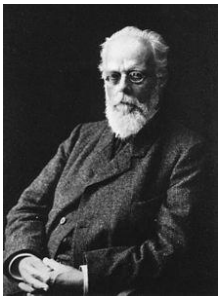
<u>Lecture 4.</u> Chromosome theory of inheritance. Sex determination and the inheritance of sex-linked traits.

1. Chromosome theory of inheritance.
2. Chromosome mapping.
3. Sex determination and the inheritance of sex-linked traits.

In **1865 Gregor Mendel** has discovered laws of heredity. But he came to the conclusion of the heredity principles without the knowledge of genes and chromosomes. Over the next decades after Mendel's findings cytological bases of heredity become more understandable.

In **1869 Johannes Friedrich Miescher** was the first researcher to isolate and identify nucleic acid in pus cells.

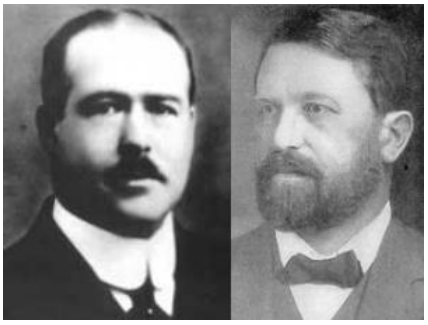
In 1878 Walther Flemming described chromatin threads in cell nucleus and behavior of chromosomes during mitosis.



In **1890 August Weismann** described role of meiosis for reproduction and heredity.

In **1888 Heinrich Waldeyer** has coined the term "chromosome" to describe basophilic stained filaments inside the cell nucleus.

The speculation that chromosomes might be the key to understanding heredity led several scientists to examine Mendel's publications and re-evaluate his model in terms of the behavior of chromosomes during mitosis and meiosis.

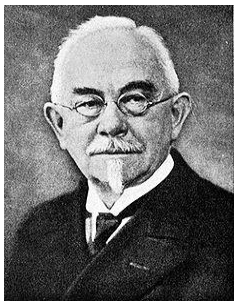


In **1902, Theodor Boveri** (right) observed that proper embryonic development of sea urchins does not occur unless chromosomes are present. That same year, **Walter Sutton** (left) observed the separation of chromosomes into daughter cells during meiosis. Together, these observations led to the development of the <u>Chromosomal Theory of Inheritance</u>, which identified chromosomes as the genetic material responsible for Mendelian inheritance.

The Chromosomal Theory of Inheritance was consistent with Mendel's laws and was supported by the following observations:

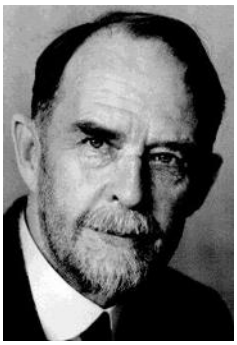
- During meiosis, homologous chromosome pairs migrate as discrete structures that are independent of other chromosome pairs.

- The sorting of chromosomes from each homologous pair into pre-gametes appears to be random.
- Each parent synthesizes gametes that contain only half of their chromosomal complement.
- Even though male and female gametes (sperm and egg) differ in size and morphology, they have the same number of chromosomes, suggesting equal genetic contributions from each parent.
- The gametic chromosomes combine during fertilization to produce offspring with the same chromosome number as their parents.



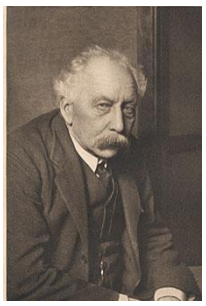
In **1909 Wilhelm Johannsen** introduced the term **«gene».**

Despite compelling correlations between the behavior of chromosomes during meiosis and Mendel's abstract laws, the Chromosomal Theory of Inheritance was proposed long before there was any direct evidence that traits were carried on chromosomes. Critics pointed out that individuals had far more independently segregating traits than they had chromosomes. It was only after several years of carrying out crosses with the fruit fly, *Drosophila melanogaster*, that **Thomas Hunt Morgan** provided experimental evidence to support the Chromosomal Theory of Inheritance.



He studied and explained the following questions:

1) Importance of chromosomes as carriers of hereditary information;
2) Linkage of genes;
3) Crossing-over and chromosome mapping;
4) Chromosomal definition of sex;
5) Sex-linked inheritance.



But before, in the early **1900s, William Bateson** (left) and **R. C. Punnett** (right) were studying inheritance in the sweet pea. They studied two genes: one affecting flower color (P, purple, and p, red) and the other affecting the shape of pollen grains (L, long, and l, round). They crossed pure lines P/P · L/L (purple, long) × p/p · l/l (red, round), and selfed the F_1 P/p · L/l heterozygotes to obtain an F_2.

Table 1. shows the proportions of each phenotype in the F_2 plants.

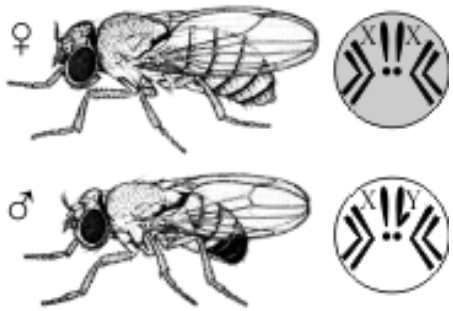
Table 1. Sweet Pea Phenotypes Observed in the F_2 by Bateson and Punnett

		NUMBER OF PROGENY
Phenotype (and genotype)	**Observed**	**Expected from 9:3:3:1 ratio**
purple, long (P/– · *L*/–)	4831	3911
purple, round (/– *P*· *l*/*l*)	390	1303
red, long (*p*/*p* · *L*/–)	393	1303
red, round (*p*/*p* · *l*/*l*)	1338	435
	6952	6952

The F_2 phenotypes deviated strikingly from the expected 9:3:3:1 ratio. This does not appear to be explainable as a modified Mendelian ratio. Two phenotypic classes are larger than expected: the purple, long phenotype and the red, round phenotype. As a possible explanation for this, Bateson and Punnett proposed that the F_1 had actually produced more P · L and p · l gametes than would be produced by Mendelian independent assortment. Because these genotypes were the gametic types in the original pure lines, the researchers thought that physical **coupling** between the dominant alleles *P* and *L* and between the recessive alleles *p* and *l* might have prevented their independent assortment in the F_1. However, they did not know what the nature of this **coupling** could be.

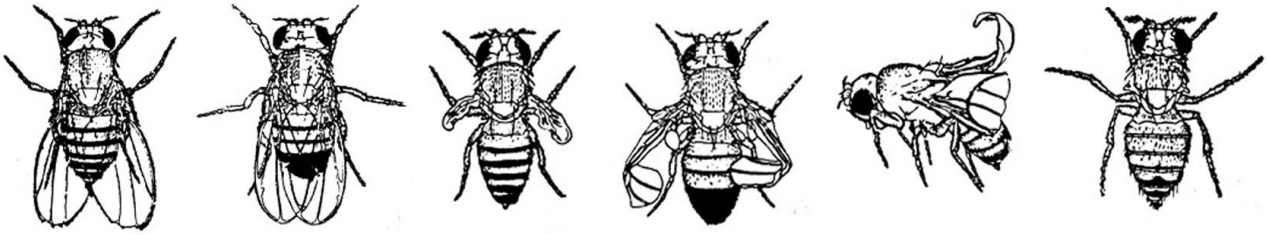
The confirmation of Bateson and Punnett's hypothesis had to await the development of *Drosophila* as a genetic tool.

In 1910, Thomas Hunt Morgan started his work with *Drosophila melanogaster*, a fruit fly.



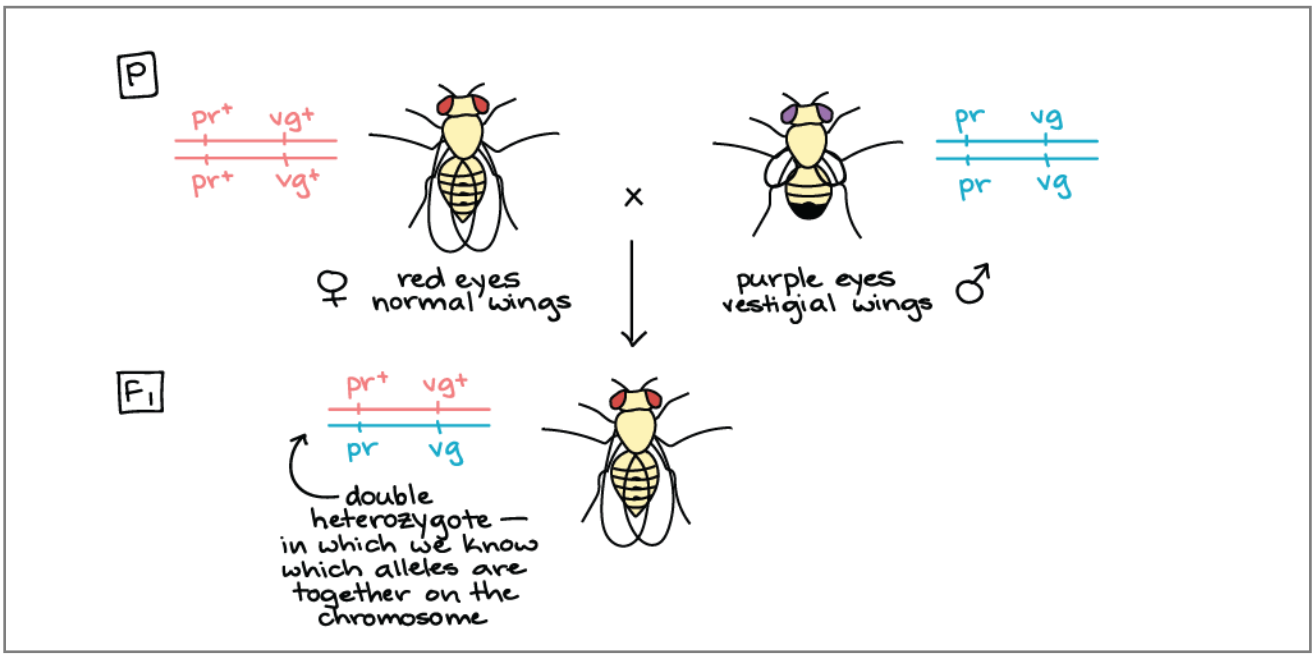
He chose fruit flies because:

1) they can be cultured easily,
2) are present in large numbers,
3) have a short generation time (breeds rapidly, attaining maturity in 12 days. One can receive 30 generations of *Drosophila* for a year),
4) have only four pair of chromosomes (relatively simple karyotype) and polytene chromosomes that can be easily identified under the microscope,
5) This fly has clearly marked characters: different colors of body and eyes, size and shape of wings.



