6 Pedigree Analysis and Applications

*1. Joe is colorblind. His mother and father both have normal vision, but his mother's father (Joe's maternal grandfather) is colorblind. All of Joe's other grandparents have normal color vision. Joe has three sisters—Patty, Betsy, and Lora—all with normal color vision. Joe's oldest sister Patty is married to a man with normal color vision; they have two children, a 9-year-old colorblind boy and a 4-year-old girl with normal color vision.

a. Using correct symbols and labels, draw a pedigree of Joe's family.

b. What is the most likely mode of inheritance for colorblindness in Joe's family?

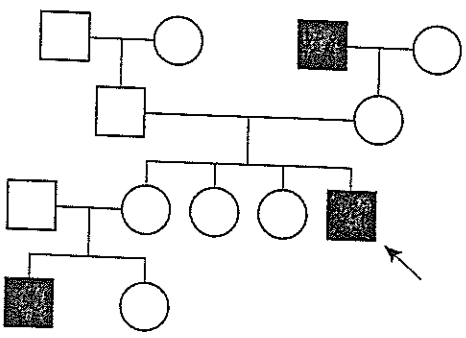
c. If Joe marries a woman who has no family history of colorblindness, what is the probability that their first child will be a colorblind boy?

d. If Joe marries a woman who is a carrier for the colorblind allele, what is the probability that their first child will be a colorblind boy?

e. If Patty and her husband have another child, what is the probability that it will be a colorblind boy?

Answer

a.



b. X-linked recessive is the most likely mode of inheritance for colorblindness in Joe's family for the following reasons: The trait appears only in males; the colorblind males do not produce colorblind offspring; and the trait appears to be passed through females who do not express it (and are therefore carriers).

c. If Joe marries a woman who has no family history of colorblindness, there is no chance that the first born would be colorblind (unless a new mutation occurs). Male offspring would receive a Y chromosome from their father and their X chromosome from their mother. The Y chromosome does not carry the gene. Therefore, as long as the mother's family has no history of colorblindness, the X chromosome of the son would not carry the colorblind allele.

d. Joe is hemizygous for the colorblind allele and the woman he marries is heterozygous, so the cross is as follows.

$X^cY \times X^+X^c$

↓

$^1/_4$ X^+X^c	normal female
$^1/_4$ X^+Y	normal male
$^1/_4$ X^cX^c	colorblind female
$^1/_4$ X^cY	colorblind male

The probability that their first child will be a colorblind boy is $^1/_4$.

e. Patti must be a carrier (X^+X^c), as she and her husband already have one child with colorblindness. Her husband is unaffected (X^+Y), so the cross is as follows.

$X^+X^c \times X^+Y$

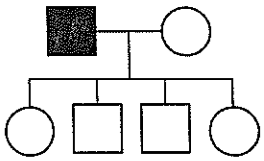
↓

$^1/_4$ X^+X^+	normal female
$^1/_4$ X^+X^c	normal female
$^1/_4$ X^+Y	normal male
$^1/_4$ X^cY	colorblind male

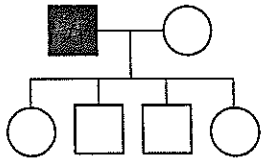
The probability that their child will be a colorblind boy is $^1/_4$.

**2. A man with a specific unusual genetic trait marries an unaffected woman and they have four children. Pedigrees of this family are shown below, but the presence or absence of the trait in the children has not been indicated. For each type of inheritance, indicate how many children of each sex are expected to express the trait by coloring in the appropriate circles and squares. Assume that the trait is rare and fully penetrant.

