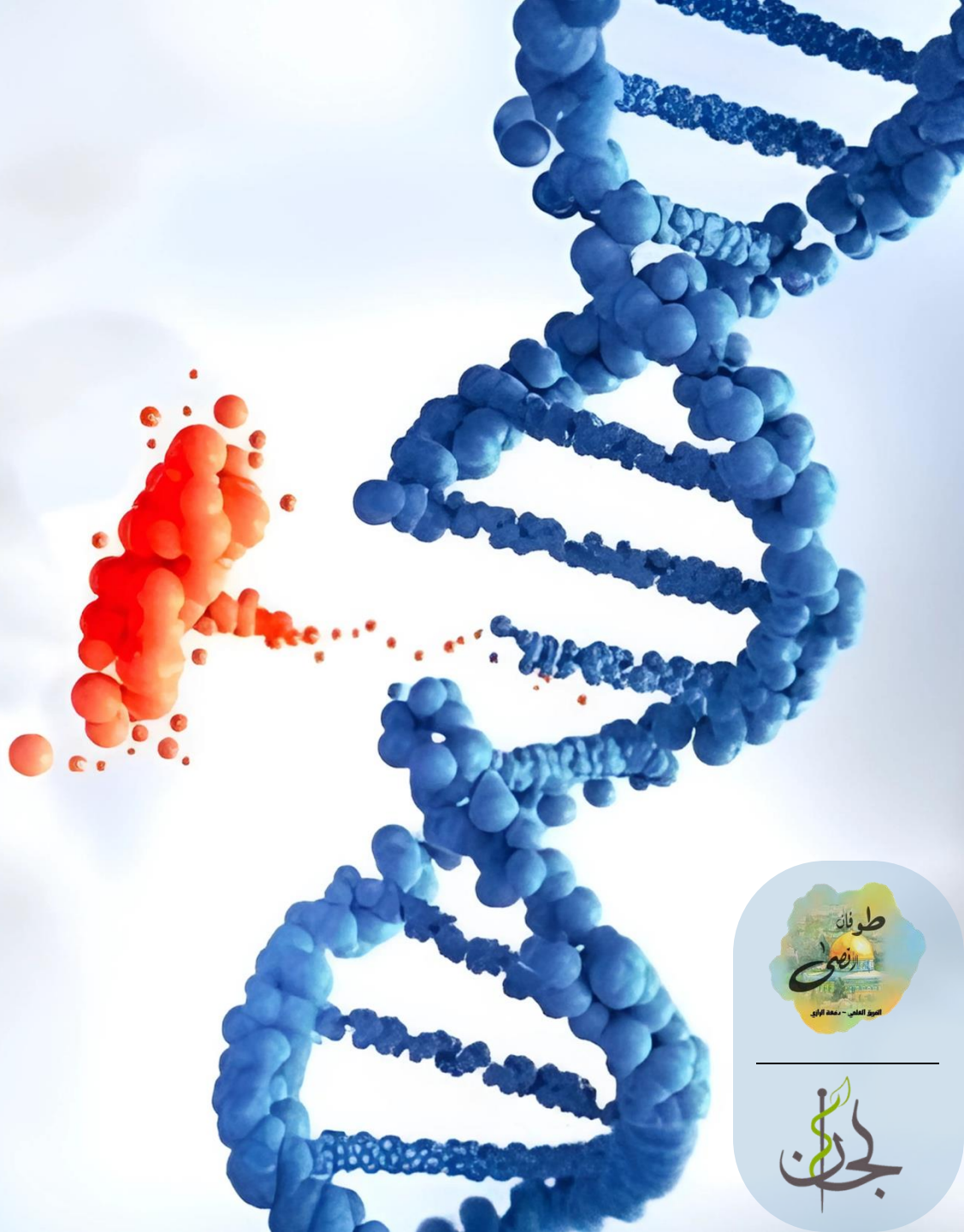
Genetics

Modified no.

Writer: Afnan Abu-Swelem
& Abdulla Al-Khawaldeh
Editor: Mais Mustafa

Doctor: Zaid Abu Rbeiha



Color code

- Slides
- Doctor
- Additional info
- Important

AUTOSOMAL DOMINANT INHERITANCE

Characteristics of Autosomal Dominant Inheritance

- Currently, there are more than 4,400 known autosomal dominant traits, most of which are rare diseases.
- Each autosomal dominant disease is rather rare in populations, however, with the most common ones having gene frequencies of about 0.001.

(One allele is enough to cause autosomal dominant disease.)

- Matings between two individuals both affected by the same autosomal dominant disease are thus uncommon. Most often, affected offspring are produced by the union of a normal parent with an affected heterozygote.

- The affected parent can pass either a disease gene or a normal gene to his or her children. Each event has a probability of 0.5. Thus, on the average, half of the children will he heterozygotes and will express the disease, while half will be normal homozygotes.

Pannett square illustrating the mating of unaffected individual (aa) with an individual who is heterozygous for an autosomal dominant disease gene (Aa). The genotype of affected offspring are shaded, 50%.
While the unshaded squares show unaffected ones 50%.

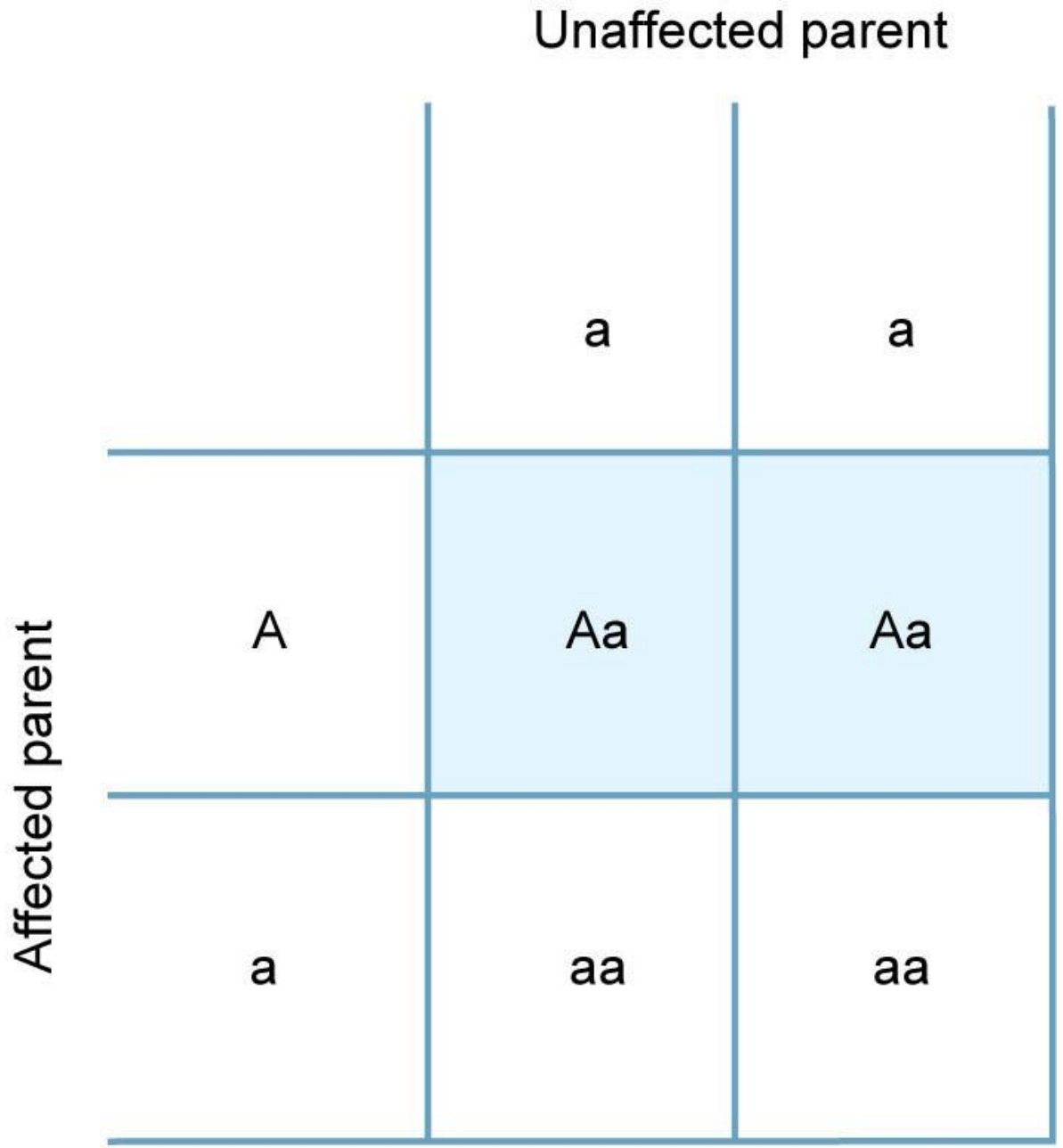


Fig. 4-2. Punnett square illustrating the mating of an unaffected individual (*aa*) with an individual who is heterozygous for an autosomal dominant disease gene (*Aa*). The genotypes of affected offspring are shaded.

