Living with Hypophosphatasia (HPP)

YOUR GUIDE TO UNDERSTANDING AN HPP DIAGNOSIS

The patient experiences represented in this brochure are not indicative of all HPP patients. HPP can present in various ways across many demographics, regardless of age or sex.

A lot of seemingly unrelated symptoms were bothering me. I just didn't understand why until they came together like puzzle pieces."

Carol

LIVING WITH HPP

DIAGNOSED WITH HPP AS AN ADULT
EXPERIENCED SYMPTOMS IN CHILDHOOD

In My Bones

HPP Defined

If you or a loved one has been recently diagnosed with HPP, you likely want to know more about this disease. You or your loved one may have experienced various symptoms over time (such as unexplained bone fractures, joint/muscle pain, or early tooth loss with the root intact) that confused you and your medical support team.

HPP is a rare, inherited metabolic disorder that impacts bone formation, but it can also affect other areas of the body, such as the brain and kidneys. The symptoms of HPP can start to become noticeable even before birth or may not be seen or noticed until adulthood. The symptoms can vary in severity depending on age as HPP is a progressive disease, meaning symptoms may get worse over time. HPP is also a chronic disease, so it will likely not go away on its own; therefore, if left undiagnosed, HPP can have a profound effect on managing daily activities.

The Picture of HPP

HPP can affect babies, children, or adults of any age or sex. Symptoms may look different, depending on what age they began. Because HPP is genetic, multiple members of your family may have a gene mutation, even though HPP symptoms may present differently in each individual or some may not have HPP at all.

Ages of HPP Onset

Prenatal HPP (Before Birth)

Prenatal HPP is diagnosed when a baby first develops symptoms *in utero* or at birth. It occurs when the skeleton doesn't form properly in the womb. It is one of the most severe forms of HPP because weak rib bones may negatively affect breathing while other features of HPP may lead to seizures in this population.

Infantile HPP (Newborn/Infant)

Newborn HPP is diagnosed when a baby first develops symptoms such as an abnormally shaped head or torso before the age of 6 months.

Juvenile HPP (Children)

Juvenile HPP is diagnosed when a child first develops symptoms such as muscle weakness or developmental delays at or after 6 months and before 18 years of age.

Adult HPP

Adult HPP is diagnosed when symptoms such as unexplained fractures or muscle and bone pain first become noticeable at or after 18 years of age.

(These are not all the symptoms someone with HPP may experience. See pages 17-18 for a more in-depth explanation of HPP-related symptoms that people may experience at different stages of life.)

Connecting the Dots

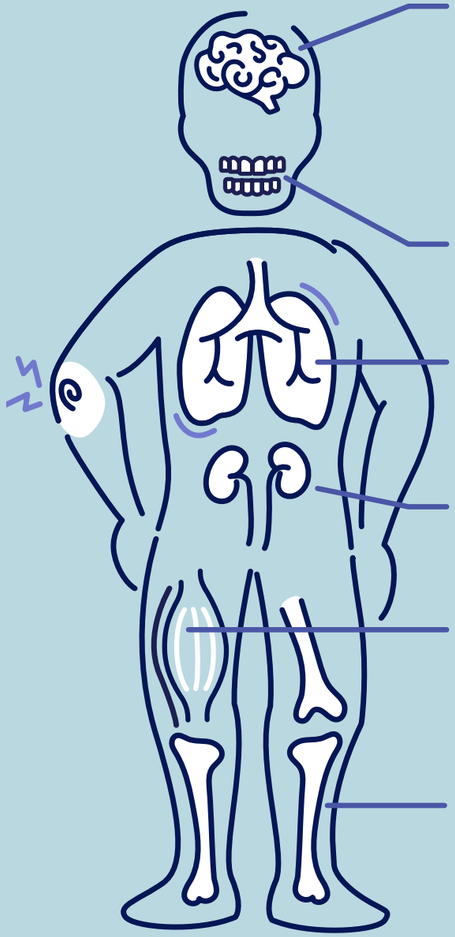
It isn't always easy to connect the symptoms one may be experiencing to HPP. The symptoms of this rare disease may vary from mild to severe and may present differently based on age of onset. Symptoms can also change within the same person over time. HPP can affect bones and teeth, but there are other perplexing symptoms of this metabolic bone disease that form a larger picture of HPP.

