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| Gene | PAH |
| Summary | Phenylalanine hydroxylase (PAH) deficiency, also known as phenylketonuria (PKU), is an autosomal recessive inborn error of metabolism caused by loss-of-function pathogenic variants in the PAH gene. Deficiency of PAH leads to elevated phenylalanine (Phe) concentrations, resulting in neurotoxicity and intellectual disability if untreated. Newborn screening enables early detection, allowing for dietary and pharmacological interventions to prevent severe neurologic sequelae. The clinical spectrum ranges from classic PKU to mild hyperphenylalaninemia, with phenotypic variability partly explained by genotype. Severe maternal hyperphenylalaninemia during pregnancy causes maternal PKU (MPKU) syndrome in offspring, including intellectual disability and congenital anomalies. Lifelong management requires dietary restriction, support from a multidisciplinary team, and careful surveillance. The worldwide incidence is approximately 1:23,930 newborns, with higher rates in some populations. |
| Clinical\_untreated | Untreated PAH deficiency manifests as severe and irreversible neurocognitive impairment (intellectual disability), microcephaly, epilepsy, neurologic symptoms (including movement disorders and seizures), neurobehavioral/psychiatric problems, decreased skin and hair pigmentation, eczema, and a musty body odor. In women with PAH deficiency who are inadequately treated during pregnancy, maternal PKU syndrome can occur in offspring, presenting with intellectual disability (>90%), microcephaly, poor neurobehavioral outcomes (including ADHD and anxiety/depression), congenital heart defects, intrauterine growth restriction, and other birth defects such as cleft palate, spina bifida, and diaphragmatic hernia. |
| Clinical\_treated | When treated from birth, most individuals develop normally, but mild reductions in intellectual functioning, executive skills, attention, and fine motor skills may remain. There is an increased rate of anxiety and depression and possible mild neurologic issues (hypertonia, movement disorders, seizures), which typically improve or resolve with good blood Phe control. Bone mineral density may be reduced but not to the level of osteoporosis. Vitamin B12 deficiency can occur if diet is not appropriately supplemented. Regular surveillance helps detect and manage long-term or subtle neuropsychological or nutritional issues. |
| Variants | PAH deficiency spans a spectrum: - Classic PKU: Severe, with untreated plasma Phe >1,000 µmol/L; nearly complete loss of PAH activity; profound neurotoxicity if untreated. - Mild PKU and variant PKU: Intermediate Phe levels (360–1,000 µmol/L), partial enzyme activity; milder cognitive/neurological issues without treatment. - Non-PKU hyperphenylalaninemia: Phe >120 but <360 µmol/L; typically does not require treatment but monitored. Genotype-phenotype correlation is imperfect, though certain variants (biallelic null alleles) predict non-responsiveness to BH4 (sapropterin). Responsiveness to sapropterin is higher in mild/moderate forms. Maternal PKU syndrome is a distinct variant occurring in offspring of pregnant women with uncontrolled PAH deficiency. |
| Genetics | PAH deficiency results from loss-of-function biallelic variants in the PAH gene (autosomal recessive). To date, over 1,000 pathogenic or likely pathogenic mutations have been identified and validated, including missense, nonsense, splice-site variants, small deletions/insertions, and rare exonic deletions/duplications. Approximately 95%-99% of pathogenic variants can be detected by sequence analysis and 2%-3% by gene-targeted deletion/duplication analysis (e.g., MLPA). Carriers are asymptomatic. |
| Incidence | Global incidence is about 1:23,930 live births. Incidence varies by region: as high as 1:850 in the Karachay-Cherkess region of Russia; 1:4,000–1:10,000 in Europe/Middle East; 1:25,000 in the US; lower in Asia (e.g., 1:125,000 in Japan). |
| Diagnosis | Diagnosis in newborns is via newborn screening using dried blood spots (24–72 hrs after birth), measuring elevated phenylalanine and the phenylalanine-to-tyrosine (Phe:Tyr) ratio by tandem mass spectrometry. Follow-up biochemical testing confirms persistent hyperphenylalaninemia (Phe >120 µmol/L, Phe:Tyr ≥3). Exclusion of tetrahydrobiopterin (BH4) defects is recommended via pterin/DHPR assays or multigene panels. Definitive diagnosis is by molecular genetic testing showing biallelic pathogenic PAH variants. |
| Differential\_diagnosis | Differential diagnoses include other causes of hyperphenylalaninemia: disorders of tetrahydrobiopterin (BH4) synthesis or recycling (e.g., AR-GTPCH deficiency/GCH1, PTPS deficiency/PTS, DHRP deficiency/QDPR, PCD deficiency/PCBD1) and DNAJC12 deficiency. These typically present with additional neurologic signs and require distinct treatment (e.g., BH4 or neurotransmitter precursors). |
| Treatment | Lifelong, age-appropriate phenylalanine-restricted diet supplemented with Phe-free medical foods (amino acid or glycomacropeptide-based). Sapropterin dihydrochloride (synthetic BH4 cofactor) may be added for responsive individuals. Enzyme substitution therapy with pegvaliase (pegylated recombinant phenylalanine ammonia lyase) is approved for adults with poor control on dietary therapy. Large neutral amino acids (LNAA) are an adjunct for adolescents/adults but contraindicated in pregnancy. Special management is needed preconception and during pregnancy to prevent maternal PKU syndrome (strict Phe control <360 µmol/L). Avoid aspartame-containing products. Treatment is coordinated by a multidisciplinary metabolic team. |
| Prognosis | With early diagnosis and strict, lifelong treatment, affected individuals generally have normal cognitive development and quality of life, with only mild neuropsychological or neurologic issues in some. Educational, social, and occupational outcomes are favorable. Untreated or late-diagnosed cases have irreversible intellectual disability and neurologic damage. Children of women with untreated PAH deficiency are at high risk for teratogenic effects. Prognosis strongly correlates with treatment adherence and early intervention. |