



A Genetic Overview of Hypophosphatasia

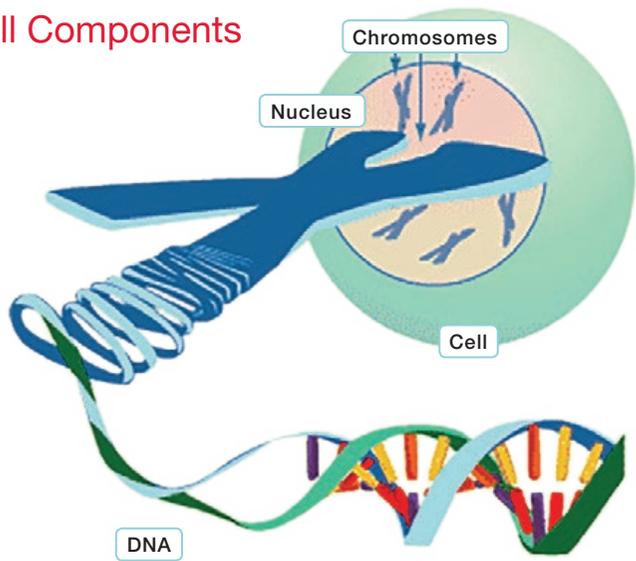
Soft  Bones
Canada



▶ A Background in Genetics

Cells are the basic building blocks of all living organisms. Our body is composed of trillions of cells. Each of these cells contains deoxyribonucleic acid (DNA), the hereditary material. DNA contains genetic instructions and tells the cell what to do and how to grow. DNA is stored in chromosomes. Humans have 23 pairs of chromosomes - a total of 46 - and each pair is designated its own number (1 to 22) or letter (X or Y for the sex chromosomes). In every individual one of each of the 23 chromosome pairs comes from one parent and one of each of the 23 pairs comes from the other parent, totalling 46 chromosomes in every human cell.

▶ Cell Components



Lisa Ormerod.¹

In the human body each cell contains approximately 25,000 genes, and each gene contains the DNA blueprint for a specific protein.

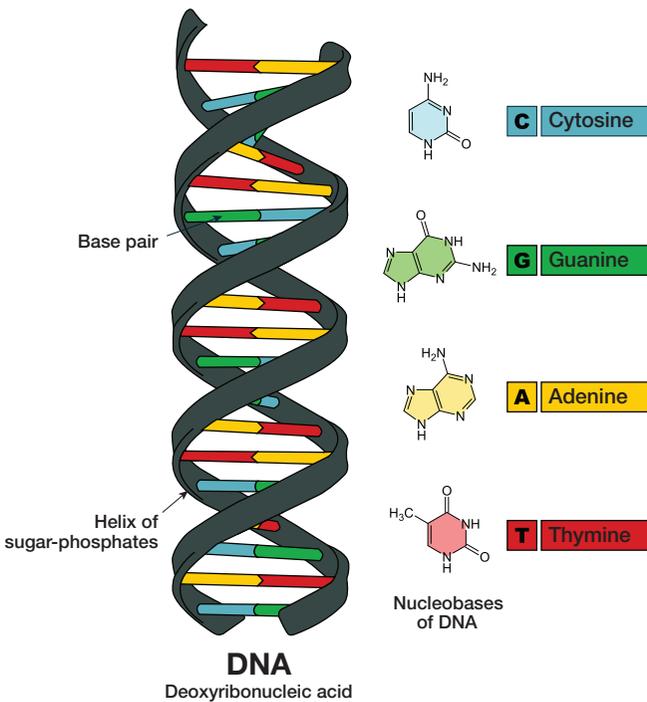
Proteins are the building blocks of all structures in the body and are needed to keep our cells healthy. Every person has two copies of each gene, one inherited from each parent.

► A Background in Genetics (CONTINUED)

Genes are made up of a specific sequence of letters known as bases: Adenine (A), Thymine (T), Cytosine (C), and Guanine (G). The sequence of these bases determines the particular amino acid sequence of a protein.

The genetic blueprint determines how these letters come together and form the DNA structure called the double helix, which resembles a twisted ladder. The order, or sequence, of these bases determines what biological instructions are contained in a strand of DNA, similar to how letters of the alphabet form words.

