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NLM Citation: Cali E, Dominik N, Manole A, et al. Riboflavin Transporter Deficiency. 2015 Jun 11 [Updated 2021 Apr 8]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Riboflavin Transporter Deficiency

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Created: June 11, 2015; Updated: April 8, 2021.

Summary

Clinical description

Riboflavin transporter deficiency (RTD), comprising RTD2 and RTD3 (caused by biallelic pathogenic variants in *SLC52A2* and *SLC52A3*, respectively) is a rare neurologic condition characterized by progressive peripheral and cranial neuronopathy that causes muscle weakness (and consequent respiratory compromise), vision loss, deafness, and sensory ataxia. Onset is usually in infancy or in childhood; however, on occasion individuals with genetically confirmed RTD present as adults and even as late as the fifth decade. When untreated, most infants with riboflavin transporter deficiency rapidly become ventilator dependent and die in the first decade of life.

In the majority of affected individuals, the initial finding is sensorineural hearing loss, which is usually progressive and severe. The time between the onset of hearing loss and the development of other manifestations varies but is usually one to two years. In some individuals an intercurrent event, usually an injury or infection, appears to precipitate the initial manifestations or worsen existing findings.

One case report (which requires additional confirmation) suggests that biallelic expression of pathogenic variants in *SLC52A1* (i.e., RTD1) is associated with infantile-onset of riboflavin-responsive seizures associated with hyperammonemia.

Diagnosis/testing

The diagnosis of RTD2 and RTD3 is established in an individual with suggestive findings and biallelic pathogenic variants in either *SLC52A2* or *SLC52A3*, respectively, identified on molecular genetic testing.

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Management

Treatment of manifestations: High-dose oral supplementation of riboflavin (vitamin B_2) between 10 mg and 50 mg/kg/day improves symptoms and signs on clinical examination, improves objective testing (vital capacity, brain stem evoked potentials, nerve conduction studies), and normalizes acylcarnitine levels. Liquid riboflavin is available but is often difficult to obtain; therefore, riboflavin capsules are often opened and mixed with food such as yogurt. The amount of riboflavin supplementation varies depending on the severity of the disease and response of the individual to the treatment. When riboflavin supplementation is given earlier in the disease course, the response can be very good; if given later in the disease course, the response is less, likely reflecting the effect of existing neuronal damage.

Because oral riboflavin supplementation is effective (and possibly lifesaving), it should begin as soon as a riboflavin transporter deficiency is suspected and continued lifelong unless molecular genetic testing fails to identify biallelic pathogenic variants in either *SLC52A2* or *SLC52A3*.

Supportive care includes respiratory support; physiotherapy to avoid contractures; occupational therapy to support activities of daily living; orthotics for limb and trunk bracing; speech and language therapy to avoid choking and respiratory problems; wheelchair as needed; low vision aids as needed; routine management of scoliosis to avoid long-term respiratory problems; and routine management of depression.

Surveillance: At three months and six months after initiation of riboflavin supplementation, routine follow-up physical and neurologic examinations, measurement of blood riboflavin/FAD/FMN, and analysis of blood acylcarnitine profile. Thereafter, follow up is usually biannually in older individuals and more frequently in younger children.

Agents/circumstances to avoid: Dietary restriction of riboflavin and strenuous physical activity.

Evaluation of relatives at risk: When the *SLC52A2* or *SLC52A3* pathogenic variants in the family are known, it is appropriate to perform molecular genetic testing on the older and younger sibs of an affected individual to identify as early as possible those who are affected and would benefit from early treatment with riboflavin supplementation and monitoring for potential complications of the disorder.

Pregnancy management: A diet rich in ribolflavin is recommended for women who have RTD or are heterozygous for a pathogenic variant in either *SLC52A2* or *SLC52A3.* If necessary, riboflavin supplements should be taken before and during pregnancy and when breast feeding to avoid inducing riboflavin deficiency in the baby.

Genetic counseling

RTD caused by biallelic pathogenic variants in either *SLC52A2* (RTD2) or *SLC52A3* (RTD3) is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an RTD-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial RTD-causing pathogenic variants. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if both RTD-causing pathogenic variants have been identified in an affected family member.

GeneReview Scope

Riboflavin transporter deficiency (RTD), comprising RTD2 and RTD3 (caused by biallelic pathogenic variants in *SLC52A2* and *SLC52A3,* respectively*)* is a well-defined phenotypic continuum of motor, sensory, and cranial nerve neuronopathy that encompasses the previously recognized phenotypes Brown-Vialetto-Van Laere (BVVL)

syndrome and Fazio-Londe syndrome [Green et al 2010, Johnson et al 2010, Johnson et al 2012, Foley et al 2014].

One case report (which requires additional confirmation) suggests that biallelic expression of pathogenic variants in *SLC52A1* (i.e., RTD1) is associated with infantile onset of riboflavin-responsive seizures associated with hyperammonemia [Kang et al 2020].

Diagnosis

Suggestive Findings

Riboflavin transporter deficiency 2 (RTD2) and **riboflavin transporter deficiency 3 (RTD3) should be suspected** in individuals with the following clinical, neurophysiologic, brain MRI, and laboratory findings.

