Genetics and Genomics in Medicine Chapter 5

Questions & Answers

Multiple Choice Questions

Question 5.1

The term phenotype can be applied to a wide range of manifestations. Which of the following properties, if any, do not constitute a phenotypic manifestation?

a) The number of digits a person has.
b) The transcriptome of a single T cell.
c) The sequence of a person's beta globin gene.
d) autistic behavior

Answer 5.1

c) The sequence of a person's beta globin gene.

Question 5.2

Which, if any, of the following is incorrect? When used in genetics, the term *character*

a) may apply to an anatomical, morphological, or physiological feature.
b) may apply to a type of behaviour.
c) may apply to any intracellular property, such as the sodium ion concentration of a cell or the mitochondrial DNA sequence.
d) implies a phenotypic feature that is not disease-associated.

Answer 5.2

c) may apply to any intracellular property, such as the sodium ion concentration of a cell or the mitochondrial DNA sequence.

Explanation 5.2

Character is a phenotypic property and although it does apply to intracellular properties it does not apply to DNA sequences (which come under the heading of *genotype.*)

Question 5.3

Which, if any, of the following is incorrect? When used in human genetics, the term *allele*

a) describes any individual gene variant.
b) refers to a nuclear gene at a locus on a single chromosome

c) primarily means an individual DNA sequence copy at a locus that is common to two homologous chromosomes.
d) is often used loosely at the protein level to describe a protein made by a single copy of a nuclear gene.

Answer 5.3

a) describes any individual gene variant.
b) refers to a nuclear gene at a locus on a single chromosome

Explanation 5.3

a) Applies only to loci present on maternal and paternal homologous chromosomes (and so does not apply to mitochondrial DNA or Y-specific DNA)
b) Not just genes, can be any single copy of a DNA sequence that is present at a locus that is found on maternal and paternal homologous chromosomes.

Question 5.4

Which, if any, of the following is incorrect? When used in human genetics, the term *heterozygote*

a) applies even if a person possesses two alleles that differ by just one nucleotide out of a million
b) consistently applies to Y-specific loci because men must be heterozygotes at these loci, having a very different sequence on the X chromosome.
c) may apply to a person with a recessive disease when the two mutant alleles are not identical.
d) does not apply to loci on the X chromosome in women because in each of a woman's cells one X chromosome is inactivated.

Answer 5.4

b) consistently applies to Y-specific loci because men must be heterozygotes at these loci, having a very different sequence on the X chromosome.
d) does not apply to loci on the X chromosome in women because in each of a woman's cells one X chromosome is inactivated.

Explanation 5.4

Heterozygous means having two different alleles at the *same* locus on homologous chromosomes, but loci on the Y-specific region are not present on the X chromosome. X-inactivation is an epigenetic phenomenon and does not change the position that women have paternal and maternal alleles on their X chromosomes.

Question 5.5

Which, if any, of the following is incorrect? When used in human genetics, the term *hemizygous* is a property that

a) applies to all loci on the X chromosome in males.
b) applies to Y-specific DNA because loci here are exclusively paternally inherited
c) applies to loci on mitochondrial DNA because they are exclusively maternally inherited.
d) does not apply to loci in the pseudoautosomal regions.

Answer 5.5

a) applies to all loci on the X chromosome in males.
c) applies to loci on mitochondrial DNA because they are exclusively maternally inherited.

Explanation 5.5

a) Loci in pseudoautosomal regions at the tips of the X and Y chromosomes are shared and the DNA sequences can recombine (so that they are not X-specific or Y-specific sequences).
c) Diploid loci are necessarily nuclear loci, but mitochondrial loci are not (because of matrilineal inheritance).

Question 5.6

Which, if any, of the following is incorrect? When used in human genetics,

a) the terms *dominant* and *recessive* apply equally to alleles and phenotypes.
b) *dominant* describes a phenotype that is manifested in the heterozygote, that is, the phenotype is attributable to just a single allele.
c) *recessive* describes a phenotype that is manifest as a result of the combined effects of both alleles at a locus.
d) the AB blood group is an example of a co-dominant phenotype.

Answer 5.6

a) the terms *dominant* and *recessive* apply equally to alleles and phenotypes.

Explanation 5.6

The terms *dominant* and *recessive* apply to phenotypes not alleles. We may speak of a *dominantly-acting allele* (one that contributes to a dominant phenotype in the absence of any contribution by the other allele at that locus) or a *recessively-acting allele* (one that contributes to a phenotype only when the other allele simultaneously makes a contribution to the phenotype) but not of a dominant allele or a recessive allele.

