

# UNDERSTANDING BETA ( $\beta$ )-THALASSEMIA ON A GENETIC LEVEL



**AN INFORMATIONAL  
RESOURCE FOR PATIENTS**



**THE PURPOSE OF THIS BROCHURE** is to help you learn more about how  $\beta$ -thalassemia (thal) affects your body at the genetic level. Since  $\beta$ -thalassemia is caused by a change to a gene, it's important to understand the role of genes in your disease.

In the first few pages, we will review terms that provide a basis for understanding your body at the genetic level. Then, we will use those terms to learn more about:

- The effects  $\beta$ -thalassemia has on red blood cells and hemoglobin
- How  $\beta$ -thalassemia can affect your body
- Different ways to talk about your disease
- Treatment options for  $\beta$ -thalassemia

These topics can help you as you talk with your doctor about living with  $\beta$ -thalassemia and the goals you are working toward.



MY DOCTOR KNOWS A LOT ABOUT THAL, BUT I DIDN'T TELL HER ABOUT MY GOALS UNTIL NOW. I'M GLAD I'M TALKING WITH HER TODAY ABOUT HOW TO MANAGE MY DISEASE AND WORK TOWARD MY FUTURE PLANS.

Actor portrayals throughout. Not real patients.





## MY THAL. My today.

I'M WORKING HARD TOWARD BECOMING A PASTRY CHEF, BUT SOMETIMES MY TEACHER THINKS I'M JUST BEING LAZY. EVEN WHEN MY THALASSEMIA MAKES ME EXHAUSTED, I WILL NEVER LET THAT BE A REASON TO QUIT.

THIS CULINARY PROGRAM IS GONNA TAKE A LOT OUT OF ME, BUT IT'S GONNA BE WORTH IT.

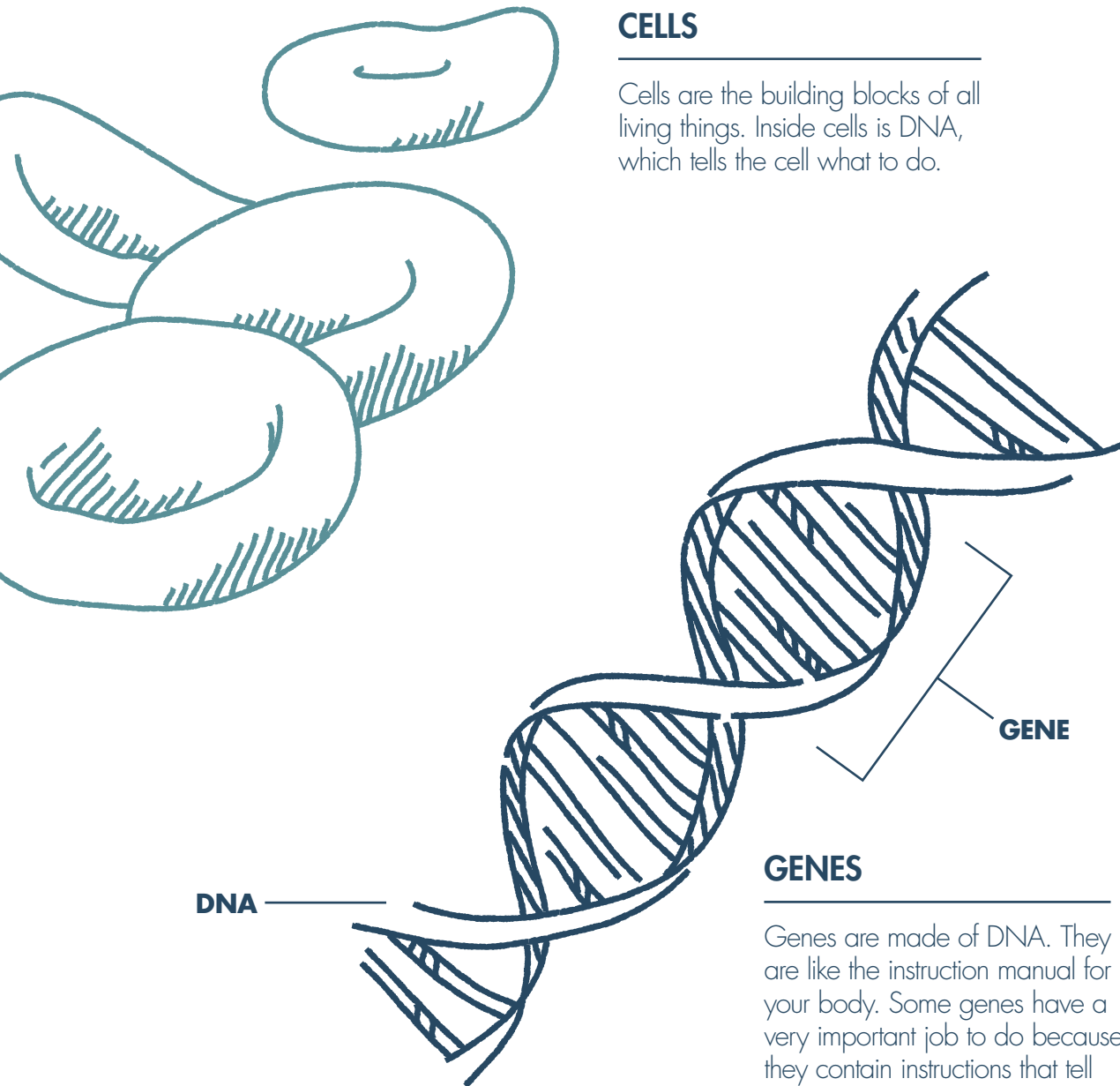
MY DOCTOR AND I ARE WORKING ON WHAT I CAN DO TO MANAGE MY DISEASE AND STILL ACCOMPLISH MY GOALS.