Clinical features. Progressive, usually childhood onset (range: a few months to early teen years; very rarely adulthood) of the following:

- **Cranial neuronopathy**
  - Very frequently affecting cranial nerves II (optic atrophy with bilateral symmetric optic nerve pallor, variably associated nystagmus) and VIII (sensorineural hearing loss is one of the initial findings)
  - Frequently affecting cranial nerves IX and X (bulbar palsy), and XII (tongue fasciculations, weakness, and atrophy)
  - Occasionally affecting cranial nerves III (ptosis) and VII (facial weakness)
- **Motor neuropathy**
  - Affecting upper limbs more than lower limbs, resulting in weakness involving proximal and distal limb musculature, often with severe distal wasting. Deep tendon reflexes are consistently absent
  - Resulting in axial weakness, manifest as severe trunk and neck weakness requiring trunk bracing and difficulty with holding the head up
  - Resulting in paralysis of the diaphragm, which can result in respiratory insufficiency
- **Sensory neuropathy** manifesting as gait ataxia

Cognition is usually preserved.

Neurophysiologic studies

- Electromyogram shows chronic partial denervation.
- Nerve conduction studies show a sensory > motor axonal neuronopathy. Motor nerve conduction velocities are usually normal.
- Sensory nerve action potentials are often absent.
- Visual evoked potentials are frequently abnormal.
- Brain stem audiometry evoked response has universally shown sensorineural deafness.
- EEG (electroencephalogram) may show an excess of theta activity or slow waves [Rosemberg et al 1982].

Brain MRI. Usually normal; however, in a small number of affected individuals cerebellar atrophy and abnormal T_2-weighted hyperintensity in the cerebellar, cortical, subcortical, and brain stem regions are observed.

Laboratory findings

- Acylcarnitine profile in blood is abnormal with accumulation of short- and medium-chain (and sometimes long-chain) acylcarnitine in some but not all individuals with molecularly confirmed RTD [Bosch et al 2012, Foley et al 2014].

- Note: Even in children with RTD diagnosed in the first months of life with abnormal acylcarnitine profiles, newborn screening bloodspots demonstrated normal acylcarnitine profiles, probably due to sufficient maternal riboflavin supply to the unborn infant [Bosch et al 2011].

Riboflavin transporter deficiency 1 should be considered (based on preliminary observations) in an infant with recurrent seizures with unexplained hyperammonemia [Kang et al 2020].

As soon as riboflavin transporter deficiency is suspected, begin oral riboflavin supplementation, an effective (and possibly lifesaving) treatment, and continue it lifelong unless molecular genetic testing fails to identify biallelic pathogenic variants in either *SLC52A2* or *SLC52A3*.

Establishing the Diagnosis

The diagnosis of riboflavin transporter deficiency (RTD) **is established** in a proband with suggestive clinical, neurophysiologic, neuroimaging, and laboratory findings and biallelic pathogenic (or likely pathogenic) variants in either *SLC52A2* (RTD2) or *SLC52A3* (RTD3) on molecular genetic testing (Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of either biallelic *SLC52A2* or *SLC52A3* variants of uncertain significance (or of one known *SLC52A2* or *SLC52A3* pathogenic variant and one *SLC52A2* or *SLC52A3* variant of uncertain significance) does not establish or rule out a diagnosis of the disorder. (3) In the only child reported to date with presumed RTD1, the complex genotype requires further investigation (see Molecular Genetics).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using multigene panel testing (see Option 1), whereas those in whom the diagnosis of RTD has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Hearing loss panels, myopathy panels, motor neuron disease panels, inborn error of metabolism panels, neuropathy panels and other multigene panels now include *SLC52A2* and *SLC52A3* along with other genes of interest (see Differential Diagnosis). Multigene panels are 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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 Riboflavin Transporter Deficiency (RTD)

Gene [1]	Proportion of RTD Attributed to Pathogenic Variants in Gene [2]	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
SLC52A2	~44%	60/60 probands [7]	No large deletions/duplications [8]
SLC52A3	~56%	76/76 probands [9]	No large deletions/duplications [8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Abbas et al [2018], Bamaga et al [2018], Garg et al [2018], Gorcenco et al [2019], Mutlu et al [2019], O'Callaghan et al [2019], Shi et al [2019], Carreau et al [2020], Kranthi et al [2020], Pillai et al [2020], Rabbani et al [2020], Gayathri et al [2021], Khani et al [2021]
3. See Molecular Genetics for information on variants.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
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 gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Kang et al [2020]
7. Bamaga et al [2018], Gorcenco et al [2019], O'Callaghan et al [2019], Shi et al [2019], Carreau et al [2020], Kranthi et al [2020], Pillai et al [2020]
8. No large deletions/duplications have been identified using chromosome microarray analysis (CMA) [Amir et al 2020].
9. Abbas et al [2018], Garg et al [2018], Mutlu et al [2019], O'Callaghan et al [2019], Carreau et al [2020], Rabbani et al [2020], Gayathri et al [2021], Khani et al [2021]

Clinical Characteristics

Clinical Description

Riboflavin transporter deficiency 2 (caused by biallelic *SLC52A2* pathogenic variants) and riboflavin transporter deficiency 3 (caused by biallelic *SLC52A3* pathogenic variants) are clinically characterized by motor neuropathy, sensory neuropathy, and cranial neuronopathy [Bandettini Di Poggio et al 2014, Foley et al 2014, Manole et al 2014]. Motor neuropathy manifests as proximal and distal limb weakness (often with severe distal wasting and breathing problems due to paralysis of the diaphragm), sensory neuropathy as gait ataxia, and cranial neuronopathy as optic atrophy, sensorineural hearing loss, and bulbar palsy.

In contrast, RTD1 (possibly caused by biallelic *SLC52A1* pathogenic variants), reported in a single case report, may manifest in infancy as generalized or focal tonic-clonic seizures, metabolic acidosis, and hyperammonemia, responsive to riboflavin supplementation [Kang et al 2020].

