Mendelian Genetics and its Extension
(Principles of inheritance)

Genetics is the study of heredity. It is an ancient discipline. At least 4000 years ago, in Sumeria, Egypt and other parts of the world, farmers recognised that they could improve their crops and their animals by selective breeding. Their knowledge was based on experience and they recognised that many features of plants and animals were passed on from generation to generation. Furthermore, they were aware that desirable traits - such as size, speed and weight of animals could sometimes be combined by controlling mating, and that in plants, crop yield and resistance to arid conditions could be combined by cross pollination, The ancient breeding programmes were not based on experimental studies because nothing was known of genes or any of the principles of heredity.

Birth of Genetics:

Modern genetics originated with Gregor Mendel's (Fig. 1.1) work. It is based on this paper entitled ***"Experiments*** in ***Plant Hybridisation"*** published in 1866 in the Proceedings of the Society of Natural History in Bmo. Mendel carried out detailed investigations of inheritance in garden pea. He performed elaborate plant hybridisation experiments and kept accurate pedigree records of his results. With the data obtained, he was able to formulate the basic principles of inheritance.

Mendel proposed the concept of hereditary units. According to him equal number of these units (factors) inherited from each parent determined the observable characters of the offspring. **This** was the first conceptualisation of what is now referred to ***particulate*** inheritance. Characteristics themselves are not inherited but the particles, units or factors that determine or control the observable traits are transmitted from parents to offspring. The appearance of the character in the offspring is determined by the particular combination of factors inherited from the two parents. **This** was the beginning of the concept of a gene, which is the modern term for the hereditary units or particles originally described by Mendel.

Mendel's work was not appreciated by the rest of the scientific community until 1900, when three botanists Carl Correns in Germany, Hugo de Varies in the Netherlands and **Erich** von Tschermak in Austria, rediscovered his work after each had independently reached similar conclusions. They all found Mendel's report while scanning the literature for related work and cited it in their own publications.

William Bateson, an English scientist, coined the term "genetics" in 1905 for this developing science. The term was derived from Greek word which means 'to generate". Many consider Bateson as the real founder of genetics as he was the first to have Mendel's papers translated into English and the first one to show that Mendel's theory was also applicable to animals.

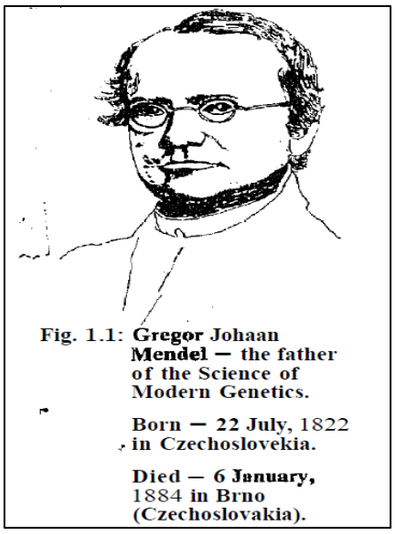


Fig. 1.1: Gregor Johaan Mendel — the father of the Science of Modern Genetics.

Born — 22 July, 1822 in Czechoslovekia.

Died — 6 January, 1884 in Brno (Czechoslovakia).

Mendel was born in a small village and was the only son of a peasant family. He had all insatiable curiosity about the natural and the physical world and was keen interested in the diversity of living beings. His parents could not afford his higher education. He joined monastery of St. Thomas, which was at that time in Austria and now in Czechoslovakia. His interest in Botany began early in life, as farming and the development of new varieties of apples were his family's chief occupation. His early interest was further stimulated by his formal education which centred round mathematics, physics, botany and zoology. The monastery provided him a stimulating environment, as it was a centre of cultural, intellectual and religious life, and its members and visitors included many notable scholars and scientists of that period. In 1851, he joined the University of Vienna and upon completing his course he returned to his teaching responsibilities at Brno. His experiments in plant hybridization were carried out in the monastery garden for several years. Beginning from 1826 Mendel combined his talent, background and interests in a series of experiments with garden peas. His experiments are now recognised as classic example of carefully planned and executed scientific research.

