

## Lecture 4: Introduction to Genetics. Human Genetics

1. Heredity and Genetics: Definitions
2. The origin of genetics. Gregor Mendel's experiments
3. Monohybrid Crosses
4. Dihybrid Crosses
5. Mendel's Laws of Inheritance
6. Rediscovery of Mendel's Laws
7. Genetics of Human Diseases
8. Modes of Inheritance

For much of human history people were unaware of the scientific details of how babies were conceived and how **heredity** worked. Clearly they were conceived, and clearly there was some hereditary connection between parents and children, but the mechanisms were not readily apparent.

**Heredity** is the genetic transmission of traits from one generation to the next, from parents to offspring

**Genetics** is a branch of Biology devoted to understanding *how* characteristics are transmitted from generation to generation; it is scientific study of heredity and hereditary variations.

### The origin of genetics:

The study of genetics begins when **Gregor Mendel**, in 1865, addressed the question "How are characters passed on from one generation to the next?" Mendel was the first to make a serious attempt of experimentally answering the question of heredity and not only his answers were correct, they were a complete and compelling proof.

#### G. Mendel's Biography

G. Mendel (1822-1884) grew up on his parents' small farm in a region of Austria that is now part of Czech Republic.

In 1843, Mendel entered an Augustinian monastery.

He studied Science and Mathematics (including Statistics) at the University of Vienna (1851-1853). Mendel's knowledge of Statistics later proved valuable in his research on Heredity.

Mendel was interested in understanding variances in plants and between 1856 and 1863 he cultivated and tested some 28,000 pea plants.

He was the first to identify discrete units of heredity - hereditary factors. He brought an experimental and quantitative approach to genetics.

His experiments brought forth two generalizations which later became known as *Mendel's Laws of Heredity* or *Mendelian inheritance*. These are described in his paper "*Experiments on Plant hybridization*" that was published in 1866.

His work was unrecognized until 1900 when rediscovered independently by three different researchers.

Mendel grew and tended the pea plants he used for his experiments. He observed as many offspring as possible. For a cross that required him to count the number of round seeds to wrinkled seeds, he observed and counted a total of 7,324 peas!

Mendel reasoned an organism for genetic experiments **should have**:

1. a number of different traits that can be studied;
2. plant should be self-fertilizing and have a flower structure that limits accidental contact;
3. offspring of self-fertilized plants should be fully fertile.

Mendel chose the **garden pea**, *Pisum sativum*, because peas were

- (i) easy to cultivate,
- (ii) had a short generation time, and
- (iii) could be cross-pollinated.

The male parts of the pea flower are termed the **anthers**. They produce **pollen**, which contains the male gametes (sperm). The female parts of the flower are the **stigma**, **style**, and **ovary**. The egg (female gamete) is produced in the ovary. The process of **pollination** (the transfer of pollen from anther to stigma) occurs prior to the opening of the pea flower. The pollen grain grows a **pollen tube** which allows the sperm to travel through the stigma and style, eventually reaching the ovary. The ripened ovary wall becomes the fruit (in this case the pea pod). Most flowers allow cross-pollination, which can be difficult to deal with in genetic studies if the male parent plant is not known. Since pea plants are self-pollinators, the genetics of the parent can be more easily understood. Peas are also self-compatible, allowing self-fertilized embryos to develop as readily as out-fertilized embryos. Mendel tested all 34 varieties of peas available to him through seed dealers.

When Mendel performed crosses, he brushed pollen from one plant onto the stigma of another plant. After sperm fertilized eggs, the ovules developed into seeds (peas).

Mendel studied **seven traits**, or characters. Each trait studied had two distinct contrasting forms

1. flower color . purple or white
2. flower position along stem . axial or terminal
3. seed or pea color - yellow or green
4. seed texture or shape . round (smooth) or wrinkled
5. pod color . green or yellow
6. pod appearance or shape . inflated or constricted
7. plant height - long or short stems

## Monohybrid Crosses

Mendel studied the inheritance of seed shape first.

A cross involving only one trait is referred to as a monohybrid cross.

