AACC Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

Tyrosinemias: Biochemistry and Clinical Laboratory Investigation

Kwabena A. N. Sarpong, Ph.D.
Clinical Chemistry Fellow
Division of Laboratory Medicine, Department of Pathology
University of Virginia School of Medicine

DOI:10.15428/CCTC.2018.292755

CCTC Clinical Chemistry Trainee Council

Overview

- Discuss the biochemical pathway for tyrosine metabolism
- Identify enzyme mutations/protein deficiencies leading to tyrosinemias
- Management and laboratory diagnosis of tyrosinemias

Disorders of Tyrosine Metabolism

Caused by the lack of an enzyme needed to metabolize tyrosines

- results in the build up of tyrosine or other harmful metabolites in the blood

Tyrosinemia I or Hereditary Infantile Tyrosinemia or Hepatorenal Tyrosinemia

More common and affects about 1 in 100,000 individuals (1 in 16,000 in Quebec, Canada)

Most common in French Canadian (1 in 1846) , Norway (1 in 74,800) and Finnish descent (1 in 60,000)

Tyrosinemia II or Oculocutaneous tyrosinemia or Richner-Hanhart syndrome

Occurs in fewer than 1 in 250,000 individuals worldwide

More common in Arab and Mediterranean populations

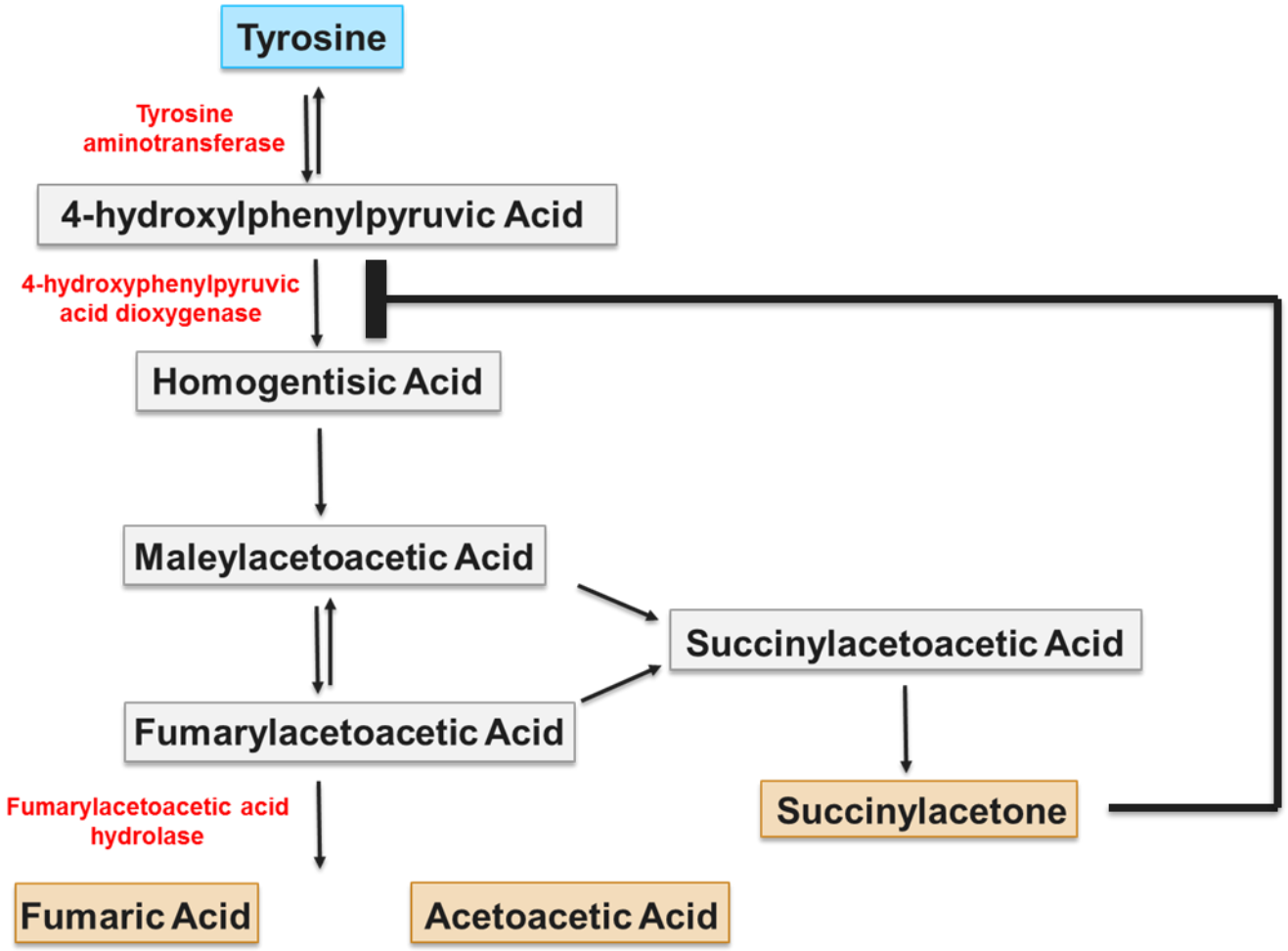
Tyrosinemia III or 4-alpha hydroxyphenylpyruvic acid oxidase deficiency