After the idea of coupling was first proposed by Bateson and Punnett, Thomas Hunt Morgan found a similar deviation from Mendel's second law while studying two autosomal genes in *Drosophila.*

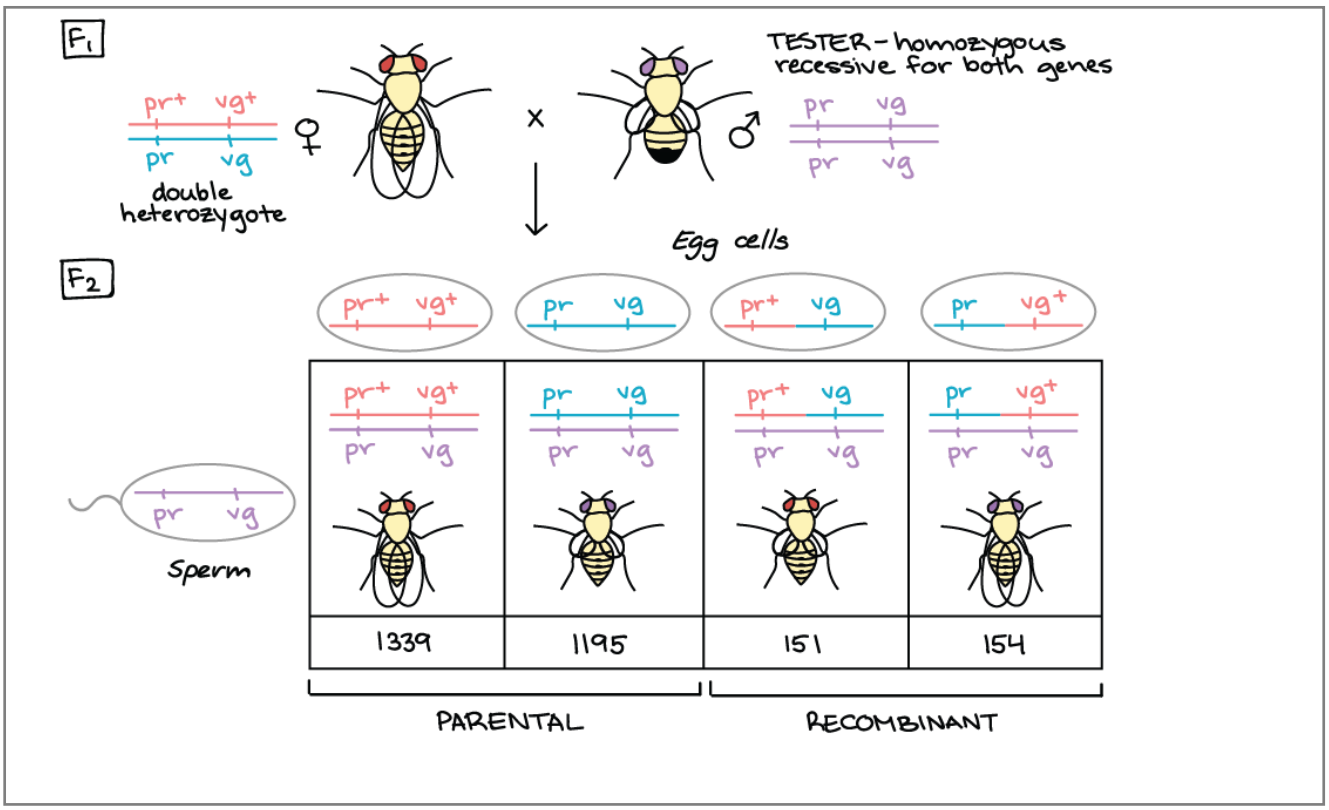
One of these genes affects eye color (*pr*, purple, and pr^+, red), and the other affects wing length (*vg*, vestigial, and vg^+, normal). The wild-type alleles of both genes are dominant. Morgan crossed *pr*/*pr* · *vg*/*vg* flies with $pr^+/pr^+ \cdot vg^+/vg^+$.



Then he **testcrossed** the doubly heterozygous F_1 females: $pr^+/pr \cdot vg^+/vg$ ♀ × $pr/pr \cdot vg/vg$ ♂.

The use of the **testcross** is extremely important. Because one parent (the tester) contributes gametes carrying only recessive alleles, the phenotypes of the offspring reveal the gametic contribution of the other, doubly heterozygous parent. Hence, the analyst can concentrate on meiosis in one parent and forget about the other. This contrasts with the analysis of progeny from an F_1 self, where there are two sets of meioses to consider: one in the male parent and one in the female. Morgan's results follow; the alleles contributed by the F_1 female specify the F_2 classes:

$pr^+ \cdot vg^+$	1339
$pr \cdot vg$	1195
$pr^+ \cdot vg$	151
$pr \cdot vg^+$	154
	2839



Obviously, these numbers deviate drastically from the Mendelian prediction of a 1:1:1:1 ratio, and they indicate a **coupling** of genes. The two largest classes are the combinations $pr^+ \cdot vg^+$ and $pr \cdot vg$, originally introduced by the homozygous parental flies. You can see that the testcross clarifies the situation. It directly reveals the allelic combinations in the gametes from one sex in the F_1, thus clearly showing the coupling that could only be inferred from Bateson and Punnett's F_1 self. The testcross also reveals something new: there is approximately a 1:1 ratio not only between the two parental types, but also between the two nonparental types.

Now let us consider what may be learned by repeating the crossing experiments but changing the combinations of alleles contributed as gametes by the homozygous parents in the first cross. In this cross, each parent was homozygous for one dominant allele and for one recessive allele. Again F_1 females were testcrossed:

P $pr^+/pr^+ \cdot vg/vg \times pr/pr \cdot vg^+/vg^+$

↓

F_1 $pr^+/pr \cdot vg^+/vg$

$pr^+/pr \cdot vg^+/vg$ ♀ × $pr/pr \cdot vg/vg$ ♂

The following progeny were obtained from the testcross:

$pr^+ \cdot vg^+$	157
$pr \cdot vg$	146
$pr^+ \cdot vg$	965
$pr \cdot vg^+$	1067
	2335

Again, these results are not even close to a 1:1:1:1 Mendelian ratio. Now, however, the largest classes are those that have one dominant allele or the other rather than, as before, two dominant alleles or two recessives. But notice that once again the allelic combinations that were originally contributed to the F_1 by the parental flies provide the most frequent classes in the testcross progeny. In the early work on coupling, Bateson and Punnett coined the term **repulsion** to describe this situation, because it seemed to them that, in this case, the nonallelic dominant alleles "repelled" each other — the opposite of the situation in coupling, where the dominant alleles seemed to "stick together." What is the explanation of these two phenomena: **coupling** and **repulsion**? Morgan suggested that the genes governing both phenotypes are located on the same pair of homologous chromosomes. Thus, when *pr* and *vg* are introduced from one parent, they are physically located on the same chromosome, whereas *pr+* and *vg+* are on the homologous chromosome from the other parent (Figure 1).

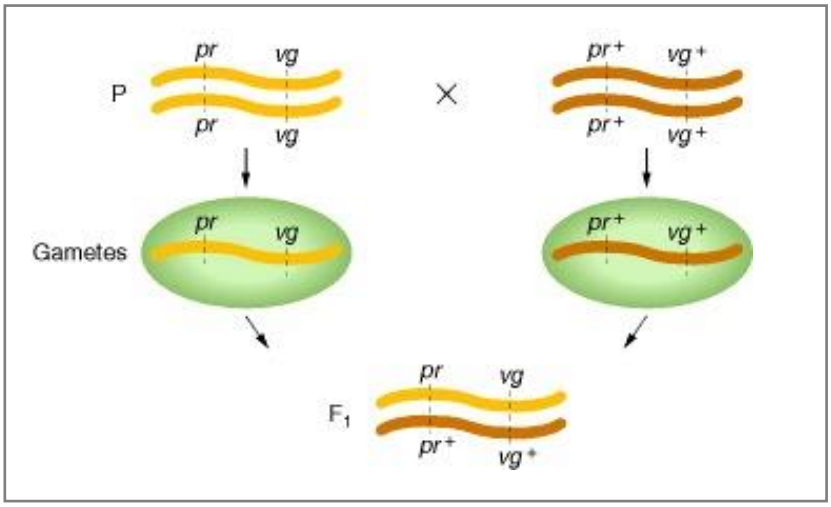


Figure 1. Simple inheritance of two pairs of alleles located on the same chromosome pair.

