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Biotinidase Deficiency

Synonym: Late-Onset Multiple Carboxylase Deficiency

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Summary

Clinical description

Individuals with biotinidase deficiency who are diagnosed before they have developed symptoms (e.g., by newborn screening) and who are treated with biotin have normal development. Symptoms including seizures, developmental delay, cutaneous manifestations (skin rash, alopecia), optic atrophy, hearing loss, and respiratory problems occur only in those individuals with biotinidase deficiency prior to biotin treatment. Symptoms of untreated profound biotinidase deficiency (<10% mean normal serum biotinidase activity) usually appear between ages one week and ten years, typically with optic atrophy, hypotonia, seizures, hair loss, and skin rash. Affected children often have ataxia and developmental delay. Individuals with partial biotinidase deficiency (10%-30% of mean normal serum biotinidase activity) may develop symptoms only when stressed, such as during infection. Some symptoms, such as feeding issues, cutaneous manifestations, and respiratory issues, usually resolve with biotin therapy, whereas other manifestations presenting prior to biotin treatment, such as optic atrophy, hearing loss, and developmental delay, may improve but are usually not completely reversible with the initiation of biotin therapy. Untreated adolescents and adults usually exhibit myelopathy and optic neuropathy and are often initially diagnosed with multiple sclerosis. Most of these individuals experience improvement in their symptoms with biotin supplementation.

Diagnosis/testing

The diagnosis of biotinidase deficiency is established in a proband whose newborn screening or biochemical findings indicate multiple carboxylase deficiency based on EITHER of the following:

- Detection of deficient biotinidase enzyme activity in serum/plasma
- Identification of biallelic pathogenic variants in *BTD* on molecular genetic testing when the results of enzymatic testing are ambiguous

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Management

Treatment of manifestations: All individuals with profound biotinidase deficiency (<10% mean normal serum enzyme activity) and those with partial biotinidase deficiency (10%-30% of mean normal serum enzyme activity) should be treated with oral biotin in the free form as opposed to the protein-bound form; biotin therapy is lifelong.

Targeted therapy: Oral biotin of 5-10 mg/day for those who have <10% mean normal serum enzyme activity and 2.5-10 mg/day in those who have 10%-30% of mean normal serum enzyme activity.

Supportive care in symptomatic individuals: Hydration and bicarbonate in those with metabolic decompensation and acidosis, although biotin therapy can rapidly resolve the metabolic derangements within hours to days; supportive developmental therapies and educational resources for those with developmental delay; subspecialist ophthalmologic care for those with optic atrophy; hearing aids and, if severe, consideration of cochlear implants for those with hearing loss.

Prevention of primary manifestations: Adherence to biotin therapy can prevent symptom development, and also improves symptoms in symptomatic individuals.

Surveillance: Evaluation by a clinical geneticist or metabolic specialist annually for those with profound biotinidase deficiency and every two years for those with partial biotinidase deficiency. If symptoms return with biotin therapy, consider obtaining urine organic acids analysis to evaluate for non-adherence to biotin therapy. Measurement of growth parameters, assessment for new manifestations (seizures, changes in tone, movement disorders), monitoring of developmental progress and educational needs, and assessment for cutaneous manifestations (eczematous rash, alopecia, thrush, and/or candidiasis) at each visit. Ophthalmology and audiology evaluations annually for those with profound biotinidase deficiency and every two years for those with partial biotinidase deficiency.

Agents/circumstances to avoid: Raw eggs should be avoided because they contain avidin, an egg white protein that binds biotin, thus decreasing its bioavailability. However, thoroughly cooked eggs present no problem because heating inactivates avidin, rendering it incapable of binding biotin.

Evaluation of relatives at risk: If prenatal testing has not been performed, a newborn with an older sib with biotinidase deficiency should be treated at birth with biotin pending results of the definitive biotinidase enzyme activity assay and/or molecular genetic testing (if the *BTD* pathogenic variants in the family are known). The genetic status of older sibs (even if asymptomatic) of a child with biotinidase deficiency should be clarified by assay of biotinidase enzyme activity or molecular genetic testing (if the *BTD* pathogenic variants in the family are known) so that biotin therapy can be instituted in a timely manner.

Pregnancy management: There have been females with profound biotinidase deficiency who are taking biotin therapy who have had normal pregnancies and offspring.

Genetic counseling

Biotinidase deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *BTD* 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. Molecular genetic carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

Diagnosis

No consensus clinical diagnostic criteria for biotinidase deficiency have been published.

Suggestive Findings

Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for biotinidase deficiency is primarily based on either fluorescent or colorimetric tests for biotinidase activity on dried blood spots.

Putative positive samples have biotinidase activities below cutoff values established by the respective screening laboratory.

Confirmational testing requires follow-up measurement of biotinidase activity in serum/plasma.

Note: False positive newborn screening test results may occur in premature infants and in samples placed in plastic prior to sufficient drying.

If the follow-up biotinidase enzyme activity supports the diagnosis of biotinidase deficiency, additional molecular genetic testing is available (see Establishing the Diagnosis).

Biotin supplementation should begin immediately on receipt of an abnormal NBS result while additional testing is performed to determine if it is a true positive NBS result and to establish the diagnosis of biotinidase deficiency definitively.

