Phenylketonuria (PKU)

It is caused by genetic defect in **phenylalanine hydroxylase**, the first enzyme in the catabolic pathway for phenylalanine.

Results in elevated levels of phenylalanine in the blood (hyperphenylalaninemia). Accumulation of phenylalanine or its metabolites in early life impairs normal development of the brain, causing severe intellectual deficits. This may be caused by excess phenylalanine competing with other amino acids for transport across the blood-brain barrier, resulting in a deficit of required metabolites.

This enzyme is called mixed-function oxidases all of which catalyze simultaneous hydroxylation of a substrate by an oxygen atom of O_2 and reduction of the other oxygen atom to H_2O. Phenylalanine hydroxylase requires the cofactor tetrahydrobiopterin, which carries electrons from NADPH to O_2 and becomes oxidized to dihydrobiopterin in the process. It is subsequently reduced by the enzyme dihydrobiopterin reductase in a reaction that requires NADPH.

In individuals with PKU, a secondary pathway of phenylalanine metabolism comes into play. In this pathway phenylalanine undergoes transamination with pyruvate to yield phenylpyruvate. Phenylalanine and phenylpyruvate accumulate in the blood and tissues and are excreted in the urine— hence the name “phenylketonuria. Phenylpyruvate can be catabolized into phenylacetate and phenyllactate. Phenylacetate imparts a characteristic odor to the urine, which nurses have traditionally used to detect PKU in infants.

Diet of PKU individuals: diet must supply only enough phenylalanine and tyrosine to meet the needs for protein synthesis. Consumption of protein-rich foods must be curtailed.

Artificial sweetener aspartame is a dipeptide of aspartate and the methyl ester of phenylalanine. Therefore, it should be avoided by PKU individuals.

Phenylketonuria can also be caused by a defect in the enzyme that catalyzes the regeneration of cofactor tetrahydrobiopterin. The treatment in this case is more complex than restricting the intake of phenylalanine and tyrosine. Tetrahydrobiopterin is also required for the formation of L-3,4-dihydroxyphenylalanine (L-dopa) and 5-hydroxytryptophan—precursors of the neurotransmitters norepinephrine and serotonin, respectively—and in phenylketonuria of this type, these precursors must be supplied in the diet. Supplementing the diet with tetrahydrobiopterin itself is ineffective because it is unstable and does not cross the blood-brain barrier.

Alkaptonuria

This genetic disorder is due to defect in **homogentisate dioxygenase** enzyme (marked in the figure below with pink outline).

Large amounts of homogentisate are excreted and its oxidation turns the urine black. Individuals with alkaptonuria are also prone to develop a form of arthritis.

Archibald Garrod was the first to make a connection between an inheritable trait and an enzyme.

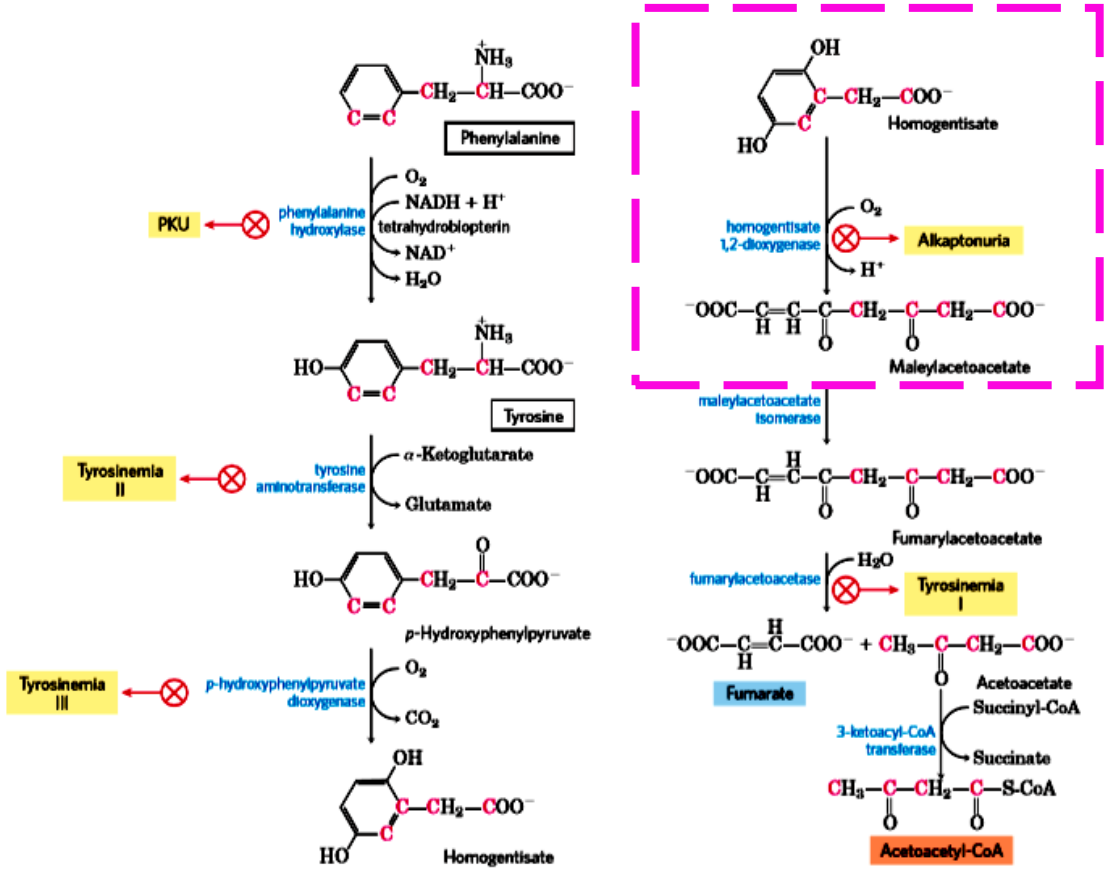

FIGURE 18–23 Catabolic pathways for phenylalanine and tyrosine. In humans these amino acids are normally converted to acetoacetyl-CoA and fumarate. Genetic defects in many of these enzymes cause inheritable human diseases (shaded yellow).

- Also Refer to Table 18-2: Some Human Genetic Disorders Affecting Amino Acid Catabolism (Page No. 717 Lehninger).
- Refer to pathways given in chapter-18 Lehninger related to the topic.