► Nucleic Acids

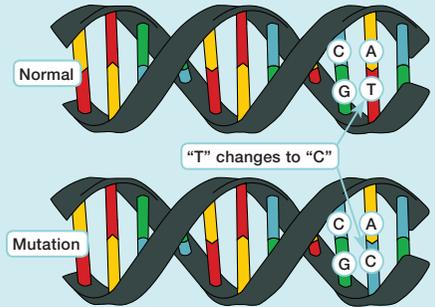


Adapted from: *Chemical structures of nucleobases* by Roland1952.²

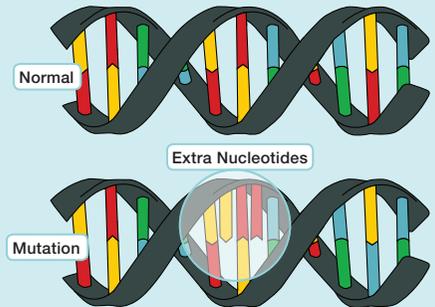
Sometimes there are misprints or changes in the sequence of letters in the DNA. These errors are known as mutations, which can affect a single gene, or multiple genes. Point mutations are changes in only one letter in the DNA sequence of a gene. There can also be larger insertions or deletions in the gene that affect the length and organization of DNA chain. Some of these changes can cause the gene to malfunction, which can impact the specific protein that the gene normally makes. Single gene disorders like HPP are caused in whole, or in part, by changes in the DNA sequence of that gene.



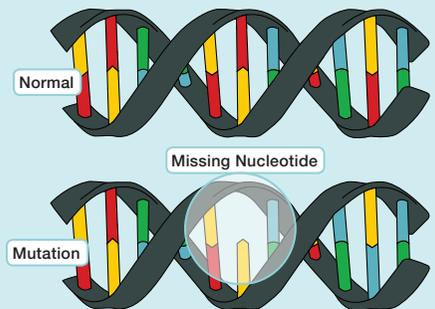
DNA Mutations



Point Mutation



Insertion Mutation



Deletion Mutation

► Genetic Basis of Hypophosphatasia

Hypophosphatasia (HPP) is an inherited disorder caused by one or more mutations in a gene called ALPL (alkaline phosphatase, liver/bone/kidney). The ALPL gene contains the DNA blueprint that codes for the tissue non-specific alkaline phosphatase enzyme (TNSALP). TNSALP plays a critical role in the healthy development of our bones and teeth.

Nearly 300 types of mutations discovered so far in the ALPL gene prevent the gene from working properly. Most of the mutations causing HPP are single point mutations. These mutations prevent bones and teeth from being able to absorb important minerals and calcium. Mineralization is critical for the formation of bones and teeth that are strong and rigid. In addition, a compound called PPI (inorganic pyrophosphate) accumulates when there is a deficiency of TNSALP. PPI further weakens HPP bones by inhibiting calcium deposition in bone. The disorder weakens and softens the bones, making them more likely to fracture. Severity of HPP varies greatly from patient to patient. Bone changes of HPP are similar to those seen in rickets in infants and children, and in osteomalacia in adults.

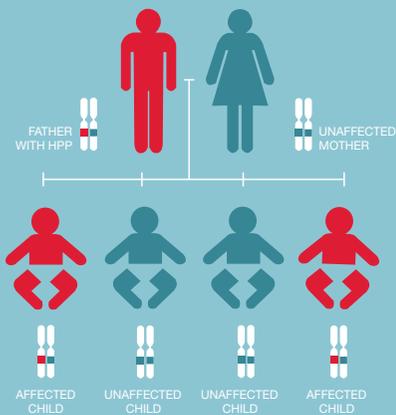
HPP follows either an autosomal recessive or an autosomal dominant pattern of inheritance. HPP in most families is caused by autosomal recessive inheritance. Autosomal recessive inheritance means that an affected individual has two non-working copies of the ALPL gene. Most likely, each parent passes down a non-working copy and is known as a carrier. A carrier of one ALPL gene mutation usually does not have signs or symptoms of HPP although a carrier has a low TNSALP level in the blood. However, carriers may pass the altered mutant gene to their children. If two carriers have a child together, their children each have a 25% chance of inheriting HPP in a recessive pattern, one mutation being inherited from each parent. The more severe perinatal and infantile forms of HPP are inherited in an autosomal recessive manner. Many milder juvenile and adult onset forms are inherited in an autosomal recessive pattern as well, but also can be inherited in an autosomal dominant fashion.

