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Phenylalanine Hydroxylase Deficiency

Synonym: PAH Deficiency

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Summary

Clinical characteristics

Phenylalanine hydroxylase (PAH) deficiency results in intolerance to the dietary intake of the essential amino acid phenylalanine and produces a spectrum of disorders. The risk of adverse outcome varies based on the degree of PAH deficiency. Without effective therapy, most individuals with severe PAH deficiency, known as classic PKU, develop profound and irreversible intellectual disability. Affected individuals on an unrestricted diet who have phenylalanine levels above normal but below 1,200 µmol/L (20 mg/dL) are at much lower risk for impaired cognitive development in the absence of treatment.

Diagnosis/testing

PAH deficiency can be detected by newborn screening in virtually 100% of cases based on the presence of hyperphenylalaninemia using tandem mass spectrometry on a blood spot obtained from a heel prick. The diagnosis of PAH deficiency is established in a proband with:

- A plasma phenylalanine concentration persistently above 120 µmol/L (2 mg/dL) and altered ratio of phenylalanine to tyrosine in the untreated state with normal BH4 cofactor metabolism;

  and/or

- The finding of biallelic pathogenic variants in *PAH* by molecular genetic testing.

Management

Treatment of manifestations: Classic PKU: a low-protein diet and use of a Phe-free medical formula as soon as possible after birth to achieve plasma Phe concentrations of 120-360 µmol/L (2-6 mg/dL). A proportion of individuals with PKU benefit from adjuvant therapy with sapropterin. Large neutral amino acid (LNAA) transporters may also decrease the plasma Phe concentration in affected adolescents and adults. Non-classic HPA: individuals with plasma Phe concentrations above 600 µmol/L are treated in most centers. It is debatable whether those with plasma Phe concentrations consistently below 600 µmol/L (10 mg/dL) require dietary

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treatment. Neuropsychiatric testing may be considered to identify learning differences in affected individuals with referral to developmental services, as indicated.

Surveillance: Regular monitoring of plasma Phe, Tyr, and plasma amino acid concentrations in individuals with classic PKU; regular assessment of growth and micronutrient needs; assessment of developmental progress and screening for mental illness at every visit.

Agents/circumstances to avoid: Aspartame, an artificial sweetener that contains phenylalanine.

Evaluation of relatives at risk: Newborn sibs of an individual with PAH deficiency who have not been tested prenatally should have blood concentration of Phe measured shortly after birth (in addition to newborn screening) to allow earliest possible diagnosis and treatment.

Pregnancy management: To minimize or prevent teratogenic effects of phenylalanine, women with PAH deficiency should follow a Phe-restricted diet for at least several months prior to conception in order to maintain plasma Phe concentrations between 120 and 360 µmol/L (2-6 mg/dL); after conception, continuous nutritional guidance and weekly or biweekly measurement of plasma Phe concentration to assure that target levels are met in addition to adequate energy intake with the proper proportion of protein, fat, and carbohydrates. Evaluation for fetal anomalies using high-resolution ultrasound and fetal echocardiogram.

Genetic counseling

PAH deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the *PAH* pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Phenylalanine hydroxylase (PAH) deficiency **should be suspected** in an individual with the following newborn screening results, clinical features (by age), neuroimaging, and supportive laboratory findings:

Newborn screening results

- Positive newborn screen by tandem mass spectrometry (MS/MS) using dried blood spots collected after 24 hours of age. This method is used in most if not all states in the USA for newborn screening.
- The ability of current tests to accurately measure Phe concentrations in infants before age 24 hours is a concern, since hyperphenylalaninemia (HPA) manifests itself as a time-dependent increase of Phe concentration in the blood. However, recognition of an altered ratio of phenylalanine and tyrosine may still identify the affected newborn.

Postnatal clinical findings in a newborn. No physical signs of hyperphenylalaninemia (HPA)

Clinical findings in an untreated, older individual (infancy to adulthood)

- Epilepsy
- Any level of intellectual disability and behavior problems, including autistic features
- Parkinson-like features (particularly in an adult)
- Musty body odor
- Eczema
- Decreased skin and hair pigmentation

- Female with no prior normal offspring who has a history of recurrent pregnancy loss and/or offspring with malformations including any combination of small size, microcephaly / brain malformations, congenital heart defect, limb malformations, and/or tracheoesophageal fistula

Neuroimaging. Progressive white matter disease on brain MRI; observed in 90% of individuals with PAH deficiency even without evidence of neurologic deterioration

- Advanced-age affected individuals off diet or with poor compliance and those who are untreated have the most severe MRI findings.
- It is proposed that in untreated affected individuals, Phe prevents myelination and in early-treated affected individuals, myelin is normally made but may be functionally impaired [Anderson & Leuzzi 2010].

