratios. This lack of adherence to Mendel's rules doesn't mean that Mendel was wrong; rather, it demonstrates that Mendel's principles are not, by themselves, sufficient to explain the inheritance of all genetic characteristics. Our modern understanding of allelic relations and factors affecting their expression and inheritance has been greatly enriched by the discovery of a number of modifications and extensions of Mendel's basic principles, which are the focus of the following part.

A- Neither Allele Is Dominant

1) Incomplete, or Partial, Dominance

The character is controlled by a couple of alleles, neither of which is dominant over the other. Heterozygote exhibits an intermediate phenotype between those of homozygote dominant and recessive. For example, if a snapdragon plant with red flowers is crossed with a white-flowered plant, the offspring have pink flowers. Because some red pigment is produced in the F1 intermediate-colored plant, neither the red nor white flower color is dominant. If the phenotype is under the control of a single gene and two alleles, where neither is dominant, the results of the F1 (pink) × F1 (pink) cross can be predicted. The resulting F2 generation shown in the following Figure confirms the hypothesis that only one pair of alleles determines these phenotypes.

One of methods used to refer to alleles is using initial letter of the name of a recessive trait, lowercased and italicized, denotes the recessive allele. The same letter in uppercase refers to the dominant allele. Thus, in the case of tall and dwarf, where dwarf is recessive: *d* allele responsible for the trait dwarf and *D* allele responsible for the trait tall. Because neither allele is recessive, we can not use upper- and lowercase letters as symbols. **Instead,** R^1 and R^2, W^1 and W^2 or C^W and C^R, where *C* indicates "color" and the *W* and *R* superscripts indicate white and red, respectively.

The most accurate way is to consider gene expression in a quantitative way. The allele C^R encodes enzyme that participates in a reaction leading to the synthesis of a red pigment. C^W encodes enzyme that cannot catalyze the reaction leading to pigment. The end result is that the heterozygote produces only about half the pigment of the red-flowered plant and the phenotype is pink.

Genotype	**Phenotype**
C^WC^W	**White**
C^WC^R	**Pink**
C^RC^R	**Red**

P

$C^W C^W$

$C^R C^R$

C^W C^R

F1

100% Pink flower

$C^W C^R$

Self-crossing

F2

♀ / ♂	C^W	C^R
C^W	$C^W C^W$ 	$C^W C^R$ 
C^R	$C^W C^R$ 	$C^R C^R$ 

(1 Red : 2 Pink : 1 White)