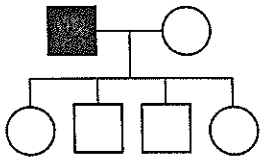
a. Autosomal recessive trait



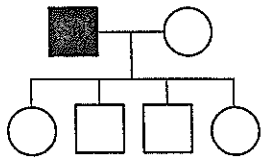
b. Autosomal dominant trait



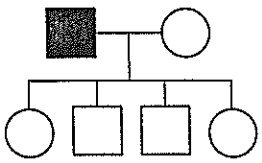
c. X-linked recessive trait



d. X-linked dominant trait

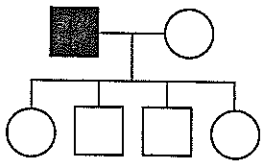


e. Y-linked trait



Answer

a. Autosomal recessive trait



The affected male parent must have genotype *aa*. If the trait is rare, then the female parent is most likely genotype A^+A^+, so the cross is:

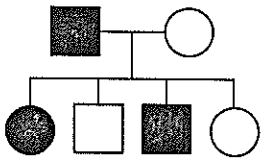
$$aa \quad \times \quad A^+A^+$$

$$\downarrow$$

all A^+a (unaffected).

All the offspring carry the gene (are heterozygous), but are phenotypically unaffected.

b. Autosomal dominant trait



If the trait is rare, the affected male parent is most likely heterozygous (Aa^+); the unaffected parent must be homozygous for the recessive (normal) allele (a^+a^+).

$$Aa^+ \quad \times \quad a^+a^+$$

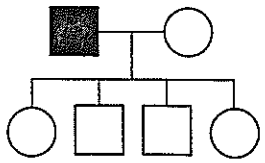
$$\downarrow$$

$^1/_2$ Aa^+ (affected)

$^1/_2$ a^+a^+ (unaffected)

Thus, one-half of the offspring, both males and females, should be affected.

c. X-linked recessive trait



The affected male parent must be hemizygous for the trait (X^aY). As the trait is rare, the female parent is most likely homozygous for the normal allele (X^+X^+), so the cross is:

$X^aY \quad \times \quad X^+X^+$

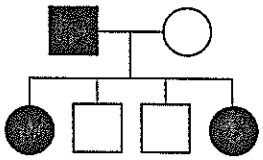
$\downarrow$

$^1/_2\ X^+X^a$ (unaffected female)

$^1/_2\ X^+Y$ (unaffected male)

All of the offspring will be phenotypically unaffected, although all females will be carriers of the trait.

d. X-linked dominant trait



The affected male parent is hemizygous for the trait (X^AY) and the female must be homozygous for the recessive normal allele (X^+X^+), so the cross is:

$X^AY \quad \times \quad X^+X^+$

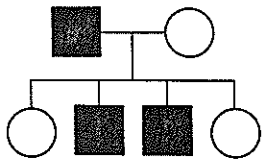
$\downarrow$

$^1/_2\ X^AX^+$ (affected female)

$^1/_2\ X^+Y$ (unaffected male)

Thus, all sons will be unaffected and all females will be affected.

e. Y-linked trait



The affected male parent carries the gene for the trait on his Y chromosome (genotype XY^a). The female has no Y chromosome and therefore does not carry a gene for the trait.

$XY^a \quad \times \quad XX$

$\downarrow$

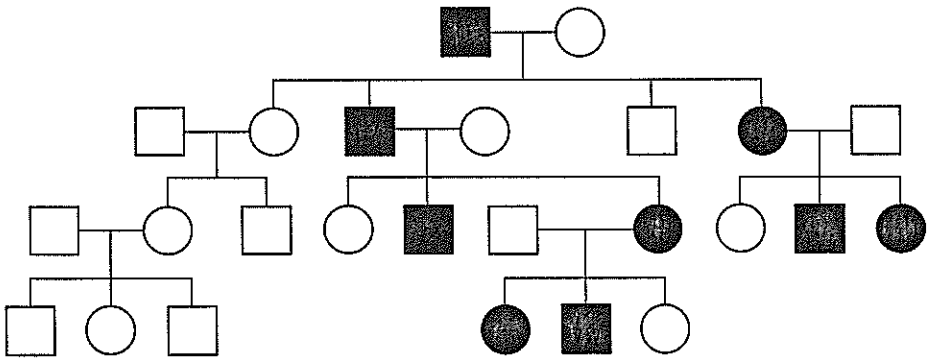
$^1/_2\ XX$ (unaffected female)