This hypothesis also explains repulsion. In that case, one parental chromosome carries *pr* and *vg+* and the other carries *pr+* and *vg*. Repulsion, then, is just another case of coupling: in this case, the dominant allele of one gene is coupled with the recessive allele of the other gene. This hypothesis explains why allelic combinations from P remain together, but how do we explain the appearance of **nonparental combinations**?

Morgan suggested that, when homologous chromosomes pair in meiosis, the chromosomes occasionally exchange parts in a process called **crossing-over.** Figure 2 illustrates this physical exchange of chromosome segments. The two new combinations are called **crossover products**.

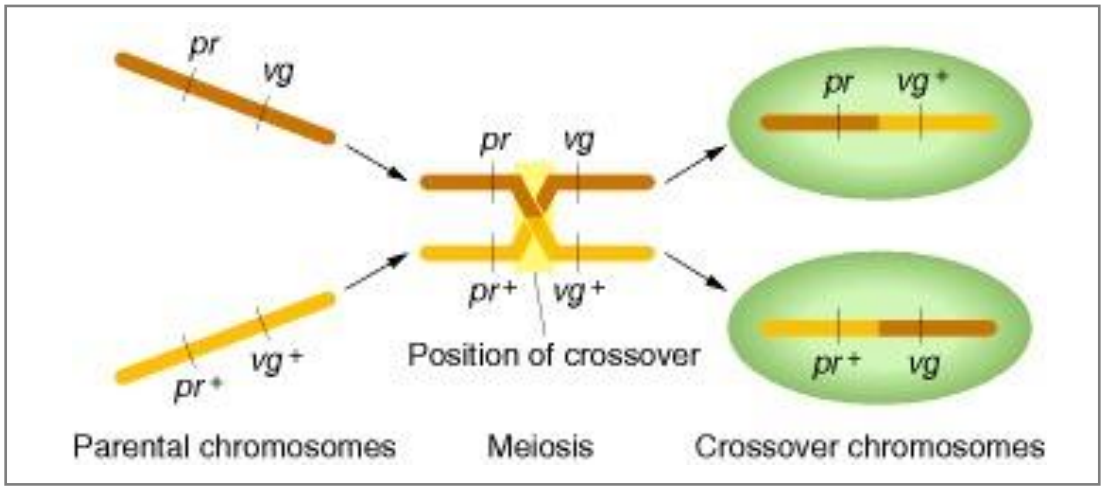


Figure 2. Crossing-over in meiosis.

An individual offspring receives one homolog from each parent. The exchange of parts by crossing-over may produce gametic chromosomes whose allelic combinations differ from the parental combinations.

Morgan's hypothesis that homologs may exchange parts may seem a bit farfetched. Is there any cytologically observable process that could account for crossing-over? In meiosis, when duplicated homologous chromosomes pair with each other, two nonsister chromatids often appear to cross each other, as diagrammed in Figure 3. The resulting cross-shaped structure is called a **CHIASMA.**

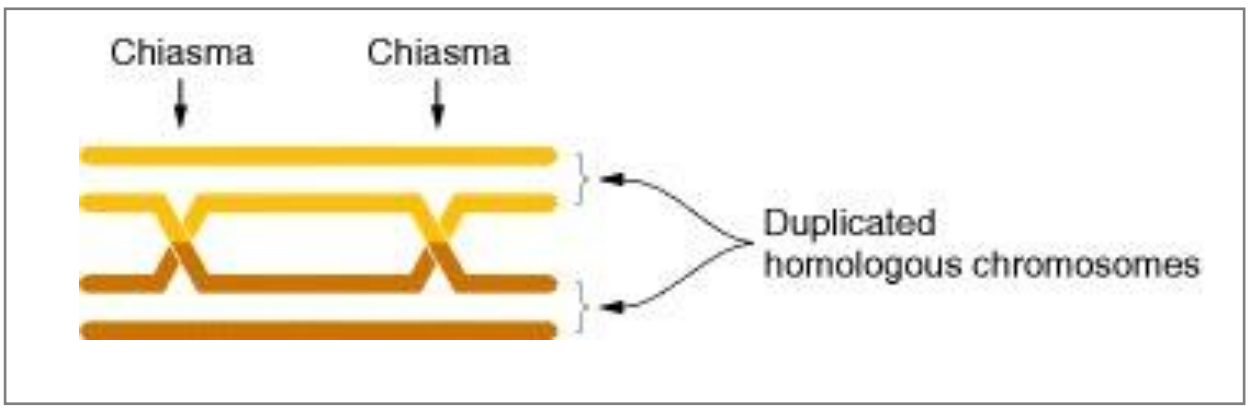


Figure 3. Diagrammatic representation of **chiasmata** at meiosis.
Each line represents a chromatid of a pair of synapsed chromosomes.

Thus, chiasmata are the visible manifestations of crossovers.

To Morgan, the appearance of the chiasmata visually corroborated the concepts of **crossing-over**. Morgan did not arrive at this interpretation out of nowhere; he was looking for a physical explanation for his genetic results.

His achievement in correlating the results of breeding experiments with cytological phenomena thus emphasizes the importance of the chromosome theory as a powerful basis for research.

Data like those just presented, showing coupling and repulsion in testcrosses and in F_1 selfs, are commonly encountered in genetics. Clearly, results of this kind are a departure from independent assortment. Such exceptions, in fact, constitute a major addition to Mendel's view of the genetic world.

To conclude, **when two genes are close together on the same chromosome pair, they do not assort independently.** The residing of genes on the same chromosome pair is termed linkage. Two genes on the same chromosome pair are said to be linked.

It is also proper to refer to the linkage of specific alleles: for example, in one A/a · B/b individual, A might be linked to b; a would then of necessity be linked to B. These terms graphically allude to the existence of a physical entity linking the genes—that is, the chromosome itself. You may wonder why we refer to such genes as "linked" rather than "coupled"; the answer is that the words coupling and repulsion are now used to indicate two different types of linkage conformation in a double heterozygote, as follows:

Coupling conformation $\frac{pr \quad vg}{pr^+ \quad vg^+}$

Repulsion conformation $\frac{pr \quad vg^+}{pr^+ \quad vg}$

In other words, **coupling** refers to the linkage of two dominant or two recessive alleles, whereas **repulsion** indicates that dominant alleles are linked with recessive alleles. To ascertain whether a double heterozygote is in coupling or repulsion conformation, an investigator must testcross the double heterozygote or consider the genotypes of its parents.

Based on the results of his experiments T.H.Morgan in 1915 published "The mechanism of Mendelian Heredity" in which formulated the main principles of chromosome theory of inheritance.

Postulates of the **Chromosome Theory of Heredity** are the following:

- The genes are located on chromosomes in the linear order.
- Each gene occupies a certain place (locus) on chromosome.
- Each homologous chromosome contains only one allelic gene from the allelic pair.
- Genes of one chromosome form a group of linkage and are inherited together.
- The number of linkage groups is equal to the number of the haploid set of chromosomes of the species.
- Linkage of genes can be interrupted during meiosis by crossing over (recombination). It is the exchange of allelic genes between homologous chromosomes.
- The percentage of crossing-over is directly proportional to the distance between genes.
- The distance between genes on a chromosome can be estimated from the proportion of recombinant offsprings.

- Genes of non-homologous chromosomes can independently assort from each other.

In **1933 Thomas H. Morgan** was awarded the **Nobel Prize** in Physiology and Medicine "***for his discoveries concerning the role played by chromosome in heredity***".

Genetic linkage occurs when particular genes are inherited together. Linkage can be **complete** (when **crossing-over does not occur**) and **incomplete** (when **crossing-over** occurs) *(Figure 4).*

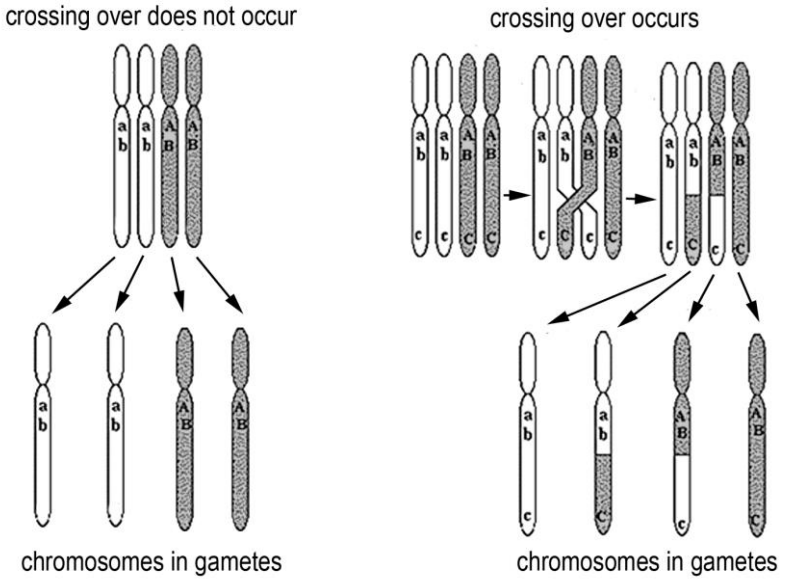


Figure 4. Types of gene linkage.