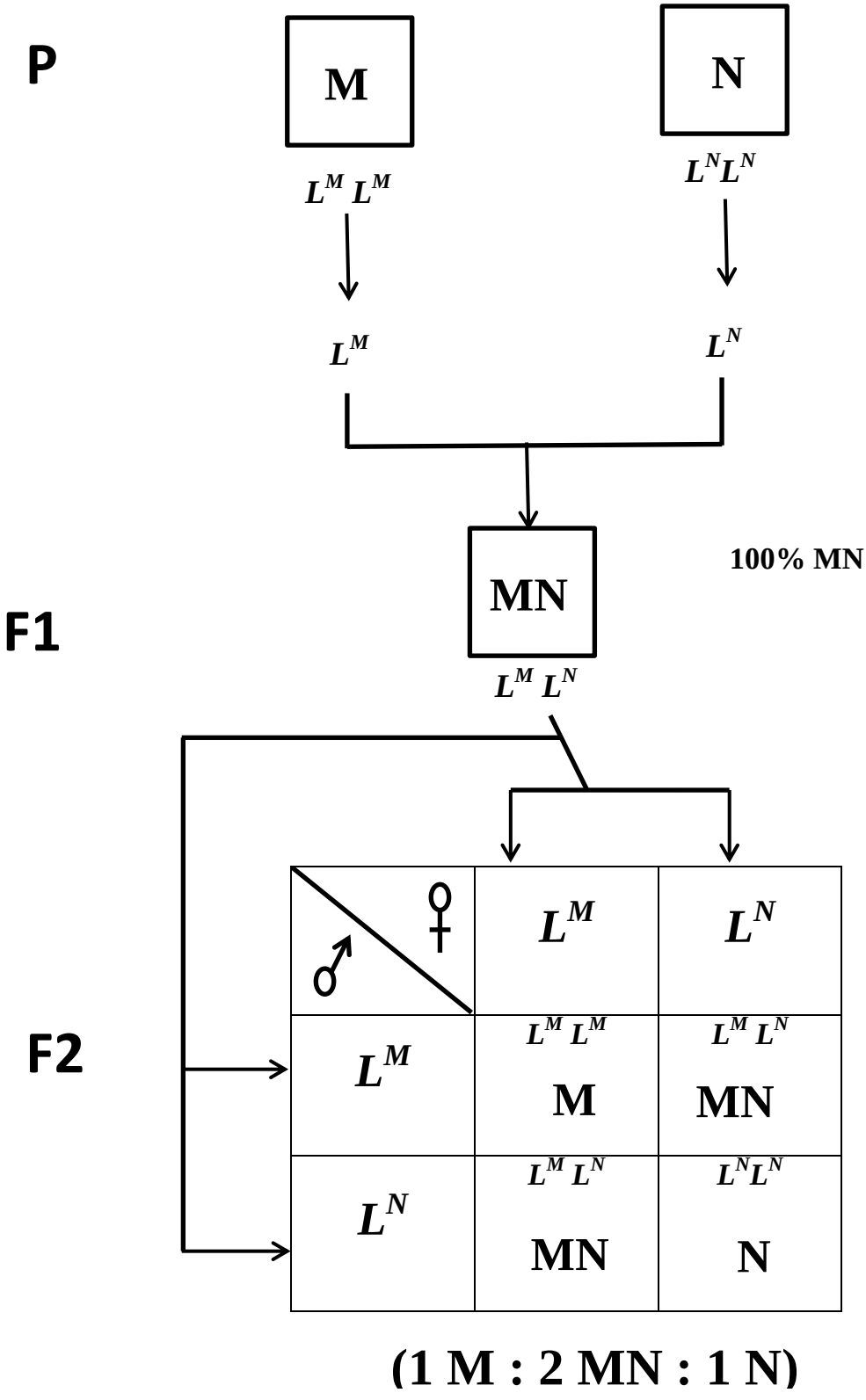
2) Codominance

Alleles of a single gene are responsible for producing two distinct, detectable gene products. It is the joint expression of both alleles in heterozygotes. The Influence of both alleles in a heterozygote is clearly evident. It is a situation different from incomplete dominance or dominance/recessiveness arises.

The **MN blood group** in humans illustrates this phenomenon. A glycoprotein molecule found on the surface of red blood cells that acts as a native antigen, providing biochemical and immunological identity to individuals. In the human population, two forms of this glycoprotein exist, designated M and N; an individual may exhibit either one or both of them. Two alleles designated L^M and L^N. Because humans are diploid, three combinations are possible, each resulting in a distinct blood type:

Genotype	**Phenotype**
$L^M L^M$	**M**
$L^M L^N$	**MN**
$L^N L^N$	**N**

As predicted, a mating between two heterozygous MN parents may produce children of all three blood types, as follows:



In partial and incomplete dominance, phenotypic ratio equals the genotypic one (1 : 2 : 1) as heterozygous has a phenotype that can be distinct from homozygous.