Growth of Genetics: From Mendel to Genetic Engineering

Genetics has come a long way and at present is a mature and dynamic science. The science of genetics was built on the foundation laid by Mendel but is owes its present stature to the contributions of a large number of scientists. In fact, the history and development of genetics is a subject worthy of study. We will be studying about the important contributions of various researchers in different units of this course. Nevertheless, a list of salient developments/contributions in the field has been compiled in Table 1.1 to give you some idea of their chronology.

Table 1.1 : The Genetics Time Line (modified from Gardner et al., 1991).

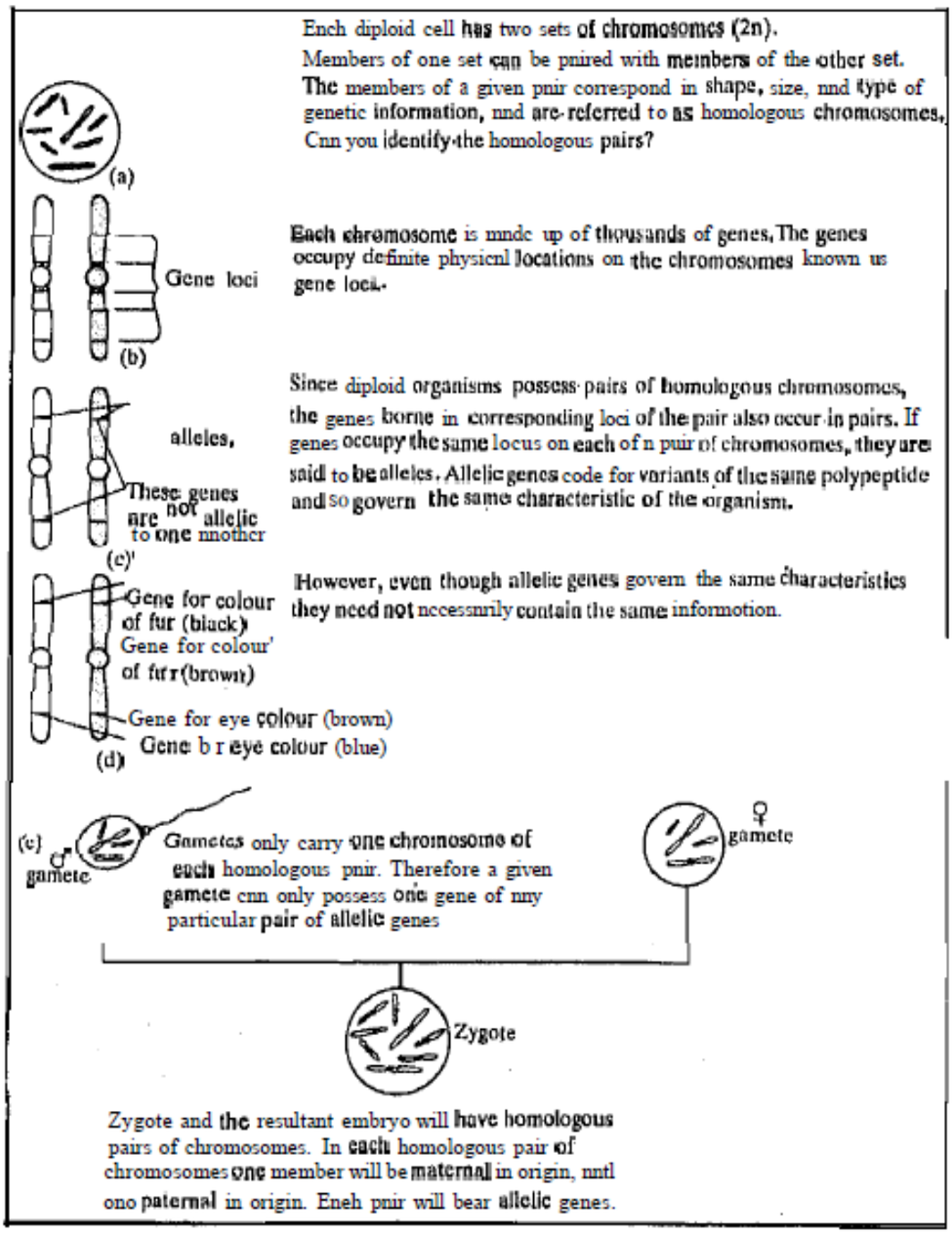
Year	Scientists (S)	Contribution
1865	Mendel	read his paper to the Brünn Society for Natural History
1866	Mendel	his paper published in the Proceedings of the Brünn Society for Natural History
1868	Miescher	first study of DNA
1900	De Vries, Correns, and Tschermak	Mendel's work discovered
1902	Boveri & Sution	demonstrated the presence of paired chromosomes (homologs) in diploid species
1905	Bateson	named the science genetics
1908	Hardy & Weinberg	formulated the "Hardy Weinberg Law" relating genotypic frequencies to gene frequencies in randomly mating populations
1909	Johannsen	introduced the term gene
1909	Garrod	book on Inborn Errors of Metabolism
1910	Morgan	established the sex-linked inheritance of white eyes in *Drosophila melanogaster (Nobel Prize 1933)*
1911	Morgan	postulated the chromosomal basis of linkage
1913	Sturtevant	construction of a genetic map
1927	Muller	reported the use of the *ClB* technique to demostrate that X-rays are mutagenic *(Nobel Prize*, 1946)
1928	Griffith	discovery of transformation in *Diplococcus pneumoniae*
1931	Creighton & McClintock	demonstrated that genetic recombination is correlated with the exchange of morphological markers on chromosomes.
1940	Oliver	demonstration of recombination within the lozenge functional unit in *Drosophila*
1941	Beadle and Tatum	one gene one enzyme concept *(Nobel Prize 1958)*
1944	Avery, MacLeod & McCarty	demonstrated that the pneumococcal "transforming principle" is DNA
1946	Lederberg & Tatum	discovered conjugation in bacteria *(Nobd Prize 1958)*
1950	McClintock	first to present a paper on "Transposable elements" in Maize *(Nobel* Prize *1983)*
1952	Hershey & Chase	demostrated that the genetic material of bacteriophage T2 is DNA *(Nobel Prize 1969)*
1952	Zinder & Lederberg	discovered the phage-mediated transduction in bacteria
1953	Watson & Crick	worked out the double-helix structure of DNA using the X-ray diffraction data of Wilkins and the base composition data of Chargaff *(Nobel Prize 1962)*