$^1/_2\ XY^a$ (affected male)

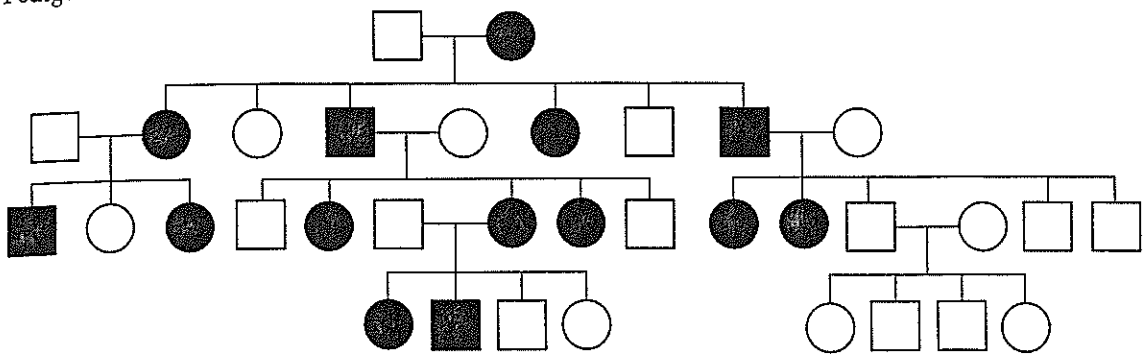
No daughters will be affected but all sons will be affected.

*3. For each of the pedigrees (*a*, *b*, *c*, *d*, *e*) shown below, give the most likely mode of inheritance assuming that the trait is rare. Carefully explain your reasoning.