B- Multiple alleles

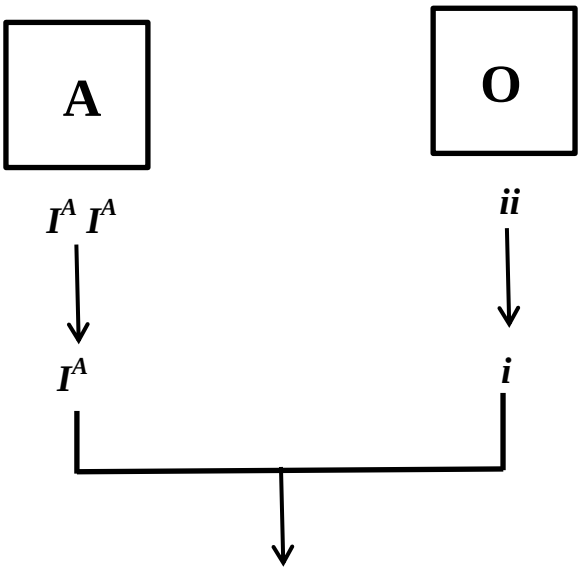
It means presence of more than 2 alleles for a gene in population. However, every diploid individual has 2 alleles for such gene. Thus, among members of a species, numerous alternative allelic combinations of the same gene can exist. The simplest case of multiple alleles occurs when three alternative alleles of one gene exist. This situation is illustrated in the inheritance of the **ABO blood groups** in humans. The ABO system, like the MN blood types, is characterized by the presence of antigens (A & B) on the surface of red blood cells. The A and B antigens are distinct from the M & N antigens and are under the control of a different gene. As in the MN system, one combination of alleles in the ABO system exhibits a codominant mode of inheritance. Each individual has one of four phenotypes. Each individual has either the A antigen (A phenotype), the B antigen (B phenotype), the A and B antigens (AB phenotype), or neither antigen (O phenotype).

Although different designations can be used, we will use the symbols I^A, I^B, and *i* to distinguish these three alleles. The *I* designation stands for *isoagglutinogen*, another term for antigen. If we assume that the I^A and I^B alleles are responsible for the production of their respective A and B antigens and that *i* is an allele that does not produce any detectable A or B antigens, we can list the various genotypic possibilities and assign the appropriate phenotype to each:

Genotype	Antigen	Phenotype
I^AI^A	A	A
I^Ai	A	A
I^BI^B	B	B
I^Bi	B	B
I^AI^B	AB	AB
ii	-	O

In these assignments, the I^A and I^B alleles are dominant to the *i* allele, but codominant to each other.

