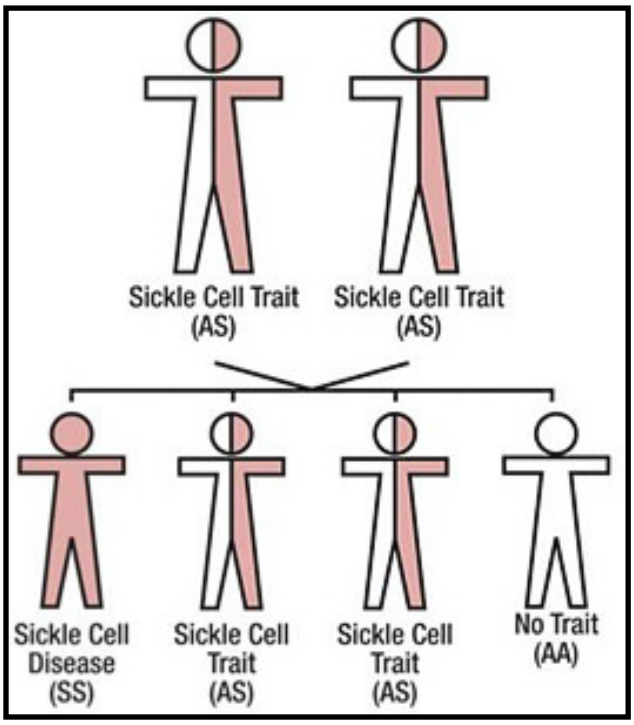
What a Difference a Valine Makes

Adapted from Robert L. Gering (Ward's Nautral Science), and Benjamin Wedro, MD, FACEP, F (MedicineNet)

People can dream, but their road to success can be derailed in the most unusual ways, perhaps none as strange as that which affected Ryan Clark of the Pittsburgh Steelers. When his team plays in Denver, the Mile High City, so named because it sits at an altitude of 5,280 feet, Clark is sidelined. This is because of an incident in 2007 in which Clark ended up critically ill requiring emergency surgery because of his genetics; he suffers from sickle trait, a condition that affects the shape and function of red blood cells. So when his teammates compete in the Mile High City, Clark is relegated to the sidelines.

Red blood cells are manufactured in the bone marrow. Their unique biconcave shape (think of squeezing a marshmallow between your fingers) increases their storage capacity for hemoglobin molecules that carry oxygen. They also make the cells pliable and soft so they can squeeze through the tiniest blood vessels in the body. In sickle disease, the red blood cells form an abnormal crescent shape that is rigid, causing the red blood cells to be damaged. The cells aren't malleable enough to get through tight spaces, and this can increase the risk of forming blood clots in the small capillaries of different organs causing the potential for organ damage.

Sickle cell disease is a genetic disease that most commonly affects people whose heritage is usually African or Caribbean. Patients with full blown sickle cell anemia have inherited a sickle gene from each parent and are usually diagnosed in childhood as having this autosomal recessive disease. Autosomal means that the gene is not located on either the X or Y sex chromosome. Recessive means that you need to have two copies of the involved gene to have the disease. If only one parent passes on that "bad gene," the disease may not be present, or in the case of sickle disease, the patient is said to have sickle trait. People with sickle trait usually live normal lives and have very few, if any, symptoms. Unfortunately, that is not always the case.



In the U.S., full-blown sickle cell anemia affects about 100,000 people, but almost two million more have the sickle trait. In sickle trait, symptoms rarely occur but are usually are brought on by exercise, presumably because of lactic acid production as the body moves from aerobic to anaerobic production. This may be why Mr. Clark became ill playing football in Denver. There is less oxygen available in the air at high altitudes and the intense exercise and dehydration caused his normally-shaped red blood cells to morph into the sickle shape.

Perhaps one of the most affected organs of the body in sickle disease is the spleen, whose job it is to filter the blood, get rid of debris, and to remove damaged red blood cells. Sickled red blood cells clog up the filter system and can cause the spleen to become enlarged, swell with blood, and cause shock. And a variety of other organs can also be involved, most often causing a pain crisis because the blood supply is interrupted when the sickle cells obstruct the small capillaries. Catastrophes like stroke, loss of vision, kidney failure, and other complications may occur. There are too many complications to discuss here, but commonly in sickle disease, spleen function is gradually lost as blood vessels become blocked and the spleen dies or infarcts. The role of the spleen in the immune system is also lost, and immunizations may be needed to fight off common causes of infection, especially the pneumococcus bacteria. This same immunization is also given to any patient who has needed a splenectomy (an operation to remove the spleen).

