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HST.161 Molecular Biology and Genetics in Modern Medicine  
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## Lecture 11

## PKU

PKU is an inborn (genetic) error of metabolism.

We know:

- biochemical phenotype
- genetic mutations
- clinical phenotype
- newborn screening (PKU was the first thing for which newborn screening was developed)
- preventative treatment
- teratogenicity from maternal PKU
- prenatal diagnosis (not well utilized, but available)
- very good animal model (encompasses just about all the characteristics of PKU)

Clinical phenotype:

- before 1962, PKU patients were severely mentally retarded, hyperactive
- discovered in 1934: 2 children were severely retarded; their mother believed their retardation was caused by the same thing - they both had an odor to their bodies and their urine. Brought them to Dr. Folling who specialized in studying the urine of diabetic patients; he added ferric chloride to the urine and saw a reaction, and realized that something must be wrong with the metabolism of phenylalanine.
- Untreated:
  - o Developmental delay; usually apparent in first few months of life. Very characteristic agitation, more colds than normal babies.
  - o Eczema (itchy skin rash; severe in PKU)
  - o Autism (first signs at 6-8 months of age). PKU is one of the few known causes of autism.
  - o Light complexion – blond, blue-eyed

Biochemical phenotype:

- phenylalanine is usually metabolized, by phenylalanine hydroxylase, to tyrosine. In PKU, this metabolism is blocked, and you get a large buildup of phenylpyruvic acid, which breaks down into phenyllactic acid and phenylacetic acid.
- Cofactor, BH<sub>4</sub>, donates hydrogen groups to phenylalanine during its normal metabolism. There are some variants of PKU that are due to reductions in levels of BH<sub>4</sub>. (Most versions of PKU involve mutations of the PAH itself).

Genotype:

- over 500 mutations now identified as being responsible
- there are points at which a mutation makes more difference than at another location.
- Mutations are recessive.

Newborn screening:

- very important, since once mental retardation has set in, it won't go away with treatment (the other symptoms – eczema, autism, and complexion – will all disappear).
- Phenylalanine in the blood is how you detect PKU in the screen.
- All done in the same way, initially:
  - o Baby's heel is stuck; blood is collected on filter paper, dried, and tested.
- at birth, the baby is not affected by PKU because the placenta acts as a dialysis machine, and transports the excess PKU from the baby's blood into the mother, where it's metabolized (assuming the mother doesn't have PKU). Thus, the blood has to be taken 24-48 hours after birth, so that PKU will have built up in the blood enough to be detected.
- Guthrie test: bacterial growth test on the dried blood to indicate high levels of PKU.

#### Treatment of PKU:

- dietary:
  - o low-protein foods, both natural and special. 5% of protein is Phe.
  - o Earlier diet treatments were too restrictive; patients became catabolic and broke down their own proteins, releasing Phe into their bloodstream.
  - o Phe-free amino acid mix was developed; solved this problem.
- Very restrictive diet; imposes a lot on the family.
- “everything we like, they can't have”

#### Effects of maternal PKU on baby:

- Mental retardation
- microcephaly
- congenital heart disease
- intrauterine growth retardation
- Treatment: mother should be on an even more restricted diet than normal to prevent problems with the baby.
- Mothers with PKU can't completely breastfeed; they have to go on an alternating schedule of breastfeeding and formula feeding, to prevent giving the baby too much Phe (which is present in the protein she provides it; treatment just clears the free Phe levels in the blood)

#### Additional genetic errors of metabolism (these are all detectable by newborn screening):

##### Glutaric Acidemia:

- macrocephaly
- encephalopathic episodes; damage to basal ganglia
- dystonia

##### Maple Syrup Urine Disorder

##### Citrullinemia

##### Tandem Mass Spectrometry:

- measures many metabolites in one test; can identify many disorders

Frequency: 1/12000, with exceptions for various ethnic groups – not present in Ashkenazi Jews or Africans; present in double in Turks (1/6000)