Very rare; less than 20 cases reported

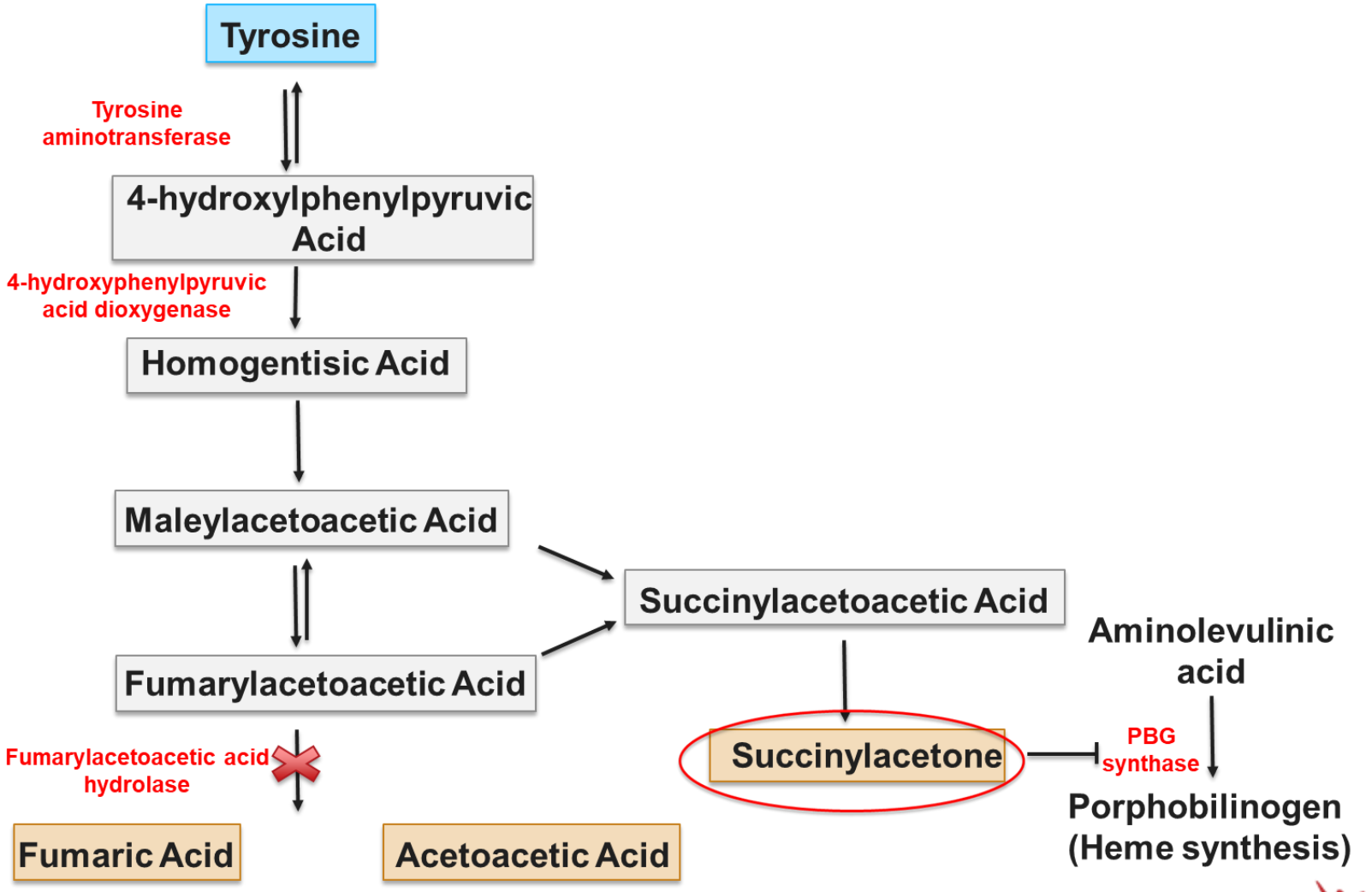
These conditions are inherited in an autosomal recessive manner