Mendel crossed pure-breeding (= true-breeding) **smooth-seeded** plants **with** a variety that had always produced **wrinkled seeds**.

He found that, all of the F<sub>1</sub> (the first generation) were identical to one of the parents: all resulting seeds were smooth!

The following year, Mendel planted these seeds and allowed them to self-fertilize. He recovered 7324 seeds: 5474 smooth and 1850 wrinkled. To help with record keeping, generations were labeled and numbered. The parental generation is denoted as the P<sub>1</sub> generation. The offspring of the P<sub>1</sub> generation are the F<sub>1</sub> generation (first filial). The self-fertilizing F<sub>1</sub> generation produced the F<sub>2</sub> generation (second filial).

P<sub>1</sub>: smooth × wrinkled

F<sub>1</sub>: all smooth (100%)

F<sub>2</sub>: 5474 smooth and 1850 wrinkled

Mendel coined **two terms** to describe the relationship of the two phenotypes (the observable characteristics of an individual organism) based on the results of F<sub>1</sub> and F<sub>2</sub>: **dominant** and **recessive**.

**Dominant** traits were defined by Mendel as those which appeared in the F<sub>1</sub> generation in crosses between true-breeding strains (*smooth* - **S**).

**Recessive** were those which "skipped" a generation, being expressed only when the dominant trait is absent (wrinkled - **s**).

Upon statistically analyzing the F<sub>2</sub> generation, Mendel determined the **ratio** of smooth and wrinkled seeds **was** approximately **3:1** (3 dominant : 1 recessive). Mendel's plants exhibited **complete dominance**, in which the phenotypic expression of alleles was either dominant or recessive, not "in between".

Wrinkle-seeded plants have skipped the F<sub>1</sub> generation, and show up in the F<sub>2</sub> and succeeding generations. Mendel concluded that the traits under study were governed by discrete (separable) factors. The factors were inherited in pairs, with each generation having a pair of trait factors. We now refer to these trait factors as alleles. Having traits inherited in pairs allows for the observed phenomena of traits "skipping" generations.

### Summary of Mendel's Results:

1. The F<sub>1</sub> offspring showed only one of the two parental traits, and always the same trait.
2. Results were always the same regardless of which parent donated the pollen (was male).
3. The trait not shown in the F<sub>1</sub> reappeared in the F<sub>2</sub> in about 25% of the offspring.
4. Traits remained unchanged when passed to offspring: they did not blend in any offspring but behaved as separate units.
5. Reciprocal crosses showed each parent made an equal contribution to the offspring.

### Mendel's Conclusions:

1. Evidence indicated factors could be hidden or unexpressed, these are the recessive traits.
2. The term **phenotype** refers to the outward appearance of a trait, while the term **genotype** is used for the genetic makeup of an organism.
3. Male and female contributed equally to the offsprings' genetic makeup: therefore the number of traits was probably two (the simplest solution).
4. Upper case letters are traditionally used to denote dominant traits, lower case letters for recessives.

G.Mendel reasoned that factors must segregate from each other during gamete formation (remember, meiosis was not yet known!) to retain the number of traits at 2. The **Principle of Segregation** (now known as **The First Mendelian Law**) *proposes the separation of paired factors during gamete formation, with each gamete receiving one or the other factor, usually not both. Organisms carry two alleles for every trait. These traits separate during the formation of gametes.*

## Dihybrid Crosses

When Mendel considered two traits per cross (**dihybrid**, as opposed to single-trait-crosses, monohybrid), the resulting (F<sub>2</sub>) generation did not have 3:1 dominant:recessive phenotype ratios. The two traits, if considered to inherit independently, fit into the principle of segregation. Instead of 4 possible genotypes from a monohybrid cross, dihybrid crosses have as many as 16 possible genotypes (4×4=16).

Mendel realized the need to conduct his experiments on more complex situations. He performed experiments tracking two seed traits: shape and color. A cross concerning two traits is known as a dihybrid cross.

Smooth seeds (**S**) are dominant over wrinkled (**s**) seeds.