Scenario 2: Symptomatic Individual

A symptomatic individual may have either atypical findings associated with partial biotinidase deficiency or untreated profound biotinidase deficiency resulting from any of the following: NBS not performed, false negative NBS result, caregivers not adherent to recommended treatment following a positive NBS result.

Biotinidase deficiency **should be considered** in individuals with the following clinical, supportive laboratory, and family history findings.

Clinical features

- Features more specific to untreated profound biotinidase deficiency:
  - Eczematous skin rash
  - Alopecia
  - Conjunctivitis
  - Candidiasis
  - Ataxia
- Other features of untreated profound biotinidase deficiency:
  - Seizures
  - Hypotonia
  - Respiratory problems including hyperventilation, laryngeal stridor, and apnea
  - Developmental delay
  - Hearing loss
  - Vision problems such as optic atrophy
- Features of **untreated partial biotinidase deficiency** may be the same as listed above but are mild and occur only when the person is stressed, such as with a prolonged infection.

Supportive laboratory findings

- Metabolic ketolactic acidosis

- Organic aciduria (usually with the metabolites commonly seen in multiple carboxylase deficiency [see Differential Diagnosis]; however, 3-hydroxyisovalerate may be the only metabolite present)

  Note: Urinary organic acids can be normal even in individuals with biotinidase deficiency who are symptomatic.

- Hyperammonemia (usually mildly elevated up to several hundred µmol/L of ammonia in plasma)

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of biotinidase deficiency **is established** in a proband whose newborn screening or biochemical findings indicate multiple carboxylase deficiency based on EITHER of the following:

- Detection of deficient biotinidase enzyme activity in serum/plasma
- Identification of biallelic pathogenic (or likely pathogenic) variants in *BTD* on molecular genetic testing (see Table 1) when the results of enzymatic testing are ambiguous (e.g., in differentiating profound biotinidase deficiency from partial biotinidase deficiency and in differentiating heterozygosity for profound biotinidase deficiency from partial biotinidase deficiency)

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 variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) does not establish or rule out the diagnosis.

Biotinidase enzyme activity in serum. The working group of the American College of Medical Genetics Laboratory Quality Assurance Committee has established technical standards and guidelines for the diagnosis of biotinidase deficiency [Strovel et al 2017] (full text).

- Profound biotinidase deficiency: <10% mean normal serum biotinidase activity
- Partial biotinidase deficiency: 10%-30% of mean normal serum biotinidase activity
- Note: (1) With appropriate controls, biochemical testing is definitive for confirming the diagnosis. It is important that a normal unrelated control sample and samples from the parent(s) accompany the serum/plasma sample from the proband to the diagnostic laboratory for accurate interpretation of enzymatic results [Neto et al 2004]. (2) An increasing problem of enzymatic deterioration (false positives) is almost certainly the result of inadequate storage of samples either prior to shipping to commercial laboratories or at some laboratories [Wolf 2003].

Molecular genetic testing is performed by **single-gene testing.** Sequence analysis of *BTD* is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

Note: Targeted analysis for the pathogenic c.1330G>C (p.Asp444His) and c.1368A>C (p.Gln456His) variants can be performed first in individuals of Amish ancestry (see Table 8).

Table 1. Molecular Genetic Testing Used in Biotinidase Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
BTD	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	See footnote 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. Almost all individuals with partial biotinidase deficiency have the pathogenic variant p.Asp444His in one allele of *BTD* in combination with a pathogenic variant for profound deficiency in the other allele [Swango et al 1998].
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.
6. Two large *BTD* deletions have been reported in affected individuals [Senanayake et al 2015, Wolf 2016].

Clinical Characteristics

Clinical Description

Individuals with biotinidase deficiency who are diagnosed before they have developed symptoms (e.g., by newborn screening) and who are treated with biotin have normal development [Möslinger et al 2001, Weber et al 2004, Wolf 2017, Tankeu et al 2023] (see also Management, Targeted Therapy and Table 5). Neurologic problems, including seizures, optic atrophy, and hearing loss, occur only in those individuals with biotinidase deficiency who have recurrent symptoms and metabolic compromise prior to biotin treatment.

Untreated Profound Biotinidase Deficiency

Early onset. Symptoms of untreated profound biotinidase deficiency (<10% mean normal serum biotinidase activity) usually appear between ages one week and ten years, with a mean age of 3.5 months [Wolf et al 1985].

Some children with biotinidase deficiency manifest only a single finding, whereas others exhibit multiple neurologic and cutaneous findings.

Neurologic findings. The most common neurologic features in individuals with untreated profound biotinidase deficiency are seizures and hypotonia [Wolf 2011]. Older affected individuals often have ataxia and developmental delay.

- **Seizures** are usually myoclonic but may be generalized and/or focal. Infantile spasms have also been observed.
- **Hypotonia.** The degree of hypotonia varies but usually improves with biotin therapy. The degree of spasticity also varies but may not be reversible even after biotin intervention.
- **Spinal cord involvement.** Some untreated older children and adolescents have exhibited progressive spastic paresis, limb weakness, and myelopathy [Wolf 2015a].
- **Developmental delay / intellectual disability.** Developmental delays may be global or specific, often with intellectual disabilities and speech-language issues, which if present prior to biotin treatment may or may not improve with biotin therapy.