Alkaptonuria, Hawkinsinuria and Transient Tyrosinemia would be discussed later

Tyrosine Metabolism Pathway



Enzyme Defect Leading to Tyrosinemia I



Pathological Effects of Tyrosinemia I

Clinical findings of patients with Tyrosinemia I

- Severe liver disease
- Repeated neurological crisis
- Renal tubular dysfunction
- Rickets (hypophosphatemic)
- Hepatocellular carcinoma
- Death (due to liver failure or hepatocellular carcinoma)

Laboratory Findings in Patients with Tyrosinemia I

- Increased succinylacetone concentration in the blood
- Increased urinary excretion of succinylacetone
- Elevated urinary concentration of tyrosine metabolites
- Elevated plasma concentration of tyrosine, methionine and phenylalanine
- Increased urinary excretion of aminolevulinic acid
- Marked changes in liver function (AFP concentrations of 160,000 ng/ml, prolonged PT and PTT)

Diagnosis of Tyrosinemia I

Newborn Screening

- Elevated concentration of succinylacetone (plasma and urine)
  - Urine organic acid screen (qualitative)
  - Tandem mass spectrometry on newborn blood spot
  - Reference interval <5 µM in blood
- Elevated methionine or tyrosine concentration
  - Reference interval (Tyrosine 26-115 nmol/ml, methionine 11-35 nmol/ml)
  - Elevated tyrosine can also result from tyrosinemia I, II, transient tyrosinemia of newborn or liver diseases
  - Elevated methionine can indicate methionine metabolism defects, homocystinuria or liver problems
  - First newborn sample might show normal-to-modestly elevated concentrations of tyrosine and methionine
- Low aminolevulinic dehydratase (PBG synthase) enzyme activity

Molecular Diagnosis of Tyrosinemia I

Molecular Genetic Testing

- Four common pathogenic variants of *FAH* gene
  - IVS12+5G>A (33.7% of disease-causing alleles worldwide and accounts for ~90% of all disease-causing alleles in affected French Canadians)
  - IVS6-1G>T(common in central and western Europe, and accounts for 29% of all disease-causing alleles in Europe and 6.7% in North America)
  - Pro261Leu mutation (accounts for ~99% of affected individuals of Ashkenazi Jewish descent)
  - IVS7-6T>G
- Gene-target deletion/duplication analysis

  Performed if only one or no pathogenic variant is found

Management of Tyrosinemia I

Currently, no cure for this condition

Treatments

- Nutritional
  - Restricted diet (tyrosine and phenylalanine)
- Liver transplantation – children with severe liver failure
- Pharmaceutical
  - Nitisinone (Orfadin®), 2-(2-nitro-4-trifluoromethylbenzyol)-1,3 cyclohexanedione (NTBC)
    - Blocks 4-hydroxyphenylpyruvic acid dioxygenase

Retrospective studies shows success in patients treated with NTBC

- 45 French patients treated with NTBC
  - 97.5% overall survival rate
  - 1 patient died of transplantation complications
  - 3 patients underwent secondary liver transplantation

Management of Tyrosinemia I

Nutritional management

- High protein foods contain high tyrosine and phenylalanine
  - Avoid milk, meat, poultry, fish, eggs, cheese, nuts and beans

- Milk substitutes
  - Special formula (TYROS and TYREX-1)
  - Phenylalanine- and Tyrosine-Free

TYROS

- **BY MEAD JOHNSON**
- **MEDICAL FOOD FOR INFANTS**
- **PHENYLALANINE- AND TYROSINE-FREE**
- **NUTRITION FOR INFANTS WITH DOCUMENTED TYROSINEMIA**