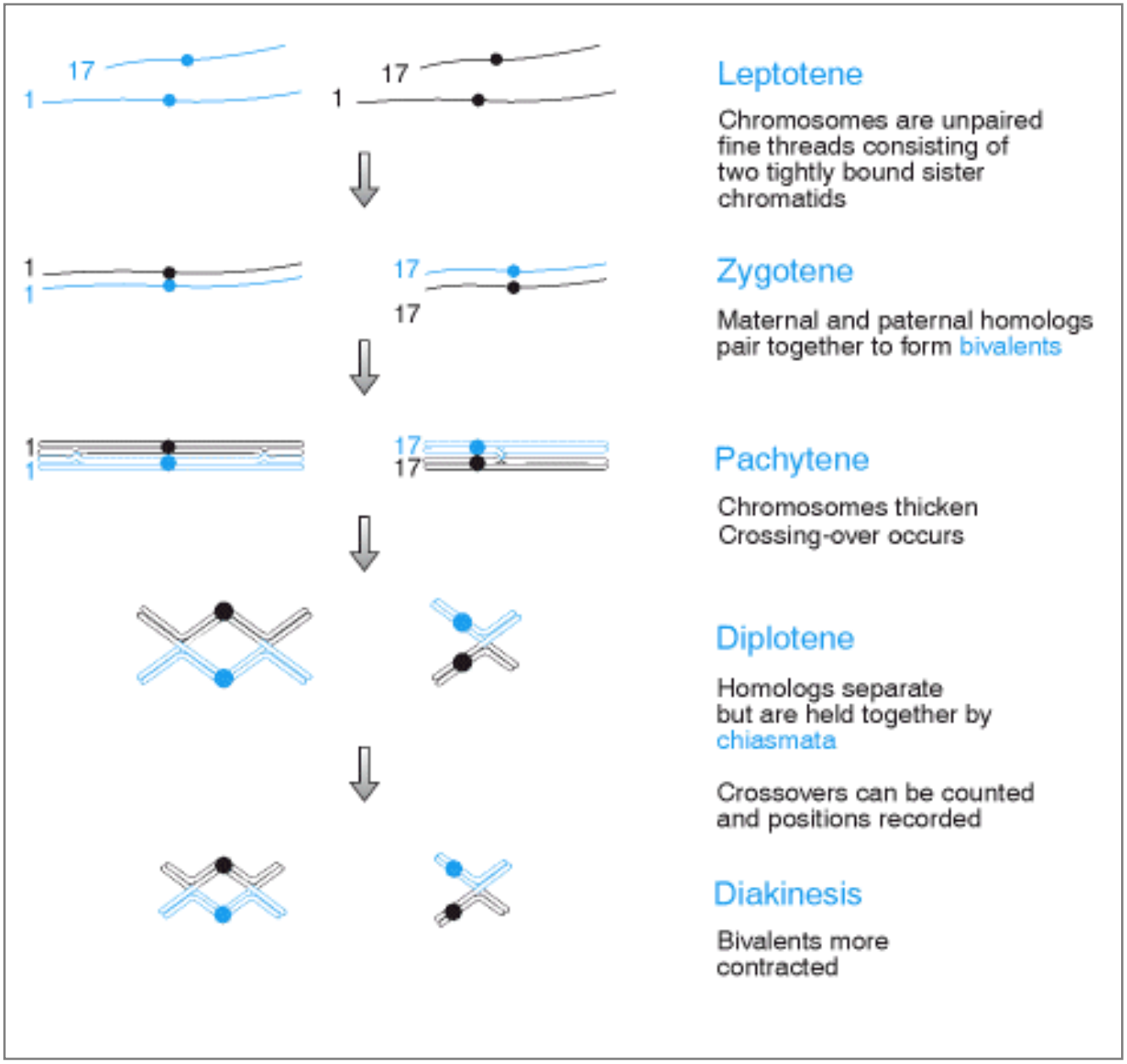
Examples of **complete linkage** in humans are**:**

- Inheritance of RH-factor genes (RHD and RHCE);
- Inheritance of MN and Ss blood groups;
- Inheritance of HLA antigen.

Examples of **incomplete linkage** in humans are**:**

- Inheritance of RH-factor genes and gene of elliptocytosis (oval shape of erythrocytes) that are in the first chromosome at the 3% crossing-over distance;
- Inheritance of red-green color blindness and hemophilia that are in the X chromosome at the 9.8% crossing-over distance.

Crossing over is the exchange of homologous regions between homologous chromosomes. Crossing-over happens in Pachytene phase of the Prophase I (The First Meiotic division). It can be in one or several parts of the chromosome.



Crossing-over is genetically determined process. In most number of species crossing-over may occur in both males and females, but in some species (like drosophila) it occurs only in homogametic sex (females).

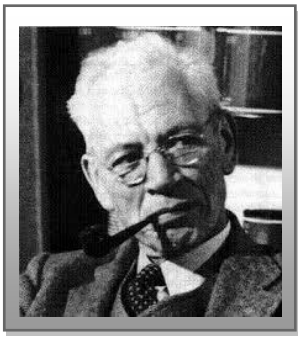
Significance of crossing-over:

- it is molecular basis of genetic variation (gene recombination);
- analysis of gene linkage allows composing genetic maps of chromosomes.

SINCE THE PROBABILITY OF CROSSING-OVER IS LOW, A NUMBER OF NON-CROSSOVER GAMETES FORMED IS ALWAYS MORE THAN CROSSOVER ONES IN INCOMPLETE LINKAGE.

FRACTION OF INDIVIDUALS WITH NEW COMBINATIONS OF TRAITS (CROSSOVERS) IS LESS THAN 50% OF THE TOTAL NUMBER OF OFFSPRING.

A study of the linkages between many genes enables the creation of a **linkage map** or **genetic maps**.



The observation by Tomas Hunt Morgan that the amount of crossing-over between linked genes differs, led to idea that crossover frequency might indicate the distance separating genes on the chromosome. Morgan's student **Alfred Sturtevant** developed the first genetic map, also called a linkage map or genetic map.

Genetic map is the arrangement of genes on chromosome.

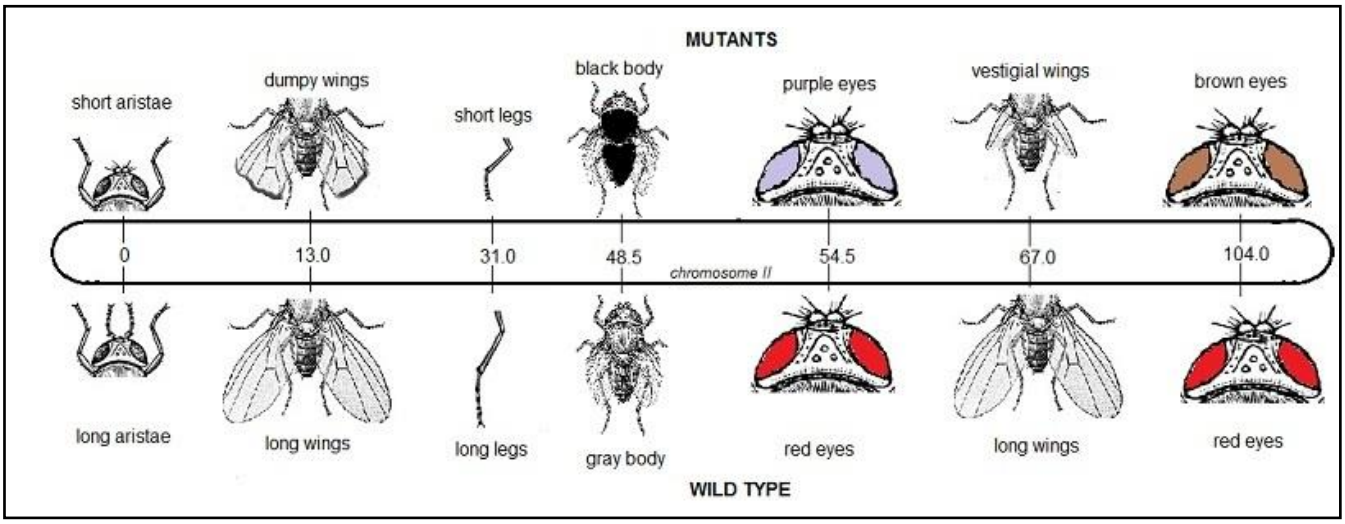


Figure 5. Chromosome 2 of Drosophila Melanogaster (fruit fly)

Sturtevant postulated:

- genes are arranged in a linear series on chromosome;
- genes which are close together will be separated by crossing over less frequently than genes which are father apart;
- it should be possible, by determining the frequencies of crossovers, to plot the sequence of the genes along the chromosome and the relative distance between them.

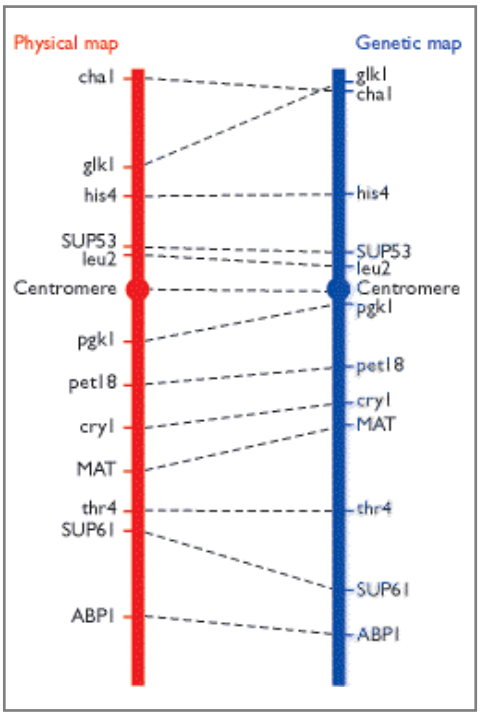
As standard unit of measure, he arbitrarily took the distance that would give (on the average) one crossover per 100 fertilized eggs. Thus, genes with 10 percent crossover would be 10 units apart. Unit of distance was named as **centimorgan (cM)** in honor of his teacher.