1955	Benzer	first to present a paper on the fine structure of the Phage T4rII locus
1956	Tjio & Levan	established that the normal diploid chromosome number in human is 46
1957	Fraenkel-Conrat & Singer	demonstrated that the genetic information of tobacco mosaic virus is stored in RNA
1958	Meselson & Stahl	demonstrated that DNA replication is semi-conservative
1958	Kornberg	isolated DNA polymerase I from *E.Coli (Nobel Prize 1959)*
1959	Ochoa	discovered RNA polymerase *(Nobel Prize 19-59)*
1961	Jacob & Monod	proposed the "Operon Model" for regulating gene expression *(Nobel Prize 1965)*
1964	Yanofsky & colleagues; Brenner & colleagues	established colinearity between polypeptide products
1964	Temin	proposed the DNA provirus from RNA tumour viruses (Nobel *Prize 1975)*
1965	Holley	worked out the first complete nucleotide sequence of a tRNA *(Nobel Prize 2968)*
1966	Nirenberg, Khorana & coworkers	established the complete genetic code *(Nobel Prize 1968)*
1970	Nathans & Smith	isolated the first restriction endonuclease *(Nobel Prize 1978)*
1970	Baltimore	identified reverse transcriptase of RNA tumour viruses *(Nobel Prize 1975)*
1972	Berg	produced first recombinant DNA *(Nobel Prize 1980)*
1976	Bishop & Varmus	demonstrated the protooncogene to oncogene relationship *prize 1989)*
1976	Hozumi & Tonigawa	demonstrated somatic rearrangements of gene encoding antibodies
1977	Breathnach, Mandel & Chambon; Jeffreys & Flavell	demonstrated the presence of introns in eukaryotic genes
1977	Maxam & Gilbert; Sanger, Nicklen& Coulson	description of the DNA sequencing techniques
1977	Sanger & colleagues	worked out the complete 5387 nucleotide sequence of phage ΦX174
1978	Three different laboratories	discovered "splicing" of adenovirus RNAs
1982	Sanger & colleagues	worked out the complete 48,502 nucleoticle-pair sequence of phage lambda
1983	Cech & Altman	established the existence of catalytic RNAs *(Nobel Prize 1989)*
1985	Jeffery	DNA finger-printing
1988	Watson	coordinated the "human genome-project"
1989	NIH Recombinant DNA Advisory Committee	recommended approval of first-human "gene transplant" experiment
1989	Tsui, Collins & colleagues	coloned the "cystic fibrosis gene"
1990	Saiki	Polymerase chain reaction