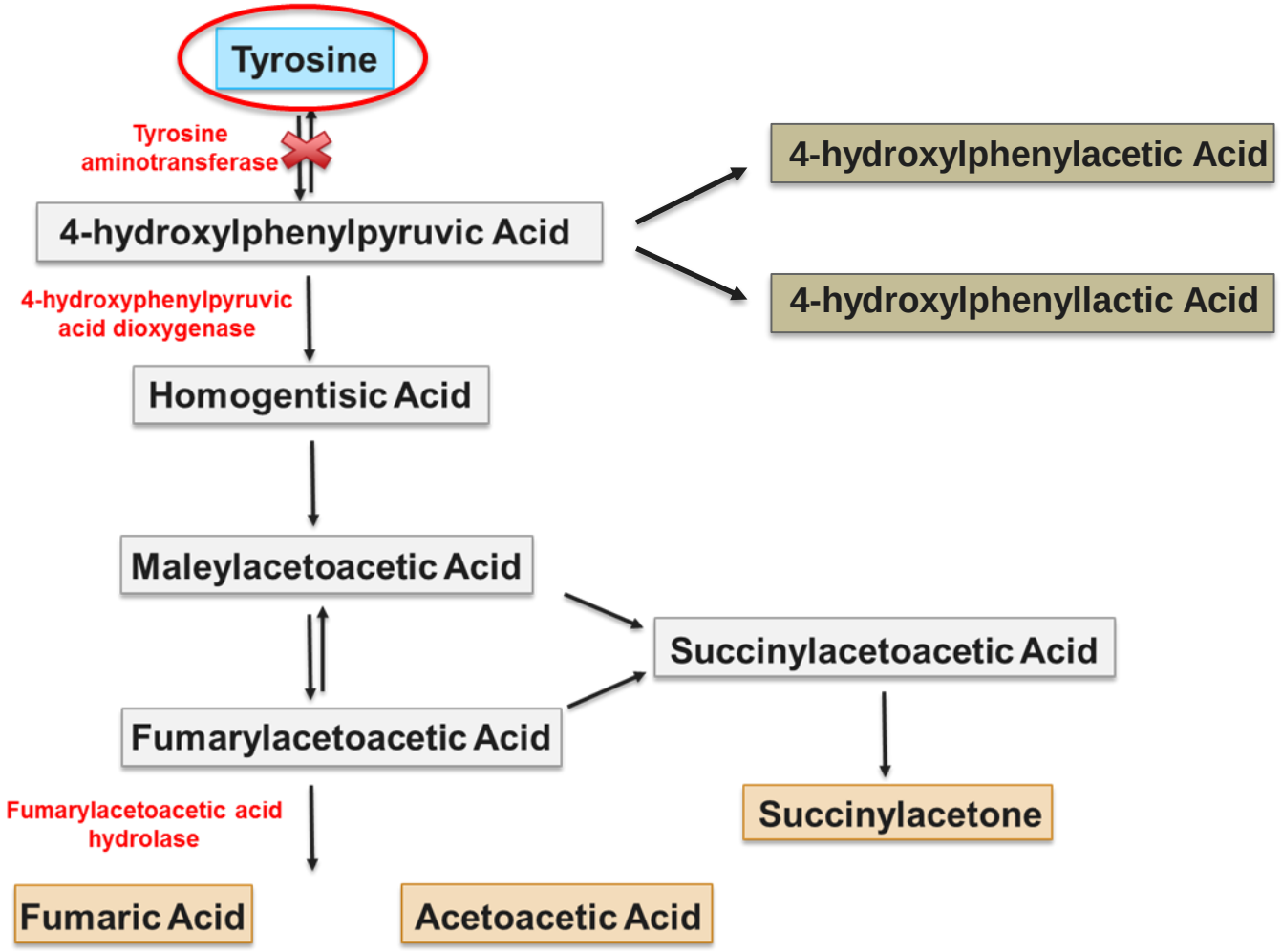
Composition: Corn syrup solids, vegetable oil (palm olein oil, coconut oil, soy oil, high oleic sunflower oil), **amino acids (L-glutamine, L-leucine, potassium aspartate, L-lysine hydrochloride, L-proline, L-valine, L-alanine, L-isoleucine, L-arginine, L-threonine, L-serine, glycine, L-histidine, L-methionine, L-tryptophan, L-cystine)**, modified corn starch, sugar, calcium phosphate and less than 1%: *Mortierella alpina* oil‡, *Crypthecodinium cohnii* oil§, ethyl vanillin, sodium citrate, potassium citrate, magnesium oxide, ferrous sulfate, potassium chloride, zinc sulfate, cupric sulfate, manganese sulfate, sodium iodide, sodium selenite, choline chloride, inositol, ascorbic acid, niacinamide, calcium pantothenate, vitamin B_6 hydrochloride, thiamin hydrochloride, riboflavin, vitamin D_3, folic acid, biotin, vitamin K_1, vitamin E acetate, vitamin A palmitate, vitamin B_{12}, taurine, L-carnitine.