*Aiden*



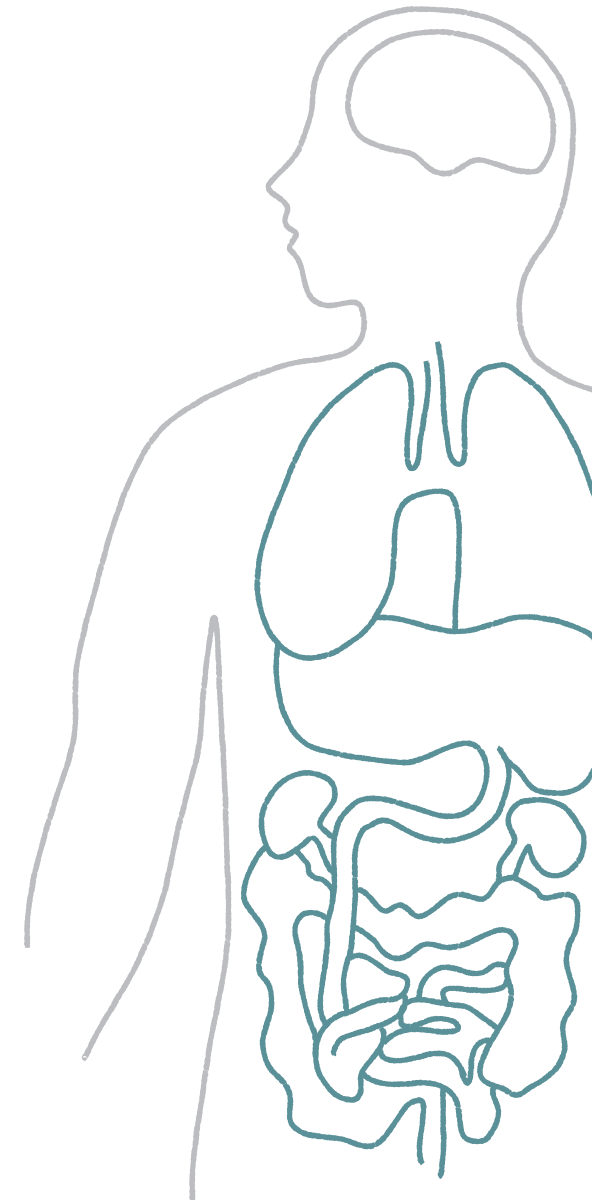
## WHERE TO START: CELLS, GENES, PROTEINS, AND YOUR BODY

Let's start by talking about terms—cells, DNA, genes, and proteins. It is important to know these terms so that you can understand how your body works. Then, you can learn how genetic diseases like  $\beta$ -thalassemia affect the functions of your body.



