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NLM Citation: Arnold G, Vockley J. Phenylalanine Hydroxylase Deficiency. 2000 Jan 10 [Updated 2025 Mar 13]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Phenylalanine Hydroxylase Deficiency

Synonyms: Hyperphenylalaninemia, PAH Deficiency, Phenylketonuria (PKU)

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Created: January 10, 2000; Updated: March 13, 2025.

Summary

Clinical characteristics

The phenotypes in individuals with PAH deficiency include PAH deficiency treated from birth and late-diagnosed or untreated PAH deficiency. Maternal PKU (MPKU) syndrome occurs in offspring of mothers with inadequately treated PAH deficiency during pregnancy and results from the toxic effects of elevated blood phenylalanine (Phe) concentrations on the developing fetus.

PAH deficiency treated from birth is characterized by the following, even with adherence to a low Phe diet: (1) a modest but measurable decrease in intellectual functioning as well variable impairments in executive function, attention, and fine motor functions; (2) an increased prevalence of mental health concerns including anxiety and depression; and (3) neurologic problems (including hypertonia, paraplegia, movement disorders, and seizures), which may improve or resolve with lowering blood Phe concentration.

Late-diagnosed or untreated PAH deficiency is characterized by irreversible neurocognitive impairment (intellectual disability), neurobehavioral/psychological issues, neurologic manifestations (motor disturbances including movement disorders and seizures), and microcephaly. Although lowering blood Phe concentration sometimes improves neurobehavioral/psychological issues and motor disturbances, it does not reduce neurocognitive impairment.

MPKU syndrome is characterized by intellectual disability, neurobehavioral/psychiatric manifestations, congenital heart defects, and other birth defects.

Diagnosis/testing

The diagnosis of PAH deficiency is established in all neonates following an out-of-range newborn screening result with (1) biochemical testing (plasma amino acid analysis) and (2) molecular genetic testing to identify the causative biallelic *PAH* pathogenic variants to confirm the biochemical diagnosis of PAH deficiency and inform clinical management and genetic counseling.

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Management

Targeted therapies: Lifelong treatment of all individuals with an untreated blood Phe concentration greater than 360 µmol/L with an age-appropriate Phe-restricted diet and Phe-free protein supplementation with medical foods (amino acid or glycomacropeptide based). In certain individuals, FDA-approved pharmacologic therapies may include the Phe hydroxylase activator/cofactor sapropterin dihydrochloride and/or enzyme substitution therapy (pegvaliase).

Supportive care: Because treatment for affected individuals of all ages can be difficult, the support of an experienced health care team consisting of physicians, metabolic dietitians, genetic counselors, social workers, nurses, nurse practitioners, and psychologists is essential for all individuals with PAH deficiency and their parents/caregivers. Teaching should include information on malnutrition and growth failure, the side effects of dietary treatment. Therapy needs are greater for individuals with late diagnosis and resultant neurodevelopmental deficits. As PAH deficiency is a lifelong disorder with varying age-related implications, smooth transition of care of affected individuals from a pediatric setting is essential for long-term management and should be organized as a well-planned, continuous, multidisciplinary process integrating resources of all relevant subspecialties.

Surveillance: Regular individualized screening for early identification of the manifestations of PAH deficiency treated from birth and late-diagnosed or untreated PAH deficiency is required.

Agents/circumstances to avoid: Aspartame, an artificial sweetener often added to soft drinks, foods, and some medications, is metabolized in the gastrointestinal tract into Phe and aspartate. Persons with PAH deficiency should either (1) avoid products containing aspartame or (2) when using such products calculate total Phe intake in order to adapt diet components accordingly.

Evaluation of relatives at risk: If the *PAH* pathogenic variants in the family are known, molecular genetic prenatal testing of a fetus at risk can be performed via amniocentesis or chorionic villus sampling to allow for treatment at birth of an infant known to be affected. Any at-risk newborn sib who did not have prenatal testing should be evaluated immediately after birth for PAH deficiency by measuring blood Phe concentration to allow for earliest possible diagnosis and treatment. Older at-risk sibs – even those who are apparently asymptomatic – should be evaluated for PAH deficiency given the significant variability in the clinical manifestations of previously undiagnosed PAH deficiency.

Preconception, pregnancy, and postpartum care: Preconception: achieve and maintain maternal blood Phe concentration at <360 µmol/L for three months prior to conception; provide genetic counseling regarding the teratogenic effects of elevated maternal blood Phe concentration on the developing fetus. Pregnancy: maintain maternal blood Phe concentration at 120-360 µmol/L during pregnancy and monitor dietary intake to ensure that dietary nutrients are adequate. Postpartum: monitor blood Phe concentrations of mother and infant as needed.

Genetic counseling

PAH deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PAH* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *PAH* pathogenic variants. Children born of one parent with PAH deficiency and one parent with two normal *PAH* alleles are obligate heterozygotes. If the mother is the affected parent, MPKU syndrome is a critical issue. Females with PAH deficiency should receive counseling regarding the teratogenic effects of elevated maternal plasma Phe concentration (i.e., MPKU syndrome) when they reach childbearing age. Once the PAH pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing for PAH deficiency are possible.

Diagnosis

Recently published recommendations from the American College of Medical Genetics and Genomics (ACMG) for the diagnosis and management of phenylalanine hydroxylase (PAH) deficiency [Smith et al 2025] supplement the published ACMG guidelines [Vockley et al 2014].

Suggestive Findings

A diagnosis of PAH deficiency should be suspected due to an out-of-range newborn screening (NBS) result prior to onset of suggestive findings (see Scenario 1) or manifestations of PAH deficiency (see Scenario 2).

Scenario 1: Out-of-Range Newborn Screening (NBS) Result

NBS for PAH deficiency is primarily based on use of dried blood spots collected between 24 and 72 hours after birth to quantify phenylalanine (Phe) and tyrosine (Tyr) concentrations by tandem mass spectrometry (MS/MS). For information on NBS by state in the United States (US), see www.newbornscreening.hrsa.gov/your-state.

In the US most NBS laboratories determine their own cutoff levels for out-of-range test results; thus, newborns with an NBS result with elevated Phe concentrations must undergo additional testing as soon as possible to determine its etiology (see Establishing the Diagnosis, Biochemical Testing and Molecular Genetic Testing).

For recommendations on presumptive treatment while awaiting diagnostic confirmation, consult a metabolic specialist to discuss immediate care needs. If a metabolic specialist is not available, the following treatment should be considered (see Management):

- Verify the abnormal result with the state screening laboratory.
- Ascertain that the infant is clinically well.
- Consult the ACMG ACT sheet.
- Obtain follow-up plasma or serum amino acid analysis and urine/blood pterin analysis.

Note: Do not initiate dietary Phe restriction before confirmatory testing is sent.

Scenario 2: Symptomatic Individual

A symptomatic individual can have either (1) typical findings associated with late-diagnosed PAH deficiency or (2) untreated infantile-onset PAH deficiency resulting from any of the following: NBS not performed, false negative NBS result, clinical findings prior to receiving NBS result, or caregivers not adherent to recommended treatment after a positive NBS result. PAH deficiency **should be considered** in probands with the following clinical, laboratory, and imaging findings and family history.

Clinical findings (infancy to adulthood)

- Epilepsy
- Any level of irreversible intellectual disability and neurobehavioral/psychiatric manifestations including emotional and social problems and autistic features
- Neurologic findings including movement disorders, sensory manifestations, tremors, and Parkinson-like features (particularly in adults)
- Musty body odor
- Eczema
- Decreased skin and hair pigmentation

Supportive biochemical findings could include (if obtained) those in Establishing the Diagnosis, Biochemical Testing.

Brain imaging findings

- White matter abnormalities, particularly parietal and frontal with some temporal involvement (involving mostly periventricular and central white matter)
- Occasional cerebral or cerebellar atrophy [Bako & Çıkı 2023]
- Restricted diffusion

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of PAH deficiency **is established** in all neonates following an out-of-range NBS result with (1) biochemical testing (plasma amino acid analysis) and (2) molecular genetic testing [Smith et al 2025]. Molecular genetic testing is strongly recommended to confirm the biochemical diagnosis of PAH deficiency, inform clinical management, and allow genetic counseling.

