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Tyrosinemia Type II

Synonyms: Oculocutaneous Tyrosinemia, Richner-Hanhart Syndrome, TAT Deficiency, Tyrosine Aminotransferase Deficiency

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Summary

Clinical characteristics

Tyrosinemia type II is characterized by corneal dystrophy, painful palmoplantar hyperkeratosis, and variable intellectual disability. Individuals diagnosed and treated from early infancy may be asymptomatic or have only mild ocular and skin manifestations. Individuals with delayed diagnosis or lack of treatment present with ocular, skin, and variable cognitive manifestations.

Diagnosis/testing

The diagnosis of tyrosinemia type II is established in a proband by identification of biallelic pathogenic variants in *TAT* on molecular genetic testing or – in limited instances – significantly reduced activity of the enzyme tyrosine aminotransferase in liver.

Management

Targeted therapy: Lifelong restriction of dietary tyrosine and phenylalanine with low-protein diet combined with age-appropriate amino acid (phenylalanine-free and tyrosine-free), vitamin, and mineral supplements.

Supportive care: Lubricating eye drops and ointment; ocular surgery as needed to treat bilateral corneal ulcers; pyridoxine phosphate or a systemic retinoid may be beneficial for skin manifestations; developmental and educational support.

Surveillance: Quantitative analysis of plasma tyrosine and phenylalanine concentrations at each visit; ophthalmology evaluation annually or as needed; evaluation by ophthalmic subspecialist annually or as recommended by ophthalmologist; skin assessment for hyperkeratotic plaques as clinically indicated; monitoring of developmental milestones, neuropsychological testing using age-appropriate standardized assessment batteries, and standardized quality-of-life assessment tools for affected individuals, parents, and/or

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caregivers annually or at each visit; measurement of plasma calcium, phosphorus, and 25-hydroxyvitamin D concentrations annually or as clinically indicated.

Agents/circumstances to avoid: Increased dietary protein.

Evaluation of relatives at risk: Testing of at-risk sibs of any age is warranted to allow for early diagnosis and treatment.

Genetic counseling

Tyrosinemia type II is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *TAT* pathogenic variant, each sib of an affected individual has at conception 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 the *TAT* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for tyrosinemia type II have been published.

Suggestive Findings

Tyrosinemia type II is caused by deficiency of the enzyme tyrosine aminotransferase (TAT) (see Figure 1). Tyrosinemia type II **should be suspected** in individuals with either abnormal newborn screening (NBS) results or clinical and laboratory findings suggestive of tyrosinemia type II. Note: Tyrosinemia type II is not typically included in NBS panels, but may be detected when screening for tyrosinemia type I.

Scenario 1: Abnormal NBS Result

NBS for hepatorenal tyrosinemia (tyrosinemia type I) is typically based on quantification of tyrosine in dried blood spots. Elevated tyrosine above the cutoff reported by the screening laboratory is considered positive and requires follow-up biochemical testing. The identification of an infant with elevated tyrosine without the presence of succinylacetone (which is seen in tyrosinemia type I) should prompt investigation of other defects in tyrosine metabolism, including tyrosinemia type II.

Additional supportive laboratory findings of tyrosinemia type II include the following:

- Markedly elevated plasma tyrosine concentration

  Note: Elevated plasma tyrosine concentration can be a nonspecific indicator of liver damage or immaturity.
- Normal succinylacetone measured directly from the newborn blood spot by tandem mass spectroscopy
- Absence of succinylacetone in the blood and urine
- Elevated urinary concentration of tyrosine metabolites (e.g., 4-hydroxyphenylpyruvate, 4-hydroxyphenyllactate, 4-hydroxyphenylacetate, N-acetyltyrosine, and 4-tyramine)

If the follow-up biochemical testing supports the likelihood of tyrosinemia type II, additional testing is required to confirm the diagnosis (see Establishing the Diagnosis).

Upon identification of high tyrosine levels on NBS (typically >500 µmol/L and may exceed 1,000 µmol/L), consultation with a metabolic physician / biochemical geneticist and specialist metabolic dietitian should be obtained while additional testing is performed to determine whether the result is a true positive NBS and to definitively establish the diagnosis of tyrosinemia type II.