Question 5.7

With respect to autosomal dominant inheritance in human genetics, which, if any, of the following statements is incorrect?

a) One of the parents of an affected person will be affected.
b) Both parents of an affected person may be unaffected, but one of them at least will carry the mutant allele in all of their nucleated cells.
c) A child born to an affected parent and a normal parent has a 50% chance of inheriting the mutant allele.
d) The term *dominant* applies equally to the phenotype of affected individuals with one mutant allele (heterozygotes) and individuals with two mutant alleles because in practice the phenotypes are essentially identical.

Answer 5.7

a) One of the parents of an affected person will be affected.
b) Both parents of an affected person may be unaffected, but one of them at least will carry the mutant allele in all of their nucleated cells.
d) The term *dominant* applies equally to the phenotype of affected individuals with one mutant allele (heterozygotes) and individuals with two mutant alleles because in practice the phenotypes are essentially identical.

Explanation 5.7

a) One of the parents of an affected child may carry the mutant allele but it may not be expressed (for example, by imprinting) and so they may not be affected.
b) The disease-causing mutation may arise *de novo* during gametogenesis or in the very early embryo.
d) No distinction is made in human genetics between these possibilities because affected individuals with two mutant alleles are extremely rare, but when they are identified the phenotype is usually more severe than that of affected heterozygotes.

Question 5.8

With respect to autosomal recessive inheritance, which, if any, of the following statements is incorrect?

a) Affected individuals normally have unaffected parents.
b) For unaffected parents who have a previously affected child, there is a 1 in 4 risk of having an affected child on each occasion that they produce a new child.
c) Heterozygotes are always asymptomatic carriers.
d) Some affected individuals have alleles with identical pathogenic mutations but many have two different mutant alleles and are described as compound heterozygotes.

Answer 5.8

c) Heterozygotes are always asymptomatic carriers.

Explanation 5.8

Sometimes the heterozygote may have some mild symptoms. For example, carriers of the sickle-cell mutation are not quite asymptomatic. The sickle-cell allele produces a mutant β-globin that is co-dominantly expressed with the normal β-globin, and heterozygotes can have mild anemia (*sickle-cell trait*). However, under intense, stressful conditions such as exhaustion, hypoxia (at high altitudes), and/or severe infection, sickling may occur in heterozygotes and result in some of the complications associated with sickle-cell disease. Note that whereas sickle-cell disease is recessively inherited, the sickle-cell trait is expressed in the heterozygote and is therefore regarded as a dominant trait.

Question 5.9

With respect to X-chromosome inactivation in females, which, if any, of the following statements is incorrect?

a) X-inactivation first occurs in the preimplantation female mammalian embryo.
b) One of the two X chromosomes in each diploid cell of a normal woman is randomly selected to undergo X-inactivation and becomes highly condensed.
c) The process involves epigenetic silencing of each gene on one of the two X chromosomes, either the maternal X chromosome or the paternal X chromosome.
d) Once the decision is made to inactivate a paternal X or the maternal X in a cell, all descendant cells will continue with that pattern of X-inactivation.

Answer 5.9

c) The process involves epigenetic silencing of each gene on one of the two X chromosomes, either the maternal X chromosome or the paternal X chromosome.

Explanation 5.9

In humans, about 15% of genes on the inactivated X chromosome somehow escape being silenced by X-inactivation.

Question 5.10

With respect to X-linked recessive inheritance, which, if any, of the following statements is false?

a) Males with just one mutant allele are affected because, lacking a second X chromosome, they do not have a normal allele.
b) Women are always asymptomatic.
c) The disorder is not transmitted from fathers to sons.

d) Each child born to a normal man and a carrier woman has a risk of 1in 4 of being affected.

Answer 5.10

b) Women are always asymptomatic.

Explanation 5.10

Women can occasionally be *manifesting heterozygotes,* where the X chromosome carrying the harmful allele is inactivated in a high proportion of cells associated with the disease phenotype. Note that in (d) each child has a 1 in 4 risk but it is sex-dependent: females are not at risk and males have a 1 in 2 risk.

Question 5.11

With respect to X-linked dominant inheritance, which, if any, of the following statements is false?

a) There are significantly more affected females than males.
b) Each child born to an affected mother has a risk of 1 in 2 of being affected.
c) Each daughter born to an affected father has a risk of 1 in 2 of being affected.
d) Each boy born to an affected father has a negligible risk of being affected.

