Understanding Pyruvate Kinase (PK) Deficiency

“My family understands—if you don't feel good, that's okay.”

Molly, 32
Diagnosed with PK deficiency at 9 months old

Information for caregivers

agios

Caring for someone with PK deficiency

As the parent or caregiver of someone with PK deficiency, you have many roles to fill.

Appointments, emotional support, sick days… the calendar can become very full, very quickly. And then there are other roles you may play: coworker, spouse, parenting other children.

Our goal for this brochure is to help you understand PK deficiency and the impact living with the condition can have on someone's life. Your doctor will provide medical advice, but having a good knowledge base helps ensure clear communication as you work with them to get your loved one the care they need. It also helps make sure everyone else on your loved one's team—family, friends, and teachers—is on the same page when it comes to responding to challenges your loved one may face.

Sometimes you may need someone to make a quick trip to the grocery store, or listen and provide emotional support.

It's also a good idea to have a family member or friend who understands your loved one's condition, to help out if there's ever a time when you simply can't be in two places at once.

So while you're building a team to help support your loved one, find a few key players who can back you up, too.

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At Agios, people living with genetically defined diseases are at the center of everything we do and every decision we make. Agios is a company committed to knowing more about PK deficiency and how it feels for those living with the disease.

Contents

What is PK deficiency?

PK deficiency is a rare, inherited enzyme deficiency that affects red blood cells (RBCs).

PK deficiency causes hemolytic anemia. Hemolytic anemia happens when RBCs are broken down faster than they are made.

Key Terms

Red blood cells (RBCs or erythrocytes): Cells that carry oxygen throughout the body

Anemia: A condition in which the blood has lower-than-normal levels of RBCs or hemoglobin

Hemoglobin: A protein that helps RBCs carry the oxygen your body needs

Hemolytic anemia: A type of anemia that is caused by the early breakdown of RBCs in the bloodstream or by the spleen

Hemolysis: The breakdown of RBCs, which leads to the release of hemoglobin into the blood and production of bilirubin

Chronic: Lasting a long time

Catalyze: To increase the rate of a chemical reaction

Enzyme: A protein that catalyzes chemical reactions that occur inside the body

Gene mutation: A permanent change in the DNA sequence of a gene, altering the gene's ability to make a protein and causing the protein to stop working properly