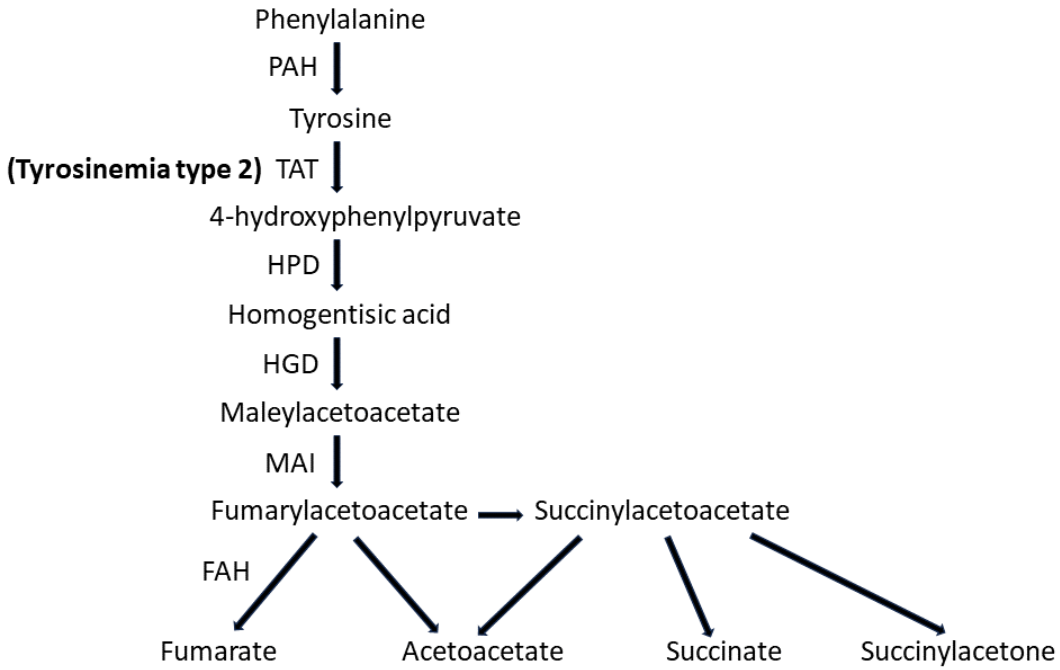

Figure 1. The tyrosine catabolic pathway

FAH = fumarylacetoacetate hydrolase; HGD = homogentisate 1,2-dioxygenase; HPD = 4-hydroxyphenylpyruvic acid dioxygenase; MAI = 4-maleylacetoacetate cis-trans-isomerase; PAH = phenylalanine hydroxylase; TAT = tyrosine aminotransferase

Scenario 2: Symptomatic Individual

A symptomatic individual who has either (1) atypical findings associated with later-onset tyrosinemia type II or (2) untreated infantile-onset tyrosinemia type II may present with the following supportive clinical findings, preliminary laboratory findings, and family history.

Clinical findings

- Ocular manifestations such as increased tearing, photophobia, pain, redness, and bilateral keratitis
- Skin manifestations such as progressive, painful, nonpruritic, and hyperkeratotic plaques on soles and palms, often associated with hyperhidrosis; usually begin after first year of life
- Developmental delay, particularly in those with high blood tyrosine concentration
- Variable intellectual disability

Laboratory findings

- Elevated plasma tyrosine concentration
- Elevated 4-hydroxyphenylpyruvate, 4-hydroxyphenyllactate, and 4-hydroxyphenylacetate and presence of small quantities of N-acetyltyrosine and 4-tyramine on urine organic acid analysis.
- Serum transaminase levels are usually normal.

Note: Because these laboratory findings are not specific to tyrosinemia type II, additional testing is required to establish the diagnosis.

Family history may suggest autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not exclude the diagnosis.

Establishing the Diagnosis

The diagnosis of tyrosinemia type II **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *TAT* on molecular genetic testing (see Table 1) or – in limited instances – significantly reduced activity of the enzyme tyrosine aminotransferase in liver. Because of its relatively high sensitivity, *TAT* molecular genetic testing can obviate the need for enzymatic testing and, thus, is increasingly the preferred confirmatory test for tyrosinemia type II [Beyzaei et al 2022].

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *TAT* variants of uncertain significance (or of one known *TAT* pathogenic variant and one *TAT* variant of uncertain significance) does not establish or rule out the diagnosis.

