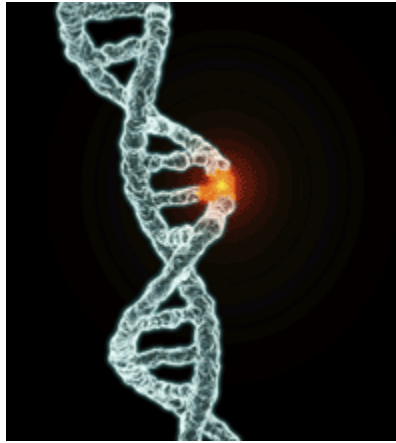


Genetics in Special Education Series

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Thalassemia

What do we know about heredity and thalassemia?

Thalassemia is actually a group of inherited diseases of the blood that affect a person's ability to produce hemoglobin, resulting in anemia. Hemoglobin is a protein in red blood cells that carries oxygen and nutrients to cells in the body. About 100,000 babies worldwide are born with severe forms of thalassemia each year. Thalassemia occurs most frequently in people of Italian, Greek, Middle Eastern, Southern Asian and African Ancestry.

The two main types of thalassemia are called "alpha" and "beta," depending on which part of an oxygen-carrying protein in the red blood cells is lacking. Both types of thalassemia are inherited in the same manner. The disease is passed to children by parents who carry the mutated thalassemia gene. A child who inherits one mutated gene is a carrier, which is sometimes called "thalassemia trait." Most carriers lead completely normal, healthy lives.

A child who inherits two thalassemia trait genes - one from each parent - will have the disease. A child of two carriers has a 25 percent chance of receiving two trait genes and developing the disease, and a 50 percent chance of being a thalassemia trait carrier.

Most individuals with alpha thalassemia have milder forms of the disease, with varying degrees of anemia. The most severe form of alpha thalassemia, which affects mainly individuals of Southeast Asian, Chinese and Filipino ancestry, results in fetal or newborn death.

A child who inherits two copies of the mutated gene for beta thalassemia will have beta thalassemia disease. The child can have a mild form of the disease, known as thalassemia intermedia, which causes milder anemia that rarely requires transfusions.

Thalassemia Major: A Serious Disorder

The more severe form of the disease is thalassemia major, also called Cooley's Anemia. It is a serious disease that requires regular blood transfusions and extensive medical care.

Those with thalassemia major usually show symptoms within the first two years of life. They become pale and listless and have poor appetites. They grow slowly and often develop jaundice. Without treatment, the spleen, liver and heart soon become greatly enlarged. Bones become thin and brittle. Heart failure and infection are the leading causes of death among children with untreated thalassemia major.

The use of frequent blood transfusions and antibiotics has improved the outlook for children with thalassemia major. Frequent transfusions keep their hemoglobin levels near normal and prevent many of the complications of the disease. But repeated blood transfusions lead to iron overload - a buildup of iron in the body - that can damage the heart, liver and other organs. Drugs known as "iron chelators" can help rid the body of excess iron, preventing or delaying problems related to iron overload.

Thalassemia has been cured using bone marrow transplants. However, this treatment is possible only for a small minority of patients who have a suitable bone marrow donor. The transplant procedure itself is still risky and can result in death.

Gene Therapy Offers Hope for a Cure

Scientists are working to develop a gene therapy that may offer a cure for thalassemia. Such a treatment might involve inserting a normal beta globin gene (the gene that is abnormal in this disease) into the patient's stem cells, the immature bone marrow cells that are the precursors of all other cells in the blood.

Another form of gene therapy could involve using drugs or other methods to reactivate the patient's genes that produce fetal hemoglobin - the form of hemoglobin found in fetuses and newborns. Scientists hope that spurring production of fetal hemoglobin will compensate for the patient's deficiency of adult hemoglobin.

Is there a test for thalassemia?

Blood tests and family genetic studies can show whether an individual has thalassemia or is a carrier. If both parents are carriers, they may want to consult with a genetic counselor for help in deciding whether to conceive or whether to have a fetus tested for thalassemia.

Prenatal testing can be done around the 11th week of pregnancy using chorionic villi sampling (CVS). This involves removing a tiny piece of the placenta. Or, the fetus can be tested with amniocentesis around the 16th week of pregnancy. In this procedure, a needle is used to take a sample of the fluid surrounding the baby for testing.

Assisted reproductive therapy is also an option for carriers who don't want to risk giving birth to a child with thalassemia. A new technique, pre-implantation genetic diagnosis (PGD), used in conjunction with in vitro fertilization, may enable parents who have thalassemia or carry the trait to give birth to healthy babies. Embryos created in-vitro are tested for the thalassemia gene before being implanted into the mother, allowing only healthy embryos to be selected.