Biochemical Testing

The biochemical diagnosis of PAH deficiency is established in a proband with the following [Vockley et al 2104, Smith et al 2025]:

- Blood phenylalanine concentrations >120 umol/L
  - Blood phenylalanine concentrations >360 umol/L require treatment in some form for life (see Management, Treatment of Manifestations).
  - Blood phenylalanine concentrations >120 umol/L but <360 umol/L require regular monitoring for at least the first two years of life as dietary protein intake increases, followed by monitoring every one or two years as indicated (see Management, Evaluations Following Initial Diagnosis, **Individuals with benign hyperphenylalaninemia**).

  Note: Because blood Phe concentrations rise in the days after delivery, these recommendations are based on follow-up blood testing obtained after the NBS result.
- Phenylalanine-to-tyrosine (Phe:Tyr) ratio ≥3
- Absence of defects in biopterin synthesis or recycling* based on quantitative assay of pterins. Note: Because these assays are best performed in specialized centers and are not readily available in many countries, follow up of abnormal NBS result with molecular genetic testing is increasingly common.
  - Quantitative assay of pterins (neopterin and biopterins) in urine or blood. If abnormal, reflex to quantitative assay of erythrocyte dihydropterine reductase (DHPR) activity if available (typically on dried blood spot). Reference values are available for different age groups.
  - Abnormal pterin concentrations in urine or reduced red blood cell DHPR activity (from dried blood spots) should prompt enzyme testing for possible deficiencies of the following enzymes: GTP cyclohydrolase (AR-GTPCH), 6-pyruvoyl-tetrahydropterin synthase (PTPS), DHPR, or pterin carbinolamine-4α-dehydratase (PCD).

  * Smith et al [2025] and van Spronsen et al [2021] emphasize that all neonates with persistent hyperphenylalaninemia must be screened for the tetrahydrobiopterin (BH4) deficiencies via biochemical testing or a multigene panel to identify pathogenic variants in genes known to cause hyperphenylalaninemia (see Differential Diagnosis).

Molecular Genetic Testing

The molecular diagnosis of PAH deficiency **is established** in a proband with biallelic *PAH* pathogenic (or likely pathogenic) variants identified by molecular genetic testing (see Table 1). Molecular analysis of PAH variants is not required to initiate (and should not delay) treatment; however, genotype can provide clinical information including prediction of severity and potential biopterin response as well as assisting with genetic counseling.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *PAH* variants of uncertain significance (or of one known *PAH* pathogenic variant and one *PAH* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include single-gene testing, use of a multigene panel, or comprehensive genomic testing.

- **Single-gene testing** can be considered in probands with a biochemical diagnosis of PAH deficiency. Sequence analysis of *PAH* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications might not be detected. If only one or no *PAH* variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *PAH* and other genes associated with hyperphenylalaninemia (see Differential Diagnosis) is most likely to identify the genetic cause of hyperphenylalaninemia while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) 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. (2) Some multigene panels might include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options might include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel might include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Comprehensive genomic testing,** which does not require the clinician to determine which gene is likely involved, can be considered in a symptomatic individual who is not known to have PAH deficiency because the phenotype of untreated PAH deficiency is indistinguishable from many other inherited disorders characterized by epilepsy, intellectual disability, and neurologic findings characterized by movement disorders. Exome sequencing is most commonly used; genome sequencing is also possible. To date, most *PAH* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. However, because the spectrum of *PAH* variants is great, noncoding variants should be considered if biochemical testing is positive and no or only one *PAH* pathogenic variant has been found.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Phenylalanine Hydroxylase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
PAH	Sequence analysis [3]	95%-99% [4]
	Gene-targeted deletion/duplication analysis [5]	2%-3% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Hillert et al [2020]
5. 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Ninety-seven percent of individuals with PAH deficiency can be identified by sequencing all exons and flanking intron regions; exon deletion/duplication identified by MLPA accounts for 2%-3% of pathogenic *PAH* alleles [Li et al 2015, Yan et al 2016, Liu et al 2017, Rajabi et al 2019, Vela-Amieva et al 2021, Gao et al 2022].

Clinical Characteristics

Clinical Description

The phenotypes in individuals with phenylalanine hydroxylase (PAH) deficiency include PAH deficiency treated from birth and late-diagnosed or untreated PAH deficiency. In addition, maternal PKU (MPKU) syndrome is important to consider in offspring of mothers with inadequately treated PAH deficiency during pregnancy, as elevated blood phenylalanine (Phe) concentrations are toxic to the developing fetus [Smith et al 2025].

PAH Deficiency Treated from Birth

Intelligence. Even with adherence to a low Phe diet, there is a modest but measurable decrease in intellectual functioning as well variable impairments in executive function, attention, and fine motor functions [Christ et al 2020, Adams et al 2023, Pardo et al 2024]. The correlation between early elevated blood Phe concentrations and long-term decreases in IQ has been well studied. A review of 55 studies from 1991 to 2021 and a meta-analysis of 14 studies noted significantly higher IQs in individuals who maintained blood Phe concentrations <360 umol/L throughout life [Adams et al 2023].

Neuropsychological issues. In individuals with early-treated PKU, certain psychological problems are increased as compared to control groups, unaffected sibs, or individuals with other chronic diseases [Brumm et al 2010, Bilder et al 2013, Adams et al 2023]. Individuals with early-treated PKU perform more poorly on tests of executive function, processing speed, and motor speed; there is a strong correlation of these findings with blood Phe concentrations [Christ et al 2023, Clocksin et al 2023].

Individuals with early-treated PKU also have an increased prevalence of mental health concerns, including anxiety and depression [Jahja et al 2016, Manti et al 2016, Waisbren et al 2017, Trefz et al 2019].

Evidence is emerging that lowering blood Phe concentrations in adults who have had persistently elevated blood Phe concentrations can improve both neuropsychological function [Burgess et al 2021, Bilder et al 2022, Manti et al 2023, Thomas et al 2023] and the related MRI changes [Clocksin et al 2021, Rocha et al 2023, Rovelli & Longo 2023, Pardo et al 2024].

Neurologic abnormalities associated with elevated blood Phe concentrations include increased deep tendon reflexes, ankle and patellar clonus, tremor, hypertonia, paraplegia or hemiplegia, progressive supranuclear palsy, choreiform or athetoid hyperkinesia, and seizures. Lowering blood Phe concentration often improves or resolves these neurologic manifestations [Jaulent et al 2020, Merkel et al 2023, Rovelli & Longo 2023].

Osteopenia. Numerous studies have indicated that individuals with PAH deficiency have bone mineral density that is below average or osteopenic, but not to a level of frank osteoporosis (as measured by dual-energy x-ray absorptiometry scan) [Walter 2011, Demirdas et al 2015, Demirdas et al 2017, Lubout et al 2020, Daly et al 2021, Christ et al 2024].

Vitamin B_{12} deficiency can occur in individuals with complete or near-complete deficiency of PAH activity, particularly when they relax their Phe-restricted diet in adolescence [Robinson et al 2000, Walter 2011, Akış et al 2020]. Vitamin B_{12} is found in natural animal protein; affected individuals who decrease their amino acid supplementation provided by their medical food (formula) and still choose low-protein foods are at risk for vitamin B_{12} deficiency [Kose & Arslan 2019].

Late-Diagnosed or Untreated PAH Deficiency

Persistent severe hyperphenylalaninemia is characterized by irreversible neurocognitive impairment (intellectual disability), neurobehavioral/psychological issues, neurologic manifestations (motor disturbances including movement disorders and seizures), and microcephaly. Although treatment (see Management, Treatment of Manifestations) sometimes improves neurobehavioral/psychological issues and motor disturbances, it does not reduce neurocognitive impairment.

Decreased skin and hair pigmentation result from associated inhibition of tyrosinase and low blood tyrosine concentrations.

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

MPKU Syndrome

Elevated blood Phe concentrations are teratogenic during pregnancy. MPKU syndrome results from exposure of a fetus of a woman who has PAH deficiency to blood Phe concentrations >360umol/L due either to poorly treated or untreated PAH deficiency during pregnancy. Rarely, a woman can be unaware of her diagnosis of PAH deficiency and, thus, bear children with MPKU syndrome [Alghamdi et al 2023].