Riboflavin Deficiency 2 and 3

While most individuals with RTD2 or RTD3 (caused by biallelic pathogenic variants in *SLC52A2* or *SLC52A3*, respectively) present early in life, late onset (ages 10-30 years) has been reported in persons with RTD3. Males and females are equally affected. Table 2 summarizes the frequency of select features in 136 individuals with molecularly confirmed RTD2 and RTD3.

Table 2. Riboflavin Transporter Deficiency 2 and 3: Select Features

Feature		% of Persons w/Feature		
		RTD2 (n=60)	RTD3 (n=76)	RTD2 & RTD3 (n=136)
Age of onset		Mean 3.2 yrs	Mean 8.5 yrs	
Peripheral neuropathy		92%	84%	80%-90%
Motor neuropathy (weakness, hypotonia)		77%	80%	80%
Sensory neuropathy (gait abnormality, ataxia)		60%	13%	34%
Cranial neuronopathy	**Optic nerve atrophy / ophthalmoplegia**	43%	19%	
	Facial weakness	34%	55%	
	Hearing loss	85%	82%	
	Bulbar palsy	55%	62%	
Respiratory involvement		48%	57%	
Feeding difficulties		23%	41%	
Abnormal cranial MRI		19% (7/37)	22% (13/60)	

Based on O'Callaghan et al [2019]
RTD2 = riboflavin transporter deficiency caused by biallelic *SLC52A2* pathogenic variants; RTD3 = riboflavin transporter deficiency caused by biallelic *SLC52A3* pathogenic variants

The phenotype of individuals with riboflavin deficiency 2 and 3 at onset usually includes hearing impairment and/or sensory ataxia, followed by progressive upper limb weakness, optic atrophy, bulbar weakness, and respiratory failure.The time between the disease onset and the development of other manifestations varies but is usually one to two years. In some individuals an intercurrent event, usually an injury or infection, appears to precipitate the initial manifestations or worsen existing findings [Bandettini Di Poggio et al 2014].

Note: When the onset occurs in infancy, after a symptom-free first few weeks (or in some cases months) of life, infants become floppy with failure to thrive and rapidly developing respiratory insufficiency due to paralysis of the diaphragm, followed (in order of appearance) by:

- Infantile- or early childhood-onset nystagmus
- Early childhood-onset sensory (gait) ataxia
- Early-childhood onset progressive and severe sensorineural hearing loss
- Weakness and atrophy of the upper limbs (first distally then proximally)
- Weakness of neck extensors and later trunk muscles
- Tongue fasciculations and atrophy with increased swallowing problems
- Respiratory insufficiency due to muscle weakness

Other initial presenting features can include stridor, slurring of speech, and facial weakness. Visual problems due to optic atrophy are common [Bandettini Di Poggio et al 2014, Foley et al 2014, Manole et al 2014, Srour et al 2014, Bamaga et al 2018, Amir et al 2020, Kranthi et al 2020].

Motor neuropathy has been described in 80% of affected individuals. Limb weakness is frequently accompanied by atrophy and involves the upper extremities more than the lower extremities in RTD2. Many also developed axial weakness, with severe weakness of neck extensor and trunk muscles.

Electrophysiologic studies, when performed, were suggestive of peripheral neuropathy in most individuals with RTD, showing chronic denervation and anterior horn dysfunction. Nerve conduction studies suggest an axonal rather than demyelinating neuropathy.

Sensory neuropathy was reported in 34% of individuals. However, most individuals with gait abnormalities/ataxia had RTD2, while only 13% of those with RTD3 had sensory symptoms. Vibration and proprioception are the most severely affected.

Ophthalmologic involvement, the result of optic nerve atrophy, usually manifests as reduced visual acuity and visual field impairment; a few individuals also experience color blindness. Vision loss can progress rapidly or slowly [Bamaga et al 2018, Gorcenco et al 2019, Kranthi et al 2020].

When present, torsional/horizontal nystagmus is one of the early signs of optic atrophy prior to vision loss; thus, RTD should be considered in children with new-onset nystagmus [Amir et al 2020].

Facial weakness. Fifty-five per cent of individuals with RTD3 presented with facial weakness caused by degeneration of cranial nerve VII; this feature was rarely observed in RTD2.

Hearing loss, a presenting manifestation in many individuals, falls within the auditory neuropathy spectrum disorder (ANSD) and is a consequence of cranial nerve VIII degeneration. Otoacoustic emissions (OAE) are usually present while auditory brain stem reflexes (ABR) are abnormal or absent. The hearing loss is usually progressive and severe and can result in complete bilateral deafness (hearing loss >81 decibels). The time between the onset of ANSD and the development of other manifestations of RTD varies but is usually one to two years. Very rarely affected individuals do not develop any hearing impairment, and sometimes it appears later in the disease course [Anderson et al 2019, Mutlu et al 2019, Amir et al 2020].

Bulbar palsy. Signs and symptoms of bulbar palsy are common, being reported in more than 50% of individuals. Most individuals report dysarthria and feeding difficulties resulting from dysphagia. Tongue wasting/fasciculations are common on neurologic examination.

Respiratory involvement, a consequence of neurogenic diaphragm paralysis, is often an early manifestation. Many affected individuals present with breath-holding spells within the first year of the disease course. Therefore, respiratory insufficiency, secondary to muscle weakness, can also be one of the late manifestations of untreated RTD. Artificial respiratory support may be required.