Scenario 1: Abnormal newborn screening (NBS) result. When NBS results and other laboratory findings suggest the diagnosis of tyrosinemia type II, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *TAT* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *TAT* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Scenario 2: A symptomatic individual. When the diagnosis of tyrosinemia type II has not been considered (because an individual has atypical findings associated with later-onset tyrosinemia type II or untreated infantile-onset tyrosinemia type II resulting from NBS not performed or false negative NBS result), **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *TAT* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Tyrosinemia Type II

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
TAT	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	<5% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Beyzaei et al [2022] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Maydan et al [2006] and Legarda et al [2011] reported large deletions involving *TAT*.

Clinical Characteristics

Clinical Description

Tyrosinemia type II is characterized by corneal dystrophy, painful palmoplantar hyperkeratosis, and variable intellectual disability. Individuals diagnosed and treated from early infancy may be asymptomatic or have only mild ocular and skin manifestations. Individuals with delayed diagnosis or lack of treatment present with ocular, skin, and variable cognitive manifestations [Gliagias et al 2022]. To date, more than 70 individuals have been identified with tyrosinemia type II [Beyzaei et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of Tyrosinemia Type II

Feature	% of Persons w/Feature		Comment
	Diagnosis & treatment in early infancy	Later diagnosis w/delayed or no treatment	
Ocular manifestations	75%	~75%-85%	↑ tearing, photophobia, eye redness, dendritic epithelial ulcers
Skin manifestations	35%	80%	Palmoplantar hyperkeratosis, hyperkeratotic plaques
Intellectual disability	Rare	~60%	
Developmental delay	Rare	~10%	

Based on Al-Ratrout et al [2005], Viglizzo et al [2006], Legarda et al [2011], El-Shabrawi & Kamal [2013]

Ocular manifestations can appear in the first months or first year of life or as late as the fourth decade [Viglizzo et al 2006]. Ocular symptoms include epiphora (increased tearing), photophobia, pain, and blepharospasm. Ocular signs include corneal clouding, pseudodendritic corneal lesions (usually bilateral), dendritic ulcers, and, rarely, corneal or conjunctival plaques. The dendritic lesions on the cornea stain poorly with fluorescein.

- Bacterial, viral, and fungal cultures are typically negative.

- Ocular manifestations may undergo spontaneous remission and/or recurrence and may occur independently of other clinical manifestations.
- Individuals are often misdiagnosed with herpes simplex keratitis [Soares et al 2017].
- Bilateral corneal lesions unresponsive to antiviral therapies should alert the clinician to the possible diagnosis of tyrosinemia type II, even in the absence of skin lesions [Macsai et al 2001].
- Some individuals with tyrosinemia type II report isolated burning and redness of the eyes since childhood [Ghalamkarpour et al 2020].
- Asynchronous bilateral eye disease was the sole clinical feature reported in one child age 15 months with negative NBS for tyrosinemia type II [Gliagias et al 2022]. Following diet modification, tyrosine levels decreased, resulting in significant resolution of ocular symptoms [Gliagias et al 2022].
- Dietary treatment (see Management, Targeted Therapy) has resulted in significant improvement of ocular manifestations in most affected individuals within the first week of treatment [El-Shabrawi & Kamal 2013, Tekin et al 2015].
- Corneal lesions recurred in one individual after discontinuation of dietary restrictions [Macsai et al 2001].

Skin manifestations can appear in the first months of life or be delayed until the second decade [Rabinowitz et al 1995]. They typically present as progressive painful hyperkeratotic plaques on the soles and palms, often associated with hyperhidrosis [da Silva et al 2024]. The fingertips and weightbearing areas of the soles are commonly affected by keratoderma.

- One individual had vesicular lesions on the fingertips [Peña-Quintana et al 2017].
- Skin manifestations rarely resolve spontaneously and often recur.
- The pain experienced with palmoplantar keratoderma is a key diagnostic feature, and it can be severe enough to hinder walking [Viglizzo et al 2006].
- A skin biopsy from a plantar callus showed hyperkeratosis, hypergranulosis, and acanthosis [Al-Ratrout et al 2005].
- Dietary restriction of tyrosine and phenylalanine is a highly effective treatment; significant improvement of skin manifestations in most individuals occurs within the first week of treatment [Tekin et al 2015].
- In one individual, the toenails showed subungual hyperkeratosis and secondary nail dystrophy [Madan & Gupta 2006].