- Postaxial polydactyly, the presence of an extra digit next to the fifth digit, can be inherited as an autosomal dominant trait.

(postaxial polydactyly) is an example of autosomal dominant diseases, where patients have 6 or 7 digits.

- Let A symbolize the gene for polydactyly, and let a symbolize the normal allele. The pedigree illustrates several important characteristics of autosomal dominant inheritance.

→ First, the two sexes exhibit the trait in approximately equal proportions and males and females are equally likely to transmit the trait to their offspring. This reflects the fact that this is an autosomal disease (as opposed to a disease caused Y and X chromosome mutation, in which these proportions typically differ).

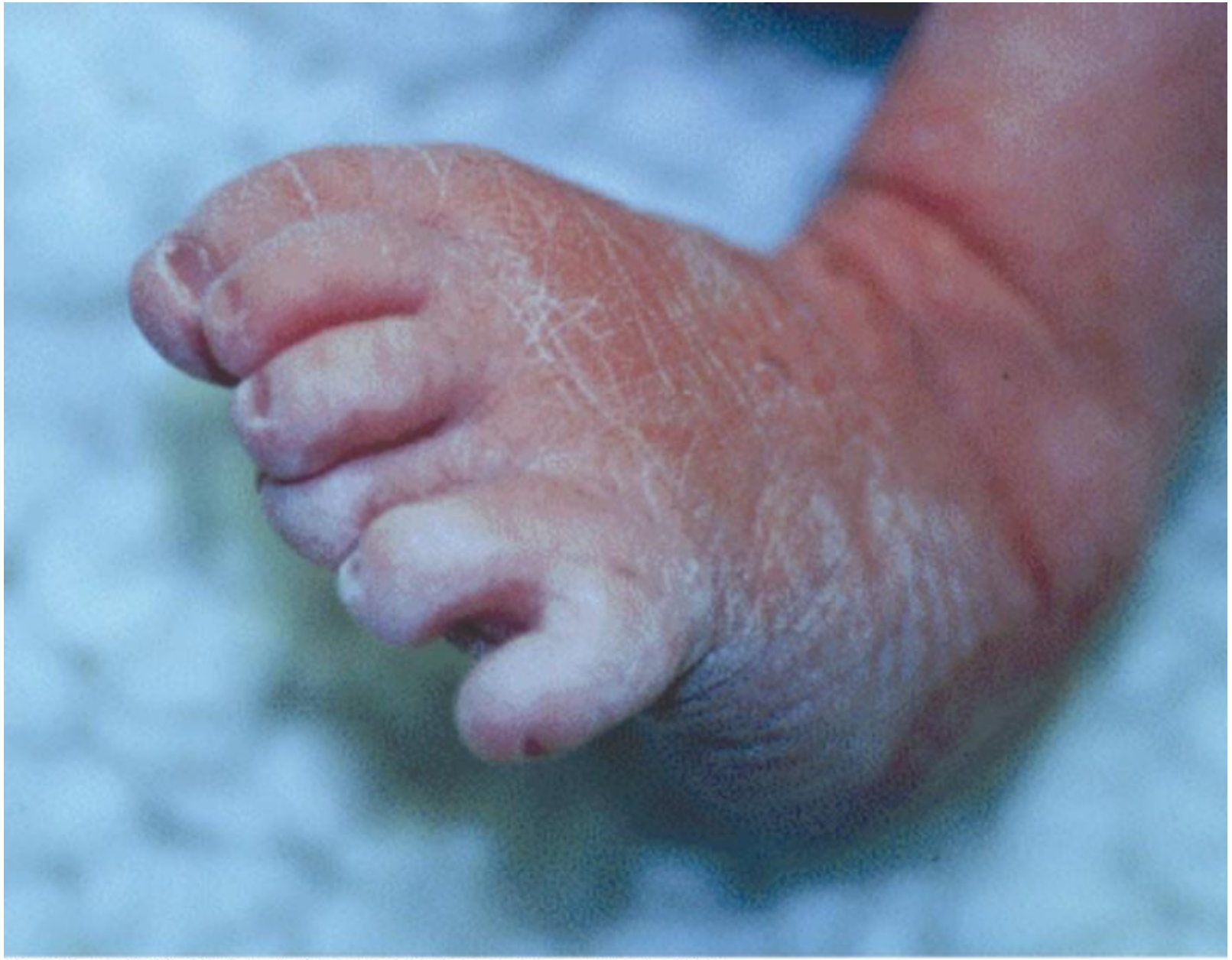


Fig. 4-3. Postaxial polydactyly. An extra digit is located next to the fifth digit.

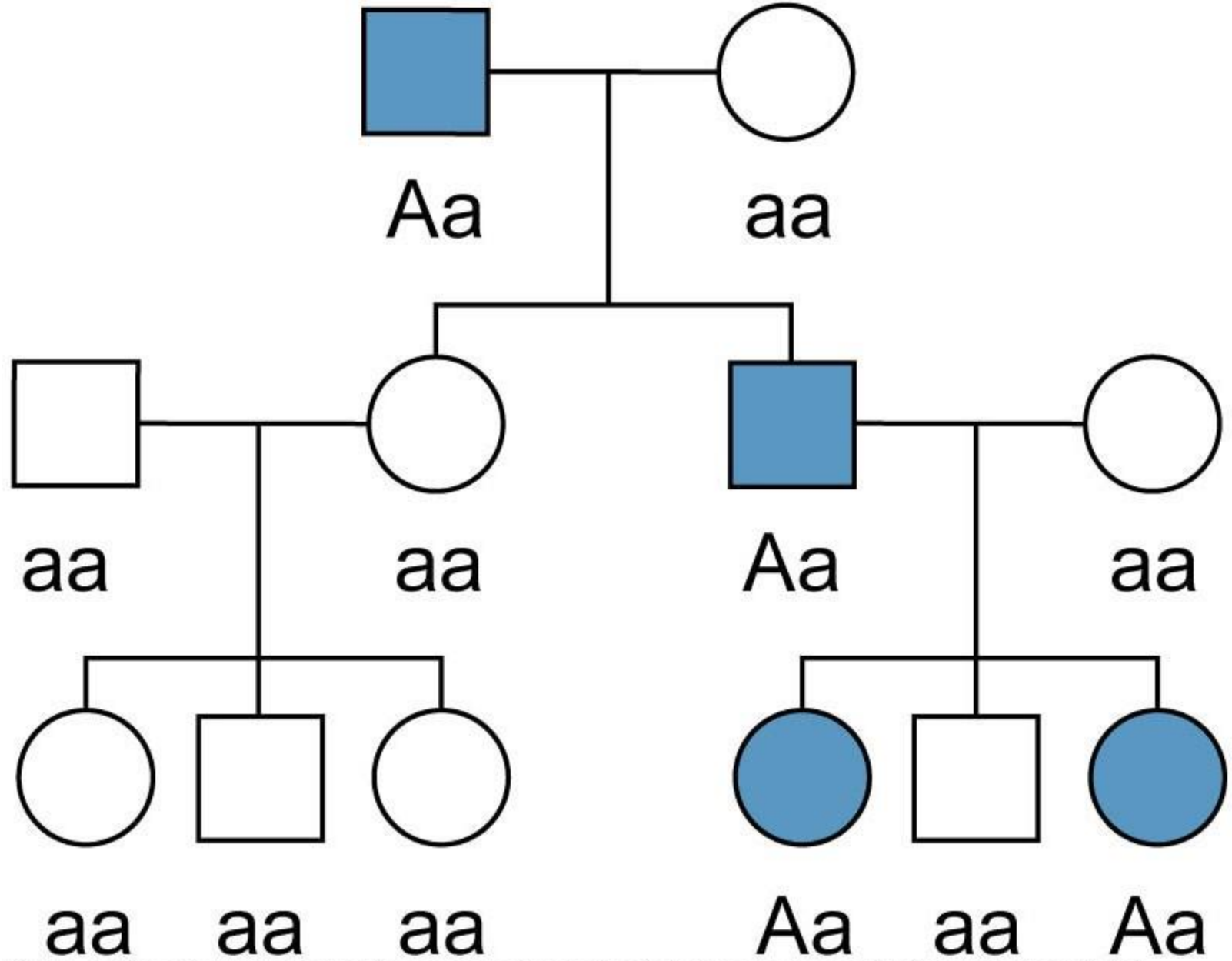


Fig. 4-4. Pedigree illustrating the inheritance pattern of postaxial polydactyly, an autosomal dominant disorder. Affected individuals are represented by shading.

