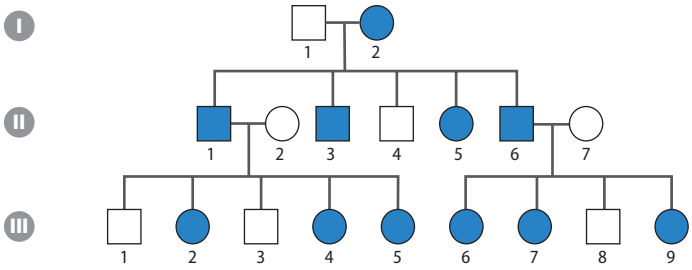
Questions and Answers for Genetics and Genomics in Medicine Chapter 5

Question 1

What is the likely inheritance pattern in the pedigree below?

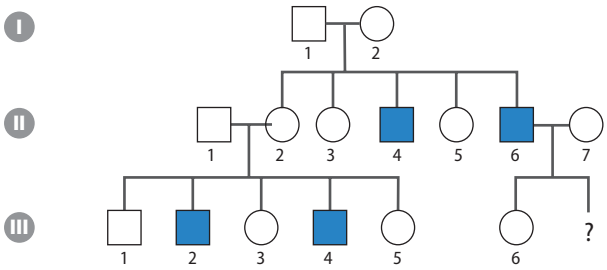


Answer

This is clearly not a recessive disorder. It could be an autosomal dominant disorder on the basis that both sexes are affected and affected individuals have an affected parent. But there are six affected females and three unaffected males in generation III, each of whom had an affected father, suggesting the possibility of an X-linked dominant condition.

Question 2

What is the likely inheritance pattern in the pedigree below? II-7 is pregnant again. What is the risk that the child will be affected?



Answer

It might conceivably be an autosomal dominant disorder in which there is non-penetrance with two asymptomatic gene carriers (II-2 and one of the grandparents in generation I). However, the presence of affected males is compatible with an X-linked recessive disorder in which affected males are able to reproduce, such as hemophilia. In that case, I-2 and II-2 can be expected to be carriers, and for each of the sisters in generations II and III plus III-6 there will be a 50% chance of being a carrier.

In the case of X-linked recessive inheritance, II-7's risk of having an affected child would be negligible: the affected father must pass a Y chromosome to each son, and so a son could not be

affected. There is a 50% chance that the affected father, II-6, will transmit an X chromosome with the mutant allele to a daughter, but in that case she would be a carrier but would not be affected.

Question 3

In X-linked recessive inheritance, women carriers may sometimes show disease symptoms. How does that happen?

Answer

Because of random X-inactivation, some women by chance might have inactivated the normal X chromosome in a high proportion of cells in the tissues that normally manifest disease. On rare occasions the disorder might occur through an X-autosome translocation in which the breakpoint on the X severs a gene or disturbs its normal expression. That results in nonrandom X-inactivation: the normal X is consistently silenced (otherwise there would be the danger of silencing autosomal genes on the hybrid X-autosome).

Question 4

What is meant by pseudoautosomal regions and pseudoautosomal inheritance?

Answer

Pseudoautosomal regions (PARs) are short gene-containing homologous sequences found at the tips of the short and long arms of the X and Y chromosomes. In male meiosis, recombination between the X and the Y is confined to the PARs, and as a result of crossover between homologous PARs, genes in these regions get swapped between the X and the Y in much the same way that recombination allows the swapping of genes between autosomal homologs. As a result, the sequences of these regions are not X-specific or Y-specific.

Some single-gene disorders are due to mutations in certain genes of the PARs, and the inheritance of the condition shows the same characteristics as autosomal dominant or autosomal recessive inheritance. Hence although the disease gene loci are on the sex chromosomes, the inheritance is referred to as pseudoautosomal inheritance.

Question 5

Sickle-cell disease is an autosomal recessive disorder. Nevertheless, carriers of a sickle-cell disease mutation may not be asymptomatic. Explain why.

Answer

Hemoglobin is a tetramer with two α-globin and two β-globin chains. In sickle-cell disease, both copies of the β-globin gene are mutated, producing a specific mutant β-globin polypeptide. The resulting mutant hemoglobin, HbS, causes red blood cells to develop a characteristic sickle shape that results in anemia.

In carriers of the sickle-cell mutation, the two alleles are co-dominantly expressed to give a normal β-globin and the specific mutant β-globin, both of which can be incorporated into hemoglobin molecules. Occasionally, therefore, when two mutant β-globin chains are incorporated into the hemoglobin, some HbS will be made (if the normal and mutant β-globin were to be produced in equal amounts, about 25% of the hemoglobin might be expected to be HbS). As a result, carriers of the sickle-cell mutation develop mild anemia (a trait that is known as sickle-cell trait; because it is expressed in the heterozygote, this is a dominant trait). Under certain stressful conditions, such as hypoxia and so on, the trait is exacerbated, resulting in some of the complications associated with sickle-cell disease.

Question 6

New mutations are rare in recessive disorders, but for severe, X-linked recessive disorders, about 1 in 3 mutations occur *de novo*. Why is that?

Answer

For the frequency of a single-gene disorder to remain constant in a population over time, there is a balance between mutant alleles that are lost from the population (because they are not transmitted for some reason, such as ill health, early death, personal circumstances, or personal choice) and mutant alleles that are introduced by *de novo* mutation.

Irrespective of the severity of the condition, new mutations are rare in autosomal recessive disorders. That is so because the carriers greatly outnumber the small number of affected individuals. For each affected individual who does not reproduce, there will be many unaffected carriers who are able to do so. As a result, only a small proportion of mutant alleles are lost when affected individuals do not reproduce, and so the rate of *de novo* mutation does not need to be very high to maintain a constant frequency of mutant alleles in the population.