Supportive laboratory findings

- **Plasma amino acid analysis.** In the untreated state, an elevated plasma phenylalanine (Phe) concentration persistently higher than 120 µmol/L (2 mg/dL) with phenylalanine levels higher than tyrosine (Tyr) levels
  - A normal Phe:Tyr ratio is typically <1; a ratio of >3 is considered useful in the diagnosis of PAH deficiency [Vockley et al 2014].
  - Most severely affected individuals with complete enzyme loss (also called "classic PKU") have untreated levels of phenylalanine (Phe) of >1,200 µmol/L. If diagnosed early and if treatment is begun in the first or second week of life, most severely affected individuals do not attain Phe levels this high.
- **BH4 (tetrahydrobiopterin) cofactor analysis and/or challenge**
  - Normal urine or dried blood spot pterins (neopterin and biopterins) studies using liquid chromatography
  - Normal dihydropterine reductase measurement in erythrocytes, typically from a dried blood spot

Establishing the Diagnosis

The diagnosis of PAH deficiency **is established** in a proband with a plasma phenylalanine concentration persistently above 120 µmol/L (2 mg/dL) and altered ratio of phenylalanine to tyrosine in the untreated state, with normal BH_4 cofactor metabolism; and/or the finding of biallelic pathogenic variants in *PAH* by molecular genetic testing (see Table 1).

Note: (1) It is important that a low phenylalanine diet be initiated prior to receiving the results of the pterins or molecular genetic studies. (2) See Genotype-Phenotype Correlations for information on the clinical utility of a molecular diagnosis.

Molecular testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *PAH* is performed first followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

  Targeted analysis for common pan ethnic pathogenic variants (see Table 2), as well as targeted analysis for founder pathogenic variants, may be performed. Note that founder variants in specific populations may be the same as those found in pan ethnic populations.

- **A multigene panel** that includes *PAH* and other genes of interest (see Differential Diagnosis) may also be considered. Note: The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Phenylalanine Hydroxylase Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
PAH	Sequence analysis [3]	97%-99%
	Gene-targeted deletion/duplication analysis [4]	<1%-3% [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. This technique has been used to detect abnormal dosage in 20% of uncharacterized PKU alleles [Gable et al 2003] and therefore duplications and deletions may account for up to 3% of pathogenic variants in the Czech population [Kozak et al 2006].

Enzyme analysis is not usually indicated in the diagnosis of PAH deficiency because PAH is a hepatic enzyme and accurate, less invasive methods of diagnosis are available.

Clinical Characteristics

Clinical Description

Phenylalanine hydroxylase (PAH) deficiency results in intolerance to the dietary intake of the essential amino acid phenylalanine and produces a spectrum of disorders [Vockley et al 2014]. Many terms have been used to describe the various clinical phenotypes that result from PAH deficiency (see Nomenclature). This *GeneReview* will follow the American College of Medical Genetics and Genomics (ACMGG) recommended convention.

The risk of adverse outcome varies based on the degree of PAH deficiency. Without effective therapy, most individuals with severe PAH deficiency, known as classic PKU, develop profound and irreversible intellectual disability. Affected individuals on an unrestricted diet who have phenylalanine levels above normal but below 1,200 µmol/L (20 mg/dL) are at much lower risk for impaired cognitive development in the absence of treatment. However, current understanding of these issues is not complete.

Untreated Individuals with Persistent Severe Hyperphenylalaninemia (i.e., Classic PKU)

Affected individuals almost always show impaired brain development. Signs and symptoms include nearly invariable severe intellectual disability and behavior problems with a high frequency of seizures and variable microcephaly.

The excretion of excessive phenylalanine and its metabolites can create a musty body odor and skin conditions such as eczema.

The associated inhibition of tyrosinase and low tyrosine levels are responsible for decreased skin and hair pigmentation.

Affected individuals also have decreased myelin formation, leading eventually to white matter changes on head MRI.

Significantly elevated Phe levels decrease dopamine, norepinephrine, and serotonin production and can be reflected in electroencephalographic changes, which are reversible if the Phe level is reduced.

Individuals with Classic PKU Identified and Treated from Birth

Intelligence. The correlation between early elevated Phe levels and long-term decreases in IQ has been well studied. The benefit of normalized Phe levels on IQ throughout life has also been shown in studies of affected adults.

- Those who decrease their adherence to a Phe-restricted diet in adulthood have a small drop in IQ, further supporting the current advice of "diet for life" (see Management) [Brumm & Grant 2010, Vockley et al 2014, Jahja et al 2016].
- However, even with strict adherence to a low phenylalanine (Phe) diet, adults may still have some underlying sequelae and suboptimal cognitive outcomes affecting language skills, memory, learning skills, and executive function [Moyle et al 2007, Waisbren et al 2007, Antshel 2010, Burton et al 2013].

Neuropsychological issues. In treated individuals, certain psychological problems are increased – as compared to unaffected sibs or children with other chronic diseases [Brumm et al 2010, Bilder et al 2013].

- Adults who have increased Phe levels typically due to relaxed Phe-restricted diet tend to have a reduced attention span, slow information-processing abilities, and slow motor reaction time [Channon et al 2007, Moyle et al 2007]. These findings appear to be related to both current and historical phenylalanine levels [Huijbregts et al 2002, Fonnesbeck et al 2013].
- There is also a higher incidence of anxiety, depression, phobias, and panic attacks in early-treated individuals who discontinued therapy in the second decade of life [Koch et al 2002].

Neurologic. Early-treated adults who discontinue diet are also at risk for minor neurologic abnormalities such as tremor and brisk reflexes [Pietz et al 1998] and, in some cases, more severe neurologic dysfunction, including paralysis. Return to diet often resolves these neurologic symptoms [Camp et al 2014].

