Summary

Clinical characteristics
If untreated, young children with profound biotinidase deficiency usually exhibit neurologic abnormalities including seizures, hypotonia, ataxia, developmental delay, vision problems, hearing loss, and cutaneous abnormalities (e.g., alopecia, skin rash, candidiasis). Older children and adolescents with profound biotinidase deficiency often exhibit motor limb weakness, spastic paresis, and decreased visual acuity. Once vision problems, hearing loss, and developmental delay occur, they are usually irreversible, even with biotin therapy. Individuals with partial biotinidase deficiency may have hypotonia, skin rash, and hair loss, particularly during times of stress.

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 detection of deficient biotinidase enzyme activity in serum/plasma OR identification of biallelic pathogenic variants in BTD on molecular genetic testing.

Management
Treatment of manifestations: All symptomatic children with profound biotinidase deficiency improve when treated with 5-10 mg of oral biotin per day. All individuals with profound biotinidase deficiency, even those who have some residual enzymatic activity, should have lifelong treatment with biotin. Children with vision problems may benefit from vision aids; those with hearing loss will usually benefit from hearing aids or cochlear implants, and those with developmental deficits from appropriate interventions.

Prevention of primary manifestations: Children with biotinidase deficiency identified by newborn screening should remain asymptomatic if biotin therapy is instituted early and continuously lifelong.

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Surveillance: Annual vision and hearing evaluation, physical examination, and periodic assessment by a metabolic specialist.

Agents/circumstances to avoid: Raw eggs because they contain avidin, an egg-white protein that binds biotin and decreases the bioavailability of the vitamin.

Evaluation of relatives at risk: Testing of asymptomatic sibs of a proband ensures that biotin therapy for affected sibs can be instituted in a timely manner.

**Gene Review**

Biotinidase deficiency is inherited in an autosomal recessive manner. With each pregnancy, a couple who has had one affected child has a 25% chance of having an affected child, a 50% chance of having a child who is an asymptomatic carrier, and a 25% chance of having an unaffected child who is not a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are options if the pathogenic variants in the family are known.

**Diagnosis**

Clinical issues and frequently asked questions regarding biotinidase deficiency have been addressed in a review [Wolf 2010].

**Suggestive Findings**

Biotinidase deficiency should be suspected in infants with positive newborn screening results, untreated individuals with clinical findings, and persons with suggestive preliminary laboratory findings [Wolf 2012]:

**Positive Newborn Screening Results**

Virtually 100% of infants with either profound biotinidase deficiency or partial biotinidase deficiency can be detected in the US by newborn screening (see National Newborn Screening Status Report).

Newborn screening utilizes a small amount of blood obtained from a heel prick for a colorimetric test for biotinidase activity:

- False positive test results may occur in premature infants and in samples placed in plastic prior to sufficient drying.
- Measurement of biotinidase enzyme activity in serum/plasma is warranted in infants whose initial screening tests are abnormal.

**Clinical Findings**

Children or adults with untreated profound biotinidase deficiency usually exhibit one or more of the following nonspecific features (which are also observed in many other inherited metabolic disorders):

- Seizures
- Hypotonia
- Respiratory problems including hyperventilation, laryngeal stridor, and apnea
- Developmental delay
- Hearing loss
- Vision problems, such as optic atrophy

Features more specific to profound biotinidase deficiency include the following:

- Eczematous skin rash
Older children and adolescents may exhibit limb weakness, paresis, and scotomata. Some have exhibited findings suggestive of a myelopathy and have been initially incorrectly diagnosed and treated as having another disorder before biotinidase deficiency is correctly diagnosed [Wolf 2015].

**Children or adults with untreated partial biotinidase deficiency** may exhibit any of the above signs and symptoms, but the manifestations are mild and occur only when the person is stressed, such as with a prolonged infection.

**Preliminary Laboratory Findings**

The following findings are suggestive of biotinidase deficiency:

- Metabolic ketolactic acidosis
- Organic aciduria (usually with the metabolites commonly seen in multiple carboxylase deficiency; 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

**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 variants in *BTD* on molecular genetic testing (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)

**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 [Cowan et al 2010] (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.
Table 1. Molecular Genetic Testing Used in Biotinidase Deficiency

<table>
<thead>
<tr>
<th>Gene</th>
<th>Method</th>
<th>Proportion of Probands with Pathogenic Variants Detectable by Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTD</td>
<td>Sequence analysis</td>
<td>~99%</td>
</tr>
<tr>
<td></td>
<td>Gene-targeted deletion/duplication analysis</td>
<td>See footnote 6</td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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.
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 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] (see also Management, Prevention of Primary Manifestations). Neurologic problems occur only in those individuals with biotinidase deficiency who have recurrent symptoms and metabolic compromise prior to biotin treatment.

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 three and one-half months [Wolf et al 1985b]. Some children with biotinidase deficiency manifest only a single finding, whereas others exhibit multiple neurologic and cutaneous findings.

The most common neurologic features in individuals with untreated, profound biotinidase deficiency are seizures and hypotonia [Wolf et al 1983a, Wolf et al 1985b, Wastell et al 1988, Wolf 1995, Wolf 2011]. The seizures are usually myoclonic but may be grand mal and focal; some children have infantile spasms [Salbert et al 1993b]. Some untreated children have exhibited spinal cord involvement characterized by progressive spastic paresis and myelopathy [Chedrawi et al 2008]. Older affected children often have ataxia and developmental delay.