For severe X-linked recessive disease, affected boys do not reproduce, but unaffected female carriers do.

Question 7

Give four alternative explanations for variable expression (including non-penetrance) in monogenic disorders.

Answer

- Imprinting. For a small minority of genes, the expression of a mutant allele is routinely silenced if it is maternally inherited, and for some others a paternally inherited mutant allele is silenced. As a result, the effect of the mutant allele is not observed in some gene carriers.
- Mitochondrial heteroplasmy. If a woman is heteroplasmic for a pathogenic mitochondrial DNA mutation associated with a single-gene disorder, some of her mtDNA molecules will carry the mutation and others will not. When she transmits eggs to the next generation, by chance the proportion of mutant mtDNAs might be very low so that the gene carrier does not show obvious clinical symptoms.

- The effect of modifier genes. By interacting with an allele from some other modifier locus, the mutant allele may be suppressed in some way. Some family members may have the mutant suppressor allele at the modifier locus, but others may have another allele and show clinical symptoms.
- Dynamic mutations. Certain pathogenic mutations are unstable and can slowly change to have more harmful effects over long periods. An affected person can therefore transmit a more harmful mutant allele than the one he or she inherited. The classic examples are pathogenic unstable expansions of tandem oligonucleotide repeats that are associated with diseases such as Huntington disease, myotonic dystrophy, and fragile X syndrome. In this case, mutant alleles have an increased number of tandem repeats compared with normal alleles, and this affects gene expression. However, the alleles are unstable and can increase in size; when they do, the clinical symptoms can increase.

Question 8

The Hardy–Weinberg equilibrium is an important principle in population genetics. Explain what it means and how it can be usefully applied to Mendelian disorders.

Answer

The Hardy–Weinberg equilibrium relates allele and genotype frequencies within a population.

If a locus has two alleles only, the Hardy–Weinberg equilibrium gives the frequency of each homozygous genotype as the square of the allele frequency, and the frequency of the heterozygous genotype as twice the product of the individual frequencies. Imagine we have two alleles: allele *A* with a frequency of *p* and allele *a* with a frequency of *q*. According to the Hardy–Weinberg equilibrium, the genotype frequencies will be as follows: $AA - p^2$, $Aa - 2pq$, and $aa - q^2$.

The most useful application of the Hardy–Weinberg equilibrium to Mendelian disorders is in calculating carrier risk in autosomal recessive conditions. Here, the frequency of normal alleles in the population is given as *p*, and the frequency of all mutant alleles for the condition is given as *q*. The frequency of affected people is therefore p^2 (because they have two mutant alleles) and the frequency of carriers is $2pq$. If we are given the frequency of an autosomal recessive disorder ($= p^2$), we can calculate the square root to get *p* and that then allows us to calculate the carrier frequency. Because $p + q = 1$, the carrier frequency is $2p(1 - p)$. Because calculation of genetic risk for autosomal recessive disorders is based on calculating carrier risks, the Hardy–Weinberg equilibrium is especially useful here.

Question 9

An autosomal recessive disorder has a frequency of 1 in 3600 in a certain population. A woman who has two affected sibs with this condition has recently married an unrelated man from the same population group and is expecting a child by him. Deduce from a combination of the principles of Mendelian segregation and from the Hardy–Weinberg equilibrium what the risk is that any child that the couple have will be affected. [Hint: use Mendelian segregation to work out her risk of being a carrier, then use the Hardy–Weinberg equilibrium to work out what her prospective husband's risk of being a carrier is, and finally use Mendelian segregation to work out the chance of having an affected child if both are carriers.]

Answer

From Mendelian segregation principles, the chance that she is a carrier is 2/3 (not 1 in 4). That is so because if we imagine the normal allele to be ***A*** and the mutant allele to be ***a*** and that the paternal alleles are blue and the maternal alleles are red, there are four possible combination of the parental alleles: **AA**, **aA**, **Aa**, and **aa**. Because she is unaffected, she cannot be **aa**. So she must be **AA** (not a carrier), **aA** (carrier), or **Aa** (carrier), giving two chances out of three that she is a carrier.
The chance that her husband is a carrier comes from the Hardy–Weinberg equilibrium. The frequency of the autosomal recessive disorder is 1/3600. If we define p as the frequency of normal alleles and q as the frequency of any mutant alleles so that $p + q = 1$, then the proportion of people who are homozygous for the normal allele (**AA**) is p^2, the proportion of carriers (either **aA** or **Aa**) is $2pq$, and the proportion of affected individuals (**aa**) is q^2. We are told that the proportion of affected individuals is 1 in 3600 and so $q^2 = 1/3600$, giving $q = 1/\sqrt{3600} = 1/60$.

The chance that both husband and wife are carriers is the product of their individual risks of being a carrier, namely $2/3 \times 1/60 = 1/90$. If they are both carriers, the chance of having an affected child is 1 in 4. Therefore the risk of being affected for each child born to this couple is $1/4 \times 1/90 = 1/360$ (or roughly 0.3%)

Question 10

What is meant by balancing selection? How does it explain the high frequencies of certain recessive conditions?

Answer

Balancing selection occurs when a heterozygote has greater biological fitness (that is, has a greater capacity for survival and reproductive success) than either homozygote. Balancing selection explains why some recessive conditions can have particularly high frequencies in some populations: carriers of the mutant allele are more successful at reproducing than both normal homozygotes and affected individuals (heterozygote advantage). In malaria-infested regions, for example, carriers of certain recessive blood disorders have a greater biological fitness than both normal homozygotes (who are more susceptible to malaria) and mutant homozygotes (who suffer from the recessive blood disorder).