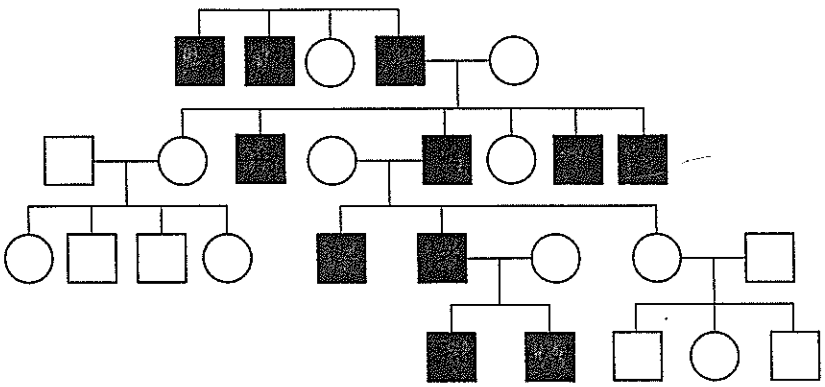
Pedigree *a*



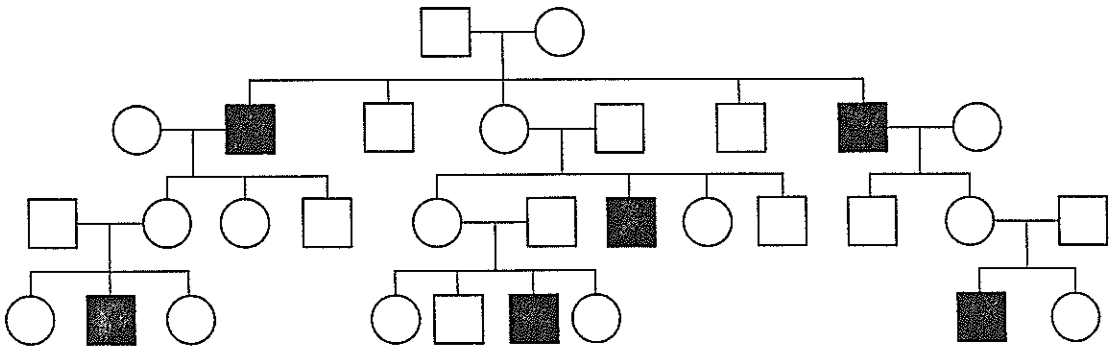
Pedigree *b*



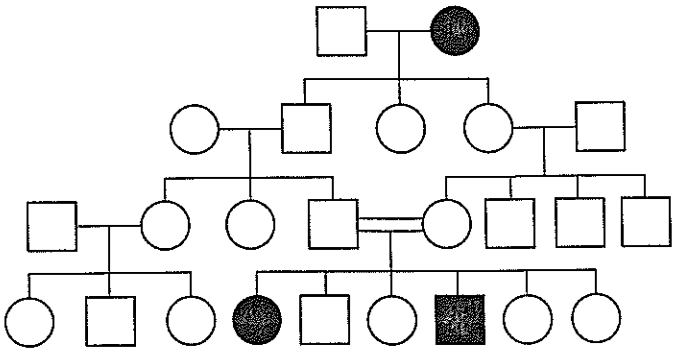
Pedigree *c*



Pedigree *d*



Pedigree *e*



Answer

a. Males and females are affected in equal numbers, suggesting an autosomal gene determines the trait. If one parent is affected, on the average $^1/_2$ of the offspring are affected. In addition, all affected children have at least one affected parent. These findings would indicate that the trait is inherited as an autosomal dominant trait.

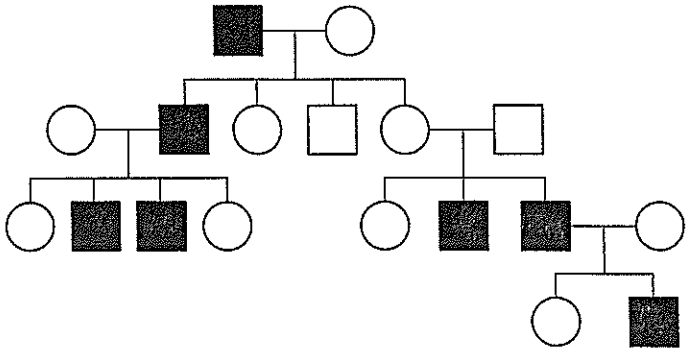
b. If the mother is affected, the male and female offspring are affected in equal numbers. All affected children have at least one affected parent. When the father is affected, all the daughters are affected, but none of the sons are affected. These findings would indicate that the trait is inherited as an X-linked dominant trait.

c. This pedigree shows that the trait affects only males and, if the father is affected, all of the male offspring express the trait. This would indicate the inheritance of a Y-linked trait.

d. This trait affects only males in this pedigree. However, there is no male-to-male transmission, ruling out Y-linked inheritance and suggesting X-linked inheritance. Affected males typically have unaffected parents, suggesting a recessive inheritance pattern. These findings are consistent with an X-linked recessive trait.

e. Both sexes appear to be affected in equal numbers, suggesting an autosomal trait, although the number of affected individuals is small. Affected children have unaffected parents, suggesting recessive inheritance. The example of a first cousin marriage (III-IV and III-V) would increase the homozygosity of the genomes of the offspring. This pattern of inheritance is consistent with an autosomal recessive trait.

*4. The trait shown in the pedigree below is expressed only in the males of the family. Is the trait Y-linked? Why or why not? If you believe the trait is not Y-linked, propose an alternate explanation for its inheritance.



Answer

The trait is probably not Y-linked. Y-linked traits should be passed directly from father to son, and they should not skip a generation. In this pedigree, only 50% of the sons of I-1 are affected. Also, the daughters of I-1 are unaffected, yet one daughter married to an unaffected male produces two affected sons. It could be a Y-linked trait with incomplete penetrance. It could also be an autosomal dominant trait that is sex-limited (expressed only in males) or is dominant in males and recessive in females.

**5. A geneticist studies a series of characteristics in monozygotic twins and dizygotic twins, obtaining the concordances shown below. For each characteristic, indicate whether the rates of concordance suggest genetic influences, environmental influences, or both. Explain your reasoning.