Recombination is defined as the occurrence of progeny with combinations of genes other than those that occurred in the parents due to independent assortment or crossing over. The frequency of crossing over (recombination frequency) is calculated from the proportion of recombinants over total offspring:

$$\text{Frequency of crossing over} = \frac{\text{number of recombinants}}{\text{total number of offspring}} \times 100\%$$

If among the offspring 80 per cent have the parental combination of dominant genes A and B, and 20 per cent have a new combination of genes A and B not found in either parent, the genes are said to show 20 per cent recombination, i.e., they are 20 map units apart.

Distances between any two genes are measured in terms of map units (m.u.), one map unit is also known as a **centimorgan (cM)**, being equal to 1 per cent of crossing over. The frequency of recombination gives the frequency of crossing over and thereby the distance, between any two loci on a given chromosome, in map units.



Modern DNA technologies permit direct identification of gene location on a chromosome and determination of distance between the genes in base pairs. Maps composed by direct DNA studying are called **physical maps.**

Genetic and **physical** maps are similar, but non-identical. Number of base pairs corresponding to one centimorgan varies between males and females (crossing-over in females is more frequent) and between different regions of chromosome. One centimorgan matches to about one million base pairs in human on average.

Linkage mapping by recombination in humans

Progress in **mapping** was initially slow for several reasons.

- First, it is not possible to make controlled crosses in humans, and geneticists had to try to calculate recombinant frequencies from the occasional dihybrids that were produced by chance in human matings. Crosses that were the equivalent of testcrosses were extremely rare.
- Second, human progenies are generally small, making it difficult to obtain enough data to calculate reliable map distances.
- Third, the human genome is immense, which means that on average the distances between the known genes are large.

DNA markers have been particularly helpful in mapping human chromosomes.

The human X chromosome has always been more amenable to mapping by recombination analysis than the autosomes, and the first human chromosome map was for the X chromosome. The reason for this success is that males are hemizygous for X-linked genes, and, just as we did for Drosophila, if we look only at male progeny of a dihybrid female, we are effectively sampling her gametic output. In other words, we have a close approximation to a testcross. Consider the following situation concerning the rare X-linked recessive alleles for defective sugar processing (g) and, at another locus, for color blindness (c). A doubly affected male (c

g/Y) marries a normal woman (who is al-most certainly C G/C G). The daughters of this mating are coupling-conformation heterozygotes. The male children of women of this type will provide an opportunity for geneticists to measure the frequency of recombinants issuing from the maternal meioses (Figure 6). However, silent DNA markers also can be used in this type of X-chromosome mapping.

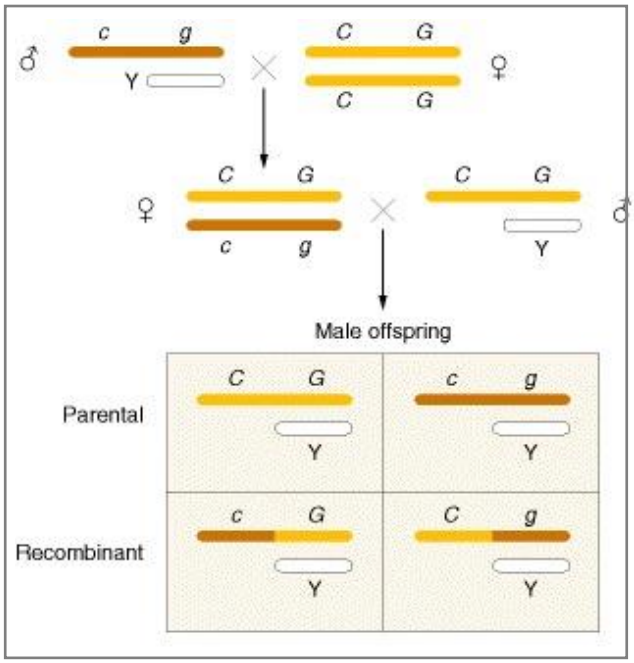


Figure 6. The phenotypic proportions in male children of women heterozygous for two X-linked genes can be used to calculate recombinant frequency.

Thus, the X chromosome can be mapped by combining such pedigrees.

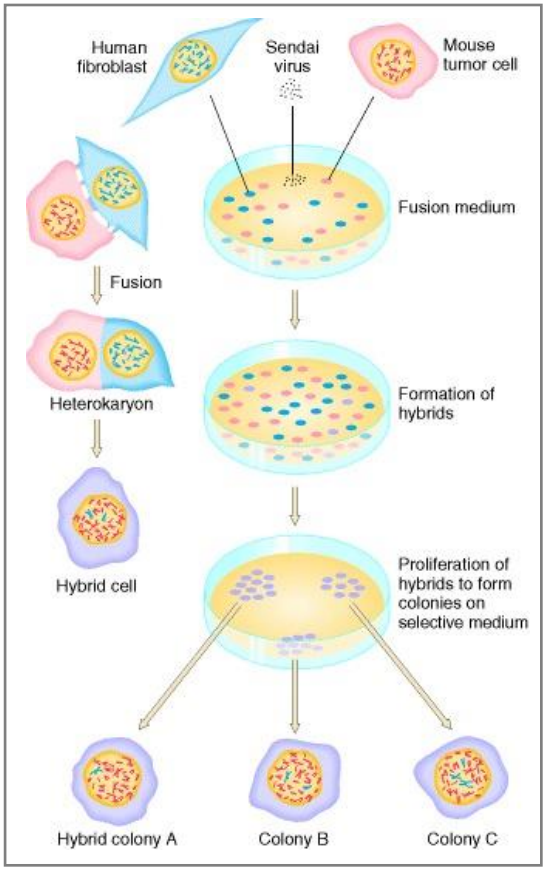
Lod score for linkage testing by pedigrees

The small numbers of progeny in human families mean that it is impossible to determine linkage on the basis of single matings. To obtain reliable RF (recombination frequency) values, large sample sizes are necessary. However, if the results of many identical matings can be combined, then a more reliable estimate can be made. The standard way of doing so is to calculate Lod scores. Lod stands for “log of odds.” The method simply calculates the probability of obtaining a set of results in a family on the basis of independent assortment and a specific degree of linkage. Then the ratio (odds) of the two probabilities is calculated, and the logarithm of this number is calculated, which is the Lod. Because logarithms are exponents, the Lod score has the useful feature that scores from different matings for which the same markers are used can be added, hence providing a cumulative set of data either supporting or not supporting some particular linkage value.

Mapping human genes by using human–rodent somatic cell hybrids

The technique of somatic cell hybridization is extensively used in human genome mapping. The procedure uses cells growing in culture. A virus called the ***Sendai virus*** has a useful property that makes the mapping technique possible. Each Sendai virus has several points of attachment, so it can simultaneously attach to two different cells if they happen to be close together. However, a virus is very small in comparison with a cell, so the two cells to which the virus is attached are held very close together indeed. In fact, the membranes of the two cells may fuse together and the two cells become one — a **binucleate heterokaryon**. If suspensions of human and

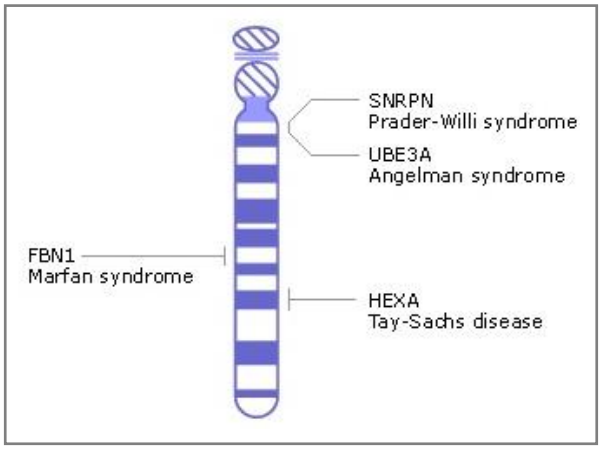
mouse cells are mixed together in the presence of Sendai virus that has been inactivated by ultraviolet light, the virus can mediate fusion of the cells from the different species. When the cells have fused, the nuclei subsequently fuse to form a uni-nucleate cell line composed of both human and mouse chromosome sets. Because the mouse and human chromosomes are recognizably different in number and shape, the two sets in the hybrid cells can be readily distinguished. However, in the course of subsequent cell divisions, for unknown reasons the human chromosomes are gradually eliminated from the hybrid at random. The loss of human chromosomes can be arrested in the following way to encourage the formation of a stable partial hybrid **(Figure 7)**.



Chromosome stains such as quinacrine and Giemsa reveal a pattern of banding within the chromosomes. The size and the position of these bands vary from chromosome to chromosome, but the banding patterns are highly specific and invariant for each chromosome. Thus, it is easy to identify the human chromosomes that are present in any hybrid cell. Different hybrid cells are grown separately into lines; eventually a bank of lines is produced that contains, in total, all the human chromosomes. With a complete bank of chromosomes, we can begin to assign genes or markers to chromosomes.

Figure 7.Cell-fusion techniques applied to human and mouse cells produce colonies, each of which contains a full mouse genome plus a few human chromosomes (blue).

If the human **chromosome** set is homozygous for a human molecular marker—such as an allele that controls a cell-surface antigen, drug resistance, a nutritional requirement, a specific protein, or a DNA marker — then the presence or absence of this genetic marker in each line of hybrid cells can be correlated with the presence or absence of certain human chromosomes in each line.