Yellow seed color (**Y**) is dominant over green (**y**).

Mendel started with true-breeding plants that had smooth, yellow seeds and crossed them with true-breeding plants having green, wrinkled seeds. All seeds in the F<sub>1</sub> had smooth yellow seeds. The F<sub>2</sub> plants self-fertilized, and produced 4 phenotypes:

315 smooth yellow (**SSYY**, **SsYy**, **SsYY**, and **SSYy**)

108 smooth green

101 wrinkled yellow

32 wrinkled green (**ssyy**)

Result was: ratio 9:3:3:1

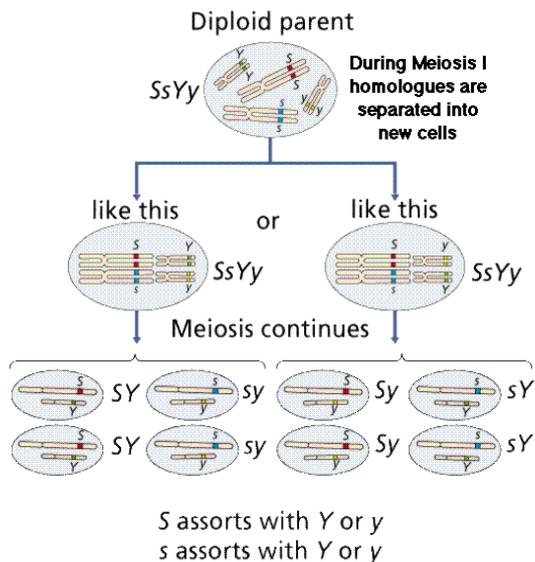
The data from these more complex crosses showed that traits produced by dominant factors do NOT necessarily appear together.

Mendel concluded that the factors for different characteristics are NOT connected.

Mendel analyzed each trait for separate inheritance as if the other trait were not present. The 3:1 ratio was seen separately and was in accordance with the **Principle of Segregation**. The segregation of **S** and **s** alleles must have happened independently of the segregation of **Y** and **y** alleles. The chance of any gamete having a **Y** is  $\frac{1}{2}$ ; the chance of any one gamete having **S** is  $\frac{1}{2}$ . The chance of a gamete having both **Y** and **S** is the product of their individual chances (or  $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$ ). The chance of two gametes forming any given genotype is  $\frac{1}{4} \times \frac{1}{4} = \frac{1}{16}$  (remember, the product of their individual chances). Since there are more possible combinations to produce a smooth yellow phenotype (**SSYY**, **SsYy**, **SsYY**, and **SSYy**), that phenotype is more common in the F<sub>2</sub>.

From the results of the 2<sup>nd</sup> experiment, Mendel formulated the **Principle of Independent Assortment** (now known as **The Second Mendelian Law**). *that when gametes are formed, alleles assort independently.* If traits assort independent of each other during gamete formation, the results of the dihybrid cross can make sense. Since Mendel's time, scientists have discovered chromosomes and DNA. We now interpret the *Principle of Independent Assortment* as *alleles of genes on different chromosomes are inherited independently during the formation of gametes.* This was not known to Mendel.

The inheritance of two traits on different chromosomes can be explained by meiosis (see figure).



### Mendel's Laws of Inheritance

Mendel's historic experiments led him to the conclusion that inherited characteristics were carried in discrete, independent units (later named **genes**).

In Mendel's interpretation, hereditary characteristics occurred in pairs of factors that had specific relationships.

- **Principle of Segregation:** The factors of inheritance (genes) normally are paired, but are separated or segregated in the formation of gametes (eggs and sperm).
- **Principle of Independent Assortment:** Each factor's distribution in the gametes is not related to the distribution of any other factor.

