

Introduction

The heterozygote advantage, otherwise known as overdominance, is the term used for when a heterozygote for some gene mutation has an advantage over the homozygotes. For example, a recessive genetic disorder that can be fatal when the person is a homozygote can give a heterozygote added resistance to infection or an diminished symptoms to common diseases. The heterozygote advantage has been used to explain why some mutations that scientists would expect to die out have survived. They expected that the homozygotes with the recessive gene would have a decreased chance of reproducing while the heterozygotes would just become rarer. For this not to happen, there would inherently have to be some advnatage to being a heterozygote that would keep the gene from leaving the gene pool.

Sickle Cell Anemia and Malaria

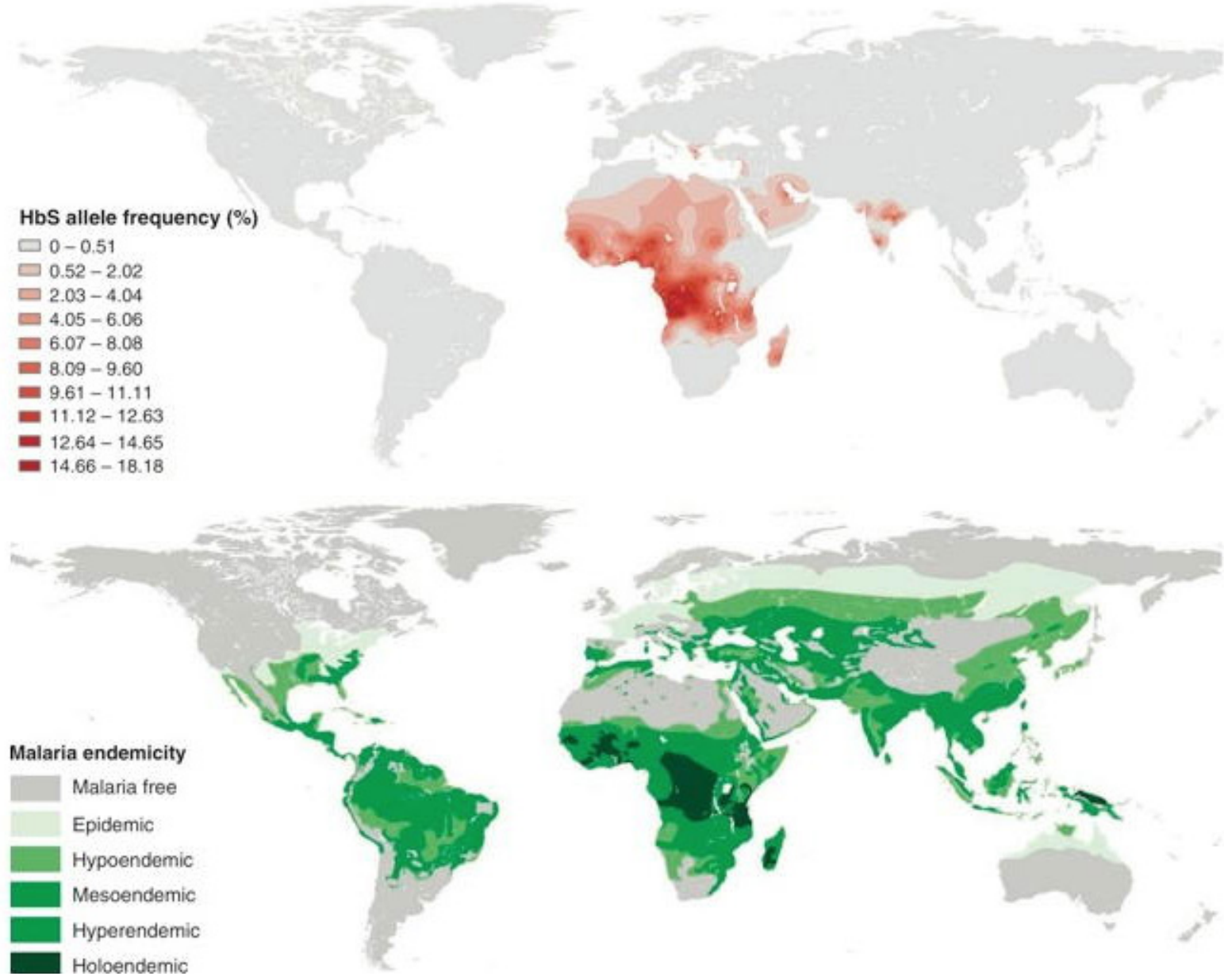
Sickle Cell Cell Anemia is an incompletely recessive hereditary blood disorder where the red blood cells take on abnormal crescent (sickle) shape, as seen below. Sickled cells reduce the flexibility and make the person prone to many different complications. The sickled cells occur, because of an abnormal hemoglobin protein, which is the oxygen-carrying molecule in my blood. The abnormality will cause the cell to lose oxygen and warp into the sickle shape. With the complications, it'd be expected that Sickle Cell Anemia would be quite rare, but that far from the case. Scientists studying this disorder noted that it was most prevalent in areas of the world with a lot of Malaria. In some areas, up to 40% of people carry the gene.