→ Second, there is no skipping of generations: if an individual has polydactyly, one parent must also have it. This leads to a vertical transmission pattern, in which the disease phenotype is usually seen in one generation after another. Also, if neither parent has the trait, none of the children have it.

→ Third, father-son transmission of the disease gene is observed. Although father-son transmission is not required to establish autosomal dominant inheritance, its presence in a pedigree excludes certain other modes of inhentance (particularly X-linked inheritance).

→ Finally, an affected heterozygote transmits the trait to approximately half of his or her children. However, since gamete transmission, like coin tossing, is subject to chance fluctuations, it is possible that all or none of the children of an affected parent will have the trait.

Homozygous autosomal dominant conditions are very rare and result in a severe form of the disease. Consequently, individuals with such conditions often face health challenges, which can impact their ability to live a normal life and pursue activities such as marriage.

Recurrence Risks

- Parents at risk for producing children with a genetic disease are often concerned with the question: What is the chance that our future children will have this disease?

- When one or more children have already been born with a genetic disease, the parents are given a recurrence risk. This is the probability that subsequent children will also have the disease.
- If the parents have not yet had children, but are known to be at risk for having children with a genetic disease, an occurrence risk can be given.

- When one parent is affected by an autosomal dominant disease (heterozygote) and the other is normal, the occurrence and recurrence risks for each child are 1/2. It is important to keep in mind that each birth is an independent event, as in the coin-tossing examples.

- Thus, even though parents may have already had a child with the disease, their recurrence risk remains 1/2. Even if they have had several children, all affected (or all unaffected) with the disease, the law of independence dictates that the probability that their next child will have the disease still ½.

AUTOSOMAL RECESSIVE INHERITANCE

- Autosomal recessive diseases are fairly rare in populations.

Autosomal recessive diseases are rare because they require both parents to be carriers in order to produce an affected child.

- Heterozygous carriers for recessive disease genes are much more common than affected homozygotes.

- The parents of individuals affected with autosomal recessive diseases are usually both heterozygous carriers.

- As the Punnett square demonstrates, one fourth of their offspring will be normal homozygotes, half will be phenotypically normal heterozygous carriers, and one fourth will be homozygotes affected with the disease (on average).

Here two carrier parents

-75% of their offsprings won't be affected
-50% will get parents' genotype (carrier but not affected)
-25% will be affected

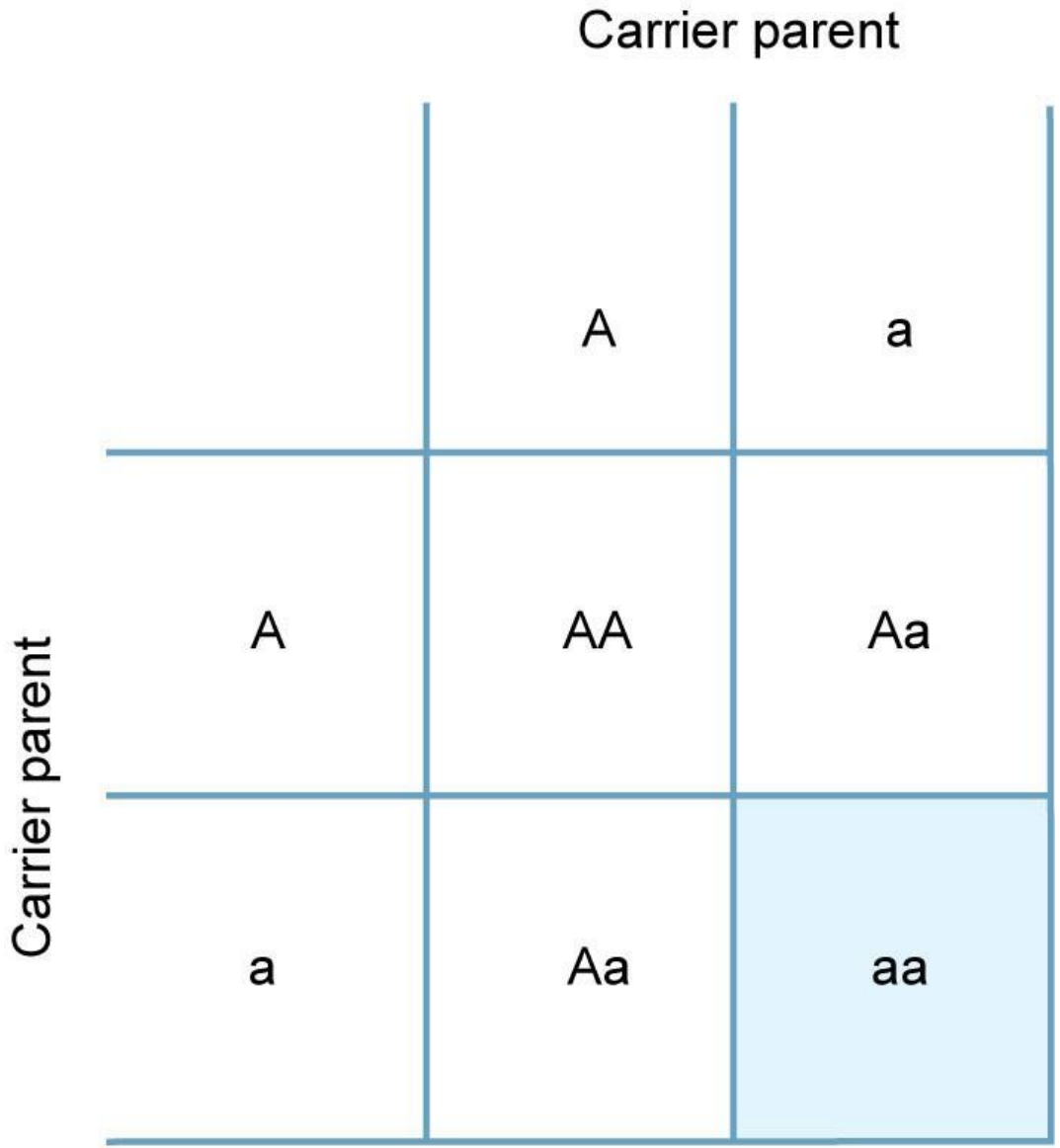


Fig. 4-5. Punnett square illustrating the mating of two heterozygous carriers of an autosomal recessive gene. The genotype of the affected offspring is shaded.

Characteristics of Autosomal Recessive Inheritance

- A pedigree showing the inheritance of an autosomal recessive form of albinism that results from mutations in the gene that encodes tyrosinase, a tyrosine-metabolizing enzyme.
- The resulting tyrosinase deficiency creates a block in the metabolic pathway that normally leads to the synthesis of melanin pigment. Consequently, the affected individual has very little pigment in the skin, hair, and eyes.
- Because melanin is also required for the normal development of the optic fibers, albinos may also display nystagmus (rapid uncontrolled eye movement), strabismus (deviation of the eye from its normal axis), and reduced visual acuity.
- The pedigree demonstrates most of the important criteria for distinguishing autosomal recessive inheritance.

This Pedigree shows that autosomal recessive disease appears in late generation, not in every generation such as in autosomal dominant disease.