Characteristic	*Monozygotic concordance (%)*	*Dizygotic concordance (%)*
Migraine headaches	60	30
Eye color	100	40
Measles	90	90
Clubfoot	30	10
Blood pressure	70	40
Handedness	70	70
Tuberculosis	5	5

Answer

For migraine headaches, the concordance for monozygotic twins is twice that for dizygotic twins. This suggests a genetic influence. The monozygotic concordance of 60% suggests that environment also plays a role in the development of migraines.

For eye color, the monozygotic concordance is 100%, more than twice that of the dizygotic concordance. This suggests a genetic influence. Because the concordance of monozygotic twins is 100% and that of dizygotic twins is about 50%, there is no evidence of environmental influence.

For measles, the concordance values for monozygotic and dizygotic twins are identical. This suggests an environmental influence.

For clubfoot, the monozygotic concordance is 30%, which would seem to indicate that there is more than just a genetic component. The dizygotic concordance is 10%. This would suggest that genetics plays some role in the development of a clubfoot, but environmental influences also contribute.

For blood pressure, the monozygotic concordance is 70%, which is almost twice that of the dizygotic concordance. This indicates a strong genetic influence. As the monozygotic concordance is less than 100%, environmental influence is also suggested.

For handedness, the concordance values for monozygotic and dizygotic twins are identical. This suggests that only environmental factors influence variation in the trait.

For tuberculosis, the concordance values for monozygotic and dizygotic twins are identical. This suggests an environmental influence.

*6. In a study of schizophrenia (a mental disorder involving disorganization of thought and withdrawal from reality), Kety et al. (1978) looked at the prevalence of the disorder in the biological and adoptive parents of individuals who were adopted as children. They found the following results.

		Prevalence of schizophrenia (%)	
		Biological parents	*Adoptive parents*
Adopted persons	With schizophrenia	12	1
	Without schizophrenia	6	4

From Kety, S. S., et al. 1978. The biological and adoptive families of adopted individuals who become schizophrenic: Prevalence of mental illness and other characteristics. In L. C. Wynne, R. L. Cromwell, and S. Matthysse (eds.), *The Nature of Schizophrenia: New Approaches to Research and Treatment* (pp. 25–37). New York: Wiley.

What conclusions can you make from these results concerning the role of genetics in schizophrenia? Explain your reasoning.

Answer

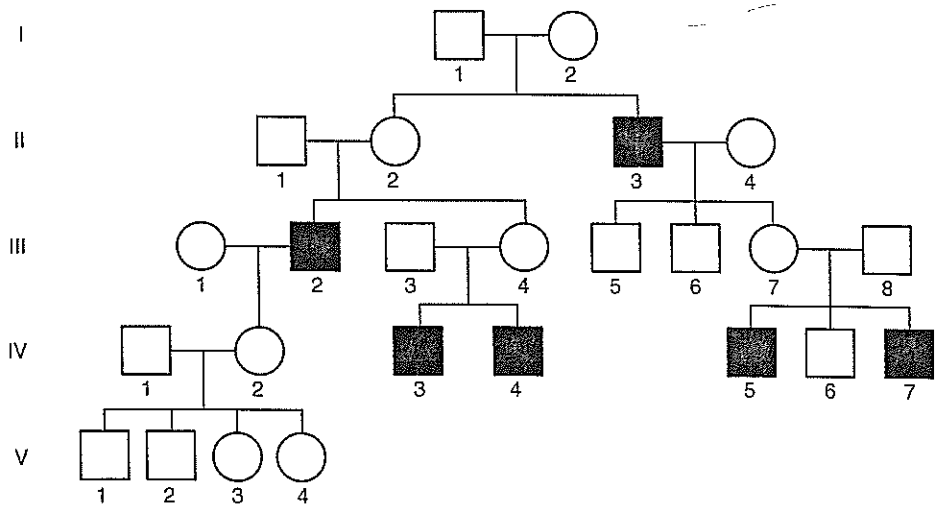
Schizophrenia is most likely to occur in offspring whose biological parents had schizophrenia. This suggests that there is a strong genetic component in the predisposition to schizophrenia. However, only 12% of the biological parents of a person with schizophrenia have schizophrenia, so environment must also play an important role.