Neuroimaging. Most brain imaging studies are normal. However, a variety of central nervous system abnormalities on brain MRI or CT have been reported [Wolf et al 1983b, Wastell et al 1988, Lott et al 1993,

Salbert et al 1993, Grünewald et al 2004]. The most characteristic abnormalities include cerebral atrophy and ventricular dilatation. These findings may improve or resolve after biotin treatment.

Hearing impairment. Approximately 76% of untreated symptomatic individuals with profound biotinidase deficiency have sensorineural hearing loss that usually does not resolve or improve but remains static with biotin treatment [Wolf et al 2002]. Depending on the degree and/or pattern of hearing loss, children usually require hearing aids or even cochlear implants (see Management, Supportive Care).

Ophthalmologic involvement may include optic atrophy and scotoma [Salbert et al 1993].

Cutaneous manifestations include skin rash, alopecia, and recurrent viral or fungal infections caused by cellular immunologic dysfunction. These symptoms usually resolve with biotin therapy.

Respiratory problems including hyperventilation, laryngeal stridor, and central apnea can occur. These symptoms usually resolve with biotin therapy.

Gastrointestinal/feeding issues. Although feeding issues may occur prior to biotin treatment, they resolve with biotin therapy.

Late onset. A number of children with untreated profound biotinidase deficiency were asymptomatic until adolescence or adulthood, when they developed sudden loss of vision with progressive optic neuropathy, peripheral neuropathy, and spastic paraparesis [Ramaekers et al 1992, Lott et al 1993, Ramaekers et al 1993, Wolf 2015a, Deschamps et al 2018, Kellom et al 2021]. After several months of biotin therapy, the eye findings may improve or resolve and the spastic paraparesis may improve.

Untreated Partial Biotinidase Deficiency

Individuals with untreated partial biotinidase deficiency (10%-30% of mean normal serum biotinidase activity) may develop symptoms only when stressed, such as during infection.

One child with partial biotinidase deficiency who was not treated with biotin exhibited hypotonia, skin rash, and hair loss during an episode of gastroenteritis at approximately age six months. When treated with biotin, the symptoms resolved.

Prognosis

Because newborn screening (NBS) was rapidly incorporated into all state programs in the United States and in many countries, the window of opportunity to study symptomatic children has been limited compared to that of many other inherited metabolic disorders. Symptomatic children, if treated early enough, may experience reversal of all of their symptoms with biotin treatment.

- The biochemical abnormalities and seizures rapidly resolve after biotin treatment, followed by improvement of the cutaneous abnormalities.
- Hair growth returns over a period of weeks to months in children who have alopecia.
- Optic atrophy and hearing loss may be resistant to therapy, especially if a long period has elapsed between their onset and the initiation of treatment.
- Some treated children have rapidly achieved developmental milestones, whereas others have continued to show delays.
- Many symptomatic children who experienced developmental delay, optic atrophy, and/or hearing loss prior to biotin treatment may find that the degree of the problem becomes static (i.e., does not progress), but also does not completely resolve. Children identified by NBS and treated shortly after birth, some in their fourth decade, have had successful outcomes [Wolf 2017].

Early reported deaths in a few symptomatic individuals were due to severe metabolic compromise. Diagnosis of biotinidase deficiency and/or treatment with biotin was usually too late. Currently, such cases are fortunately rare due to NBS or to inclusion of the disorder in the differential diagnosis of symptomatic children. A normal life span is expected for both initially symptomatic children and those identified by NBS as long as they continue lifelong biotin supplementation. One death initially thought to be caused by sudden infant death syndrome was subsequently attributed to biotinidase deficiency [Burton et al 1987].

Genotype-Phenotype Correlations

Genotype-phenotype correlations are not well established. However, certain genotypes correlate with profound biotinidase deficiency and others with partial biotinidase deficiency. There is a single report from Turkey in which symptomatic individuals with pathogenic null variants predicted to lead to profound enzyme deficiency had hearing loss, whereas those who had some residual enzyme activity did not [Sivri et al 2007].

Profound biotinidase deficiency (<10% mean normal serum biotinidase activity):

- Most *BTD* pathogenic variants cause complete loss or near-complete loss of biotinidase enzyme activity. These alleles are considered profound biotinidase deficiency alleles and are more likely to be deletions, insertions, or nonsense pathogenic variants. The combination of two such alleles, whether homozygous or compound heterozygous, results in profound biotinidase deficiency. Affected individuals are likely to develop symptoms if not treated with biotin.
- Those with absence of all biotinidase enzyme activity are likely to be at increased risk for earlier onset of symptoms.
- In one study, children with symptoms of profound biotinidase deficiency with null pathogenic variants were more likely to develop hearing loss than those with pathogenic missense variants, even if those with pathogenic missense variants were not treated for a period of time [Sivri et al 2007].

Partial biotinidase deficiency (10%-30% of mean normal serum biotinidase activity). Compound heterozygotes for the p.Asp444His pathogenic variant and a pathogenic variant that results in profound biotinidase deficiency are expected to have approximately 20%-25% of mean normal serum biotinidase enzyme activity [Swango et al 1998].

Homozygotes for the p.Asp444His pathogenic variant are expected to have approximately 45%-50% of mean normal serum biotinidase enzyme activity (which is similar to the activity of heterozygotes for profound biotinidase deficiency) and do not require biotin therapy.

Penetrance

Almost all children with profound biotinidase deficiency become symptomatic or are at risk of becoming symptomatic if not treated.

