



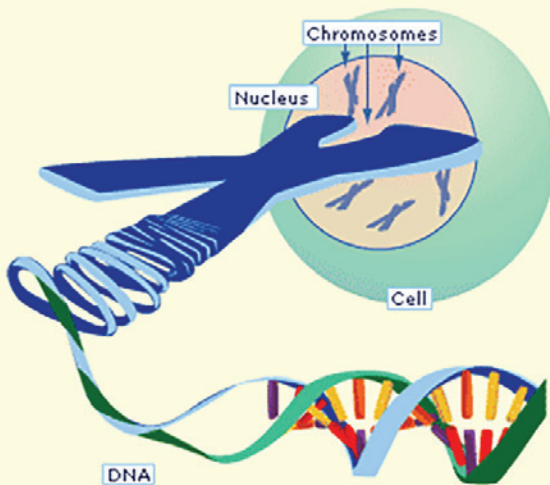
A Genetic Overview of **Hypophosphatasia**

Soft  Bones
Finding the Key to HPP

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 labeled with its own number or letter for the X and Y sex chromosomes. Each set of chromosomes comes from each of our parents.

» Cell Components



Lisa Ormerod.¹

Genes are located on chromosomes and determine our physical features. Genes are made up of DNA and they make molecules called proteins, the building blocks of all structures in the body.

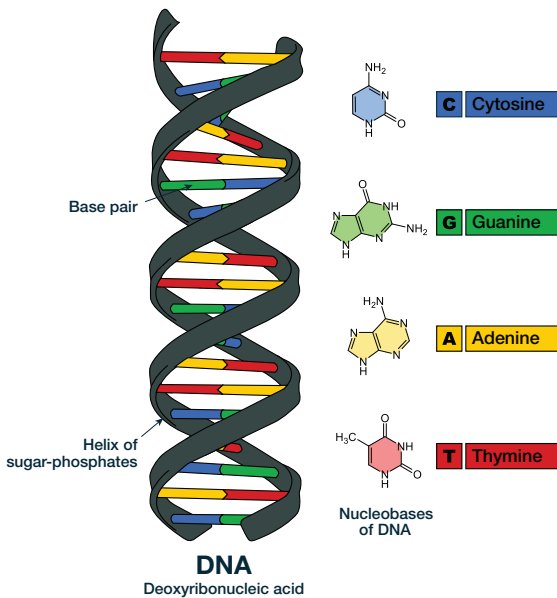


A Background in Genetics (continued)

In the human body every gene contains a code that acts as a blueprint for the cell. Cells use this blueprint to make a certain protein that is necessary to keep our bodies healthy. Every person has two copies of each gene, one inherited from each parent.

Genes are made up of combinations of nucleic acids: Adenine (A), Thymine (T), Cytosine (C) and Guanine (G). 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 nucleic acids determines what biological instructions are contained in a strand of DNA, similar to how letters of the alphabet form words.

» Nucleic Acids

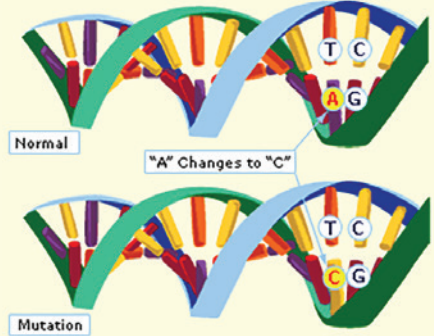


Adapted from: *Chemical structures of nucleobases* by Roland1952.²

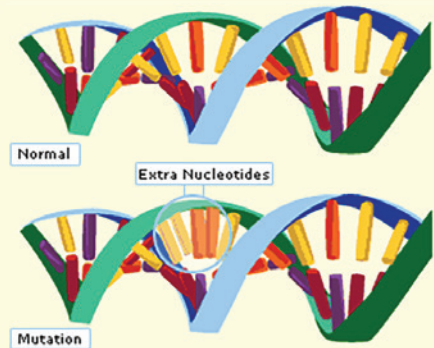


» DNA Mutations

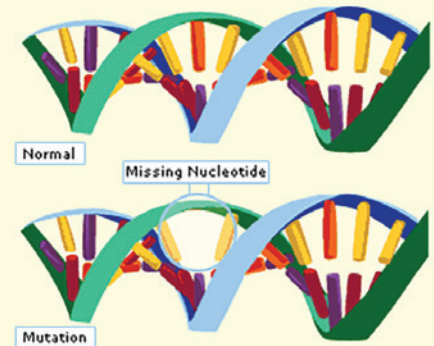
Sometimes there are mistakes or changes in the pattern of letters in the DNA sequence. These errors are known as mutations, which can affect a single gene or multiple genes. Point mutations are changes in one of the DNA's letters. There can also be larger insertions or deletions in the gene that affect the entire DNA chain. Some of these changes can cause the gene to malfunction, which can impact the specific protein that the gene normally makes. Genetic disorders are caused in whole or part by a change in the DNA sequence.