The Long-Term Effects

Over the course of a lifetime, symptoms of HPP can progressively worsen. HPP can therefore cause a high burden of illness as symptoms develop over time. Untreated HPP can result in the constant management of symptoms and can impact quality of life regardless of age at onset with issues such as fatigue, fractures, depression, and mobility limitations.

(See pages 17-18 for a more in-depth explanation of the HPP-related symptoms that people may experience at different stages of life.)

Symptoms of HPP[a]



SKULL/BRAIN

- Premature closure of skull bones, leading to abnormally shaped head[b]
- Brain fog/problems with thinking or memory
- Seizures[b]
- Headaches
- Fatigue

TEETH

- Early tooth loss with the root intact
- Gum disease

LUNGS

- Improper development of ribs and chest deformities[b]
- Difficulty breathing and the need for breathing support[b]
- Pneumonia

KIDNEYS

- Calcium buildup in the kidneys
- Kidney failure

JOINTS/MUSCLES

- Weakness
- Pain
- Arthritis
- Gout-like symptoms
- Muscle fatigue
- Missed motor milestones
- Mobility issues that may require an assistive device

BONES

- Rickets
- Chronic bone pain
- Frequent or slow-healing fractures
- Weak bones or bowed legs

a. This is not an exhaustive list of HPP signs and symptoms.
b. Symptoms commonly seen in infants and young children.

Knowing others with HPP and having a sister who also lives with it helps validate my own experiences. I'm not the only one who lives in a weird reality where some days my legs don't work properly—other people can relate."

Suzanne

LIVING WITH HPP

DIAGNOSED WITH HPP AS AN ADULT

EXPERIENCED SYMPTOMS IN CHILDHOOD

Amy (left), Suzanne (right), both living with HPP

In My Genes

The Root Cause of HPP

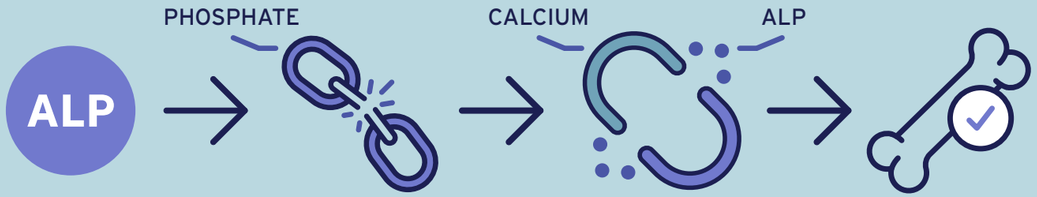
Getting to a diagnosis of hypophosphatasia can often be a long and difficult journey because symptoms can vary greatly. Understanding the underlying cause of HPP can be eye-opening. HPP is caused by a genetic mutation (a change in your DNA) in the *ALPL* gene. Normally the *ALPL* gene provides instructions to your body to make an enzyme called alkaline phosphatase (ALP). ALP is necessary to build healthy bones; however, for people with this *ALPL* gene mutation, the body does not create adequate ALP for sufficient bone development. This results in an inability for bones to reach standard hardness, strength, and size.

**HPP is caused by a genetic mutation in the *ALPL* gene.
For people with this *ALPL* gene mutation, the body does not create adequate ALP for sufficient bone development.**

ALP & What It Means for HPP

For the majority of the population, a sufficient amount of ALP enzyme is in the body. One of the purposes of ALP is to help break down minerals in the body, freeing phosphate, so it can combine with calcium to form hydroxyapatite — the building block for healthy bones. Without ALP, bones can't form properly.

People with HPP generally have low levels of ALP all the time, which can also be referred to as persistently low ALP. With this condition, the minerals that ALP breaks down will build up and there won't be enough free phosphate for bone formation. This prevents the development of strong bones and causes symptoms of HPP such as weak bones or muscles.