Answer 5.11

c) Each daughter born to an affected father has a risk of 1 in 2 of being affected.

Explanation 5.11

Each daughter will inherit a paternal X chromosome carrying the mutant allele and so would be expected to be affected.

Question 5.12

With respect to mitochondrial inheritance, which, if any, of the following statements is false?

a) Affected individuals can be of either sex.
b) Mitochondrial disorders are transmitted virtually exclusively through the maternal line.
c) Both the sperm and the egg contribute mitochondrial DNA to the zygote.
d) Clinical variability is a common feature of mitochondrial DNA disorders.

Answer 5.12

None.

Explanation 5.12

All are true. Although the sperm does contribute some mitochondrial DNA molecules to the zygote they are selectively destroyed.

Question 5.13

With respect to mosaicism, which, if any, of the following statements, is false?

a) Any person who has two or more cells that have a different genetic constitution is a mosaic
b) All women are genetic mosaics
c) Every person is a genetic mosaic.
d) Mosaicism is the inevitable consequence of germline mutations.

Answer 5.13

d) Mosaicism is the inevitable consequence of germline mutations.

Question 5.14

An individual single gene disorder can show different levels of genetic heterogeneity, and different mutations in a single gene can sometimes result in a very wide range of different phenotypes. Which, if any, of the following statements, is false?

a) Allelic heterogeneity describes a situation where any of a range of different mutations in one gene can result in the same disorder
b) Sickle cell anemia is an outstanding example of allelic heterogeneity.
c) Locus heterogeneity means that a disease phenotype is manifest only as a result of the additive contributions of genetic variants at multiple loci.
d) The situation where different mutations in a single gene result in quite different diseases can be described as phenotype heterogeneity.

Answer 5.14

b) Sickle cell anemia is an outstanding example of allelic heterogeneity.
c) Locus heterogeneity means that a disease phenotype is manifest only as a result of the additive contributions of genetic variants at multiple loci.

Explanation 5.14

Sickle cell anemia is caused by very specific mutations that cause a change in just one amino acid. Locus heterogeneity means that certain mutations in any of two or more loci produce the same disease.

Question 5.15

Purifying selection removes harmful alleles from the population because a proportion, at least, of people who carry the harmful alleles have reduced biological fitness (manifesting by reduced reproductive success rates). For any inherited disorder, the frequency of mutant alleles in the population is usually stable: mutant alleles that are eliminated from the population (because the

people that have them do not reproduce, or reproduce less efficiently), and new mutant alleles are created by *de novo* mutation. Link individual types of single gene disorder a) to e) to one of the values i) to iv) for the percentage of mutant alleles that arise by de novo mutation.

Disorder (*f* = biological fitness of affected person)

a) A severe autosomal dominant disorder (affected individuals do not have children; $f = 0$)
b) Achondroplasia (autosomal dominant; $f = 0.2$)
c) Huntington disease (a late onset autosomal dominant disorder)
d) A severe X-linked recessive disorder, ($f = 0$)
e) A severe autosomal recessive disorder ($f = 0$)

Percentage of mutant alleles arising by de novo mutation

i) very low
ii) 33.3%
iii) 80%
iv) 100%

Answer 5.15

a) iv)
b) iii)
c) i)
d) ii)
e) i)

Essay and List Questions

Question 5.16

The human X and Y chromosomes are thought to have evolved from what used to be a pair of autosomes. Unlike homologous pairs of autosomes, the current X and Y chromosomes are very different in many ways, including their DNA composition, DNA sequence classes, and gene content. Comment on the degree of DNA sequence sharing between these two chromosomes, and the consequences of having very different sex chromosomes in males.

Answer 5.16

Most of the X and Y chromosomes contain unrelated DNA sequences, and because of that pairing of the X and Y chromosomes during male meiosis is extremely limited and confined to the terminal regions of the chromosomes.

Two prominent regions of sequence homology lie at the terminal regions. At the very tips of the short arms, just internal to the telomere DNA repeats, there is a conserved major pseudoautosomal region, that contains 2.6 Mb of DNA with multiple genes. And, at the very tips of the long arms, there is a conserved minor pseudoautosomal region that is 0.32 Mb long with just a few genes. The pseudoautosomal regions are conserved because these two regions are involved in X-Y recombination in male meiosis and so can swap sequences by recombination between these two chromosomes. The sequences behave much like alleles at autosomal loci and, as a result, the sequences on the X and Y in these regions are essentially the same, just like autosomal alleles (hence the name *pseudoautosomal*).