When a person is a heterzygote, they have a mixed phenotype where some of the cells have the abnormal shape, but not a large enough percent to negatively affect the person. When a heterzygote's red blood cells are infected with the Malaria parasite, the cells sickle. The spleen is able to identify and cull these sickled cells, eliminating the parasite before it is able to kill the person. The person is not immune, rather they have a higher chance of survival.



Sickle - cell anemia and malaria

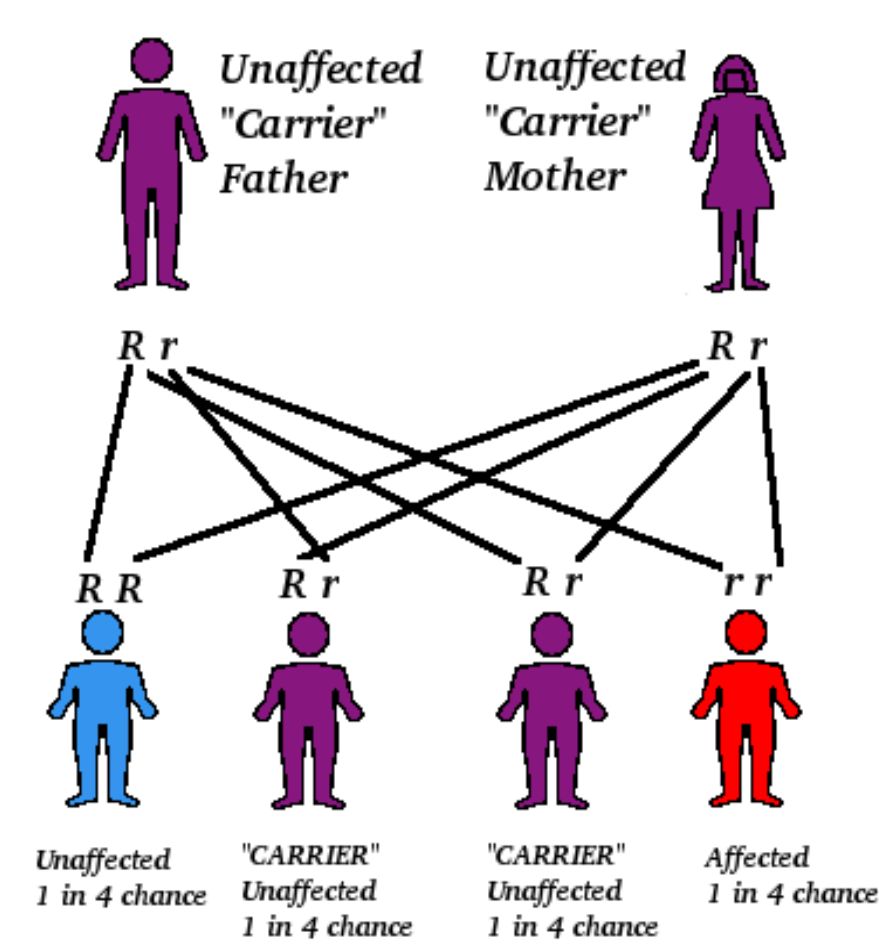
Piel *et al*
Nature Communications
1:104, 2010



