Medical Genetics

LECTURE 3
MODE OF INHERITANCE

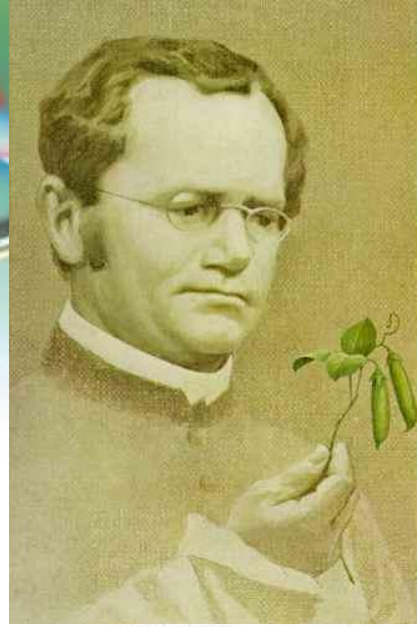
Lecture Objectives

By the end of this lecture, students should be able to:

- Assess Mendel's laws of inheritance
- Understand the bases of Mendelian inheritance
- Define various patterns of single gene inheritance using family pedigree and Punnett's squares

Father of Genetics

- Monk and teacher
- Discovered some of the basic laws of heredity
- Presentation to the Science Society in1866 went unnoticed
- He died in 1884 with his work still unnoticed
- His work rediscovered in 1900.



Gregor Mendel
Monk and Scientist

Mendel's breeding experiments: Interpretation of his results

- The plant characteristics being studied were each controlled by a pair of factors, one of which was inherited from each parent.
- The pure-bred plants, with two identical genes, used in the initial cross would now be referred to as homozygous.
- The hybrid F1 plants, each of which has one gene for tallness and one for shortness, would be referred to as heterozygous.
- The genes responsible for these contrasting characteristics are referred to as *allelomorphs*, or alleles for short.

Genotypes and Phenotypes

- Homozygous dominant:
  Homo (same)

- Homozygous recessive:

Alleles

- Heterozyous:
  Hetero (different)

Punnett Square

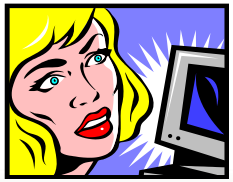
Each parent can only contribute one allele per gene

These genes are found on the chromosomes carried in the sex cells.

Offspring will inherit 2 alleles to express that gene

Male gametes

T t



Female gametes

T t

	T	t
T	T T	T t
t	T t	t t

COMPLETE DOMINANCE - one allele is dominant to another allele

RECALL MENDEL'S 1st EXPERIMENTS

Punnett Squares

CROSS: Purebred purple female x White male

P1 generation = **PP** x **pp**

Female gametes

Male gametes

	P	P
p	Pp	Pp
p	Pp	Pp

F1 generation

Genotypic ratio = 1Pp

Phenotypic ratio = 1 purple

RECALL MENDEL'S 2nd EXPERIMENT

Punnett Squares

CROSS: Two F1 generation offspring with each other.

