**MENDELIAN INHERITANCE IN MAN**

**What are the reasons for which study of human inheritance is not possible in man?**

**OR**

# State the reasons for which direct study of human inheritance in man is not possible in man.

Answer:

Some of the reasons which impede the study of human inheritance directly on man are:

i. The time span between the two generations is so lengthy that it is not possible to collect comprehensive and detailed data of several generations for understanding the mechanism of the inheritance.

ii. The size of the family is very small and for which to test the applicability of Mendelian laws is not possible.

iii. There are several traits in human beings which are controlled and influenced by more than one gene.

iv. Prolonged period of human growth and development.

v. Controlled breeding is not possible in man due to ethical reasons and cannot be made laboratory specimen.

**Is Mendelian inheritance in man is applicable to man? Discuss it with examples.**

Yes, Mendelian inheritance in man is applicable to man. The discovery of Mendel’s laws has made it possible to a great extent. The first demonstration of application of Mendel laws in man was made in 1903 by William Curtis Farabee (1865-1925). He studied the inheritance pattern of Brachydactyly in a family and found that the number of the family members with, and without brachydactyly followed the Mendelian pattern of inheritance. Since then onwards, several studies were carried out by scholars and they have proved that Mendel’s laws are fundamental and can be universally applicable to all forms of life, including man. In man, till now there are more than 5000 known human phenotypes that are inherited according to the Mendelian laws of inheritance

**What is a Mendelian trait?**

A Mendelian trait is one that is controlled by a single allele in an inheritance pattern. The inheritance of the trait is depends on the nature of the gene (dominant or recessive) and on the chromosome (autosomes and sex chromosomes) where it is located. In Mendel’s experiment, and heterozygous condition and the recessive gene (gene for dwarfness) express its trait only in homozygous condition.

**What is Autosomal Dominant trait? Discuss its pattern of inheritance with examples**.

Human chromosomes are of two types, autosomes and sex-chromosomes, and therefore the pattern of inheritance of the trait determined by the gene present in the autosomes will differ from the trait that is determine by the gene present in the sex-chromosome. The trait that is determined by the gene or allele present in the autosome is called Autosomal trait.

**Autosomal Dominant Inheritance**

The Autosomal inheritance refers to the mode of inheritance of a trait which occurs due to the presence of an affected gene in an autosome. Based on the nature of the genes, autosomal traits are again of two types, autosomal dominant and autosomal recessive trait. The autosomal dominant trait, as the name implies, is determined a single affected gene in the autosome of an individual and the mode of inheritance of the trait is called autosomal dominant inheritance. The various study carried out in man have shown that the autosomal dominant traits always follow the Mendelian pattern of inheritance. To understand better, let us consider a genetic situation where one of the parents (irrespective of sex) carries a single autosomal dominant gene *D* along with a normal gene *d* for a particular autosomal dominant trait. On the other hand, the genetic composition of the other parent is totally normal (dd). In this situation, it is observed that the dominant gene D is transmitted to the 50 percent of the offspring, while 50 percent of the offspring are totally normal. Thus, in dominant autosomal inheritance when one of the parents is affected (heterozygote), 50 percent of the children will inherit normal gene from their parents and will not show the trait. On the other hand, 50 percent of the children will inherit the defective gene from the parents and the trait will appear on them (Fig.41 A).

If we consider another situation, where the defective autosomal dominant gene D is present in both the parents, then also, it is observed that the trait is inherited according to the Mendelian laws of inheritance. In such a mating, one out of every four children (25%) does not carry the defective gene (dd). On the other hand, 2 out of every four children (50%) carries the gene in heterozygotic condition and one out of every four (25%) are homozygote for the gene (DD). Thus, in such combination, there is 25 percent chance that children will

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1. (B)

  **Fig.41: Dominant pattern of inheritance**

be normal (dd), 50 percent of the children will inherit one copy of normal and one copy of dominant gene and 25 percent of the children will inherit both copies of the affected gene from the parents (Fig.41 B). Again in some rare cases, when one of the parents is homozygote (DD) for the dominant gene, in such condition, all the offspring will have one dominant and one normal gene. Thus, autosomal dominant traits are inherited vertically from one generation to the next. It is also further noticed that half of the offspring of the affected parents bears the trait, while none of the offspring of the unaffected parents carries the trait. However, there are certain exceptions in which an affected offspring may not have affected parents. This is due to new mutation or a case of non-penetrance of the gene in the parents.