Developmental delay. Infants diagnosed and treated in early infancy typically have normal development. Untreated individuals can have global developmental delay including poor feeding with poor appetite and reduced oral intake [Gliagias et al 2022].

Mild developmental delay with hemiparesis and seizures has been reported in one individual [Charfeddine et al 2006].

Intellectual disability. About half of individuals with tyrosinemia type II have mild intellectual disability, but early dietary treatment may reduce this risk [Legarda et al 2011, Nakamura et al 2015, da Silva et al 2024]. Mild language disorder has been reported in three individuals [Charfeddine et al 2006]. Intellectual disability may be prevented by early dietary restriction of tyrosine and phenylalanine. Language development was reported to improve with dietary treatment [Tsai et al 2006].

Nutritional deficiencies can appear in individuals due to limitations of certain amino acids (phenylalanine, tyrosine, and methionine) in the diet. Deficiency of calcium, phosphorus, and 25-hydroxyvitamin D have been observed.

Other

- Isolated geographic tongue with otherwise normal clinical findings (1 individual) [Bouyacoub et al 2013]

- Self-harm (agitation with paroxysms of head banging and hand and tongue biting) and diffuse plantar keratoderma (1 individual) [Madan & Gupta 2006]

Genotype-Phenotype Correlations

Precise genotype-phenotype correlations are difficult to determine, as most *TAT* pathogenic variants reported to date are not recurrent [Beyzaei et al 2022].

The most common variant reported to date, p.Arg57Ter, has been reported in ten affected individuals from three families [Peña-Quintana et al 2017, Beyzaei et al 2022]. Individuals homozygous for this pathogenic variant typically present in the neonatal period and have eye and skin manifestations.

Nomenclature

Tyrosinemia type II was previously referred to as keratosis palmoplantaris with corneal dystrophy.

Prevalence

Tyrosinemia type II is rare, with an incidence of less than one in 250,000 [Bouyacoub et al 2013]. Fewer than 100 affected individuals from various ethnic backgrounds have been reported to date [Janakiraman et al 2006, El-Shabrawi & Kamal 2013].

Founder pathogenic variants have been reported in populations from northern Italy (Lombardy and Tuscany; p.Arg57Ter), Tunisia (p.Cys151Tyr), Lebanon (p.Arg297Ter), Palestine (p.Arg417Ter), and Gran Canaria (p.Pro406Leu), which has a population of Mediterranean ancestry primarily from continental Spain and northern Africa [Peña-Quintana et al 2017, Beyzaei et al 2022]. Consanguinity is frequently reported in parents of affected individuals, which may contribute to the higher prevalence of this disorder among Arab populations [Charfeddine et al 2006].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TAT*.

Differential Diagnosis

Hypertyrosinemia. Other causes of hypertyrosinemia include genetic tyrosine metabolism disorders (see Table 3) and acquired conditions such as the following:

- Transient tyrosinemia of the newborn
- Immature liver
- Hypertyrosinemia due to liver disease

Corneal lesions. Because ocular features are often the initial manifestations of tyrosinemia type II, pseudodendritic keratitis is often mistaken for herpes simplex keratitis.

Genetic disorders of interest in the differential diagnosis of tyrosinemia type II are listed in Table 3.

Table 3. Genes of Interest in the Differential Diagnosis of Tyrosinemia Type II

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/tyrosinemia type II	Distinguishing from tyrosinemia type II
FAH	Tyrosinemia type I	AR	Hypertyrosinemia	• Liver & kidney dysfunction • ↑ succinylacetone concentration in blood & urine • Hypoglycemia • High alkaline phosphatase • Moderately ↑ plasma concentration of tyrosine, phenylalanine, & other amino acids, esp methionine (due to secondary inhibition of methionine adenosyltransferase)
HPD	Tyrosinemia type III (OMIM 276710)	AR	Hypertyrosinemia	• Moderately ↑ plasma concentration of tyrosine • Low activity of enzyme HPD in liver biopsy • Ataxia & seizures • Absence of skin & ocular lesions
MBTPS2 *PERP* *TRPV3*	Olmsted syndrome (OMIM PS614594)	AD XL	Palmoplantar keratoderma w/ periorificial keratotic plaques	• Sparse hair & onychodystrophy • Joint abnormalities • Hypotrichosis

