GENEReviews

Tyrosinemia Type 1

[*FAH Deficiency, Hepatorenal Tyrosinemia, Hereditary Tyrosinemia Type I , Fumarylacetoacetase Deficiency, Fumarylacetoacetate Hydrolase Deficiency*]

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Summary

Disease characteristics. Untreated tyrosinemia type I usually presents either in young infants with severe liver involvement or later in the first year with liver dysfunction and renal tubular dysfunction associated with growth failure and rickets. Untreated children may have repeated, often unrecognized, neurologic crises lasting one to seven days that can include change in mental status, abdominal pain, peripheral neuropathy, and/or respiratory failure, requiring mechanical ventilation. Death in the untreated child usually occurs before the age of ten years, typically from liver failure, neurologic crisis, or hepatocellular carcinoma. Combined treatment with nitisinone and a low-tyrosine diet has resulted in a greater than 90% survival rate, normal growth, improved liver function, prevention of cirrhosis, correction of renal tubular acidosis, and improvement in secondary rickets.

Diagnosis/testing. Tyrosinemia type I results from deficiency of the enzyme fumarylacetoacetate hydrolase (FAH), encoded by the gene *FAH*. Typical biochemical findings include: increased succinylacetone concentration in the blood and urine; and elevated plasma concentrations of tyrosine, methionine, and phenylalanine; elevated urinary concentration of tyrosine metabolites and the compound δ-ALA. Assay of FAH enzyme activity is possible in skin fibroblasts but not readily available. Molecular genetic testing by targeted mutation analysis for the four common *FAH* mutations and sequence analysis are clinically available and can detect mutations in more than 95% of affected individuals.

Management. Nitisinone (Orfadin®), 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione (NTBC), which blocks parahydroxyphenylpyruvic acid dioxygenase *(p*-HPPD), the second step in the tyrosine degradation pathway, prevents the accumulation of fumarylacetoacetate and its conversion to succinylacetone. Nitisinone should be prescribed as soon as the diagnosis of tyrosinemia type I is confirmed. Because nitisinone increases the blood concentration of tyrosine, dietary management with controlled intake of phenylalanine and tyrosine should be started immediately upon diagnosis to prevent tyrosine crystals from forming in the cornea. If the blood concentration of phenylalanine becomes too low (<20 umol/L), additional phenylalanine should be added to the diet. Prior to the availability of nitisinone,

the only definitive therapy for tyrosinemia type I was liver transplantation, which now should be reserved for those children who have severe liver failure at presentation and fail to respond to nitisinone therapy or have documented evidence of malignant changes in hepatic tissue. Guidelines for routine surveillance of individuals with tyrosinemia type I have been developed.

Genetic counseling. Tyrosinemia type I is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. If both disease-causing alleles of an affected family member are known, carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at 25% risk are possible by molecular genetic testing.

Diagnosis

Clinical Diagnosis

Tyrosinemia type I, a disorder of tyrosine metabolism, classically presents as severe liver disease in young infants. Children older than age six months may come to medical attention with signs of rickets or neurologic crises.

Testing

Deficiency of fumarylacetoacetate hydrolase (FAH) (EC 3.7.1.2) results in tyrosinemia type I [Lindblad et al 1977, Fallstrom et al 1979]. FAH is the terminal enzyme in the tyrosine catabolic pathway (Figure 1). In FAH deficiency, the immediate precursor, fumarylacetoacetate (FAA):

- Appears to accumulate in hepatocytes, causing cellular damage and apoptosis (identified in an animal model by Endo & Sun 2002);

- Is diverted into succinylacetoacetate and succinylacetone. Succinylacetone interferes with the activity of the following hepatic enzymes:

  - Parahydroxyphenylpyruvic acid dioxygenase *(p*-HPPD), resulting in elevation of plasma tyrosine concentration

  - PBG synthase, resulting in (1) reduced activity of the enzyme δ-ALA dehydratase in liver and circulating red blood cells, (2) reduced heme synthesis, (3) increased δ-aminolevulinic acid (δ-ALA), which may induce acute neurologic episodes [Sassa & Kappas 1983], and (4) increased urinary excretion of δ-ALA [Mitchell et al 1990]

Tyrosinemia type I is characterized by the following biochemical findings:

- **Increased succinylacetone concentration in the blood and excretion in the urine**

  Note: (1) Increased excretion of succinylacetone in the urine of a child with liver failure or severe renal disease is pathognomonic of tyrosinemia type I. (2) Many laboratories require that measurement of succinylacetone be specifically requested when ordering urine organic acids.