Other features variably seen:

- **Epilepsy.** Some affected individuals had a single seizure-like episode that resolved before the diagnosis of RTD was established and before beginning treatment with riboflavin [Pillai et al 2020, Rabbani et al 2020].
- **Progressive mental and motor regression** [Shi et al 2019, Pillai et al 2020]
- **Anemia.** Although two individuals had riboflavin-responsive severe macrocytic anemia, riboflavin deficiency had been previously associated with mild-moderate anemia [Amir et al 2020, Pillai et al 2020].
- **Depression.** To date, only associated with RTD3 [Rabbani et al 2020, Khani et al 2021]

While the RTD2 and RTD3 phenotypes are difficult to differentiate, in RTD2 early-onset weakness in the upper limbs and neck is almost invariable, in contrast to RTD3 or genetically unclassified Brown-Vialetto-Van Laere (BVVL) syndrome, in which the onset of weakness is often more generalized [Green et al 2010, Bosch et al 2011, Bosch et al 2012, Foley et al 2014].

Life expectancy. Untreated, most infants diagnosed with RTD rapidly become ventilator dependent (often for some years at home or in intensive care units) and most die before age 12 years [Bandettini Di Poggio et al 2014, Foley et al 2014, Manole et al 2014].

Previous data suggest that in 70% of individuals receiving riboflavin supplementation, muscle strength, motor abilities, respiratory function, and cranial nerve deficits improve [O'Callaghan et al 2019]. Death was reported in some individuals if the treatment was discontinued or started too late in the disease course [Jaeger & Bosch 2016].

With improved disease management and riboflavin treatment (see Management), life span is likely to increase; however, the experience with riboflavin supplementation has only been since 2010 [Bosch et al 2011, Horvath 2012, Bandettini Di Poggio et al 2014, Foley et al 2014, Manole et al 2014].

Pathology. Few pathologic descriptions are available. Sural nerve biopsies in individuals with RTD2 and RTD3 previously showed axonal neuropathy and degeneration. In one study, clinical manifestations and MRI findings supported neuronal loss and degeneration in cranial nerve nuclei and tracts and in the brain stem, cerebellum, and spinal cord of individuals with RTD3 [O'Callaghan et al 2019].

Genotype-Phenotype Correlations

See Table 2 for a comparison of select clinical findings by gene.

Nomenclature

Other terms used to refer to riboflavin transporter deficiency:

- Brown-Vialetto-Van Laere (BVVL) syndrome (corresponding with either *SLC52A3*- or *SLC52A2*-related disease) and Fazio-Londe syndrome (a BVVL-like syndrome without deafness caused by *SLC52A3* pathogenic variants)
- *SLC52A2*-related riboflavin transporter deficiency may be referred to as spinocerebellar ataxia with blindness and deafness type 2 (SCABD2)[Babanejad et al 2018].

Prevalence

Although riboflavin transporter deficiency (RTD) is relatively rare, the advent of molecular genetic testing has improved diagnostic capabilities, making RTD appear more prevalent than previously thought [Foley et al 2014].

It is difficult to establish the prevalence of RTD. It may be underdiagnosed and misdiagnosed; however, it is estimated that RTD affects one in 1,000,000 people in the general population.

SLC52A2. The founder pathogenic variant c.916G>A;p.Gly306Arg has been described in the Lebanese population [Foley et al 2014, Srour et al 2014].

SLC52A3. No founder variants have been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known (or presumed) to be associated with biallelic germline pathogenic variants in *SLC52A1*, *SLC52A2,* or *SLC52A3*.

Sporadic tumors (including esophageal squamous cell carcinomas) occurring as single tumors in the absence of any other findings of riboflavin transporter deficiency frequently harbor somatic pathogenic variants in *SLC52A3* that are **not** present in the germline; thus, predisposition to these tumors is not heritable.

Differential Diagnosis

Table 3. Genes and Disorders of Interest in the Differential Diagnosis of Riboflavin Transporter Deficiency

Gene(s)	Disorder	MOI	Clinical Features	Distinguishing Features
AAAS	Achalasia-addisonianism-alacrimia syndrome (AAAS) (OMIM 231550)	AR	Prominent bulbar features; however, achalasia, alacrimia, adrenal problems & autonomic symptoms are the primary manifestations. [1]	Persons w/AAAS have an abnormal, small fissured tongue similar to that in ALS. [2]
BSCL2 *GARS1*	*BSCL2*- or *GARS1*-related distal hereditary motor neuropathy (HMN)	AD	Axonal neuropathy w/upper limb-predominant involvement	*BSCL2*- & *GARS1*-related distal HMN are not assoc w/optic atrophy, hearing loss, or bulbar dysfunction. [3]
C9orf72 *FUS* *SOD1* *TARDBP* *UBQLN2* [4] (~30 genes [5])	Amyotrophic lateral sclerosis (ALS)	AD AR XL [6]	Progressive, fatal, neurodegenerative disease involving both brain & spinal cord. Death most often results from failure of respiratory muscles. RTD has been described as an AR juvenile form of ALS since both RTD & ALS have bulbar & LMN involvement.	ALS features that differentiate it from RTD: absence of hearing loss, less prominent bulbar presentations, later onset, asymmetric early presentations, & usually more rapid progression [7]
ETFA *ETFB* *ETFDH*	Neonatal-onset multiple acyl-CoA dehydrogenase deficiency (MADD)	AR	Usually fatal; severe hypoketotic hypoglycemia, metabolic acidosis, multisystem involvement, & excretion of large amts of fatty acid- & amino acid-derived metabolites (biochemical profile similar to RTD)	MADD usually presents w/metabolic decompensation or muscle weakness. Hearing loss has not been described in MADD.
IGHMBP2	Spinal muscular atrophy with respiratory distress 1 (SMARD1) (OMIM 604320)	AR	Typically early-onset (infantile onset is most common) severe axonal polyneuronopathy w/distal muscle & lower-limb weakness & respiratory failure due to diaphragmatic paralysis; ± autonomic involvement, pneumonia, & hypotonia	Deafness has not been described in SMARD1. [8]
SMN1	Spinal muscular atrophy	AR	Muscle weakness & atrophy due to progressive degeneration & irreversible loss of anterior horn cells in spinal cord & brain stem nuclei. Onset of weakness ranges from before birth to adulthood; weakness is symmetric, proximal > distal, & progressive.	RTD is limited to lower cranial nerves & progresses to death in 1-5 yrs if not treated.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Distinguishing Features
VWA1	10-bp repeat expansion in *VWA1* assoc w/HMN	AR	Axonal motor neuropathy w/upper & lower limb involvement, distal & proximal wasting, & tongue fasciculations/atrophy [9]	Unlike RTD, which has predominantly upper limb involvement, *VWA1*-assoc HMN more frequently affects lower limbs (upper limb involvement is usually secondary) & most affected persons present w/foot deformities. *VWA1*-assoc HMN is not assoc w/other bulbar manifestations, optic atrophy, or hearing loss. [9]