P

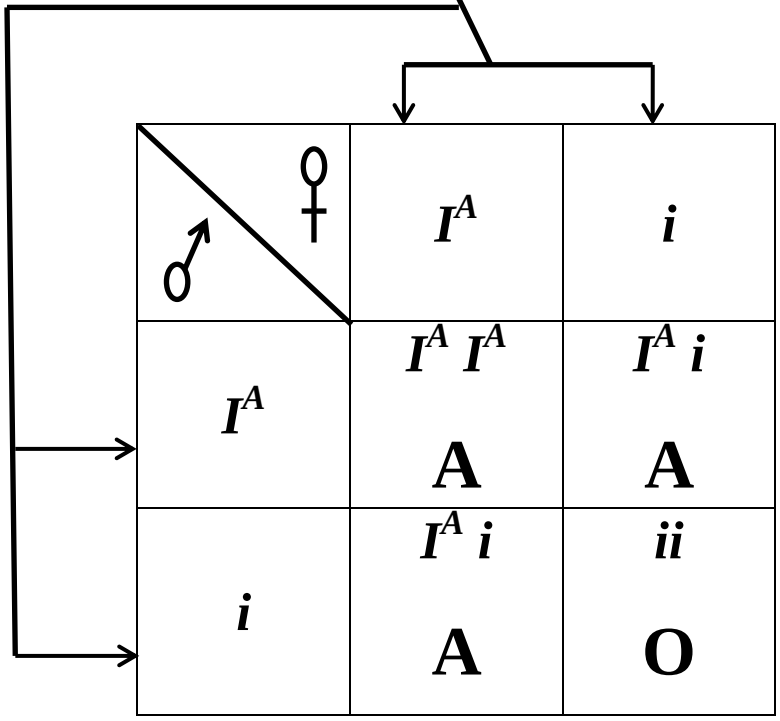


F1

100% A

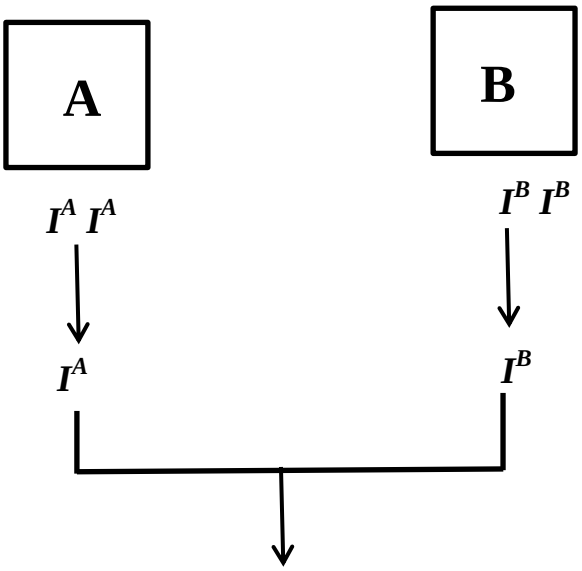
I^Ai

F2

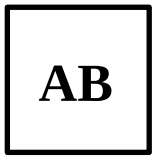


(3 A : 1 O)

P



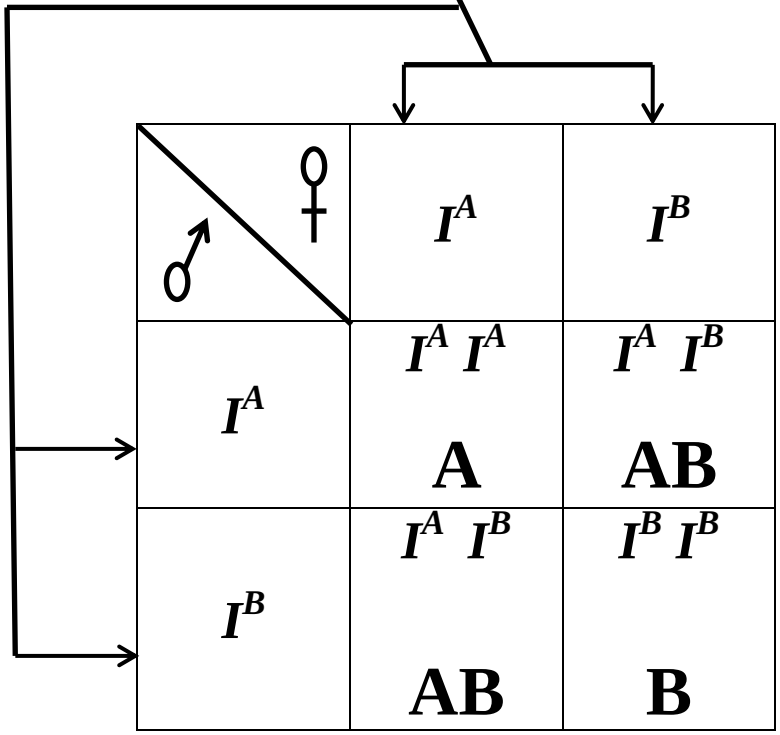
F1



100% AB

$I^A\ I^B$

F2



♀ / ♂	I^A	I^B
I^A	$I^A\ I^A$ **A**	$I^A\ I^B$ **AB**
I^B	$I^A\ I^B$ **AB**	$I^B\ I^B$ **B**

(1 A : 2 AB : 1 B)