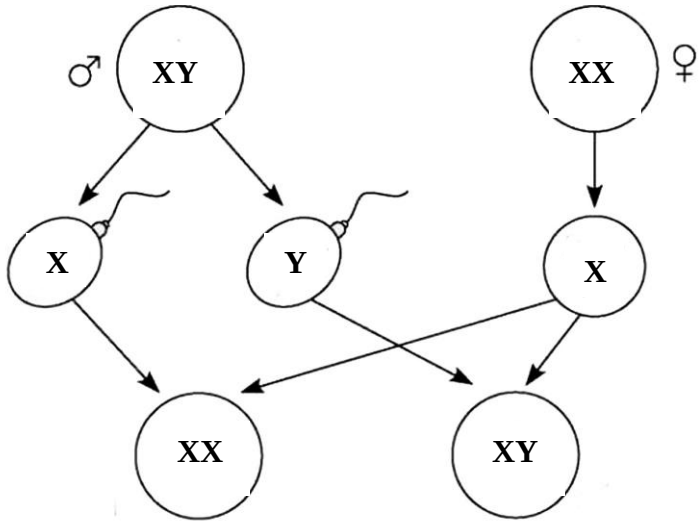
For example, chromosome 15 - contains approximately 1200 genes, approximately 100 million base pairs, of which over 80% have been determined.

SEX DETERMINATION AND THE INHERITANCE OF SEX-LINKED TRAITS.

Sex is set of features, which provide recombination of genetic material during reproduction. Sex is hereditary determined trait.

Human cells have 23 pairs of chromosomes – 22 pairs of **autosomes (A -** the same for males and females) and 1 pair of **sex chromosomes (**marked **XX** and **XY)**.

The female produce one kind of gametes with X chromosome and are termed as **homogametic**. Males produce two kinds of gametes (50% sperms contain X chromosome and 50% - Y chromosome) and are termed as **heterogametic**.

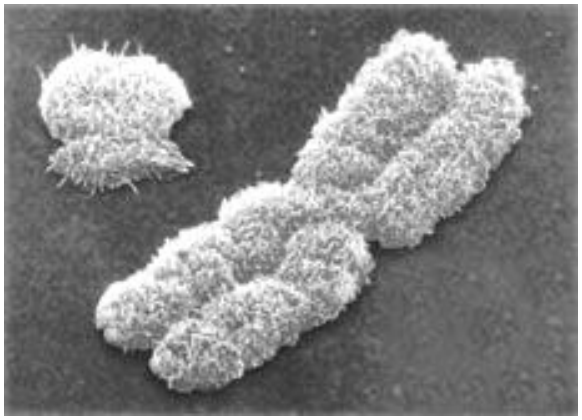


The sex is determined at the moment of fertilization by the kind of sperm that fuses with an ovum!!!

Gender ratio at birth corresponds about 1:1.

In fact, sex ratio of males to females born is 106:100. Possible explanation of this fact is based on different size, so sperm carrying it moves faster and quite often reaches egg first.

There are other variants of chromosomal determination of sex. In birds and some reptiles females are heterogametic (referred as ZW) and males are homogametic (referred as ZZ). In some insects males have only one X chromosome (XO), and males have two X chromosomes (XX). In honey bee females develop from fertilized diploid egg and males develop by parthenogenesis from non-fertilized haploid eggs.



The **X chromosome** is a **submetacentric** chromosome belonged to group C. There are about 2000 human X-linked genes. It is about 6% of the total DNA. The **Y chromosome**, a member of group G, is a small **acrocentric** chromosome and contains just 78 genes. Traits coded for by genes on the Y chromosome are said to be *holandric*.

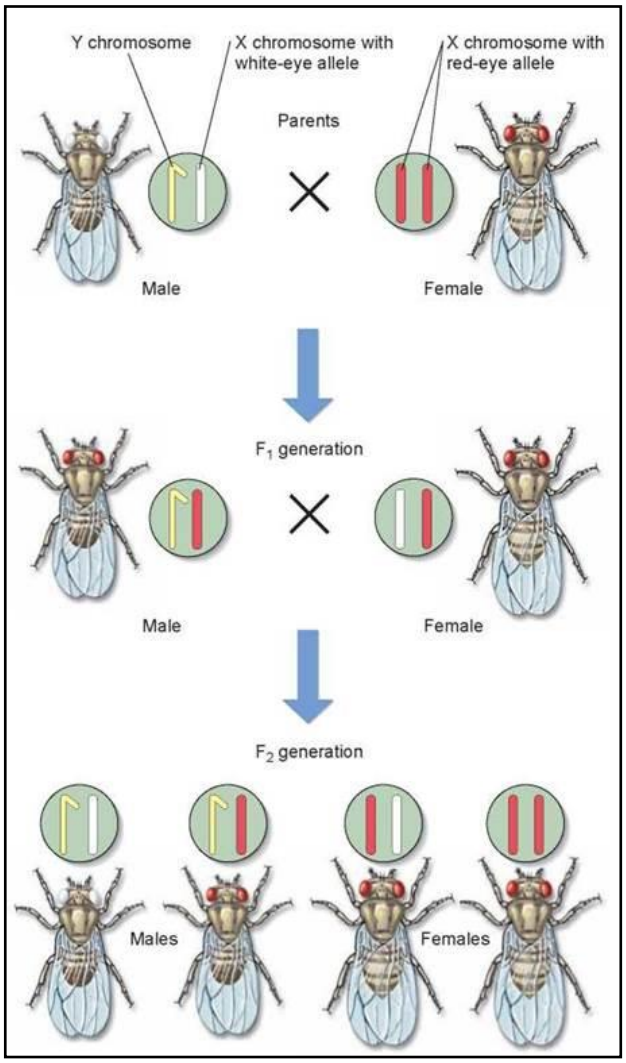
The sexual identity of an individual is determined at several levels:

Level	*Events*	*Timing*
Chromosomal / genetic	XY = male XX = female	Fertilization
Gonadal sex	Undifferentiated structure becomes testis or ovary	9-16 weeks after fertilization
Phenotypic sex	Development of external and internal reproductive structures continues as male or female in response to hormones	8 weeks after fertilization
Gender identity	Strong feeling of being male or female develop	From childhood, possibly earlier

Discovery of the sex-linked traits.

In 1910, Morgan published details of his research in an article titled **"Sex Limited Inheritance in Drosophila".**

Just before Morgan's discovery of the white-eyed, male fly, some careful work had been done on the cells of Drosophila. They have three pair of **autosomes** (three pairs of chromosomes which are the same for male and female) and a pair of **sex chromosomes**. In the female, the fourth pair is made up of identical, rod-shaped chromosomes called X chromosome. In the male there is only one X chromosome. The other member of the pair is a hook-shaped chromosome called Y chromosome.



First**, Morgan** took the white mutant and bred it with pure red-eyed female flies. All of the females that resulted from that breeding had red eyes. Morgan then took those red-eyed females and mated them with the original white-eyed mutant male to determine whether or not the inheritance of eye color followed Mendel's inheritance patterns. If Mendel's patterns applied to Morgan's flies, there would be one white-eyed fly to every three red-eyed flies in the resulting generation of flies, regardless of sex. Although Morgan did observe one white-eyed fly to every three red flies, that inheritance pattern was not shared equally across males and females. Most of the white-eyed flies were male. That result indicated that the flies did not follow Mendel's ratio in a traditional sense.

After observing the white-eye inheritance pattern, Morgan hypothesized that a factor, or gene, controlling eye color was located on the X chromosome. Female flies have two X chromosomes, and males have one X chromosome and one Y chromosome. If a trait, like eye color, correlated with a specific factor on the X chromosome, then the trait was called

X-linked. Because males only have one X chromosome, they display all X-linked traits. Females, on the other hand, often need an X-linked trait to exist on both X chromosomes to display that trait. Morgan hypothesized that, in his breeding experiment, the first generation of flies contained males only with white eyes because the gene controlling eye color was on the X chromosome. Males displayed the white eye trait because the trait was present on their only X chromosome. Females did not display the white eye trait because the trait was only present on one of their X chromosomes.

Sex traits in human can be categorized into three types of inheritance:

1) sex-linked,
2) sex-limited,
3) sex-influenced.

Sex-linked traits are controlled by genes present on X and Y chromosomes.

Sex of human beings influences on some other characters, the development of which is determined by the genes located in autosomes of both sexes.

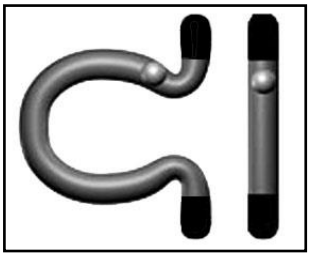
Difference	***Kind of character***	
	Sex limited traits	*Sex influenced traits*
Expression (Manifestation)	Traits expressed in only one sex. (It may be controlled by sex linked or autosomal loci).	They are expressed in both men and women, but variously (different degree of expressivity).
Examples	All secondary sexual characters. Genes determining beard growth or mammary glands (breast size).	Pattern baldness is a condition which is dominant in men but recessive in women; kind of human singing voice (bass, baritone, tenor, soprano, mezzo-soprano, contralto)

All genes of **sex chromosomes** could be divided into **three groups**:

1) genes of X chromosome present on the regions which do not have homologous regions on Y chromosome (such genes do not have allelic pair in Y chromosome, they exist only in one copy in heterogametic gender (males) and called **hemizygous**);

2) genes of non-homologous region of Y chromosome (traits encoded by these genes are said to be **holandric –** they are present only in males and passed from father to son**);**

3) genes of homologous regions of X and Y chromosomes - (**pseudoautosomal regions**) – at the ends of chromosomes.