F1 generation = **Pp** x **Pp**

Female gametes

Male gametes

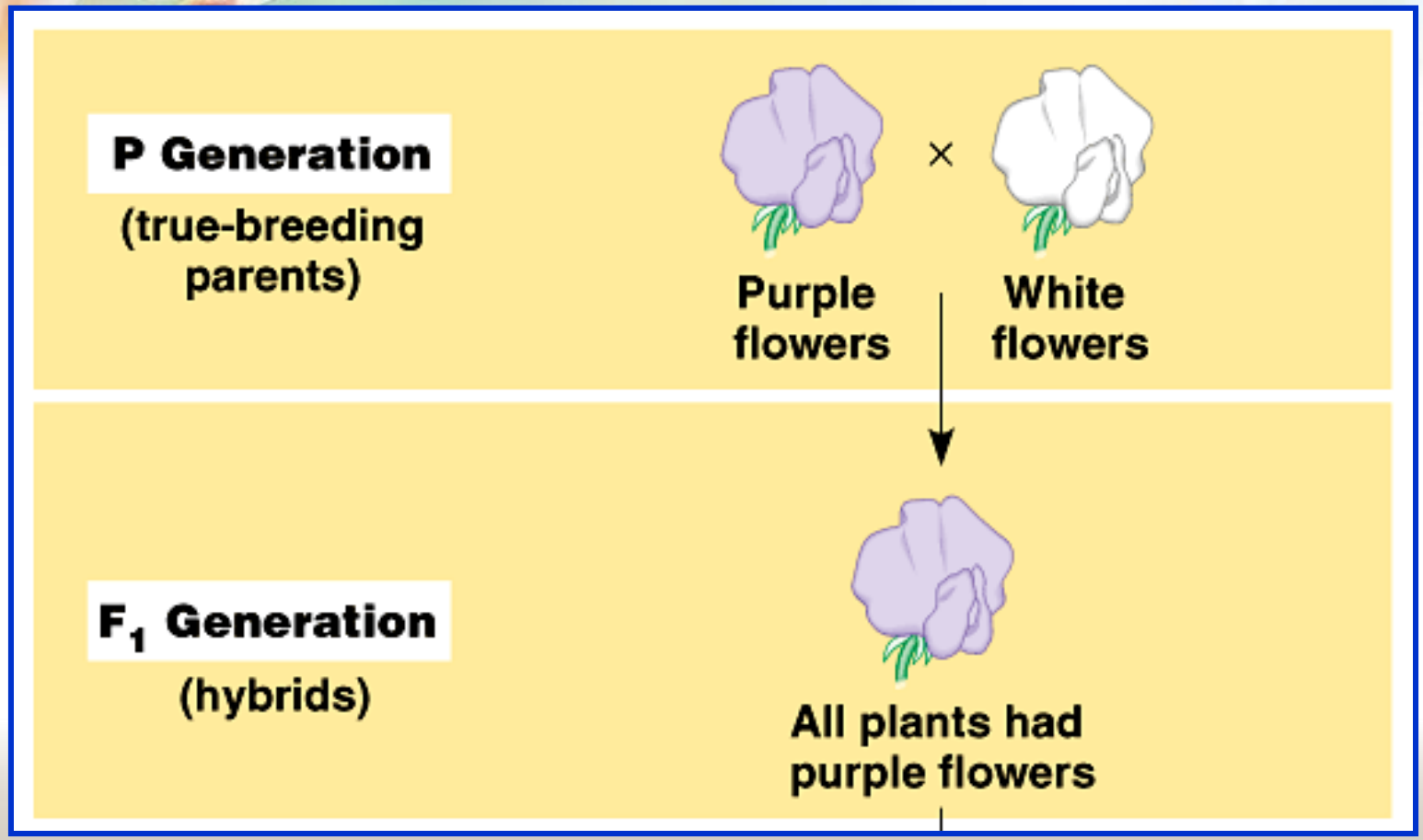
	P	p
P	PP	Pp
p	Pp	pp

F2 generation

- **Genotypic ratio** = 1PP:2Pp:1pp
- **Phenotypic ratio** = 3 purple:1 white

Law of Dominance

In the monohybrid cross (mating of two organisms that differ in only one character), one version disappeared.