AD = autosomal dominant; ALS = amyotrophic lateral sclerosis; AR = autosomal recessive; LMN = lower motor neuron; MOI = mode of inheritance; RTD = riboflavin transporter deficiency; XL = X-linked
1. Flokas et al [2019]
2. Manole et al [2014]
3. Rossor et al [2012]
4. Of note, a *UBQLN1* variant was identified in an individual with a clinical diagnosis of Brown-Vialetto-Van Laere (BVVL) syndrome and atypical early-onset ALS with bulbar palsy & hearing loss. Although the pathogenicity of this variant is uncertain, this finding highlights the overlap of the BVVL and ALS phenotypes [González-Pérez et al 2012].
5. The ALS-related genes that have been identified and that account for at least half of ALS that occurs in families with a history of more than one affected relative. Thirty genes have been associated with genetic ALS; *C9orf72*, *FUS*, *SOD1*, and *TARDBP* are the four most robust and common genes.
6. Determination of the mode of inheritance is based on family history and molecular genetic testing.
7. Yedavalli et al [2018], Khani et al [2021]
8. Saladini et al [2020]
9. Pagnamenta et al [2021]

Transient neonatal riboflavin deficiency. In the reports of transient riboflavin deficiency in two newborns of mothers heterozygous for an *SLC52A1* pathogenic variant, the mothers were asymptomatic whereas the infants had clinical and biochemical features of multiple acyl-CoA dehydrogenase deficiency (MADD) that resolved with riboflavin supplementation. When riboflavin supplementation was discontinued, children both showed normal psychomotor development. In the report of Ho et al [2011] only the mother was heterozygous for the *SLC52A1* variant, whereas in the report of Mosegaard et al [2017], both the mother and infant were heterozygous.

Disorders of unknown cause to consider in the differential diagnosis of riboflavin transporter deficiency include the following:

- **Nathalie syndrome** (OMIM 255990) has no lower cranial nerve signs but includes deafness and weakness in addition to spinal muscular atrophy (SMA), cataracts, hypogonadism, and cardiac conduction defects.
- **Madras motor neuron disease (MMND)** (also referred to as Madras pattern motor neuron disease), a rare disorder with early-onset progressive neuromuscular disease with a relatively benign course, has predominantly been observed in southern India. Multiple cranial nerve palsies involve predominately the seventh and ninth to 12th cranial nerves. Hearing impairment is present in all; optic atrophy is present in some. While the majority are simplex cases (i.e., a single occurrence in a family), a few familial cases have been reported. The etiology is unknown; pathogenic variants in *SLC52A2* and *SLC52A3* as well as *C9orf72* have been excluded [Nalini et al 2013].
- **Facial-onset sensory motor neuronopathy (FOSMN)** is a rare, slowly progressive, lower motor neuron disease with sensory compromise, involving mainly the face, bulbar region, and upper limbs. FOSMN syndrome represents a primary neurodegenerative variant of motor neuron disease with TAR DNA-binding protein (TDP)-43 aggregation. While most individuals have an insidious clinical course over the fifth to seventh decades of life, childhood and juvenile onset have been reported [Pinto et al 2019].

Management

No clinical practice guidelines for riboflavin transporter deficiency have been published.

Note: Because *SLC25A1*-related riboflavin-responsive hyperammonemic seizures have been described in a single individual to date [Kang et al 2020], current information is insufficient to provide management recommendations.

When riboflavin transporter deficiency is suspected during the diagnostic evaluation, begin oral riboflavin supplementation (see Treatment of Manifestations) immediately and continue it lifelong unless the diagnosis is excluded by molecular genetic testing.