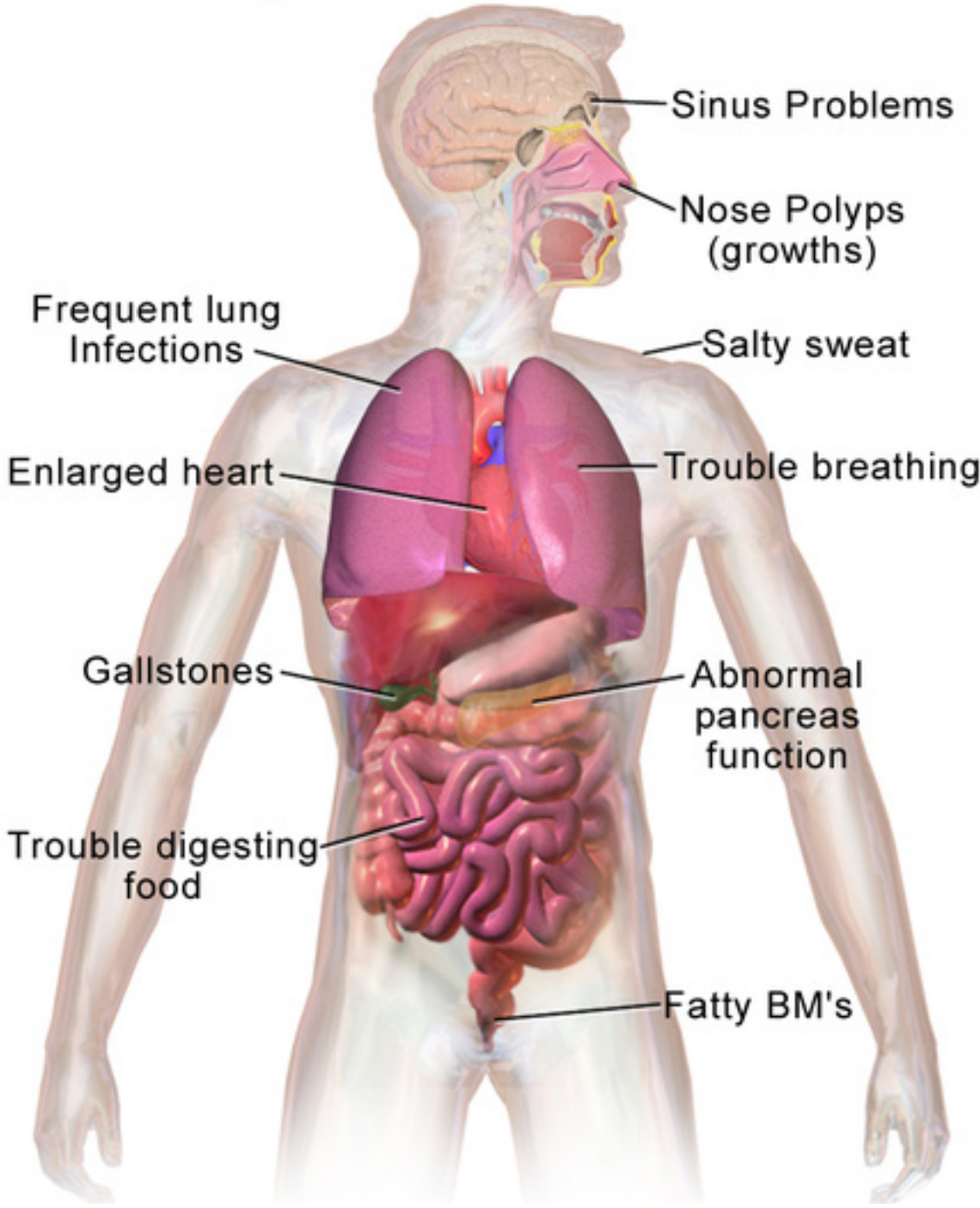
Heterozygote Advantage

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Principles of Modern Biology



Health Problems with Cystic Fibrosis



Cystic Fibrosis

Cystic fibrosis is a life-threatening, recessive genetic disease. The mutation occurs in the CFTR gene, which handles the transport of chlorine and sodium ions into and out of cells. Cystic fibrosis causes poor growth, poor weight gain, respiratory issues, and sticky mucus to build up in the lungs, digestive tract and other parts of the body. Just like Malaria, scientists would expect the mutation to disappear, but it has been found to be common in European countries.

To explain cystic fibrosis' prevalence, scientists have suggested multiple diseases where being a heterozygote for cystic fibrosis might be advantageous. None of the diseases have been conclusively confirmed. Some scientists believe a heterozyote who gets cholera or typhoid fever will not lose as much fluid to diarrhea. Other claims have been made being a heterozygote gives some resistance to tuberculosis These diseases are international, though, so some scientists theorize that the advantage conferred by cystic fibrosis is cancelled out by an increased loss in salt from sweat. Europe, with its milder climate, is one of the few places where the advantage can be truly effective.

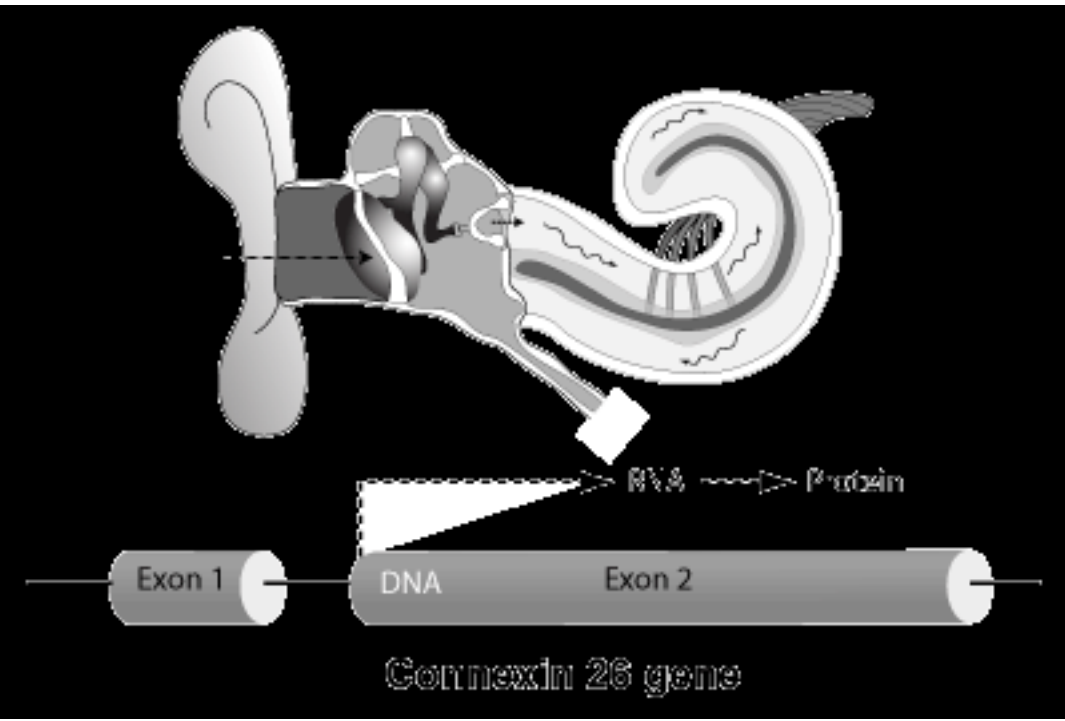
Species (breed)	Trait	Gene	Heterozygote	Homozygote
Cat (Manx)	Taillessness	<i>M</i>	Short tail	Lethal
Dog (boxer)	White spotting	<i>MITF</i>	White spotting pattern	Deafness
Dog (ridgeback)	Hair ridge	<i>FGF</i>	Dorsal hair ridge	Dermoid sinus
Dog (whippet)	Muscle (myostatin)	<i>MSTN</i>	More muscle, fast racer	Double muscle (euthanized)
Pig	Halothane sensitivity	<i>RYR1</i>	High lean-meat content	Porcine stress syndrome
Sheep	Fecundity	<i>BMP15</i> , <i>GDF9</i>	Increases fecundity	Infertility
Horse*	Leopard complex spotting	<i>TRPM1</i>	Leopard complex spotting	Congenital night blindness
Wolf*	Black coat	<i>CBD103</i>	Black	Low survival and recruitment

*In wild populations.

Deafness and Decreased Infection Risk

The most common cause for non-syndromic deafness (deafness not associated with other symptoms) is caused by a recessive mutation in a gene called GJB2. This gene codes for the protein Connexin 26. This mutation accounts for 50% of genetic, non-syndromic deafness is found in as many as 1 in 30 Americans. This high carrier frequency lead researchers to look for a heterozygote advantage.

Researchers have found that heterozygotes will not experience deafness, but will have a thickened skin layer and an increased capacity for cell repair, both of which help the person fight off infections.



Lysomal Storage Disorders

Four recessive lysomal storage disorders have been claimed to be examples of the heterozygote advantage. Tay Sachs, Gaucher's, Niemann-Pick and mucopolidosis type IV lead to excessive storage by lysosomes of sphingolipids, a substance that promotes growth of neural axons. The extra sphingolipids could then increase learning capacity. In Israel, it has been found being an engineer or scientist is 6 times more common among people with Gaucher's compared to the rest of the population.

MHC heterozygosity and Scent

There have been a multiple studies that show that women prefer the scent of men who who are heterozygotes for all three of the MHC genes (Major Histocompatibility Complex). Some scientists argue that this heterozygosity allows the person to fight a wider range of diseases, which has been partially confirmed in mice.

Criteria for Heterozygote Advantage

While all these examples, claim to show the heterozygote advantage, not all have been proven to show it. Some are just claimed examples of the heterozygote advantage. To officially be a heterozygote advantage, the following is necessary (according to one researcher):

- The gene and alleles must be identified.
- The relative fitness of each genotype must be known (and heterozygotes must have the highest relative fitness)
- The mechanism of selection is clear and proven so the basis for higher fitness is known.

References

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