- **Elevated plasma concentration of tyrosine, methionine, and phenylalanine**

  Note: (1) Plasma tyrosine concentration in affected infants can be normal in cord blood and during the newborn period. (2) Elevated plasma tyrosine concentration can also be a nonspecific indicator of liver damage or immaturity, for example, in infants taking a high-protein formula [Techakittiroj et al 2005], including undiluted goat's milk [Hendriksz & Walter 2004].

- **Elevated urinary concentration of tyrosine metabolites** *p*-hydroxyphenylpyruvate, *p*-hydroxyphenyllactate, and *p*-hydroxyphenylacetate detected on urine organic acid testing

- **Increased urinary excretion of the compound δ-ALA** secondary to inhibition of the enzyme δ-ALA dehydratase by succinylacetone in liver and circulating red blood cells [Sassa & Kappas 1983, Mitchell et al 1990]

Untreated tyrosinemia type I is characterized by the following changes in liver function:

- **Markedly elevated serum concentration of alpha-fetoprotein (average 160,000 ng/mL)** (normal: <1000 ng/mL for infants age 1-3 months and <12 ng/mL for children age 3 months to 18 years)

- **Prolonged prothrombin and partial prothromboplastin times**

Note: (1) Changes in serum concentration of AFP (alpha-fetoprotein) and PT/PTT (prothrombin time/partial thromboplastin time) are more severe in tyrosinemia type I than in nonspecific liver disease and are often the presenting findings in tyrosinemia type I. (2) Transaminases and bilirubin are only modestly elevated, if at all. (3) Presence of normal serum concentration of AFP and normal PT/PTT in an individual with liver disease has a low probability of tyrosinemia type I.

Fumarylaceteoacetic acid hydrolase (FAH) enzyme activity. Assay of FAH enzyme activity is possible in skin fibroblasts but not readily available. Affected individuals have very low or undetectable FAH enzyme activity; specific reference ranges vary between laboratories.

Note: Homozygosity for the pseudodeficiency allele (R341W) or compound heterozygosity for the pseudodeficiency allele and a pathologic allele results in low FAH enzyme activity but no clinical symptoms and normal serum concentration of tyrosine, thus potentially complicating the interpretation of FAH enzyme activity particularly in prenatal testing. This potential difficulty is now avoided because assay of FAH enzyme activity is no longer in routine use.

For laboratories offering biochemical testing, see **Testing** .

Newborn screening

- **Blood tyrosine or methionine concentration.** Elevated concentration of tyrosine or methionine in the blood suggests tryrosinemia type I and should be further evaluated by quantification of urinary succinylacetone.

  Note: (1) Infants with tyrosinemia type I may have only modestly elevated or normal blood concentrations of tyrosine and methionine when the first newborn screening sample is collected. (2) Elevated tyrosine concentration on newborn screening can be the result of transient tyrosinemia of the newborn, tyrosinemia type II or III, or other liver disease. (3) Elevated methionine concentration can indicate liver dysfunction, defects in methionine metabolism, or homocystinuria (see cystathionine beta-synthetase deficiency).

- **More sensitive and specific indicators** of tyrosinemia type I:

  - **Succinylacetone,** measured directly from the newborn blood spot by tandem mass spectroscopy [Allard et al 2004, Rashed et al 2005]

  - **Delta-ALA-dehydratase (PBG synthase) enzyme activity,** measured in the newborn screening program in Quebec, Canada [Giguère et al 2005].

Succinylacetone is then measured in the urine of infants with apparent δ-ALA dehydratase deficiency [Schulze et al 2001].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *FAH* is the only gene known to be associated with tyrosinemia type I.

Molecular genetic testing: Clinical uses

- Diagnostic confirmation
- Carrier testing
- Prenatal testing

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis**
    - The four common *FAH* mutations (IVS12+5 G>A, IVS6-1 G>T, IVS7-6 T>G, P261L) account for approximately 60% of mutations in tyrosinemia type I in the general US population [CR Scott, unpublished data].
    - The P261L mutation accounts for nearly 100% of mutations responsible for tyrosinemia type I in the Ashkenazi Jewish population [Elpeleg et al 2002].
    - IVS12+5 G>A accounts for 87.9% of mutations in the French Canadian population [Poudrier et al 1996].
- **Sequence analysis.** If neither or only one disease-causing allele is detected by targeted mutation analysis and if biochemical testing has confirmed the diagnosis of tyrosinemia type I, sequence analysis may be performed on *FAH* to identify rare mutations. Sequence analysis is available on a clinical basis for affected individuals only.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Tyrosinemia Type 1

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis	*FAH* mutations: IVS12+5 G>A, IVS6-1 G>T, IVS7-6 T>G, P261L	60% in general US population [1, 2]	Clinical **Testing**
Sequence analysis	*FAH* sequence alterations	>95%	

1. P261L accounts for >99% of the mutations in the Ashkenazi Jewish population [Elpeleg et al 2002].
2. IVS12+5 G>A accounts for 87.9% of mutations in the French Canadian population [Poudrier et al 1996].