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Riboflavin Transporter Deficiency 2 and 3

System/Concern	Evaluation	Comment
Constitutional	Measure height, weight, & head circumference.	Weight loss reported in some persons
Motor/sensory neuropathy	Neuromuscular specialist	Assess proximal & distal muscle strength (Rankins scale, MRC strength scale), sensory loss, & gait disturbance (SARA ataxia scale).
Epilepsy	Medical history; EEG	
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To assess: • Gross motor & fine motor skills • Spine for scoliosis • Mobility, ADL, & need for bracing &/or adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Optic atrophy	Experienced ophthalmologist	Assess extraocular movement, best corrected visual acuity, color vision testing (Farnsworth test), visual field testing (Goldman perimetry), visual evoked potentials, OCT, fundus exam
	Vision specialist	Assess for need for visual aids, preferential seating in school.
Sensorineural hearing impairment	Audiologic exam	Incl: • ABRs to confirm pathology & provide baseline • Evoked OAEs to identify type of hearing impairment • Speech discrimination tests • Behavioral tests
Speech & language	Speech & language assessment	As indicated
Bulbar dysfunction		Assess for swallowing disorder (dysphagia).
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	Assess aspiration risk & nutritional status; consider eval for gastric tube placement in those w/dysphagia &/or aspiration risk.
Autonomic dysfunction	Physical exam, medical history	Assess heart rate, temperature, medical history for syncope.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Respiratory involvement	Pulmonary consultation	Sleep study / polysomnography
Depression	Psychiatric consultation	If present
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of riboflavin transporter deficiency in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ABR = auditory evoked brain stem response; ADL = activities of daily living; MOI = mode of inheritance; OAE = otoacoustic emission; OCT = optical coherence tomography; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

High-dose supplementation of riboflavin (vitamin B_2). Riboflavin supplementation is effective and possibly lifesaving. It is recommended that treatment begin as soon as RTD is suspected and continue lifelong unless molecular genetic testing fails to identify biallelic pathogenic variants in either *SLC52A2* or *SLC52A3*. Before initiating riboflavin supplementation, perform the assessments in Table 4.

High-dose supplementation of riboflavin (10-50 mg/kg/day) has been effective in individuals with molecularly confirmed riboflavin transporter deficiency and, also in some individuals in whom the genetic basis of riboflavin transporter deficiency has not been established.

The amount of riboflavin given varies depending on the severity and response of the individual to the treatment. It has been reported that doses <10 mg/kg/day are ineffective [O'Callaghan et al 2019], whereas doses >80 mg/kg/day may have minimal side effects.

Oral riboflavin supplementation should be given in gradually increasing doses in order to establish the optimal dose:

1. Riboflavin 10 mg/kg/day in 3 doses for 1 month
2. Riboflavin 20 mg/kg/day in 3 doses for 1 month
3. Riboflavin 30 mg/kg/day in 3 doses for 1 month
4. Riboflavin 40 mg/kg/day in 3 doses for 1 month
5. Riboflavin 50 mg/kg/day in 3 doses for 1 month

Note: Theoretically, parenteral administration of riboflavin may increase uptake and effect [Gorcenco et al 2019].

Side effects reported after high-dose riboflavin supplementation, when present, can include diarrhea, increased urination, and urine discoloration. Allergic reactions have been described rarely. Side effects, problems, or deterioration at any point require discussion with the treating clinician.

Open-label studies have reported improvement of motor symptoms or neurophysiologic measurements or hearing level in a third of individuals treated with up to 500 mg riboflavin three times per day. However, no randomized controlled trials have been performed [Foley et al 2014, Jaeger & Bosch 2016].

Positive clinical response to the treatment could occur with some latency; thus, riboflavin therapy should be continued in all suspected or genetically diagnosed RTD cases even when there is no apparent initial clinical improvement [O'Callaghan et al 2019].

Better response to the treatment is reported when given earlier in life or in the disease course. Adulthood-onset or late treatment are frequently associated with non-improvement, likely reflecting neuronal damage.

Supportive care by multidisciplinary specialists including the following are recommended: pulmonology; orthopedics, rehabilitation medicine, physical therapy and occupational therapy; speech and language therapy; feeding team including gastroenterology, nutritionists; low vision specialist; and mental health specialists (see Table 5).

Table 5. Supportive Care for Individuals with Riboflavin Transporter Deficiency 2 and 3

Manifestation/ Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Dysphagia		• Determine exact cause of swallowing malfunction; modify food types & consistency, head positioning during swallowing, & exercises to improve swallowing. • Attn to oral hygiene & dental care, as dysphagia may → impaired clearance of organisms & pathogenic colonization
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for orthotics for limb & trunk bracing, positioning & mobility devices, & disability parking placard.
Reduced vision	Low vision aids; per ophthalmologist & low vision specialist	Community vision services through early intervention or school district
Ptosis	Per treating ophthalmologist	
Sensorineural hearing impairment	Treatment of SNHL depends on degree of hearing impairment. [1]	Educational intervention for the hearing impaired; cochlear implants or hearing aids may be required.
Dysarthria	Speech-language pathologist	Help maintain vocal control; improve speech, breathing techniques, & communication in general
Depression	Depending on severity, treatment may be required.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; no one ASM has been demonstrated effective specifically for RTD. • Education of parents/caregivers [2]
Family needs / social support	Educational services; home nursing care; palliative care consultation	

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy; SNHL = sensorineural hearing loss
1. See Hereditary Hearing Loss and Deafness Overview for details about treatment options.
2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Educational Services for Those with Motor and Language Disabilities

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

Table 6. Recommended Surveillance for Individuals with Riboflavin Transporter Deficiency 2 and 3

System/Concern	Evaluation	Frequency
Riboflavin supplementation	• Discussion of any problems w/riboflavin supplementation • Blood sample for riboflavin/FAD/FMN; acylcarnitine analysis (if previous/y abnormal) to determine if they are normalizing	3 mos, 6 mos, & 12 mos after initiation of riboflavin supplementation, then annually or as needed
Neurologic exam	Focused on motor/sensory findings	
Musculoskeletal	• Orthopedic eval of spine/scoliosis • Physical medicine & rehab; OT/PT eval of fine & gross motor skills, ADL	
Sensorineural hearing impairment	Audiogram	
Epilepsy	Assess new episodes; EEG.	
Autonomic dysfunction	Physical exam	
Vision loss	Ophthalmologic exam	
Speech & language	Eval by speech-language pathologist; consider need for alternative communication.	As needed
Bulbar dysfunction	Assess safety of oral feeding vs need for gastrostomy tube.	
Feeding	Assess nutrition, dietary needs.	
Respiratory involvement	Assess need for ventilation.	
Family support/ resources	Discussion of any problems	

ADL = activities of daily living; FAD = flavin adenine dinucleotide; FMN = flavin mononucleotide; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Avoid dietary restriction of riboflavin and consume riboflavin-rich foods such as meat, eggs, and milk.

