Phenylketonuria

**Alternative Names**
PKU
Phenylalanine Hydroxylase Deficiency
PAH Deficiency
Oligophrenia Phenylpyruvica
Folling Disease
Phenylalanine Hydroxylase
PAH
PKU1
Hyperphenylalaninemia, Mild
HPA
Phenylalaninemia

**Record Category**
Disease phenotype

**WHO-ICD**
Endocrine, nutritional and metabolic diseases >
Metabolic disorders

**Incidence per 100,000 Live Births**
6-10

**OMIM Number**
261600

**Mode of Inheritance**
Autosomal recessive

**Gene Map Locus**
12q24.1

**Description**
Phenylketonuria (PKU) is a genetic metabolic disorder characterized by complete or near-complete deficiency of an important enzyme known as phenylalanine hydroxylase (PAH). PAH is the enzyme necessary to convert the amino acid phenylalanine into the amino acid tyrosine. Tyrosine is necessary for the production of certain hormones, neurotransmitters, and melanin. Patients with PKU must have restricted dietary phenylalanine to live without PKU complications. These complications include mental retardation, hypopigmentation, and psychological problems such as agoraphobia. However, agoraphobia is noticed in patients with or without dietary treatment. Seizures, delayed development, and movement disorders are also common. Affected individuals may have a musty or mouse-like odor due to excess phenylalanine in the body.

It is found that approximately 1% of the mentally retarded patients are affected by PKU. The diet can be gradually enlarged, but metabolic control must be performed during the first ten years of life. Phenylalanine is toxic to fetal development, therefore pregnant women with high phenylalanine level must have special diet and they must be observed to save fetus life. Pharmacological doses of tetrahydrobiopterin (BH4), a cofactor of PAH, are found to be effective for some patients with PKU.

Classic PKU affects about one of every 10,000 to 20,000 Caucasian or Oriental births. PKU is rare in blacks. A high incidence is reported in Turkey, regions of Northern and Eastern Europe, the Yemenite Jewish population, Italy, Estonia, China, and former Yugoslavia. A low prevalence is reported in Finland.

**Molecular Genetics**
Mutations in the phenylalanine hydroxylase (PAH) gene cause a primary deficiency of the enzyme PAH. To date, over 450 different mutations have been identified in the PAH gene which cause PKU. On the other hand, about 31 different polymorphisms which cause minor changes in the gene sequence have been detected and they have neutral effect on the produced enzyme (PAH). The PAH gene contains 13 exons and spans 90 kilobases.

**Epidemiology in the Arab World**
**Algeria**
Lyonnet et al. (1989) studied 37 patients with permanent hyperphenylalaninemia. One of the patients, an Algerian boy, born to consanguineous parents, was diagnosed with a variant form of the disease. He had a dietary phenylalanine tolerance of above 350 mg/d, plasma phenylalanine levels below 1.5 mmol/L, and residual PAH activity 2-6% of normal controls. RNA analysis showed normal PAH mRNA quantity. However, sequencing of the PAH cDNA revealed a c.280 (G>A; Glu>Lys) mutation. PCR amplification of the PAH gene in the remaining patients identified another patient from North Africa to be a homozygote for the same mutation. Both patients were found to be homozygous for haplotypes 38, showing a complete concordance between haplotypes 38 and the 280 (Glu>Lys) mutation. Additionally, both patients showed the same variant phenotype of the disease. This mutation was screened for in 33 additional patients from DNA extracted from their Guthrie cards. Two heterozygotes and two homozygotes for the mutation could be detected, all of whom were Arabs, originating from either Algeria or Tunisia.

Egypt
Shawky et al. (1998) assessed the regional cerebral blood flow in patients with PKU compared to age and sex matched healthy children using SPECT (Single Photon Emission Computed Tomography). That assessment was followed by studying the possible association between behavioral and neurological disorders in PKU subjects and the changes in cerebral blood flow. The study included nine males and seven females who were proved to be PKU patients. For comparison of brain SPECT results, five healthy children were also included. The ages ranged from two to 11 in both groups. PKU patients were subjected to full clinical history, clinical examination, intelligence quotient (IQ) assessment, EEG recording, Ferric chloride test, and SPECT. Paper chromatography was performed to detect plasma phenylalanine (Phe) level. The consanguinity rate among the patients was 62.5% of which 50% were between first cousins. It was found that the mean age of onset of dietary therapy was considerably late (32.46 ± 25.56 months); therefore most cases had significant brain damage before being diagnosed and treated. Also, only five patients followed such therapy regularly. Shawky et al. (1998) attributed those results to the lacking of a proper screening program, and the unavailability and high cost of low Phe diet in Egypt. The most common complaint recorded among the patients was delayed physical and mental milestones (62.5%) and 50% of the cases were moderately mentally retarded. It is noted that the higher the plasma Phe, the lower the IQ and the later the age of dietary therapy onset, the lower the IQ and vice versa. Behavioral disorders were observed in 11 patients (68.75%) in the form of hyperactivity (36.36%), irritability (27.27%), autistic criteria (27.27%), and agoraphobia (9.09%). Neurological disorders were detected in 12 patients (75%) and those included pyramidal tract signs (91.67%) and convulsions (25%). Qualitative analysis of the brain SPECT results showed that 15 cases (93.9%) had changes in regional cerebral blood flow compared to none of controls. The most common were tempoparietal hyperperfusion (68.75%) and frontal hyperperfusion (50%). Patients with behavioral disorders had higher tempoparietal hyperperfusion compared to patients without behavioral disorders. The findings revealed that changes in regional cerebral blood flow (perfusion) occurred in PKU patients regardless the age of dietary therapy onset or plasma Phe level. Four years later, Shawky et al. (2002) analyzed the polymorphism caused by the variation in the number of short tandem repeats (STRs) as markers to detect PKU carriers in Egyptian families and also determined the degree of heterozigosity of this system in the Egyptian population. The study included sixteen unrelated families, each with at least one child with PKU. The PKU kindred studied included 16 PKU index cases, four affected sibs and three affected first cousins; 37 PKU carriers and 15 normal individuals as controls. At least one family was consanguineous. PCR was used to amplify STR alleles. Among the subjects, only eight STR alleles were identified. These alleles differed only in the number of the basic TCTA repeat and they had allele sizes starting from 230 to 258 bp. Thus, Shawky et al. (2002) suggested that the polymorphic nature of this system is a consequence of insertions or deletions of four basepair repeat units. STR heterozygosity of normal and mutant chromosomes was respectively 0.7441 and 0.7819. There was a statistically significant difference between normal and mutant chromosomes in the distribution of STR alleles. The 250-bp allele was the commonly associated with wild-type chromosomes (42%), whereas the 246-bp allele was the most frequent on mutant chromosomes (35.7%). In addition, the 254-bp allele had the second highest frequency (25%) on mutant chromosome.