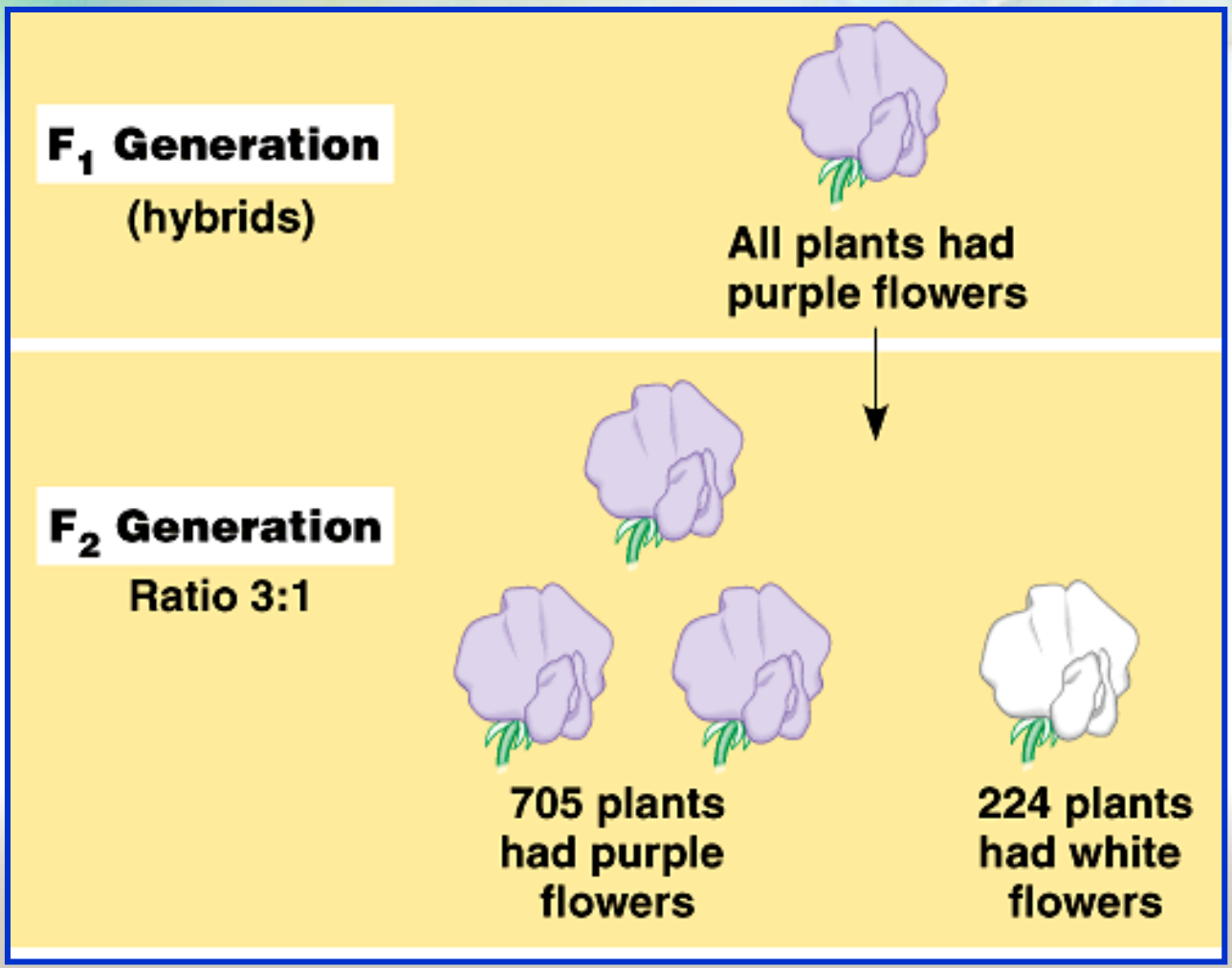


What happens when the F1's are crossed?

Genotype versus phenotype.

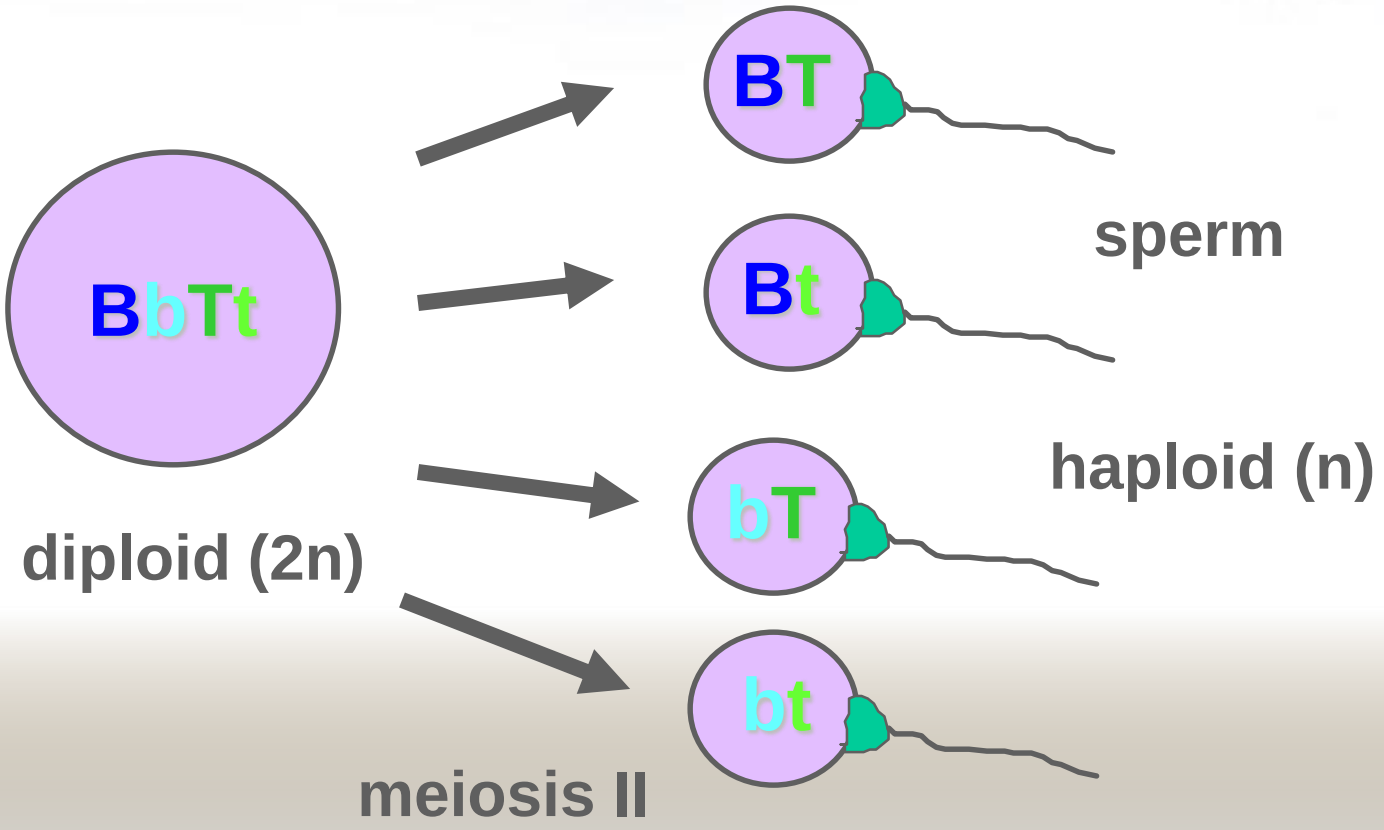
The F1 crossed produced the F2 generation and the lost trait appeared with predictable ratios.