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

1 Measurement of serum concentration of AFP and prothrombin time/partial thromboplastin time (PT/PTT)

2 If #1 is markedly abnormal, evaluation of urine organic acids for tyrosine metabolites and succinylacetone

3 Molecular genetic testing for diagnostic confirmation in individuals with biochemical findings consistent with tyrosinemia type I

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *FAH*.

Clinical Description

Natural History

Untreated tyrosinemia type I usually presents either in young infants with severe liver involvement or later in the first year with liver dysfunction and significant renal involvement, growth failure, and rickets. Growth failure results from chronic illness with poor nutritional intake, liver involvement, and/or chronic renal disease. Death in the untreated child usually occurs before age ten years, typically from liver failure, neurologic crisis, or hepatocellular carcinoma.

Liver involvement. Untreated children presenting before age six months typically have acute liver failure with initial loss of synthetic function for clotting factors [Lindstedt et al 1992, Croffie et al 1999]. PT and PTT are markedly prolonged and not corrected by vitamin K supplementation; factor II, VII, IX, XI, and XII levels are decreased; factor V and factor VIII levels are preserved. Paradoxically, serum transaminase levels may be only modestly elevated and serum bilirubin concentration may be normal or only slightly elevated, in contrast to most forms of severe liver disease, in which marked elevation of transaminases and serum bilirubin concentration occur **concomitantly** with prolongation of PT and PTT. Resistance of affected liver cells to cell death may explain the observed discrepancy in liver function [Vogel et al 2004].

This early phase can progress to liver failure with ascites, jaundice, and gastrointestinal bleeding. Children may have a characteristic odor of "boiled cabbage" or "rotten mushrooms." Infants occasionally have persistent hypoglycemia; some have hyperinsulinism [Baumann et al 2005]. Others have chronic low-grade acidosis [CR Scott, unpublished data]. Untreated affected infants may die from liver failure within weeks or months of first symptoms.

Renal tubular involvement. In the more chronic form of the untreated disorder symptoms develop after age six months; renal tubular involvement is the major manifestation. The renal tubular dysfunction involves a Fanconi-like renal syndrome with generalized aminoaciduria, phosphate loss, and for many, renal tubular acidosis. The continued renal loss of phosphate is believed to account for rickets; serum calcium concentrations are usually normal.

Neurologic crises. Untreated children may have repeated neurologic crises similar to those seen in acute intermittent porphyria. These crises include change in mental status, abdominal pain, peripheral neuropathy, and/or respiratory failure, requiring mechanical ventilation. Crises can last one to seven days. Repeated neurologic crises often go unrecognized. Mitchell et al (1990) reported that 42% of untreated French Canadian children with tyrosinemia type I had experienced such episodes. In an international survey, Van Spronsen et al (1994) reported that 10% of deaths in untreated children occurred during a neurologic crisis.

Hepatocellular carcinoma. Those children who are not treated with nitisinone and a low-tyrosine diet and who survive the acute onset of liver failure are at high risk for developing and succumbing to hepatocellular carcinoma.

Survival in untreated children. Van Spronsen et al (1994) found the two-year survival rate for untreated infants diagnosed before two months of age to be 29%. Those diagnosed at two to six months of age had a 74% two-year survival rate, and a 96% survival rate after two years was noted for those diagnosed after age six months. After more than five years, however, the survival rate of the group diagnosed at age two to six months dropped to approximately 30% and that of the group diagnosed after age six months dropped to approximately 60% (Figure 2).

The natural history of tyrosinemia type I in children who are treated with nitisinone is markedly different from that in untreated children. Furthermore, the natural history of tyrosinemia type I in children who are treated before age two years with the combination of nitisinone and low-tyrosine diet is markedly different from the natural history in those treated with low-tyrosine diet alone. The combined nitisinone and low-tyrosine diet treatment has resulted in a greater than 90% survival rate, normal growth, improved liver function, prevention of cirrhosis, correction of renal tubular acidosis, and improvement in secondary rickets.

