



What is Phenylalanine Hydroxylase Deficiency?

Phenylalanine hydroxylase (PAH) deficiency is an inherited disease of variable severity. When untreated, the most severe form of PAH, called phenylketonuria (PKU), is characterized by microcephaly, epilepsy, severe mental retardation, and behavioral problems. It involves defects in the enzyme phenylalanine hydroxylase, which is responsible for the breakdown of phenylalanine, one of the essential amino acids that is found in a variety of foods, including proteins and some artificial sweeteners. Major symptoms associated with PAH are due to the build-up of phenylalanine to toxic levels in the body, particularly affecting the brain.¹

What are the symptoms of Phenylalanine Hydroxylase Deficiency and what treatment is available?

Phenylalanine hydroxylase deficiency is a disease with variable severity, even within families. There are two main categories of phenylalanine hydroxylase deficiency based on levels of phenylalanine (Phe) found in the blood and the subsequent risk for mental retardation.²

The most severe, classic form of PAH deficiency is called PKU. Affected individuals appear normal at birth, although they may have microcephaly (small head size) and light skin and hair color.¹ When untreated, symptoms of PKU may include^{1,2}:

- High levels of Phe in blood
- Mental retardation
- Eczema
- Musty or “mousy” body odor
- Seizures
- Developmental delays
- Behavior problems and/or psychiatric disorders
- Osteopenia (low bone mineral density)

The less severe form is called non-PKU hyperphenylalaninemia (non-PKU HPA). When untreated, affected individuals may have similar symptoms to classic PKU but with moderate levels of Phe in blood and a lower risk of mental retardation.² There are some individuals who—even when untreated—have only mildly elevated levels of Phe in blood and appear at lower risk for mental retardation.²

There is no cure for any form of phenylalanine hydroxylase deficiency; however, with early detection and treatment, mental retardation and other neurological damage can be prevented. As the severity of the disease varies, the treatment is typically managed by physicians and nutritionists familiar with PAH deficiency. A lifelong, phenylalanine-restricted diet is essential in classic PKU. Special formula and other dietary supplements have been developed specifically for people with PAH deficiency. Medications may also be recommended. In addition, foods containing the artificial sweetener aspartame should be avoided as it contains phenylalanine.²

High levels of phenylalanine in a pregnant woman can cause birth defects in a developing fetus, including poor growth, heart defects, and mental retardation. Consequently, women affected with PAH deficiency should work with their physician several months prior to conception and during pregnancy to determine an appropriate diet.²

Phenylketonuria is included on the newborn screening panel in all 50 states.³



How is Phenylalanine Hydroxylase Deficiency inherited?

Phenylalanine hydroxylase deficiency is an autosomal recessive disease caused by mutations in the *PAH* gene.¹ An individual who inherits one copy of a *PAH* gene mutation is a “carrier” and is not expected to have related health problems. An individual who inherits two mutations in this gene, one from each parent, is expected to be affected with PAH deficiency.

If both members of a couple are carriers of a mutation in the *PAH* gene, the risk for an affected child is 25% in each pregnancy; therefore, it is especially important that the reproductive partner of a carrier be offered testing.

Who is at increased risk for PAH deficiency?

Phenylalanine hydroxylase deficiency can occur in individuals of all races and ethnicities. It is most common in Turkish, Irish, and Caucasian individuals.²

Carrier Frequency and Incidence in Select Populations²

Population	Carrier Rate	Incidence
Turkish	1/26	1/2,600
Irish	1/33	1/4,500
Caucasian	1/50	1/10,000

Having a relative who is a carrier or is affected can increase an individual’s risk of being a carrier. Consultation with a genetics health professional may be helpful in determining carrier risk and appropriate testing.

What does a positive test result mean?

If a gene mutation is identified, an individual should speak to a physician or genetics health professional about the implications of the result and appropriate testing for the reproductive partner and at-risk family members.

What does a negative test result mean?

A negative result reduces, but does not eliminate, the possibility that an individual carries a gene mutation. The likelihood of being a carrier is also influenced by family history, medical symptoms, and other relevant test results.

Where can I get more information?

- March of Dimes: http://www.marchofdimes.com/baby/birthdefects_pku.html
- Screening, Technology and Research in Genetics: <http://www.newbornscreening.info/Parents/aminoacid disorders/PKU.html>
- National PKU News: <http://www.pkunews.org/>

References

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2. Mitchell, J and Scriver, C Phenylalanine Hydroxylase Deficiency *GeneReviews* Available at: <http://www.ncbi.nlm.nih.gov/books/NBK1504/> Accessed on: December 12, 2011
3. National Newborn Screening Status Report, Updated 2/15/12. Available at: <http://genes-r-us.uthscsa.edu/nbsdisorders.pdf>