Mendel used a term **factor** of inheritance but we use the special terms and definitions of Genetics:

1. **Gene:** a unit of genetic information that occupies a specific position on a chromosome (locus) and comes in multiple versions called alleles.
2. **Allele:** one alternative of a pair or group of genes that could occupy the same position on homologous chromosomes and cover the same trait
3. **Phenotype:** (appearance) the physical or observable characteristics of an organism.
4. **Genotype:** the genetic constitution of an organism (genetic makeup).
  - a) **Homozygous:** having a genotype with two identical alleles (one from each parent) for a particular characteristic (**AA, aa**)
  - b) **Heterozygous:** having a genotype with two different and distinct alleles for the same trait (**Aa**)

In 1910, Punnett developed a simple method of depicting the possible genotypes one could get from various matings. We call it the Punnett Square. **Punnett square** . probability diagram illustrating the possible offspring of a mating. Its use in predicting the genotypic ratios in the offspring is illustrated below for Mendel's dihybrid cross. Thus, in this case the Punnett Square has 16 boxes.

Gametes	SY	sY	Sy	sy
SY	SSYY	SsYY	YySS	SsYy
sY	SsYY	ssYY	SsYy	ssYy
Sy	SSYy	SsYy	SSyy	Ssyy
Sy	SsYy	ssYy	Ssyy	ssyy

### Rediscovery of Mendel's Laws

Although Mendel published in 1866, little attention was paid to his work until 1900, when it was simultaneously rediscovered by three scientists. They were

1. German botanist and geneticist *Carl Correns*,
2. Dutch plant physiologist *Hugo de Vries*, and
3. Austrian agronomist *Erich von Tschermak-Seysenegg*.

The scientific community caught up to Mendel's ideas because the cellular basis of inheritance had been worked out between 1865 and 1900. There are often impressions that Mendel was removed from the scientific community, or that his papers were not well circulated. This was not true. All three of Mendel's rediscoverers had read Mendel's work prior to publishing their own work. The lack of attention paid to Mendel is even more mysterious considering the clarity of the ideas presented in his original work.

In 1902, the German scientist *Theodor Boveri* and the American scientist *Walter S. Sutton*, working independently, suggested that chromosomes could be shown to bear the material of heredity. Their works provided sound cytological evidence for the individuality of the chromosomes. Boveri's "The Chromosomes in Heredity" was published in 1903.

The Boveri . Sutton's *Chromosome Theory of Inheritance*, as it came to be known, was discussed and debated during the first years of the twentieth century.

The Chromosome Theory of Inheritance is supported in several ways:

1. Both chromosomes and factors (alleles) exist in pairs in diploid cells.
2. Both homologous chromosomes and alleles of each pair segregate during meiosis so that gametes have one-half the total number.
3. Both homologous chromosomes and alleles of each pair segregate independently so that gametes contain all the possible combinations.
4. Fertilization restores both the diploid chromosome number and the paired condition for alleles in the zygote.

Mendel hypothesized the existence of chromosomes 37 years before Sutton observed them. Compare Mendel's factors with Sutton's chromosomes.

**1866**

Mendel used statistics to hypothesize the action of trait carriers, which he called factors.

**1903**

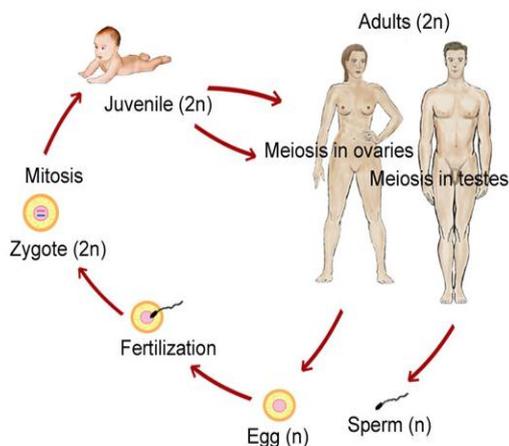
Sutton used a microscope and observed that chromosomes behaved like Mendel's factors.

Mendel's Factors	Chromosomes
Occur in pairs	Occur in pairs
Segregate in gamete production	Separate during meiosis
Pairs sort independently	Pairs sort independently



## Human Life Cycle

In sexual reproduction new individuals are produced by the fusion of *haploid* gametes to form a *diploid* zygote.