(look at the red arrow) This double line illustrates marriage between relatives or cousins.

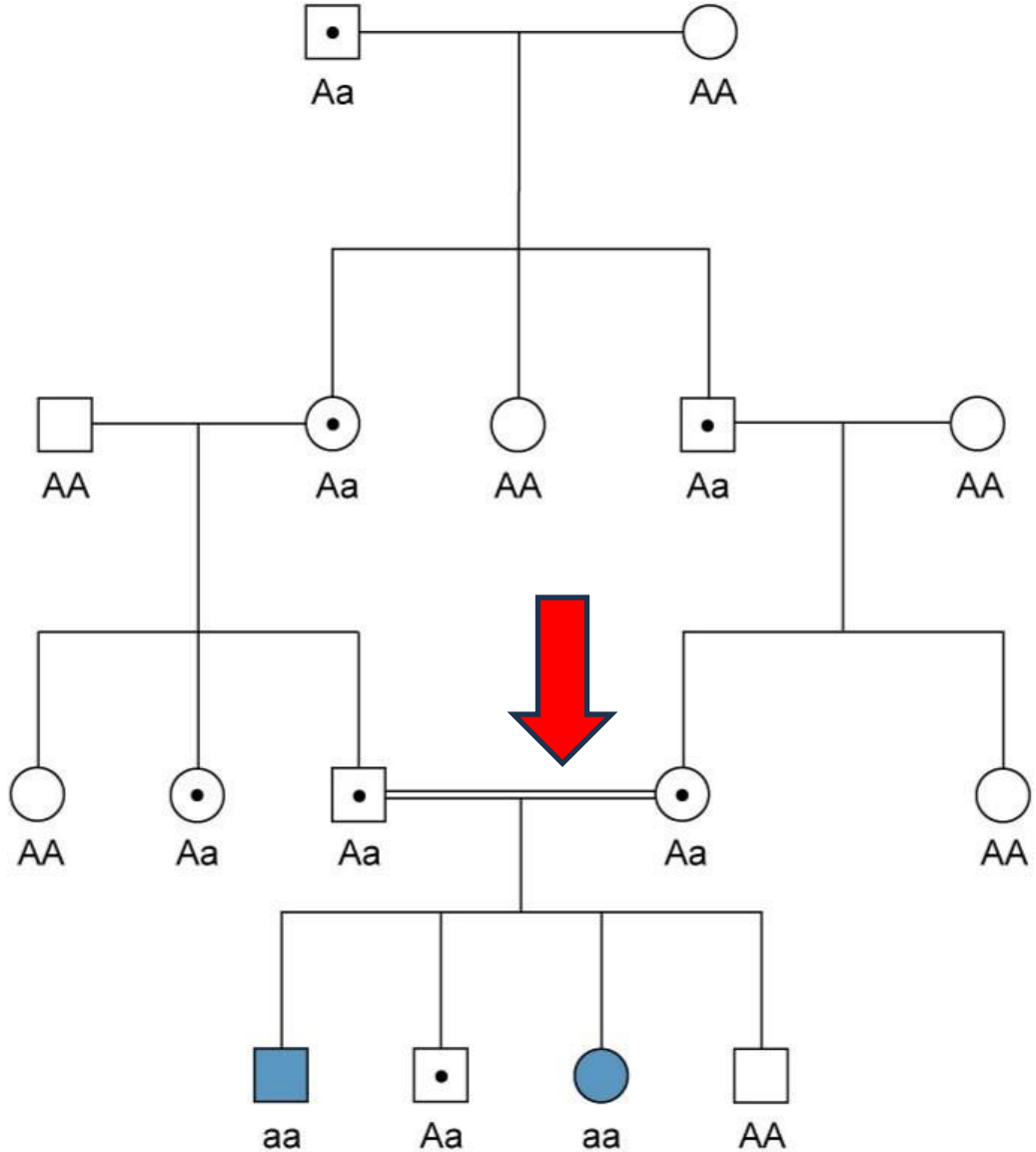
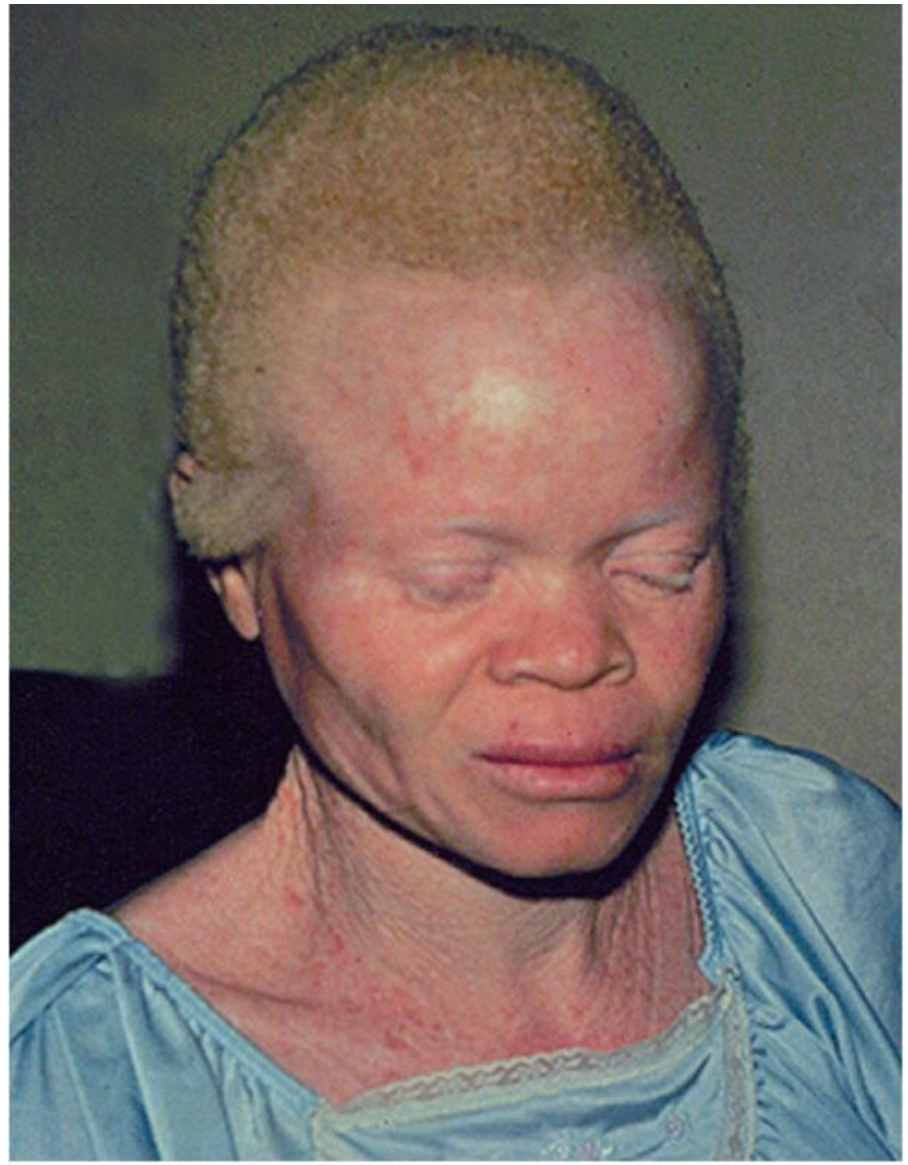


Fig. 4-6. Pedigree showing the inheritance pattern of tyrosinase-negative albinism, an autosomal recessive disease. Consanguinity in this pedigree is denoted by a double bar connecting the parents of the affected individuals.



(Courtesy of Dr. Phil Fischer, Mayo Clinic.)

Fig. 4-7. An African woman with oculocutaneous albinism, illustrating a lack of pigmentation in the hair and skin. She is looking away from the camera because her eyes are more sensitive to light than are those of persons with normally pigmented retinas.

Homozygous recessive are rarely to get married because they represent severe disease.