## BODY

In order to work properly, your body relies on the ways that cells, genes, and proteins work together. For instance, some genes instruct some cells to make proteins that facilitate communication between cells in different parts of your body.





# GENES AND GENOTYPES

In this section, we will go into more detail about 2 terms we just reviewed: **genes** and **proteins**. To better understand how genes and proteins work together, it may be helpful to first look at an example that is not related to  $\beta$ -thalassemia. One example of how genes and proteins work together is eye color.

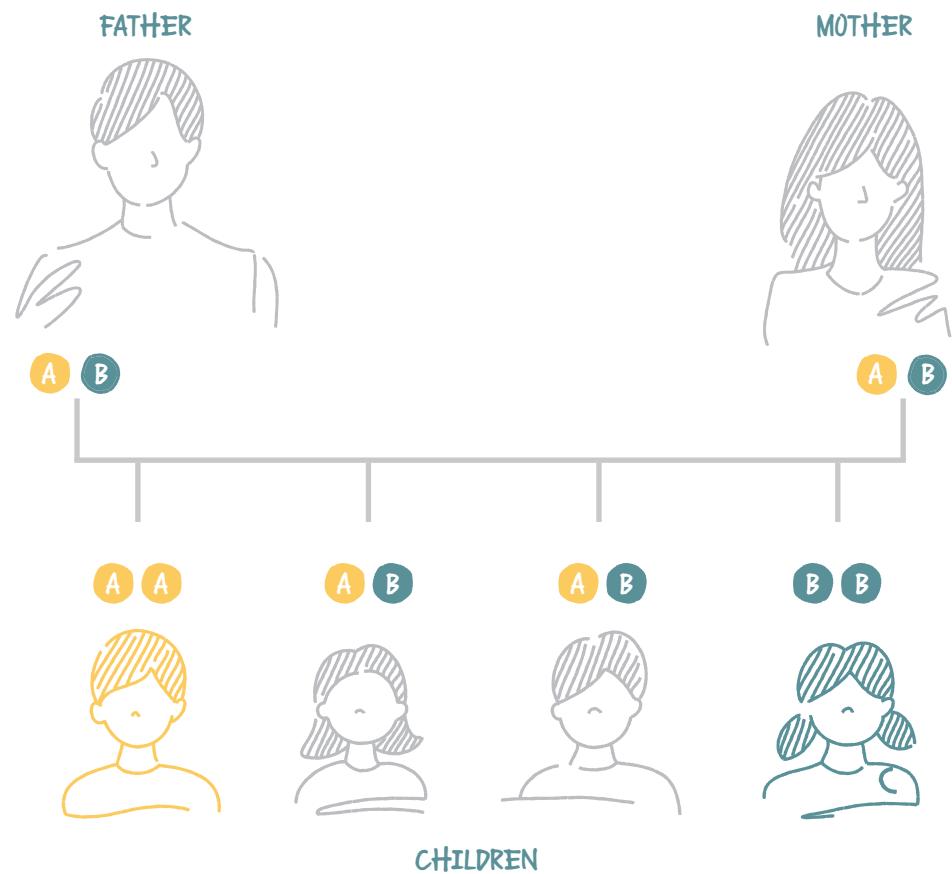
Based on the instructions from your unique genes, proteins create an eye color that is unique to you. In other words, genes instruct proteins that are involved in the expression of a physical trait (like eye color).

People receive genes from their parents. This is why children often look like their parents—they share physical traits (and other characteristics) from their parents' genes.

Genes usually come in pairs: 1 copy of the gene from your mother and 1 copy of the gene from your father. In the example below, the genes are represented by the letters A and B. Each child receives a unique pair of these letters, one from each parent. This pair of letters is called a **genotype**.

A genotype can be used to describe the general way a characteristic you inherit will show up in you. However, it is important to remember that your genes are unique to you. Even if you share the same genotype with other people, the inherited characteristic may not show up in the same way.

Later, we will talk about genotypes in  $\beta$ -thalassemia. First, we will learn more about how  $\beta$ -thalassemia affects your blood.



I LOVE PLAYING SOCCER WITH MY FRIENDS AFTER SCHOOL, BUT SOME DAYS, I JUST DON'T HAVE THE ENERGY. MAYBE I CAN TALK TO MY DOCTOR ABOUT HOW I CAN BE MORE ACTIVE.