SOME BASIC GENETIC TERMINOLOGY:

1. Genes and Alleles:

The inheritance of any character can be studied only when there are two contrasting conditions, such as yellow versus green seed colour **(as** observed by Mendel in peas), normal pigmentation versus absence of pigmentation **(albinism)** in humans and other animals, and brown versus black coat colour in guinea pigs. An individual expresses one or the other, but not both contrasting conditions at the same time. **Genes that govern variations of the same characteristic and that occupy corresponding loci on homologous chromosomes are termed alleles.**



Geneticists use the term *allele* to emphasise that there are two or more alternative forms of a gene that can occur at corresponding specific loci. The possible variants of a gene at any given locus are known as alleles, each of which

is assigned a single letter (or a group of letters) as its symbol. In the example below, we shall consider the trait - height of pea plant. Tall forms are denoted by T and the short ones are denoted by t. T and t are alleles of the same gene. Since they are present in pairs they are represented as TT, tt or Tt.

2. Homozygous and heterozygous:

In an individual two identical alleles may exist or a given character and, hence, the individual is referred to as *Homozygous* (e.g. AA and aa). If there are two non-identical or different alleles for a given character, the individual is referred to as *heterozygous* (e.g. Aa).

Let us examine a situation where both the parents' are homozygous. The male is homozygous recessive aa, and female is homozygous dominant AA. During meiosis in the male the two 'a' alleles separate from each other so that each sperm has only a single 'a' allele. Similarly, in the female parent each egg has one **'A'** allele. The fertilisation of the 'A' egg by 'a' sperm results in **heterozygous animal** with 'Aa'.

The form of gene which occurs in an individual in nature is called the **'wild type'** while a **'mutant type'** is the one in which the genetic material is somewhat altered. The alleles which express themselves in both homozygous and heterozygous conditions are known as the **dominant alleles.** For example, **TT** represents tallness (homozygous). The individuals having the alleles TT, and Tt would be tall as T is a **dominant** allele and it can express itself in both homozygous and heterozygous conditions. Some alleles express themselves only in homozygous condition and are referred to as **recessive alleles.** In the height characteristic, dwarfness can be seen in individuals that have the alleles 'tt', i.e., **recessive alleles** are expressed in homozygous condition only.

3. Phenotype and Genotype:

in an organism by just looking at it. The **phenotype** is the term used to specify the appearance of an individual in a given environment with respect to a certain inherited trait. The *genetic constitution* of that organism, most often expressed in symbols, is its **genotype.**

Using the same example as above let us understand the concepts of phenotype and genotype. If the female parent has the genotype TT (homozygous, dominant) can you guess the phenotype? Yes! It is Tall. If the male parent is homozygous recessive 'tt' can you tell what is its phenotype? The answer is dwarf. If these two parents are crossed then what would be the genotype and phenotype of the offspring? The genotype would be 'Tt' and phenotype would be tall.