PAH with Milder Biochemical and Clinical Phenotypes

Individuals with PAH deficiency and **plasma Phe between 600 and 1,200 µmol/L (10-20 mg/dL)** on an unrestricted diet have not been extensively studied. However, it is well documented that individuals with classic PKU who have levels in this range have both acute and chronic neuropsychological problems. Therefore, treatment with a Phe-restricted diet is recommended for individuals with Phe levels in this range.

Individuals with PAH deficiency who have plasma **Phe concentrations consistently below 600 µmol/L (10 mg/dL)** on an unrestricted diet are considered by many experts not to be at higher risk of developing intellectual, neurologic, and neuropsychological impairment than are individuals without PAH deficiency. However, since evidence suggests that individuals with classic PKU have demonstrable neurophysiologic changes when Phe levels are between 360 and 600 µmol/L (6 to 10 mg/dL), other experts recommend Phe restriction for any individual who has Phe levels >360 µmol/L (6 mg/dL) on an unrestricted diet. A very small number of programs begin therapy for individuals with Phe levels >240 µmol/L (4 mg/dL). As Phe is an essential amino acid, having inadequate phenylalanine leads to growth restriction, microcephaly, and developmental problems. The safety of dietary restriction of Phe for individuals with the milder PAH deficiency has not been systematically studied. Practices vary around the world [Blau et al 2010].

In a few case reports untreated individuals with mild PAH deficiency who had normal intelligence were diagnosed in adulthood as a result of sudden and severe psychiatric deterioration [Weglage et al 2000, Camp et al 2014].

Other

Osteopenia. While numerous studies indicate that individuals with PAH deficiency have a high incidence of osteopenia (as measured by DXA, dual-energy x-ray absorptiometry) [Zeman et al 1999, Pérez-Dueñas et al

2002, Modan-Moses et al 2007], a recent meta-analysis showed that the combined data do not support a high risk based on World Health Organization and International Society for Clinical Densitometry measurement guidelines [Demirdas et al 2015]. Studies to explore the mechanism of low bone density and clinical significance are under way. Until additional studies are performed, it is important to continue to closely monitor the bone health of individuals with PAH deficiency. A recent study of individuals with PAH deficiency by Coakley et al [2016] identified risk factors for lower Z-scores, with the highest significance for dietary prescription compliance in an adult population.

Vitamin B_{12} deficiency can occur when individuals with PKU relax their diet in adolescence [Robinson et al 2000]. This vitamin is found in natural animal protein; when affected individuals decrease their amino acid supplementation, they often still choose low-protein foods and are therefore at risk for vitamin B_{12} deficiency.

Children Born to Women with PAH Deficiency

The abnormalities that result from exposure of a fetus to high maternal plasma Phe concentration are the result of maternal PAH deficiency. Risks include the following [Vockley et al 2014]:

- **Intellectual disability** (>90%).The threshold for this finding is a maternal Phe concentration consistently above 360 µmol/L during pregnancy with an inverse relationship between cognitive function and maternal Phe level above 360 µmol/L.
- **Poor behavioral outcomes**
- **Microcephaly.** The risk is 5%-18% in pregnancies in which the maternal Phe level is optimized prior to ten weeks' gestation and increases to 67% if appropriate Phe levels are not achieved by 30 weeks' gestation.
- **Congenital heart defect and other malformations.** Due to the early formation of the heart, consistently elevated maternal Phe concentrations (>600 µmol/L) during early gestation leads to an approximately 8%-12% risk of cardiac malformations. Minor dysmorphic features and other birth defects have also been reported in infants born to women with maternal PKU, including tracheoesophageal fistula.
- **Intrauterine growth restriction (IUGR).** Frequency is not different from that in the general population if maternal Phe levels are controlled by week ten of gestation; the risk of IUGR increases if the Phe concentration is optimized later in pregnancy.

Genotype-Phenotype Correlations

More than 900 pathogenic variants have been described in *PAH* (see www.biopku.org). While both genetic (particular pathogenic variant) and environmental (dietary consumption) components contribute to an affected individual's total plasma Phe level, knowledge of the specific genetic cause can offer insight helpful for long-term management [Zschocke & Hoffmann 2000, National Institutes of Health Consensus Development Panel 2001, Güttler & Guldberg 2006, Santos et al 2010].

In compound heterozygotes with functional hemizygosity (null/missense paired alleles), the less severe of the two *PAH* pathogenic variants determines disease severity. However, when two pathogenic variants associated with similar severity are present, the phenotype may be milder than predicted by either allele [Kayaalp et al 1997, Guldberg et al 1998, Waters et al 1998].

In general, affected individuals with milder *PAH* pathogenic variants have a better response to sapropterin (B6BH4, Kuvan™) (see Management). The current guidelines recommend that all affected individuals (except those with two pathogenic null variants *in trans*) be offered a trial with sapropterin (B6BH4, Kuvan™) because of the difficulty of predicting the phenotype from the genotype [Vockley et al 2014]. See Molecular Genetics for more information on common pathogenic variants in *PAH* and their reported responsiveness to sapropterin therapy.