## WHY IS THIS IMPORTANT TO KNOW?

Understanding the role that genes, proteins, and genotypes play in your body can help you better understand how  $\beta$ -thalassemia affects your body in a unique way.

# β-THALASSEMIA AND BLOOD CELLS

Here, we talk about a specific type of cells called red blood cells. We describe what makes up healthy red blood cells and how β-thalassemia affects these cells in people living with the disease.

## RED BLOOD CELLS AND HEMOGLOBIN

Red blood cells play an important role in your body. Their job is to carry oxygen from the lungs to the cells throughout your body. Oxygen is like your body's fuel—it is used to create energy.

Like all cells, red blood cells rely on a protein within the cell to do the actual work. In red blood cells, this protein is called **hemoglobin**. The hemoglobin in your red blood cells does the work of carrying oxygen throughout your body. When your red blood cells are healthy, each cell is densely packed with hemoglobin.

## HOW HEMOGLOBIN IS FORMED

The formation of hemoglobin starts with special cells called **blood stem cells**. These cells are most often found in the bone marrow. Blood stem cells form all types of blood cells, including red blood cells, white blood cells, and platelets. As blood stem cells become red blood cells, the genes inside the cells provide instructions to build hemoglobin.

Hemoglobin is made up of 4 smaller parts: 2 β-globin proteins and 2 alpha (α)-globin proteins. There must be an equal balance of β-globin and α-globin in order for adult hemoglobin to form properly. Each of the 4 proteins also includes iron. Iron is important because it holds onto oxygen so that it can be delivered to your body.

## WHAT CAUSES β-THALASSEMIA?

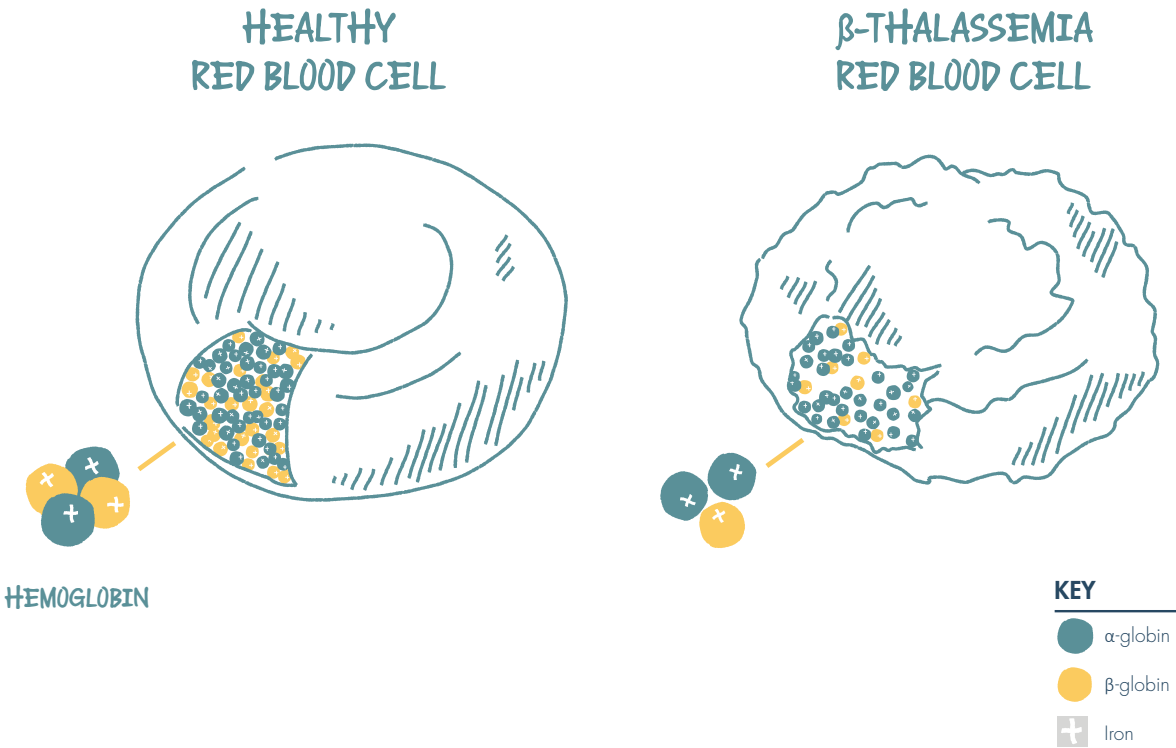
β-thalassemia is caused by a change in a specific gene called the *HBB* gene.