Similarly, an individual has alleles that govern hair colour. These specific alleles constitute the individual's genotype for hair colour. The actual hair colour that the individual exhibits is its phenotype (black, brown, red, blonde etc.). The crux of the above discussion is that the *genetic constitution* of an individual is referred to as its **genotype** and the expression of these genes as its **phenotype.**

1.4 MENDEL'S CLASSICAL EXPERIMENTS WITH PEA

Mendel's studies provide an outstanding example of good scientific technique. He chose research material well suited for the study of the problem at hand, designed his experiments carefully, collected large amount of data and used mathematical analysis to show that the results were consistent with his explanatory hypothesis.

1.4.1 Choice of Material

Before Mendel, several investigators carried out research work to understand the principles of inheritance, but they failed to reach meaningful conclusions because of the unsuitability of the system they were studying. The garden pea with which Mendel worked has several suitable features. The foremost were that these plants were cheap, easy to obtain, required little space, had shorter generation time, produced many offspring and could be crossed easily. The pea flowers are bisexual and are usually self-fertilised, that is, the ovule (female gamete) is fertilised by pollen (male gamete) from the same flower as both the male and female parts of the flower are closed in a petal box or keel (see Fig. 1.5). Pollen from another plant can be experimentally introduced to the stigma of a flower to bring about cross-pollination.

Cross-pollination can be encouraged experimentally either by removing stamens from female parent and placing pollen from another variety on the stigma of its flowers (Fig. 1.6a), or by placing the pollen from the male parent on the stigma of a different plant, whose stamens have been removed (Fig. 1.6b). Therefore, with the common pea plant, the geneticists can perform crosses in the way they choose and can easily establish lineage or pedigree of each plant in a particular cross.

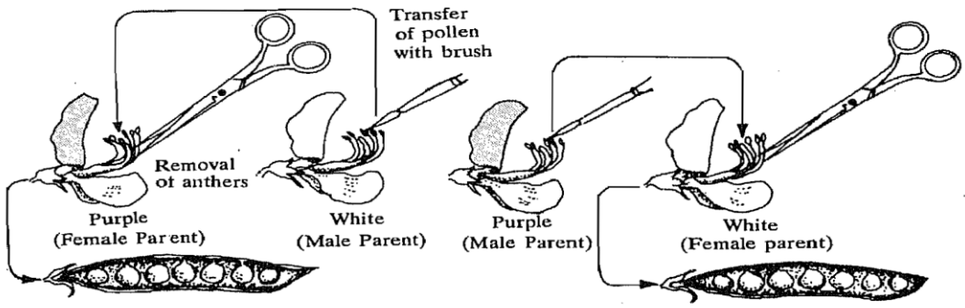


Fig. 1.6 (a,b) : Cross pollination in pea. In a) the anthers are removed in the purple flowers to prevent self-pollination. Similarly, in b) anthers are removed in the white flowers and it is usd for cross-pollination.

The pea plants varied with respect to a number of characteristics such as plant height, seed texture, used colour and flower colour. Such a variation is essential if anything at all is to be learned about the inheritance of any character. If, for example, all pea plants were of the same height and had the same flower colour, generation after generation, no information would be gained from following plant height and flower colour in genetic studies. A characteristic must have alternative traits or variant forms that can be followed if insight is to be gained regarding the inheritance pattern.