Point Mutation



Insertion Mutation



Deletion Mutation

Lisa Ormerod.¹



Genetic Basis of Hypophosphatasia

Hypophosphatasia (HPP) is an inherited disorder caused by one or more mutation to a gene called alkaline phosphatase, tissue-nonspecific isozyme (ALPL). ALPL tells the cell to make a protein called tissue-nonspecific alkaline phosphatase (ALP). ALP is essential in the healthy development of teeth and bones.

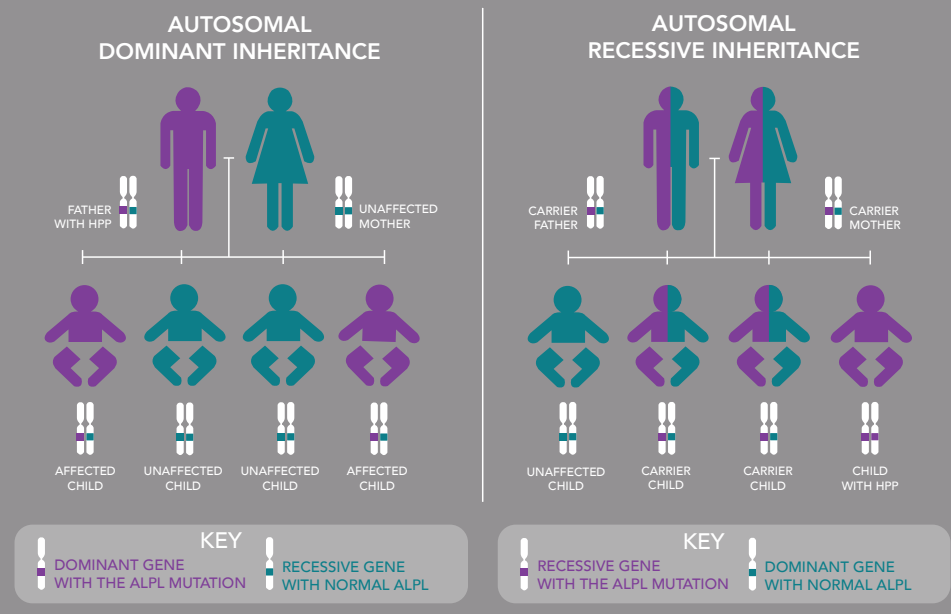
Nearly 300 types of mutations discovered so far in ALPL prevent the gene from working properly. These mutations prevent bones and teeth from being able to absorb important minerals and calcium. Mineralization is critical for the formation of bones and teeth that are strong and rigid. In addition, a chemical inhibitor called inorganic pyrophosphate (PPi) accumulates in the body causing defective calcification of bones. The disorder weakens and softens the bones, making them more likely to fracture. Severity of the disorder varies greatly from patient to patient. Bone changes are similar to rickets in infants and children and osteomalacia in adults.

HPP follows both an autosomal dominant and autosomal recessive pattern of inheritance. Autosomal dominant inheritance means that an individual has one working copy and one non-working copy of ALPL. 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 has a 50% chance of having low ALP.

Not everyone with low ALP develops HPP. Both adults and children with the mild form of HPP tend to be inherited in an autosomal dominant manner. Ondonto-HPP, which only affects the teeth, is usually autosomal dominant.

Autosomal recessive inheritance means that an individual has two non-working copies of ALPL. Most likely, each parent passed down a non-working copy. The parents usually have low ALP and mild unrecognized HPP symptoms. They are considered carriers of HPP. A carrier has one gene with a mutation but may not have obvious symptoms of the disease. However, carriers may pass the altered 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. The more severe perinatal and infantile forms of HPP are inherited in an autosomal recessive manner. Some milder juvenile and adult onset forms are inherited in an autosomal recessive pattern as well.