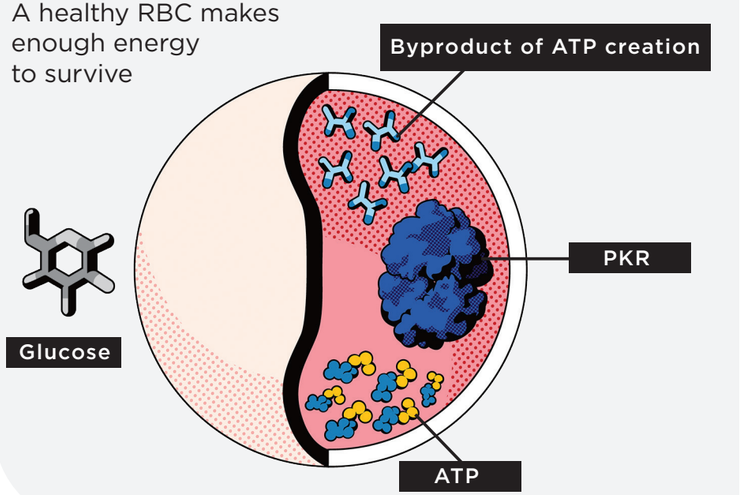
Deficiency: A shortage of something

PKR (pyruvate kinase in RBC): The pyruvate kinase enzyme

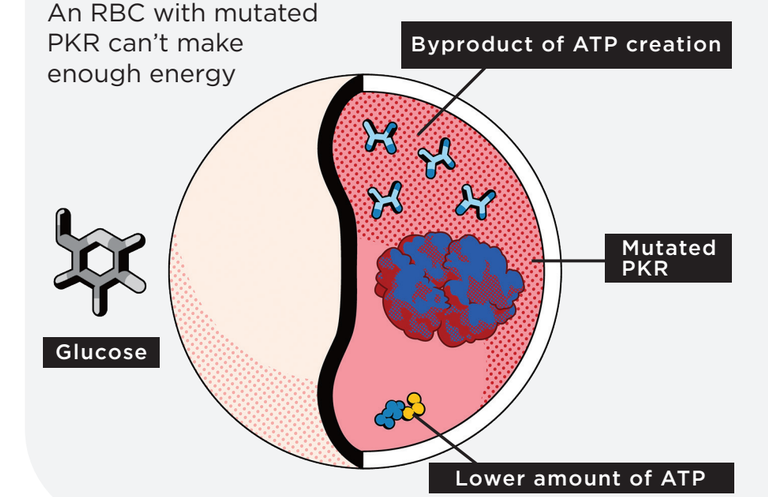
Glycolysis: The process of RBCs converting glucose (sugar) into pyruvate and ATP

ATP: The primary source of energy for cells

Healthy RBC



PK-deficient RBC



The PKR enzyme performs the last step of glycolysis. RBCs convert glucose (a sugar) into pyruvate to make ATP. Too little PKR means less ATP produced, so RBCs have less energy.

Healthy RBCs

After healthy RBCs are produced, they travel through the lungs, and oxygen binds to a molecule in the cells called hemoglobin. The RBCs then transport oxygen to the rest of the body. Healthy RBCs have enough ATP, or energy, made by the pyruvate kinase R (PKR) enzyme to survive this trip throughout the body.

Each RBC lives for about 120 days before being broken down and removed from circulation.

PK-deficient RBCs

RBCs that do not have enough PK, or that do not have properly working PK, have less ATP, so they die more quickly. The low levels of ATP can cause chronic hemolytic anemia (low RBC counts or low levels of hemoglobin).

DID YOU KNOW?

While healthy RBCs typically last 120 days, a PK-deficient RBC doesn't have as much energy, so it may only last a few days to weeks.

What causes PK deficiency?

PK deficiency is a genetic disease caused by a mutation in the *PKLR* gene. More specifically, it's an autosomal recessive mutation passed down from parents to their children. Genes are stretches of DNA that carry genetic information. They are found in long strips of DNA called chromosomes.

The *PKLR* gene tells the body how to make an enzyme called pyruvate kinase R, or PKR. In PK deficiency, the mutated gene creates PKR that doesn't work properly. As a result, RBCs can't make enough energy and die too soon.

Key Terms

Gene: Stretches of DNA. Different genes have different jobs, but many genes tell the proteins in our bodies how to work

Chromosome: A very long strand of DNA that's stored in the cell's nucleus and contains its genetic information. Each chromosome may contain hundreds to thousands of genes

DNA: The genetic material that tells a cell how to grow and what its job is

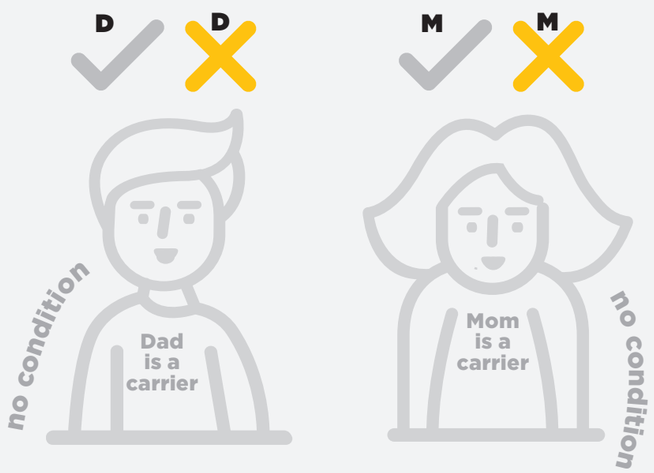
Autosomal recessive gene inheritance: A genetic disease that is inherited from receiving 2 nonworking copies of a gene