Risks to the offspring of a woman with high blood Phe concentrations during pregnancy include the following [Waisbren et al 2015, Adams et al 2023, Smith et al 2025]:

- **Intellectual disability** (>90%). The threshold for this finding is a maternal blood Phe concentration consistently >360 µmol/L during pregnancy.
- **Poor neurobehavioral/psychiatric outcomes.** Reports include increased prevalence of attention-deficit/hyperactivity disorder (ADHD) (22% of individuals with MPKU syndrome were on ADHD medication) and anxiety and/or depression in 34% of individuals with MPKU syndrome.
- **Microcephaly**
  - Risk of microcephaly is 5%-18% when maternal blood Phe concentration is optimized prior to ten weeks' gestation.
  - Risk of microcephaly is 67% if appropriate maternal blood Phe concentrations are not achieved by 30 weeks' gestation.
  - Risk of microcephaly is >90% if appropriate maternal blood Phe concentrations are never achieved during the pregnancy.

- **Congenital heart defects.** Consistently elevated maternal blood Phe concentrations (>600 µmol/L) during early gestation result in an 8%-12% risk of cardiac malformations [Levy et al 2001, Lupo et al 2024]. A recent review of the Texas birth defects registry noted the highest odds ratios associated with elevated phenylalanine-to-tyrosine (Phe:Tyr) ratios and transposition of the great vessels, atrioventricular septal defects, coarctation of the aorta, tetralogy of Fallot, hypoplastic left heart, and pulmonary valve stenosis/atresia [Lupo et al 2024].
- **Other birth defects** reported with increased frequency associated with elevated Phe:Tyr ratios include tracheoesophageal fistula / esophageal atresia, gastroschisis, large or small intestinal atresia, spina bifida, diaphragmatic hernia, and cleft lip with or without cleft palate [Prick et al 2012, Lupo et al 2024].
- **Intrauterine growth restriction (IUGR).** The frequency of IUGR does not differ from that in the general population when maternal blood Phe concentrations are controlled by 10 weeks' gestation; however, the risk of IUGR increases when maternal blood Phe concentration is not optimized until later in the pregnancy or if maternal blood Phe concentration is too low [Teissier et al 2012].

Genotype-Phenotype Correlations

Although genotype can be predictive of sapropterin dihydrochloride responsiveness (see Management, Targeted Therapies), genotype-phenotype correlations to date are imperfect; thus, all individuals with PAH deficiency except those with biallelic null *PAH* pathogenic variants should be offered a trial of sapropterin dihydrochloride therapy to assess responsiveness [Adams et al 2023]. Muntau et al [2019] reviewed 23 studies of sapropterin trials and noted a high level of sapropterin responsiveness in individuals classified as having mild or moderate PAH deficiency, and low levels of responsiveness in individuals with classic PAH deficiency.

Nomenclature

"Traditional" PAH terminology is not used in the 2023 ACMG practice guideline for PAH deficiency diagnosis and management [Smith et al 2025] but is often utilized in historical publications.

- "Phenylketonuria (PKU)" refers specifically to severe PAH deficiency associated, in an untreated state, with plasma Phe concentrations >1,000 µmol/L [Kayaalp et al 1997].
- "Non-PKU hyperphenylalaninemia (non-PKU HPA)" describes plasma Phe concentrations consistently above normal (i.e., >120 µmol/L) but <1,000 µmol/L when an individual is on a normal diet [Kayaalp et al 1997].
- "Variant PKU" refers to individuals who do not fit the description for either PKU or non-PKU HPA [Kayaalp et al 1997].
- "Mild hyperphenylalaninemia (HPA)" refers to individuals with an untreated blood phenylalanine concentration of 360-600 µmol/L.

The term "classic PKU" is most often used to refer to severe PAH deficiency associated with a complete or near-complete deficiency of PAH activity [Guldberg et al 1998].

Prevalence

Hillert et al [2020] estimated the incidence of PAH deficiency worldwide at 1:23,930 newborns. The highest incidence is described in the Karachay-Cherkess region of Russia (1:850), with relatively higher incidences in Europe and some Middle Eastern countries (approximately 1:4,000 to 1:10,000). Incidence is somewhat lower in Asia outside of China (1:125,000 in Japan). Incidence in the United States is estimated at 1:25,000.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Tetrahydrobiopterin (BH_4) deficiency. Hyperphenylalaninemia (HPA) can result from the impaired synthesis or recycling of tetrahydrobiopterin (BH_4), the cofactor in the phenylalanine, tyrosine, and tryptophan hydroxylation reactions. The HPAs caused by BH_4 deficiency (see Table 2) account for approximately 2% of individuals with elevated blood Phe concentrations in most populations. However, for persons with an elevated blood Phe concentration from populations in which phenylalanine hydroxylase (PAH) deficiency is less common (e.g., Japanese individuals), the risk to the affected individual of having a disorder of pterin metabolism is much higher. Note that Phe concentrations can be normal in some individuals with BH_4 deficiency.

In principle, BH_4 deficiencies are treatable. Treatment requires the normalization of BH_4 availability and 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 dihydropterine reductase (DHPR) deficiency. However, residual neurologic manifestations such as movement abnormalities can persist. The treatment should be initiated early and probably continued for life [Blau et al 2011, Opladen et al 2020].

DNAJC12 deficiency. HPA can also result from DNAJC12 deficiency. *DNAJC12* encodes a co-chaperone of HSP70, which interacts with PAH, tyrosine hydroxylase, and tryptophan hydroxylase (see Table 2).

Table 2. Autosomal Recessive Disorders Known to Cause Hyperphenylalaninemia

Disease Mechanism	Gene	Disorder	Abbreviation	Clinical Characteristics
BH_4 deficiency	*GCH1*	Autosomal recessive GTP cyclohydrolase I deficiency (OMIM 233910)	AR-GTPCH deficiency	• Typical (severe) forms have the following variable but common findings: ID, convulsions, disturbance of tone & posture, drowsiness, irritability, abnormal movements, recurrent hyperthermia w/o infections, hypersalivation, & swallowing difficulties. • Microcephaly is common in PTPS & DHPR deficiencies. Plasma Phe concentrations can vary from slightly above normal (>120 µmol/L) to as high as 2,500 µmol/L. • Note: Mild forms of BH_4 deficiency have no clinical signs.
	PTS	6-pyruvoyl-tetrahydrobiopterin synthase deficiency (OMIM 261640)	PTPS deficiency	
	QDPR	Dihydropteridine reductase deficiency (OMIM 261630)	DHRP deficiency	
	PCBD1	Pterin-4-alpha-carbinolamine dehydratase deficiency (OMIM 264070)	PCD (or PCBD) deficiency [1]	• Benign transient HPA • Affected persons are at risk for MODY-type diabetes at puberty.
Co-chaperone deficiency	*DNAJC12*	DNAJC12 deficiency (OMIM 617384)	DNAJC12 deficiency	• Phenotypic spectrum ranges from mild autistic features or hyperactivity to severe ID, dystonia, & parkinsonism. • Blood Phe concentrations are ↑ w/low concentrations of biogenic amine in CSF. • Late diagnosis results in permanent neurologic disability, while early diagnosis & treatment w/ levodopa/carbidopa & 5-hydroxytryptophan allows normal development. • Phe concentrations return to normal w/BH_4 treatment.

BH_4 = tetrahydrobiopterin; CSF = cerebrospinal fluid; HPA = hyperphenylalaninemia; ID = intellectual disability; MOI = mode of inheritance; Phe = phenylalanine

1. Sometimes referred to as "primapterinuria"

Management

Recently published guidelines for the diagnosis and management of phenylalanine hydroxylase (PAH) deficiency in the United States (US) [Smith et al 2025] supplement the published guidelines of Vockley et al [2014]. European guidelines have also been published [van Spronsen et al 2017, van Wegberg et al 2017]. Most other international guidelines largely align with the US recommendations with some variation in the acceptable blood Phe concentrations, especially in older individuals (i.e., adults).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PAH deficiency, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Newborns with an out-of-range newborn screening (NBS) result. Refer to a metabolic specialty center that includes a metabolic physician / biochemical geneticist and metabolic dietitian to establish the diagnosis and begin an age-appropriate low-phenylalanine (Phe) diet as soon as elevated blood Phe concentrations have been documented (see Establishing the Diagnosis). If a referral is not immediately practical, see Treatment of Manifestations for treatment guidelines. Ideally the low-Phe diet should be initiated within the first week of life, with a goal of having blood Phe concentration in the treated range within the first two weeks of life [Smith et al 2025].