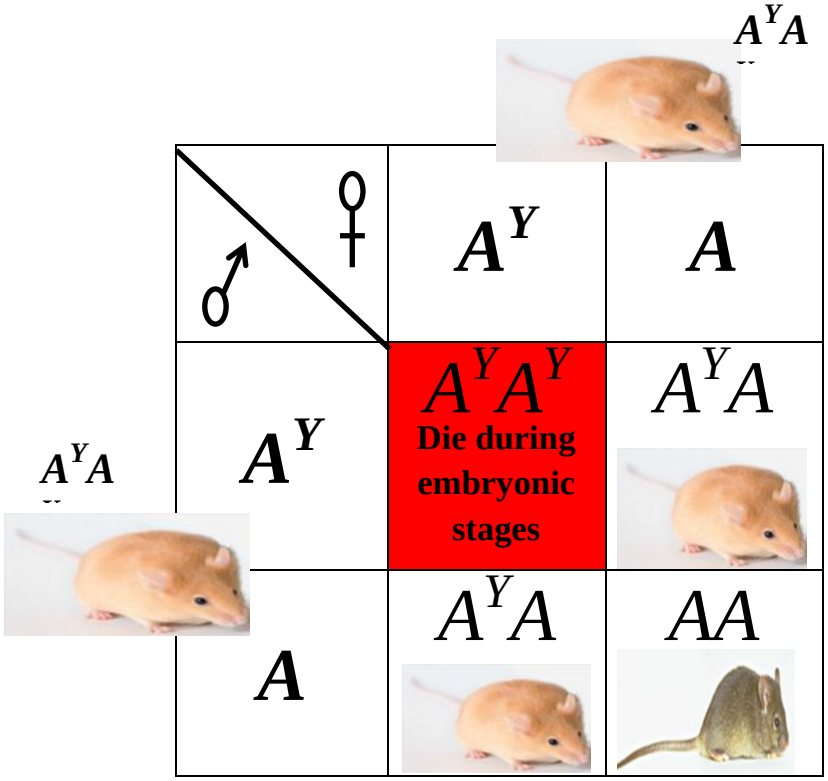
Q: What are the expected blood groups for children whose parents have:

- AB and O blood groups.
- AB and A blood groups.

C- Lethal Alleles

Presence of certain alleles may cause death of their carriers. If 2 copies of a lethal allele are required for death, the allele is called **recessive lethal allele**. If death occurs before birth some genotypes may not appear among the progeny. Consequently, Mendelian ratios will be modified.

In rats, a mutation produced an allele (A^Y) that causes death in case of homozygotes. The mutation was associated with appearance of yellow coat instead of agouti coat. The allele is recessive for lethality where 2 copies are required for death while it is dominant for color where only one copy of it is enough to produce yellow color. Matting of 2 yellow rats gives yellow and agouti in 2:1 ratio. The modification of Mendelian ratio is attributed to death of rats carrying (A^YA^Y) genotype that constitutes 1/3 of expected yellow rats die during embryonic stages.



(2 yellow : 1 agouti)

A^Y is recessive lethal allele were it is lethal in homozygotes only though it encodes dominant trait (yellow) of color. It is clear that all yellow rats are heterozygotes (Why?). Also, A^Y has no effect on agouti X agouti and agouti X yellow (Why?).

If only one copy of lethal alleles is enough for death, the allele is thus called dominant leathal allele. Both of homozygotes and heterozygotes die. Truly dominant lethal alleles cannot be transmitted unless they are expressed after the onset of reproduction, as in Huntington disease in humans,

Huntington disease is due to a dominant autosomal allele *H*, where the onset of the disease in heterozygotes (*Hh*) is delayed, usually well into adulthood. Affected individuals then undergo gradual nervous and motor degeneration until they die. This lethal disorder is particularly tragic because it has such a late onset, typically at about age 40. By that time, the affected individual may have produced a family, and each of their children has a 50 percent probability of inheriting the lethal allele, transmitting the allele to his or her offspring, and eventually developing the disorder.

Dominant lethal alleles are rarely observed. For these alleles to exist in a population, the affected individuals must reproduce before the lethal allele is expressed, as can occur in Huntington disease. If all affected individuals die before reaching reproductive age, the mutant gene will not be passed to future generations, and the mutation will disappear from the population unless it arises again as a result of a new mutation.

D) A Single gene has multiple phenotypic effects (pleiotropy).

