Guide to Understanding HPP Genetic Variations

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Does Having a Genetic Variant Mean That I Have Hypophosphatasia?

One of the hardest parts of having hypophosphatasia (HPP) is the lack of information/understanding around a prognosis and answering the question so many of us have: **"What will the future hold?"**

The answer to that question is not simple. In fact, it's fairly complex. Some may even blame their doctors for not knowing enough about HPP, but the truth is that the genotype (one or more genetic variant(s) in the ALPL gene) and the phenotype (how the disease presents itself and symptoms evolve over time, etc.) are not very well understood. The good news is that it is a focus of ongoing research, and every year we are increasing our knowledge about genetic variants/mutations and HPP.

Important considerations are below.

Having a Genetic Variant Does Not Mean You Have HPP

- Many people have ordered 23andMe® or other genetic screenings and discovered that they carry an ALPL variant. Some may have searched the **JKU ALPL Gene Variant Database** and found that their variant is associated with a certain form of HPP, or is in fact classified benign.
- There are 5 types of variants: ***benign*** *(1),* ***likely benign*** *(2),* ***uncertain significance*** *(3),* ***likely pathogenic*** *(4), and* ***pathogenic*** *(5).* A variant can be called a mutation if it is classified as pathogenic (types 4 and 5), meaning it has the potential to cause disease.
- Fact is – there are many healthy, asymptomatic people carrying ALPL variants. **Having one ALPL mutation alone is not enough to diagnose HPP.**

HPP is Not a Lab-Only Diagnosis

- We know that a low ALP in the blood is a typical sign of HPP. However, **there are many conditions and situations where ALP is low for unrelated reasons.** In fact, over 99.9% of low ALP in large laboratory screening studies were not due to HPP.
- You may even have an ALPL mutation, a low ALP, and high vitamin B6 ("the biochemical signature of HPP"), and **still have no clinical symptoms of HPP.** This is now known as subclinical HPP—meaning you have all the laboratory signs, but no outward symptoms of HPP. You may not have HPP now, but it may (or not) possibly show up in the future.
- **If you have this biochemical signature**, it is important that you see an endocrinologist, bone specialist, or a geneticist who is familiar with HPP (or is willing to learn more about it) and monitor your symptoms.
- **The myHPP app is a great place to keep track of aches and pains to help document a potential onset of disease** to a point where therapeutic options should be discussed.

You Do Not Always Need Two Genetic Variants to Have HPP

- People with severe, **early-onset forms of HPP** (perinatal/infantile) have mutations in both copies of the ALPL gene (2 mutations, one on each gene copy).
- **One mutation can be enough to produce clinical symptoms. Affected individuals most often present as late-onset forms.**
- This is an area of evolving research. We have learned that in genetic diseases, such as cystic fibrosis, that are deemed "recessive" (meaning they only manifest if 2 mutations are present, affecting both gene copies), even having a single mutation can produce symptoms. The most frequent cause in this scenario is that the mutation is "dominant negative", meaning that the mutated gene product suppresses the healthy copy. This leads to dominant (as opposed to recessive) inheritance. The **JKU ALPL Gene Variant Database** provides this information. For example, some cystic fibrosis parents who carry a gene mutation have a history of recurrent respiratory infections or other symptoms. This is similar to late-onset HPP.

You May Not Have HPP At All

- HPP has been called a disease with one of the widest spectrums of severity known. Some people have genetic mutations but are truly asymptomatic carriers who may never have a low ALP or a high Vitamin B6 or exhibit clinical symptoms at all.
- **However, carriers should be aware of their mutations for family planning purposes.** About 1 in 250 people carry an ALPL variant; hence, genetic counseling should be sought when planning a family.

Your Genetic Mutation Does NOT Equal Your Fate

- **It's important to understand the purpose of the JKU ALPL Gene Variant Database**. It was created to:
  1. *Provide a global resource of all known ALPL variants, all genotypes, and all associated phenotypes*
  2. *Help clinicians and geneticists to better counsel their patients and also healthy individuals with ALPL variants.*
- **The database is constantly growing.** It grows by clinical researchers publishing data on individual patients, so that genotype and phenotype can be added. It also grows by submission of cases from clinicians or geneticists to the research team at JKU. That way, the database expands and meets its aim to be a comprehensive resource of absolutely all manifestations of the condition, including the benign/asymptomatic spectrum associated with ALPL variants.
- **The form of HPP that is assigned to your mutation does not mean that you will definitely have this particular form of HPP.** Your phenotype may not have been reported to date, and thus, the JKU team should be informed. For example, individuals carrying one particular mutation may be completely asymptomatic, have subclinical HPP, or be/become symptomatic with odonto HPP or adult HPP. Similarly, genetically identical twins with hypophosphatasia (HPP) can have different forms or severities of the disease, even though they share the same ALPL gene mutations. This is a fascinating and well-documented example of **variable expressivity**, meaning the same genotype can lead to different clinical outcomes.
- The ALPL gene variant database shows all phenotypes (HPP forms) that have ever been reported for a particular variant and genotype. **Please encourage your doctors to report your case to the JKU team if your variant, genotype, or phenotype is not yet listed in the database.** Doing this can ensure the database grows and can benefit other people.

Use Any Genetic/Clinical Database With Caution: More Than Mutations May Be at Play

- First, the database is a resource for medical and genetic experts, not necessarily patients or individuals seeking advice.
- Mutations only tell part of the story.
- Modifier genes, which can impact how a gene is translated from genotype to phenotype, can influence how severe or mild HPP can present.
- Epigenetics, or the study of how the body turns genes on or off, can also influence how and when HPP can show up.
- Environmental factors, including nutrition, physical activity, stress, and more, may potentially also impact how HPP manifests.
- These are all areas that are currently being studied by scientists and geneticists through our myHPP app and by the ALPL Gene Variant Consortium.

We know it can be frustrating to live with uncertainty, especially when you're trying to plan for your child's or your own future. Our understanding of HPP is growing quickly, and as we learn more, we promise to keep sharing. Together, through science, collaboration with experts and researchers, advocacy, and shared experience, we'll continue to push forward.

For more information, please contact the Soft Bones Foundation
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