**Haploid** ( $n$ ) is having the same number of sets of chromosomes as a germ cell or half as many as a somatic cell (body cell). **Diploid** ( $2n$ ) is having two sets or a pair of chromosomes, as normally found in the somatic cell of higher organisms. A diploid cell has one chromosome from each parent.

Sperm produced by male testes are male gametes, ova (ovum singular) produced by female ovaries are female gametes. Meiosis produces cells that are genetically distinct from each other; fertilization is the fusion of two such distinctive cells that produces a unique new combination of alleles, thus increasing variation on which natural selection can operate. One gamete comes from each parent to produce the genotype of the offspring.

Human set of chromosomes has 46 chromosomes where 44 chromosomes (22 pairs) are autosomes and 2 chromosomes (1 pair) are sex chromosomes. Autosomes are common for both men and women. Set of sex chromosomes are different for man and woman: XY for man and XX for woman.

Sexual reproduction offers the benefit of generating genetic variation among offspring, which enhances the chances of the population's survival.

## Human Genetics

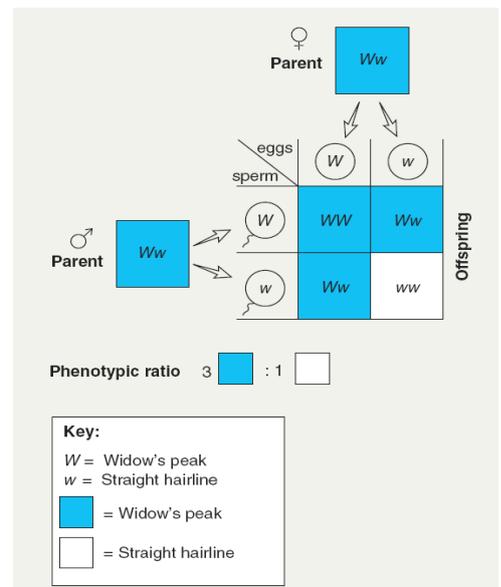
Although Mendel's Laws were first tested in pea plants and fruit flies, evidence quickly mounted that they applied to all living things.

In 1902, *Archibald E. Garrod*, an English prominent physician, demonstrated that human traits were transmitted according to Mendel's laws.

The simple concept of eye color inheritance . brown is dominant, blue is recessive . was published in 1907; however, scientists now believe that several genes are involved

Now more than 3500 human genetic traits are known (for some examples see a table below).

Dominant	Recessive
Curled Up Nose	Roman Nose
Can Roll Tongue	Can't Roll Tongue
Widow's Peak	No Widow's Peak
Facial Dimples	No Facial Dimples
Earlobe hangs	Earlobe attaches at base
Short fingers	Long fingers
Oval face	Square face
Cleft chin	No cleft chin
Broad eyebrow	Slender eyebrow
Separated eyebrows	Joined eyebrows
Long eyelashes	Short eyelashes
Almond eyes	Round eyes
Freckles	No freckles



### Monohybrid cross with a human trait

In humans, widow's peak ( $W$ ) is dominant over straight hairline ( $w$ ). The Punnett Square is constructed as follows (see a figure above).

When the parents are heterozygous ( $Ww$ ), each child has a 75% chance of having the dominant phenotype and a 25% chance of having the recessive phenotype. classic Mendelian ratio 3:1.

### Genetics of Human Diseases

In human, some genetic diseases are inherited in accordance with Mendel's Laws. Such disorders are called *Mendelian traits*. Most of our genes are on the *autosomes*, so they show *autosomal inheritance*. That means that male and female progeny have an equal chance to be affected.

The disorders are determined by dominant or recessive alleles.

Recessive inheritance was first discovered for *alkaptonuria* (1902) described by Archibald E. Garrod and *albinism* (1903). Among the first dominant disorders discovered were *brachydactily* (short fingers, 1905), *congenital cataract* (1906), and *Huntington's chorea* (1913).

**Autosomal dominants** are rare, although they are (by definition) more commonly expressed.

Autosomal dominant diseases are inherited from a single affected parent.