This led to the formulation of the current model of inheritance.



Mendel's 3rd Law of Inheritance

Principle of Independent Assortment: **the alleles for different genes usually separate and inherited independently of one another. So, in dihybrid crosses you will see more combinations of the two genes.**



	RG	Rg	rG	rg
RG	**RRGG**	**RRGg**	**RrGG**	**RrGg**
Rg	**RRGg**	**RRgg**	**RrGg**	**Rrgg**
rG	**RrGG**	**RrGg**	**rrGG**	**rrGg**
rg	**RrGg**	**Rrgg**	**rrGg**	**rrgg**

Phenotypic ratio: **9** round, green: **3** round, yellow: **3** wrinkled, green: **1** wrinkled, yellow → (9:3:3:1)

Genotypic ratio: 1 RRGG: 2 RRGg: 2 RrGG: 4 RrGg: 1 RRgg: 2 Rrgg: 2 rrGg: 1 rrGG: 1 rrgg

THE LAW OF UNIFORMITY

It refers to the fact that when two homozygotes with different alleles are crossed, all the offspring in the F1 generation are identical and heterozygous.

"The characteristics do not blend, as had been believed previously, and can reappear in later generations."

THE LAW OF SEGREGATION

It refers to the observation that each individual possesses two genes for a particular characteristic, only one of which can be transmitted at any one time.

Rare exceptions to this rule can occur when two allelic genes fail to separate because of chromosome non-disjunction at the first meiotic division.

THE LAW OF INDEPENDENT ASSORTMENT

- It refers to the fact that members of different gene pairs segregate to offspring independently of one another.

- In reality, ***this is not always true***, as genes that are close together on the same chromosome tend to be inherited together, i.e. they are 'linked‘.

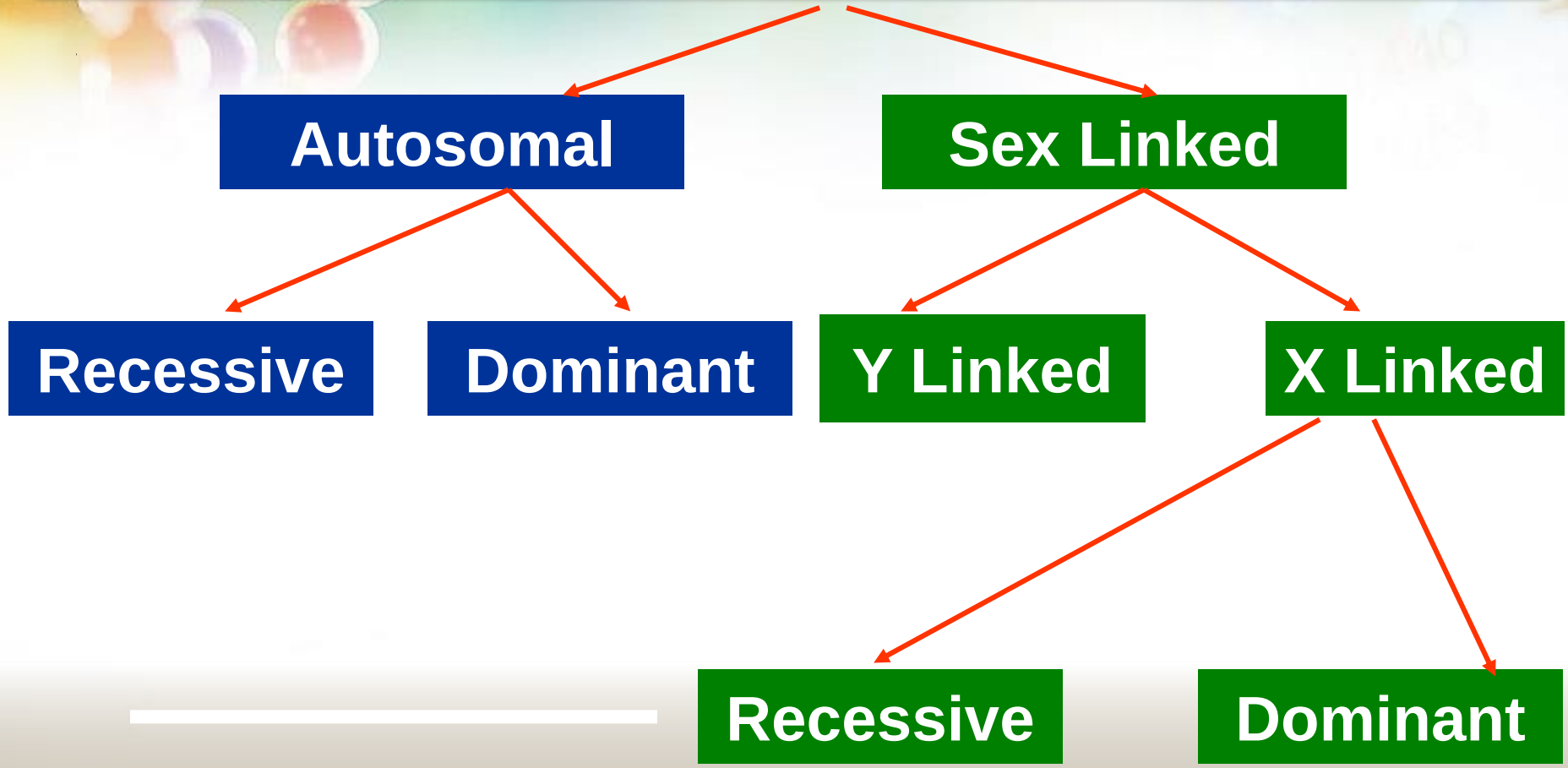
MENDELIAN INHERITANCE (simple pattern of inheritance)