**7. The pedigree below illustrates the inheritance of Nance-Horan Syndrome, a rare genetic condition in which affected individuals have cataracts and abnormally shaped teeth.

a. On the basis of this pedigree, what do you think is the most likely mode of inheritance for Nance-Horan Syndrome?

b. If couple III-7 and III-8 have another child, what is the probability that the child will have Nance-Horan Syndrome?

c. If III-2 and III-7 mated, what is the probability that one of their children would have Nance-Horan Syndrome?



Pedigree adapted from Stambolian, D., Lewis, R. A., Buetow, K., Bond, A., and Nussbaum, R. 1990. Nance-Horan syndrome: Localization within the region Xp21.1–Xp22.3 by linkage analysis. *American Journal of Human Genetics* 47:13–19.

Answer

a. X-linked recessive is the most likely mode of inheritance for this trait. The observation that only males are affected might suggest Y-linked inheritance, but this can be eliminated because not all sons of affected males express the trait (III-5, 6). Although the trait appears only in males, it seems to be passed through an unaffected female. This suggests X-linked recessive inheritance.

b. Individual III-7 must be a carrier of the recessive X-linked allele that causes Nance-Horan Syndrome (X^+X^h) because she has two affected sons. III-8 must have the normal allele on his X chromosome (X^+Y) because he is unaffected. The cross between III-7 and III-8 is:

$X^+X^h \times X^+Y$

↓

$^1/_4$ X^+X^+ unaffected female
$^1/_4$ X^+Y unaffected male
$^1/_4$ X^+X^h unaffected female
$^1/_4$ X^hY male with Nance-Horan Syndrome

So the probability is $^1/_4$.

c. III-2 is an affected male (X^hY), and III-7 is a heterozygous female (X^+X^h) because she has two affected sons. The outcome of this cross is:

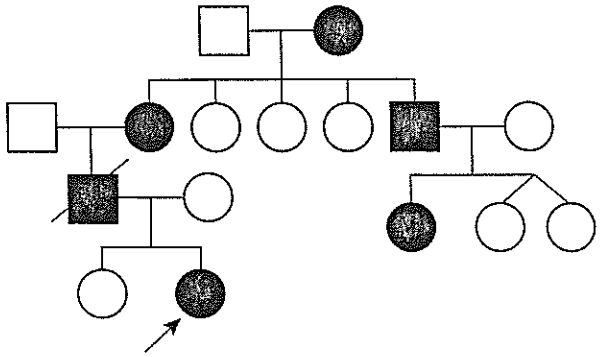
$X^hY \times X^+X^h$

↓

$^1/_4$ X^+X^h unaffected female
$^1/_4$ $X^h X^h$ female with Nance-Horan Syndrome
$^1/_4$ X^+Y unaffected male
$^1/_4$ X^hY male with Nance-Horan Syndrome

The probability that they would have an affected offspring is $^1/_2$.

*8. The following pedigree illustrates the inheritance of ringed hair, a condition in which each hair is differentiated into light and dark zones. What mode(s) of inheritance are possible for the ringed-hair trait in this family?

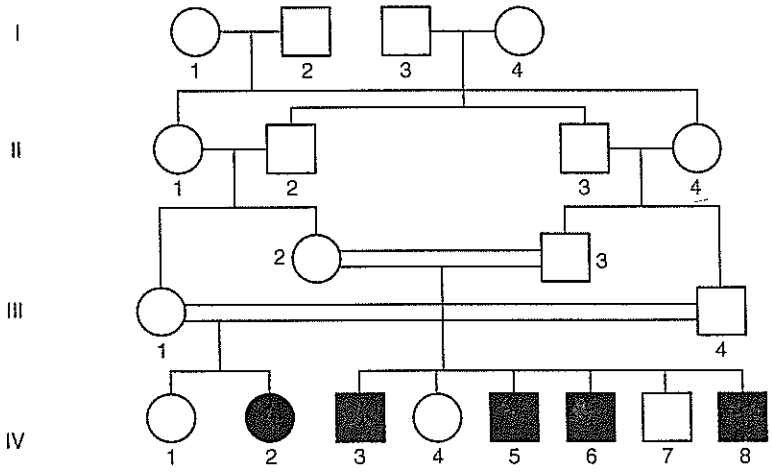


Pedigree adapted from Ashley, L. M. and Jacques, R. S. 1950. *Journal of Heredity* 41:82–84.