Several reports describe adults with profound biotinidase deficiency who have offspring who also have profound biotinidase deficiency identified by NBS but who have never had symptoms [Wolf et al 1997, Baykal et al 2005]. In addition, several enzyme-deficient sibs of symptomatic individuals have apparently never exhibited symptoms. It is possible that these individuals would become symptomatic if stressed, such as with a prolonged infection.

Nomenclature

Profound and partial biotinidase deficiency is the accepted nomenclature for this disorder.

Individuals with partial biotinidase deficiency were previously described as having late-onset or juvenile multiple or combined carboxylase deficiency.

Biotinidase deficiency should not be confused with holocarboxylase synthetase deficiency (see Differential Diagnosis), previously referred to as early-onset or infantile multiple or combined carboxylase deficiency.

Prevalence

Based on the results of worldwide screening of biotinidase deficiency [Wolf 1991], the incidence of the disorder is:

- One in 137,401 for profound biotinidase deficiency;
- One in 109,921 for partial biotinidase deficiency;
- One in 61,067 for the combined incidence of profound and partial biotinidase deficiency.

The incidence of biotinidase deficiency is generally higher in populations with a high rate of consanguinity (e.g., Turkey, Saudi Arabia).

The incidence appears to be increased in the Hispanic population [Cowan et al 2012] and it may be lower in the African American population.

Carrier frequency in the general population is approximately one in 120.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Clinical features including vomiting, hypotonia, and seizures accompanied by metabolic ketolactic acidosis or mild hyperammonemia are often observed in inherited metabolic diseases. Individuals with biotinidase deficiency may exhibit clinical features that are misdiagnosed as other disorders (e.g., isolated carboxylase deficiency) before they are correctly identified [Suormala et al 1985, Wolf & Heard 1989]. Other symptoms that are more characteristic of biotinidase deficiency (e.g., skin rash, alopecia) can also occur in children with nutritional biotin deficiency, holocarboxylase synthetase deficiency, zinc deficiency, or essential fatty acid deficiency (see Figure 1).

Nutritional biotin deficiency can usually be diagnosed by dietary history. Individuals with biotin deficiency may have a diet containing raw eggs or protracted parenteral hyperalimentation without biotin supplementation.

Inherited Metabolic Disorders

Isolated carboxylase deficiency. Urinary organic acid analysis is useful for differentiating isolated carboxylase deficiencies from the multiple carboxylase deficiencies that occur in biotinidase deficiency and holocarboxylase synthetase deficiency (see Table 2).

Holocarboxylase synthetase deficiency (OMIM 253270). Both biotinidase deficiency and holocarboxylase synthetase deficiency are characterized by deficient activities of the three mitochondrial carboxylases in peripheral blood leukocytes prior to biotin treatment. In both disorders, these activities increase to near-normal or normal after biotin treatment.

Organic acid abnormalities in biotinidase deficiency and holocarboxylase synthetase deficiency are similar and may be reported as consistent with multiple carboxylase deficiency. However, the tandem mass spectroscopic methodology that is being incorporated into many newborn screening programs should identify metabolites that are consistent with multiple carboxylase deficiency. Because most children with holocarboxylase synthetase