- Over 11,000 traits/disorders in humans exhibit single gene ***unifactorial*** or ***Mendelian*** *inheritance*.

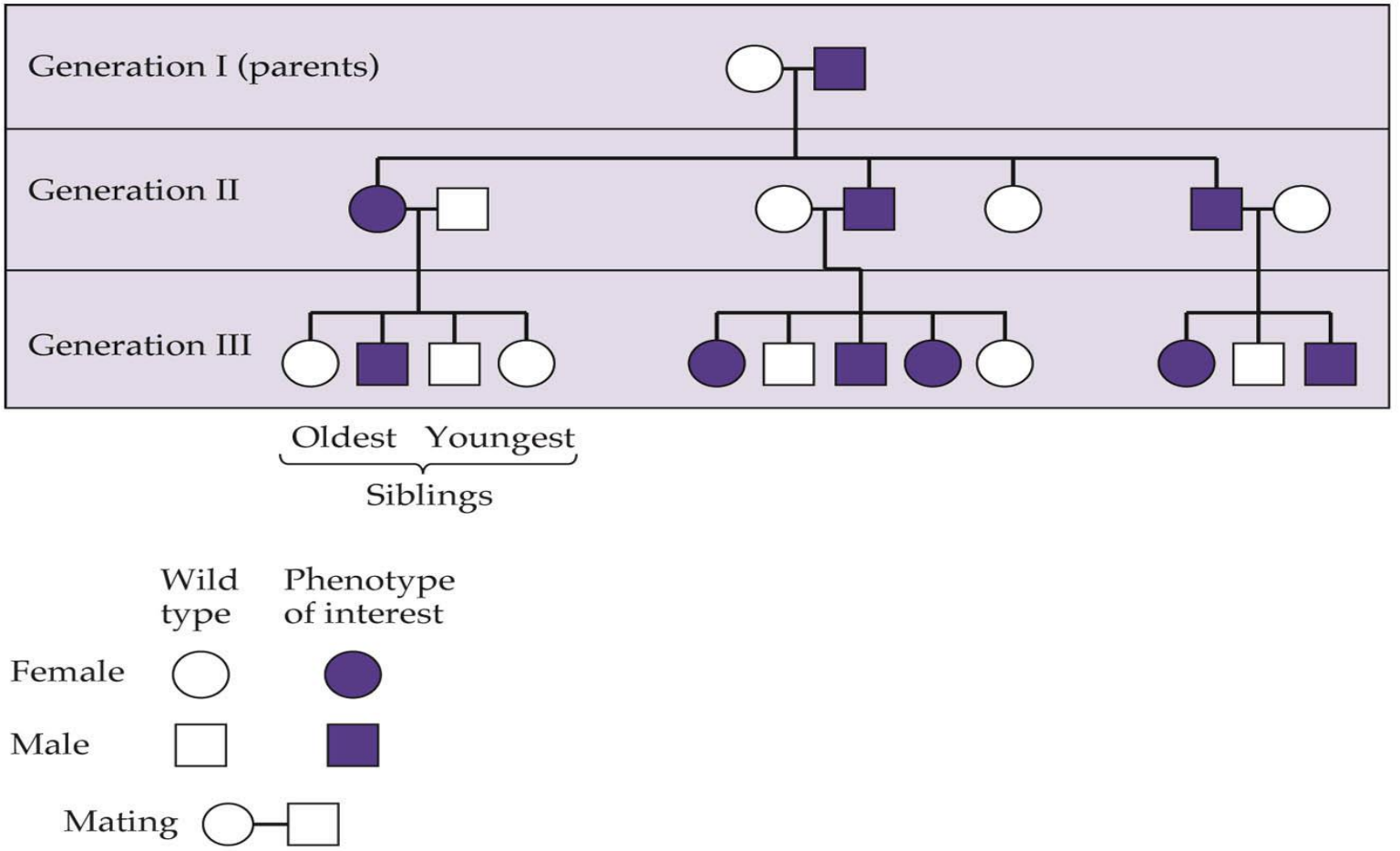
- A trait or disorder that is determined by a gene on an ***autosome*** is said to show ***autosomal inheritance.***

- A trait or disorder determined by a gene on one of the ***sex*** chromosomes is said to show ***sex-linked inheritance***.