Some of the common Autosomal dominant genetic conditions in man which are inherited in Mendelian pattern are:

Huntington chorea: It is a genetic brain disorder that caused by an autosomal dominant gene. A person having this trait gradually looses the ability to think, talk and move.

Achondroplasia: It is a trait associated with dwarfism, caused either by sporadic mutation or by an autosomal dominant genetic disorder.

Polydactyly: This trait refers to the genetic condition in which the individual posses extra fingers and toes

What is **Autosomal Recessive Trait? Discuss its pattern of Inheritance (AR) with examples.**

**OR**

**What is Autosomal Recessive Inheritance? Discuss it with examples.**

Human chromosomes are of two types, autosomes and sex-chromosomes, and therefore the pattern of inheritance of the trait determined by the gene present in the autosomes will differ from the trait that is determine by the gene present in the sex-chromosome. The trait that is determined by an autosomal recessive gene is called autosomal recessive trait and their mode of inheritance is called Autosomal recessive inheritance.

Unlike autosomal dominant trait, which requires only one copy of gene to produce phenotype, in autosomal recessive inheritance, both copies of the gene are required to produce the phenotype. A person with only one mutated recessive gene cannot exhibits the trait because the normal copy of the gene is capable of producing enough normal protein to carry out the needed functions.

 

**Fig. 42: Mode of transmission of a recessive trait when both the parents are carrier**

 inheritance. The autosomal recessive trait may appear in any individuals despite their parents are normal. This is only possible when both the parents carry the defective gene in heterozygote condition. Let us consider a situation where both the normal parents (Dd) carry the defective gene‘d’. In the figure, it shows that the parents are normal, but they are carriers. The mode of inheritance shows that the possibility of having the trait in such a condition is according to the Mendelian ratio of 3/4 (75%) normal and 1/4th (25%) affected. The genotype DD and Dd represents the normal homozygous and heterozygous carrier, respectively. The Dd genotype carries the defective gene, but phenotypically they are normal. The genotype dd represents the affected recessive individual

It can be conclude that the both the parents of the affected offspring must have the defective gene, either it may be in homozygous or heterozygous conditions. This is because; both the parents must contribute one copy of the gene to get expressed among the offspring. As far estimates, till now there are 4000 known autosomal recessive diseases in man. Studies have found that many rare AR disorders are due to the result of a consanguineous mating. The rarer the recessive phenotype, the more likely the parents are to be consanguineous. Some AR traits are also called as "ethnic diseases" because the gene responsible for the trait is more prevalent in a particular ethnic group. Examples are *sickle cell disease* in African Americans, *Thalassaemia* in Mediterranean people, *Tay Sachs* and *Gaucher disease* in Ashkenasi Jews and *cystic fibrosis* in Northern Europeans. Some of the rare autosomal recessive traits found among human population groups are:

Sickle cell anaemia: Sickle cell anaemia is an autosomal recessive trait. The defective genes are produced due to a mutation present in the chromosome 11 that bears the code for beta subunit of haemoglobin.

Thalassaemia: It is a form of inherited autosomal recessive blood disorder characterised by abnormal formation of haemoglobin. Thalassaemia is caused by variant or missing gene that adversely influences the formation of normal haemoglobin.

**What is Sex-Linked Inheritance?**

In man, out of 23 pairs of autosomes, the last 23rd pair of chromosome is called sex chromosome and the gene present in this pair of chromosome is called Sex-linked gene and the trait determine by these genes are called Sex-linked trait. In females, both copies of the sex chromosomes are designated as X chromosome, while in male, one copy of chromosome is called X chromosome and the other copy is called Y chromosome. The genes present in the X and Y chromosome are called X- linked and Y- linked genes, respectively, and the trait produced by these genes are called *sex linked traits* and their mode of inheritance is called sex-linked inheritance.Again, genes present in the sex chromosomes may be dominant or recessive. Thus, on the basis of the genes present in the sex chromosomes (X and Y chromosomes) and their mode of inheritance, they can be categorised in following manner:

i. X- linked recessive inheritance

ii. X-linked dominant inheritance and

ii. Y-linked inheritance

### Discuss about X Linked Recessive Inheritance (XR)in man with examples.

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i. X- linked inheritance and