Table 2. Common Pathogenic Changes in *PAH* and Their Responsiveness to Sapropterin

cDNA	Protein	Cases in PAHdb	Responsive to Sapropterin
c.1222C>T	p.Arg408Trp	6.7%	<10%
c.1066-11G>A (IVS10-11G>A)		5.3%	<10%
c.194T>C	p.Ile65Thr	4.1%	89%
c.782G>A	p.Arg261Gln	3.6%	78%
c.842C>T	p.Pro281Leu	2.9%	None [Leuders et al 2014, biopku.org]
c.1315+1G>A (IVS12+1G>A)		2.8%	12.5% [biopku.org] None [Leuders et al 2014]
c.473G>A	p.Arg158Gln	2.7%	<10%

Data obtained from: PAHdb accessed 5/8/2016 (biopku.org); and Leuders et al [2014]. All changes with >2.5% frequency in the PAHdb database were included. In database searches, homozygosity was assumed for calculations; however, this is a rare finding in consanguineous individuals. It is recommended that all affected individuals be tested for personal responsiveness. Genetic changes shown affect >2.5% of the database population. See biopku.org for the most up-to-date information and additional references.

However, genotype-phenotype correlation becomes more complex when clinical outcomes are also taken into account. While DiSilvestre et al [1991] found that genotype does predict biochemical phenotype (i.e., by Phe loading tests), it does not always predict clinical phenotype (i.e., occurrence of intellectual disability). Some untreated individuals with PAH deficiency and biallelic *PAH* pathogenic variants that usually result in classic PKU have elevated plasma Phe concentration but normal intelligence. In other instances, sibs with the same genotype have different clinical and metabolic phenotypes. While mechanisms that cause dissimilarities in pathogenesis at the level of the brain in spite of comparable plasma Phe concentrations are not fully understood [Scriver & Waters 1999], there is evidence that variation in transport of Phe across the blood-brain barrier is at least one relevant factor [Weglage et al 2002].

Nomenclature

The 2014 American College of Medical Genetics and Genomics guidelines on the diagnosis and management of PAH (PKU) recommends the term "phenylalanine hydroxylase (PAH) deficiency" to describe all affected individuals, in order to best recognize that there is a spectrum of PAH deficiency. The guideline recognizes that the most severe expression of that spectrum will continue to be termed "classic PKU." They also recognized that other classification schema in historical use suggested the use of the term "hyperphenylalaninemia" (hyperPhe or HPA) for those who have Phe levels on an unrestricted diet that are above normal but below 1,200 µmol/L (20 mg/dL) [Vockley et al 2014].

Alternative Nomenclature Systems

In the early literature there was no universal system of nomenclature; thus, it was necessary to understand how terms were used in a given report to interpret the significance of the observations regarding PAH activity. In response to this difficulty, various systems of nomenclature have been proposed.

Camp et al [2014] provide, as part of an NIH systematic review of PKU, a recommendation for terminology of PAH deficiency (from most to least severe) of "classic PKU," "moderate PKU," "mild PKU," "mild HPA-gray zone," and "mild HPA-NT" (no treatment), and a table mapping the various terms to the level of blood Phe when untreated, to the dietary tolerance of Phe, and to the observed or expected level of PAH activity. This table of nomenclature will be of particular value to those wishing to understand the relationship between the various historical systems of nomenclature. See Table 2 in Camp et al [2014].

An early classification scheme proposed by Kayaalp et al [1997] was intended to simplify the nomenclature. In this system:

- **Phenylketonuria (PKU)** is the most severe of the three types and in an untreated state is associated with plasma Phe concentrations >1,000 µmol/L and a dietary Phe tolerance of <500 mg/day. PKU is associated with a high risk of severely impaired cognitive development.
- **Non-PKU hyperphenylalaninemia (non-PKU HPA)** is associated with plasma Phe concentrations consistently above normal (i.e., >120 µmol/L) but lower than 1,000 µmol/L when an individual is on a normal diet. Individuals with non-PKU HPA are at a much lower risk for impaired cognitive development in the absence of treatment.
- **Variant PKU** includes those individuals who do not fit the description for either PKU or non-PKU HPA.

A classification scheme proposed by Guldberg et al [1998] subdivides PAH deficiency into the following four categories:

- **Classic PKU** is caused by a complete or near-complete deficiency of PAH activity. Affected individuals tolerate less than 250-350 mg of dietary phenylalanine per day to keep plasma concentration of Phe at a safe level of ≤300 µmol/L (5 mg/dL). Without dietary treatment most individuals develop profound, irreversible intellectual disability.
- **Moderate PKU.** Affected individuals tolerate 350-400 mg of dietary phenylalanine per day.
- **Mild PKU.** Affected individuals tolerate 400-600 mg of dietary phenylalanine per day.
- **Mild hyperphenylalaninemia (MHP).** Affected infants have plasma Phe concentrations <600 µmol/L (10 mg/dL) on a normal diet.

Prevalence

PAH deficiency varies in frequency from more than 1:5,000 (Turkey, Ireland) to approximately 1:10,000 in those of northern European and East Asian origin (lower in Finland and Japan). Classic PKU was once the most common identifiable etiology of severe intellectual disability in institutions for the developmentally disabled in Europe and North America, but since the adoption of universal newborn screening in many countries, symptomatic classic PKU is less frequently seen. The predicted incidence of severe intellectual disability resulting from PKU in screened populations – fewer than one in a million live births – reflects those children not detected by newborn screening. See Table 3.