***PKLR*:** The gene for pyruvate kinase

Enzyme assay: A measurement, determined by a blood test, of how active an enzyme is

Autosomal recessive inheritance

Carrying mutated *PKLR*



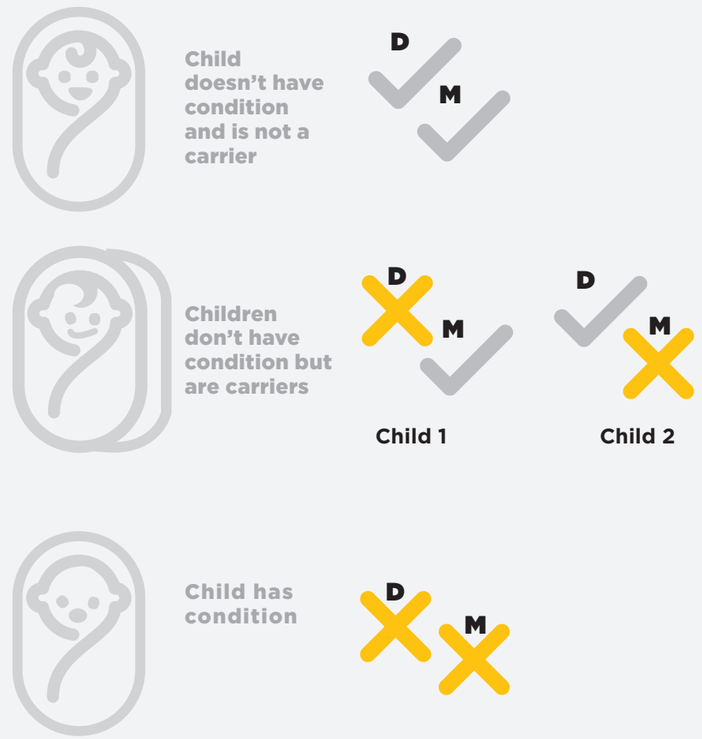
Working *PKLR* gene

Mutated *PKLR* gene

D Dad

M Mom

Inheriting PK deficiency



Doctors test for PK deficiency in 2 ways. They can test enzyme levels with an enzyme assay, and they can perform genetic tests to identify PKLR *gene mutations.*

AnemiaID *is an Agios-sponsored free testing program. Learn more in the Resources section.*

In an autosomal recessive gene inheritance, carriers, or parents, each have one copy of the mutated gene that they pass down to their child. Parents themselves do not usually have PK deficiency. To inherit the condition, a child receives a mutated *PKLR* gene from both parents.

DID YOU KNOW?

Over 300 different mutations of the *PKLR* gene have been identified. Approximately 25% of people diagnosed with PK deficiency have versions of the gene mutation that are newly discovered.

How does PK deficiency affect everyday life?

Signs and symptoms of PK deficiency are different for everyone and can change over time. Even siblings with PK deficiency can have different experiences.

Key Terms

Bilirubin: A substance created from hemoglobin when RBCs break down, which can cause jaundice and scleral icterus

Jaundice: Yellowing of the skin caused by high levels of bilirubin in the body

Scleral icterus: Yellowing of the whites of the eyes caused by high levels of bilirubin in the body

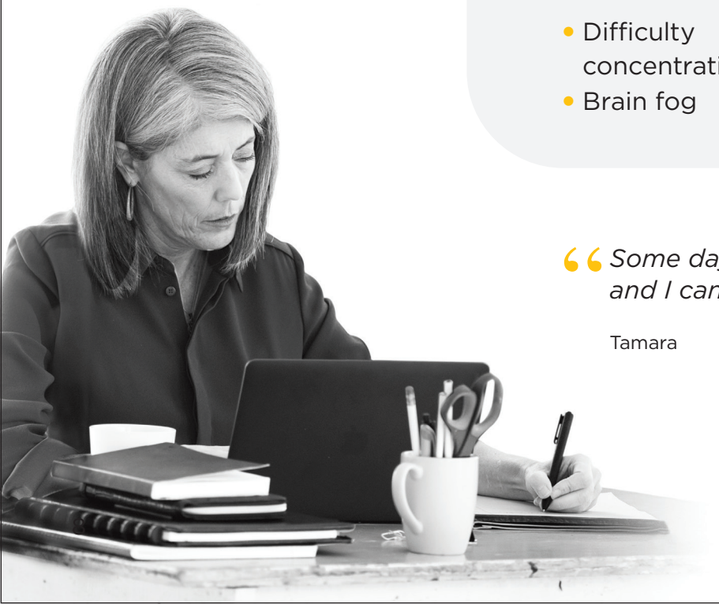
Cognitive difficulties: Problems associated with memory, language, thinking, and judgment