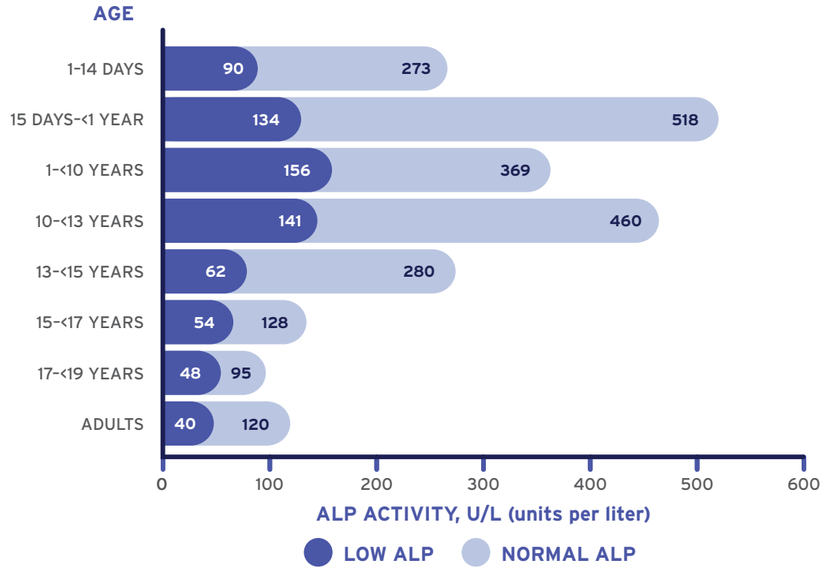
ALP breaks down minerals and frees phosphate, so phosphate can combine with calcium and form hydroxyapatite. Without this process, bones can't form properly.

Image created for illustrative purposes.

Testing for ALP

If HPP is suspected due to perplexing symptoms, your doctor can order a comprehensive metabolic panel (CMP) — a common blood test — to help confirm a diagnosis. Normal ALP levels change throughout one's life, so your doctor will check if your level is normal for your age and sex. Medications or other medical conditions can affect ALP levels. Your doctor will likely measure your ALP level multiple times based on these factors.

FEMALE AGE- AND SEX-ADJUSTED ALP REFERENCE INTERVALS (U/L)*

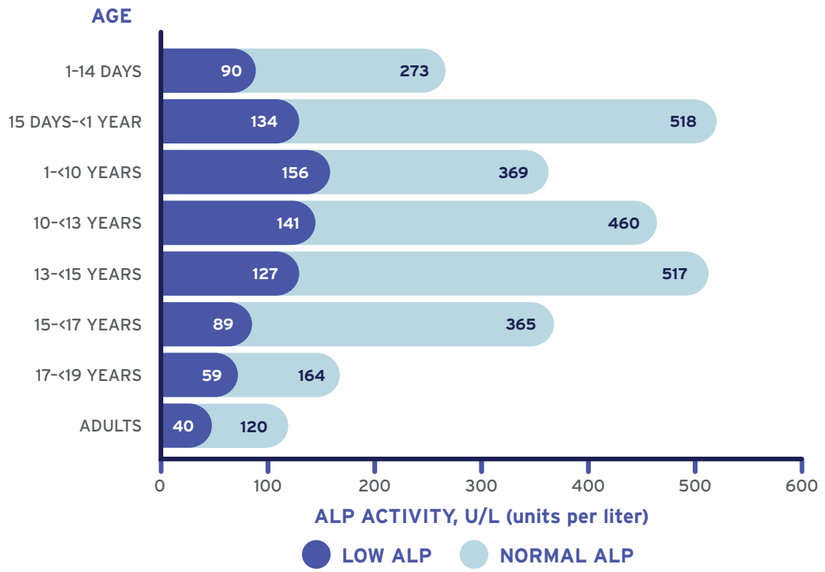


*Low ALP is not conclusive for HPP diagnosis; check with your doctor for lab's appropriate age- and sex-adjusted reference interval. Pediatric ranges were adapted from the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) project (Colantonio et al, 2012). (*Continued on page 12.*)

Do you know your alkaline phosphatase level?

Scan or click on this code to learn more about ALP levels.

MALE AGE- AND SEX-ADJUSTED ALP REFERENCE INTERVALS (U/L)*



*(*Continued from page 11.*)
Caliper samples from 1072 male and 1116 female participants (newborn to 18 years) were used to calculate age- and sex-specific reference intervals. Reference intervals shown were established on the Abbott ARCHITECT C8000 analyzer.

