

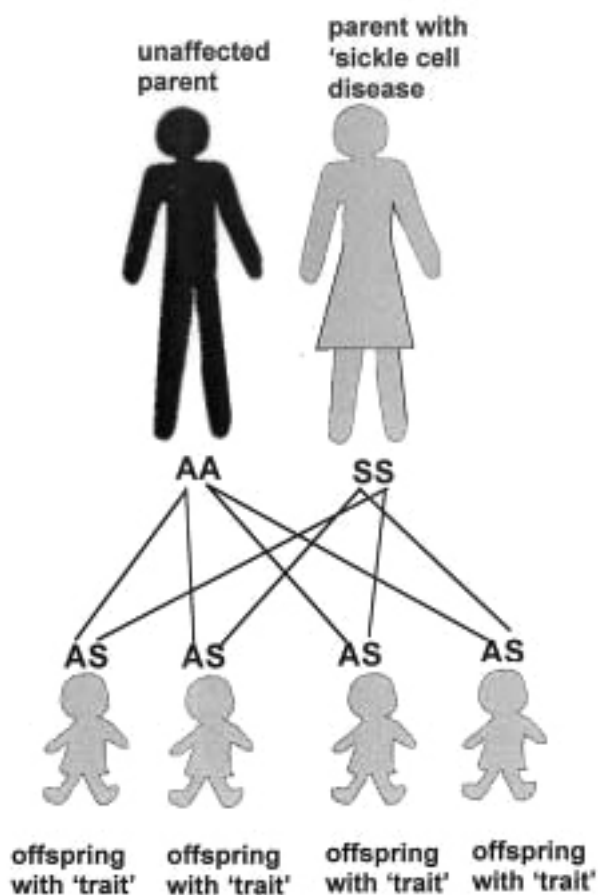
Genetics of sickle cell anaemia

Introduction

This activity is based on an article explaining the genetics. Several activities are included on the student sheet to focus their engagement with the text. You may not wish to do all of these.

The activity

1.



- (a) none
- (b) 100% /all of them
- (c) none

Science explanations

Gb The mechanism which explains evolution is natural selection. There is always variation between individuals in the same species. Some individuals will have characteristics which give them a better chance of surviving in a particular environment. Those individuals that survive will reproduce and pass on their characteristics to the next generation. The genes for the advantageous characteristic will become more common.

Gc Natural selection leads, over many generations, to a gradual change in the characteristics of a whole population.

2.

Genetic make-up: of individual	Characteristic of individual	Likely outcome with no malarial infection	Likely outcome with malarial infection
AA	unaffected	survives	dies young
AS	sickle cell trait	survives	survives
SS	sickle cell disease	dies young	dies young

3 The sickle cell allele only becomes common in areas where it gives an advantage to people carrying the allele.

In countries, such as Africa where there is malaria, carriers of the sickle cell allele (AS) are less likely to die of malaria than unaffected people (AA). The A allele becomes less common as AA people die young of malaria, and the S allele becomes more common because heterozygotes (AS) survive. In Northern Europe, the S allele gives no advantage, so remains rare.

4 Examples of ethical issues/ questions arising from the text:

(a) Often we judge the 'seriousness' of a genetic disease in terms of how easily it can be treated, and how much support a person with the disease may need from their family and the community. Social and economic factors may override judgements on the quality of the person's life from their point of view.

(b) How do decisions about which embryos should/ should not survive affect our attitude to people in the population with the disease being considered?

(c) Once a disease can be successfully treated, should we allow affected people to pass on their genes to future generations despite the potential economic implications of an increase in disease alleles?

(d) Do we have the right to judge the potential 'quality of life' of people with genetic disease?

(e) Germ line therapy would deliberately alter the human genome, so is 'playing God' to a greater extent than somatic gene therapy.

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Introduction

What is sickle cell disease?

Sickle cell anaemia was the first genetic disease to be described in terms of a gene mutation. The mutation changes the molecule haemoglobin, causing the red blood cells (RBC's) to become stiff and sometimes sickle-shaped when they release oxygen to the body tissues. The sickled cells tend to get stuck in narrow blood vessels, blocking the flow of blood. As a result, those with sickle cell disease suffer painful "crises" in their joints and bones. They may suffer strokes, blindness, or damage to the lungs, kidneys, or heart. They must often be hospitalized for blood transfusions and are at risk for a life-threatening complication called acute chest syndrome. Although many sufferers of sickle cell disease die before the age of 20, modern medical treatments can sometimes prolong these individuals' lives into their 40's and 50's.