The instructions from the *HBB* gene create β-globin (a part of hemoglobin). With the change in the *HBB* gene, the instructions for β-globin are incorrect, and your body produces reduced or no β-globin. This affects how your red blood cells work.

# HEMOGLOBIN AND β-THALASSEMIA

When hemoglobin has an equal balance of β-globin and α-globin, it can do the job of delivering oxygen to your body. People with β-thalassemia do not have an equal balance of β-globin and α-globin.

Without the correct amount of β-globin, there is an excess amount of α-globin, which clumps together and causes your red blood cells to die early. Additionally, less β-globin means that less hemoglobin can form properly, causing your red blood cells to be smaller and become abnormally shaped. Due to these problems with your red blood cells, you do not have enough healthy red blood cells to carry oxygen to your body to meet its needs; this condition is called anemia.



In the next few pages, we will talk about how the lack of hemoglobin caused by β-thalassemia can affect your body.



## HOW $\beta$ -THALASSEMIA AFFECTS YOUR BODY

As you just learned,  $\beta$ -thalassemia affects how your red blood cells deliver oxygen to your body. If  $\beta$ -thalassemia is not treated, or poorly treated, it can lead to:

- Anemia (or lack of red blood cells)
- Fatigue and weakness
- Poor nutrition and failure to grow in children
- Pale or yellowing skin
- Deformity of the face and skull
- Infections
- Organs that do not function properly and become enlarged (usually the liver or spleen)
- Weakening and fragile bones that can cause pain

The effects of  $\beta$ -thalassemia differ from person to person based on how much  $\beta$ -globin your body is actually producing. Some people with  $\beta$ -thalassemia may get very sick when they are infants, while others do not have problems until they get older. There are people who can go their whole lives without ever having any symptoms.

Many people with  $\beta$ -thalassemia are treated with regular blood transfusions (see pages 16 and 17) that may lead to too much iron in their organs (iron overload [see callout below]). High levels of iron in the heart and liver can lead to life-threatening complications. It is important to keep talking with your doctor about what works best for you and keeps you healthy.

Understanding the genetic information behind your  $\beta$ -thalassemia can help you understand how the disease may affect you. In the coming section, you will see some of the ways that people talk about  $\beta$ -thalassemia, one of which connects directly to genes and genotypes—terms we've previously reviewed.

### WHAT ABOUT IRON OVERLOAD?

People with  $\beta$ -thalassemia may have high iron levels in their organs, including the heart and liver. This is sometimes called iron overload and may be part of the disease or result from treatment with transfusions.



# 3 WAYS TO TALK ABOUT β-THALASSEMIA

It can be confusing to understand the different ways people describe β-thalassemia. They are all ways of trying to group similar experiences together, but none of them is perfect. Each person living with β-thalassemia is completely unique and has their own experience of how the disease affects them.

## 01 TYPES OF β-THALASSEMIA

Historically, β-thalassemia has been classified into 3 main groups, based on the symptoms a person has and when they first started to show signs of the disease. The 3 main types are:

- **Thalassemia major**  
People show serious symptoms of disease between the ages of 6 months and 2 years; without regular transfusions, most of these people do not survive childhood
- **Thalassemia intermedia**  
People may show symptoms of disease later than thalassemia major, possibly not until adulthood, and may have no symptoms or have milder symptoms that do not require transfusions or only occasionally require transfusions
- **Thalassemia minor**  
(also called "β-thalassemia trait")  
Even though these people carry the disease (they may, in fact, be called "carriers"), they usually do not have any symptoms, although some people may experience mild anemia

## 02 GENOTYPES IN PEOPLE WITH β-THALASSEMIA

There are nearly 200 different changes in the *HBB* gene that can cause β-thalassemia. The different changes are grouped and represented by one of the letters shown below. When paired, these letters then create a genotype.

- β<sup>0</sup>: no β-globin is produced
- β<sup>+</sup>: a reduced amount of β-globin is produced
- β<sup>E</sup>: a reduced amount of β-globin is produced and the shape of hemoglobin is also affected; this genotype is most common in Southeast Asia

As discussed earlier, genotypes are often written as 2 letters, with 1 letter for the copy of the gene from each parent. People with β-thalassemia can have any mix of the 3 genotypes above. They may have 2 copies of β<sup>0</sup> (known as a β<sup>0</sup>/β<sup>0</sup> genotype), or 1 copy or no copies of β<sup>0</sup> (known as a non-β<sup>0</sup>/β<sup>0</sup> genotype).