The **pseudoautosomal region** is homologous section of X and Y chromosomes, i.e., a region of similarity between sex chromosomes. The region is responsible for pairing the X and Y chromosomes during meiotic prophase I. In this region genes are present in two copies in males and females and thus are inherited

like autosomal genes, whereas other Y-linked genes are passed on only from father to son.

These genes are also known as incompletely sex-linked because crossing over may occur in the homologous sections of X and Y chromosomes. Certain examples of such "XY-linked genes" in humans are *achromatopsia (total colour blindness), nephritis, xeroderma pigmentosum*, etc.

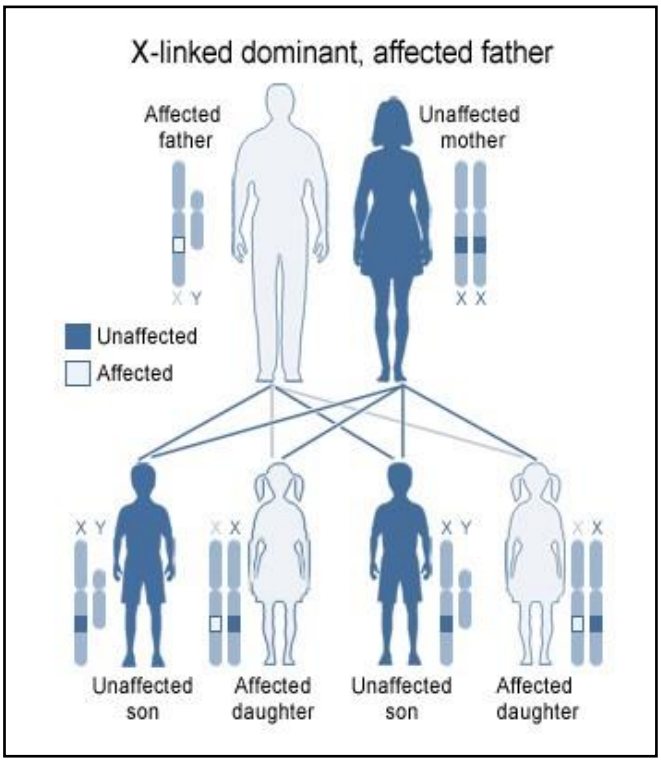
There are **X-linked** (dominant or recessive) and **Y-linked** patterns of inheritance.

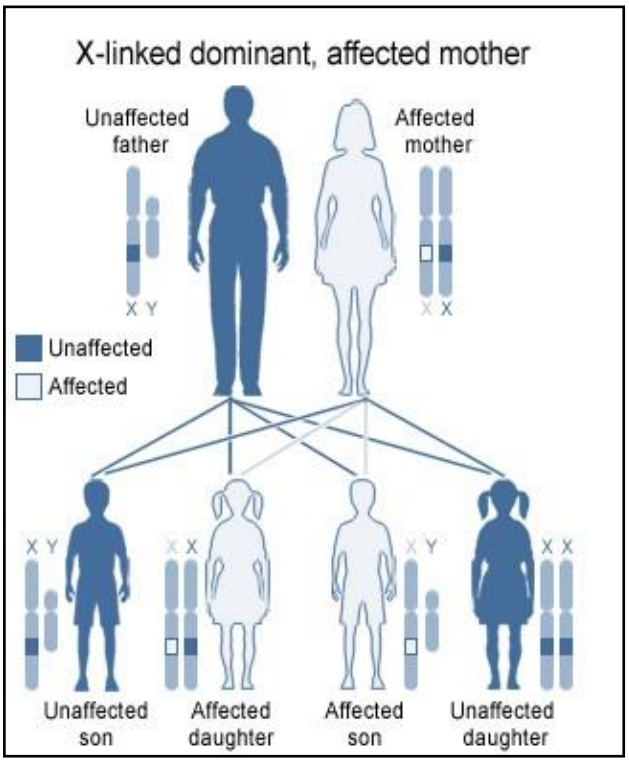
<u>X-linked dominant mode of inheritance</u>:

- females are affected more often;
- a dominant gene on the X chromosome causes a characteristic to be manifested in the offspring;
- When the **father alone** is the carrier of a defective gene associated with a disease or disorder, he too will have the disorder. His children will inherit the disorder as follows:

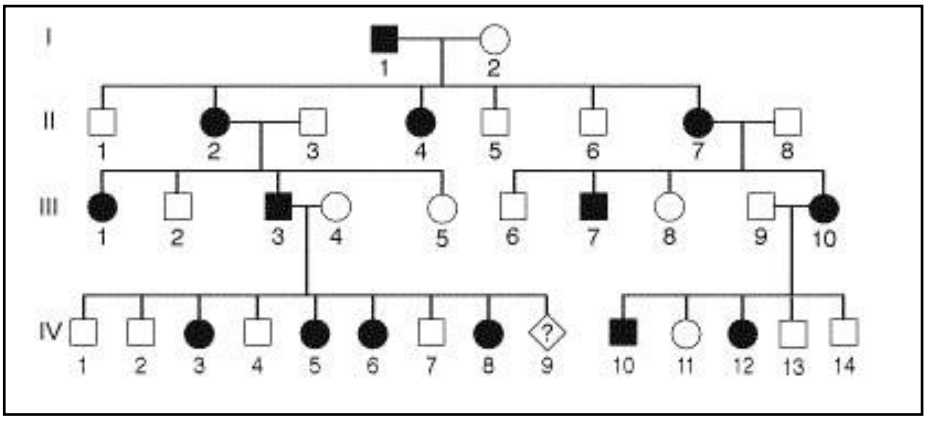
- His **<u>daughters: 100%</u>** will have the disorder, since all of his daughters will receive one copy of his single X chromosome.
- His **<u>sons: none</u>** will have the disorder; sons do not receive an X chromosome from their father.

- when the mother alone is the carrier of a mutated gene, her daughters and sons: 50% will have the disorder, 50% will be completely unaffected.





X-linked dominant mode of inheritance

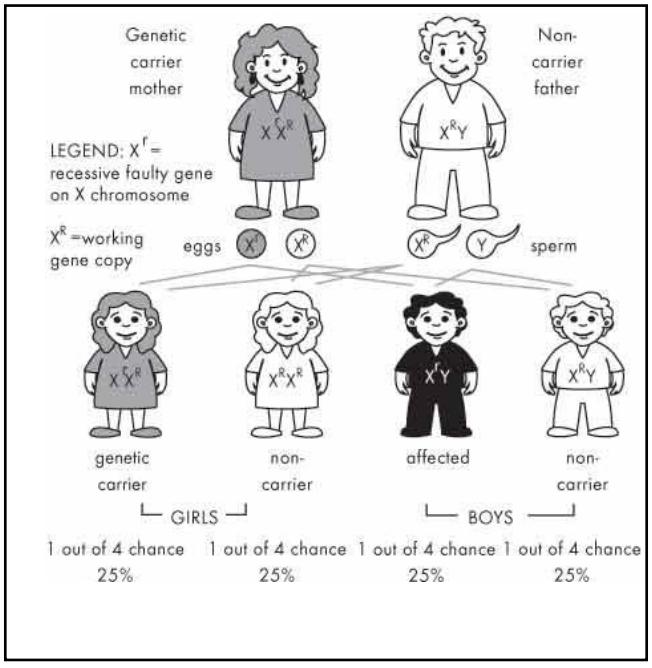


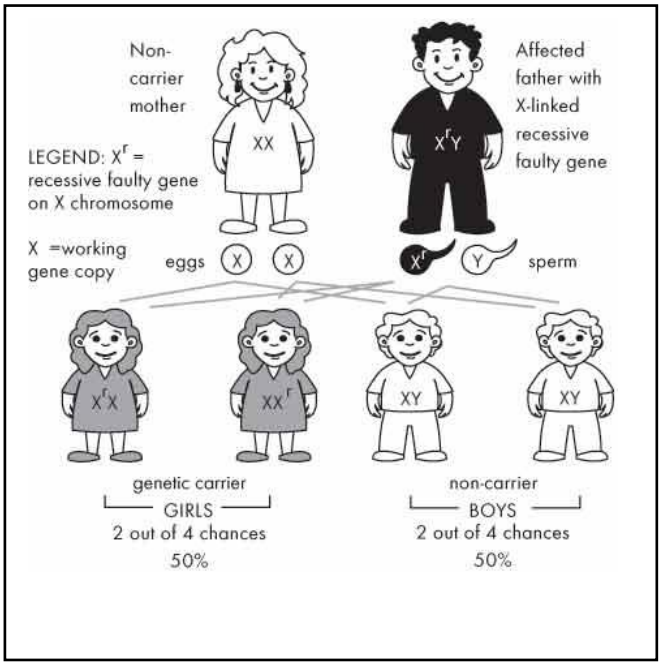
X-linked recessive mode of inheritance

X-linked recessive disease **usually occurs in males** who have inherited a recessive X-linked mutation **from their mother**. Rarely, the disease may be seen in females who have inherited mutations in the same gene X-linked from both parents. More typically, the mother is a carrier and is unaffected, although it is not uncommon for female carriers of X-linked disorders to have mild clinical manifestations related to the disorder.