Common symptoms

- Debilitating fatigue
- Exercise intolerance
- Jaundice
- Scleral icterus

Some symptoms are cognitive

- Difficulty concentrating
- Brain fog
- Memory loss



“Some days are great and some are horrible and I can’t control it.”

Tamara

As with adults, symptoms and complications can vary widely between children.

Additional signs and symptoms

- Due to fatigue, babies may not be as interested in feeding
- Underfeeding, plus the fatigue PK deficiency can cause, may lead to irritability
- Talk to your child's doctor about how this could affect growth, so you can put a plan in place

- A parvovirus infection can cause the body to stop producing new RBCs (aplastic crisis). The virus usually causes fever and a rash on the face
- Stressors like infections can also cause hemolytic episodes. These can lead to the worsening of everyday symptoms
- Both aplastic crises and hemolytic episodes tend to be more frequent in childhood

- Jaundice can be difficult for children and teens because of others' reactions
- Enlist family and friends in supporting your child by helping them to understand why jaundice occurs. Let teachers know this symptom might trigger bullying
- Increased jaundice is a sign of RBCs breaking down. This breakdown may be accompanied by other symptoms, like fatigue
- In addition to jaundice, high bilirubin levels may cause gallstones. Symptoms include abdominal pain, nausea, and vomiting

It’s important to know what symptoms to look for, so you can keep your child’s healthcare team informed. New or worsening symptoms can mean PK deficiency isn’t under control. This could mean it’s time to reevaluate the management plan.

DID YOU KNOW?

As your child gets older, encourage them to interact directly with their healthcare team. It’s important that they feel comfortable asking questions, or for more explanation. Care for their PK deficiency will be a constant, so making sure they can speak up for themselves when they’re younger may make managing the responsibility easier in adulthood.

What are the complications of PK deficiency?

Different symptoms and complications can arise due to the effect PK deficiency has on RBCs. Complication severity can vary from person to person.

PK deficiency can cause iron overload in the blood. Iron can collect in the tissues of the body and damage the liver and heart. It may also contribute to other symptoms, such as fatigue and abdominal pain.

Key Terms

Spleen: An organ that filters blood, helps support the immune system, and removes old or damaged blood cells from the body

Splenomegaly: An enlarged spleen

Aplastic crisis: When the production of new RBCs temporarily stops

Gallbladder: An organ that stores and concentrates bile between meals

Gallstones: Small stones that form in the gallbladder

Iron overload: An excess of iron in the body

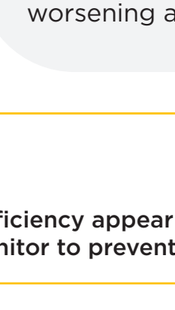
Ferritin: A blood protein that contains iron

Osteopenia: A decrease in bone mass or bone mineral density. In severe cases it can progress to osteoporosis

Osteoporosis: A disease in which the density and strength of bones are reduced

Endocrinopathies: Diseases of the body system that makes hormones

Complications of chronic hemolysis



A lack of healthy RBCs
Low amounts of RBCs reduce the amount of oxygen in the body, causing stress on the heart and lungs.