MODES OF INHERITANCE OF SINGLE GENE DISORDERS



A Pedigree Analysis for Huntington's Disease

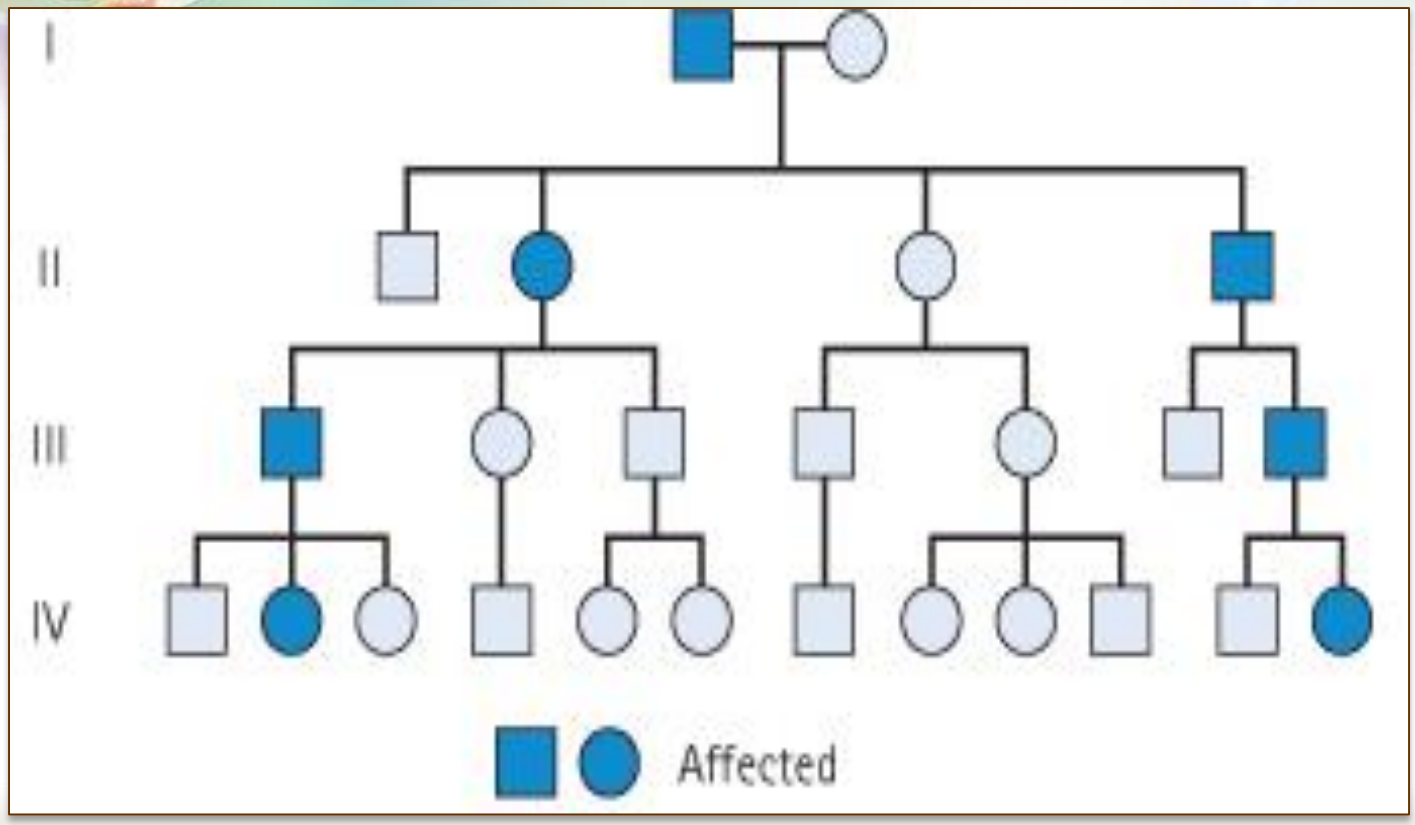


LIFE: THE SCIENCE OF BIOLOGY, Seventh Edition, Figure 10.10 Pedigree Analysis and Dominant Inheritance

Autosomal Dominant Mode of Inheritance

- **The trait (character, disease) appears in every generation.**
- **Unaffected persons do not transmit the trait to their children.**
- **Examples: Huntington disease, Myotonic dystrophy, Neurofibromatosis type 1, Marfan syndrome etc.**

Family Tree of an Autosomal Dominant Mode of Inheritance



Note the presence of male-to-male (i.e. father to son) transmission

Autosomal Recessive Mode of Inheritance

- **The trait (character, disease) is recessive**
- **The trait expresses itself only in homozygous state**
- **Unaffected persons (heterozygotes) may have affected children (if the other parent is heterozygote)**
- **The parents of the affected child maybe related (consanguineous)**
- **Males and female are equally affected**
- **Examples:**

  Cystic fibrosis, Phenyketonuria, Sickle cell anaemia, Thalassaemia etc.