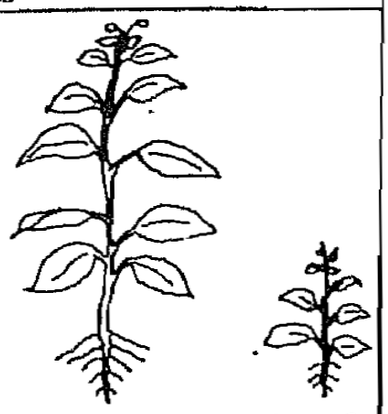
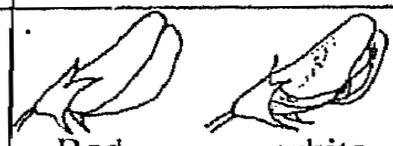
	Characteristics	Traits
a	Height	 Tall vs dwarf
b	Seed shape	 Round vs wrinkled
c	Seed colour	 Yellow vs green
d	Flower colour	 Red vs white
e	Flower position	 Axial vs terminal
f	Pod colour	 Green vs yellow
g	Pod shape	 Inflated vs constricted

Fig. 1.7: The seven characteristics (a-g) in pea plant studied by Mendel. Each character has two well defined phenotypes that are easily recognised.

MENDEL'S LAWS OF INHERITANCE:

Gregor Johann Mendel was born on July 22, 1822 to peasant parents in a small agrarian town in Czechoslovakia. He is considered as the father of genetics. Through his hybridization experiments on garden pea plant (Pisum sativum), in the year 1865 he presented some basic ideas on inheritance in a research paper. This remarkable piece of work unfortunately remained unrecognized for 34 long years. In the year 1900, Mendel's work was rediscovered by three botanists namely Hugo de Vries, Carl Correns and Erich Von Tschermak. Interestingly, it was not Mendel but Correns, one of the discoverers of Mendel's work, who proposed this work as Mendelian laws of Inheritance. These laws of heredity are listed below.

1) Law of uniformity.
2) Law of segregation or Law of purity of gametes.
3) Law of independent assortment or Law of free recombination.

From the monohybrid crosses, in which crosses were made between parents, each of which exhibited one of two contrasting forms of the characters, Mendel suggested as follows.

Genetic characters are controlled by unit factors (later called genes) that occur in pairs on homologous chromosomes in individual organism.

When two unlike unit factors responsible for a single character are present in a single individual, one unit factor may be dominant over the other, which is referred to as recessive.

1. Law of Uniformity:

Mendel's first law states that when plants with two contrasting characters are crossed (mated), the characters do not blend. If any character does not express in the first generation, it may reappear without any change in subsequent generations.

2. Law of Segregation:

The second law states that in a heterozygote the dominant and recessive factors (genes or alleles) remain together throughout life without contaminating or mixing with each other and finally separate or segregate from one another so that each gamete receives only one factor either dominant or recessive. For explanation, see the following figures.