This can lead to:
- Tiredness and fatigue
- Headaches
- Shortness of breath
- An inability to exercise
- Cognitive difficulties
- Aplastic crisis
- Osteopenia/osteoporosis

The breakdown of RBCs
RBCs break down and release bilirubin into the bloodstream, causing:
- Jaundice and scleral icterus
- Bilirubin to build up in the gallbladder, creating gallstones

The removal of RBCs
As the spleen removes old or damaged RBCs, they may collect in the organ, causing splenomegaly. Working RBCs may also be removed, leading to worsening anemia.

Complications of iron overload

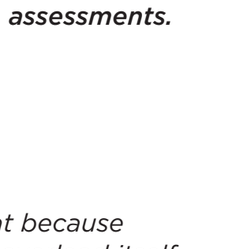
Everyone with PK deficiency is at risk for iron overload. While iron overload can be caused by frequent blood transfusions, many people with PK deficiency who don't get regular transfusions can also develop it—it can occur at any age, with any hemoglobin level.

- **Liver cirrhosis:**
  Scarring of the liver

- **Heart issues and pulmonary hypertension:**
  High blood pressure that affects the arteries in the lungs and right side of the heart

- **Osteopenia/osteoporosis:**
  In addition to iron overload and treatments for it, bone disease and/or bone fragility may be caused by the bone marrow expanding while trying to create new blood cells at a high rate

- **Endocrine/hormone problems**
  This includes testing for diabetes



Regular monitoring for iron overload is very important. Most hematologists recommend testing ferritin levels once or twice a year.

By testing the blood for ferritin (Fe), doctors can see how much iron is building up in the body. If ferritin levels exceed a certain amount (for example, ferritin greater than 500 nanograms per milliliter), be prepared to take action and ask about potential follow-up assessments.

DID YOU KNOW?

Some complications of PK deficiency appear later on in life, and may not have any signs. It's important to regularly monitor to prevent future risk.

> *"Iron overload is something to monitor and proactively treat because otherwise you would run into all the complications of iron overload itself, including liver disease, cardiac disease, and endocrinopathies."*
>
> S.S., PK deficiency specialist

How is PK deficiency managed?

There is no cure for PK deficiency. Your loved one's doctor may recommend some of the following options to manage symptoms and complications. Talk to your loved one's doctor to find out more.

Treatment effects on health can vary, and may impact other aspects of life. It's important to meet with your loved one's hematologist regularly so that management decisions are both timely and appropriate.

Key Terms

Transfusion: The process of putting blood into the bloodstream by intravenous (IV, meaning through the veins) infusion into the arm

Splenectomy: Surgical removal of the spleen

Cholecystectomy: Surgical removal of the gallbladder

Managing hemolytic anemia

RBC transfusions
To boost RBC levels, donated blood cells can be added to the bloodstream. The degree of anemia and symptoms that come with it are evaluated before adding transfusions to a management plan.

The need for transfusions can change over time. Young children may need them frequently and then outgrow them, while adults who have never had transfusions may find they need them as they age.

Splenectomy
The spleen may become enlarged due to RBCs breaking down. The spleen also sometimes removes RBCs that still work.

A splenectomy may be considered to increase RBC counts or prevent further complications. But people who have their spleen removed may be at higher risk for certain bacterial infections.

If a splenectomy is recommended for your child or loved one, make sure you both understand the risks and how to minimize them. Typically, splenectomies are not recommended for children under the age of 5.

Managing complications

Cholecystectomy
To prevent the ongoing risk of gallstones due to continued hemolysis, the removal of the gallbladder may be considered. Gallstones can cause nausea, stomach pain, or other forms of gallbladder disease.

Chelation therapy
To manage iron overload, a type of medicine called a chelation agent may be prescribed. Chelation agents bind with iron in the bloodstream to form a substance the body can remove more easily.

There are trade-offs in choosing management methods. For example, transfusions can help with fatigue but they can be time-consuming and have additional risks.

To learn more about management options, talk to a healthcare professional or download the* Fast Facts *brochure from KnowPKDeficiency.com.

> *I want everyone with PK deficiency to have a doctor who listens, and is there to give us what we need.*
>
> Molly

DID YOU KNOW?