Punnett square showing autosomal recessive inheritance:

(1) Both Parents Heterozygous:

25% offspring “affected Homozygous”

50% Trait “Heterozygous normal but carrier”

25% Normal

Mother

Father	A	a
A	AA	Aa
a	Aa	aa

(2) One Parent Heterozygous:

Female

	A	a
A	AA	Aa
A	AA	Aa

50% normal but carrier “Heterozygous”

50% Normal

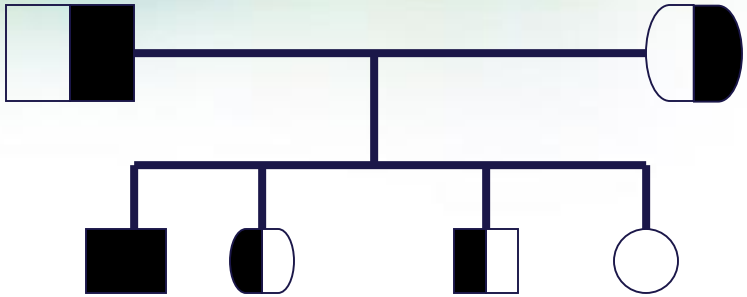
(3) One Parent Homozygous:

Female

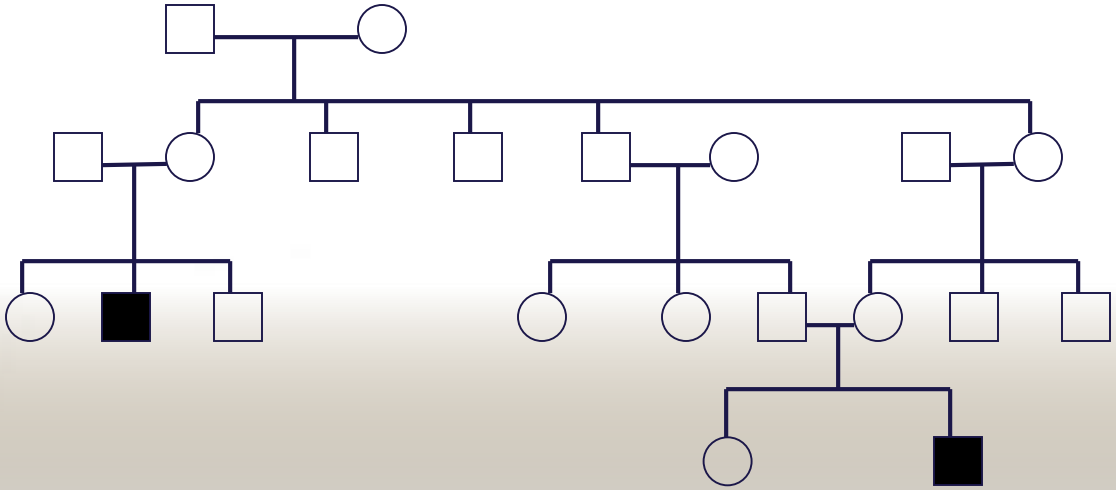
	A	A
a	Aa	Aa
a	Aa	Aa

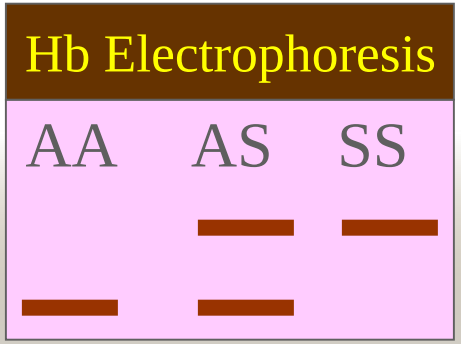
100% offspring carriers.

Family tree of an Autosomal recessive disorder Sickle cell disease (SS)



A family with sickle cell disease -Phenotype



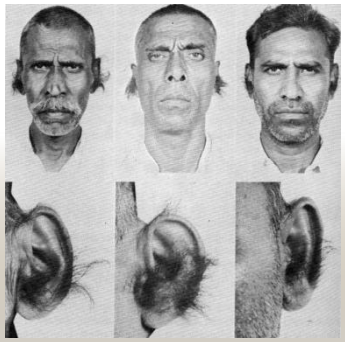


Sex – Linked Inheritance

- This is the inheritance of a gene present on the sex chromosomes.
- The Inheritance Pattern is different from the autosomal inheritance.
- Inheritance is different in the males and females.