TYREX-1

- **BY ABBOTT**
- **MEDICAL FOOD FOR INFANTS**
- **PHENYLALANINE- AND TYROSINE-FREE**
- **NUTRITION FOR INFANTS AND TODDLERS WITH TYR I, II & III**

Composition: Corn Syrup Solids, High Oleic Safflower Oil, Coconut Oil, Soy Oil. Less than 2% of the Following: L-Leucine, L-Proline, L-Lysine Acetate, Calcium Phosphate, L-Arginine, DATEM, L-Glutamine, L-Valine, L-Isoleucine, L-Alanine, Potassium Phosphate, Glycine, L-Asparagine, L-Serine, L-Threonine, Sodium Citrate, Potassium Citrate, Magnesium Chloride, L-Histidine, L-Methionine, Calcium Carbonate, L-Glutamic Acid, Ascorbic Acid, L-Cystine Dihydrochloride, L-Tryptophan, L-Aspartic Acid, Choline Chloride, Taurine, m-Inositol, Ferrous Sulfate, Zinc Sulfate, Ascorbyl Palmitate, L-Carnitine, dl-Alpha-Tocopheryl Acetate, Niacinamide, Mixed Tocopherols, Calcium Pantothenate, Salt, Cupric Sulfate, Thiamine Chloride Hydrochloride, Manganese Sulfate, Vitamin A Palmitate, Riboflavin, Pyridoxine Hydrochloride, Folic Acid, Beta-Carotene, Potassium Iodide, Biotin, Phylloquinone, Sodium Selenate, Chromium Chloride, Sodium Molybdate, Vitamin D3, and Cyanocobalamin.

Enzyme Defect Leading to Tyrosinemia II



Pathological Effects of Tyrosinemia II

Clinical findings of patients with Tyrosinemia II

- Developmental delay
- Corneal opacity
- Intellectual disability
- Palmoplantar keratoderma
- Hyperhidrosis (excessive sweating)
- Photophobia

Laboratory findings and diagnosis of Tyrosinemia II

- Elevated concentration of tyrosine in urine and plasma amino acid analysis

- Elevated concentration of tyrosine and 4-hydroxypyruvate metabolites in organic acid analysis (in the absence of succinylacetone)
    - 4-hydroxyphenylpyruvate
    - 4-hydroxyphenyllactate
    - 4-hydroxyphenylacetate
    - N-acetyltyrosine
    - 4-tyramine

- Molecular Genetic Testing for mutations in the *TAT* gene (encodes tyrosine aminotransferase)