A Hidden Clue

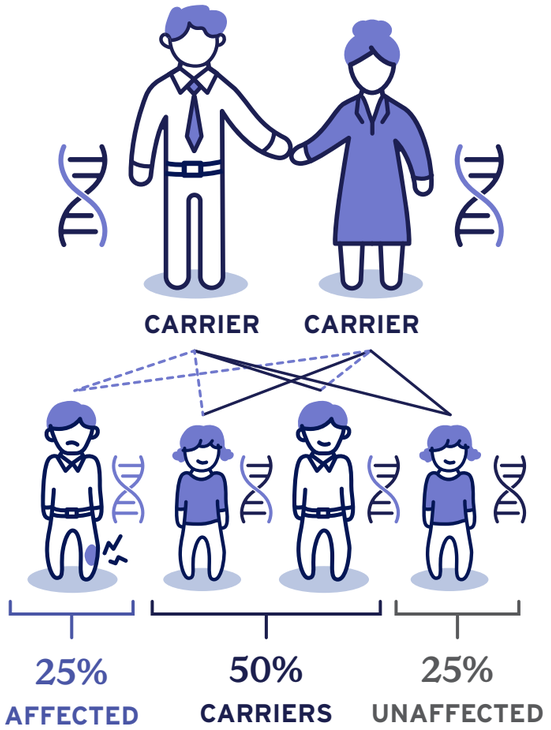
HPP is an inherited disease, meaning that you can get it from one or both of your parents. Understanding your unique genetic picture may provide even more insight into your diagnosis.

HPP can be inherited in an autosomal recessive or autosomal dominant pattern. Autosomal means the mutation is located on a non-sex gene.

Autosomal recessive means that a child must receive two copies of the mutated gene to be affected. A person may be a carrier if they receive only one copy, but will most likely not show any HPP signs or symptoms. Conversely, autosomal dominant means that only one copy of the gene is needed to cause HPP symptoms.

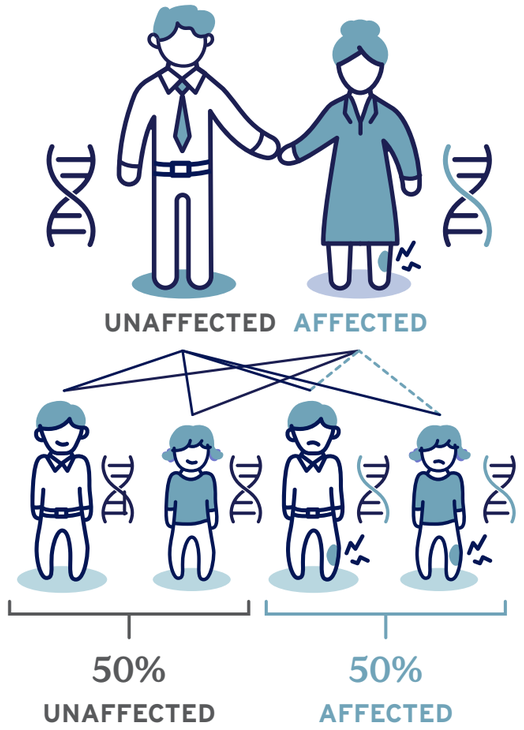
Autosomal Recessive Inheritance

A child needs to inherit two copies of the mutated *ALPL* gene — one from each parent — in order to have HPP.



Autosomal Dominant Inheritance

A child only needs to inherit one copy of the mutated gene to cause HPP. In this case, the child inherits a normal *ALPL* gene from one parent and a mutated *ALPL* gene from the other.



Images adapted from *Mornet Orphanet J Rare Dis* 2007 and *MedlinePlus*_Hypophosphatasia

HPP & Genetic Testing

Genetic testing can give you information about your specific mutation and how it was inherited. Because it's in your genes, you can pass it on to your children. Genetic counseling can be a valuable resource when deciding to get tested and in understanding your results.

Genetic testing is not required to confirm an HPP diagnosis, and a negative genetic test doesn't mean you don't have HPP. Typically, this testing is only used for confirmation when a doctor wants more clarification on symptoms.

Suzanne (bottom left), Amy (bottom center) & family

When we were very young, we didn't really talk about the symptoms. It's just the way we were. It wasn't until we got older that we started to really search for the answers."