Sickle Cell Disease

What do we know about heredity and sickle cell disease?

Sickle cell disease is the most common inherited blood disorder in the United States. Approximately 80,000 Americans have the disease.

In the United States, sickle cell disease is most prevalent among African Americans. About one in 12 African Americans and about one in 100 Hispanic Americans carry the sickle cell trait, which means they are carriers of the disease.

Sickle cell disease is caused by a mutation in the hemoglobin-Beta gene found on chromosome 11. Hemoglobin transports oxygen from the lungs to other parts of the body. Red blood cells with normal hemoglobin (hemoglobin-A) are smooth and round and glide through blood vessels.

In people with sickle cell disease, abnormal hemoglobin molecules - hemoglobin S - stick to one another and form long, rod-like structures. These structures cause red blood cells to become stiff, assuming a sickle shape. Their shape causes these red blood cells to pile up, causing blockages and damaging vital organs and tissue.

Sickle cells are destroyed rapidly in the bodies of people with the disease, causing anemia. This anemia is what gives the disease its commonly known name - sickle cell anemia.

The sickle cells also block the flow of blood through vessels, resulting in lung tissue damage that causes acute chest syndrome, pain episodes, stroke and priapism (painful, prolonged erection). It also causes damage to the spleen, kidneys and liver. The damage to the spleen makes patients - especially young children - easily overwhelmed by bacterial infections.

A baby born with sickle cell disease inherits a gene for the disorder from both parents. When both parents have the genetic defect, there's a 25 percent chance that each child will be born with sickle cell disease.

If a child inherits only one copy of the defective gene (from either parent), there is a 50 percent chance that the child will carry the sickle cell trait. People who only carry the sickle cell trait typically don't get the disease, but can pass the defective gene on to their children.

New Treatments Prolong Life:

Until recently, people with sickle cell disease were not expected to survive childhood. But today, due to preventive drug treatment, improved medical care and aggressive research, half of sickle cell patients live beyond 50 years.

Treatments for sickle cell include antibiotics, pain management and blood transfusions. A new drug treatment, hydroxyurea, which is an anti-tumor drug, appears to stimulate the production of fetal hemoglobin, a type of hemoglobin usually found only in newborns. Fetal hemoglobin helps prevent the "sickling" of red blood cells. Patients treated with hydroxyurea also have fewer attacks of acute chest syndrome and need fewer blood transfusions.

Bone Marrow Transplantation: The Only Cure:

Currently the only cure for sickle cell disease is bone marrow transplantation. In this procedure a sick patient is transplanted with bone marrow from healthy, genetically compatible sibling donors. However only about 18 percent of children with sickle cell disease have a healthy, matched sibling donor. Bone marrow transplantation is a risky procedure with many complications.

Gene Therapy Offers Promise of a Cure:

Researchers are experimenting with attempts to cure sickle cell disease by correcting the defective gene and inserting it into the bone marrow of those with sickle cell to stimulate production of normal hemoglobin. Recent experiments show promise. In December 2001, scientists at Harvard Medical School and MIT, supported by the National Institutes of Health (NIH), announced that they had corrected sickle cell disease in mice using gene therapy.

Researchers used bioengineering to create mice with a human gene that produces the defective hemoglobin causing sickle cell disease. Bone marrow containing the defective hemoglobin gene was removed from the mice and genetically "corrected" by the addition of the anti-sickling human beta-hemoglobin gene. The corrected marrow was then transplanted into other mice with sickle cell disease. The genetically corrected mice began producing high levels of normal red blood cells and showed a dramatic reduction in sickled cells. Scientists are hopeful that the techniques can be applied to human gene transplantation using autologous transplantation, in which some of the patient's own bone marrow cells would be removed and genetically corrected.

Is there a test for sickle cell disease?

Doctors diagnose sickle cell through a blood test that checks for hemoglobin S - the defective form of hemoglobin. To confirm the diagnosis, a sample of blood is examined under a microscope to check for large numbers of sickled red blood cells - the hallmark trait of the disease.

In more than 40 states, testing for the defective sickle cell gene is routinely performed on newborns.

Sickle cell disease can also be detected in an unborn baby. Amniocentesis, a procedure in which a needle is used to take fluid from around the baby for testing, can show whether the fetus has sickle cell disease or carries the sickle cell gene. If the test shows that the child will have sickle cell disease, some parents may choose not to continue the pregnancy. Genetic counselors can help parents make these difficult decisions.

A new technique used in conjunction with *in vitro* fertilization, called pre-implantation genetic diagnosis (PGD), enables parents who carry the sickle cell trait to test embryos for the defective gene before implantation, and to choose to implant only those embryos free of the sickle cell gene.