Table 3. Prevalence of PAH Deficiency by Population

Population	PAH Deficiency in Live Births	Carrier Rate	Reference
Turks	1:2,600	1/26	Ozalp et al [2001]
Irish	1:4,500	1/33	DiLella et al [1986]
Northern European origin, East Asian	1:10,000	1/50	Scriver & Kaufman [2001]
Japanese	1:143,000	1/200	Aoki & Wada [1988]
Finnish, Ashkenazi Jewish	1:200,000	1/225	Scriver & Kaufman [2001]

Click here (pdf) for a historical perspective.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants of *PAH*.

Differential Diagnosis

Tetrahydrobiopterin (BH_4) deficiency. Hyperphenylalaninemia may also result from the impaired synthesis or recycling of tetrahydrobiopterin (BH_4), the cofactor in the phenylalanine, tyrosine, and tryptophan hydroxylation reactions. All of the HPAs caused by BH_4 deficiency are inherited in an autosomal recessive manner. They account for approximately 2% of individuals with elevated Phe levels in most populations. However, for individuals with elevated Phe from populations in which PAH is less common (e.g., Japan), the risk to the affected individual of having a disorder of pterin metabolism is much higher. BH_4 is also involved in catecholamine, serotonin, and nitric oxide biosynthesis (see biopku.org).

- Defects in BH_4 synthesis result from guanosine triphosphate cyclohydrolase (GTPCH) deficiency (OMIM 233910) caused by biallelic pathogenic variants in *GCH1* or from 6-pyruvoyl tetrahydrobiopterin synthase (PTPS) deficiency (OMIM 261640) caused by biallelic pathogenic variants in *PTS*.
- Impaired recycling of BH_4 is caused by dihydropteridine reductase (DHPR) deficiency (OMIM 261630) caused by biallelic pathogenic variants in *QDPR* or by pterin-4 acarbinolamine dehydratase (PCBD) deficiency (OMIM 264070) caused by biallelic pathogenic variants in *PCBD1*.

Vockley et al [2014] emphasize that all neonates with persistent hyperphenylalaninemia must be screened for the BH_4 deficiencies. The following tests are best performed in specialized centers. Prenatal diagnosis is possible for all forms of BH_4 deficiencies. The following screening tests are essential:

- Pterins are measured in urine or blood.
- Erythrocyte dihydropterine reductase should be measured on whole blood spotted on filter paper. A quantitative assay for urinary neopterin and biopterin can confirm results obtained from the filter paper samples. Reference values are available for different age groups.
- Abnormal pterin levels and ratios should prompt enzyme testing for possible deficiencies of: GTP cyclohydrolase, 6-pyruvoyl-tetrahydropterin synthase, dihydropteridine reductase, or pterin carbinolamine-4α-dehydratase.

The typical (severe) forms of GTPCH, PTPS, and DHPR deficiency have the following variable, but common, findings: intellectual disability, convulsions, disturbance of tone and posture, drowsiness, irritability, abnormal movements, recurrent hyperthermia without infections, hypersalivation, and swallowing difficulties. Microcephaly is common in PTPS and DHPR deficiencies. Plasma phenylalanine concentrations can vary from slightly above normal (>120 µmol/L) to as high as 2,500 µmol/L. Mild forms of BH_4 deficiency have no clinical signs.

PCD deficiency, sometimes referred to as "primapterinuria," is associated with benign transient hyperphenylalaninemia and patients are at risk for MODY-type diabetes at puberty.

In principle, BH_4 deficiencies are treatable. Treatment requires the normalization of BH_4 availability and of blood Phe concentration and restoration of the BH_4-dependent hydroxylation of tyrosine and tryptophan. This is achieved by BH_4 supplementation along with dietary modification, neurotransmitter precursor replacement therapy, and supplements of folinic acid in DHPR deficiency. The treatment should be initiated early and probably continued for life [Blau et al 2001, Ponzone et al 2006].

More information on the BH_4 deficiencies can be found at www.biopku.org.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with phenylalanine hydroxylase (PAH) deficiency, the following evaluations are recommended:

- Medical biochemical genetics consultation, if not already done, and evaluation by a metabolic dietician able to begin a low-Phe, age-appropriate diet
- Blood phenylalanine concentration and estimation of phenylalanine tolerance [Kayaalp et al 1997, Guldberg et al 1998]. Because the PAH genotype may not always predict phenotype (see Genotype-Phenotype Correlations), the individual's diet should be tailored to the estimated phenylalanine tolerance irrespective of genotype.
- For individuals diagnosed outside the newborn period, formal developmental, behavioral, neuropsychological, and mental health evaluation

Treatment of Manifestations

Treatment for affected individuals of all ages can be difficult and is enhanced with the teaching and support of an experienced health care team consisting of physicians, nutritionists, genetic counselors, social workers, nurses, and psychologists. See ACMG Management Guidelines for PKU.

Treatment of Classic PKU

Restriction of dietary phenylalanine. The generally accepted goal of treatment for individuals with PAH deficiency is normalization of the concentrations of Phe (phenylalanine) and Tyr (tyrosine) in the blood and thus prevention of the cognitive deficits that are attributable to this disorder [Burgard et al 1999].

Genetic Metabolic Dieticians International (GMDI) has PKU Nutrition Management Guidelines that are continually updated.

