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My46 Trait Profile

Hypophosphatasia

Other Names: Rathbun disease

Hypophosphatasia is a genetic condition in which the bones are not mineralized properly. It is caused by mutations in the ALPL gene which makes the alkaline phosphatase enzyme.

Characteristics of Hypophosphatasia

Hypophosphatasia (HPP) is a genetic condition in which the bones are not mineralized properly. Mineralization is important to maintain bone and teeth strength. There is a wide range of severity, ranging from stillbirth with no mineralized bone and breathing problems to the less severe cases of early loss of teeth without bone problems. Although the condition is a spectrum, there are six overlapping clinical forms that are recognized. These forms reflect the severity of the condition and the age at which the bony problems are first found.

In the perinatal (lethal) form, signs are identified prior to birth by prenatal ultrasound. Along with obvious impaired mineralization, there are often skin-covered osteochondral spurs (i.e. bony growths) protruding from the forearms or legs, which are often diagnostic of this lethal form of HPP. The perinatal (benign) form also has signs identified on prenatal ultrasound, however there is typically improvement of these signs, either through the pregnancy or after birth. In the third form, infantile HPP, signs usually appear in the first six months of life, and can include widespread bone demineralization, breathing problems and early closing of the skull soft spots. The childhood form is characterized by skeletal abnormalities, including rickets, short stature and a waddling gait (i.e., walking with short steps and the weight tilting from one foot to the other). The fifth form, adult HPP, includes stress fractures. Foot and/or thigh pain are often the first symptoms of these stress fractures. The last form, odontohypophosphatasia, usually only affects the teeth and does not have other bony involvement. In this form, there is early loss of baby teeth and/or severe dental cavities.

Diagnosis/Testing

HPP is caused by changes or mutations in the ALPL gene. This gene makes the alkaline phosphatase enzyme that is responsible for mineralization in developing bones and teeth. Mutations in ALPL gene affect both how, and how much enzyme is made. It is thought that less enzyme made leads to the more severe forms of HPP. Some ALPL mutations cause little to no enzyme being made which results in the more severe forms of HPP. Other mutations cause low, but not absent levels of the enzyme being made, resulting in the milder forms of HPP. All individuals with HPP either have one or both of their ALPL genes working improperly. Radiographs (x-rays) can also be helpful in working towards a diagnosis.

Management/Surveillance

The treatment is based on treating the signs and symptoms individually, as well as monitoring for the problems associated with HPP. It is recommended that individuals be followed by a healthcare provider familiar with HPP. This specialist can outline a specific plan of management for the patient’s local healthcare providers.

Mode of inheritance

HPP can be inherited in an autosomal dominant or autosomal recessive pattern.

An autosomal dominant pattern means inheriting one ALPL mutation is enough for an individual to be affected and show signs of HPP. The mutation can be inherited from an affected parent or it can occur brand new (de novo) in an affected child.

In other cases, the inheritance is autosomal recessive. This means that an individual has to inherit two ALPL mutations (i.e., one from each parent) to be affected with HPP. If both parents are carriers of a ALPL mutation, they have a 1 in 4 (25%) chance with each pregnancy of having a child with HPP.

Risk to family members

The overall risk to family members for any symptoms of the condition is complicated and depends on the exact mutations in the family.

In general, if a couple has a child with the perinatal lethal or infantile form, there is a 25% chance each additional child will have a very similar form of HPP.

Special considerations

None

Resources

HPP
http://www.hypophosphatasia.com
Soft Bones: The US Hypophosphatasia Foundation
http://www.softbones.org/
Genetics Home Reference: Hypophosphatasia
http://ghr.nlm.nih.gov/condition/hypophosphatasia
Canadian Hypophosphatasia Contact
http://hypophosphatasia.homestead.com/files/index.html

References

Mornet, E. (2007)."Hypophosphatasia." Orphanet Journal of Rare Diseases 2: 40.
Mornet E, Nunes ME. (Updated 10 November 2011). Hypophosphatasia. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.ncbi.nlm.nih.gov/books/NBK1150/. [Accessed 02/20/2013].
Mornet, E. et al. (2011)."Clinical utility gene card for: hypophosphatasia." European Journal of Human Genetics 19(3).
Whyte MP. Hypophosphatasia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B, eds. The Metabolic and Molecular Bases of Inherited Disease (OMMBID). New York, NY: McGraw-Hill. Chap 207. Available at http://www.ommbid.com//OMMBID/the_online_metabolic_and_molecular_bases_o.... [Accessed 02/20/2013].

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