Consultation with a clinical geneticist, certified genetic counselor, certified genetic nurse, or genetics advanced practice provider (nurse practitioner or physician assistant) to inform affected individuals and their families about the nature, mode of inheritance, and implications of PAH deficiency to facilitate medical and personal decision making is recommended.

Assess the need for family support and resources including community or online resources such as Parent to Parent and National PKU Alliance (NPKUA); social work involvement for parental support; and home nursing referral.

Individuals with late-diagnosed or untreated hyperphenylalaninemia (HPA). Refer to a metabolic specialty center that includes a metabolic physician / biochemical geneticist and metabolic dietitian to begin appropriate treatment based on the specific diagnosis, age of the individual, and other extenuating circumstances.

Individuals in this group need to be evaluated for the medical issues associated with untreated PAH deficiency such as epilepsy, intellectual disability, neurobehavioral/psychiatric manifestations, and movement disorders. These evaluations and their management follow standard medical practice and are not discussed further in this *GeneReview*.

Individuals with benign HPA (i.e., untreated blood Phe concentration between 120 and 360 µmol/l). Although immediate treatment is not recommended for these individuals, their blood Phe concentration should be measured regularly while on a non-protein-restricted diet until at least age two years to ensure that blood Phe concentrations do not reach the threshold for which treatment would be recommended. See Surveillance for recommended follow up after age two years.

Treatment of Manifestations

There is no cure for PAH deficiency. However, gene therapy trials are currently under way (see Therapies Under Investigation).

ACMG guidelines recommend lifelong treatment of all individuals with untreated blood Phe concentrations >360 µmol/L [Smith et al 2025].

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

The mainstay of treatment for individuals with an untreated Phe blood concentration >360 umol/L is lifelong treatment with an age-appropriate Phe-restricted diet. Dietary therapy includes dietary protein restriction and Phe-free protein supplementation with medical foods (amino acid or glycomacropeptide based). In certain individuals, FDA-approved pharmacologic therapies may include the Phe hydroxylase activator/cofactor sapropterin dihydrochloride and/or enzyme substitution therapy (pegvaliase) [Smith et al 2025] (see Table 3).

Table 3. Phenylalanine Hydroxylase Deficiency: Targeted Therapies

Treatment Class	Mechanism of Action	Specific Drug	Dose
Diet / Medical food	Phe-restricted diet to prevent ↑ blood Phe concentrations	Phe-free metabolic formulas	• Lifelong & age appropriate • Implementation of Phe-restricted diet for infants requires use of Phe-free metabolic infant formula in combination w/breast milk &/or infant formula. • Phe is an essential amino acid; thus, measured amounts of dietary Phe are required to meet daily requirements while maintaining blood Phe concentrations w/in treatment range.
Cofactor supplementation	PAH activator/cofactor	Sapropterin dihydrochloride (synthetic form of naturally occurring BH_4)	• Determination of clinical/biochemical responsiveness to sapropterin should be documented prior to implementation of patient-specific treatment plan. • As 25%-50% of persons w/PAH deficiency are sapropterin responsive, all persons w/PAH deficiency should be offered the opportunity to determine their sapropterin dihydrochloride responsiveness. [1]
Enzyme substitution therapy	Phe-metabolizing enzyme	Pegvaliase	• Approved for adults in US who have uncontrolled blood Phe concentrations >600 µmol/L on existing mgmt • PEGylated recombinant Phe ammonia lyase enzyme administered via subcutaneous injection • Requires an induction, titration, & maintenance dosing schedule based on individual's drug tolerance [2]
Supplementation		Large neutral amino acids (LNAA)	Treatment w/LNAAs is currently limited to adolescents & adults & should be excluded in pregnant women.

Based on Lowe et al [2020], Tables 2 and 3

BH_4 = tetrahydrobiopterin; PAH = phenylalanine hydroxylase; Phe = phenylalanine

1. Although genotype could be predictive of sapropterin dihydrochloride responsiveness, to date genotype-phenotype correlations are imperfect. Thus, all individuals with PAH deficiency (except those with biallelic null *PAH* pathogenic variants) should be offered a trial of sapropterin dihydrochloride therapy to assess responsiveness [Muntau et al 2019, Smith et al 2025].

2. Longo et al [2019]

Supportive Care

Supportive treatment should be provided for individuals with PAH deficiency and their parents/caregivers. Treatment for affected individuals of all ages, which can be difficult, is enhanced with the teaching and support of an experienced health care team consisting of physicians, metabolic dietitians, genetic counselors, social workers, nurses, nurse practitioners, and psychologists [Smith et al 2025]. This should include information on the side effects of dietary treatment (i.e., malnutrition and growth failure). Therapy needs are greater for individuals with late diagnosis and resultant neurodevelopmental deficits.

Regular individualized screening for early identification of manifestations of PAH deficiency is recommended (see Surveillance).

Developmental Delay / Intellectual Disability Management Issues

Individuals with PAH deficiency should be monitored closely with screening testing for developmental delay/intellectual disability. The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country and may not be indicated for individuals with PAH deficiency without apparent developmental concerns.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. If indicated, consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) should be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children might qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Transition of Care from Pediatric to Adult-Centered Multidisciplinary Care Settings

As PAH deficiency is a lifelong disorder with varying age-related implications, smooth transition of care of affected individuals from a pediatric setting is essential for long-term management and should be organized as a well-planned, continuous, multidisciplinary process integrating resources of all relevant subspecialties. Because most centers in the US do not have metabolic physicians who specialize in adult care, the primary metabolic care provider is likely to remain unchanged. However, transition of other specialty services can still be transitioned to adult-oriented providers, and older teenagers and young adults can be taught the skills needed to identify the services provided by adult medical care providers. In the US, two formal transition curricula have been developed:

- The Cristine Trahms Program for Phenylketonuria Transition Curriculum at the University of Washington (accessed 2-12-25)
- Boston Children's Hospital Transition Toolkit (accessed 2-12-25)

A transitional care process has been developed in Italy in which adult internal medicine specialists initially see individuals with PAH deficiency together with pediatric metabolic experts, dietitians, psychologists, and social workers [Biasucci et al 2022].

As the long-term course of pediatric metabolic diseases in this age group is not yet fully characterized, continuous supervision by a center of expertise with metabolic diseases with sufficient resources is essential.

Preconception, Pregnancy, and Postpartum Care

Offspring of women with PAH deficiency who have received appropriate treatment throughout childhood and adolescence and during pregnancy have normal physical development and essentially normal intellectual and behavioral development. However, if the woman has elevated blood Phe concentrations during pregnancy, the

fetus is at high risk for maternal PKU (MPKU) syndrome, including malformations and intellectual disability, since Phe is a potent teratogen (see Clinical Description, MPKU Syndrome) [Rouse & Azen 2004, Prick et al 2012].

Preconception Care

The American College of Obstetrics and Gynecology Committee Opinion on the Management of Women with Phenylalanine Hydroxylase Deficiency (Phenylketonuria) and the American College of Medical Genetics and Genomics (ACMG) guidelines on the diagnosis and management of PAH deficiency [Smith et al 2025] suggest the following management of an affected woman prior to pregnancy.

- Genetic counseling regarding the teratogenic effects of elevated maternal blood Phe concentration on the developing fetus and recurrence risks for PAH deficiency in the fetus
- Achievement and maintenance of maternal blood Phe concentration at <360 µmol/L for three months prior to conception. Note: Maternal Phe concentrations tend to decrease in the third trimester of pregnancy, presumably due to increased protein accretion in the developing fetus.
- Some evidence suggests that poorly treated or untreated maternal PAH deficiency during pregnancy can result in an increased risk of miscarriage [Lenke & Levy 1980, Adams et al 2023]; however, to date this has not been well studied.

Psychosocial support. Specialized metabolic centers should offer specific counseling and support services for females with PAH deficiency of childbearing age. Above all, they should receive training on the need for metabolic control and education on the consequences of elevated blood Phe concentrations on the developing fetus and the risk of giving birth to a child with MPKU syndrome [Rohde et al 2021]. This training should include partners and families.

Pregnancy Care

Maintain maternal blood Phe concentration at 120-360 µmol/L during pregnancy. Maternal blood Phe concentration should be monitored in conjunction with a metabolic dietitian and metabolic physician from a metabolic center with experience in managing a pregnant woman with PAH deficiency.