Any provider managing the diet of an individual with PAH deficiency should use these resources and work closely with a dietician knowledgeable in the care and management of a person with this diagnosis.

Singh et al [2014] provide the following dietary recommendations:

- Maintain blood Phe between 120 and 360 µmol/L throughout the life span.
- Monitor blood Phe most frequently during times of increased anabolism: infancy, childhood, and pregnancy. The NIH recommends measurement of blood phenylalanine levels on a weekly basis for the first year of life, on a biweekly basis until age 13 years, and on a monthly basis thereafter [Camp et al 2014]. Care must be taken to avoid long periods of low blood Phe concentration, which is also harmful to brain development and function.
- Monitor blood Phe consistently, preferably two to three hours after eating.
- Evaluate individual nutritional needs, ability to adhere to recommendations, and access to treatment options when choosing appropriate interventions (medical food, modified low-protein food, large neutral amino acids [LNAAs], and sapropterin) to achieve blood PHE in the target range.
- Include breast milk [Vockley et al 2014] and/or infant formula as sources of Phe in the diet of an infant with PAH deficiency.
- Recommend that medical food be consumed throughout the day for optimal metabolic control.
- Track Phe intake by any of several methods, including counting milligrams or exchanges of PHE or grams of protein.
- Maintain blood Tyr in the normal range.

- Maintain other nutrients and micronutrients at RDA levels, including calcium, vitamin D, iron, and B vitamins. Due to the protein-restricted dietary components, micronutrients found in animal products must be carefully monitored and supplemented, as needed.
- Provide counseling and education specific to the needs of the individual with PAH deficiency (and/or his/her caregivers) to help maintain appropriate blood Phe throughout the life span.

Sapropterin (Kuvan®). BH_4 responsiveness, as determined by a 30% decrease in Phe plasma levels on plasma amino acid analysis, is determined based on response to a pharmacologic dose of BH_4 (10-20 mg/kg per day):

- All affected individuals except those with two *trans* pathogenic null variants should ideally undergo a trial with sapropterin supplementation. The trial needs to be conducted when Phe levels have been stable and dietary intake can remain unchanged, so that any change in Phe level is the result of the medication; for some affected individuals it is a challenge to conduct a trial of therapy. The most common dose given is 20 mg/kg per day. Lower trial doses may lead to false negative responsiveness results [Vockley et al 2014].
- Affected individuals who are responsive should continue this medication with compensatory dietary Phe liberalization, as needed, to maintain a safe Phe level between 120 and 360 µmol/L.
- The majority of individuals with mild or moderate PKU may be responsive to sapropterin while up to 10% of individuals with classic PKU show a response [Bernegger & Blau 2002, Pérez-Dueñas et al 2004, Zurflüh et al 2006]. Reviewed in Ho & Christodoulou [2014].

Click here (pdf) for more information on the proposed mechanism of action of sapropterin.

Large neutral amino acids (LNAA) transporters. LNAA may decrease the plasma Phe concentration in affected adolescents and adults; however, it should not be used in women of childbearing age (see Pregnancy Management).

Click here (pdf) for more information on the proposed mechanism of action of LNAA.

Treatment for Non-Classic Hyperphenylalaninemia

While debate continues, many experts believe that dietary treatment is unnecessary for many of the individuals in this class.

- Individuals with **Phe levels >600 µmol/L (10 mg/dL)** are treated by most centers, in recognition of the finding of head MRI changes and neuropsychological findings in at least some affected individuals.
- Treatment in individuals with **Phe levels consistently <600 µmol/L but >360 µmol/L** remains controversial [Weglage et al 2001, Hanley 2011, van Spronsen 2011].
  - Thirty-one individuals with PAH deficiency who were never treated and whose plasma Phe concentrations did not exceed 600 µmol/L had normal cognitive neuropsychological development.
  - The American College of Medical Genetics and Genomics guidelines on the diagnosis and management of PAH (PKU) state: "…treatment of infants with sustained blood Phe levels >360 µmol/L is recommended following appropriate review of the controversy with patients."
- If the **Phe levels remain between 120 and 360 µmol/L**, treatment is not recommended; however, children should be followed for plasma Phe levels closely during the first two years of life, then on an annual or biennial basis [Vockley et al 2014].
- Care should be taken so that women of childbearing age in this group receive proper counseling about the teratogenic effects of elevated maternal plasma Phe concentration (i.e., "maternal HPA/PKU") on the developing fetus [Weglage et al 2001] (see Pregnancy Management).

Other

Neuropsychiatric testing may be considered to identify learning differences. Referral to appropriate developmental services is indicated to optimize developmental outcome.

Bone health assessment. Current literature regarding the utility of DXA (dual-energy x-ray absorptiometry) scans is controversial; however, bone health should be considered in the overall health of an affected individual [Coakley et al 2016].

Prevention of Primary Manifestations

See Treatment of Manifestations.

Surveillance

Plasma Phe and Tyr concentrations in individuals with classic PKU must be monitored regularly [National Institutes of Health Consensus Development Panel 2001] (see Treatment of Manifestations).

- In infants, frequent in-clinic visits are recommended until Phe levels are stabilized, followed by weekly blood level monitoring of Phe and tyrosine levels until age one with closer monitoring during periods of rapid growth or diet transitions. In addition, plasma amino acid levels should be regularly monitored to foster optimal growth during the first year of life.
- Between ages one and 12 years, biweekly to monthly sampling may be adequate.
- In adolescents and adults who are stable and well controlled, blood level monitoring can be monthly.