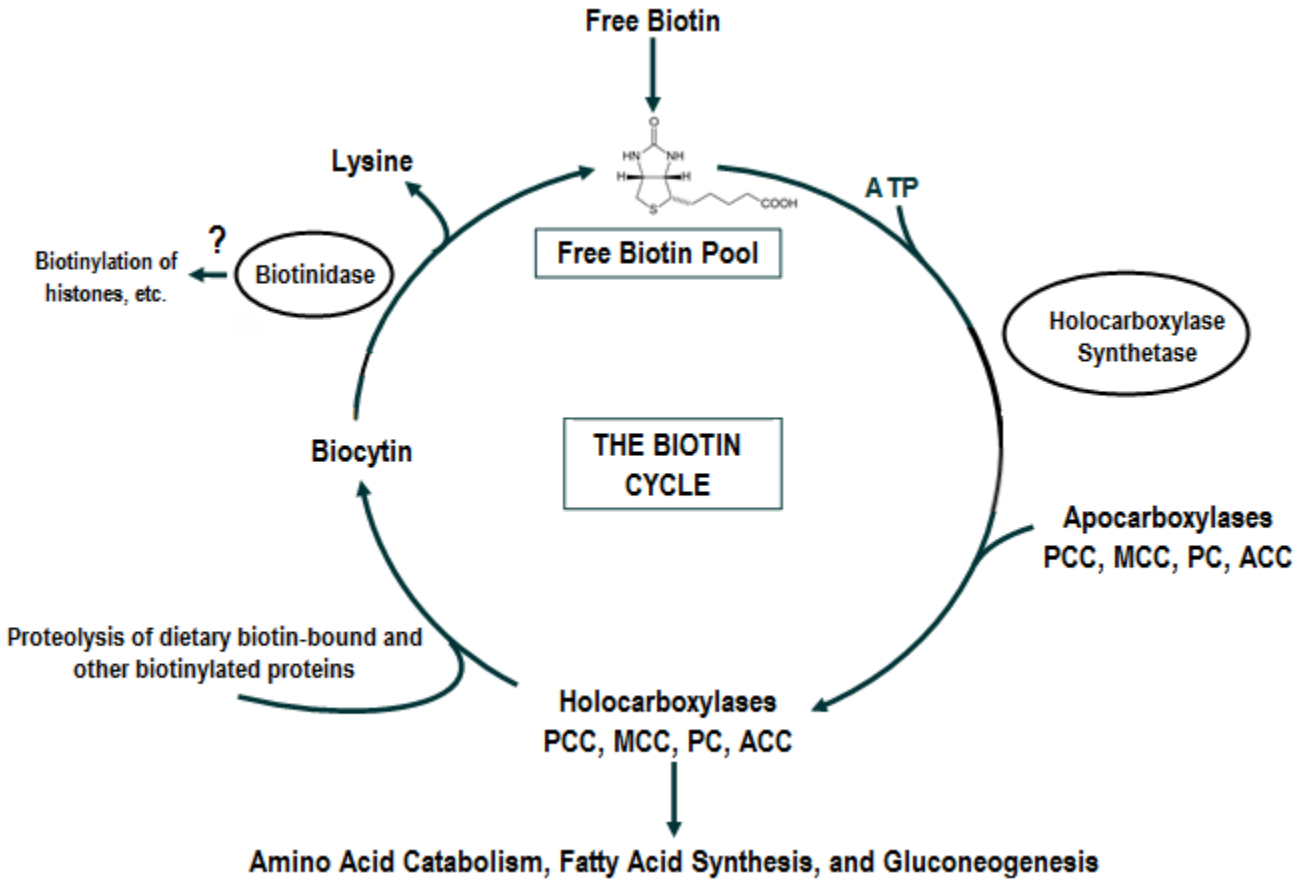

Figure 1. The biotin cycle

Free biotin enters the cycle from dietary sources or from the cleavage of biocytin or biotinyl-peptides by the action of biotinidase. The free biotin is then covalently attached to the various apocarboxylases, propionyl-CoA carboxylase (PCC), beta-methylcrotonyl-CoA carboxylase (MCC), pyruvate carboxylase (PC), and acetyl-CoA carboxylase (ACC) by the action of biotin holocarboxylase synthetase, thereby forming active holocarboxylases. The holocarboxylases are subsequently proteolyzed to biocytin and/or biotinyl-peptides, which are then further cleaved by biotinidase, thus recycling the biotin. The liberated biotin can then enter the free biotin pool. Isolated deficiencies of each of the carboxylases and deficiencies of both holocarboxylase synthetase and biotinidase can occur.

deficiency excrete these metabolites in the newborn period, the disorder should be identifiable using this technology.

Definitive enzyme determinations are required to distinguish between biotinidase deficiency and holocarboxylase synthetase deficiency (see Table 2).

Table 2. Inherited Metabolic Disorders in the Differential Diagnosis of Biotinidase Deficiency

Disorder		Gene	Clinical and Supportive Laboratory Features	Urinary Organic Acid Analysis	Enzyme Analysis
Multiple carboxylase deficiency (biotin responsive [1])	Biotinidase deficiency (topic of this *GeneReview*; included for reference)	*BTD*	• The symptoms of biotinidase deficiency & HLCS deficiency are similar & clinical differentiation is often difficult. • Age of onset of symptoms may be	• Lactic acid • 3-hydroxyisovaleric acid • 3-methylcrotonic acid • 3-methylcrotonylglycine • 3-hydroxy-propionic acid • Methylcitric acid	Deficient biotinidase enzyme activity in serum/plasma

Table 2. continued from previous page.

Disorder		Gene	Clinical and Supportive Laboratory Features	Urinary Organic Acid Analysis	Enzyme Analysis
	Holocarboxylase synthetase (HLCS) deficiency (OMIM 253270)	*HLCS*	useful for distinguishing between the disorders: HLCS deficiency usually presents age <3 mos, whereas biotinidase deficiency usually presents age >3 mos; however, there are exceptions for both disorders.		• Normal biotinidase enzyme activity [2] • Deficient activities of the 3 mitochondrial carboxylases in extracts of fibroblasts that are incubated in medium containing only the biotin contributed by fetal calf serum (low biotin), whereas persons w/biotinidase deficiency have normal carboxylase activities in fibroblasts • The activities of the carboxylases in fibroblasts of persons w/HLCS deficiency become near-normal to normal when cultured in medium supplemented w/ biotin (high biotin).

Table 2. continued from previous page.

Disorder		Gene	Clinical and Supportive Laboratory Features	Urinary Organic Acid Analysis	Enzyme Analysis
Isolated carboxylase deficiency (not biotin responsive [1])	Isolated beta-methylcrotonyl-CoA carboxylase deficiency (OMIM PS210200)	*MCCC1* *MCCC2*	• Seizures, lethargy, hypotonia, developmental delay • Metabolic acidosis	• 3-methylcrotonic acid • 3-methylcrotonylglycine • 3-hydroxyisovaleric acid	Isolated carboxylase deficiency can be diagnosed by: • Deficient enzyme activity of 1 of the 3 mitochondrial carboxylases in peripheral blood leukocytes (prior to biotin therapy) or in cultured fibroblasts grown in low biotin-containing medium; & • Normal activity of the other 2 carboxylases.
	Propionic acidemia	*PCCA* *PCCB*	• Seizures, lethargy, hypotonia, developmental delay • Metabolic acidosis, hyperammonemia	• Lactate • 3-hydroxy-propionic acid • Methylcitric acid	
	Pyruvate carboxylase deficiency	*PC*	• Seizures, lethargy, hypotonia, developmental delay • Lactic acidosis, hypoglycemia	Lactate	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. A trial of biotin can be useful for discriminating between the disorders.
2. Biotinidase enzyme activity is normal in serum of individuals with holocarboxylase synthetase deficiency; therefore, the enzymatic assay of biotinidase activity used in newborn screening is specific for biotinidase deficiency and does not identify children with holocarboxylase synthetase deficiency.