Neurologic crises observed in treated children have always been associated with a prolonged interruption in nitisinone treatment [CR Scott, unpublished data].

Children with acute liver failure require support prior to and during the initiation of treatment with nitisinone. Improvement generally occurs within one week of starting nitisinone treatment.

Corneal crystals. Nitisone blocks the tyrosine catabolic pathway such that succinylacetone is not produced but tissue tyrosine levels are raised. Blood tyrosine concentration greater than 500 mol/L confers risk of precipitation of tyrosine as bilateral, linear, branching subepithelial corneal opacities [Ahmad et al 2002], causing photophobia and itchy, sensitive eyes. The crystals resolve once tyrosine levels are reduced.

Hepatocellular carcinoma. Although Holme & Lindstedt (2000) and van Spronsen et al (2005) reported hepatocellular carcinoma in individuals after years of nitisinone therapy, it is estimated that fewer than 5% of children placed on nitisinone therapy before age two years will develop hepatocellular carcinoma by age ten years [CR Scott, unpublished data]. In Quebec, where tyrosinemia type I is included in the newborn screening program, hepatocellular carcinoma has not been reported in those placed on nitisinone therapy prior to 30 days of age. The longest period of treatment in this group is seven years [G Mitchell, preliminary data].

Genotype-Phenotype Correlations

No correlation is observed between clinical presentation and genotype. Both acute and chronic forms have been seen in the same families, and in unrelated individuals with the same genotype [Poudrier et al 1998].

One mechanism that explains this clinical variation is "gene reversion." Hepatic nodules removed from livers of individuals with the chronic form of tyrosinemia type I have been shown to have cells that are immunologically positive for FAH protein and to have enzymatic activity for FAH [Kvittingen et al 1994, Grompe 2001]. These "normal" cells appear to have arisen by "gene reversion," that is, the spontaneous self-correction of the germline mutation to the normal gene during somatic cell division. Spontaneous somatic mutation that suppresses the pathologic mutations and allows for normal or near-normal gene expression in these cells has also been

reported [Bliksrud et al 2005]. These are true reversions and not the result of maternal cell colonization or maternal cell fusion [Bergeron et al 2004]. The normal (reverted) cells have a selective growth advantage because they are no longer at risk for apoptosis from the accumulation of fumarylacetoacetate. These foci of revertent cell colonies comprise many of the liver nodules in untreated persons with chronic tyrosinemia type I who have a milder biochemical and clinical phenotype [Kim et al 2000, Demers et al 2003]. However, the continued production of succinylacetone and fumarylacetoacetate by the non-revertent cells places the individual at continued risk for hepatocellular carcinoma [Kim et al 2000].

Nomenclature

Previously used terms referring to tyrosinemia type I include tyrosinosis.

Prevalence

Tyrosinemia type I affects approximately one in 100,000 to 120,000 births [Mitchell et al 2001]. Because of the inconsistent and confusing nature of its clinical presentation, it is estimated that fewer than 50% of affected individuals are diagnosed while alive.

In the general US population, the carrier frequency is estimated to be 1/150 to 1/100.

Two regions of the world have a higher than expected frequency of tyrosinemia type I:

- In Norway (IVS 12+5 G>A and/or G337S) and Finland (W262X), the birth prevalence is estimated to be one in 60,000 live births.

- A founder effect from colonization by French settlers is present in the province of Quebec, Canada [Grompe et al 1994]. The IVS12+5 G>A mutation accounts for 87% of gene mutations in this population [Poudrier et al 1996].

  The birth prevalence in the province of Quebec is 1/16,000; in the Saguenay-Lac Saint-Jean region of Quebec, it is one in 1,846 live births.

  The overall carrier frequency in Quebec is 1/66 based on newborn screening data. The carrier frequency in the Saguenay-Lac St-Jean region is 1/16-1/20.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Children with any of the following presenting findings should be evaluated for tyrosinemia type I (Table 2):

Table 2. Differential Diagnosis of Tyrosinemia Type I in Infants by Presenting Finding

