PHENYLKETONURIA

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Biochem 118Q

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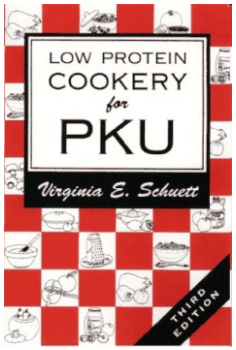
About PKU

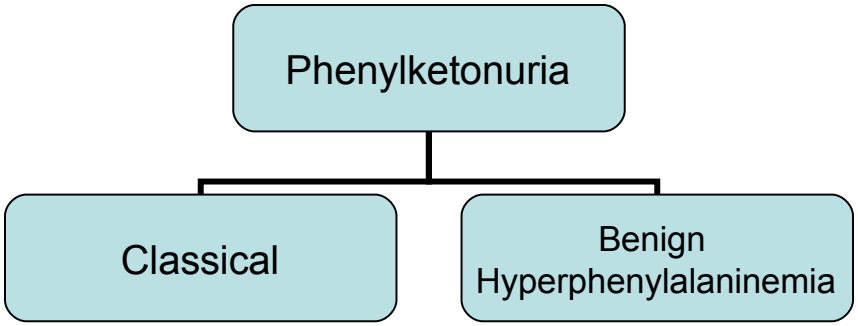
- Deficiency of an enzyme that processes the essential amino acid known as "phenylalanine“
  - Phenylalanine is externally received
  - Build up of phenylalanine is toxic
- Early diagnosis is important



Symptoms In Classical Diagnosis

- Mental retardation
  - Phenylalanine builds up in the bloodstream
  - If not treated, PKU will lead to mental retardation within the first year of life
- Delayed mental and social skills
- ADHD
- ‘Mousy' odor
  - Due to build up of phenylalanine
- Hyperactivity
- Epilepsy
- Eczema
- Light pigmentation
  - Phenylalanine plays a role in melanin production

Incidence



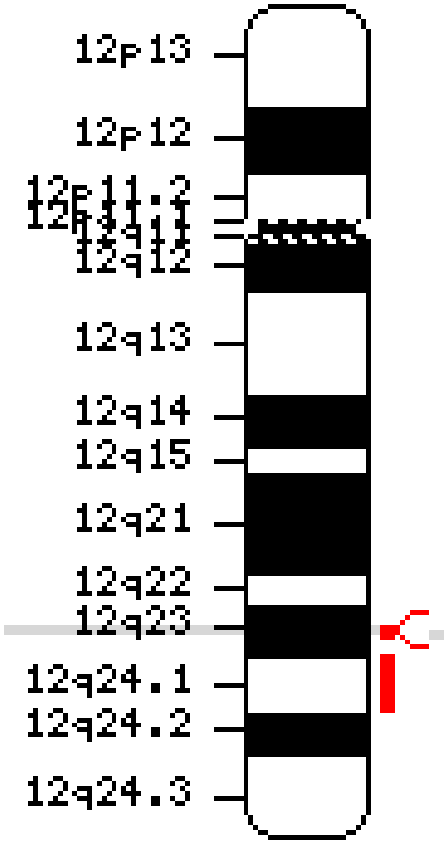
- Classical PKU affects about one of every 14,000 babies
- More common in individuals of Northern European and Native American ancestry than in those of African-American, Hispanic and Asian ancestry
- Equally frequent in males and females

Classical Diagnosis and Treatment

- Classical diagnosis: blood test which checks phenylalanine levels
  - Clue: Child usually starts to vomit consistently after 3-4 months of age
  - Clue: Untreated child will show clear abnormal movement at 1 yr of age
- Classical treatment: very restricted diet
  - No milk, eggs, artificial sweeteners, and most protein complexes
  - This diet used to be recommended up until adulthood (but not during)

Molecular Genetics

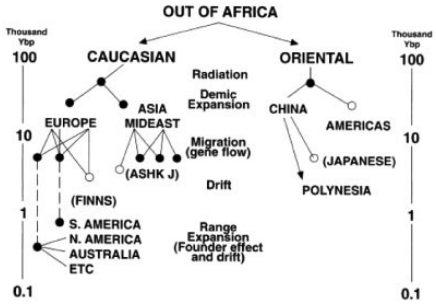
- Chromosome 12
  - PAH gene
    - Successfully cloned in the 1980s
- Autosomal recessive
  - Mendelian
- Screened by Tandem Mass Spectrometry
  - Babies affected by PKU have high levels of phenylalanine
  - If test is positive, then a confirmation test will occur
    - Confirmation test can be enzyme assays, DNA testing or tandem mass spectrometry
- While genotype–phenotype relationships in PKU often show no robust correlation
- Main explanation for PKU phenotype is a mutation in the major locus (PAH)



Benefits of Screening

- Preventative
  - Little to no brain damage
  - 1st genetic disease to enter public health domain
    - Net benefits (cost benefit anaylsis) for detecting and treating one individual with PKU were $208,000 ($292,000-$84,000)
    - Now all newborns are screened at 3 days of age
- "Curative"
  - genetics allows us to pursue other therapies
  - BH_4 is a protein co-factor. Adding BH_4 to the diet may decrease symptoms of PKU
  - New Treatment (2007)
    - Kuvan acts exactly like BH_4
      - Recently KUVAN has been tested in 579 PKU patients.In studies, side effects in patients taking KUVAN generally occurred at a similar rate as they did in patients who received placebo (a pill without any medicine in it).

Added Benefits



- Analysis of human descent
- Participants in the PKU story have benefited from learning that "besides its obvious intrinsic value, knowledge of population history, and of the demographic and evolutionary changes that accompany it, **has proven fundamental to address applied research in genetics**" [Barbujani and Goldstein, 2004].