Sensorineural Hearing Loss

Sensorineural hearing loss (see Hereditary Hearing Loss and Deafness Overview) has many causes. Biotinidase deficiency can be excluded as a cause by determining biotinidase enzyme activity in serum. This test should be performed specifically on children with hearing loss who are exhibiting other clinical features consistent with biotinidase deficiency.

Late-Onset Biotinidase Deficiency

Older children, adolescents, and adults ultimately found to have biotinidase deficiency often exhibit symptoms different from those of younger children with the disorder [Ferreira et al 2017, Wolf 2018, Wolf 2019a, Van-Winckel et al 2020]. They usually present with ophthalmologic issues such as optic neuropathy and varying degrees of myelopathy [Wolf 2018]. Biotin therapy can reverse many of the optic findings and some or all of the myelopathy, if diagnosed in a reasonable time period. These individuals often are initially diagnosed with neuromyelitis optica spectrum disorder or multiple sclerosis. It has been recommended that any person diagnosed with these disorders be tested for biotinidase deficiency because of its treatability.

Management

No clinical practice guidelines for biotinidase deficiency have been published. However, Strovel et al [2017] (full text) refers to some basic recommendations.

When biotinidase deficiency is suspected during the diagnostic evaluation (i.e., due to decreased biotinidase activity on a newborn blood spot), biotin treatment should be initiated immediately. Biotinidase deficiency or

other biotin-related disorders, such as holocarboxylase synthetase deficiency (see Differential Diagnosis), should be excluded before biotin supplementation is discontinued.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an **asymptomatic infant diagnosed with biotinidase deficiency following newborn screening**, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Biotinidase Deficiency: Recommended Evaluations Following Initial Diagnosis Detected by Newborn Screening in an Asymptomatic Infant

System/Concern	Evaluation	Comment
Genetics / Genetic counseling	Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian	
	Genetic counseling by genetics professionals [1]	To inform affected persons& their families re nature, MOI, & implications of biotinidase deficiency to facilitate medical & personal decision making
Constitutional	Measurement of growth parameters	To screen for poor growth
Neurologic	Neurologic eval	• To incl assessment for hypotonia & seizures • Consider EEG if seizures are a concern.
Hearing	Audiologic eval	Assess for hearing loss by audiography. [2]
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

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse
2. Newborn hearing screening should not be used as a substitute for this hearing evaluation.

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

Table 4. Biotinidase Deficiency: Recommended Evaluations Following Initial Diagnosis in a Symptomatic Individual

System/Concern	Evaluation	Comment
Genetics / Genetic counseling	Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian	
	Genetic counseling by genetics professionals [1]	To inform affected persons& their families re nature, MOI, & implications of biotinidase deficiency to facilitate medical & personal decision making
Constitutional	Measurement of growth parameters	To screen for poor growth
Gastrointestinal/ Feeding	Nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl assessment for hypotonia, ataxia, & seizures • Consider EEG if seizures are a concern.
Eyes	Ophthalmologic eval	To assess for optic atrophy, scotoma, conjunctivitis, etc.
Integument	Full skin & mucosal exam	To assess for eczematous rash, alopecia, thrush, &/or candidiasis
Respiratory	Clinical assessment for breathing issues incl stridor, hyperventilation, & apnea	
Development	Developmental assessment	• To incl motor & feeding-speech eval • Eval for early intervention service needs
Hearing	Audiologic eval	Assess for hearing loss.
Immunologic	Assess for history of recurrent viral or fungal infections.	Untreated affected persons are at ↑ risk of immune dysfunction; however, this typically resolves w/biotin therapy, so no formal immunologic studies are typically required.
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

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

Treatment of Manifestations

There is no cure for biotinidase deficiency. Biotin therapy is lifelong.

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

All individuals with profound biotinidase deficiency (<10% mean normal serum enzyme activity) and those with partial biotinidase deficiency (10%-30% of mean normal serum enzyme activity) should be treated with oral biotin in the free form as opposed to the bound form (see Table 5).

Note: (1) Over the years it has become important, especially during infancy, to ensure that the child is ingesting a uniform and complete dose of the biotin. Various methods for administration of biotin to assure the appropriate dosage have been described [Wolf 2022]. (2) A protein-restricted diet is not necessary. (3) Because genotype-phenotype correlations in biotinidase deficiency are not well established, decisions regarding treatment should be based on the results of enzyme activity rather than molecular genetic testing.