Presenting Finding	Differential Diagnosis
Hypertyrosinemia	−High-protein diet [1, 2] −Tyrosinemia type II −Tyrosinemia type III −Other liver disease
Hypermethioninemia	−Homocystinuria −Disorders of methionine metabolism −Other liver disease
Liver disease	−Galactosemia −Hereditary fructose intolerance −Fructose 1, 6 diphosphatase deficiency −Niemann Pick C disease −Wilson disease −Neonatal hemochromatosis −Hemophagocytic lymphohistiocytosis −Mitochondrial cytopathies −Congenital disorders of glycosylation −Acetaminophen toxicity −Bacterial infections (sepsis, salmonella, TB) −Viral infections (such as CMV, Hepatitis A, B) −Mushroom poisoning [3] −Herbal medicines [3] −Idiosyncratic drug reaction, toxin, vascular/ischemic or infiltrative process [3]
Renal syndrome	−Lowe syndrome −Cystinosis −Renal tubular acidosis −Fanconi syndrome
Rickets	−Hypophosphatasia −Vitamin D deficiency (nutritional/genetic) −Hypophosphatemic rickets −Vitamin D-dependent rickets −Fanconi syndrome
Neurologic crisis	−Cerebral hemorrhage/edema −Bacterial/viral meningitis −Hypernatremic dehydration −Acute intermittent porphyria

1. Techakittiroj et al 2005

2. Undiluted goat's milk [Hendriksz & Walter 2004]

3. Bansal & Dhawan 2004

Tyrosinemia type II is caused by a defect in tyrosine aminotransferase (TAT:EC 2.6.1.5) [Goldsmith et al 1973]. Establishing the diagnosis of tyrosinemia type II relies on the following:

- Plasma tyrosine concentration typically greater than 500 μM that may exceed 1000 μM (the concentration of other amino acids is normal)

- Increased excretion of *p*-hydroxyphenylpyruvate, *p*-hydroxyphenyllactate, and *p*-hydroxyphenylacetate and presence of small quantities of *N*-acetyltyrosine and 4-tyramine on urine organic acid analysis

Affected individuals have painful non-pruritic and hyperkeratotic plaques on the soles and palms. The plantar surface of the digits may show marked yellowish thickening associated with the hyperkeratosis [Rehak et al 1981]. Ophthalmologic involvement is recalcitrant pseudodendritic keratitis [Macsai et al 2001]. Although developmental delay appears to be common, it is unclear if ascertainment bias accounts for this and the reports of neurologic symptoms.

Findings improve on a diet restricted in tyrosine and phenylalanine [Ellaway et al 2001].

Tyrosinemia type III, the rarest of the tyrosine disorders, is caused by a deficiency of *p*-hydroxyphenylpyruvic acid dioxygenase (EC.1.13.11.27) [Endo et al 1983, Cerone et al 1997]. Plasma concentration of tyrosine ranges from 350 to 650 µM. Excretion of 4-hydroxyphenylpyruvic acid, 4-hydroxyphenyllactate, and 4-hydroxyphenylacetate is increased. The precise quantities vary with protein intake.

Few individuals have been identified with the disorder, and its clinical phenotype remains ill defined. The first affected individuals came to medical attention because of mental retardation or ataxia; another was detected on routine screening [Mitchell et al 2001]. These individuals, like those with tyrosinemia type II, have no liver involvement but have skin or ocular changes. It remains unclear if tyrosinemia type III is truly associated with cognitive delays or if the association has resulted from ascertainment bias [Cerone et al 1997, Ellaway et al 2001].

A diet low in phenylalanine and tyrosine can lower plasma tyrosine concentration.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- CBC with platelet count; electrolytes; prothrombin time (PT), partial thromboplastin time (PTT); serum bilirubin concentration; liver enzyme concentrations: AST, ALT, GGT, alkaline phosphatase; serum alpha-fetoprotein (AFP) concentration; BUN, creatinine

- Baseline abdominal CT or MRI with contrast to evaluate the liver for adenomas or nodules (see Dubois et al 1996)

- X-ray of wrist to document presence or absence of rickets

- Renal ultrasound examination to evaluate for nephromegaly

Treatment of Manifestations

Acute management of liver failure. Children may require respiratory support, appropriate fluid management, and blood products for correction of bleeding diathesis.

Nitisinone (Orfadin®). 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione (NTBC) was approved by the Food and Drug Administration in April 2002 for treatment of tyrosinemia type I [Schwetz 2002]. Nitisinone blocks parahydroxyphenylpyruvic acid dioxygenase *(p*-HPPD), the second step in the tyrosine degradation pathway, and prevents the accumulation of fumarylacetoacetate and its conversion to succinylacetone (Figure 1).

Nitisinone should be prescribed as soon as the diagnosis of tyrosinemia type I is confirmed.

Nitisinone is generally prescribed at 1.0 mg/kg/day; individual doses may vary. Dosage should be adjusted to maintain blood nitisinone levels between 40 and 60 µmol/L, which theoretically blocks greater than 99% of *p*-HPPD activity. Nitisinone is typically given in two divided doses but because of the long half-life (30 hours), affected individuals who are older and more stable may maintain adequate therapy with once per day dosing. As long as blood concentration of nitisinone is within the therapeutic range, urine succinylacetone does not need to be measured.