ii. Y-linked inheritance

 In this question, I will discussed about the X-linked inheritance. X-linked trait are of two types, namely X-linked recessive trait and X-linked dominant trait. Gene present in the X chromosome are different in both the sexes. In males there is only one X chromosome and for which there is only one copy of each of the genes, while the females have two copies of X chromosome and therefore two copies of genes are always present in a single locus. These two copies of gene may be in homozygous or in heterozygous conditions. Thus in females, X linked recessive genes are expressed only if there are two copies of gene (one on each X chromosome). For this reasons, women are rarely affected by X linked diseases. On the other hand, in males a single copy of gene in the X-chromosome is sufficient enough to exhibit the trait phenotypically because they do not have a normal copy of gene to compensate the influence of the gene present in the X chromosome. This condition of inheritance in male is called *hemizygous*. Women who carry one copy of the gene are called *carriers*. To understand better about the mode of inheritance of X-linked recessive trait, let us consider a marriage between an affected male and normal woman. In this case, all the sons from this marriage will be normal, because father will transmit the Y chromosome to the sons, whereas all the daughters will receive the defective X allele from the father and normal X allele from the mother. In such cases, all the daughters XX will be heterozygous carrier, but phenotypically normal . Let us assume a carrier women (XX) marries a normal man (XY). In this case, 50 percent of the sons will received the X chromosome with defective gene and will be affected, while 50 percent will be normal. Daughters have also the same 50 percent chance of inheriting the mutant gene, but they will get a normal X chromosome from the father for which they will be carrier, but phenotypically normal. Thus, the above pattern of inheritance demonstrated a 'criss-cross' pattern, where an affected male has an unaffected daughter, who in turn has an affected son. The trait skips a generation. In another typical mating, when an affected male (XY) marries a carrier women (XX), 50 percent of the daughters will be affected (XX), while 50 percent will be normal but carriers XX. On the other hand, 50 percent of the sons will have the probability of being totally normal (XY), and 50 percent of them will have the chance of being affected XY.



 A B

Fig.43: Mode of the transmission of the trait (A) when an affected male marries a normal women (B) when a carrier woman marries a normal man

Examples of X-linked recessive traits

Haemophilia

An example of human trait with an X linked pattern of inheritance is Haemophilia. It is a genetically X linked inherited genetic disorder where the blood cannot clot properly due to a deficiency of a clotting factor called Factor VIII.

Red-green color blindness: Red-green color blindness is another best example of recessive X linked inheritance in man. Individuas suffering from this trait simply cannot distinguish shades of red and green (usually blue-green).

**Discuss about X-linked Dominant Inheritance**

Like X linked recessive gene, X linked dominant genes are also located in the X chromosome of both male and female, but they are dominant in nature. A single copy of allele present in the X chromosome is sufficient enough to cause the disorder. Males are always hemizygous for X- linked traits and a single mutant allele is sufficient to produce a mutant phenotype in the male, irrespective of the fact that the gene is dominant or recessive. Unlike the X - linked recessive trait which affects more males than the females, X-linked dominant traits do not necessarily affect males more than females. The exact pattern of inheritance varies, depending on whether the father or the mother has the trait. For better understanding the inheritance pattern of X-linked dominant gene, let us consider a marriage between an affected male with a normal female (Fig 44 A). The defective X-linked gene is represented by X, while the normal gene is represented by ‘X’. The affected male will be designated by XY and the normal female is represented by XX. This means that one copy of the gene is working (X) and producing the correct gene product however the other copy (X) is not working. In this particular case, all the daughters will inherit the mutant gene from the father and all will be affected, but none of his sons will be affected. This is because father always contributes one X chromosome to the daughters and Y chromosome to the sons. Males will only receive an X chromosome from their mother while females get an X chromosome from both parents. As a result females result from this type of marriage tends to show higher prevalence of X-linked disorders than the males.



 (A) (B) (C)

Fig.44: Pattern of X-linked dominant inheritance showing marriage between (A) An affected male with normal female. (B) An affected female with normal male (C) An affected male with affected female.

(The defective X-linked gene is represented by ‘X’, the normal gene by ‘X’)

In another typical mating, when an affected women marries a normal males, there is the probability of inheritance of the defective gene by the 50 percent of the sons and daughters, whereas, 50 percent of the offspring will be normal. The affected female will be designated by XX and the normal male is represented by XY. This means that one copy of the gene is working (X) and producing the correct gene product however the other copy (X) is not working. The half of the sons and half of the daughters which bear the defective gene will exhibit the trait (Fig.44 B)

Again when both the parents are affected by an X-linked dominant gene, half of the daughters will receive two copies of the X chromosome and half of them will receive a single copy. However, though all the daughters will inherit the trait, but those where genes are in homozygous conditions, trait will appear in severe form. However, it is very rare for a woman to have a dominant gene mutation on both copies of her X chromosome. On the other hand, half of the sons will be normal and half of them will be affected.