Table 5. Biotinidase Deficiency: Targeted Treatment

Targeted Treatment	Degree of Enzyme Deficiency	Dosage in Infants/ Children [1, 2]	Considerations
Oral biotin [3]	Profound (<10% mean normal serum enzyme activity)	5-10 mg/day	• Biotin is usually dispensed as a tablet or a capsule (most of which is filler: the quantity of biotin is minute relative to the quantity of filler). [4, 5] • To administer biotin to an infant or young child, the tablet can be crushed or the contents of the capsule can be mixed with breast milk or formula in a spoon, medicine dispenser, or syringe. [6]
	Partial [7] (10%-30% of mean normal serum enzyme activity)	2.5-10 mg/day	• Because there is no known toxicity for biotin, children w/partial biotinidase deficiency are usually treated. • Different perspectives on biotin treatment exist; some centers treat partial biotinidase deficiency for only the first few months of life, while other centers do not treat partial biotinidase deficiency at all. The author recommends treatment for life [Wolf 2015b].

1. More data are required to determine the dosage of biotin that is necessary for older children with either profound or partial biotinidase deficiency, but essentially all children have tolerated 10 mg/day of oral biotin with no side effects.
2. Anecdotally, two girls with profound biotinidase deficiency developed hair loss during adolescence that resolved following an increase of their biotin dosages from 10 mg/day to 15 or 20 mg/day.
3. There are no known adverse side effects from pharmacologic doses of biotin.
4. Although biotin occasionally is dispensed as a solution or syrup, these liquid preparations are not recommended because the mixture – which is a suspension – tends to settle (especially upon refrigeration) and to grow bacteria upon storage.
5. The liquid preparations usually do not provide a consistent dose and should not be added to milk in a bottle.
6. The contents of the tablet or capsule should not be put into a bottle because the mixture will stick to the bottle and/or fail to pass through the nipple, thus delivering inconsistent doses.
7. Only a few anecdotal reports exist regarding symptoms in children with partial biotinidase deficiency who were not treated with biotin.

Note: High doses of biotin, such as that used to treat biotinidase deficiency, can interfere with laboratory tests that use biotin-streptavidin technologies [Wolf 2019b]. It is important to check with the laboratories that perform these diagnostic tests to determine the best methods to avoid this interference. Fortunately, most laboratories are aware of this problem.

Supportive Care

Supportive care in **symptomatic individuals** is summarized in Table 6.

Table 6. Biotinidase Deficiency: Treatment of Manifestations in Symptomatic Individuals

Manifestation/Concern	Treatment	Considerations/Other
Metabolic decompensation [1]	• Hydration (typically intravenous) for dehydration • Bicarbonate for acidosis	Biotin therapy (see Table 5) can rapidly resolve the metabolic derangement & improve many of the clinical symptoms w/in hours to days.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	Supportive developmental therapies & educational resources	• Speech therapy, occupational therapy, & physical therapy may be beneficial, depending on specific needs. • Consider referral to developmental specialist. • Special education, incl IEP or 504 plans, may be considered. [2, 3]
Optic atrophy	Ophthalmic subspecialist	
	Low vision services	• Children: through early intervention programs &/or school district • Adults: Low vision clinic &/or community vision services / occupational therapy / mobility services
Hearing loss	• Hearing aids may be helpful per otolaryngologist. • In select instances, cochlear implants may be considered.	Community hearing services through early intervention or school district
Family/Community	• Ensure appropriate social work involvement to connect families w/ local resources& support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Consider involvement in adaptive sports or Special Olympics.

IEP = individualized educational plan

1. Although newborn screening for biotinidase deficiency has resulted in almost complete ascertainment of children with biotinidase deficiency in the United States and in many other countries, occasionally a child who has not been screened or has been mistakenly thought to have normal biotinidase activity on newborn screening will present with clinical symptoms.

2. Individualized education plans (IEPs) are specific to the United States. An IEP provides specially designed instruction and related services to children who qualify.

3. A 504 plan is specific to the United States (Section 504: a US federal statute that prohibits discrimination based on disability). It 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.

Prevention of Primary Manifestations

Adherence to biotin therapy (see Table 5) can prevent symptom development and also improves symptoms in symptomatic individuals.

Surveillance

To monitor existing manifestations, the individual's response to targeted and supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Biotinidase Deficiency: Recommended Surveillance

System/Concern	Evaluation	Frequency
Genetics	Eval by clinical geneticist or metabolic specialist	• Annually for those w/profound biotinidase deficiency • Every 2 yrs for those w/partial deficiency
	Eval of urinary organic acids [1]	If symptoms return w/biotin therapy (most commonly the result of non-adherence)
Constitutional	Measurement of growth parameters	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Development	Monitor developmental progress & educational needs.	
Integument	Assess for eczematous rash, alopecia, thrush, &/or candidiasis.	
Eyes	Ophthalmology eval	• Annually for those w/profound biotinidase deficiency • Every 2 yrs for those w/partial deficiency
Hearing	Audiology eval	
Family/Community	Assess family need for social work support, care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

1. Measurement of biotin concentrations in blood or urine is not useful except to determine adherence to therapy.

Agents/Circumstances to Avoid

Raw eggs should be avoided because they contain avidin, an egg white protein that binds biotin, thus decreasing its bioavailability. However, thoroughly cooked eggs present no problem because heating inactivates avidin, rendering it incapable of binding biotin.

Evaluation of Relatives at Risk

Prenatal testing of a fetus at risk. When the pathogenic variants causing biotinidase deficiency 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 has not been performed, a newborn with an older sib with biotinidase deficiency should be treated at birth with biotin pending results of the definitive biotinidase enzyme activity assay and/or molecular genetic testing (if the *BTD* pathogenic variants in the family are known).