While some doctors do provide RBC transfusions at their offices, many times they are administered at a transfusion center in a hospital or at a stand-alone location. One transfusion typically takes 1 to 4 hours.

Build a management plan with the right team

Studies show that patients who communicate well with their healthcare team are happier with their treatment and receive better care. Many different healthcare professionals will play an important role in managing PK deficiency.

Key Terms

Extramedullary hematopoiesis: Blood cell production occurring outside of the bone marrow, in organs such as the liver or spleen

DXA (or DEXA) scan: An X-ray performed to assess bone strength

MRI: A scan performed to look for iron overload in the liver and heart

Abdominal ultrasound: A test performed to look for gallstones or other complications involving the gallbladder

Echocardiogram (echo): A test assessing heart function and signs of pulmonary hypertension

Building a healthcare team

Hematologist
A doctor who specializes in blood disorders

Pediatrician, family doctor, or general practitioner
The doctor your loved one sees for checkups and yearly flu shots or other wellness visits

Registered nurse
In addition to nurses at your loved one's doctor's office, there are nurses who specialize in giving transfusions

Counselor or psychologist
Living with PK deficiency can cause stress and anxiety. It may help your loved one to have a support group or a mental health professional to talk to

DID YOU KNOW?

The need and timing of tests varies for everyone. Download the monitoring tool from KnowPKDeficiency.com and use it to help guide conversations about how often assessments should be done.

Regular evaluations help ensure your loved one is getting the right care. Many assessments to monitor for PK deficiency are done on a yearly basis, but some are done more often based on transfusion frequency, the need for chelation therapy, and discoveries from previous tests.

Know the tests for monitoring complications

Annual blood tests for:
- Degree of anemia (hemoglobin levels)
- Reticulocyte count (number of newly developing RBCs)
- Iron overload (ferritin levels)
- Vitamin D levels (to help assess bone health)
- Hormone changes (to check for diabetes, thyroid problems, or sex hormone levels)
- Viruses, such as HIV, and hepatitis A, B, and C (for people who receive transfusions)

Gallstones
Monitored by ultrasound if there is new or worsening abdominal pain, or if bilirubin levels are consistently high.

Iron damage to the heart or liver
Monitored by a yearly T2* MRI scan. Patients who receive regular transfusions, or who need chelation therapy, may need to be assessed more frequently.

Osteopenia and osteoporosis
A DXA should be done in early adulthood. Results of the scan determine how often the test should be repeated.

Pulmonary hypertension
An echocardiogram should be done after age 30. Doctors determine if the test needs to be repeated based on what the picture shows.

Extramedullary hematopoiesis
A visual exam is performed regularly, with further testing if there is unexplained swelling or symptoms that indicate signs of nerve damage, such as numbness, tingling, burning, or shooting pain.

PK deficiency affects more than just the body

Navigating a chronic condition can feel overwhelming. Symptoms and treatments of PK deficiency may have effects on mental health, but there are ways to find support.

If you are a parent or caregiver of a child or adolescent with PK deficiency, it may fall on you to communicate your child's emotions.

Encourage open discussions about feelings. Support groups for people caring for children with a chronic condition may be a resource for guiding these kinds of conversations.

Common mental health challenges

People with PK deficiency and their caregivers participated in a poll* and reported feeling:

Anxiety 84%

Depression 55%

Low self-esteem 61%

Social isolation 58%

If your loved one no longer takes enjoyment in activities, if everyday tasks seem too much, or feelings of sadness, emptiness, or guilt about their condition persist, it could be a sign of depression. It's important to talk to a healthcare provider about these feelings.

*Poll results found in *Voice of the Patient Report: Pyruvate Kinase Deficiency" from the National Organization for Rare Disorders.

DID YOU KNOW?

When asked about PK deficiency management methods, only 11% of participants responded that their current methods work very well. Continue gathering information and advocating for your loved one to find the right plan and team.

Because the impact of PK deficiency goes beyond physical symptoms, it's also important that the healthcare team understands your loved one's ability to cope with everyday activities. Physical plus emotional symptoms help paint the full picture.