In unplanned pregnancies, measure maternal blood Phe concentration immediately. If elevated, reduce the blood Phe concentration using dietary management or pharmacologic therapy.

Monitor dietary intake of pregnant women with PAH deficiency at every clinic visit to ensure that dietary nutrients are adequate with the proper proportion of protein, fat, and carbohydrates.

Evaluate for fetal anomalies by high-resolution ultrasound examination and fetal echocardiogram at appropriate gestational ages.

Targeted therapies (see Table 3)

- Despite limited data available to date, sapropterin can be continued in addition to dietary therapy due to the risk of elevated maternal blood Phe concentration if discontinued.
- There is limited experience with pegvaliase in pregnancy. In a single report, 14 infants (six females and eight males) had no congenital anomalies, and all infants had normal growth parameters [Bier et al 2024]. Four of 11 infants (excluding triplet pregnancies) were delivered preterm (36%), a higher rate than the general population (12%). The recently updated ACMG management guidelines for PAH deficiency found insufficient evidence to either recommend or discourage use of pegvaliase in pregnant women with PAH deficiency [Smith et al 2025].
- Large neutral amino acid (LNAA) treatment should be avoided in pregnant women because (1) its effects on fetal growth and central nervous system development is not well understood and (2) it does not

sufficiently lower blood Phe concentration to the range that is safe for fetal development [Smith et al 2025].

Postpartum Care

Provide coordinated care, including monitoring of blood Phe concentrations of mother and infant as needed, implementation of Phe-restricted diet if the infant has PAH deficiency, and follow-up echocardiogram in infants if indicated.

Dietary management, sapropterin dihydrochloride, and/or pegvaliase should be continued for the mother to maintain blood Phe concentrations in the recommended range. Monitoring of the mother for postpartum mental health issues and ability to breastfeed and follow the Phe-restricted diet is recommended [Ford et al 2018].

Breastfeeding may be pursued if the infant does not have PAH deficiency.

Surveillance

For those with untreated blood Phe concentrations >360 µmol/L, the ACMG recommendations for monitoring of blood Phe concentration and nutritional status are summarized in Table 4 [Vockley et al 2014].

Table 4. Phenylalanine Hydroxylase Deficiency: Recommended Biochemical Monitoring

Age Group	Phe Monitoring	Type/Timing of Routine Nutritional Monitoring	Routine Clinical Visit Follow Up
Infants (age ≤1 yr)	Weekly	• Plasma amino acids: monthly to every 3 mos • Complete blood count: once • Albumin: once • Prealbumin: once • Ferritin: once • 25-hydroxyvitamin D: once	Monthly
Children age <12 yrs	Every 2 weeks or monthly	• Plasma amino acids: each clinic visit • Complete blood count: yearly • Albumin: every 6-12 mos • Prealbumin: every 6-12 mos • Ferritin: yearly • 25-hydroxyvitamin D: yearly	• Age 1-7 yrs: monthly to every 6 mos • Age 8-18 yrs: every 6-12 mos
Adolescents	Once a month		
Adults age >18 yrs			Every 6-12 mos

Based on Vockley et al [2014]
Phe = phenylalanine

For those with untreated blood Phe concentrations >120 µmol/L, the recommendation is monitoring blood Phe concentration at least until age two years [Vockley et al 2014]. The frequency of monitoring depends on blood Phe concentrations and may extend beyond age two years as needed. If treatment is not required before age two years, monitoring annually or every two years is adequate for subsequent assessment.

Other manifestations. Although most individuals with PAH deficiency will have normal development if blood Phe concentrations are appropriately controlled, developmental, neuropsychological, and psychosocial concerns merit careful attention to assure that needs are being met across the life span. Assessment by the appropriate specialists involved in providing supportive care should be considered when concerns arise, including: (1) acquisition of developmental milestones and overall developmental progress; (2) educational needs; (3) neuropsychologic issues; (4) neurologic abnormalities; (5) osteopenia and bone health; and (6) family need for social work support, care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).

Agents/Circumstances to Avoid

Aspartame, an artificial sweetener that is often added to soft drinks, foods, and some medications, is metabolized in the gastrointestinal tract into Phe and aspartate. Persons with PAH deficiency should either avoid products containing aspartame or calculate total Phe intake when using such products in order to adapt diet components accordingly [Maler et al 2023].

Note: Some medications (such as antibiotics) contain aspartame. Depending on the condition being treated, antibiotic treatment might need to be altered if no other alternatives are readily available.

Evaluation of Relatives at Risk

Prenatal testing of a fetus at risk. If the *PAH* pathogenic variants in the family are known, molecular genetic prenatal testing of a fetus at risk can be performed via amniocentesis or chorionic villus sampling to allow for treatment at birth of an infant known to be affected.

Newborn sib of a proband with PAH deficiency. If prenatal testing has not been performed, each at-risk newborn sib should be evaluated immediately after birth for PAH deficiency by measuring blood Phe concentration to allow for earliest possible diagnosis and treatment.

The initial newborn screening (NBS) measurement of blood Phe concentration is collected when the newborn is on a normal formula / breast milk diet.

In most circumstances, the results of NBS blood Phe concentration will be available before the results of molecular genetic testing, even if the familial pathogenic variants are known. Molecular genetic testing can be used to confirm the diagnosis in a newborn with an out-of-range NBS result. Note that molecular genetic testing in this circumstance is most informative if the familial *PAH* pathogenic variants are known. It should also be noted that if molecular testing is performed, carrier status will also be determined; thus, appropriate genetic counseling when testing a minor should also be included in any discussion.

Older at-risk sibs. Because of the significant variability in the clinical manifestations of previously undiagnosed PAH deficiency, even apparently asymptomatic sibs of an individual with PAH deficiency could be affected. If the at-risk sib underwent NBS, review of the sib's NBS result is recommended to clarify the status of at-risk sibs; if NBS was not performed, the following evaluations are recommended [Smith et al 2025]:

- Measure blood Phe concentrations;
- Perform molecular genetic testing if the *PAH* pathogenic variants in the family are known.

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

Therapies Under Investigation

Multiple modalities are now in clinical trials or being prepared for clinical trial, including gene therapy (NCT04480567, NCT06332807), mRNA therapy (NCT06147856), Phe uptake receptor blocker (NCT05781399), sepiapterin (NCT06302348), and multiple diet and dietary supplement studies. It is expected that multiple options for treatment of PAH deficiency will be available in coming years.

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 presumed to be heterozygous for a *PAH* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *PAH* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *PAH* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *PAH* pathogenic variants.
- Significant intrafamilial variability has been observed in PAH deficiency; thus, the clinical phenotype observed in the proband might not be consistent with or predicative of the clinical phenotype in affected sibs [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 PKU (MPKU) syndrome is a critical issue (see Clinical Description, MPKU Syndrome).

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. American College of Medical Genetics and Genomics (ACMG) guidelines recommend the use of

molecular genetic testing to identify carriers in a family with a known *PAH* pathogenic variant [Smith et al 2025].

Related Genetic Counseling Issues

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

Family planning

- Young women with PAH deficiency should receive counseling regarding the teratogenic effects of elevated maternal plasma Phe concentration (e.g., MPKU syndrome) when they reach childbearing age (see Management, Preconception Care).
- The optimal time for determination of genetic risk 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.
- Partners of an individual affected with PAH deficiency or known to be a carrier of a *PAH* pathogenic variant may be interested in carrier testing. Molecular genetic testing of *PAH* can be offered, with appropriate counseling about limits of sensitivity. Founder variants have been identified in the Bukharan Jewish, Sephardic Jewish, Ashkenazi Jewish, Amish, Romani, and Mennonite populations.
- The ACMG includes PAH deficiency among those disorders for which carrier screening should be offered to all individuals who are pregnant or planning a pregnancy [Gregg et al 2021].