Autosomal dominant inheritance means that an affected individual has one working copy and one non-working copy of the ALPL gene. The gene copy with the mutation in one copy alone is sufficient to cause signs and symptoms. A person with the dominant form of HPP can pass down either the non-working copy or the working copy of the gene to their offspring. This means each child born to a parent with a dominant form of HPP has a 50% chance of having dominant HPP and low TNSALP. Dominant HPP usually is milder than autosomal recessive forms of HPP.

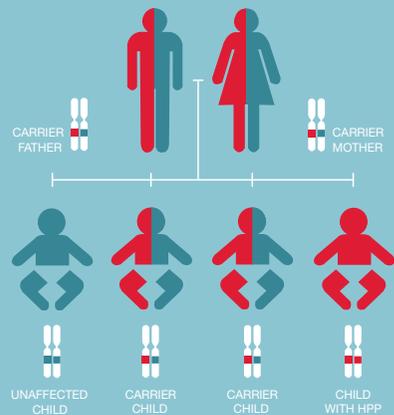
Not everyone with low TNSALP develops HPP. It should be noted that with Odontohypophosphatasia (odonto-HPP), only teeth are affected, and patients have low levels of TNSALP, but have no signs or symptoms in other parts of the bony skeleton. Odonto-HPP usually follows an autosomal dominant pattern of inheritance.

▶ Autosomal Inheritance

AUTOSOMAL DOMINANT INHERITANCE



AUTOSOMAL RECESSIVE INHERITANCE



KEY
 **DOMINANT GENE WITH THE ALPL MUTATION**
 **RECESSIVE GENE WITH NORMAL ALPL**

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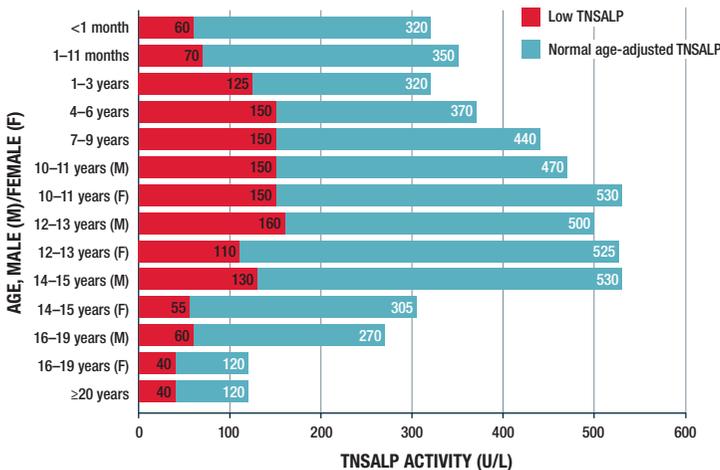
► Diagnosis of Hypophosphatasia

Hypophosphatasia is usually diagnosed by measuring TNSALP levels in the blood. Physicians refer to an age- and gender-adjusted tool that provides the normal range of TNSALP blood levels. A low TNSALP blood level alone often can confirm a HPP diagnosis.

While low TNSALP is the hallmark of HPP, it is not the only biochemical marker of HPP. Therefore, it is usually important to confirm an HPP diagnosis through additional measurements such as abnormally high levels of a form of vitamin B6 known as PLP.

Doctors look for other symptoms when diagnosing HPP, including premature loss of baby teeth, muscle weakness and bone deformity. Independently, these signs and symptoms do not confirm HPP, but when they present with low serum TNSALP levels a confident diagnosis can be made.

► Age and Gender Adjusted TNSALP Reference Ranges



Adapted from: ARUP Laboratories. Alkaline phosphatase isoenzymes, serum or plasma: 0021020. Available at: <http://tld.aruplab.com/tests/pub/0021020>



► Genetic Testing for HPP

Should I seek genetic testing for HPP?

Before undergoing genetic testing, it is important to understand how the test is performed, as well as the possible benefits, risks and limitations of the test. A laboratory will require your informed consent - your knowledge of the risks and benefits - before performing the test. A clinical geneticist, or a genetic counselor who specializes in HPP can help explain how the test is performed and what the results mean.

Benefits

Genetic testing can be done during pregnancy to confirm a diagnosis of HPP. Genetic testing can also help families who have a child with HPP understand the risk of inheritance for their future children. In rare circumstances when signs and symptoms do not clearly signify HPP, genetic testing may be useful. Genetic testing during pregnancy can help couples better plan for when the baby is born and alleviate uncertainty about a genetic disorder. A negative test result can bring greater peace of mind. Parents can make more informed decisions with genetic test results.