> ***My parents got me into horses when I was 10. I couldn't do the swimming and the tennis and all the stuff that my sister did. The horses I could do, so I excelled at them. It gave me an outlet to not think about the bullying, the disease, and I was able to compete in an athletic event like other kids and do as well as them.***
>
> Robin

> ***There are different points in your life where it's harder versus other times where it's easier. That's important to know.***
>
> Tamara

> ***I ultimately found a physician willing to work with me; one who saw me as a person and who read the resources I shared with them. If you don't get that, it's okay to walk away and seek a second opinion. Ultimately, it was my body, my choices, and my life.***
>
> Molly

At the beginning of each school year, consider talking to your child's teacher and the school nurse about your child's condition. This can help them understand how PK deficiency may affect your child's participation. Visit KnowPKDeficiency.com to download a template for a "cheat sheet" you can share with them.

When should I talk to my child about PK deficiency?

The best time to talk to your child about their condition is when they start to ask you about it. At the beginning it may be enough to say, “because there are special cells in your body that don’t work the way they should.”

When the simplest answer isn’t enough, these questions and answers can be the start of building their knowledge. As your child grows, you can share other pages of this brochure that, together with conversations with your child’s healthcare team, can help increase their understanding.

Why do I have PK deficiency?
Everyone is born with certain traits, such as the color of their eyes or the shape of their nose. Traits come from your parents. For example, your eye color depends on what traits you get from both of your parents. PK deficiency is another trait you can be born with.

Why doesn’t everyone in my family have PK deficiency?
For someone to be born with PK deficiency, both of their parents have to have a trait that causes it. Sometimes, kids may only get one trait or no traits from their parents. Kids who are born with PK deficiency received the trait from both of their parents.

What causes PK deficiency?
Every cell in your body has a job to do. If one type of cell can’t do its job right, it can make you sick. With PK deficiency, red blood cells go away too quickly. That means you don’t have as many red blood cells as you need.

What are red blood cells?
Red blood cells are tiny cells that move through your blood. They deliver oxygen to every part of your body. Our body needs oxygen to work properly. We get oxygen by breathing air into our lungs. Red blood cells take the oxygen from our lungs and carry it to all the parts of our body, such as our brains, our hearts, and even our fingers.

Why do I get so tired?
All the parts of your body need oxygen to do their jobs. Because you have PK deficiency, you don’t have enough RBCs. Without enough RBCs to carry oxygen, your body doesn’t get enough energy. This makes you tired.

Why do my skin and eyes become yellow?
When red blood cells go away too quickly, they can leave substances behind in your blood. One of these substances is called bilirubin (bil-ih-roo-bin). Too much bilirubin can turn your skin and eyes yellow.

Why do I get blood transfusions?
A blood transfusion is a way to give you more red blood cells. Red blood cells can be added (transfused) into your blood. There, they help take the place of ones that went away too soon. They work with the red blood cells you have and help them do their job.

Not everyone with PK deficiency needs transfusions. Your doctor will recommend what’s right for you.

Why do I get chelation therapy?
When red blood cells go away too soon, they can also leave behind iron (also called ferritin) in your bloodstream. Too much iron can make you sick or hurt your heart or liver. So, your doctor gives you medicine that chelates (key-ates) the iron. That means it binds to the iron, so that you can get rid of it when you go to the bathroom. Transfusions can cause iron to build up too.

Why do I have to go to the doctor so much?
Your doctor needs to check on your health, and the health of your blood, to help prevent problems. When your blood cells break down too fast, they can make you sick in other ways. Your doctor wants to see you often to help you stay as healthy as you can be.

myagios™

Introducing a patient support program for people living with PK deficiency and their caregivers.

Tailored support

Everyone's experience with PK deficiency is different. We will listen to understand your specific needs and interests, and work with you over time to deliver customized education and support.

Educational resources

Whether you're newly diagnosed or you've been living with PK deficiency for a while, we will share resources that can help you or your family better understand the disease. This will help you communicate with your healthcare team.