Some X-linked dominant conditions are:

Rett syndrome (RTT), originally termed Cerebroatrophic Hyperammonemia, is a rare genetic postnatal neurological disorder of the grey matter of the brainthat almost exclusively affects females but has also been found in male patients.

X-linked hypophosphatemia (XLH) is an X-linked dominant form of rickets that differs from most cases of rickets. It can cause bone deformity including short stature and bowed legs.

**Write short notes about**

1. **Y- Linked inheritance or Holandric inheritance**
2. **Sex-limited trait**
3. **Sex-controlled or Sex influenced trait.**

**Y-linked inheritance**

**It** is also known as holandric inheritance that refers to a condition where the expression of a phenotypic trait is determined by an allele (or gene) present on the Y chromosome. Since Y chromosome is found only in male, Y-linked traits are passed only from father to son or any mutations in the Y chromosome would result in all sons of an affected male and none to his daughters. Since Y chromosome is smaller compared to the X-chromosomes, the number of genes present in the chromosome is also less and therefore Y- linked diseases are also rare. Till now only 20 abnormal traits have been found to be caused by the Y-linked genes, whereas more than 250 abnormal traits have been coded for the X chromosome. The concept of dominant and recessive is not applicable to the Y-linked traits or genes, because a single allele is present in the Y-chromosome. This condition is called as hemizygous.

Some of the traits caused by the gene present in the Y chromosome are:

1. Azoospermia (Sertoli cell-only syndrome): It is a genetical Y-linked trait in which the individuals failed to produce sperm. This trait is due to deletion of azoospernia factor (azf) in USpqy gene in the Y chromosome..
2. Absent testicular Development (ATD): This trait is occurred when sex determining region of the Y-chromosome is deleted. An individual with ATD suffers from a wide range of defect in the testicular development often resulting in ambiguous genitalia formation of gonads.

In many textbooks, Hypertrichosis Pinnae or Hairy Pinna and Retinisa pigmentosa have been referred as Y-linked trait. But, now it is clear that these two traits are not Y-linked.

**Sex Limited Traits in Man**

Unlike sex-linked genes which is found in the sex chromosomes, the genes responsible for sex-limited and sex controlled traits are found in the autosomes. These sex limited genes are present in both male and female, but expressed in only one sex. The difference comes only in the expression of the genes in the phenotype of the individuals. Their expression is determined by the presence or absence of one of the sex hormones and, thereof, these genes are expressed in only one sex. They used to appear in both the sexes equally, but later modified (repressed or promoted) in one sex only by modifier or regulatory elements. Sex limited genes have 100 percent penetrance in one sex and also zero penetrance in the opposite sex. These sex limited genes generally control the expression of the primary and the secondary sexual characteristics. One of the best examples is the production of milk by a lactating mother when she gave birth to a baby. There are genes which influence the production of milk in a lactating mother. These genes are carried by both males and females, but only females ever express them. The beard development, the deep voice and the strong musculature in males are the sex limited traits, while breast development, feminine voice and comparatively weak musculature are sex limited traits found in females. Any abnormalities in the secretion of the hormone may result in the beard development in female or breast enlargement in male.

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**Sex Controlled or Sex Influenced Trait**

Sex controlled traits (also called as sex influenced traits) are the autosomal trait determined by the genes present in the autosomes and their mode of inheritance is in accordance to Mendelian laws of inheritance. The basic differences of sex controlled trait with that of sex limited trait is that it is expressed in both the sexes, but more common in one sex, while sex limited trait is restricted to one sex only. In general, it is found that the sex controlled gene is dominant in one sex and the same gene is recessive in opposite sex. One classic example of a sex influenced trait is pattern baldness in humans (sometimes called “male pattern baldness,” though the condition isn’t restricted to males). This is a form of baldness where hair loss spreads out from the crown of the head, and is controlled by a single gene with two alleles ‘B’ and ‘b’. In male the B allele is dominant and thus heterozygotes Bb are also bald, but in females, it is recessive and therefore it is not common. The behaviors of the products of these genes are highly influenced by the hormones in the individual, particularly by the hormone testosterone. In the presence of high levels of testosterone, the baldness allele has a very powerful influence. In the presence of low levels of testosterone, this allele is quite ineffectual in female. All humans have testosterone, but males have much higher levels of this hormone than females do. Another example of sex controlled trait in human is the short length of index finger. This short fingerdness of index finger is due to the presence of a gene, which is dominant in male but recessive in female.