AD = autosomal dominant; AR = autosomal recessive; HPD = 4-hydroxyphenylpyruvic acid dioxygenase; MOI = mode of inheritance; XL = X-linked

Management

No clinical practice guidelines for tyrosinemia type II have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

When tyrosinemia type II is suspected during the diagnostic evaluation due to high levels of tyrosine (typically >500 µmol/L and may exceed 1,000 µmol/L), metabolic treatment should be initiated immediately (see Targeted Therapy).

Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require a multidisciplinary approach including multiple subspecialists, with oversight and expertise from a specialized metabolic center and the involvement of a dietitian with specialized training.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with tyrosinemia type II, the evaluations summarized Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Tyrosinemia Type II: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	To assess for epiphora, photophobia, & blepharospasm & more complex findings (e.g., corneal clouding, corneal lesions, & dendritic ulcers) that may require referral for subspecialty care &/or low vision services
Skin	Skin exam	To assess for hyperkeratotic plaques on soles, palms (esp thenar & hypothenar areas), & fingertips

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Metabolic	Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian	To initiate dietary restriction of tyrosine & phenylalanine
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of tyrosinemia type II to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Restriction of dietary tyrosine and phenylalanine. Targeted therapy for tyrosinemia type II aims to reduce plasma tyrosine concentration and consists of a low-protein diet with age-appropriate amino acid (tyrosine- and phenylalanine-free), vitamin, and mineral supplements.

- Treatment is a lifelong tyrosine- and phenylalanine-restricted diet. Initially this is in the form of a prescribed infant formula. After weaning, a low-protein diet is prescribed and age-appropriate amino acid (tyrosine- and phenylalanine-free), vitamin, and mineral supplements are given.
- A diet that is low in tyrosine and phenylalanine can help correct chemical abnormalities and lead to significant improvement in skin and eye lesions.
- Early dietary restriction of tyrosine can help prevent intellectual disability [El-Shabrawi & Kamal 2013, Murphy 2016].

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Tyrosinemia Type II: Treatment of Manifestations

Principle/Manifestation	Treatment	Considerations/Other
Ocular manifestations	• Lubricating eye drops & ointment • Ocular surgery to treat bilateral corneal ulcers	Ocular manifestations improve & may resolve w/ dietary restriction of tyrosine & phenylalanine (see Targeted Therapy).

Table 5. continued from previous page.

Principle/Manifestation	Treatment	Considerations/Other
Skin manifestations	Pyridoxine phosphate or systemic retinoid may be beneficial.	Skin manifestations often resolve w/dietary restriction of tyrosine & phenylalanine (see Targeted Therapy).
Developmental delay / Intellectual disability	Developmental & educational support as needed	

Surveillance

In addition to regular evaluations by a metabolic specialist and metabolic dietician, the evaluations summarized in Table 6 are recommended to monitor existing manifestations, the individual's response to targeted therapy and supportive care, and the emergence of new manifestations.

Table 6. Tyrosinemia Type II: Recommended Surveillance

Manifestation	Evaluation	Frequency/Comment
Metabolic/ Nutrition	Quantitative analysis of plasma tyrosine & phenylalanine concentrations	At each visit
Ocular manifestations	Eval by ophthalmologist to assess for epiphora, photophobia, blepharospasm, & keratitis	Annually or as needed
	Eval by ophthalmic subspecialist to assess for more complex findings (e.g., corneal clouding, pseudodendritic corneal lesions, dendritic ulcers, & corneal or conjunctival plaques)	Annually or as recommended by ophthalmologist
Skin manifestations	Skin assessment for hyperkeratotic plaques	As clinically indicated
Delayed acquisition of developmental milestones	• Monitoring of developmental milestones • Neuropsychological testing using age-appropriate standardized assessment batteries • Standardized quality-of-life assessment tools for affected persons & parents/caregivers	Annually or at each visit
Nutritional deficiencies	Measurement of plasma calcium, phosphorus, & 25-hydroxyvitamin D concentrations	Annually or as clinically indicated

Agents/Circumstances to Avoid

Avoid increased dietary protein.