Your genotype can be determined by a blood test and may help your doctor with treatment decisions. Many people with β-thalassemia learn their genotype when they are first diagnosed. If you're not sure what your genotype is, you can ask your doctor.

## 03 TRANSFUSION DEPENDENT OR NON-TRANSFUSION DEPENDENT

There are people living with β-thalassemia who receive regular red blood cell transfusions to help make up for their lack of healthy red blood cells. Some doctors are starting to categorize β-thalassemia based on whether or not a person depends on regular blood transfusions to survive and function. If a person needs regular transfusions, it is sometimes called transfusion-dependent β-thalassemia, or TDT. For patients who do not receive regular transfusions, the term non-transfusion dependent β-thalassemia (or NTD) may be used.

### DO YOU HAVE TDT?

The most straightforward way to talk about your β-thalassemia may be about whether you receive regular transfusions or not. If you are dependent on transfusions to manage your β-thalassemia, transfusion-dependent β-thalassemia (TDT) may be the most direct way to describe your disease.

Now that you know more about how β-thalassemia affects your blood and your body, as well as the different ways that people describe the disease, we will talk about treatments for people with TDT.



# TREATMENTS FOR TRANSFUSION-DEPENDENT $\beta$ -THALASSEMIA (TDT)

For people with TDT, there are currently 2 standard options for treatment:

- Regular blood transfusions, which help with the symptoms of TDT (anemia) but do not address the disease at the genetic level
- Stem cell transplant, which addresses TDT at the genetic level

Please note that the information here about treatment is for general educational purposes only. You should always speak to your doctor about the possible risks and side effects associated with treatments for  $\beta$ -thalassemia.

## GLOSSARY

### $\beta$ -thalassemia:

a genetic blood disorder that reduces or eliminates the production of  $\beta$ -globin

### Blood stem cell:

an immature cell that has the potential to develop into all types of blood cells, including white blood cells, red blood cells, and platelets

### Chelation therapy:

medicine that helps to reduce the amount of iron in your body

### DNA:

a material that is in almost all living things that carries genetic information

### Gene:

a sequence of DNA responsible for controlling inherited traits

### Genetic disease:

a disease that is caused by a genetic change

### Genotype:

your genetic makeup for any trait, which may be labeled with a pair of letters, each representing the copy of a gene inherited from one of your parents

### Hemoglobin:

a protein in your red blood cells that helps carry oxygen throughout your body; healthy adult hemoglobin contains iron and a balanced amount of  $\beta$ -globin and  $\alpha$ -globin

### Protein:

the working component of your cells that is required for the structure, function, and regulation of your body's tissues and organs

### Red blood cell:

a hemoglobin-containing cell that carries oxygen throughout your body

### Trait:

an inherited characteristic

### Transfusion-dependent $\beta$ -thalassemia (TDT):

a form of  $\beta$ -thalassemia that requires regular transfusions of red blood cells

# 2 STANDARD TREATMENTS FOR TDT

## BLOOD TRANSFUSIONS

People with TDT require regular blood transfusions in order to manage their symptoms. Blood from a donor contains working red blood cells that help to treat anemia. The new blood is able to deliver the oxygen (fuel) the body needs. After a blood transfusion, the level of healthy red blood cells in the body eventually becomes too low again and another transfusion is needed. Many people need a blood transfusion every 2 to 5 weeks to maintain a proper amount of red blood cells. While transfusions can help people with TDT, they do not treat the disease at the genetic level.

### Side effects from regular blood transfusions

Red blood cell transfusions with healthy red blood cells can contain a lot of iron—sometimes more than your body can naturally get rid of on its own. Over time, the iron from transfusions can build up on top of the excess iron you may have due to  $\beta$ -thalassemia. This iron collects in organs like the heart and the liver. Iron overload makes it difficult for the body to work properly. If iron overload is not treated, it can lead to serious complications, including damage to your organs.