A person who has sickle trait does not have any symptoms unless he or she is unlucky enough, because of unusual circumstances, to have normal red blood cells turn into sickled ones. The risk of sickle trait in athletes is well recognized. After the death of a college athlete in 2006, the NCAA began recommending testing of all athletes whose sickle status was not known (most states routinely test newborns). If sickle trait is present, adjustments in the training programs can allow the athlete to reach his or her full potential. Taking a few extra seconds to recover between sprints or repetitive training sets and having oxygen supplementation on the sidelines and at practice can decrease the buildup of lactic acid and minimize the risk of sickling.

Mr. Clark's story is a reminder that while a person may appear fit, there is always potential danger that lurks under the surface. There is a common theme that reasserts itself in medicine and in life; prevention is easier than dealing with disaster.

Finding the Basis of Sickle Cell

In 1948, L. Pauling became interested in the sickle cell anemia. Using electrophoresis, he was able to distinguish between normal hemoglobin and sickled hemoglobin.

Then V. Ingram and his associates started to determine the exact structural difference between sickle cell hemoglobin and normal hemoglobin. Using a combination of electrophoresis and paper chromatography, Ingram's group identified the difference between the two types of hemoglobin. Normal hemoglobin (Hb^A) differs from sickle hemoglobin ((Hb^A) by only one amino acid component. In order to understand what this means, we need to look at the hemoglobin molecules itself.

Each human red blood cell contains about 280 million hemoglobin molecules. The hemoglobin molecule has two equal parts: one part consists of two identical polypeptide chains, called alpha chains. The second part also consists of two identical polypeptide chains, called beta chains. Each alpha chain consists of 141 amino acids joined together in linear sequence (by peptide bonds). Each beta chain consists of 146 amino acids joined together in linear sequence (by peptide bonds). An oxygen-containing heme molecule (containing a charged iron atom) is attached to each of the 4 polypeptide chains. Thus, each hemoglobin molecule has 4 molecules of heme, as well as 4 polypeptide chains.

Ingram and his associates found that the alpha chains in both normal ((Hb^{A}) and sickle hemoglobin (Hb^{A}S are identical; and that there is only a single amino acid difference in the beta chains. Normal hemoglobin (Hb^{A}) has a glutamic acid component in position 6 from its amino terminus of the chain; whereas sickle hemoglobin (Hb^{S}) substitutes a valine component at the same position. What difference does this make? Glutamic acid has an extra carboxyl group which ionizes giving it more of a hydrophilic characteristic; valine does not – its R-group is hydrophobic. Therefore normal hemoglobin ((Hb^{A}) is slightly more ionic than sickle hemoglobin (Hb^{S}). This difference expresses itself under conditions of oxygen deficiency when sickle cell (Hb^{S}) hemoglobin becomes less soluble than normal (Hb^{A}) hemoglobin. Herein lies the answer to the distinctive characteristics of the sickle hemoglobin.

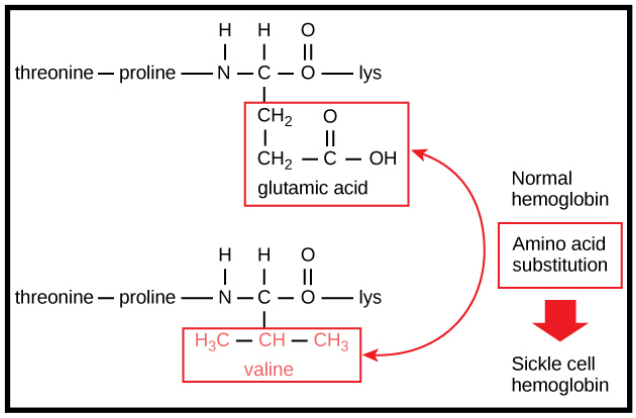
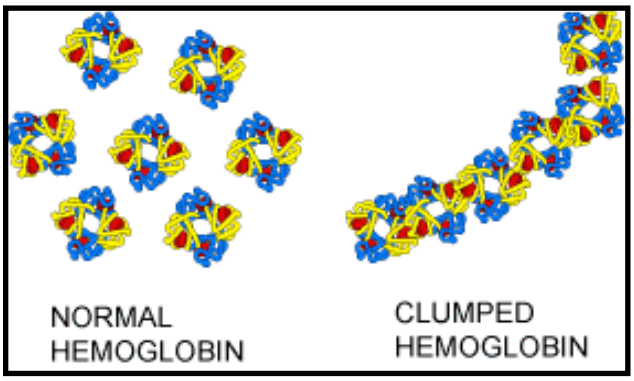


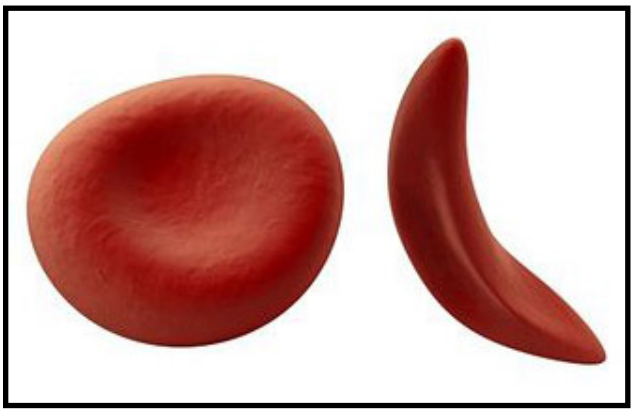
Figure: Glutamic acid, in normal hemoglobin, ionizes a proton from its carboxyl group in the cytoplasm of cells. Therefore, the carboxyl group will have a negative charge. This makes it more hydrophilic vs the hydrophobic R-group of valine.