Amy

LIVING WITH HPP

DIAGNOSED WITH HPP AS AN ADULT

EXPERIENCED SYMPTOMS IN CHILDHOOD

In My Journey

For many people, it is a long, slow process of bridging the symptoms into a clear picture of diagnosis. With such a wide variety of symptoms and range of severity, it is often a difficult journey to diagnosis.

The Diagnosis Journey

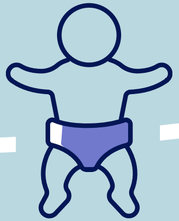
HPP can look unique, depending on your age at diagnosis and genetic factors. Different doctors may have been involved in your journey to diagnosis such as a maternal-fetal medicine specialist, neonatologist, orthopedist, endocrinologist, rheumatologist, or geneticist.

A holistic view of a person is sometimes missing in the search for a diagnosis because each doctor is an expert in the symptoms relevant to their specialty. A coordinated team-based approach may be essential to the effective management of patients with HPP.

Before Birth

A baby may show signs of poor bone formation *in utero*, which can lead to deformities of the limbs, skull, rib cage, or spine. In some cases, symptoms may improve by themselves before or at birth, but perinatal HPP can be very serious and needs to be diagnosed quickly.

Ultrasounds, magnetic resonance imaging (MRIs), and computed tomography (CT) scans can show bone abnormalities *in utero* to help diagnose prenatal HPP.



Newborns and Infants

Some babies with HPP may develop an abnormally shaped head or chest and may have life-threatening seizures or respiratory problems shortly after birth. Others may appear to develop normally until issues with feeding, inadequate weight gain, or rickets appear as the first signs of HPP.

To diagnose HPP in newborns and infants, doctors use X-rays to look for bone problems and a blood test to measure ALP levels.

Children

Early tooth loss with the root intact may be an initial sign of HPP. Young children may present with eating problems, issues with growth, weight gain, or signs of delayed development. Older children may experience muscle weakness and bone pain that make it hard to walk, run, carry things, or even chew and swallow. Kids with HPP sometimes have trouble keeping up with their peers or staying awake and alert at school due to symptoms such as weak muscles or fatigue.

To diagnose HPP in children, doctors use a blood test to check their ALP levels along with obtaining a complete picture of the child's symptoms using various methods, including X-rays.

Adults

Common symptoms of HPP in adults may include fractures or muscle and bone pain. Some adults may remember experiencing symptoms in childhood that they did not realize were related to HPP. Adults may experience pain severe enough to require medication or an assistive mobility device. If unmanaged, pain from HPP can become debilitating, make it difficult to perform daily activities, get around at home or work, and stay alert throughout the day.

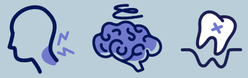
To diagnose HPP in adults, doctors look at symptoms, X-rays, and ALP blood test levels.

Remember

YOUR DOCTOR WILL LOOK FOR:

PERSISTENTLY LOW AGE- AND SEX-ADJUSTED ALP

+



ONE OR MORE HPP SYMPTOMS

=

TO MAKE AN HPP DIAGNOSIS AFTER RULING OUT OTHER CAUSES OF LOW ALP

Common Misdiagnoses

HPP is often misdiagnosed because a patient's symptoms are broad and look similar to those of other conditions. Many doctors lack experience in treating a rare disease like HPP, so they may not recognize the symptoms or realize that persistently low levels of ALP are a strong indicator of HPP. ALP levels can also be impacted by certain medications, large blood transfusions, or other conditions such as celiac disease.

Based on when your symptoms first presented, there are many possible misdiagnoses. HPP may be mistaken for the following conditions on the next page.

CHRONIC CONDITIONS

Fibromyalgia
Rickets
Brain Fog

BONE PAIN

Osteomalacia
Osteopenia/Osteoporosis
Osteogenesis Imperfecta
Osteoarthritis/Arthritis
Rheumatoid Arthritis
Pseudogout

TOOTH LOSS*

*with the root intact
Gum Disease
Dentinogenesis Imperfecta

CANCER

Leukemia
Bone Cancer

If you've been misdiagnosed in the past, be sure to report your new HPP diagnosis to your entire healthcare team. Treatment of other more common conditions could worsen HPP. For example, some vitamins and medications used to treat osteoporosis may be harmful for people with HPP.