Zaky et al. (2002) evaluated the neurological, behavioral, and psychiatric disorders in 20 PKU patients and investigated the psychosocial characteristics of their caregivers. The patients were
11 females and nine males with ages ranged between 2.5 to 15 years. All patients were subjected to medical history, clinical tests, plasma phenylalanine (Phe) level assessment, EEG, intelligence quotient (IQ) assessment, and assessments of behavioral, psychosocial and psychiatric problems. The caregivers were assessed for socioeconomic status, psychiatric disorders, and family social function. The overall consanguinity rate was 75% of which 30% was first cousin marriage, thus the prevalence of PKU among the patients’ family was high (55%). The most socioeconomic levels of the families were low level (40%) and very low level (25%). The age of establishing PKU diagnosis and dietary therapy was considerably late for most cases as only two cases were diagnosed and treated at ≥ six months. Dietary therapy was difficult to be maintained by the caregivers because of the unavailability of low Phe diet, their high cost, and bad taste. Because of these problems, only 35% of the patients had regular dietary therapy. All patients had behavior and or psychiatric disorders (100%) and the most common type of these disorders was motor excess problems (85%). EEG changes were detected in seven cases (35%). Different degrees of mental retardation were reported in 85% of PKU cases. It was noted that the lower the IQ, the higher the age at time of diagnosis and the average plasma Phe level. Zaky et al. (2002) noted that the lower the family social functioning (FSF) score, the higher is the plasma Phe value which indicated the importance of a healthy family psychosocial function in maintaining regular dietary therapy. Using the depression, anxiety, and isolation (DAI) score, 100%, 95%, 80% of studied mothers had anxiety, depression, and social isolation, respectively, compared to 70%, 50%, and 20% of studied paternal caregivers.

Kuwait
In 1987, In Kuwait, Teebi et al. found 7 cases of PKU, including a pair of siblings, among 451 institutionalized mentally retarded persons (prevalence: 1.9%). A further 13 cases from eight Arab families of different nationalities were ascertained among referral cases.

Yadav and Reavey (1988) presented a summary of the results of quantitative amino acid analysis in 800 subjects over a three-year period in Al-Sabah Hospital, Kuwait. Thirty-five patients with aminoacidopathy were identified, all but two of whom were the offspring of first-degree consanguineous marriages: nine cases of phenylketonuria, one benign hyperphenylalaninemia, seven non-ketotic hyperglycinemia, five tyrosinemia, five homocystinuria, four citrullinemia, two cystinuria, one hyperprolinemia, and one case of maple syrup urine disease were encountered.

Tunisia
See: Tunisia > Lyonett et al., 1989.

United Arab Emirates
Al-Hosani et al. (2003) performed a study to evaluate the progress of the UAE national newborn screening program and to determine the incidence of phenylketonuria (PKU) in the UAE. Blood was collected by heel prick onto a filter paper and tested for phenylalanine levels. Investigations for confirmation and cause of PKU included plasma amino acids and measurement of biotin metabolism defects. Over a period of six years, 13,8718 newborns were screened and of those, seven confirmed PKU cases were detected with an incidence 1:20050 for PKU. Data showed that coverage was acceptable in all districts except Dubai. There was a satisfactory increase in the coverage from 1998 to 2000 in all districts which reached 65%; however, this percentage was still bellow the international standard. A comparison of the timeliness of screening program indicators showed that the UAE indicators improved between 1998 and 2000 and now approximate international standard. The program protocol had an acceptable recall rate for PKU (0.04%). Apparent sensitivity (100%) and specificity (>99%) for PKU were acceptable. The positive predictive value (PPV) of 13.7% for PKU was unacceptably high.

Yemen
Avigad et al. (1987) reported a deletion of exon 3 responsible for all PKU cases among the Yemenite Jews. Using a molecular probe that detects carriers of the deletion, they identified 5 carriers among 200 randomly selected volunteers from this community who were not related to the known PKU families. Although the deleted gene was traced to 25 different locations throughout Yemen, family histories and official documents of the Yemenite Jewish community showed that the common ancestor of all the carriers of this defect lived in Sanaa, the capital of Yemen, before the eighteenth century.

References


**Related CTGA Records**
- Homocystinuria
- Maple Syrup Urine Disease

**External Links**
- http://www.genetests.org/profiles/pku
- http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=716

**Contributors**
- Abeer Fareed: 28.5.2007
- Ghazi O. Tadmouri: 29.4.2007
- Pratibha Nair: 22.4.2007
- Ghazi O. Tadmouri: 27.2.2007
- Abeer Fareed: 26.7.2006