Rare side effects of nitisinone have included transient low platelet count and transient low neutrophil count that resolved without intervention and photophobia that resolved with stricter dietary control and subsequent lowering of blood tyrosine concentrations.

Low-tyrosine diet. Nitisinone increases blood concentration of tyrosine, necessitating a low-tyrosine diet to prevent tyrosine crystals from forming in the cornea. Dietary management

should be started immediately upon diagnosis and should provide a nutritionally complete diet with controlled intakes of phenylalanine and tyrosine using a vegetarian diet with low-protein foods and a medical formula such as Tyrex® (Ross) or Tyros-1® (Mead Johnson).

Phenylalanine and tyrosine requirements are interdependent and vary from individual to individual and within the same individual depending on growth rate, adequacy of energy and protein intakes, and state of health. With appropriate dietary management, plasma tyrosine concentration should be 200-500 µmol/L, regardless of age; plasma phenylalanine concentration should be 20-80 µmol/L (0.3-1.3 mg/dL). If the blood concentration of phenylalanine is too low (<20 µmol/L), additional phenylalanine should be added to the diet from milk or foods.

Liver transplantation. Prior to the availability of nitisinone for the treatment of tyrosinemia type I, the only definitive therapy was liver transplantation.

Recent clinical experience indicates that liver transplantation should now be reserved for those children who (1) have severe liver failure at clinical presentation and fail to respond to nitisinone therapy or (2) have documented evidence of malignant changes in hepatic tissue [Mohan et al 1999].

Transplant recipients require long-term immunosuppression. Mortality associated with liver transplantation in young children is10% or higher.

Transplant recipients may also benefit from low-dose nitisinone therapy to prevent continued renal tubular and glomerular dysfunction resulting from succinylacetone generated in renal tissue [Pierik et al 2005].

Prevention of Primary Manifestations

Treatment with nitisinone (Orfadin®) should begin as soon as the diagnosis is confirmed.

Prevention of Secondary Complications

Carnitine deficiency secondary to the renal tubular Fanconi syndrome can cause skeletal muscle weakness and should therefore be evaluated and treated if necessary [Nissenkorn et al 2001].

Correction of acidosis, calcium and phosphate balance, and therapy with 25-OH-vitamin D may be necessary to treat osteoporosis and rickets that have occurred from renal tubular damage.

Surveillance

Frequent evaluation of the following parameters is typical in the management of individuals with tyrosinemia type I (Table 3).

Table 3. Guidelines for Monitoring in Tyrosinemia Type I

Evaluation	Initiation of Therapy (Baseline)	First 6 Months		After 6 Months		
		Monthly	Every 3 months	Every 3 months	Every 6 months	Yearly
CBC						
Hgb, Hct, WBC, plts	x	x			Every 6 months or yearly	
Tyrosinemia markers (blood)						
Serum AFP concentration	x	x		Every 3 or 6 months		

Blood chemistries						
Plasma concentration of methionine, phenylalanine, tyrosine	x	x		x		
Prothrombin time (PT)	x	x				
Partial thromboplastin time (PTT)	x	x		+		
Bilirubin	x					+
ALT/AST	x		x			+
GGT	x		x			+
Alkaline phosphatase	x		x			+
BUN, creatinine	x	x				x
Urine samples						
Succinylacetone	x	x				+
Renal studies						
Renal ultrasound examination (nephromegaly)	x					+
Skeletal evaluation						
X-ray of wrist (rickets)	x					+
CT evaluation						
Abdominal CT or MRI	x					x
Dosage monitoring						
Blood nitisinone concentration		x		x		

+= if indicated

Testing of Relatives at Risk

Although it is unlikely that the healthy older sibs of a newly diagnosed infant with tyrosinemia type I will also have tyrosinemia type I, it is prudent to perform organic acid analysis of urine for measurement of succinylacetone.

All subsequent newborns of parents who have had a previous child with tyrosinemia type I should have urine analyzed for succinylacetone to allow for the earliest possible diagnosis and initiation of therapy.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Tyrosinemia type I is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.

- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.

- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with tyrosinemia type I are obligate heterozygotes (carriers) for a disease-causing mutation in the *FAH* gene.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Molecular genetic testing. Carrier testing is available to at-risk relatives on a clinical basis once the mutations have been identified in the proband. For unrelated reproductive partners of carriers, molecular genetic testing for the four common mutations that account for about 60% of alleles in the general US population is available.