Management of Tyrosinemia II

Treatments

- Nutritional

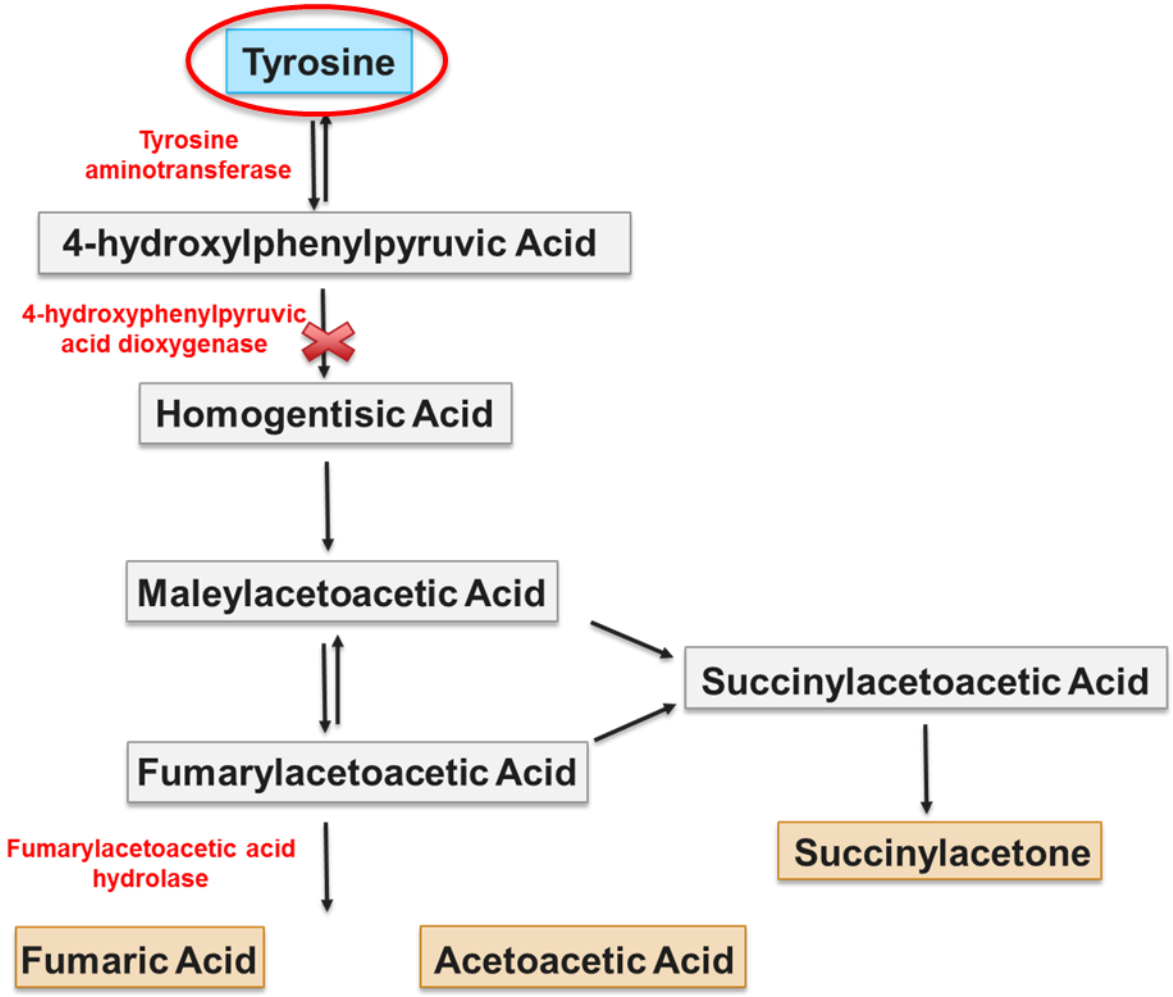
  - Restricted diet (special formulation low in tyrosine and phenylalanine)

    - Lowers plasma tyrosine concentrations and resolves oculocutaneous manifestations

- Pharmaceutical

  -Oral retinoids for treatment of skin lesions

Enzyme Defect Leading to Tyrosinemia III



Pathological Effects and Management of Tyrosinemia III

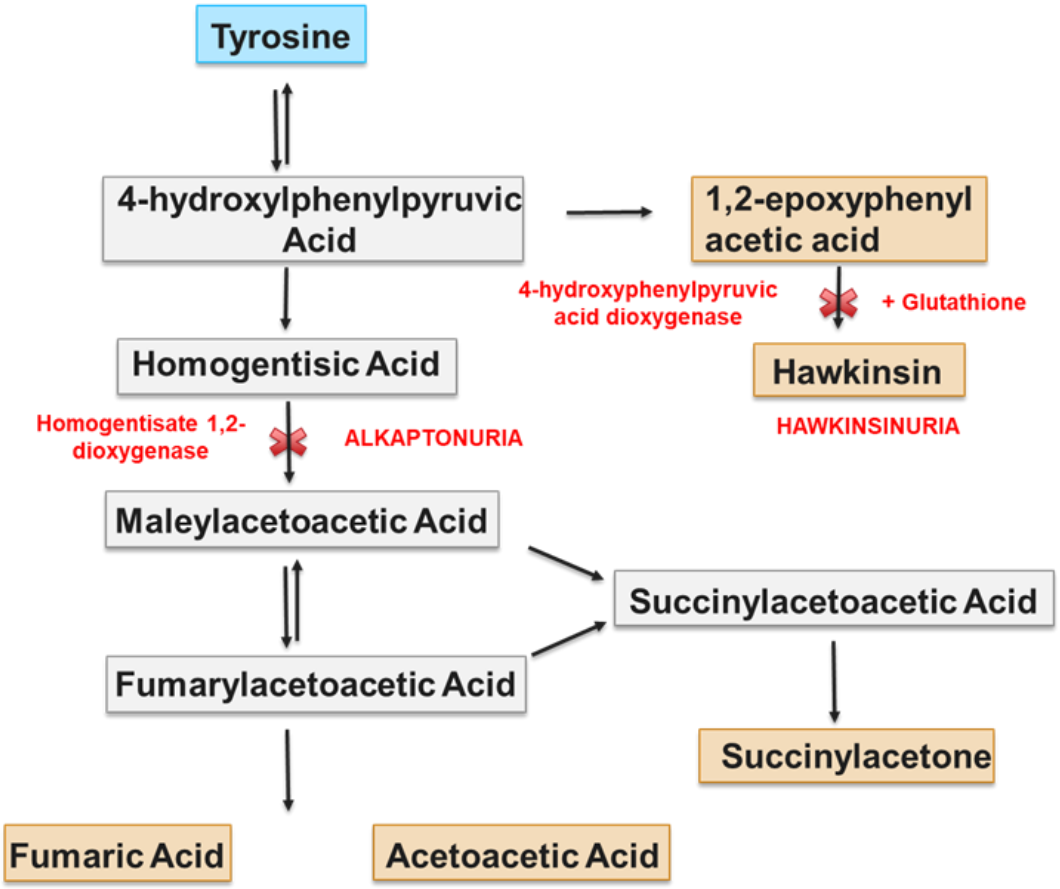
Clinical findings of patients with Tyrosinemia III