Monohybrid cross in garden pea plants

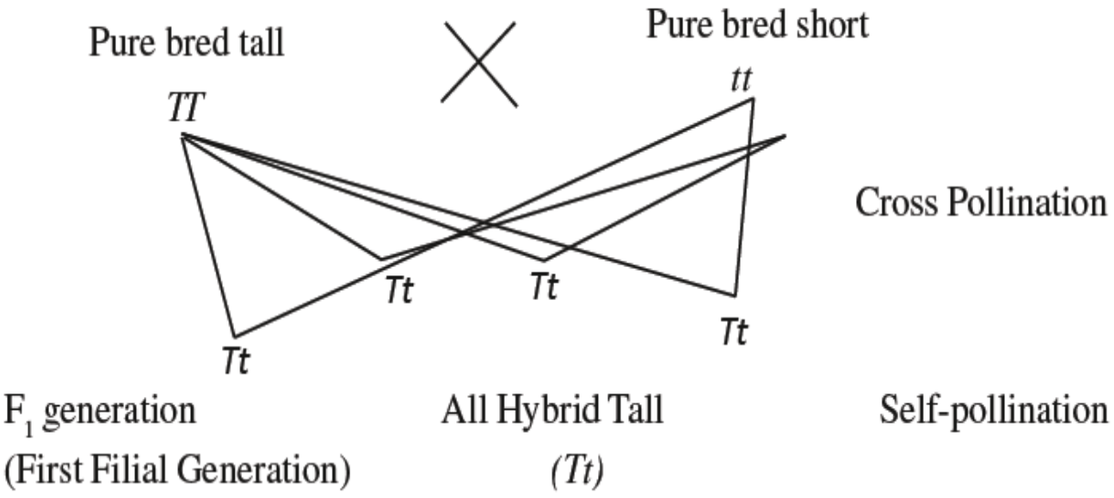


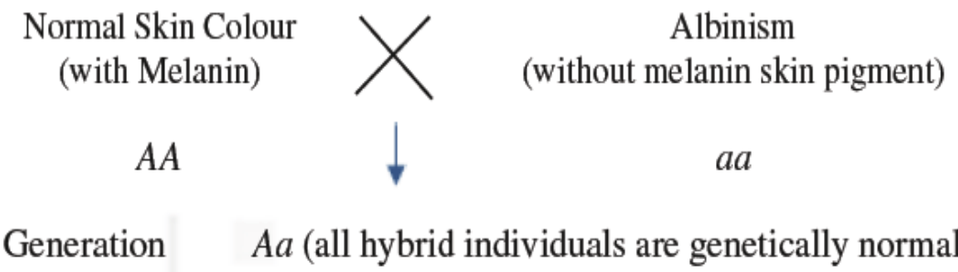
Fig. 3.1: All the plants of F_1 generation are genetically *Tt*.

To determine the types and frequencies of various offspring expected we normally use squares called Punnett Squares in genetics.

		Gametes of pure bred tall plant	
		T	*T*
Gametes of pure bred short plant	*t*	*Tt*	*Tt*
	t	*Tt*	*Tt*

Fig. 3.2: The Punnett's square showing genetic constitution of offspring resulted due to the mating between pure short and pure tall plants.

Monohybrid cross in humans



A = Normal dominant

a = Abnormal recessive

Fig. 3.3: Monohybrid cross (mating) for skin colour in Man.

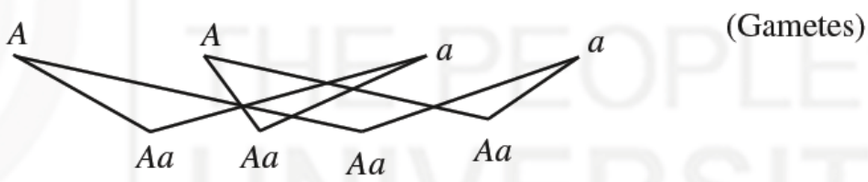


Fig. 3.4: All the individuals of F1 generation are genetically hybrid.

		Gametes of pure bred normal individuals	
		A	*A*
Gametes of pure bred albinos	*a*	*Aa*	*Aa*
	a	*Aa*	*Aa*

Fig. 3.5: The punnett squares showing the genetic contribution of the offspring resulted from mating between pure normal and pure albino individuals.

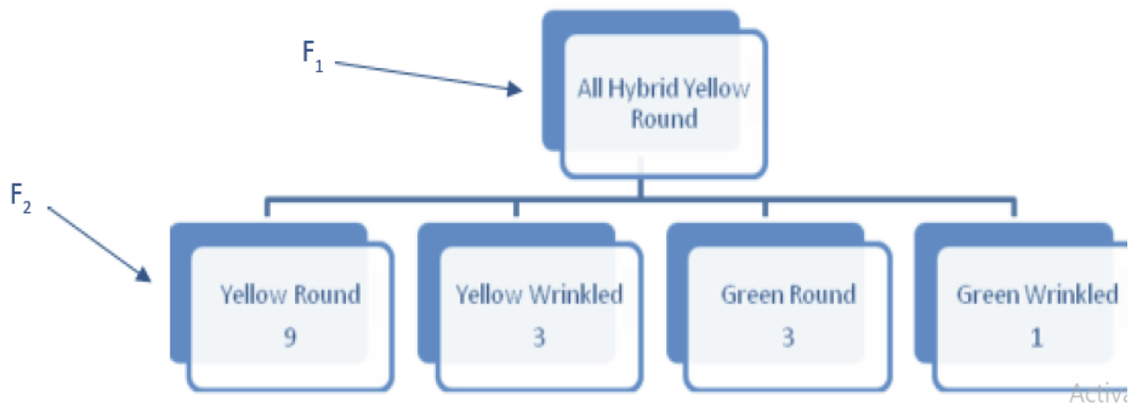
3. Law of Independent Assortment:

The law of independent assortment or recombination states that the members of different pairs of factors (genes) assort independently of each other when the gametes are formed. Because of that new combinations (or all possible combinations) of characters are produced in the offspring.

For explanation see the following figures.

Di hybrid cross in pea plants having yellow, round, green and wrinkled seeds.

YR	X	*yr*	Corss
Pure bred		Prue bred	Pollination
yellow round		green wrinkled	



Checker Board

Genotype *YyRr*

Phenotype Yellow Round

	YR	*YR*
Yr	*YyRr*	*YyRr*
Yr	*YyRr*	*YyRr*

Fig. 3.6a: Di hybrid cross F_1 generation.

	YR	*Yr*	*yR*	*yr*
YR	*YRYR*	*YRYr*	*YRyR*	*YRyr*
Yr	*YrYR*	*YrYr*	*YryR*	*Yryr*
yR	*yRYR*	*yRYr*	*yRyR*	*yRyr*
yr	*yrYR*	*yrYr*	*yryR*	*Yryr*

Fig. 3.6b: Di hybrid cross F_2 generation.

Genotypes: 9 different combinations.

Phenotypes: 9 Yellow Round : 3 Yellow Wrinkled : 3 Green Round : 1 Green Wrinkled.

In case of di hybrid cross, when mating takes place in humans showing different contrasting pairs of characters, it will be observed that assortment of genes of one pair will be independent of the other pair.

From the above figure it is revealed that each pair of contrasting characters behaves independently and bears no association with a particular character.

Back Cross and Test Cross:

When F1 individuals are crossed with one of the parents from which they are obtained, such cross is called back cross. In such back crosses, when F1 is back crossed to the parent with dominant phenotype, no recessive individuals are derived in the offspring. But when F1 progeny is back crossed with its recessive parent, both phenotypes (i.e. dominant and recessive) appear in the progeny. While both of these crosses are back crossed, only the cross with the recessive parent is called Test Cross.

Examples

I) Monohybrid Test Cross

In a monohybrid cross of homozygous tall (*DD*) and homozygous dwarf (*dd*) plant is crossed either with its dominant parent to perform a back cross or with its recessive parent to perform a test cross the following results are obtained

P_1

Homozygous tall (*DD*) X Homozygous dwarf (*dd*)

Heterozygous Tall *Dd*

A) Back Cross

F_1 Tall *Dd* X P_1 Tall *DD*

½ *DD*	½ *Dd*

Back Cross Progeny: Homozygous Tall (All Tall) | Heterozygous Tall

B) Test Cross

F_1 Tall *Dd* X P_1 Dwarf *dd*

½ *Dd*	½ *dd*

Test Cross Progeny: Homozygous Tall | Homozygous Dwarf

Or Test Cross ratio = 1:1

II) Di hybrid Test Cross

The test cross of heterozygous yellow round (*YyRr*) seeded pea plant with a double parent recessive parent (green wrinkled *yyrr*) yields a test cross genotypic ratio of 1 : 1 : 1 : 1 as follows.

P_1

Yellow, Round (Heterozygous) *YyRr* X Green, Wrinkled (Homozygous) *yyrr*

F_1

1*YyRr* : 1*Yyrr* (Or) : 1 *yyRr* : 1 *yyrr*

¼ Yellow round : ¼ yellow wrinkled : ¼ green round : ¼ green wrinkled