Nutritional assessment should include growth evaluation and assessment of micronutrient intake and needs.

- Some clinics perform monitoring of plasma amino acids, transthyretin, complete blood count, ferritin, and 25-OH vitamin D every six months in infants and annually thereafter even if growth is appropriate and analysis of the diet shows adequate intake.
- If there is evidence for suboptimal dietary intake or overreliance on nutritionally incomplete medical foods, evaluation of plasma amino acids (full panel), transthyretin, albumin, complete blood count, ferritin, 25-OH vitamin D, electrolytes, renal function, liver function, albumin, vitamin B_{12}, red blood cell essential fatty acids, trace minerals (zinc, copper, selenium), vitamin A, and folic acid should be considered [Singh et al 2014, Vockley et al 2014].

Assessment of developmental milestones and overall developmental progress should take place at every visit.

Screening for mental illness should be considered at every visit and performed at regular intervals by primary care providers.

Agents/Circumstances to Avoid

Aspartame, an artificial sweetener in widespread use, contains phenylalanine. Persons with PKU should either avoid products containing aspartame or calculate intake of Phe and adapt diet components accordingly.

Evaluation of Relatives at Risk

It is appropriate to evaluate sibs of a proband in order to identify as early as possible those who would benefit from initiation of treatment. Note: Because phenotypic variability may be significant, previously undiagnosed and even apparently asymptomatic sibs of an affected individual may also be affected [Vockley et al 2014].

Evaluations can include:

- Measurement of blood concentration of phenylalanine and newborn screening in newborn sibs of an individual with PKU if prenatal testing was not done;
- Molecular genetic testing if the pathogenic variants in the family are known;
- Blood concentration of phenylalanine and tyrosine to clarify the disease status of older at-risk sibs if the pathogenic variants in the family are not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Women with PAH Deficiency

Women with PAH deficiency who have received appropriate treatment throughout childhood and adolescence have normal physical and essentially normal intellectual and behavioral development. However, if the woman has elevated plasma Phe concentrations during pregnancy, the fetus is at high risk for malformations and intellectual disability, since phenylalanine is a potent teratogen (see Clinical Characteristics) [Rouse & Azen 2004, Prick et al 2012].

The American College of Obstetrics and Gynecology Committee Opinion on the Management of Women with Phenylketonuria, the American College of Medical Genetics and Genomics guidelines on the diagnosis and management of PAH deficiency [Vockley et al 2014], and Singh et al [2014] suggest the following management of an affected woman prior to and during pregnancy.

Preconception

- Genetic counseling regarding the teratogenic effects of elevated maternal Phe concentration on the developing fetus and recurrence risks for PAH deficiency in the fetus
- Achievement and maintenance of the maternal Phe concentration at less than 360 µmol/L for three months prior to conception
- Assessment of early osteopenia risk
- Discontinuation of LNAA treatment

During pregnancy

- Co-monitor in conjunction with practitioners from an experienced metabolic center.
- Maternal Phe concentration of 120-360 µmol/L during pregnancy is recommended. In unplanned pregnancies, rapid reinitiation of a Phe-restricted diet should be advised based on current knowledge of the fetal risks.
- Despite limited data, sapropterin supplementation may be appropriate in addition to dietary therapy.
- Monitor dietary intake of pregnant women with PAH deficiency to ensure nutrient adequacy with proper proportion of protein, fat, and carbohydrates.
- Evaluate for fetal anomalies by high-resolution ultrasound and fetal echocardiogram.

Post partum

- Provide coordinated care in the postpartum period
- Breastfeeding may be pursued if the infant does not have PAH deficiency.

Therapies Under Investigation

Although the treatment of PKU with phenylalanine-restricted diets has been hugely successful, the poor palatability of the diet results in poor compliance in adolescence and adulthood. A number of attempts to find other treatment modalities for PKU are ongoing.

Enzyme substitution. Under investigation is the administration of the enzyme phenylalanine ammonia lyase (PAL), a plant-derived enzyme that converts phenylalanine to trans-cinnamic acid and ammonia. The version currently under investigation is the PEGylation (conjugation with polyethylene glycol) of PAL, since it has been found to decrease the immune response to PAL [Gámez et al 2005, Sarkissian & Gámez 2005]. Clinical trials with this protected form of injectable enzyme are currently under way. The results of the Phase I trial showed effectiveness by reducing blood Phe by 54% in the participants receiving the highest dose. The Phe level nadir

was at six days and response lasted 21 days. Adverse reactions included rash, antibody accumulation to both PAL and the PEGylation component, and injection site reaction [Longo et al 2014].

Cell-directed therapies. Liver repopulation with PAH-expressing cells is being investigated. Hepatocyte transplantation has been successful in animal models and in humans for other liver-based inborn errors of metabolism, such as glycogen storage disorders and urea cycle defects. Research continues to identify the best ways to allow for transferred hepatocytes to have cell growth advantage over native hepatocytes (reviewed in Strisciuglio & Concolino [2014]).