This table shows the several gene diseases in human being determined by dominant alleles (inherited as dominant trait).

Huntington's Disease	neurological deterioration, personality changes, unsteady gait, uncontrollable movements, onset in 40's
Hydrocephalus	swelling brain, mental retardation
Malignant hyperthermia	high fever, muscle contraction, swelling, pressure on the brain, coma, and death
Osteogenesis Imperfecta	fragile bones, hearing loss, blue eye sclera
Waardenburg Syndrome	white forelock, wide-spaced, light colored eyes, hearing impairment

**Autosomal recessive diseases** (such as *sickle-cell anemia*) must be inherited from both parents (who are often carriers - i.e.,  $Aa$  types).

Mating between blood relatives often causes genetic disorders. This is because the descendants of an individual who is a carrier for a specific disease have a much greater chance of inheriting the disease than the normal person. Thus, the taboo subject of inbreeding does have validity.

There are also traits that are a result of **autosomal recessive** inheritance. Such disease becomes apparent in homozygous condition.

DISEASE	SYMPTOMS
Adrenoleukodystrophy	neurological impairment, death by age three, degenerated adrenal glands
Biotinidase Deficiency	mental retardation, seizures, skin rash, loss of hearing, vision and hair, slow growth, convulsions, and death
Congenital Hypothyroidism	mental retardation, poor growth, hearing loss
Galactosemia	muscle weakness, cerebral palsy, seizures, cataracts, liver disease, mental retardation
Homocystinuria	blood clotting, thin bones, seizures, muscle weakness, mental disturbances, and mental retardation
Hurler Disease	enlarged liver and spleen, slow growth, bone deformities, heart problems, deafness, retardation
Maple Syrup Urine Disease	lethargy, vomiting, irritability, mental retardation, coma, and death; urine has sweet odor
Phenylketonuria (PKU)	mental retardation, fair skin, musty odor, small head, heart disease, poor language skills
Porphyria	abdominal pain, red urine, fever, headache, hoarseness, insomnia, delirium, convulsions, stupor, coma, and death
Primary Adrenal Hypoplasia	hormone deficiency, delayed puberty, mental retardation, death
Tay-Sachs	nervous system degeneration, cherry spot on retina, vision, hearing, mobility loss, death
Wilson Disease	silly grin, drooling, inability to walk and talk, stomach aches, headaches, inflamed liver, greenish rings around iris, onset in early thirties

Because some of the chromosomes have a special role in determining gender, the genes on those chromosomes have a special kind of linkage called **sex-linkage**. Because there are two such chromosomes in humans and many other animals this linkage can be separated into *X-linkage* and *Y-linkage*. Y chromosome has very few genes that cause an observable phenotype, therefore most sex-linkage is in fact X-linkage.

The diseases that are caused by mutations on the sex chromosome are called *sex-linked diseases*.

In sex-linked traits, the gene for the trait is found on the X chromosome (a sex chromosome). X-linked traits affect primarily males, since they have only one copy of the X chromosome (XY). Females, who have two copies of the X chromosome, are affected only if they are homozygous for the trait. Females can, however, be carriers for sex-linked traits, passing their X chromosomes on to their sons.

The first sex-linked diseases discovered were *Duchenne muscular dystrophy* (1913), *red-green color blindness* (daltonism, 1914) and *hemophilia* (1916).