Biochemical testing. Biochemical methods of carrier detection are not available.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at 25% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed. Molecular genetic testing is the preferred method for prenatal diagnosis [Jakobs et al 1990, Grenier et al 1996].

Biochemical testing. Prenatal diagnosis for pregnancies at 25% risk is possible by detection of succinylacetone in amniotic fluid or measurement of fumarylacetoacetase in cultured amniotic cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation. Detection of succinylacetone in amniotic fluid is diagnostic; however, because false negatives have been reported this method should only be used by laboratories consistently able to identify succinylacetone at low levels by stable isotope detection.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing .

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Tyrosinemia Type 1

Gene Symbol	Chromosomal Locus	Protein Name
FAH	15q23-q25	Fumarylacetoacetase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Tyrosinemia Type 1

276700	TYROSINEMIA, TYPE I

Table C. Genomic Databases for Tyrosinemia Type 1

Gene Symbol	Entrez Gene	HGMD
FAH	2184 (MIM No. 276700)	FAH

For a description of the genomic databases listed, click here.

Normal allelic variants: The gene is approximately 35 kbp in size and consists of 14 exons [Labelle et al 1993]. A single pseudodeficiency allele (c.1021C>T) leads to decreased FAH enzyme activity and very little immunoreactive protein but normal amounts of FAH mRNA [Rootwelt et al 1994].

Pathologic allelic variants: Population-specific mutations resulting from founder effect or genetic drift:

- Ashkenazi Jewish mutation: P261L

- Finnish mutation: W262X

- French Canadian mutation: IVS 12+5 G>A

- Pakistani mutation: Q64H

- Scandinavian mutation: G337S

- Turkish mutation: D233V

- Northern European mutation: IVS 12+5 G>A

- Southern European mutation: IVS 6-1 G>T

[Grompe et al 1994, Rootwelt et al 1994, Ploos van Amstel et al 1996, Bergman et al 1998, Bergeron et al 2001, Arranz et al 2002, Elpeleg et al 2002, Heath et al 2002]

Normal gene product: Fumarylacetoacetic acid hydrolase (FAH) is a cytosolic protein that acts as a homodimer and has a molecular weight of approximately 80 kd. The wild-type FAH has a Km for fumarylacetoacetate (FAA) of about 3.5 micromolar. FAH catalyzes the conversion of FAA to fumarate and acetoacetate and the conversion of succinylacetoacetate to succinate and acetoacetate.

Abnormal gene product: Missense, nonsense, and splice site mutations result in a virtual absence of fumarylacetoacetic acid hydrolase enzyme activity, leading to an intracellular accumulation of FAA, succinylacetoacetate, and succinylacetone causing cellular damage and apoptosis.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Tyrosinemia

Save Babies Through Screening Foundation, Inc
4 Manor View Circle
Malvern PA 19355-1622
Phone: 888-454-3383
Fax: 610-647-5757
Email: email@savebabies.org
Tyrosinemia

American Liver Foundation
75 Maiden Lane Suite 603
New York NY 10038
Phone: 800-GO-LIVER (800-465-4837)
Fax: 212-483-8179
Email: info@liverfoundation.org
liverfoundation.org

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe CW2 6BG
United Kingdom
Phone: (+44) 0870 7700 326
Fax: (+44) 0870 7700 327
Email: steve@climb.org.uk
www.climb.org.uk

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. **PubMed**

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

Mitchell GA, Grompe M, Lambert M, Tanguay RM. Hypertyrosinemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 79. www.ommbid.com. modified 2002