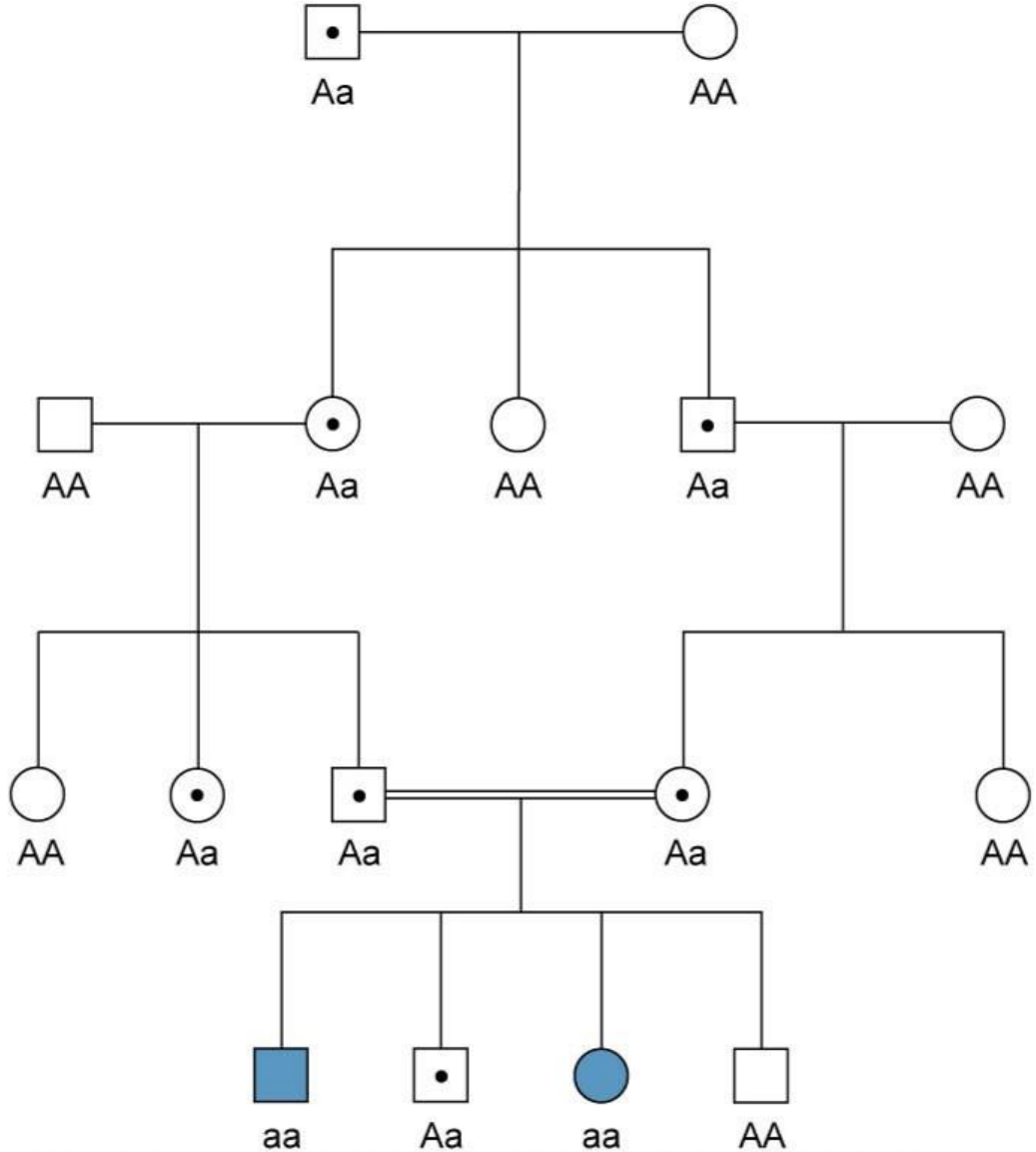


Fig. 4-6. Pedigree showing the inheritance pattern of tyrosinase-negative albinism, an autosomal recessive disease. Consanguinity in this pedigree is denoted by a double bar connecting the parents of the affected individuals.

→ First, unlike autosomal dominant diseases, in which the disease phenotype is seen in one generation after another, autosomal recessive diseases are usually seen in one or more siblings but not in earlier generations. (eg: cystic fibrosis, thalassemia, cycle cell anemia).

→ Second, as in autosomal dominant inheritance, males and females are affected in equal proportions.

→ Third, on average, one fourth of the offspring of two heterozygous carriers will be affected with the disorder.

→ Finally, consanguinity is present more often in pedigrees involving autosomal recessive diseases than in those involving other types of inheritance.

- The term consanguinity (Latin, ”with blood") refers to the mating of related individuals. It is often a factor in recessive disease because related individuals are more likely to share the same disease genes.

Consanguinity refers to marriage between relatives, such as cousins.

It's important to know the differences between autosomal recessive and dominant.

TABLE 4-1 A Comparison of the Major Attributes of Autosomal Dominant and Autosomal Recessive Inheritance Patterns

ATTRIBUTE	AUTOSOMAL DOMINANT	AUTOSOMAL RECESSIVE
Usual recurrence risk	50%	25%
Transmission pattern	Vertical; disease phenotype seen in generation after generation	Disease phenotype may be seen in multiple siblings, but usually not in earlier generations
Sex ratio	Equal number of affected males and females (usually)	Equal number of affected males and females (usually)
Other	Father-to-son transmission of disease gene is possible	Consanguinity is sometimes seen, especially for rare recessive diseases

Recurrence Risks

- The most common mating type seen in recessive disease involves two heterozygous carrier parents.

→ This reflects the relative commonness of heterozygous carriers and the fact that many autosomal recessive diseases are severe enough that affected individuals are less likely to become parents.

→ The punnett square demonstrates that one fourth of the offspring from this mating will be homozygous for the disease gene and therefore affected. The recurrence risk for the offspring of carrier parents is then 25%.

- Occasionally, a carrier of a recessive disease gene mates with an individual homozygous for the disease gene. In this case, roughly half of their children will be affected, while half will be heterozygous carriers. The recurrence risk is 50%.

→ Because this pattern of inheritance mimics that of an autosomal dominant trait, it is sometimes referred to as quasi-dominant inheritance.

→ With extended studies of pedigrees, in which carrier matings are observed, it can be distinguished from true dominant inheritance.

- When two individuals affected by a recessive disease mate, all of their children must also be affected.

→ This observation helps to distinguish recessive from dominant inheritance, since two parents both affected by a dominant disease will nearly always both be heterozygotes and thus one fourth of their children will be unaffected.

FACTORS THAT MAY COMPLICATE INHERITANCE PATTERNS

New Mutation

- If a child has been born with a genetic disease and there is no history of the disease in the family, it is possible that the child is the product of a new mutation.

New mutations mutation happen during gametes formation.

→ The gene transmitted by one of the parents underwent a change in DNA resulting in a mutation from a normal to a disease-causing allele.

→ The recurrence risk for the parents' subsequent offspring is not elevated above that of the general population.

→ The offspring of affected child may have a substantially elevated occurrence risk.

- It is estimated that 7/8 of all cases of achondroplasia are due to new mutations.