Y – Linked Inheritance

- The gene is on the Y chromosomes
- The gene is passed from fathers to sons only
- Daughters are not affected
- Hairy ears in India
- Male are Hemizygous, the condition exhibits itself whether dominant or recessive



		Father: X	Father: Y*
Mother	X	XX	XY*
Mother	X	XX	XY*

X – Linked Inheritance

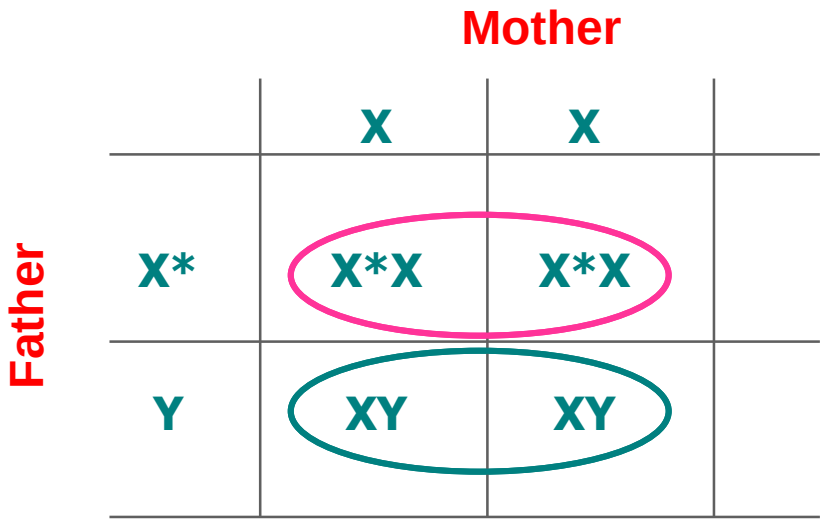
- The gene is present on the X chromosome
- The inheritance follows specific pattern
- Males have one X chromosome, and are hemizygous
- Females have 2 X chromosomes, they may be homozygous or heterozygous
- These disorders may be : recessive or dominant

X – Linked Recessive Inheritance

- The incidence of the X-linked disease is higher in male than in female
- The trait is passed from an affected man through all his daughters to half their sons
- The trait is never transmitted directly from father to sons
- An affected women has affected sons and carrier daughters
- X - Linked Recessive Disorders: Albinism, Fragile X syndrome, Hemophilia, Muscular dystrophy, Retinitis pigmentosa

X – Linked Recessive Inheritance

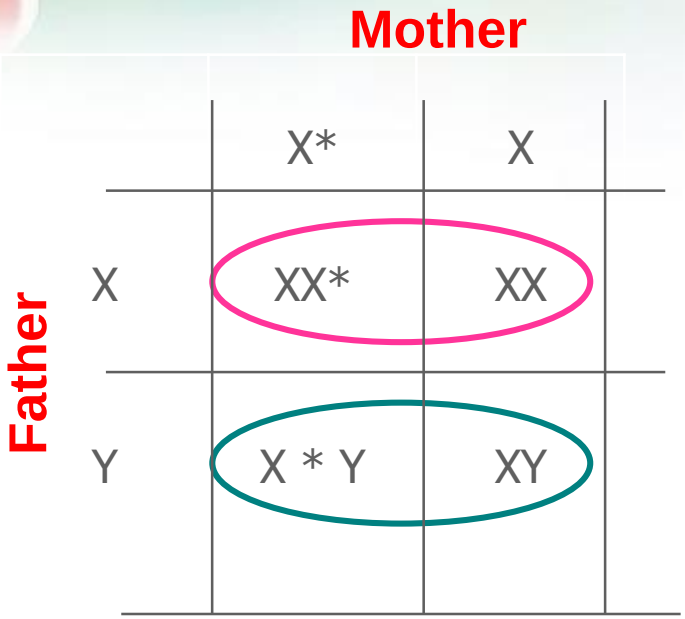
(1) Normal female, affected male



All sons are normal

All daughters carriers “not affected”

(2) Carrier female, normal male:



50% sons affected
50% daughters carriers

(3) Homozygous female, normal male:

- **All daughters carriers.**
- **All sons affected.**

X-Linked Dominant Disorders

- The gene is on X Chromosome and is dominant
- The trait occurs at the same frequency in both males and females
- Hemizygous male and heterozygous females express the disease.

Punnett square showing X – linked dominant type of Inheritance

(1) Affected male and normal female:

Father \ Mother		X	X
	X*	X*X	X*X
	Y	XY	XY

All daughters affected, all sons normal

(2) Affected female (heterozygous) and normal male:

Father \ Mother		X*	X
	X	XX*	XX
	Y	X*Y	XY

50% sons & 50% daughters are affected

TAKE HOME MESSAGE:

- An accurate determination of the family pedigree is an important part of the workup of every patient
- Pedigrees for single-gene disorders may demonstrate a straightforward, typical mendelian inheritance pattern
- These patterns depend on the chromosomal location of the gene locus, which may be autosomal or sex chromosome-linked, and whether the phenotype is dominant or recessive
- Other atypical mode of inheritance will be discussed next lecture.