» Autosomal Inheritance

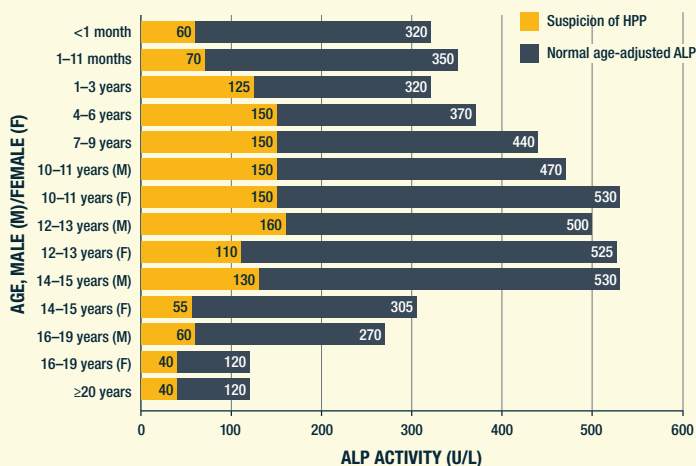




Diagnosis of Hypophosphatasia

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

» AGE- AND GENDER-ADJUSTED ALP REFERENCE RANGES



ARUP Laboratories online test directory, accessed March 31, 2014 at www.aruplab.com. Used with permission. Note: Reference levels vary somewhat by performing laboratory and testing methodology.

While low ALP is the hallmark of HPP, it is not the only indicator of low protein levels. Therefore, it is important to confirm a HPP diagnosis through additional measures such as abnormal vitamin B6 levels.

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 by themselves confirm HPP, but when they present with low serum ALP levels a confident diagnosis can be made.

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 plan better 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.

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 ALPL 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)

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.

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 ALPL 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 ALPL was found, but the meaning for that change is unknown.

Two scenarios may explain a variant of uncertain significance result: A change in ALPL may not cause HPP in a particular individual; or a change in ALPL 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.







Access to Genetic Testing

Most laboratories that screen for HPP will not offer testing directly to consumers; only a health care provider can order a genetic test. The cost of genetic testing can vary depending on the lab and the type of test. Ask your health care provider or genetic counselor about which test is best for you. On average, a single genetic test for the HPP mutation typically costs between \$800-\$1,500. When the specific mutation is known to exist, the cost is significantly less, around \$200-\$300.

Some health insurance providers may cover the cost of genetic testing for HPP. Before making plans to be tested, contact your insurance company to ask about whether genetic testing is covered and have the following information readily available:

- › The name of the test
- › The name of the lab
- › The CPT (current procedural terminology) codes

All of this information can be obtained by calling the lab. Also ask your provider about out-of-network expenses; some insurers may only cover a portion of the cost in this case.

To perform a genetic test, a DNA sample is typically collected through a blood test or less frequently a cheek swab. The sample is then sent to a lab for analysis.

Results of the test are usually available within 2-4 weeks. It is important to make a follow-up appointment with a health care provider to discuss the results and what they mean for you and your family.

Consulting a Genetic Counselor

Genetic counseling is the process of helping people understand and cope with the medical, psychological and genetic aspects of a disease. Consulting with a genetic counselor will help you make important and informed decisions about genetic testing, and also explain results and implications of genetic tests. A genetic counselor can help you understand what an ALPL mutation means and how HPP is inherited.

Resources to help locate a genetic counselor:

American Board of Genetic Counseling

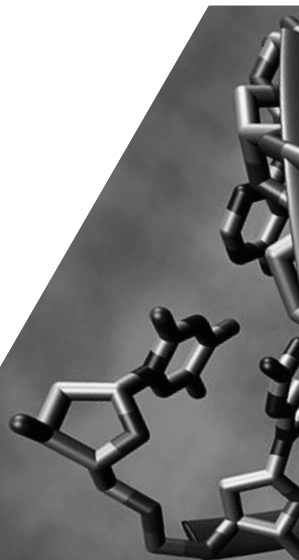
www.abgc.net

National Society of Genetic Counselors

<http://nsgc.org>

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For more information about genetics:

Genetics Home Reference

<http://ghr.nlm.nih.gov/handbook>

Diagnosing Rare Disease e-book

www.raregenomics.org/ebooks

GeneEd Web (for kids)

www.geneed.nlm.nih.gov





Notes



Soft Bones Foundation was formed in 2009 to provide information and a community to educate, empower and connect patients living with HPP, their families and caregivers.

The Foundation also promotes research of this rare bone disease through awareness and fund-raising efforts.

For more information, please contact
the Soft Bones Foundation.

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