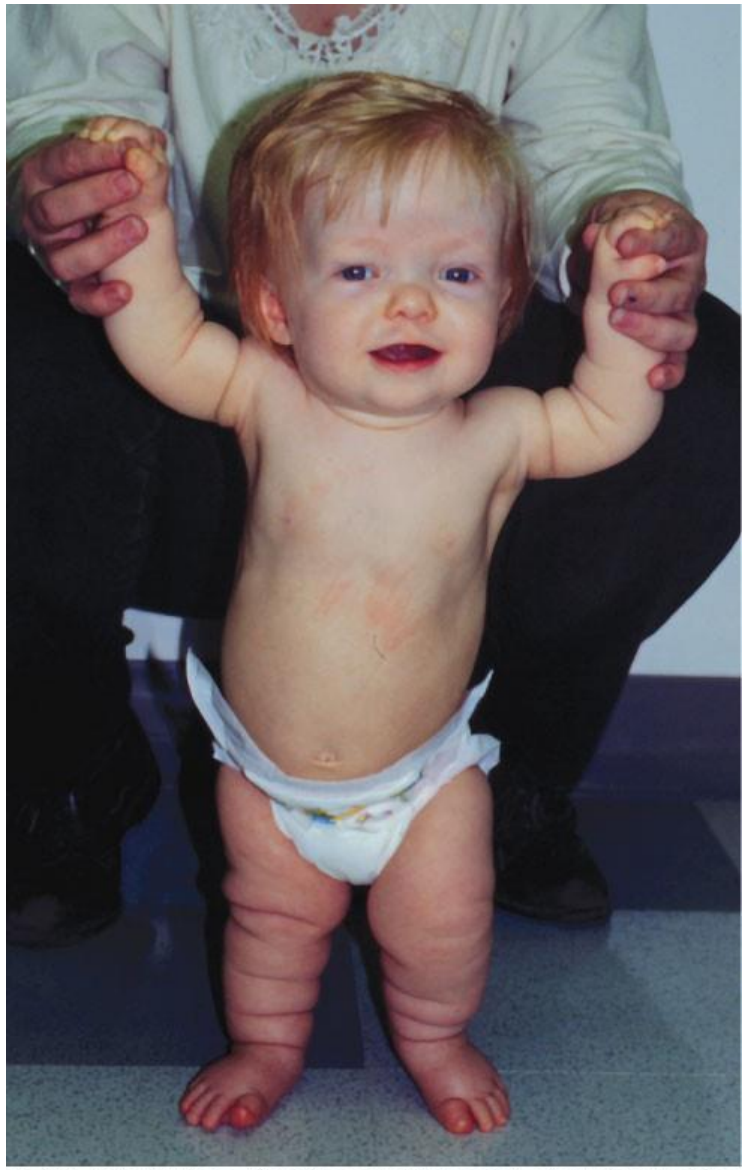


Fig. 4-8. Achondroplasia. This girl has short limbs relative to trunk length. She also has a prominent forehead, low nasal root, and redundant skin folds in the arms and legs.

This girl has short limbs relative to trunk , with a prominent forehead, redundant skin in extremities and low nasal bridge.

So this is a picture of the achondroplasia which is an autosomal dominant, but the rate for the new mutation is high 7/8.

Even though the parents may be healthy but due to a new mutation the achondroplasia appears in their children, But the already sick patients have higher rates of mutation more then 7/8.

Germline Mosaicism

- Germline mosaicism occurs when all or part of a parents germ line is affected by a disease mutation but the somatic cells are not.
- It elevates the recurrence risk for future offspring of mosaic parent.

→ During the embryonic development of one of the parents, a mutation occurred that affected all or part of the germline but few or non of the somatic cells of the embryo.

→ Osteogenesis imperfecta type II, Neurofibromatosis type I, DMD, Hemophilia A are examples.

Of germline mosaicism that once again
The somatic cells don't get affected and
the germline gets affected by a particular
percentage

Duchenne muscular dystrophy

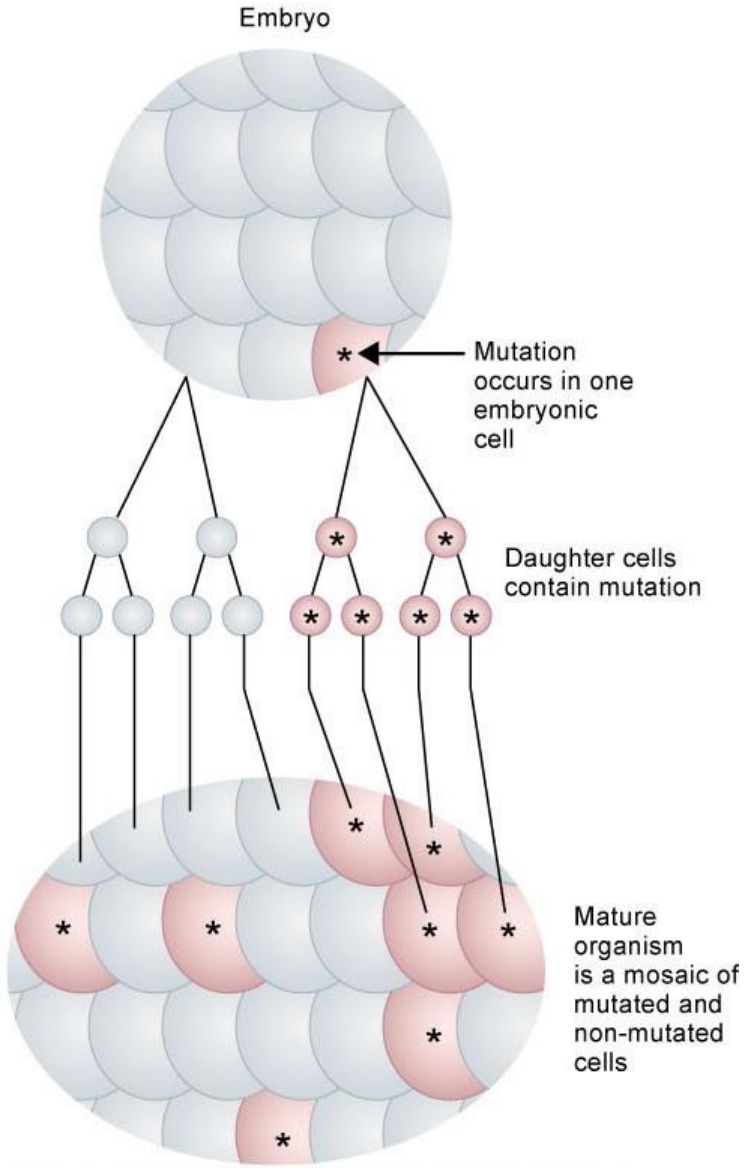


Fig. 4-9. A mutation occurs in one cell of the developing embryo. All descendants of that cell have the same mutation, resulting in mosaicism. If the first mutated cell is part of the germline lineage, then germline mosaicism results.

Once again in the embryo creation process the mutation happens :
embryo creation → involves mitosis → involves DNA replication → involve either a mutation or the repair process didn't work → daughter cells that contains the mutation and some do not contain it → some of the mature organism is mosaic and have mutated and non-mutated cells and if this affected mosaicism were in the germline (in the gametes) some of the gametes will have it and some of them won't → disease appears

Delayed age of onset

- While some genetic diseases are expressed at birth or shortly afterward, many others do not become apparent until well into adulthood.
- One of the best-known examples is Huntington's disease, a neurological disorder whose main features are progressive dementia and increasingly uncontrollable movements of the limbs.

→ Symptoms are not usually seen until age 30 or later. Thus, those who develop the disease have often had children before they are aware that they carry the gene.

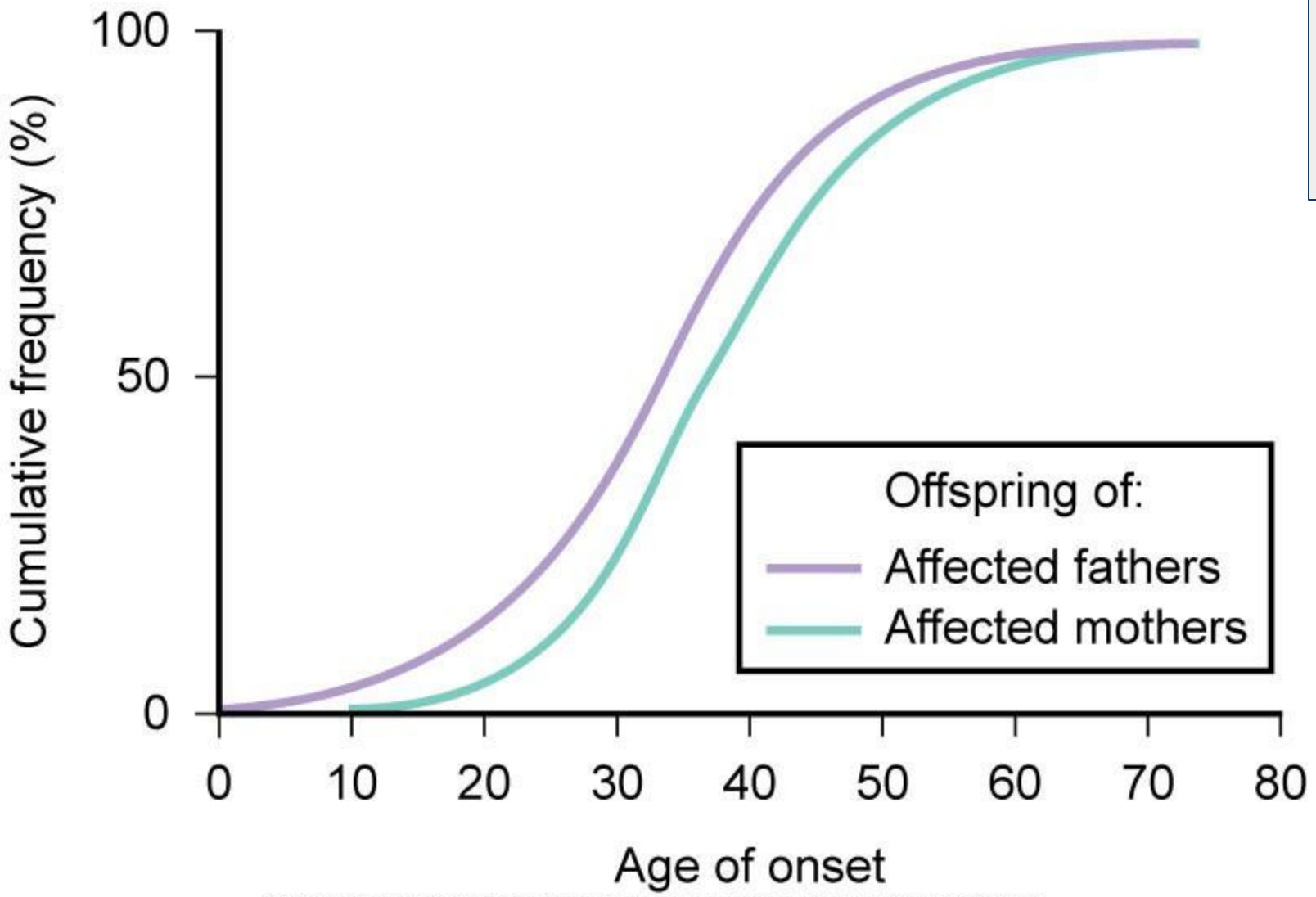
→ If the disease were present at birth, nearly all affected persons would die before reaching reproductive age, and the frequency of the gene in the population would be much lower.

→ Delaying the age of onset thus reduces natural selection against a disease gene, increasing its frequency in a population.

Most of the genetic disorders will appear during creation when the specialist exams with the ultrasound or after days or months from birth

Huntington`s Disease was described for the first time in 1872 and much later we knew that it's an autosomal dominant disease

We see that in most cases the disease appears after 30 and when the affected is the father the onset is earlier than when the mother is



(Data from Conneally PM: Huntington disease: Genetics and epidemiology. Am J Hum Genet 1984;36:520.)

Fig. 4-11. Distribution of the age of onset for Huntington disease. The age of onset tends to be somewhat earlier when the affected parent is the father.

Reduced Penetrance

- an individual who has the genotype for a disease may not exhibit the disease phenotype at all, even though he or she can transmit the disease gene to the next generation.

- Retinoblastoma, a malignant eye tumor, is a good example of an autosomal dominant disorder in which reduced penetrance is seen.

→ Family studies have shown that about 10% of the obligate carriers of the retinoblastoma susceptibility gene do not have the disease. The penetrance of the gene is then said to be 90%. Obligate carrier is the person who has a diseased son and a diseased father

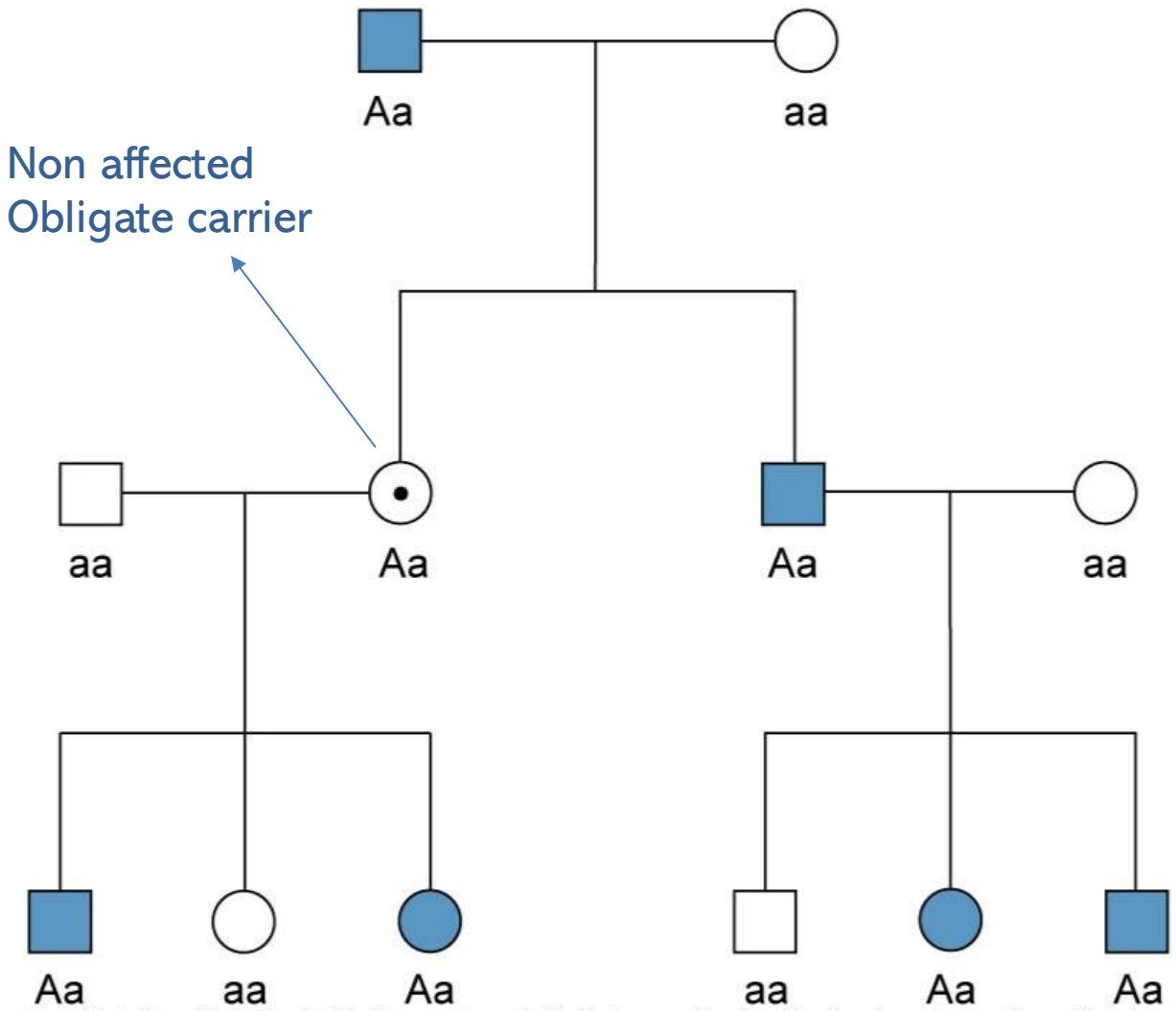


Fig. 4-10. Pedigree illustrating the inheritance pattern of retinoblastoma, a disorder with reduced penetrance. The unaffected obligate carrier, denoted by a dot, has the same genotype as the affected pedigree members.

This person must have the disease (because one allele is enough) but why doesn't he?

That's the effect of reduced penetrance

Variable Expression

- Here, the penetrance may be complete, but the severity of the disease can vary greatly.
- A well-studied example of variable expression in an autosomal dominant disease is neurofibromatosis type 1.

→ A parent with mild expression of the disease -so mild that he or she is not aware of it- can transmit the gene to a child who may have severe expression.

→ Variable expression provides a mechanism for disease genes to survive at higher frequencies in populations.

It’s expected to have environmental effects that are responsible sometimes, but if there are no certain environmental factors the gene is expressed with diminished severity or not at all.

So when we talk about variable expressions there are some possibilities :
the first one that the environmental factors have effect
2- the second thing that modifier genes (that other genes affect this gene)
3- the third thing that the molecular bases for the mutation happens…. Understood

Sometimes I have different types of mutations on certain locus;
So when I have in the locus certain mutation and in the same locus a different mutation.
Taking into consideration that the effect of the mutations differs from one another that’s called "allelic heterogeneity" different mutation on certain locus. (Mutation gives severe form and the other gives a mild form of the disease) and this complicates the inheritance pattern.

Pleiotropy and Heterogeneity

- Genes having more than one discernible effect on the body are said to be pleiotropic.
- A good example of a gene with pleiotropic effects is given by Marfan syndrome. This autosomal dominant disorder affects the eye, the skeleton, and the cardiovascular system.

→ All of the observed features of Marfan syndrome are due to unusually stretchable connective tissue.

→ Mutations in the gene encoding fibrillin, a component of connective tissue, are responsible for the multiple defects seen in this disorder.

Examples other than Marfan syndrome on pleiotropy: cystic fibrosis (affects sweat glands, lungs and pancreas) , also Osteogenesis imperfecta (affects bones, teeth, sclera) Albinism also

So I have many effects from the genetic defect

Pleiotropy and Heterogeneity

- Just as a single gene may have multiple effects, a single disease phenotype my be caused by mutations at different loci in different families.
- The causation of the same disease phenotype by mutations at distinct loci is termed locus heterogeneity.

→ Adult polycystic kidney disease (APKD), an autosomal dominant disorder in which a progressive accumulation of renal cysts is seen.

→ APKD can be caused by mutations in genes on either chromosome 16 (PKD1) or chromosome 4 (PKD2). Two loci, any mutation on one of them will lead to the phenotype.

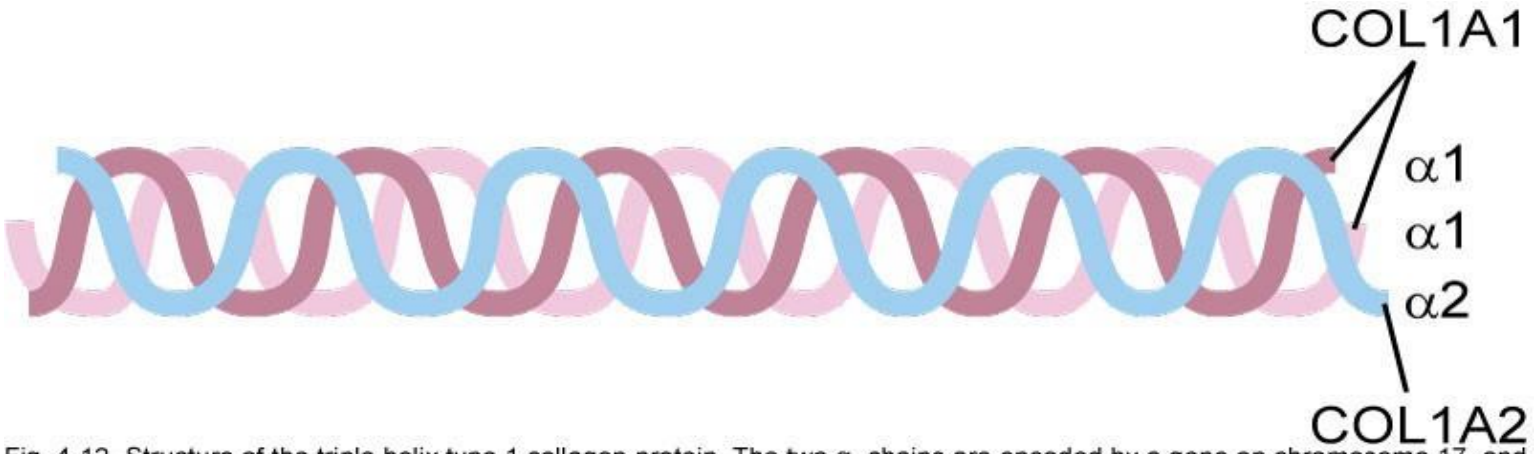


Fig. 4-12. Structure of the triple helix type 1 collagen protein. The two α_1 chains are encoded by a gene on chromosome 17, and the α_2 chain is encoded by a gene on chromosome 7.

So, thinking about type 1 collagen if there is a defect in the alpha 1 there will be a disease Or defect in the alpha 2 there will be the same disease, because the triple helix is needed for the functionality of the collagen, which is the responsibility of two different chromosomes. This was an example of type one collagen disease.

Also the Osteogenesis imperfecta is a complication of the collagen type 1 defect , and an example for the locus heterogeneity → involvement of chromosome 17 and chromosome 7

Genomic Imprinting

- Mendel's experimental work with garden peas established that the phenotype is the same whether a given allele is inherited from the mother or the father.

→ this principle does not always hold

→ A striking example is provided by a deletion of 3 to 4 Mb on the long arm of chromosome 15.

→ When this deletion is inherited from the father, the offspring manifest a disease known as Prader-Willi syndrome. The disease phenotype includes short stature, hypotonia, small hands and feet, obesity, mild to moderate mental retardation, and hypogonadism.
Micro-deletion

→ When the deletion is inherited from the mother, the off-spring develop Angelman syndrome, which is characterized by severe mental retardation, seizures, and an ataxic gait. Both diseases are seen in about 1/15,000 individuals, and in both about 70% of cases are caused by chromosome deletions.

- The differential activation of genes, depending on the parent from which they are inherited, is known as genomic imprinting.

Genes that are active when the chromosome 15 is inherited from the father will differ from the genes that are active when it's inherited from the mother which will lead to different phenotypes.

Anticipation and Repeat Expansion

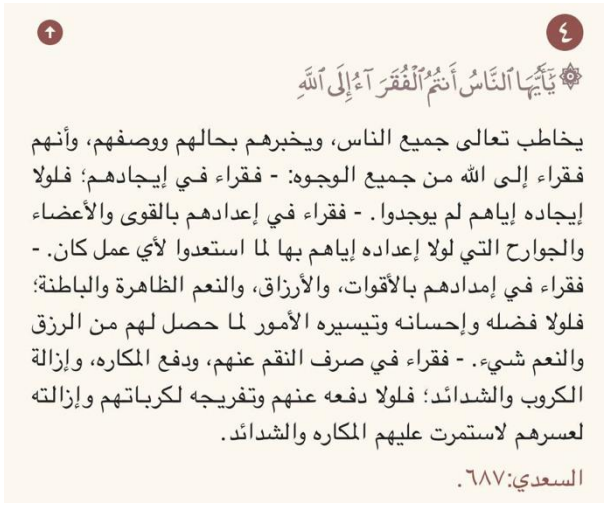
- some genetic diseases seem to display an earlier age of onset and/or more severe expression in the more recent generations of a pedigree.

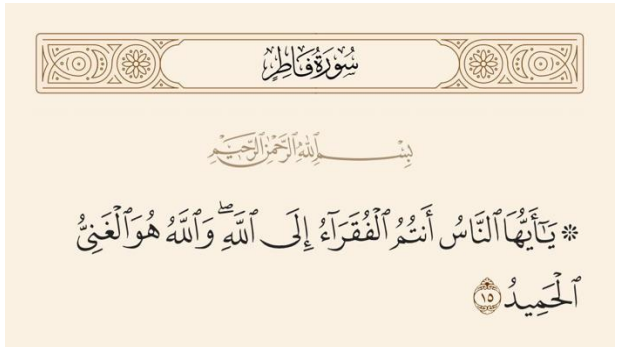
→ This pattern was termed anticipation, and it has been the subject of considerable controversy and speculation.

→ The number of these repeats is strongly correlated with severity of the disease.

- Unaffected individuals typically have 5 to 30 copies of the repeat.
- Those with 50 to 100 copies of the repeat may he mildly affected or have no symptoms.
- Those with full-blown myotonic dystrophy may have anywhere from 100 to several thousand copies of the repeat sequence.

→ The number of repeats often increases with succeeding generations: a mildly affected parent with 80 repeats may produce a severely affected offspring with more than 1,000 repeats





اللهم إنّ لنا أهلًا مستضعفين فانصرهم بنصرك واحفظهم بحفظك وأجرهم من شر الظالمين وجنودهم عزّ جارك وجلّ ثناؤك وتبارك اسمك ولا إله غيرك ,اللهم ردّ كيد أعداء دينك في نحورهم وخذهم أخذ عزيز مقتدر . اللهم انصر المسلمين واحفظهم بعينك التي لا تنام.

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!