Condition: Phenylketonuria (PKU)

Inheritance:

Autosomal recessive.

Genetic etiology:

Mutation in *PAH* gene encoding enzyme phenylalanine hydroxylase. Hyperphenylalaninemia can also be caused in rare instances by disorders of tetrahydrobiopterin synthesis.

Frequency:

Disease frequency now very low in regions of the world where newborn screening is conducted. Carrier frequency in Caucasians approximately 1/50, which predicts disease frequency of 1/10,000.

Clinical features:

Deficiency of phenylalanine hydroxylase leads to toxic accumulation of phenylalanine, and its metabolite phenylpyruvic acid. Newborns have no symptoms due to clearance of phenylalanine by the placenta, but left untreated will manifest delayed development, microcephaly, seizures, and behavioral problems. Affected individuals are hypopigmented due to deficiency of tyrosine (the product of phenylalanine hydroxylation), which is the starting point in melanin synthesis. Newborn screening is widely practiced and allows initiation of phenylalanine-restricted diet prior to onset of neurological damage.

Management:

Restriction of dietary phenylalanine; supplementation with tetrahydrobiopterin.

Genetic counseling:

Most affected children are detected by newborn screening. Parents of an affected child face a 25% recurrence risk. Genetic testing is available. Women with treated PKU need to remain on phenylalanine-restricted diet during a pregnancy, preferably before conception, to avoid congenital anomalies due to phenylalanine toxicity *in utero*.

Human Genetics and Genomics, Fourth Edition. Bruce R. Korf and Mira B. Irons.