Outside the pseudoautosomal regions, there are very few conserved regions. One is a region of roughly 99% sequence homology where the Y-linked sequence lies close to the major pseudoautosomal region and the corresponding sequence on the X is at Xp21 (see Figure 5.7). This region is a result of an evolutionarily recent X-Y transposition event where sequences were copied from one chromosome to the other.

Question 5.17

List three examples of a single gene disorder where there is extremely limited mutational heterogeneity and one example where different mutations in one gene result in a wide range of different diseases.

Answer 5.17

Sickle cell anemia results from a very limited range of mutations that each produce a change at amino acid position 6 in the beta globin chain, converting the normal glutamate to valine. Huntington disease is always caused by a modest expansion in the number of tandem CAG repeats within an array of these repeats located within exon 1. Achondroplasia is caused

exclusively by mutation at a single nucleotide, producing a glycine to arginine substitution at amino acid position 380 in the FGFR3 (fibroblast growth factor receptor type 3) protein. Different mutations in the *LMNA* (lamin A) gene can result in a wide variety of disorders, including different types of lipodystrophy, muscular dystrophy, cardiomyopathy, and progeria plus a neuropathy, Charcot-Marie-Tooth disease type 2B1.

Explanation 5.17
(see Table 5.1 on page 134 for a full list).

Question 5.18

For some single gene disorders, some members of a family who have the same genetic variants at the disease locus as strongly affected family members either show a much milder phenotype or no disease symptoms. List five explanations for why there can be a lack of penetrance or variable expressivity of a single gene disorder.

Answer 5.18

1) Epigenetic regulation. For example, lack of penetrance can occur when the disease locus is subject to imprinting and the disease allele is epigenetically silenced, according to the sex of the parent who transmitted it.
2) Heteroplasmy. For mitochondrial disorders, a woman may have a proportion of normal and mutant mtDNAs, and there may be significant variation in the ratio of mutant to normal mtDNAs in the eggs that she transmitted to her offspring.)
3) Modifier genes. Even in the case of single gene disorders the phenotype is not simply due to just a single gene. Other genes will interact with the gene at the disease locus in ways that can influence the phenotype. According to which alleles a person has at these modifier loci, the disease phenotype may be more or less severe.
4) Environmental factors. For example, dietary factors can be important in the expression of certain inborn errors of metabolism and affected cousins who are used to different diets may show significant differences in phenotype.
5) Anticipation. This observation applies to a very few disorders, such as myotonic dystrophy, where the pathogenesis is due to an unstable expansion of an oligonucleotide repeat and the pathogenesis is due to a *dynamic mutation* in which the repeat expansion increases from one generation to the next, producing an increasingly more severe phenotype.

In addition to the above, stochastic factors can explain differences in phenotype between affected individuals in the same family.

Question 5.19

What is meant by a selfish mutation? Illustrate your answer with reference to achondroplasia.

Answer 5.19

Achondroplasia is the most common form of inherited disproportionate short stature and is mutationally homogeneous in the sense that affected individuals always have a substitution at the same nucleotide position within the *FGFR3* gene that makes fibroblast growth factor receptor type 3; the substitution leads to replacement of glycine by arginine at amino acid position 380 of the FGFR3 protein.

Achondroplasia is quite common (occurring in about 1 in 30,000 live births) but the frequency of the disorder is not due to a high mutation frequency. Instead, the mutation is thought to be a *selfish mutation*: one that promotes its own transmission. De novo mutations that result in achondroplasia are always transmitted by the father, and it appears that male germ-line cells that contain the achondroplasia mutation may have a proliferative advantage and make a disproportionate contribution to sperm (so that there is a high allele frequency even although the mutation rate is not so exceptional).

Question 5.20

The Hardy-Weinberg law is an important law of population genetics that relates the frequencies of genotypes to allele frequencies. Summarize in one short sentence what it states about the relationship of genotype frequencies to allele frequencies.

Answer 5.20

It states that in a suitably ideal population the frequency of a homozygous genotype is the square of the allele frequency, and that the frequency of a heterozygous genotype is the product of the frequencies of the two alleles.

Question 5.21

What is the chief application of the Hardy-Weinberg law in clinical genetics?

