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| Field | 0 |
| Gene | PAH |
| Summary | Phenylalanine hydroxylase (PAH) deficiency is an autosomal recessive metabolic disorder caused by biallelic mutations in the PAH gene, leading to impaired conversion of phenylalanine (Phe) to tyrosine. This results in elevated Phe concentrations and toxic brain effects ranging from mild to severe intellectual disability if untreated. The spectrum includes classic phenylketonuria (PKU), less severe variants, and benign hyperphenylalaninemia. Prompt newborn screening allows early dietary and/or pharmacologic intervention, which prevents severe outcomes. PAH deficiency is among the most common inborn errors of metabolism, detected in newborns worldwide, and requires lifelong management. Untreated pregnancies in affected women can result in maternal PKU syndrome, threatening fetal development. |
| Clinical\_untreated | Untreated PAH deficiency leads to persistent severe hyperphenylalaninemia with irreversible neurocognitive impairment (intellectual disability), neurobehavioral and psychiatric issues, neurologic manifestations (such as movement disorders, hypertonia, seizures), microcephaly, decreased skin and hair pigmentation, eczema, and a musty body odor. Late-diagnosed individuals may have epileptic seizures, movement disorders, autistic features, and white matter brain abnormalities. Children exposed in utero to high maternal Phe (maternal PKU syndrome) frequently display intellectual disability, microcephaly, congenital heart defects, growth restriction, poor neuropsychiatric outcomes, and other structural malformations. |
| Clinical\_treated | Early and lifelong treatment, primarily with a Phe-restricted diet (plus medical food and, in some, sapropterin or pegvaliase), prevents most severe manifestations. Still, treated individuals may have a modest reduction in IQ, specific deficits in executive function, attention, and fine motor skills, and increased risks of psychiatric issues such as anxiety or depression. Neurologic symptoms (e.g., hypertonia, tremor, or seizures) may improve or resolve with controlled Phe levels. Bone mineral density is often below average (osteopenia). Vitamin B12 deficiency can develop if dietary adherence lapses. |
| Variants | Variants include classic PKU (untreated plasma Phe >1000 μmol/L, severe enzyme deficiency), variant PKU (intermediate, Phe >360 but <1000 μmol/L), and non-PKU hyperphenylalaninemia (untreated Phe 120–360 μmol/L, milder forms). Mild hyperphenylalaninemia is 360-600 μmol/L. Clinical severity and risk of neurotoxicity correlate with the degree of PAH functional loss; classic PKU presents earliest and most severely, whereas milder forms may require only monitoring. Genotype correlates imperfectly with phenotype but relates to sapropterin responsiveness: milder variants are more likely to respond. Distinct from PAH deficiency are BH4 deficiencies and DNAJC12 deficiency, which cause hyperphenylalaninemia via alternative mechanisms. |
| Genetics | PAH deficiency is caused by loss-of-function (LoF) mutations in the PAH gene. Over 1,000 mutations, mostly missense, but also nonsense, splice site, small insertions/deletions, and larger deletions/duplications, have been identified and functionally validated. The vast majority of affected alleles are detected by sequencing and targeted deletion/duplication analysis—about 95–99% by sequence analysis and 2–3% by deletion/duplication methods. The disease follows an autosomal recessive inheritance pattern; heterozygote carriers are asymptomatic. |
| Incidence | The global incidence is approximately 1:23,930 newborns. Regional variation exists: Karachay-Cherkess region of Russia has the highest (1:850); Europe and some Middle Eastern populations show rates of 1:4,000 to 1:10,000; the United States is about 1:25,000; and Japan has a much lower incidence (~1:125,000). |
| Diagnosis | Newborn screening (NBS) uses dried blood spots collected at 24–72 hours to measure Phe and tyrosine levels by tandem mass spectrometry. Elevated blood Phe (>120 μmol/L) and increased Phe:tyrosine ratio (≥3) are suggestive. Confirmatory diagnosis requires plasma amino acid analysis and exclusion of BH4 defects (pterin analysis), followed by molecular genetic testing to detect biallelic pathogenic PAH variants. Rapid follow-up and early initiation of diet are essential to prevent neurological damage. |
| Differential\_diagnosis | Disorders causing hyperphenylalaninemia include defects in tetrahydrobiopterin (BH4) synthesis or recycling: GCH1 (AR-GTPCH deficiency), PTS (PTPS deficiency), QDPR (DHPR deficiency), PCBD1 (PCD deficiency), and DNAJC12 deficiency. These conditions may have similar or overlapping biochemical and clinical findings (elevated Phe), but can present with additional neurologic or systemic manifestations (e.g., movement disorders, microcephaly, dystonia, parkinsonism) and require different treatments (BH4 and neurotransmitter supplementation). |
| Treatment | Lifelong, individualized therapy for those with untreated blood Phe >360 μmol/L consists of (1) a Phe-restricted diet (controlled natural protein intake), supplemented with Phe-free medical foods; (2) pharmacologic therapy in eligible patients—sapropterin dihydrochloride (synthetic BH4 cofactor) to enhance PAH activity (for responders), or pegvaliase (PEGylated phenylalanine ammonia lyase enzyme) for adults with uncontrolled Phe levels; (3) supportive care by a multidisciplinary team; (4) regular surveillance of Phe and nutritional status. Large neutral amino acid (LNAA) supplementation is another option in adolescents and adults. Aspartame-containing products should be avoided. |
| Prognosis | With early detection (via NBS) and lifelong, well-managed treatment, individuals have essentially normal growth, physical, and neurodevelopmental outcomes. Modest decreases in IQ and some executive or mental health issues may persist, but severe neurologic or intellectual disability is avoided. Early identification and treatment of women of childbearing age prevents maternal PKU syndrome in offspring. Late diagnosis or untreated disease leads to irreversible neurologic injury. |