Every allele is responsible for traits of different characters. It results in a case where traits of different characters seem to assort together i.e. do not show independent assortment. An excellent example of pleiotropy is Marfan syndrome, a human malady resulting from an autosomal dominant mutation in the gene encoding the connective tissue protein *fibrillin*. Because this protein is widespread in many tissues in the body, one would expect multiple effects of such a defect. In fact, fibrillin is important to the structural integrity of the lens of the eye, to the lining of vessels such as the aorta, and to

bones, among other tissues. As a result, the phenotype associated with Marfan syndrome includes lens dislocation, increased risk of aortic aneurysm, and lengthened long bones in limbs. Thus, lens dislocation, increased risk of aortic aneurysm and lengthened long bones in limbs will be transmitted together (not independently). This disorder is of historical interest in that speculation abounds that Abraham Lincoln was afflicted.

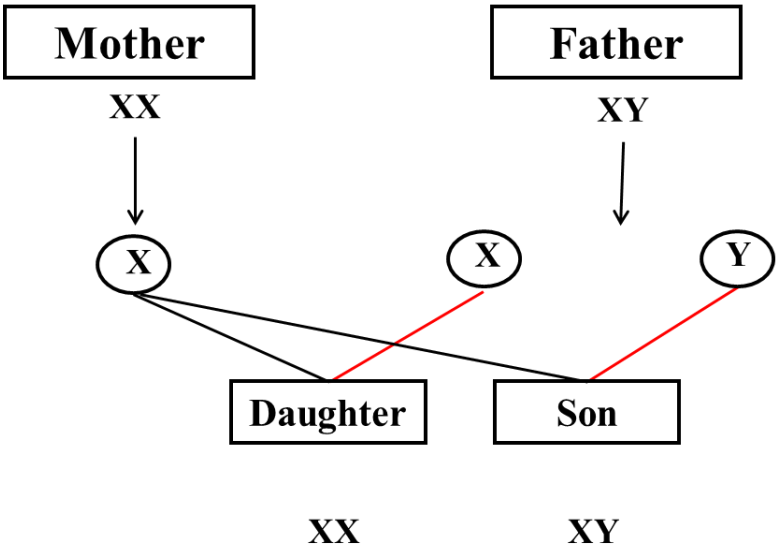
E) Impacts of sex on inheritance and expression of alleles.

It was found that sex has a great influence on either the pattern of inheritance of alleles or their expression. Generally, the influence of sex lies in the following categories:

1) Sex-linked genes （Describes Genes on the X Chromosome)

Sex determination systems vary among different organisms. The XX/XY sex-determination system is the most familiar, as it is found in humans. In the system, females have two of the same kind of sex chromosome (XX), while males have two distinct sex chromosomes (XY). The XY sex chromosomes are different in shape and size from each other, unlike the autosomes, and are termed allosomes.

Y chromosome lacks copies of most genes present on the X chromosome. As a result, genes present on the X chromosome exhibit patterns of inheritance that are very different from those seen with autosomal genes. For alleles carried on X chromosome, one copy of recessive alleles is sufficient to show the recessive phenotype in male. Females have two X chromosome (one from each parent) while males have only one X chromosome (from mother). Consequently, alleles carried on X-chromosomes pass, equally, from mother to her sons and daughters while they pass from father to his daughters only.



One of the first cases of X-linkage was documented in 1910 by Thomas H. Morgan. In Drosophila, the normal wild type red eye color is dominant to white eye color. The inheritance pattern of eye color trait was clearly related to the sex of the parent carrying each allele. Reciprocal crosses between white-eyed and red-eyed flies did not yield identical results. Analysis led to the conclusion that the locus for eye color is present on the X chromosome rather than on one of the autosomes. Both the gene and the trait are said to be X-linked. The obvious differences in phenotypic ratios in both the F1 and F2 generations are dependent on whether or not the P1 white-eyed parent was male or female. Morgan was able to correlate these observations with the difference found in the sex-chromosome composition of male and female *Drosophila*. He hypothesized that the recessive allele for white eye is found on the X chromosome, but its corresponding locus is absent from the Y chromosome. Females thus have two available gene loci, one on each X chromosome, whereas males have only one available locus, on their single X chromosome.