Metabolic stress caused by increased physical activity can decrease levels of riboflavin; therefore, excessive exercise should be limited.

Evaluation of Relatives at Risk

When the *SLC52A2* or *SLC52A3* pathogenic variants in the family are known (or if a proband is found to have biallelic *SLC52A1* pathogenic variants presumed to be associated with RTD1), it is appropriate to perform molecular genetic testing on the older and younger sibs of a proband with RTD to identify those with biallelic pathogenic variants who would benefit from early treatment with riboflavin supplementation and monitoring for potential complications of the disorder.

If the pathogenic variants are not known, riboflavin should be administered for both diagnostic and therapeutic purposes if a younger sib of a proband presents with typical symptoms or signs of RTD.

See Pregnancy Management for information about riboflavin supplementation in women who are heterozygous for an *SLC52A1, SLC52A2,* or *SLC52A3* pathogenic variant.

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

Pregnancy Management

Females with biallelic RTD-causing pathogenic variants. Females who have riboflavin transporter deficiency with biallelic pathogenic variants in either *SLC52A2* or *SLC52A3* should take riboflavin supplements before and during pregnancy and when breast feeding to avoid inducing riboflavin deficiency in the fetus and infant. Recommended dose during pregnancy is 10 mg/kg/day.

Females heterozygous for an RTD-causing pathogenic variant. The authors recommend a diet rich in riboflavin during pregnancy for females who are heterozygous for an RTD-related pathogenic variant. Young women heterozygous for an RTD-causing pathogenic variant should also receive counseling regarding the possibility of further riboflavin supplementation, if necessary, during pregnancy and when breastfeeding, to avoid risks of riboflavin deficiency in both mother and offspring.

- Transient neonatal riboflavin deficiency (see Differential Diagnosis) has been reported in offspring of a mother heterozygous for an *SLC52A1* pathogenic variant who became riboflavin deficient during pregnancy; her riboflavin-deficient newborn experienced neonatal seizures responsive to riboflavin supplementation. It is unknown if the offspring of females heterozygous for a *SLC52A2* or *SLC52A3* pathogenic variant may also be at increased risk for neonatal riboflavin deficiency.
- Although no data are available, heterozygous females may be at increased risk of developing symptoms due to an increased demand for riboflavin during pregnancy.

Few studies have evaluated for adverse fetal outcomes after excessive maternal riboflavin intake during pregnancy. Riboflavin deficiency during pregnancy, however, has been associated with an increased risk of maternal preeclampsia and preterm delivery [Carmichael et al 2013].

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

Riboflavin transporter deficiency 2 (RTD2) and RTD3 – caused by biallelic pathogenic variants in *SLC52A2* or *SLC52A3*, respectively – are inherited in an autosomal recessive manner.

Preliminary data from a single case report suggests that RTD1 is caused by biallelic pathogenic variants in *SLC25A1* and inherited in an autosomal recessive manner [Kang et al 2020]. Because further study is needed to confirm this observation, RTD1 is not discussed further in this section.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *SLC52A2* or one *SLC52A3* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC52A2* or *SLC52A3* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - 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].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Most heterozygous individuals do not have manifestations of RTD. Theoretically, heterozygotes may have manifestations of RTD if other conditions that lead to riboflavin depletion (e.g., dietary restriction, malnourishment, pregnancy, and/or illness) co-occur (see Pregnancy Management). Preliminary research data suggest that in some individuals heterozygous pathogenic variants in *SLC52A3* may be associated with RTD in the absence of conditions that lead to riboflavin depletion; however, this hypothesis requires further research [Khani et al 2021].

Sibs of a proband

- If both parents are known to be heterozygous for an *SLC52A2* or *SLC52A3* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial RTD-related pathogenic variants.
- Most heterozygous individuals do not have manifestations of RTD. Theoretically, heterozygotes may have manifestations of RTD if other conditions that lead to riboflavin depletion (e.g., dietary restriction, malnourishment, pregnancy, and/or illness) co-occur (see Pregnancy Management).Preliminary research data suggest that in some individuals heterozygous pathogenic variants in *SLC52A3* may be associated with RTD in the absence of conditions that lead to riboflavin depletion; however, this hypothesis requires further research [Khani et al 2021].

Offspring of a proband. Unless an affected individual's reproductive partner also has RTD or is a carrier, offspring will be obligate heterozygotes (carriers) for an *SLC52A2* or *SLC52A3* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC52A2* or *SLC52A3* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC52A2* or *SLC52A3* pathogenic variants in the family.