- Intellectual disability
- Seizures
- Intermittent ataxia
- Microcephaly
- Tremor
- Hypotonia

Management: Restricted diet low in tyrosine and phenylalanine

Other tyrosine disorders

Alkaptunuria and Hawkinsinuria



Transient Tyrosinemia of the Newborn

- Not an Inborn error of metabolism
- Common in premature newborns
- Delayed enzyme maturation in the tyrosine catabolic pathway
- Hypertyrosinemia, moderate hyperphenylalaninemia, and tyrosiluria
- Benign and spontaneously disappears

Summary

- Three types of tyrosinemias based on the enzyme defect
  - Type I - Defect in *FAH* gene, encodes fumarylacetoacetase
  - Type II - Defect in *TAT* gene, encodes tyrosine aminotransferase
  - Type III - Defect in *HPD* gene, encodes 4-hydroxyphenylpyruvate dioxygenase

- Screening and confirmatory tests
  - Urine organic acid screen (GC-MS)
  - Plasma amino acid analysis (MS/MS)
  - Enzyme activity
  - Molecular genetic testing

- Pharmaceutical/nutritional management for life

- Gene therapy in tyrosinemia

References

1. Chinsky JM, Singh R, Ficicioglu C, et al., Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations, Genet.Med. 2017 Epub ahead of print.
2. Sniderman King, L, Trahms, C, Scott, CR. Tyrosinemia type 1.In: Pagon, RA, Adam, MP, Bird, TD, Dolan, CR, Fong, CT, Stephens, K. (Eds.), Gene Reviews (Seattle, WA). 2017.
3. Angileri F, Bergeron A, Morrow G, Lettre F, Gray G, Hutchin T, et al. Geographical and ethnic distribution of mutations of the fumarylacetoacetate hydrolase gene in hereditary tyrosinemia type 1. JIMD Rep. 2015;19:43–58.
4. Ellaway CJ, Holme E, Standing S, Preece MA, Green A, Ploechl E, et al. Outcome of tyrosinaemia type III. J Inherit Metab Dis. 2001;24:824–832.
5. Grompe M. The pathophysiology and treatment of hereditary tyrosinemia type 1. Semin Liver Dis. 2001;21:563–571.
6. Macsai MS, Schwartz TL, Hinkle D, Hummel MB, Mulhern MG, Rootman D. Tyrosinemia type II: nine cases of ocular signs and symptoms. Am J Ophthalmol. 2001;132:522–527.

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
- **Consultant or Advisory Role:** No disclosures
- **Stock Ownership:** No disclosures
- **Honoraria:** No disclosures
- **Research Funding:** No disclosures
- **Expert Testimony:** No disclosures
- **Patents:** No disclosures

Thank you for participating in this *Clinical Chemistry* Trainee Council Pearl of Laboratory Medicine.

Find our upcoming Pearls and other Trainee Council information at www.traineecouncil.org

Download the free *Clinical Chemistry* app on iTunes today for additional content!

Follow us: