Phenylketonuria

The PAH Gene

- PAH = phenylalanine hydroxylase
- **Location:**
  - Chromosome: 12
  - Base pairs: 103,232,103 to 103,311,380
- **Length on chromosome:** 79,277 bps
- **Exons:** 13
- **Transcriptlength:** 2,681 bps
- **Translation length:** 452 residues

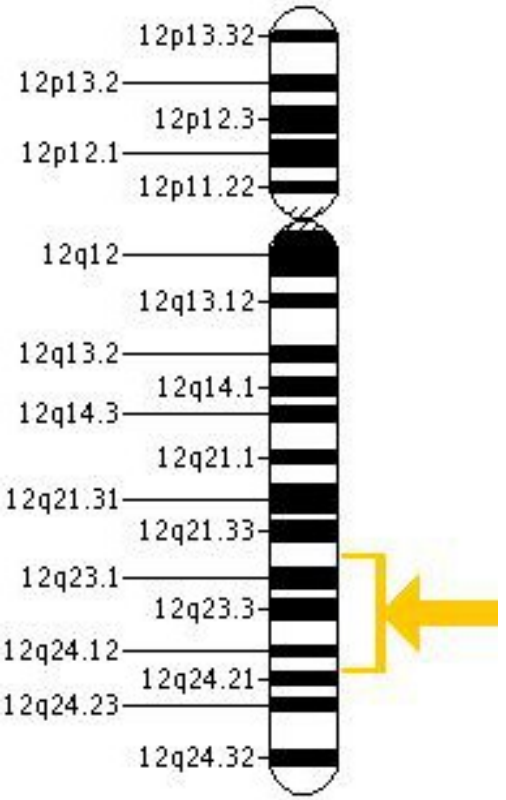

Figure taken from: http://ghr.nlm.nih.gov/gene/PAH

Phenylketonuria is inherited in an autosomal recessive fashion

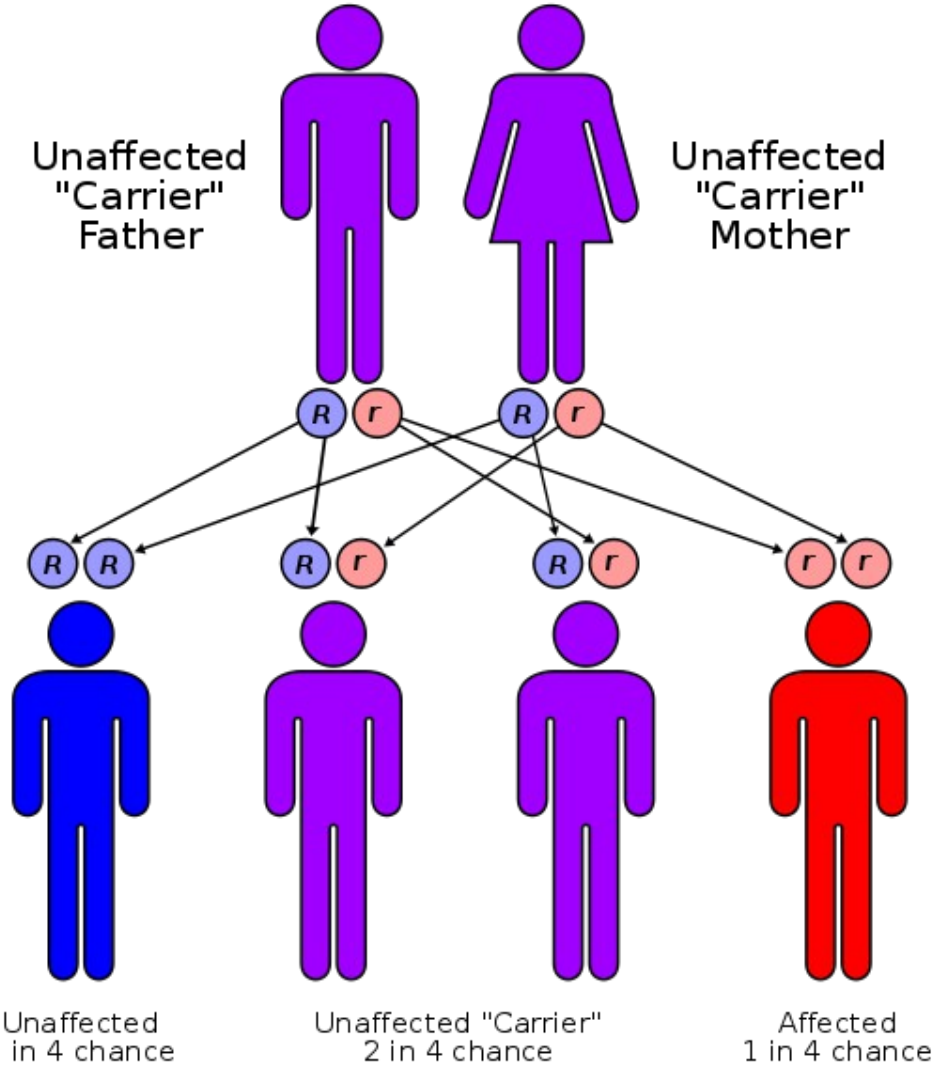

Figure taken from: http://en.wikipedia.org/wiki/Phenylketonuria

Function Of The Phenylalanine Hydroxylating System

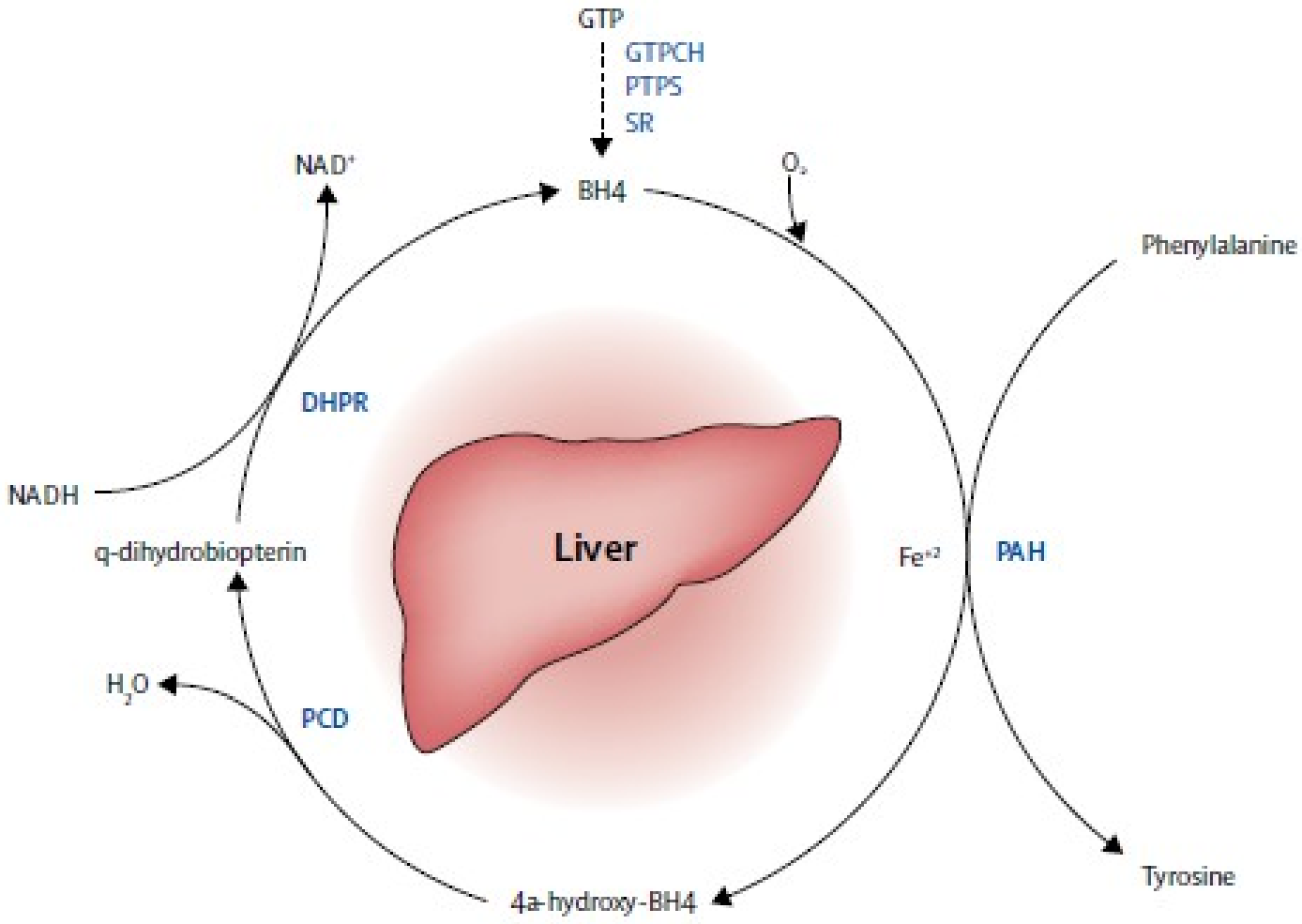

Figure taken from: *Nenad Blau, Francjan J van Spronsen, Harvey L Levy . Phenylketonuria. Lancet 2010; 376:*

Protein Structure and Location of Mutations in PAH

- **# of Mutations:** 564 (PAHdb, 2011/05/06)

- **Most Common Mutation Types:**
  - Missense: 60%
  - Deletion: 13%
  - Splice Junction: 10%

- **Position of Mutation:**
  - Catalytic Domain (Blue): 70%
  - Regulatory Domain(red): 16%
  - Tetramerisation Domain (lilac): 14%

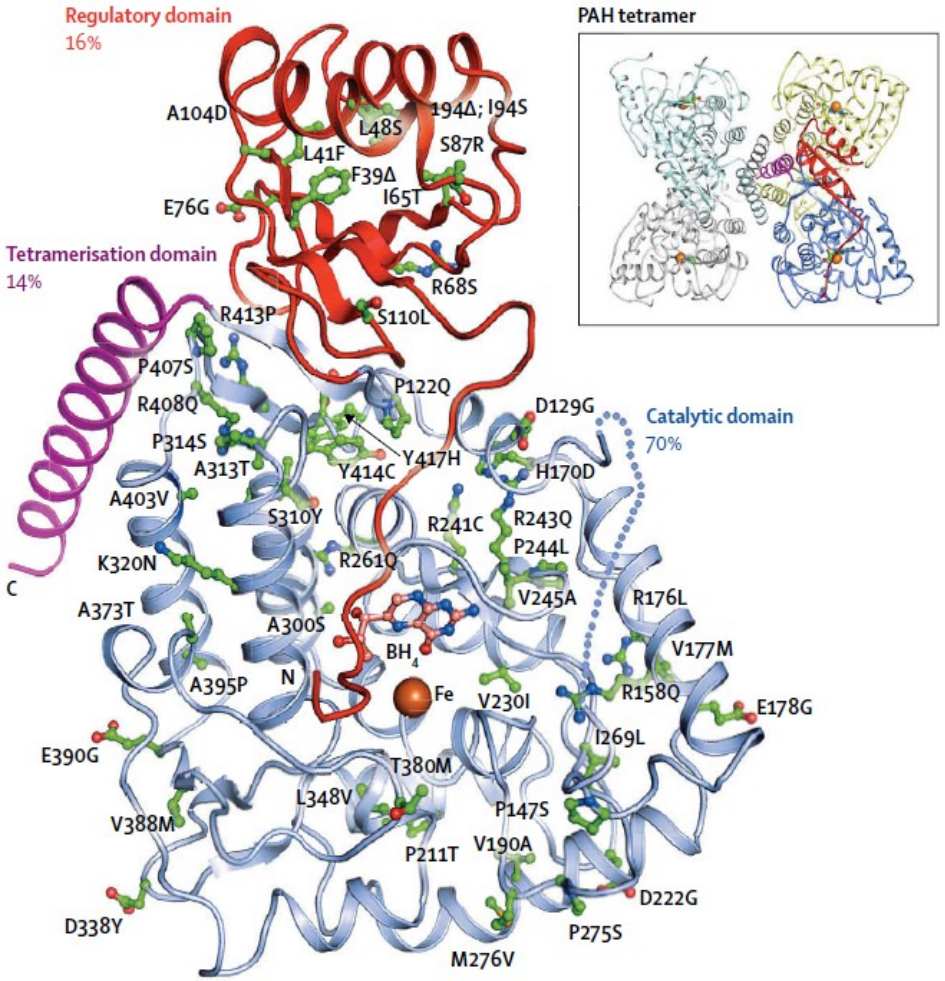

Figure taken from: *Nenad Blau, Francjan J van Spronsen, Harvey L Levy . Phenylketonuria. Lancet 2010; 376:*

General Information on Phenylketonuria

- Reduced activity of PAH
- PAH necessary to metabolize phenylalanine
- Phenylalanine accumulates
- Treatment: lifelong low-phenylalanine diet and lowering of phenylalanine-level in the blood
- Incidence: 1 in 15.000 births (Turkey 1 in 2.600 births, Finland 1 in 100.000 births)

Symptoms

- Delayed mental and social skills
- Head size significantly below normal
- Hyperactivity
- Jerking movements of the arms or legs
- Mental retardation
- Seizures
- Skin rashes
- Tremors
- Unusual positioning of hands

Physiological Background

- Phenylalanine a large, neutral amino acid (LNAA)
- Transportation of LNAAs across the blood-brain barrier (BBB) via the large neutral amino acid transporter (LNAAT)
- High concentration of phenylalanine → saturation of LNAAT → missing of other LNAAs in the brain

References

[1] Nenad Blau, Francjan J van Spronsen, Harvey L Levy . Phenylketonuria. Lancet 2010; 376: 1417–27

[2] http://ghr.nlm.nih.gov/gene/PAH

[3] http://www.ensembl.org/Homo_sapiens/Transcript/Summary?db=core;g=ENSG00000171759;r=12:103291562-103331199;t=ENST00000307000

[4] http://www.pahdb.mcgill.ca/

[5] http://en.wikipedia.org/wiki/Phenylketonuria

[6] MedlinePlus

[7] MedScape

[8] OMIM #261600