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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *PAH* pathogenic variants have been identified in an affected family member, molecular genetic prenatal 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 and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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

  bimdg.org.uk/education/temple

- **Canadian PKU and Allied Disorders Inc.**

  Canada

Phone: 877-226-7581
Email: info@canpku.org
canpku.org

- **March of Dimes**
  PKU (Phenylketonuria) in your baby
- **MedlinePlus**
  Phenylketonuria
- **National PKU Alliance**
  National PKU Alliance
- **National Society for PKU (NSPKU)**
  United Kingdom
  Phone: 030 3040 1090
  Email: info@nspku.org
  nspku.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  RareCare® Patient Assistance Programs
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  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

Molecular Pathogenesis

Phenylalanine hydroxylase (PAH) is the rate-limiting step in the conversion of phenylalanine (Phe) to tyrosine (Tyr), a reaction that requires the cofactor tetrahydrobiopterin (BH_4). PAH deficiency is an inborn error of Phe metabolism caused by biallelic *PAH* pathogenic variants resulting in reduced activity of the enzyme PAH. The main consequences of PAH deficiency are: (1) accumulation of alternative products of Phe metabolism, including phenylacetic, phenylpyruvic, and phenyllactic acid, which are toxic to brain development; and (2) reduction of Tyr, resulting in deficiency of the neurotransmitters dopamine, adrenaline, and norepinephrine, which affects the conversion to thyroxine in the thyroid gland and melanin in melanocytes.

Mechanism of disease causation. Loss-of-function *PAH* variants

Chapter Notes

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Revision History

- 13 March 2025 (bp) Comprehensive update posted live
- 20 October 2016 (ma) Comprehensive update posted live
- 31 January 2013 (me) Comprehensive update posted live
- 4 May 2010 (me) Comprehensive update posted live
- 29 March 2007 (me) Comprehensive update posted live
- 8 July 2004 (me) Comprehensive update posted live
- 13 August 2002 (me) Comprehensive update posted live
- 10 January 2000 (me) Review posted live
- 16 July 1999 (dsr) Original submission

References

Published Guidelines / Consensus Statements

Canadian Task Force on the Preventive Health Care. Screening for phenylketonuria. The Canadian Guide to Clinical Preventive Health Care. Available online. 1994. Accessed 11-17-20.

Committee on Genetics. Management of women with phenylalanine hydroxylase deficiency (phenylketonuria). American College of Obstetricians and Gynecologists Committee Opinion April 2020. Number 802. Available online. 2020. Accessed 11-17-20.

Singh RH, Rohr F, Frazier D, Cunningham A, Mofidi S, Ogata B, Splett PL, Moseley K, Huntington K, Acosta PB, Vockley J, Van Calcar SC. Recommendations for the nutrition management of phenylalanine hydroxylase deficiency. Genet Med. 2014;16:121-31. [PubMed]

Smith WE, Berry SA, Bloom K, Brown C, Burton BK, Demarest OM, Jenkins GP, Malinowski J, McBride KL, Mroczkowski HJ, Scharfe C, Vockley J; ACMG Board of Directors. Phenylalanine hydroxylase deficiency diagnosis and management: a 2023 evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2025;27:101289. [PubMed]

van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, van Rijn M, Trefz F, Walter JH, van Spronsen FJ. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017;12:162. [PubMed]

Vockley J, Andersson HC, Antshel KM, Braverman NE, Burton BK, Frazier DM, Mitchell J, Smith WE, Thompson BH, Berry SA; American College of Medical Genetics and Genomics Therapeutics Committee. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med. 2014;16:188-200. [PubMed]

Literature Cited

Adams AD, Fiesco-Roa MÓ, Wong L, Jenkins GP, Malinowski J, Demarest OM, Rothberg PG, Hobert JA; ACMG Therapeutics Committee. Phenylalanine hydroxylase deficiency treatment and management: A systematic evidence review of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25:100358. PubMed PMID: 37470789.

Akış M, Kant M, Işık İ, Kısa PT, Köse E, Arslan N, İşlekel H. Functional vitamin B12 deficiency in phenylketonuria patients and healthy controls: an evaluation with combined indicator of vitamin B12 status as a biochemical index. Ann Clin Biochem. 2020;57:291-9. PubMed PMID: 32482081.

Alghamdi MA, O'Donnell-Luria A, Almontashiri NA, AlAali WY, Ali HH, Levy HL. Classical phenylketonuria presenting as maternal PKU syndrome in the offspring of an intellectually normal woman. JIMD Rep. 2023;64:312-6. PubMed PMID: 37701331.

Bako D, Çıkı K. Phenylketonuria: a scoring system for brain magnetic resonance imaging. Turk Arch Pediatr. 2023;58:519-26. PubMed PMID: 37670551.

Biasucci G, Brodosi L, Bettocchi I, Noto D, Pochiero F, Urban ML, Burlina A. The management of transitional care of patients affected by phenylketonuria in Italy: review and expert opinion. Mol Genet Metab. 2022;136:94-100. PubMed PMID: 35589496.

Bier C, Dickey K, Bibb B, Crutcher A, Sponberg R, Chang R, Boyer M, Davis-Keppen L, Matthes C, Tharp M, Vice D, Cooney E, Morand M, Ray J, Lah M, McNutt M, Andersson HC. Outcomes in 14 live births resulting from pegvaliase-treated pregnancies in PKU-affected females. Mol Genet Metab. 2024;141:108152. PubMed PMID: 38367583.

Bilder DA, Arnold GL, Dimmock D, Grant ML, Janzen D, Longo N, Nguyen-Driver M, Jurecki E, Merilainen M, Amato G, Waisbren S. Improved attention linked to sustained phenylalanine reduction in adults with early-treated phenylketonuria. Am J Med Genet A. 2022;188:768-78. PubMed PMID: 34826353.

Bilder DA, Burton BK, Coon H, Leviton L, Ashworth J, Lundy BD, Vespa H, Bakian AV, Longo N. Psychiatric symptoms in adults with phenylketonuria. Mol Genet Metab. 2013;108:155-60. PubMed PMID: 23339767.

Blau N, Hennermann JB, Langenbeck U, Lichter-Konecki U. Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies. Mol Genet Metab. 2011;104 Suppl :S2-9. PubMed PMID: 21937252.

Brumm VL, Bilder D, Waisbren SE. Psychiatric symptoms and disorders in phenylketonuria. Mol Genet Metab. 2010;99 Suppl 1 :S59–63. PubMed PMID: 20123472.

Burgess NM, Kelso W, Malpas CB, Winton-Brown T, Fazio T, Panetta J, De Jong G, Neath J, Atherton S, Velakoulis D, Walterfang M. The effect of improved dietary control on cognitive and psychiatric functioning in adults with phenylketonuria: the ReDAPT study. Orphanet J Rare Dis. 2021;16:35. PubMed PMID: 33461585.

Camp KM, Parisi MA Acosta PB, Berry GT, Bilder DA, Blau N, Bodamer OA, Brosco JP, Brown CS, Burlina AB, Burton BK, Chang CS, Coates PM, Cunningham AC, Dobrowolski SF, Ferguson JH, Franklin TD, Frazier DM, Grange DK, Greene CL, Groft SC, Harding CO, Howell RR, Huntington KL, Hyatt-Knorr HD, Jevaji IP, Levy HL, Lichter-Konecki U, Lindegren ML, Lloyd-Puryear MA, Matalon K, MacDonald A, McPheeters ML, Mitchell JJ, Mofidi S, Moseley KD, Mueller CM, Mulberg AE, Nerurkar LS, Ogata BN, Pariser AR, Prasad S, Pridjian G, Rasmussen SA, Reddy UM, Rohr FJ, Singh RH, Sirrs SM, Stremer SE, Tagle DA, Thompson SM, Urv TK, Utz JR, van Spronsen F, Vockley J, Waisbren SE, Weglicki LS, White DA, Whitley CB, Wilfond BS, Yannicelli S, Young JM. Phenylketonuria Scientific Review Conference: state of the science and future research needs. Mol Genet Metab. 2014;112:87-122. PubMed PMID: 24667081.

Christ SE, Clocksin HE, Burton BK, Grant ML, Waisbren S, Paulin MC, Bilder DA, White DA, Saville C. Executive function in phenylketonuria (PKU): insights from the Behavior Rating Inventory of Executive Function (BRIEF) and a large sample of individuals with PKU. Neuropsychology. 2020;34:456-66. PubMed PMID: 32202818.

Christ SE, Clocksin HE, Zalik M, Goodlett BD, Sacharow SJ, Abbene EE. Neuropsychological assessment of adults with phenylketonuria using the NIH toolbox. Mol Genet Metab. 2023;139:107579. PubMed PMID: 37099821.