Chapter Notes

Author Note

University of Washington Biochemical Genetics Clinic Tyrosinemia Homepage

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Revision History

- 24 July 2006 (me) Review posted to live Web site
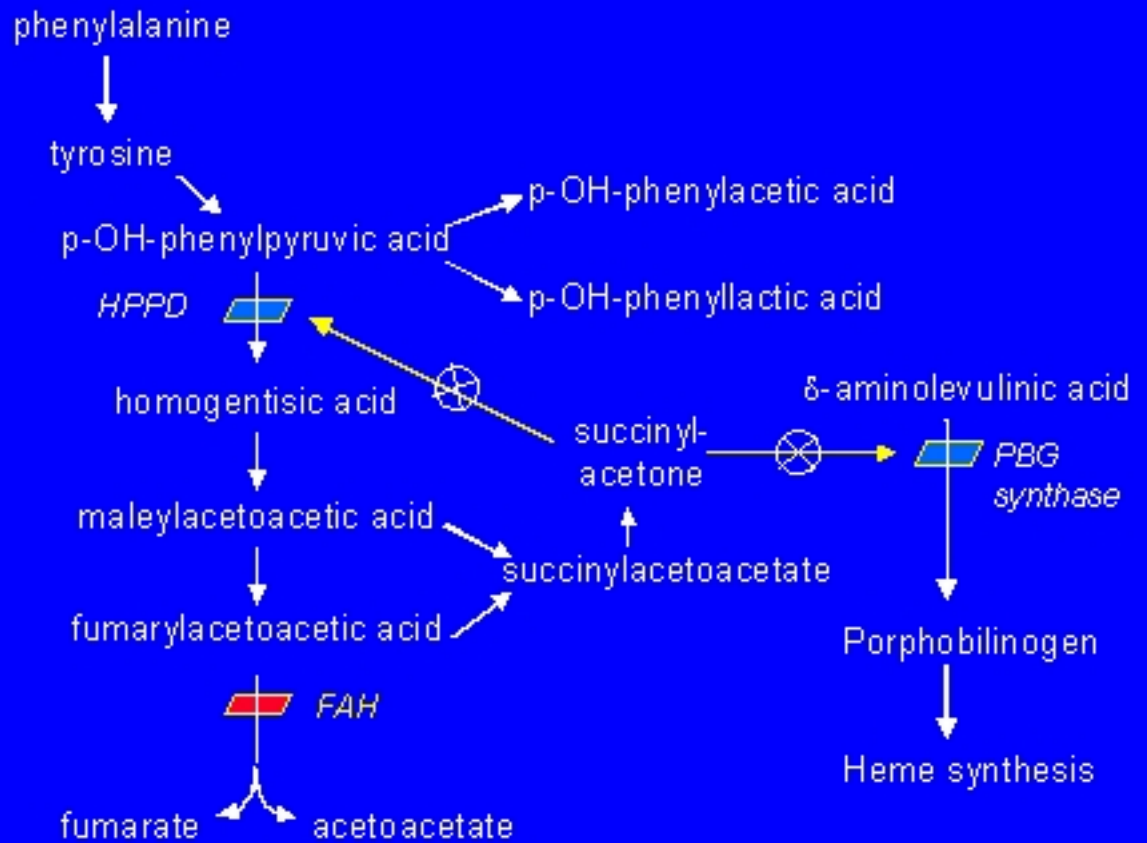- 29 June 2005 (crs) Original submission

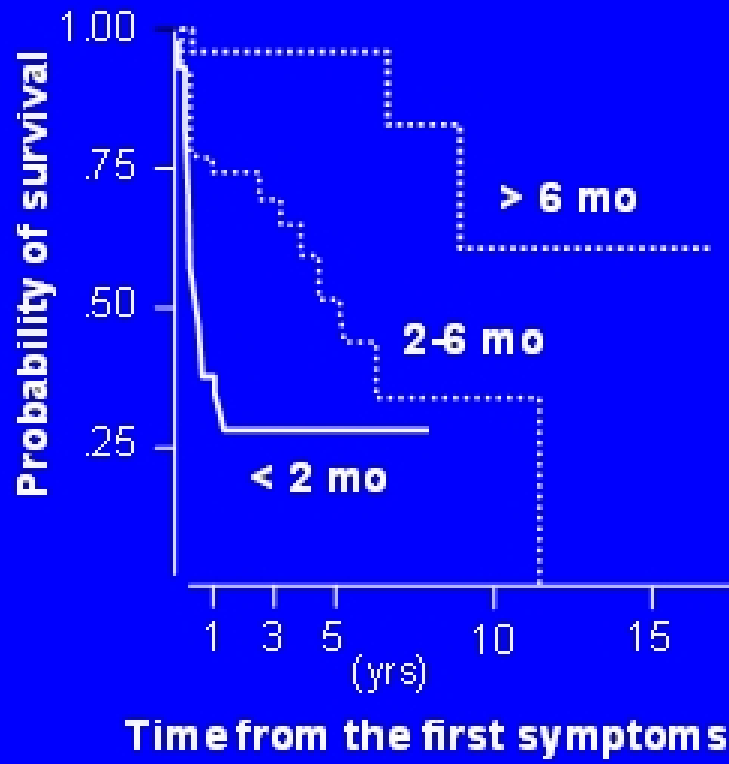**Figure 1.** The tyrosine catabolic pathway

Figure 2. Survival of children with tyrosinemia before 1992 [Van Spronsen et al 1994]