When red blood cells travel to the lungs, hemoglobin molecules bind oxygen molecules at their heme groups. At the level of the lungs, normal hemoglobin (Hb^{A}) within the cells has a solubility of 100%. Oxygenated sickle cell hemoglobin also has a solubility of about 100%. However, when normal (Hb^{A}) hemoglobin gives up its oxygen in the capillaries of the bodily tissues, its solubility is reduced about 50%, BUT still remains in solution. In contrast, because of the ionic differences mentioned above, deoxygenated sickle cell (Hb^{S}) hemoglobin loses about 98% of its solubility. Thus, in oxygen-deficient capillaries and venous blood, sickle cell hemoglobin becomes insoluble and begins to precipitate out of solutions.

Sickle cell hemoglobin tends to form into long, thick rods as it precipitates. This entails a polymerization of individual hemoglobin molecules (clumped hemoglobin).



These rods become longer than the diameter of the cell, distorting the cell into its distinctive sickle cell shape.



In the homozygous condition (Hb^{S}Hb^{S}), the victim only has sickled hemoglobin. When this hemoglobin precipitates many cells are distorted, blocking smaller blood vessels and producing localized areas of oxygen deprivation. This leads to the deleterious

long range effects of sickle cell anemia. Furthermore, many of the red blood cells are destroyed, leading to the characteristic anemia. When vascular blockage is extensive the patient suffers extremely painful “crises” which ultimately can be fatal.

On the other hand, heterozygous (Hb^AHb^S) carriers have about 40% sickle cell hemoglobin and 60% normal hemoglobin. Apparently, this proportion prevents obvious symptoms of the condition from developing, except in unusual conditions (eg. high altitudes).

What helps to keep the sickle cell allele frequency high in certain populations?

You would think that over time, the frequency of the sickle cell allele would decline as affected individuals die off (assuming that they did not reproduce). However, in certain parts of the world, the frequency of the sickle cell allele remains fairly high. This is the case in Africa Mediterranean countries, the Carribean. One might wonder, why particular regions of the world would have such a high allele frequency. For an answer to this, one must turn to the surrounding environment of these areas. These areas have high amounts of mosquitoes, insect vectors that carry the parasite underlying Malaria. Examine the correlation of sickle cell allele frequency in Africa compared to areas that have a high incidence of Malaria.

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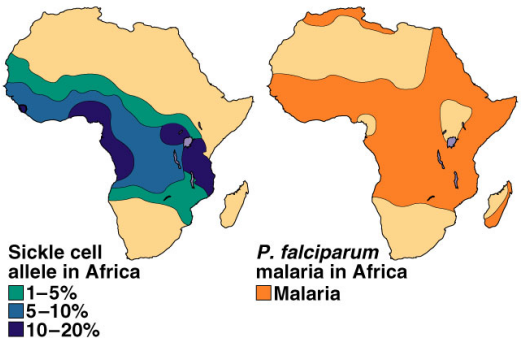

So what’s the association?

Research has shown that heterozygous carriers of the sickle cell allele are resistant to malaria. Here is one probable scenario: The parasitic malaria organisms enter some of the victim’s blood cells. The parasites’ high metabolic rate rapidly uses up oxygen in the red blood cell. The oxygen level drops below the critical level. Sickle hemoglobin present precipitates and forms rods, thereby distorting and damaging the infested red blood cell. White blood cells rush in and destroy the damaged cells along with any malaria parasites present. Thus individuals with sickle cell hemoglobin enjoy protection against and resistance to malaria. Those having only normal hemoglobin do not, and thus would succumb to malaria if infected.

Therefore, the sickle cell trait is an advantageous trait in endemic malarial areas, where its gene frequency may reach 40%. However, this advantage comes with a high price, and it is a high one; those who are homozygous (Hb^SHb^S) have sickle cell anema, and thus are likely to suffer an early and painful death.

An awesome price to pay for survival of the heterozygous (Hb^AHb^S) population. In some non-malarial countries, such as Canada, the trait loses its survival advantage. Eventually, a new gene frequency equilibrium will be established. Through this slow process the gene’s frequency among American blacks is now down to 9%.