Related Genetic Counseling Issues

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

Family planning

- Young women with RTD should receive counseling regarding riboflavin supplementation both before and during pregnancy and when breast feeding to avoid inducing riboflavin deficiency in the fetus and infant (see Pregnancy Management).
- Women found to be heterozygous (carriers) for a pathogenic variant in *SLC52A1* are recommended a diet rich in riboflavin during pregnancy, and should receive counseling regarding the possibility of riboflavin

supplementation before and during pregnancy and when breastfeeding to avoid neonatal riboflavin deficiency. Although no data are available, the same approach should be considered in women who are heterozygous for a pathogenic variant in *SLC52A2* or *SLC52A3* to avoid the possibility of riboflavin deficiency in the fetus and infant.
- 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 carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC52A2* or *SLC52A3* 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 testing. While most centers would consider use of prenatal 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.

- **Cure RTD Foundation**
  Phone: 403-244-4549
  Email: info@cureRTD.org
  www.curertd.org
- **MedlinePlus**
  Riboflavin transporter deficiency neuronopathy
- **Cure RTD Registry**
  www.curertd.org/research/rtdregistry

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. Riboflavin Transporter Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC52A1	17p13.2	Solute carrier family 52, riboflavin transporter, member 1	SLC52A1 @ LOVD	SLC52A1	SLC52A1
SLC52A2	8q24.3	Solute carrier family 52, riboflavin transporter, member 2	SLC52A2 database	SLC52A2	SLC52A2

Table A. continued from previous page.

SLC52A3	20p13	Solute carrier family 52, riboflavin transporter, member 3	SLC52A3 database	SLC52A3	SLC52A3

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 Riboflavin Transporter Deficiency (View All in OMIM)

211500	FAZIO-LONDE DISEASE
211530	BROWN-VIALETTO-VAN LAERE SYNDROME 1; BVVLS1
607882	SOLUTE CARRIER FAMILY 52 (RIBOFLAVIN TRANSPORTER), MEMBER 2; SLC52A2
607883	SOLUTE CARRIER FAMILY 52 (RIBOFLAVIN TRANSPORTER), MEMBER 1; SLC52A1
613350	SOLUTE CARRIER FAMILY 52 (RIBOFLAVIN TRANSPORTER), MEMBER 3; SLC52A3
614707	BROWN-VIALETTO-VAN LAERE SYNDROME 2; BVVLS2
615026	RIBOFLAVIN DEFICIENCY; RBFVD

Molecular Pathogenesis

SLC52A1, SLC52A2, and *SLC52A3* encode the transmembrane proteins (hRFVT1, hRFVT2, and hRFVT3, respectively) that mediate cellular uptake of riboflavin (vitamin B_2) in the intestine (as well as in the stomach, duodenum, colon, and rectum) and reabsorption in the kidney [Subramanian et al 2015, Udhayabanu et al 2016, Mosegaard et al 2020]. *SLC52A1* is highly expressed in the placenta and hRFVT1 is the only one of the three proteins to transport riboflavin to the fetus. The water-soluble vitamin riboflavin is then converted to the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are essential for mitochondrial function and electron transfer in oxidation-reduction reactions [Udhayabanu et al 2016].

Mechanism of disease causation. Loss of function. The pathogenic variants in *SLC52A2* and *SLC52A3* that cause loss of function may include missense, nonsense, frameshift, and splice site variants that reduce riboflavin uptake or riboflavin transporter protein expression [Haack et al 2012, Foley et al 2014, Manole et al 2017].

Table 7. Riboflavin Transporter Deficiency: Gene-Specific Laboratory Technical Considerations

Gene [1]	Special Consideration
SLC52A1	While a heterozygous multiexon deletion combined w/homozygous exon 3 deletion was reported in association w/RTD1, this observation may require further investigation [Kang et al 2020].
SLC52A2	To date only nonsynonymous pathogenic variants in the homozygous or compound heterozygous state have been reported in RTD2 [Bosch et al 2012, Spagnoli et al 2014].
SLC52A3	Numerous pathogenic variants have been reported in the homozygous & compound heterozygous state in RTD3. Preliminary data suggest that in some persons heterozygous pathogenic variants in *SLC52A3* may be assoc w/RTD in the absence of conditions that lead to riboflavin depletion; however, this hypothesis requires further investigation [Khani et al 2021].

RTD1 = riboflavin transporter deficiency 1; RTD2 = RTD caused by biallelic *SLC52A2* pathogenic variants; RTD3 = RTD caused by biallelic *SLC52A3* pathogenic variants

Table 8. Riboflavin Transporter Deficiency: Notable Pathogenic Variants by Gene

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
SLC52A2	NM_024531.4 NP_078807.1	c.916G>A	p.Gly306Arg	Founder variant in the Lebanese population [Foley et al 2014, Srour et al 2014]

Table 8. continued from previous page.

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
SLC52A3	NM_033409.3 NP_212134.3	c.710C>T	p.Ala237Val	Variant w/an unusual pattern of inheritance in 2 related persons of Indian ancestry [Gayathri et al 2021]
		c.986A>G	p.Tyr329Cys	Preliminary data suggest that some persons heterozygous for this variant may manifest RTD in the absence of circumstances that cause riboflavin depletion, but this hypothesis requires further investigation [Khani et al 2021].

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

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The authors are interested in neuromuscular diseases, channelopathies, and neurodevelopmental disorders; their work involves both the genetics and the functional aspects of these disorders.

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Acknowledgments

The authors would like to thank the patients and their families for their essential help with this work. This study was supported by the Medical Research Council UK, the Wellcome Trust, and the Brain Research Trust (BRT). This study was also supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre (NIHR-UCLH-BRC).

Revision History

- 8 April 2021 (bp) Comprehensive update posted live
- 11 June 2015 (me) Review posted live
- 2 September 2014 (am) Original submission

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