Living most of my life with multiple illnesses felt like I was paddling away in a pool of water trying to stay afloat. But I couldn't give up. Don't give up–that's what makes us find answers."

Carol

LIVING WITH HPP

DIAGNOSED WITH HPP AS AN ADULT

EXPERIENCED SYMPTOMS IN CHILDHOOD

Carol & her husband, Bill

In My Everyday

The Daily Impact

Life with any rare disease can have its own unique challenges. From feeling alone or misunderstood through the diagnostic process, to managing the impact on daily living. Persistently low ALP and impaired bone quality during one's growing years can also be a risk factor for long-term consequences.

Having HPP can result in:

DEVELOPMENTAL DELAYS

UNUSUAL GAIT

IMPAIRED MOBILITY

FRACTURES

FATIGUE

Being Proactive

Because HPP is a progressive disease, it can worsen over time. Symptoms can change with age, so it is important to continue to work with your doctor to monitor and manage your HPP. If left unmanaged, HPP can have an effect on the ability to carry out daily activities without assistance, such as walking. Taking a proactive role in your healthcare journey may lead to a greater understanding and empowerment over your or your loved one's health and wellbeing.

Symptom Management

Keeping a journal of your experiences, symptoms, and how they impact your daily life is a great tool to manage these changes. You can even store copies of test results and jot down questions that arise between appointments. While the journey to discovering your HPP diagnosis may have been confusing, having confirmation can bring about some clarity.

BONE, MUSCLE, OR JOINT PAIN

MISSED SCHOOL OR WORK

LIMITED ABILITY TO PERFORM EVERYDAY ACTIVITIES

DECREASED QUALITY OF LIFE

In My Life

Living with HPP

HPP is a rare disease that can be difficult to diagnose. Even though you may have known that there was something going on, no one could pinpoint what was wrong. Now that you have learned what an HPP diagnosis means and how the disease affects daily life, you may have questions for your doctor about next steps. If your primary care provider is unfamiliar with HPP, you may be referred to a specialist. Understanding your or your loved one's diagnosis, having a healthcare team you trust, advocating for yourself or them, and connecting with others in the HPP community may help you navigate your own journey.

Want to learn more?

Scan or click on this code to visit hypophosphatasia.com today

Advocating for Your Health

Figuring out how to start advocating for your or your loved one's health can feel intimidating.

Here are a few tips that may help you get started:

- Educate yourself about HPP
- Record any symptoms as well as how they affect daily activities
- Write down and prioritize any questions you have between appointments
- Get connected with the HPP community
- Keep copies of all test results for your records

Before I go to a doctor, I give myself a little pep talk. I'm going to have confidence; I'm going to speak articulately; I'm worth being treated well."

Suzanne

LIVING WITH HPP

DIAGNOSED WITH HPP AS AN ADULT
EXPERIENCED SYMPTOMS IN CHILDHOOD

HPP Advocacy & Support Resources

SOFT BONES
softbones.org
(866) 827-9937

THE AVALON FOUNDATION
kidscaringforkids.org
(419) 841-2059

GLOBAL GENES
globalgenes.org
(949) 248-RARE (7273)

NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD)
rarediseases.org
(800) 999-6673

OSTEOGENESIS IMPERFECTA (OI) FOUNDATION
oif.org
(844) 889-7579

The HPP advocacy and support resources listed above are independent, nonprofit patient service organizations. Their listing in this brochure does not imply endorsement. All logos and trademarks are the property of their respective owners.

HPP Resources from Alexion

ALEXION ONESOURCE™
alexiononesource.com
(888) 765-4747

HPP EMPOWERED EVENTS
hypophosphatasia.com/events
(844) 335-0372

PEER CONNECTS PROGRAM
(877) 576-7589

HPP STAR AMBASSADOR PROGRAM
(844) 378-2127

For additional information about hypophosphatasia (HPP), the role of ALP*, and resources available to you, please visit hypophosphatasia.com.

*alkaline phosphatase

Inside You'll Find:

- HPP Basics: Diagnosis, Symptoms, and Testing
- Genetic Factors and the ALP Connection
- Recognizing HPP
- Common Misdiagnoses and Symptom Management
- Additional Support and Resources

ALEXION®
AstraZeneca Rare Disease

US/UNB-H/0680 V1 03/2025