Christ SE, Arnold G, Lichter-Konecki U, Berry GT, Grange DK, Harding CO, Jurecki E, Levy H, Longo N, Morotti H, Sacharow S, Thomas J, White DA. Initial results from the PHEFREE longitudinal natural history study: cross-sectional observations in a cohort of individuals with phenylalanine hydroxylase (PAH) deficiency. Mol Genet Metab. 2024;143:108541. PubMed PMID: 39059270.

Clocksin HE, Abbene EE, Christ S. A comprehensive assessment of neurocognitive and psychological functioning in adults with early-treated phenylketonuria. J Int Neuropsychol Soc. 2023;29:641-50. PubMed PMID: 36134437.

Clocksin HE, Hawks ZW, White DA, Christ SE. Inter- and intra-tract analysis of white matter abnormalities in individuals with early-treated phenylketonuria (PKU). Mol Genet Metab. 2021;132:11-8. PubMed PMID: 33334682.

Daly A, Högler W, Crabtree N, Shaw N, Evans S, Pinto A, Jackson R, Ashmore C, Rocha JC, Strauss BJ, Wilcox G, Fraser WD, Tang JCY, MacDonald A. A three-year longitudinal study comparing bone mass, density, and geometry measured by DXA, pQCT, and bone turnover markers in children with PKU Taking L-amino acid or glycomacropeptide protein substitutes. Nutrients. 2021;13:2075. PubMed PMID: 34204378.

Demirdas S, Coakley KE, Bisshop PH, Hollak CE, Bosch AM, Singh RH. Bone health in phenylketonuria: a systematic review and meta-analysis. Orphanet J Rare Dis. 2015:10:17 PubMed PMID: 25758373.

Demirdas S, van Spronsen FJ, Hollak CEM, van der Lee JH, Bisschop PH, Vaz FM, Ter Horst NM, Rubio-Gozalbo ME, Bosch AM. Micronutrients, essential fatty acids and bone health in phenylketonuria. Ann Nutr Metab. 2017;70:111-21. PubMed PMID: 28334709.

Ford S, O'Driscoll M, MacDonald A. Reproductive experience of women living with phenylketonuria. Mol Genet Metab Rep. 2018;17:64-8. PubMed PMID: 30416967.

Gao J, Li X, Guo Y, Yu H, Song L, Fang Y, Yuan E, Shi Q, Zhao D, Yuan E, Zhang L. Identification of phenylketonuria patient genotypes using single-gene full-length sequencing. Hum Genomics. 2022;16:23. PubMed PMID: 35869558.

Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, Chen E, Sparks TN, Reddi HV, Rajkovic A, Dungan JS; ACMG Professional Practice and Guidelines Committee. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23:1793-806. PubMed PMID: 34285390.

Guldberg P, Rey F, Zschocke J, Romano V, François B, Michiels L, Ullrich K, Hoffmann GF, Burgard P, Schmidt H, Meli C, Riva E, Dianzani I, Ponzone A, Rey J, Güttler F. A European multicenter study of phenylalanine hydroxylase deficiency: classification of 105 mutations and a general system for genotype-based prediction of metabolic phenotype. Am J Hum Genet. 1998;63:71–9. PubMed PMID: 9634518.

Hillert A, Anikster Y, Belanger-Quintana A, Burlina A, Burton BK, Carducci C, Chiesa AE, Christodoulou J, Đorđević M, Desviat LR, Eliyahu A, Evers RAF, Fajkusova L, Feillet F, Bonfim-Freitas PE, Giżewska M, Gundorova P, Karall D, Kneller K, Kutsev SI, Leuzzi V, Levy HL, Lichter-Konecki U, Muntau AC, Namour F, Oltarzewski M, Paras A, Perez B, Polak E, Polyakov AV, Porta F, Rohrbach M, Scholl-Bürgi S, Spécola N, Stojiljković M, Shen N, Santana-da Silva LC, Skouma A, van Spronsen F, Stoppioni V, Thöny B, Trefz FK, Vockley J, Yu Y, Zschocke J, Hoffmann GF, Garbade SF, Blau N. The genetic landscape and epidemiology of phenylketonuria. Am J Hum Genet. 2020;107:234-50. PubMed PMID: 32668217.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Jahja R, van Spronsen FJ, de Sonneville LM, van der Meere JJ, Bosch AM, Hollak CE, Rubio-Gozalbo ME, Brouwers MC, Hofstede FC, de Vries MC, Janssen MC, van der Ploeg AT, Langendonk JG, Huijbregts SC. Social-cognitive functioning and social skills in patients with early treated phenylketonuria: a PKU-COBESO study J Inherit Metab Dis. 2016:39:355-62. PubMed PMID: 26914933.

Jaulent P, Charriere S, Feillet F, Douillard C, Fouilhoux A, Thobois S. Neurological manifestations in adults with phenylketonuria: new cases and review of the literature. J Neurol. 2020;267:531-42. PubMed PMID: 31701331.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Kayaalp E, Treacy E, Waters PJ, Byck S, Nowacki P, Scriver CR. Human phenylalanine hydroxylase mutations and hyperphenylalaninemia phenotypes: a metanalysis of genotype-phenotype correlations. Am J Hum Genet. 1997;61:1309–17. PubMed PMID: 9399896.

Kose E, Arslan N. Vitamin/mineral and micronutrient status in patients with classical phenylketonuria. Clin Nutr. 2019;38:197-203. PubMed PMID: 29433755.

Lenke RR, Levy HL. Maternal phenylketonuria and hyperphenylalaninemia. An international survey of the outcome of untreated and treated pregnancies. N Engl J Med. 1980;303:1202–8. PubMed PMID: 7421947.

Levy HL, Guldberg P, Güttler F, Hanley WB, Matalon R, Rouse BM, Trefz F, Azen C, Allred EN, de la Cruz F, Koch R. Congenital heart disease in maternal phenylketonuria: report from the Maternal PKU Collaborative Study. Pediatr Res. 2001;49:636-42. PubMed PMID: 11328945.

Li N, Jia H, Liu Z, Tao J, Chen S, Li X, Deng Y, Jin X, Song J, Zhang L, Liang Y, Wang W, Zhu J. Molecular characterisation of phenylketonuria in a Chinese mainland population using next-generation sequencing. Sci Rep. 2015;5:15769. PubMed PMID: 26503515.

Liu N, Huang Q, Li Q, Zhao D, Li X, Cui L, Bai Y, Feng Y, Kong X. Spectrum of PAH gene variants among a population of Han Chinese patients with phenylketonuria from northern China. BMC Med Genet. 2017;18:108. PubMed PMID: 28982351.

Longo N, Dimmock D, Levy H, Viau K, Bausell H, Bilder DA, Burton B, Gross C, Northrup H, Rohr F, Sacharow S, Sanchez-Valle A, Stuy M, Thomas J, Vockley J, Zori R, Harding CO. Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria. Genet Med. 2019:21:1851-67. PubMed PMID: 30546086.

Lowe TB, DeLuca J, Arnold GL. Similarities and differences in key diagnosis, treatment, and management approaches for PAH deficiency in the United States and Europe. Orphanet J Rare Dis. 2020;15:266. PubMed PMID: 32977849.

Lubout CMA, Arrieta Blanco F, Bartosiewicz K, Feillet F, Gizewska M, Hollak C, van der Lee JH, Maillot F, Stepien KM, Wagenmakers MAEM, Welsink-Karssies MM, van Spronsen FJ, Bosch AM. Bone mineral density is within normal range in most adult phenylketonuria patients. J Inherit Metab Dis. 2020;43:251-8. PubMed PMID: 31587319.

Lupo PJ, Archer NP, Harris RD, Marengo LK, Schraw JM, Hoyt AT, Tanksley S, Lee R, Drummond-Borg M, Freedenberg D, Shetty PB, Agopian AJ, Shumate C, Rasmussen SA, Langlois PH, Canfield MA. Newborn screening analytes and structural birth defects among 27,000 newborns. PLoS One. 2024;19:e0304238. PubMed PMID: 38968308.

Maler V, Goetz V, Tardieu M, Khalil AE, Alili JM, Meunier P, Maillot F, Labarthe F. Aspartame and phenylketonuria: an analysis of the daily phenylalanine intake of aspartame-containing drugs marketed in France. Orphanet J Rare Dis. 2023;18:142. PubMed PMID: 37291632.

Manti F, Nardecchia F, Chiarotti F, Carducci C, Carducci C, Leuzzi V. Psychiatric disorders in adolescent and young adult patients with phenylketonuria. Mol Genet Metab. 2016;117:12-8. PubMed PMID: 26655635.