## STEM CELL TRANSPLANT

A stem cell transplant (also called bone marrow transplant, or BMT) is a treatment that can potentially cure  $\beta$ -thalassemia by addressing the disease at the genetic level. A stem cell transplant aims to replace blood stem cells that contain a change to the *HBB* gene with blood stem cells from a donor who does not have the change. During a stem cell transplant, new healthy stem cells from a donor are added to the body.

Before the new cells are added, a form of treatment called conditioning (which is often chemotherapy) is used to make room in the bone marrow for the new cells. Over time, the goal of a stem cell transplant is for the healthy blood stem cells to make their way to the bone marrow and start to make new blood cells; this process is called engraftment.

In order to receive a stem cell transplant, an appropriate stem cell donor must be identified. This is so that the transplanted cells have the best chance of being accepted by your body. For the most favorable outcome, the donor should be genetically similar to the person receiving the stem cells. Generally, siblings are the people who are most genetically similar. About 25% to 30% of people have a matched sibling donor.

**If you want to know more about treatments for TDT, you should speak with your doctor about the benefits and potential risks (some of which may be severe) involved with these options.**

## HOW CAN IRON OVERLOAD BE TREATED?

You may experience iron overload either from  $\beta$ -thalassemia or from ongoing red blood cell transfusions. Your doctor may treat iron overload with special medications. This kind of treatment is called chelation (kee-LAY-shun) therapy. It is important that you take your medication for chelation therapy as prescribed by your doctor so that your iron levels are managed appropriately.



## MY THAL. My today.

SOMETIMES, THE BONE PAIN I EXPERIENCE FROM THALASSEMIA CAN GET IN THE WAY OF OUR ADVENTURES. I GET FRUSTRATED WHEN IT FEELS LIKE WE'RE NOT ABLE TO DO EVERYTHING WE HAVE PLANNED.

BUT THE IMPORTANT THING IS THAT I'M TRAVELING, AND—EVEN BETTER—I'M TRAVELING WITH HIM. I'M GOING TO CONTINUE TALKING TO MY DOCTOR ABOUT HOW TO PLAN TRIPS FOR US IN EXCITING NEW PLACES.

Emma

### WHAT ARE THE NEXT STEPS?

Now you have more information about your thal and how it affects you in a unique way. Are you ready to speak to your doctor about planning your tomorrow?



## REFERENCES

1. Baer K. A guide to living with thalassemia. Cooley's Anemia Foundation website. Accessed August 26, 2020. <http://www.cooleysanemia.org/updates/pdf/GuideToLivingWithThalassemia.pdf>
2. Baronciani D, Angelucci E, Potschger U, et al. Hematopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000–2010. *Bone Marrow Transplant*. 2016;51(4):536-541.
3. Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, eds. *Guidelines for the Management of Transfusion Dependent Thalassemia (TDT)*. 3rd ed. Nicosia, CY: Thalassemia International Federation; 2014.
4. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis*. 2010;5:11.
5. Genetics Home Reference. HBB gene. Accessed August 26, 2020. <https://ghr.nlm.nih.gov/gene/HBB>
6. Genetics Home Reference. Help me understand genetics: cells and DNA. Accessed August 26, 2020. <https://ghr.nlm.nih.gov/primer>
7. Genetics Home Reference. Help me understand genetics: how genes work. Accessed August 26, 2020. <https://ghr.nlm.nih.gov/primer>
8. Genetics Home Reference. What is DNA? Accessed August 26, 2020. <https://ghr.nlm.nih.gov/primer/basics/dna>
9. Marieb EN, Hoehn H. *Human Anatomy and Physiology*. 11th ed. Hoboken, NJ: Pearson; 2019.
10. National Cancer Institute at the National Institutes of Health. NCI dictionary of cancer terms: hematopoietic stem cell. Accessed August 26, 2020. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hematopoietic-stem-cell>
11. National Cancer Institute at the National Institutes of Health. NCI dictionary of cancer terms. Stem cell engraftment. Accessed August 26, 2020. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/stem-cell-engraftment>
12. Olivieri NF. The beta-thalassemias. *N Engl J Med*. 1999;341(2):99-109.
13. Schaefer GB, Thompson JN, Jr. *Medical Genetics: An Integrated Approach*. New York, NY: McGraw Hill Education; 2014.
14. Tiercy JM. How to select the best available related or unrelated donor of hematopoietic stem cells? *Haematologica*. 2016;101(6):680-687.