Answer 5.21

As a way of calculating the risk of being a carrier for autosomal recessive disorders. That is possible starting from surveys of birth frequency of the autosomal recessive disorder. Say, for example the birth frequency of autosomal recessive disorder X is 1 per 10,000. We can use q to represent the frequency of all disease alleles and p to represent the frequency of all normal alleles (so that $p + q = 1$). All affected individuals must have two disease alleles, and so the Hardy-Weinberg law will give frequency of affected individuals as p^2 . As a result, $p^2 = 1/10{,}000$ and so $p = 0.01$ and $q = 1 - 0.01 = 0.99$.

Carriers must have one normal allele and one disease allele, and the frequency of the heterozygous genotype is given by the Hardy-Weinberg law as $2pq$ which in this case would be 2 x 0.01 x 0.99 which is very close to 0.02. Therefore the risk that a person with no known family history is a carrier of a mutant allele for disease X would be 0.02, that is, a risk of 1 in 50.

Question 5.22

The Hardy-Weinberg law assumes an idealized population in which mating is random and allele frequencies are constant. Allele frequencies can change in human populations over time but because the changes are often slow and occur in small increments, they often have minor effects. However, certain types of non-random mating can have a major effect on the accuracy of the Hardy-Weinberg predictions. What types of non-random mating occur that can threaten the applicability of the Hardy-Weinberg Law?

Answer 5.22

- Geographical barriers to random mating. Subsets of a population can be physically separated from the main population by certain geographical features, such as mountain ranges; the isolated subpopulation can develop rather different allele frequencies.
- Assortative mating: common ethnicity etc. Within cosmopolitan cities and societies many people prefer to choose a mate from the same ethnic, cultural and/or religious background. Because breeding is less frequent between members from different communities within the population, allele frequencies can vary significantly in the different communities. Geneticists therefore need to define populations carefully and calculate genetic risk by using the most appropriate allele frequencies.
- Assortative mating: shared phenotype. We also tend to choose a mate of similar stature and intelligence to us, for example. Positive assortment mating of this type leads to an increased frequency of homozygous genotypes and a decreased frequency of heterozygous genotypes. It extends to medical conditions. People who were born deaf or blind have a tendency to choose a mate who is similarly affected.
- Inbreeding. Quite frequent in many societies, it can result in genotype frequencies that differ significantly from Hardy–Weinberg predictions. Consanguineous mating results in an increased frequency of mating between carriers and a correspondingly increased frequency of autosomal recessive disease.

Question 5.23

A locus, *A* has two alleles, a major one, *A*01*, with a frequency of 0.7, and a minor one, *A*02*, with a frequency of 0.3. In a suitably ideal population, match the individual genotypes given in a) to c) with one of the expected values for genotype frequency that are located within the possible values given in i) to v).

Genotypes	**Possible values for genotype frequency**
a) *A*01-A*01*	i) 0.21
b) *A*01-A*02*	ii) 0.09
c) *A*02-A*02*	iii) 0.18

iv) 0.42
v) 0.98
vi) 0.49

Answer 5.23

a) vi)
b) iv)
c) ii)

Explanation 5.23

The genotype frequencies in a suitably ideal population are calculated from the Hardy-Weinberg law. This gives the frequency of homozygous genotypes as the square of the allele frequencies, and the frequency of a heterozygous genotype as twice the product of the individual allele frequencies. So, the frequency of *A*01- A*01* = 0.7 x 0.7 = 0.49; that of *A*02- A*02* = 0.3 x 0.3 = 0.09; and that of *A*01- A*02* = 2 x 0.7 x 0.3 = 0.42.

Question 5.24

Allele frequencies can change from one generation to the next in different ways. Often changes in allele frequency are quite slow, but occasionally the composition of populations can change quickly, producing major shifts in allele frequency. Describe four factors that can cause comparatively rapid changes in allele frequency.