Morgan's interpretation of X-linked inheritance, shown in the next figure, provides a suitable theoretical explanation for his results. Since the Y chromosome lacks homology with almost all genes on the X chromosome, these alleles present on the X chromosome of the males will be directly expressed in the phenotype. Males cannot be either homozygous or heterozygous for X-linked genes; instead, their condition− possession of only one copy of a gene in an otherwise diploid cell−is referred to as hemizygosity. The individual is said to be hemizygous. One result of X-linkage is the *crisscross pattern of*

inheritance, in which phenotypic traits controlled by recessive X-linked genes are passed from homozygous mothers to all sons. This pattern occurs because females exhibiting a recessive trait must contain the recessive allele on both X chromosomes. Because male offspring receive one of their mother’ s two X chromosomes and are hemizygous for all alleles present on that X, all sons will express the same recessive X-linked traits as their mother.

In humans, many genes and the respective traits controlled by them are recognized as being linked to the X chromosome. Human color blindness and hemophilia are examples for such pattern of inheritance.

Male with White eye

Female with red eye

♀ \ ♂	w	♂
w^+	Female with red eye	Male with red eye
w^+	Female with red eye	Male with red eye

F1: All with red eye

Male with red eye

Female with red eye

♀ \ ♂	w^+	♂
w	Female with red eye	Male with white eye
w^+	Female with red eye	Male with red eye

F2: 3 red : 1 White

Male with red eye

♀ \ ♂		
	 Female with red eye	 Male with white eye
	 Female with red eye	 Male with white eye

Female with white eye

F1: 1 Red : 1 White

Male with white eye

♀ \ ♂		
	 Female with white eye	 Male with white eye
	 Female with red eye	 Male with red eye

Female with red eye

F2: 1 red : 1 White

2) Sex-Limited and Sex-Influenced Inheritance

In contrast to X-linked inheritance, patterns of gene expression may be affected by the sex of an individual even when the genes are not on the X chromosome. In numerous examples in different organisms, the sex of the individual plays a determining role in the expression of a phenotype. In these cases, autosomal genes are responsible for the existence of contrasting phenotypes, but the expression of these genes is dependent on the hormone constitution of the individual.

- **Sex- limited inheritance**

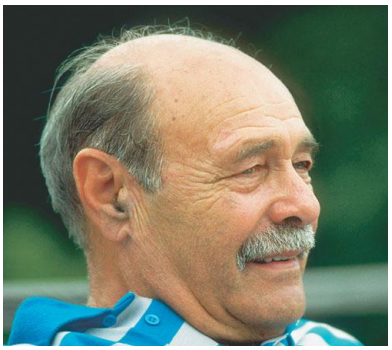
The expression of a specific phenotype is absolutely limited to one sex. In domestic fowl, tail and neck plumage is often distinctly different in males and females, demonstrating *sex-limited inheritance*. Cock feathering is longer, more curved, and pointed, whereas hen feathering is shorter and less curved. Inheritance of these feather phenotypes is controlled by a single pair of autosomal alleles whose expression is modified by the individual's sex hormones. As shown in the following chart, hen feathering is due to a dominant allele, *H*, but regardless of the homozygous presence of the recessive *h* allele, all females remain hen-feathered. Only in males does the *hh* genotype result in cock feathering.

Genotype	Phenotype	
	Male	Female
HH	Hen-feathered	Hen-feathered
Hh	Hen-feathered	Hen-feathered
hh	Cock-feathered	Hen-feathered

- **b) Sex-influenced inheritance**

The sex of an individual influences the expression of a phenotype that is not limited to one sex or the other. Cases of *sex-influenced inheritance* include pattern baldness in humans. In such cases, autosomal genes are responsible for the contrasting phenotypes,

and while the trait may be displayed by both males and females, the expression of these genes is dependent on the hormone constitution of the individual. Thus, the heterozygous genotype exhibits one phenotype in one sex and the contrasting one in the other. For example, pattern baldness in humans, where the hair is very thin or absent on the top of the head, is inherited in the following way:



Genotype	**Phenotype**	
	Male	**Female**
BB	Bald	Bald
Bb	Bald	Not Bald
bb	Not Bald	Not Bald