Opportunities

As scientists learn more about the mutations associated with HPP, improvements in the clinical management of people with the disorder and the development of new therapies can be pursued.

Risks

Potential risks of genetic testing include emotional and social consequences. People may sometimes feel angry, depressed, anxious or guilty about the results. Talking to a health care specialist or a genetic counselor may help you navigate some of these issues.

Limitations

While genetic testing can determine the existence of a mutation in the ALPL gene and the type of mutation, there is no evidence that a mutation can predict the severity of disease or how it will progress. In addition, a single test may not be able to identify all possible mutations to other genes.



► Genetic Testing for HPP (CONTINUED)

Types of Results

To date, ALPL is the only gene known to be associated with HPP. There are three different types of results: positive, negative and variant of uncertain significance.

A positive test result means that the geneticist has found a change in the ALPL gene that causes HPP. A negative test result means that a change in the ALPL gene was not found. In this case, there is no genetic basis for the patient's health concerns. A variant of uncertain significance - usually described as "maybe" - means that a change in the ALPL gene was found, but the meaning for that change is unknown.

Two scenarios may explain a variant of uncertain significance result: a change in the ALPL gene may not cause HPP in a particular individual; or a change in the ALPL gene is just a natural variant in the population and does not necessarily cause an individual to develop signs and symptoms of HPP. This type of result is less common. Results typically are positive or negative.



▶ Consulting Medical Specialists and Genetic Counselors

The diagnosis of HPP has to start with a clinical suspicion that HPP may be the cause of the baby's, child's or adult's problems. Signs and symptoms vary greatly between patients, even those within the same family. There is a correlation between age of onset and severity of symptoms. The disease is classified by age of onset of symptoms: perinatal, infantile, childhood, and adult HPP. Two other forms are odontohypophosphatasia, and benign prenatal HPP. For a more detailed description of signs and symptoms, please refer to our brochure An Overview of Hypophosphatasia, or our website: **www.softbonescanada.ca**. If the diagnosis is suspected, a health care professional expert in this condition should be consulted. This often includes a geneticist and a genetic counselor. If the history, physical examination, blood and urine test results and X-rays suggest this diagnosis, blood tests may be recommended for the parents or other family members. DNA testing looking for diagnostic mutations in the ALPL gene may be recommended, but DNA testing is not essential to make the diagnosis of HPP. Consulting with a geneticist and a certified genetic counselor will help you make important and informed decisions about testing for HPP including the pros, cons and limitations of DNA testing. The genetic counselor will also help explain results of blood and urine tests and X-rays, explain what an ALPL mutation means and implications of the test results for the affected individual, other family members and future pregnancies. Your health care professional can refer you to the specialists in your province for consultation or contact one of the members of the Soft Bones Canada Scientific Advisory Board members to assist in finding excellent resources.



► Treatment for Hypophosphatasia

Until recently management of HPP has been purely supportive with symptom management and orthopedic treatment. Now, based on promising results of clinical trials to date, and a good safety profile, Health Canada has issued a Notice of Compliance with Conditions for asfotase alfa, human recombinant bone-targeted alkaline phosphatase for the treatment of confirmed pediatric-onset HPP. This is a very promising advance for the treatment of this disorder.

Image Attributions:

1. Aetna@ Intellihealth. <http://www.intellihealth.com/article/dna-genes-and-chromosomes>.
2. Difference_DNA_RNA-DE.svg, Roland 1952. <http://commons.wikimedia.org/wiki/User:Sponk/gallery>. Creative Commons Attribution-Share Alike 3.0.



Soft Bones Canada was formed in 2013. We are a nationwide, community-based voluntary health organization dedicated to raising awareness and being a source of education, information, encouragement, and support for Canadian individuals and their families affected by Hypophosphatasia (HPP), as well as interested individuals in the medical community.

Our Mission

- » To advance education by providing courses, seminars, workshops, and educational materials about Hypophosphatasia to the public, patients and medical professionals;
- » To promote health by providing Hypophosphatasia patients and their caregivers with access to health counselling, information, and group support programs;
- » To advance education by supporting and conducting research into the causes and possible treatments of Hypophosphatasia and making the results publicly available.

Contributors

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