Gene therapies. Liver-directed gene therapy does not result in a permanent correction of PAH activity in animal models. Delivery to muscle was successful in increasing conversion of Phe to Tyr in mice (reviewed in Strisciuglio & Concolino [2014]).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Phenylalanine hydroxylase (PAH) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *PAH* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

  Significant intrafamilial variability has been observed in PAH deficiency; thus, the phenotype observed in the proband may not be consistent with or predicative of the phenotype in affected sibs [DiSilvestre et al 1991, Scriver & Waters 1999, Weglage et al 2002, Camp et al 2014].

- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Children born of one parent with PAH deficiency and one parent with two normal *PAH* alleles are obligate heterozygotes.
- If one parent is affected and the other parent is a carrier, offspring have a 50% chance of being heterozygous and a 50% chance of being affected.
- If the mother is the affected parent, maternal HPA/PKU is a critical issue (see Clinical Description, Children Born to Women with PAH Deficiency).

Other family members. Each sib of the proband's unaffected parents is at a 50% risk of being a carrier of a *PAH* pathogenic variant.

Carrier Detection

Molecular genetic testing for at-risk relatives requires prior identification of the *PAH* pathogenic variants in the family. ACMG guidelines recommend the use of molecular genetic testing to identify carriers in a family with a known *PAH* pathogenic variant [Vockley et al 2014]. If molecular genetic testing is not possible, biochemical analysis can be used.

Biochemical testing relies on plasma Phe concentration and the Phe/Tyr ratio, with or without phenylanine loading [Freehauf et al 1984, Blitzer et al 1986]. Hormones associated with pregnancy have been shown to alter the Phe/Tyr ratio; thus, biochemical analysis cannot be used to determine carrier status during pregnancy, shortly after pregnancy, or with oral contraceptive use.

Partners of an individual affected with or known to be a carrier of PAH deficiency may be interested in carrier testing. Analysis of *PAH* can be offered, with appropriate counseling about limits of sensitivity. Guidelines for biochemical carrier testing have not been established; and the predictive value of biochemical testing has been studied on a limited basis only.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- Young women affected with PAH deficiency should receive counseling regarding the teratogenic effects of elevated maternal plasma Phe concentration (i.e., "maternal HPA/PKU") when they reach childbearing age [Weglage et al 2001] (see Pregnancy Management).
- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *PAH* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for PAH deficiency are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. Prenatal diagnosis has been found by some families to be of value when decisions that will affect care of their child need to be made prenatally. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  PKU
- **Canadian PKU and Allied Disorders Inc.**
  Canada
  Phone: 877-226-7581
  Email: info@canpku.org
  www.canpku.org
- **March of Dimes**
  PKU (Phenylketonuria) in your baby
- **Medical Home Portal**
  PKU and Pterin Defects
- **MedlinePlus**
  Phenylketonuria
- **National PKU Alliance**
  National PKU Alliance
- **National PKU News**
  www.pkunews.org
- **National Society for PKU (NSPKU)**
  United Kingdom
  Phone: 030 3040 1090
  Email: info@nspku.org
  www.nspku.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org
- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  Patient Assistance Programs

- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Phenylalanine Hydroxylase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PAH	12q23.2	Phenylalanine-4-hydroxylase	PAH database Phenylalanine Hydroxylase Gene Locus-Specific Database - PAHvdb	PAH	PAH

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Phenylalanine Hydroxylase Deficiency (View All in OMIM)

261600	PHENYLKETONURIA; PKU
612349	PHENYLALANINE HYDROXYLASE; PAH

Gene structure. *PAH* contains 13 exons and spans 90 kb; the genomic sequence is known to code for a 2.6-kb mature messenger RNA. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 900 different pathogenic variants in *PAH* have been identified to date; see Table A, **Locus-Specific Databases** and **HGMD**. The majority of pathogenic variants in *PAH* are missense, nonsense, frameshift, and splice variants. Large deletions account for fewer than 1% of disease alleles in most populations, but accounted for 3% of disease alleles in the Czech population [Kozak et al 2006].

Table 4. *PAH* Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias) [1]	Predicted Protein Change	Reference Sequences
c.194T>C	p.Ile65Thr	NM_000277.1 NP_000268.1
c.473G>A	p.Arg158Gln	
c.782G>A	p.Arg261Gln	
c.842C>T	p.Pro281Leu	
c.1066-11G>A (IVS10-11G>A)		
c.1222C>T	p.Arg408Trp	
c.1315+1G>A (IVS12+1G>A)		

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
See biopku.org for gene lists and databases.
1. Variant designation that does not conform to current naming conventions

Normal gene product. The normal product of *PAH* is the protein phenylalanine hydroxylase (PAH), containing 452 amino acids (NP_000268.1). PAH enzymes can exist as tetramers and dimers in equilibrium [Hufton et al 1998]. The PAH enzyme hydroxylates phenylalanine to tyrosine, this reaction being the rate-limiting step in the major pathway by which phenylalanine is catabolized to CO_2 and water [Scriver & Kaufman 2001].

Abnormal gene product. The pathogenic variants that confer the most severe phenotypes are known or predicted to completely abolish PAH activity. These "null" variants are of various types. Missense pathogenic variants usually permit the enzyme to retain some degree of residual activity; however, it is difficult to assess severity in vivo because the in vivo activity is not the simple equivalent of the in vitro enzymatic phenotype [Waters et al 1998, Gjetting et al 2001].

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