Answer 5.24

1) *Purifying (negative) selection*. If a person affected by genetic disease is not likely to reproduce, disease alleles are lost from the population. This effect is much more pronounced in early-onset dominant conditions, in which—with the exception of non-penetrance—anyone with a mutant allele is affected by the time of puberty.
2) *New mutations.* New alleles are constantly being created by the mutation of existing alleles. Some mutations produce new disease alleles by causing genes to lose their function or to function abnormally. There are numerous different ways in which a 'forward' mutation can cause a gene to lose its function, but a 'back mutation' (*revertant* mutation) that can restore the function of a nonfunctioning allele has to be very specific and so is comparatively very rare.
3) *Influx of migrants.* If a population absorbs a large influx of migrants with rather different allele frequencies, then the overall gene pool will change.
4) *Genetic drift in small populations.* Only a certain proportion of individuals within a population reproduce. Out of all the alleles within the population, therefore, only those present in people who reproduce can be transmitted to the next generation. That is, a *sample* of the total alleles in the population is passed on and that sample is never exactly

representative of the total population for purely statistical reasons. The smaller the size of a population, the larger will be the random fluctuations in allele frequency and that can cause comparatively rapid changes in allele frequencies between generations.

Question 5.25

What is meant by biological fitness?

Answer 5.25

Biological fitness (*f*) describes a person's capacity to transmit genes to subsequent generations. It includes the capacity for a person to survive to a reproductive age plus the capacity to reproduce and bring up children that can themselves survive long enough to reproduce.

For severe, early onset inherited disorders, a person may not live long enough or be healthy enough to reproduce and would have an *f* value of 0 (whereas a normal fertile person would be assigned an *f* value of 1). For milder or late onset dominant disorders, the *f* value may be quite high and approach 1 in some cases.

For severe recessive disorders, an affected individual may have an *f* value of 0 but carriers effectively transmit mutant alleles to the next generation (they usually have an *f* value of 1).

Question 5.26

What is a founder effect? List three examples where a disorder is extremely frequent in a population as a result of a founder effect.

Answer 5.26

A founder effect means that the population frequency of an allele changes rapidly as a consequence of recent immigration. A founder effect that leads to a rise in frequency of a specific disorder can often be identified because of a high degree of mutational homogeneity in mutant alleles in affected individuals (because they originate from the same ancestral mutation or mutations). Three examples where a disorder is extremely frequent in a population as a result of a founder effect are as follows:

1) Myotonic dystrophy type I has a prevalence of 1 in 500 in the Saguenay-Lac St. Jean region of Quebec (30-60 times more frequent than in most other populations, as a result of recent immigration by French settlers.
2) Ellis van Creveld syndrome has a very high carrier frequency (of about 1 in 8) in the Amish population (which resulted from a single couple that immigrated to Pennsylvania in 1774).
3) Alzheimers type 3 (early onset) has a high frequency in remote villages in the Andes because of descent from a couple of Basque origin who settled in Colombia in the early 1700s.

Question 5.27

Certain recessive disorders appear to be common in the population as a result of balancing selection. What is meant by this? Illustrate your answer with specific examples of disorders to which this applies.

Answer 5.27

Some recessive disorders are common in the population as a result of a type of *balancing selection* in which a mutant allele is simultaneously subject to purifying selection in homozygotes and positive selection in heterozygotes. As, a result, heterozygotes with one mutant allele and one normal allele have a higher biological fitness than both mutant homozygotes (who are affected) and normal homozygotes. This situation where heterozygotes actively benefit from having a mutant allele is known as *heterozygote advantage.*

Some of the best examples of heterozygote advantage come from the high incidence of certain types of blood disorder that are found in populations who are exposed (or were recently exposed) to a high risk of contracting malaria. Sickle-cell anemia provides a classic example. It is very common in populations in which malaria caused by the *Plasmodium falciparum* parasite is endemic (or was endemic in the recent past) but is absent from populations in which malaria has not been frequent. In some malaria-infested areas of West Africa, the sickle- cell anemia allele has reached a frequency of 0.15—far too high to be explained by recurrent mutation. Sickle-cell heterozygotes have red blood cells that are inhospitable to the malarial parasite (which spends part of its life cycle in red blood cells). As a result, they are comparatively resistant to falciparum malaria. Normal homozygotes, however, frequently succumb to malaria and are often severely, sometimes fatally, affected. Heterozygotes therefore have a higher fitness than both normal homozygotes and disease homozygotes (who have a fitness close to zero because of their hematological disease).

Heterozygote advantage through comparative resistance to malaria has also been invoked for certain other autosomal recessive disorders that feature hemolytic anemia, such as the thalassemias and glucose-6- phosphate dehydrogenase deficiency. The high incidence of cystic fibrosis in northern European populations and Tay–Sachs disease in Ashkenazi Jews is also likely to have originated from heterozygote advantage, possibly through a greater resistance of carriers to infectious disease.