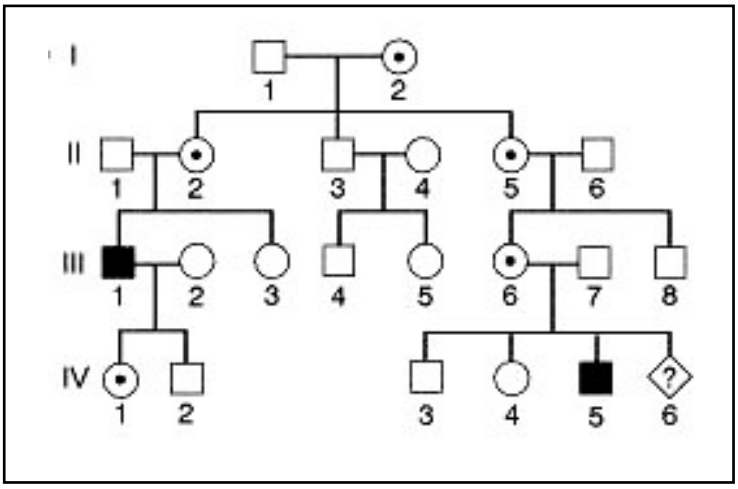
- A male child of a woman who is a carrier has a 50% risk of inheriting the disorder.
- A female child of a woman who is a carrier has a 50% risk of inheriting the gene mutation and thus being a carrier herself.
- An affected male - if able to reproduce - will pass on the gene mutation to all daughters, who are therefore **obligate** carriers. The affected male never passes the disease on to a son.

The typical family history for an X-linked recessive condition is of disease in maternal uncles. A woman who has both a brother and a son affected with an X-linked disease is also an obligate carrier.

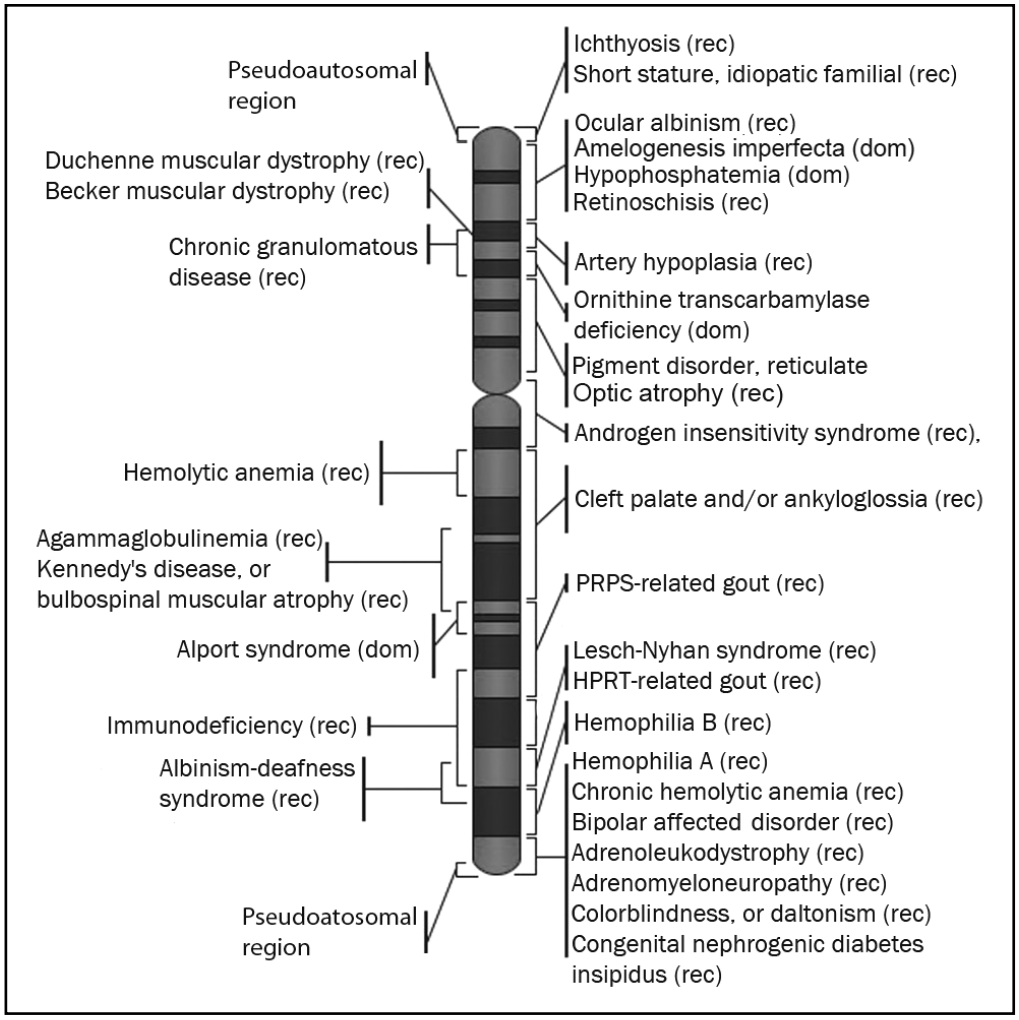




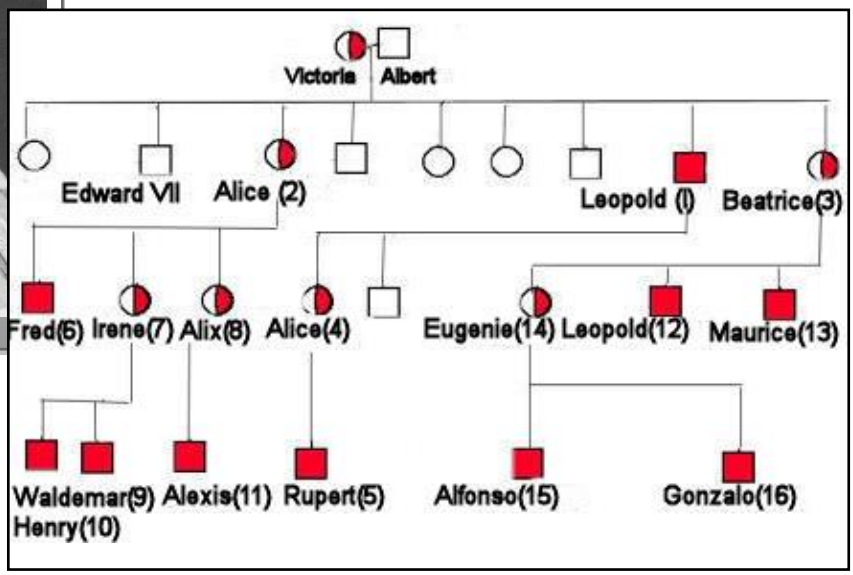
X-linked recessive mode of inheritance



More than **250 X-linked disorders** have now been identified compared to just **20 Y-linked** ones.

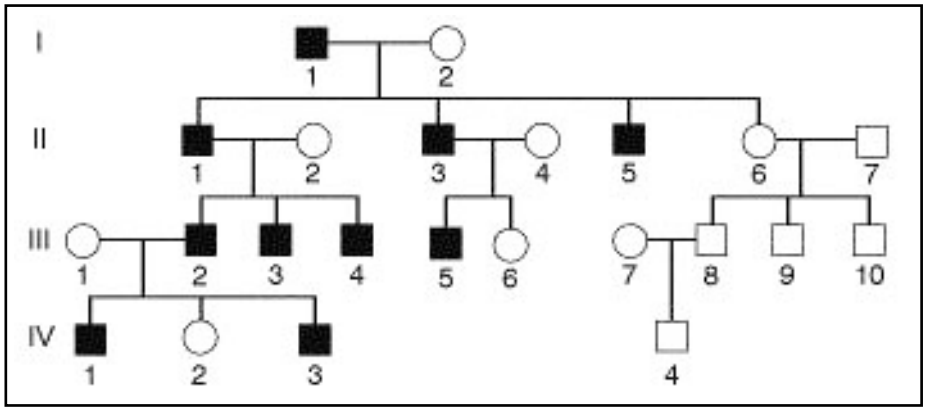


Inheritance of hemophilia in theRoyal family of **Queen Victoria**



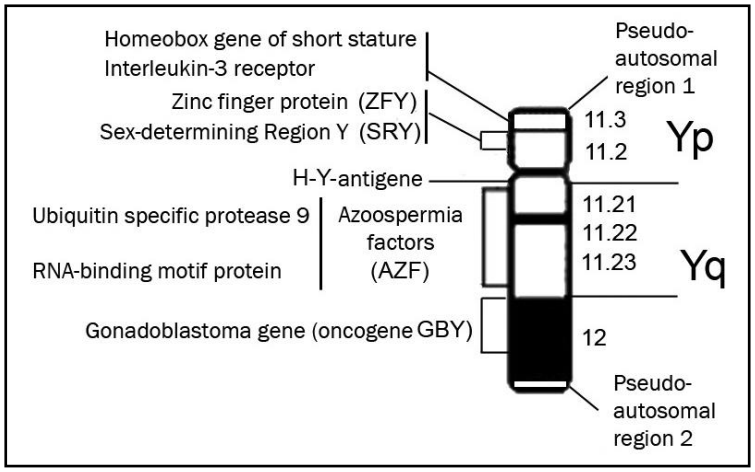
Y -linked mode of inheritance:

- only men are affected;
- genes are simply passed from father to all son;
- each affected son has affected father.



Examples: syndactily, haired pinna

Human males differ from human females in the fact that they have an Y chromosome and females do not. In 1990, the **SRY gene (which stands for Sex-Determining region Y gene)** was found. In humans, a single functional copy of the SRY gene, normally located on the Y chromosome, determines phenotypic maleness by causing gonads to differentiate into testes. This gene codes for TDF protein (Testis Determining Factor). In the absence of a functional SRY gene, gonads differentiate into ovaries and the individual is phenotypically female



An Introduction to Genetic Analysis. 7th edition. Griffiths AJF, Miller JH, Suzuki DT, et al. New York: W. H. Freeman; 2000.