How is sickle cell disease inherited?

There are two versions or **alleles** of the gene important for the inheritance of sickle cell anaemia : A and S. Individuals with two A alleles (AA) have normal haemoglobin, and therefore normal RBCs. Those with two S alleles (SS) develop sickle cell anemia. Those who are heterozygous for the sickle cell allele (AS) produce both normal and abnormal haemoglobin. Heterozygous individuals are usually healthy, but they may suffer some symptoms of sickle cell anemia under conditions of low blood oxygen, such as high altitudes or during exercise. Heterozygous (AS) individuals are said to be 'carriers' of the sickle cell gene. Both forms of haemoglobin are made in the AS heterozygotes (this is different from the situation with the more common dominant and recessive genes where either the dominant *or* the recessive characteristic is expressed). Heterozygotes are said to have 'sickle cell trait'.

Sickle cell anaemia and natural selection

In the United States, about 1 in 500 African-Americans develops sickle cell anemia. In Africa, about 1 in 100 individuals develops the disease. Why is the frequency of such a serious disease so much higher in Africa? The answer is to do with natural selection and malaria.

In the late 1940s, studies of diseases in populations suggested a connection between African populations, malaria and sickle cell disease. This is one of many examples where clinical observations led to further investigations, advancing other areas of biology such as molecular biology, genetics and physiology. The geneticist J. B. S. Haldane suggested a theory of how genetic diseases could evolve by natural selection; if the heterozygotes (AS) are protected from malaria, and the negative effects are only present in the small proportion of people who are homozygous for the affected allele (SS) the affected allele could become more common. In 1949 the molecular biologist Linus Pauling described differences between the structures of normal and sickle cell haemoglobin. It wasn't until the 1950s, when Watson and Crick proposed their model of DNA structure, that the links between genetic material (DNA), mutations, genetic diseases and proteins in cells were understood. Later studies supported Haldane's theory, showing that African children who are heterozygous for the sickle cell allele have a ten-fold reduction in their risk of getting malaria. The exact position of the sickle cell allele is now known, and gene therapy for sickle cell disease in mice has been successfully carried out early in the 21st century by treating the stem cells which give rise to red blood cells.

Malaria is characterised by chills and fever, vomiting, and severe headaches. Anaemia and death may result. Malaria is caused by a protozoan parasite (*Plasmodium*) that is transmitted to humans by mosquitoes. When malarial parasites invade the bloodstream of a person with the S allele, the red cells that contain defective haemoglobin become sickled and die, trapping the parasites inside them and reducing infection.

Compared to AS heterozygotes, people with the AA genotype (normal haemoglobin) have a greater risk of dying from malaria. AA homozygotes who die young may not pass on their genes to the next generation. Individuals with the AS genotype do not develop sickle cell anaemia and also have less chance of getting malaria. They are able to survive and reproduce in malaria-infected regions. AS heterozygotes pass on A and S alleles to the next generation, so both the A and S alleles of these people remain in the population. SS homozygotes have sickle cell anemia, which usually results in early death. S alleles are removed from the population's 'gene pool' when SS people die. In a region where malaria is common, the S allele gives a survival advantage to people who have one copy of the allele, and the otherwise harmful S allele is kept in the population at a relatively high frequency.

Is human evolution still happening?

The change in allele frequencies over time due to selection pressures is what Darwin described as 'natural selection'. The sickle cell allele gives a survival advantage only in populations living in an area where there is malaria. In all other areas, it is a disadvantage to have this allele. In the case of sickle cell anaemia, human culture changed the environment to favor an increase in the population of mosquitoes, and as a result of this an increase in malaria. From two thousand years ago, slash and burn forest clearance following the introduction of agriculture into sub-Saharan Africa produced a rapid increase in environments suitable for the mosquito. The sickle cell allele may already have appeared at several times during human evolution as the result of a mutation. Now, for the first time the allele became a valuable mutation. It was not immediately bred out of the population due to its harmful effects, as it would have been in other environments or at other times.

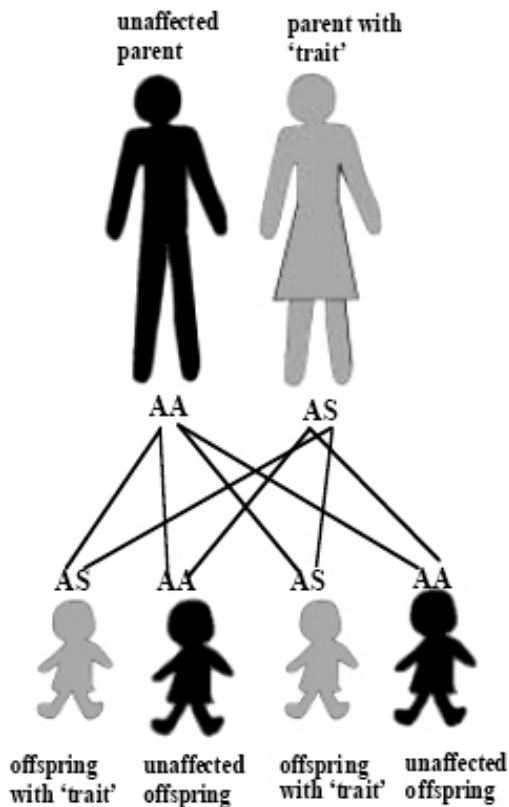
Alleles for other genetic diseases may have become common for similar reasons. The allele for cystic fibrosis was thought to have become common in Northern Europe during a period when a large percentage of deaths were due to diarrhoeal diseases such as dysentery and cholera. The allele gives some resistance to the dehydrating effects of diarrhoea, and heterozygotes are unaffected by the symptoms of cystic fibrosis.

Our attitude towards certain alleles, seen in the context of our 21st century environment, is strongly influenced by current social and economic factors. The sickle cell allele or cystic fibrosis alleles that were once an advantage in some areas may now have nothing but a negative effect on the quality of human life. Today, we have the technology to artificially remove such alleles from the population, for example by ante-natal genetic screening. Parents from families with these alleles are faced with decisions about whether it is 'right' to allow children with two copies of the allele to be born, when the technology exists to detect and abort such embryos.

Medical science is rapidly providing therapy for infectious diseases and many genetic diseases. People with diabetes or haemophilia would have died at a young age before insulin injections and clotting factor transfusions were available. Now these people can live normal lives. They can reproduce, passing on their genes to the next generation.

This generation influences human evolution, just as the Africans of 2 000 years ago influenced the frequency of the sickle cell allele. The ancient farmers did not have the knowledge or techniques available to purposely affect the human genome. The change in allele frequency was simply due to natural selection. Scientists nowadays have the technology to remove harmful alleles from the population. On the other hand, modern medical treatments and gene technology will potentially allow other harmful alleles to increase in frequency in the human population. Human intervention in human evolution may not necessarily be to the advantage of the species. Only germ-line therapy would ensure

that a 'cure' for a genetic disease is not temporary, for the lifetime of the individual with the disease, but will be passed on to future generations.



To answer

- 1 The diagram shows the alleles of parents and offspring where one of the parents is a carrier for sickle cell anaemia. Draw a similar diagram where one parent is unaffected and the other is homozygous for the sickle cell allele i.e. SS.

What proportion of the offspring from the second cross

- (a) are unaffected
 (b) have sickle cell trait (carriers)
 (c) have sickle cell anaemia?

- 2 Use the information in the text to complete the table below:

Genetic make-up of individual	Characteristic of individual	Likely outcome with no malarial infection	Likely outcome with malarial infection
AA			dies young
AS	Sickle cell trait	survives	
SS			

- 3 Explain why the frequency of sickle cell allele is so much lower in Northern Europe than in Africa.

- 4 In pairs, select one or two passages from the text where you would like to ask a question to clarify your understanding of the text. Write your question/s on a piece of paper or post-it note provided by your teacher, and display this along with the questions from the rest of the class.

Now choose a question written by another pair that you would like to try to answer. Discuss the answer with your partner. Make notes to help you when you discuss the questions in a larger group or class.

If there are any points in the text that you are still less confident about, make a note of these so you can research them for homework.