Answer

The ringed-hair trait appears to affect males and females in approximately equal numbers. This would suggest an autosomal trait. When one parent is affected, approximately 50% of the offspring are affected. This points to a dominant trait. No generations are "skipped." Ringed hair is most likely an autosomal dominant trait.

*9. Ectodactyly is a rare condition in which the fingers are absent and the hand is split. This condition is usually inherited as an autosomal dominant trait. Ademar Freire-Maia reported ectodactyly occurring in the family from Sao Paulo, Brazil, whose pedigree is shown below. Is this pedigree consistent with autosomal dominant inheritance? If not, what mode of inheritance is most likely? Explain your reasoning.



Pedigree from Freire-Maia, A. 1971. *Journal of Heredity* 62:53.

Answer

This pedigree is not consistent with autosomal dominant inheritance. Unaffected parents produce affected offspring. Males and females are affected with the trait. Affected children result from matings between related individuals. These findings are consistent with an autosomal recessive trait.

***10. Androgen insensitivity syndrome is a rare disorder of sexual development in which individuals with an XY karyotype, genetically male, develop external female features. All individuals with androgen insensitivity syndrome are infertile. In the past, some researchers proposed that androgen insensitivity syndrome is inherited as a sex-limited, autosomal dominant trait. (It is sex-limited because females cannot express the trait.) Other investigators suggested that this disorder is inherited as an X-linked recessive trait.

Draw a pedigree that would show conclusively that androgen insensitivity syndrome is inherited as a sex-limited, X-linked recessive trait, and that excludes the possibility that it is sex-limited, autosomal dominant. If you believe that no pedigree can conclusively differentiate between the two choices (X-linked recessive and sex-limited, autosomal dominant), explain why. Remember that all affected individuals are infertile.

Answer

It is not possible to conclusively differentiate between an X-linked recessive trait and a sex-limited autosomal dominant trait when the affected male is sterile.

First, assume that the trait is X-linked recessive. If males with the trait (X^iY) are sterile, then it is impossible to produce a female that is homozygous for the trait (X^iX^i), because she would have to inherit one of the X^i alleles from her father. So the only crosses possible are (1) between an unaffected male (X^+Y) and a female homozygous for the normal allele (X^+X^+); and (2) between an unaffected male and a heterozygous female (X^+X^i). The first cross does not involve any alleles for androgen insensitivity syndrome and is therefore uninformative. The second cross produces:

$X^+Y \times X^+X^i$

↓

$^1/_4$ X^+X^+	unaffected female
$^1/_2$ X^+X^i	unaffected female
$^1/_4$ X^+Y	unaffected male
$^1/_4$ X^iY	male with androgen insensitivity syndrome

The result is that all the female offspring are normal and $^1/_2$ of the male offspring have androgen insensitivity syndrome.

Now assume that the trait is sex-limited autosomal recessive. It is again impossible to have a homozygous female, because this would require that her father have the trait, which means that he would be sterile. So the only informative cross is between an unaffected male and a heterozygous female:

$A^+A^+ \times A^+A^i$

↓

$^1/_2$ A^+A^+	males and females unaffected
$^1/_2$ A^+A^i	females unaffected (because expression is limited to males) males have androgen insensitivity syndrome

Again, the result is that all female progeny would be unaffected and $^1/_2$ of the male progeny would have androgen insensitivity syndrome. The results are the same regardless of whether the mode of inheritance is X-linked recessive or sex-limited autosomal dominant.