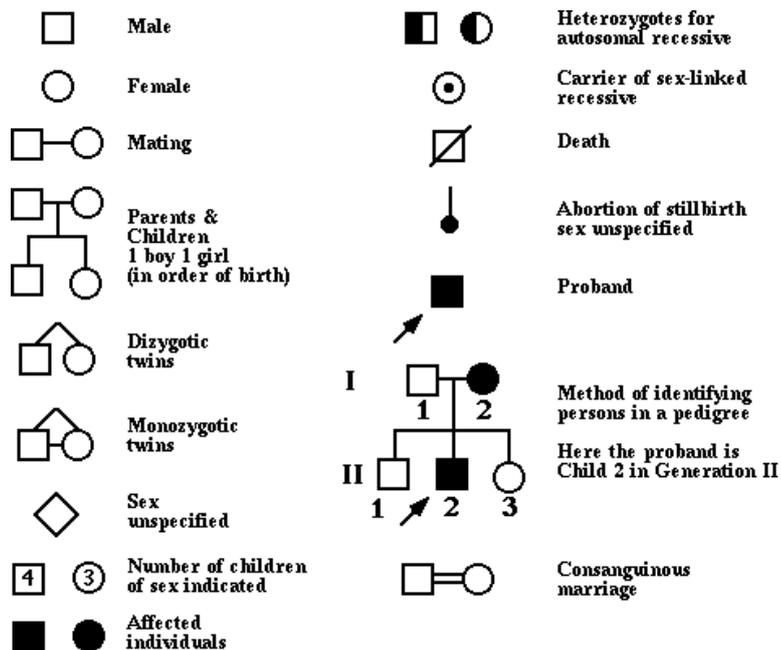
- **Red-Green color blindness (daltonism)**. The genes for the two proteins which recognize red and green light are located on the X chromosome. The two genes are located near to each other and mutations often occur which eliminate one or the other of the pair. The fact that they are located on the X means that color blindness is much more common in males
- **Hemophilia** is a group of diseases in which blood does not clot normally. Factors in blood are involved in clotting. Hemophiliacs lacking the normal *Factor VIII* are said to have *Hemophilia A*, the most common form. Normal Factor VIII can be supplied at a high dollar and health risk cost, although the development of biotechnologically engineered Factor VIII produced by bacteria lessens the health risk.

Just as mutations had provided keys to understanding fruit flies genetics, **pedigrees of families** affected by diseases provided many of the first examples of Mendelian inheritance in humans.

Why do we need to study pedigrees to understand Mendelian inheritance in humans?

- The human generation time is about 25 years.
- Humans produce relatively few offspring compared to most other species.
- Breeding programs for purpose are not possible.

Males are always represented by square symbols, females with circular symbols. A line drawn between a square and a circle represents a mating of that male and female. Two lines drawn between a square and a circle indicate a consanguineous mating, the two individuals are related, usually second cousins or closer relatives. When possible, the square should be placed on the left and the circle on the right of the mating line. Generations are connected by a vertical line extending down from the mating line to the next generation. Children of a mating are connected to a horizontal line, called the sibship line, by short vertical lines. The children of a sibship are always listed in order of birth, the oldest being on the left. Sometimes to simplify a pedigree only one parent is shown, the other is omitted. This neither signifies parthenogenic development nor does it signify divinely inspired conception, it merely means the parent left out is not from the family being studied and is genotypically homozygous normal for the trait being studied. Normal individuals are represented by an open square or circle, depending upon the gender, and affected individuals by a solid square or circle. Each generation is numbered to the left of the sibship line with Roman Numerals. Individuals in each generation are numbered sequentially, beginning on the left, with Arabic Numerals. For example, the third individual in the second generation would be identified as individual II-3.



Each generation is numbered to the left of the sibship line with Roman Numerals. Individuals in each generation are numbered sequentially, beginning on the left, with Arabic Numerals. For example, the third individual in the second generation would be identified as individual II-3.

### Modes of Inheritance

Disorders caused by single mutant genes show one of 5 simple (Mendelian) patterns of inheritance: (1) autosomal dominant, (2) autosomal recessive, (3) X-linked dominant, (4) X-linked recessive, or (5) Y-linked.

#### Example of pedigrees: X-linked recessive

England's Queen Victoria was a carrier for hemophilia (in whom it was probably a spontaneous mutation). The allele was passed to two of her daughters and one son.

Since royal families in Europe commonly intermarried, the hemophilia allele spread quickly in the Royal Houses of Europe.

The most famous case in the line is Czar Nicholas, the last Russian emperor, is only son Alexei.

Alexei suffered from hemophilia A inherited from his mother, Alexandra, who was Queen Victoria's granddaughter.