Manti F, Nardecchia F, De Leo S, Carducci C, Romani C, Palermo L, Angeloni A, Leuzzi V. Towards precision medicine for phenylketonuria: the effect of restoring a strict metabolic control in adult patients with early-treated phenylketonuria. Mol Genet Metab. 2023;140:107666. PubMed PMID: 37549444.

Merkel M, Berg D, Brüggemann N, Classen J, Mainka T, Zittel S, Muntau AC. Characterisation and differential diagnosis of neurological complications in adults with phenylketonuria: literature review and expert opinion. J Neurol. 2023;270:3675-87. PubMed PMID: 37081197.

Muntau AC, Adams DJ, Bélanger-Quintana A, Bushueva TV, Cerone R, Chien YH, Chiesa A, Coşkun T, de Las Heras J, Feillet F, Katz R, Lagler F, Piazzon F, Rohr F, van Spronsen FJ, Vargas P, Wilcox G, Bhattacharya K. International best practice for the evaluation of responsiveness to sapropterin dihydrochloride in patients with phenylketonuria. Mol Genet Metab. 2019;127:1-11. PubMed PMID: 31103398.

Opladen T, López-Laso E, Cortès-Saladelafont E, Pearson TS, Sivri HS, Yildiz Y, Assmann B, Kurian MA, Leuzzi V, Heales S, Pope S, Porta F, García-Cazorla A, Honzík T, Pons R, Regal L, Goez H, Artuch R, Hoffmann GF, Horvath G, Thöny B, Scholl-Bürgi S, Burlina A, Verbeek MM, Mastrangelo M, Friedman J, Wassenberg T, Jeltsch K, Kulhánek J, Kuseyri Hübschmann O; International Working Group on Neurotransmitter related Disorders (iNTD). Consensus guideline for the diagnosis and treatment of tetrahydrobiopterin (BH4) deficiencies. Orphanet J Rare Dis. 2020;15:126. PubMed PMID: 32456656.

Pardo J, Capdevila-Lacasa C, Segura B, Pané A, Montserrat C, de Talló Forga-Visa M, Moreno PJ, Garrabou G, Grau-Junyent JM, Junqué C; Consortium PKU. Volumetric brain reductions in adult patients with phenylketonuria and their relationship with blood phenylalanine levels. J Neurodev Disord. 2024;16:33. PubMed PMID: 38907189.

Prick BW, Hop WC, Duvekot JJ. Maternal phenylketonuria and hyperphenylalaninemia in pregnancy: pregnancy complications and neonatal sequelae in untreated and treated pregnancies. Am J Clin Nutr. 2012;95:374-82. PubMed PMID: 22205310.

Rajabi F, Rohr F, Wessel A, Martell L, Dobrowolski SF, Guldberg P, Güttler F, Levy HL. Phenylalanine hydroxylase genotype-phenotype associations in the United States: a single center study. Mol Genet Metab. 2019;128:415-21. PubMed PMID: 31623983.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Robinson M, White FJ, Cleary MA, Wraith E, Lam WK, Walter JH. Increased risk of vitamin B12 deficiency in patients with phenylketonuria on an unrestricted or relaxed diet. J Pediatr. 2000;136:545–7. PubMed PMID: 10753257.

Rocha JC, Ahring KK, Bausell H, Bilder DA, Harding CO, Inwood A, Longo N, Muntau AC, Pessoa ALS, Rohr F, Sivri S, Hermida Á. Expert consensus on the long-term effectiveness of medical nutrition therapy and its impact on the outcomes of adults with phenylketonuria. Nutrients. 2023;15:3940. PubMed PMID: 37764724.

Rohde C, Thiele AG, Baerwald C, Ascherl RG, Lier D, Och U, Heller C, Jung A, Schönherr K, Joerg-Streller M, Luttat S, Matzgen S, Winkler T, Rosenbaum-Fabian S, Joos O, Beblo S. Preventing maternal phenylketonuria (PKU) syndrome: important factors to achieve good metabolic control throughout pregnancy. Orphanet J Rare Dis. 2021;16:477. PubMed PMID: 34794480.

Rouse B, Azen C. Effect of high maternal blood phenylalanine on offspring congenital anomalies and developmental outcome at ages 4 and 6 years: the importance of strict dietary control preconception and throughout pregnancy. J Pediatr. 2004;144:235–9. PubMed PMID: 14760268.

Rovelli V, Longo N. Phenylketonuria and the brain. Mol Genet Metab. 2023;139:107583. PubMed PMID: 37105048.

Smith WE, Berry SA, Bloom K, Brown C, Burton BK, Demarest OM, Jenkins GP, Malinowski J, McBride KL, Mroczkowski HJ, Scharfe C, Vockley J; ACMG Board of Directors. Phenylalanine hydroxylase deficiency diagnosis and management: a 2023 evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2025;27:101289. PubMed PMID: 39630157.

Teissier R, Nowak E, Assoun M, Mention K, Cano A, Fouilhoux A, Feillet F, Ogier H, Oger E, de Parscau L; AFDPHE (Association Française pour le Dépistage et la Prévention des Handicaps de l'Enfant). Maternal phenylketonuria: low phenylalaninemia might increase the risk of intra uterine growth retardation. J Inherit Metab Dis. 2012;35:993-9. PubMed PMID: 22669364.

Thomas L, Olson A, Romani C. The impact of metabolic control on cognition, neurophysiology, and well-being in PKU: a systematic review and meta-analysis of the within-participant literature. Mol Genet Metab. 2023;138:106969. PubMed PMID: 36599257.

Trefz KF, Muntau AC, Kohlscheen KM, Altevers J, Jacob C, Braun S, Greiner W, Jha A, Jain M, Alvarez I, Lane P, Schröder C, Rutsch F. Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities - a retrospective study of German health insurance claims data. Orphanet J Rare Dis. 2019;14:181. PubMed PMID: 31331350.

van Spronsen FJ, Blau N, Harding C, Burlina A, Longo N, Bosch AM. Phenylketonuria. Nat Rev Dis Primers. 2021;7:36. PubMed PMID: 34017006.

van Spronsen FJ, van Wegberg AM, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, Trefz FK, van Rijn M, Walter JH, MacDonald A. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol. 2017;5:743-56. PubMed PMID: 28082082.

van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, van Rijn M, Trefz F, Walter JH, van Spronsen FJ. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017;12:162. PubMed PMID: 29025426.

Vela-Amieva M, Alcántara-Ortigoza MA, Ibarra-González I, González-Del Angel A, Fernández-Hernández L, Guillén-López S, López-Mejía L, Carrillo-Nieto RI, Belmont-Martínez L, Fernández-Lainez C. An updated PAH mutational spectrum of phenylketonuria in Mexican patients attending a single center: biochemical, clinical-genotyping correlations. Genes (Basel). 2021;12:1676. PubMed PMID: 34828281.

Vockley J, Andersson HC, Antshel KM, Braverman NE, Burton BK, Frazier, DM, Mitchell J, Smith WE, Thompson BH, Berry SA. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med. 2014;16:188-200. PubMed PMID: 24385074.

Waisbren SE, Prabhu SP, Greenstein P, Petty C, Schomer D, Anastasoaie V, Charette K, Rodriguez D, Merugumala S, Lin AP. Improved measurement of brain phenylalanine and tyrosine related to neuropsychological functioning in phenylketonuria. JIMD Rep. 2017;34:77-86. PubMed PMID: 27677920.

Waisbren SE, Rohr F, Anastasoaie V, Brown M, Harris D, Ozonoff A, Petrides S, Wessel A, Levy HL. Maternal phenylketonuria: long-term outcomes in offspring and post-pregnancy maternal characteristics. JIMD Rep. 2015;21:23-33. PubMed PMID: 25712380.

Walter JH. Vitamin B12 deficiency and phenylketonuria. Mol Genet Metab. 2011;104 Suppl :S52-4. PubMed PMID: 21824796.

Yan YS, Yao FX, Hao SJ, Zhang C, Chen X, Feng X, Yang T, Huang SZ. [Analysis of large deletion of phenylalanine hydroxylase gene in Chinese patients with phenylketonuria]. Zhonghua Yi Xue Za Zhi. 2016;96:1097-102. PubMed PMID: 27095776.

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