Older sibs. The genetic status of older sibs (even if asymptomatic) of a child with biotinidase deficiency should be clarified by assay of biotinidase enzyme activity or molecular genetic testing (if the *BTD* pathogenic variants in the family are known) so that biotin therapy can be instituted in a timely manner.

Symptomatic and non-symptomatic family members. The genetic status of any relative with symptoms consistent with biotinidase deficiency or individuals with symptoms of late-onset biotinidase deficiency should be clarified by assay of biotinidase enzyme activity or molecular genetic testing (if the *BTD* pathogenic variants in the family are known) so that biotin therapy can be instituted in a timely manner.

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

Pregnancy Management

There have been females with profound biotinidase deficiency who are taking biotin therapy who have had normal pregnancies and offspring [Wolf 2017].

The only special pregnancy management considerations for a woman who is carrying a baby with biotinidase deficiency or is at risk of having a baby with biotinidase deficiency is consideration of biotin supplementation for the mother. An optimal prenatal dose has not been determined.

See MotherToBaby for further information on medication use during pregnancy.

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

Biotinidase deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of a child with biotinidase deficiency are presumed to be heterozygous for a *BTD* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *BTD* pathogenic variant and to 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, 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.
- Heterozygotes 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 *BTD* 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.
- Sibs of an individual with biotinidase deficiency should be tested for the deficiency even if they do not exhibit symptoms (see Penetrance).

- 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 biotinidase deficiency or is a carrier (see **Family planning**), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *BTD*.
- Based on a carrier frequency of approximately one in 120 in the general population [Wolf 1991], the empiric risk to an individual with biotinidase deficiency of having a child with the disorder is about one in 240.

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

Carrier Detection

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

Biochemical genetic testing. Carriers (heterozygotes) usually have serum enzyme activity levels intermediate between those of affected and normal individuals [Wolf et al 1983a]. Using serum enzyme activity, heterozygosity can be diagnosed with approximately 95% accuracy [Weissbecker et al 1991]. However, if the *BTD* pathogenic variants in the family have been identified, molecular testing is preferred.

Note: Individuals with one profound or one partial biotinidase deficiency *BTD* pathogenic variant are carriers of biotinidase deficiency and do not exhibit symptoms. Such individuals do not require biotin therapy.

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

- 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 for reproductive partners of known carriers should be considered, particularly if consanguinity is likely and/or if both partners are of the same ethnic background. Two *BTD* founder variants have been identified in individuals of Amish ancestry (see Table 8).

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

Molecular genetic testing. Once the *BTD* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for biotinidase deficiency are possible.

Enzyme activity. Prenatal testing for pregnancies at increased risk for biotinidase deficiency is possible through measurement of biotinidase enzyme activity in cultured amniotic fluid cells and in amniotic fluid obtained by

amniocentesis [Secor McVoy et al 1984, Chalmers et al 1994]. In the United States, molecular prenatal testing is preferred.

Differences in perspective may exist among medical professionals and in 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.

- **Medical Home Portal**
  Biotinidase Deficiency
- **MedlinePlus**
  Biotinidase deficiency
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.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. Biotinidase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BTD	3p25.1	Biotinidase	Biotinidase Deficiency (BTD) BTD @ LOVD	BTD	BTD

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 Biotinidase Deficiency (View All in OMIM)

253260	BIOTINIDASE DEFICIENCY
609019	BIOTINIDASE; BTD

Molecular Pathogenesis

Biotinidase is a ubiquitously expressed enzyme essential for recycling the vitamin biotin, a water-soluble cofactor necessary for the function of several carboxylases. Biotinidase has been shown to have biotinyl-hydrolase and biotinyl-transferase activities. The enzyme is a monomeric sialylated glycoprotein with multiple isoforms resulting from differences in the degree of sialylation [Hart et al 1991]. Deficiency of biotinidase with secondary disruption of relevant carboxylases causes disruption of several pathways involved in amino acid, carbohydrate, and lipid metabolism, which leads to clinical manifestations of biotinidase deficiency.

Mechanism of disease causation. Loss of function

***BTD*-specific laboratory technical considerations.** *BTD* consists of four exons and three introns [Knight et al 1998]. Two putative translation initiation codons exist in the gene: one is encoded within exon 1 and the other within exon 2, which contains the N-terminal methionine of the mature enzyme. The presence of an intron between the two possible initiation codons could allow for alternative splicing, which could produce transcripts encoding a protein with a 41- or a 21-residue signal peptide. These transcripts may have tissue-specific expression [Strovel et al 2017].

Table 8. Selected *BTD* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001370658.1 NP_001357587.1	c.1330G>C	p.Asp444His	• Founder variant in Amish population [Strauss & Puffenberger 2009] • Persons who are homozygous for this variant typically do not require treatment w/biotin.
	c.1368A>C	p.Gln456His	Founder variant in Amish population [Strauss & Puffenberger 2009]

Variants listed in the table have been provided by the author. *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 Barry Wolf's laboratory was the first to describe biotinidase deficiency in individuals with late-onset multiple carboxylase deficiency and has characterized the clinical, biochemical, and molecular features of the disorder. They developed the method used to screen newborns for biotinidase deficiency and piloted the first newborn screening for the disorder.

Biotinidase Deficiency: A Booklet for Families and Professionals by DL Thibodeau, MS, and B Wolf, MD, PhD

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- December 1999 (bw) Original submission

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