Evaluation of Relatives at Risk

Testing of at-risk sibs of any age is warranted to allow for early diagnosis and treatment of tyrosinemia type II.

Prenatal testing of a fetus at risk. When the pathogenic variants causing tyrosinemia type II in the family are known, prenatal testing of fetuses at risk may be performed via amniocentesis or chorionic villus sampling to facilitate institution of treatment at birth.

Newborn sib. If prenatal testing was not performed – in parallel with newborn screening – testing for the familial *TAT* pathogenic variants or measurement of plasma tyrosine concentration and excretion of 4-hydroxyphenylpyruvate, 4-hydroxyphenyllactate, and 4-hydroxyphenylacetate on urine organic acid analysis can be performed.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Infants born to women with untreated tyrosinemia type II may have an increased risk of intrauterine growth deficiency and developmental delay [Cerone et al 2002]. Careful dietary control of plasma tyrosine concentration during pregnancy is recommended.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Tyrosinemia type II is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *TAT* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *TAT* pathogenic variant and allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *TAT* pathogenic variant, each sib of an affected individual has at conception 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has tyrosinemia type II or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *TAT*.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *TAT* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk sibs for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of individuals affected with tyrosinemia type II and individuals known to be carriers of a *TAT* pathogenic variant, particularly if consanguinity is likely and/or both partners are of the same ancestry (see Prevalence). *TAT* founder variants have been identified in several populations (see Table 7).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *TAT* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Tyrosinemia
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration

newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Tyrosinemia Type II: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TAT	16q22.2	Tyrosine aminotransferase	TAT database	TAT	TAT

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Tyrosinemia Type II (View All in OMIM)

276600	TYROSINEMIA, TYPE II; TYRSN2
613018	TYROSINE AMINOTRANSFERASE; TAT

Molecular Pathogenesis

TAT encodes the enzyme tyrosine aminotransferase (TAT), the first in a series of five enzymes that catalyze reversible transamination of tyrosine to 4-hydroxyphenylpyruvate. Reduced TAT function results in the accumulation of upstream byproducts of tyrosine and phenylalanine.

TAT is a homodimer and is composed of two identical polypeptide chains. It is expressed in the liver, kidneys, and brain. The enzyme has the highest activity in the liver. In TAT, the first 38 amino acids may not be involved in enzyme dimerization and are not required in the active site stability and enzyme-substrate interactions. This N-terminal fragment, however, is required for targeting by the ubiquitin-proteasome pathway, which degrades proteins to small peptides.

Mechanism of disease causation. Loss of function

Table 7. *TAT* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000353.3 NP_000344.1	c.169C>T	p.Arg57Ter	• Founder variant identified in northern Italy (Lombardy & Tuscany) • Most common variant reported to date (10 affected persons from 3 families) [Peña-Quintana et al 2017, Beyzaei et al 2022]
	c.452G>A	p.Cys151Tyr	Founder variant identified in Tunisian population [Charfeddine et al 2006]
	c.889C>T	p.Arg297Ter	Founder variant identified in Lebanese population [Peña-Quintana et al 2017]
	c.1217C>T	p.Pro406Leu	Founder variant identified in Gran Canaria population [Peña-Quintana et al 2017]
	c.1249C>T	p.Arg417Ter	Founder variant identified in Palestinian population [Maydan et al 2006]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Dr Bita Geramizadeh is a molecular pathologist. Her clinical and research interests include transplant hepatology, acute liver failure, and inherited metabolic disorders of the liver. She is the author of numerous (more than 450) original manuscripts and reviews on the subject. Her research has been in both the clinical and basic science spheres. Dr Geramizadeh has launched and established a transplant research center and national registry trial for inherited metabolic disorders with a data coordinating center at the Shiraz University of Medical Sciences. She is the vice president of the Association for Inherited Metabolic Disorders (Ibn Sina).

Dr Seyed Mohsen Dehghani is a professor of pediatric gastroenterology and hepatology with experience in inherited disorders and more than 200 highly cited published papers.

Dr Zahra Beyzaei is a molecular and biochemical geneticist. She is a staff scientist in the transplant research center at the Shiraz University of Medical Sciences. She would be happy to communicate with persons who have any questions regarding tyrosinemia type II disease. Contact Dr Beyzaei to inquire about review of *TAT* variants of uncertain significance.

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