Community connections

Living with a rare disease can mean never having met someone else with the same condition. We can provide opportunities to connect with other patients and caregivers to allow you to share your experiences with PK deficiency.

Enroll today to be connected to your dedicated Patient Support Manager.

Call 1-844-409-1141, Monday through Friday, 8 AM to 6 PM ET.

Visit myAgios.com to learn more.

For patients in the United States only. This program cannot offer medical or treatment-related advice. For these types of questions, contact your healthcare professional.

Information and resources

Visit KnowPKDeficiency.com for these and other downloadable tools and brochures

Fast Facts: Pyruvate Kinase Deficiency
In-depth information from Dr Rachael Grace, a pediatric hematologist who studies PK deficiency.

PK Deficiency Through the Decade
In-depth information about PK deficiency, plus summaries of key research papers, to help you have more proactive discussions with your loved one's healthcare team.

Monitoring Guide
A simple tool that can help you talk to your loved one's doctor about determining how often certain tests and assessments should be done.

PK Deficiency Quick Reference Guide
Background to share with your loved one's teachers and school nurse, or friends and family. You can also add additional relevant medical information.

Doctor Discussion Guide
Teens with PK deficiency may find this tool useful as they work towards learning to manage their condition themselves.

Know PK Deficiency Facebook page
You can also find support by joining the Know PK Deficiency community.

facebook.com/PKdeficiency

Anemia ID is an Agios-sponsored program that offers free genetic testing. The program can help determine the cause of hereditary anemias, confirm your diagnosis of PK deficiency, and identify family members who might be affected. Visit **AnemiaID.com** to learn more, then talk to your doctor about next steps.

This program is only available to residents of the United States. All testing provided to patients through **Anemia ID** is paid for by Agios Pharmaceuticals. While Agios provides financial support for this program, all tests and services are performed by PerkinElmer Genomics. Agios receives contact information for healthcare professionals who submit tests under this program and limited de-identified aggregate data. **Anemia ID** is sponsored by Agios in partnership with PerkinElmer Genomics. Other laboratories may also offer genetic testing.

Support for caregivers and their loved ones

PK Deficiency Foundation

A national nonprofit organization whose mission is to enhance quality of life for patients and their families by providing awareness, expanding education and promoting advocacy.

pkdeficiencyfoundation.org

Thalassemia International Federation

This advocacy group offers information about hemoglobin disorders, including PK deficiency.

thalassaemia.org.cy/pk-deficiency

National Organization for Rare Disorders (NORD®)

NORD provides resources for caregivers and people with rare diseases.

rarediseases.org/for-patients-and-families/information-resources/patient-and-caregiver-resource-center

Global Genes®

This organization, founded by friends, family, and supporters of people affected by rare disease, offers information and educational resources, including those for parents and caregivers.

globalgenes.org

Kids And Caregivers

Advice and resources specifically for caregivers of children with a chronic illness.

kidsandcaregivers.com

GEMSS

Genetics Education Materials for School Success was founded to promote awareness of and education about genetic conditions. Their resources section contains a breakdown of the accommodations and modifications available to children attending public school.

gemssforschools.org

Notes

FPO

“It is a difficult disease to have, but it is manageable.”

Tamara, 52
Diagnosed with PK deficiency
at the age of 6

Goal-setting for life with PK deficiency

PK deficiency is a rare form of hemolytic anemia in which RBCs don’t have enough energy and die more quickly. Symptoms of PK deficiency are different for everyone and can change over time, so it’s important to keep everyone on your loved one's healthcare team in the loop to help ensure the best care.

Setting up a management plan with your loved one's hematologist can help them stay ahead of their PK deficiency symptoms and ensure you’re both informed about treatment options.

Interested in more information about PK deficiency?

Agios is dedicated to understanding rare disorders such as PK deficiency, and providing educational resources to the community.

To stay informed about the latest news, resources, and research related to PK deficiency, register for updates at **KnowPKDeficiency.com**.

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