Sensorineural hearing loss and eye problems (e.g., optic atrophy) have also been described in untreated children [Wolf et al 1983b, Taizt et al 1985, Salbert et al 1993a, Weber et al 2004]. Approximately 76% of untreated symptomatic children 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].
Cutaneous manifestations include skin rash, alopecia, and recurrent viral or fungal infections caused by immunologic dysfunction.

Respiratory problems including hyperventilation, laryngeal stridor, and apnea can occur.

One death initially thought to be caused by sudden infant death syndrome was subsequently attributed to biotinidase deficiency [Burton et al 1987].

**Late onset.** A number of children with profound biotinidase deficiency were asymptomatic until adolescence, when they developed sudden loss of vision with progressive optic neuropathy and spastic paraparesis [Ramaekers et al 1992, Lott et al 1993, Ramaekers et al 1993]. After several months of biotin therapy, the eye findings resolved and the spastic paraparesis improved. In other individuals with enzyme deficiency, paresis and eye problems have occurred during early adolescence [Tokatli et al 1997, Wolf et al 1998, Wolf 2015].

**Partial Biotinidase Deficiency**

Individuals with 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.

**Genotype-Phenotype Correlations**

Genotype/phenotype correlations are not well established. Deletions, insertions, or nonsense variants usually result in complete absence of biotinidase enzyme activity, whereas missense variants may or may not result in complete loss of biotinidase enzyme activity. Those with absence of all biotinidase enzyme activity are likely to be at increased risk for earlier onset of symptoms.

Although genotype-phenotype correlations are not well established, in one study, children with symptoms of profound biotinidase deficiency with null variants were more likely to develop hearing loss than those with missense variants, even if not treated for a period of time [Sivri et al 2007].

Certain genotypes correlate with complete biotinidase deficiency and others with partial biotinidase deficiency.

**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; a 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.
- Several adults with profound biotinidase deficiency have never had symptoms and have never been treated [Wolf et al 1997] whereas some children with the same pathogenic variants have been symptomatic. Therefore, it has been speculated that some children with profound biotinidase deficiency may exhibit mild or no symptoms if left untreated. Nonetheless, it is recommended that such children be treated [Möslinger et al 2003].

**Partial biotinidase deficiency** (10%-30% of mean normal serum biotinidase activity)

- Compound heterozygotes for the p.As444His 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].

**Heterozygotes**
- Individuals with one profound or one partial biotinidase deficiency \textit{BTD} variant are carriers of biotinidase deficiency and do not exhibit symptoms [B Wolf, personal observation]. Such individuals do not require biotin therapy.

- Individuals who are homozygous 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 newborn screening, but who have never had symptoms [Wolf et al 1997, Baykal et al 2005]. In addition, several enzyme-deficient sibs of symptomatic children 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 \textit{GeneReview} are known to be associated with pathogenic variants in \textit{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.

**Biotin deficiency.** 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.

Low-serum biotin concentrations are useful in differentiating biotin and biotinidase deficiencies from holocarboxylase synthetase deficiency; however, it is important to know the method used for determining the biotin concentration as only methods that distinguish biotin from biocytin or bound biotin yield reliable estimates of free biotin concentrations.

**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:

- Beta-hydroxyisovalerate is the most commonly elevated urinary metabolite in biotinidase deficiency, holocarboxylase synthetase deficiency (OMIM 253270), isolated beta-methylcrotonyl-CoA carboxylase deficiency (OMIM PS210220), and acquired biotin deficiency.
- In addition to beta-hydroxyisovalerate, elevated concentrations of urinary lactate, methylcitrate, and beta-hydroxypropionate are indicative of the multiple carboxylase deficiencies, including the above disorders and propionic acidemia and pyruvate carboxylase deficiency.

The multiple carboxylase deficiencies are biotin responsive, whereas the isolated carboxylase deficiencies are not. A trial of biotin can be useful for discriminating between the disorders.

Isolated carboxylase deficiency can be diagnosed by demonstrating deficient enzyme activity of one of the three mitochondrial carboxylases in peripheral blood leukocytes (prior to biotin therapy) or in cultured fibroblasts grown in low biotin-containing medium, and normal activity of the other two carboxylases.

**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.

The symptoms of biotinidase deficiency and holocarboxylase synthetase deficiency are similar, and clinical differentiation is often difficult.

The age of onset of symptoms may be useful for distinguishing between holocarboxylase synthetase deficiency and biotinidase deficiency. Holocarboxylase synthetase deficiency usually presents with symptoms before age three months, whereas biotinidase deficiency usually presents after age three months; however, there are exceptions for both disorders.

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

Definitive enzyme determinations are required to distinguish between the two disorders:
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.

Individuals with holocarboxylase synthetase deficiency have deficient activities of the three mitochondrial carboxylases in extracts of fibroblasts that are incubated in medium containing only the biotin contributed by fetal calf serum (low biotin), whereas individuals with biotinidase deficiency have normal carboxylase activities in fibroblasts. The activities of the carboxylases in fibroblasts of individuals with holocarboxylase synthetase deficiency become near-normal to normal when cultured in medium supplemented with biotin (high biotin).

Sensorineural hearing loss (see Deafness and Hereditary Hearing Loss Overview). Sensorineural hearing loss 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.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in a symptomatic individual diagnosed with biotinidase deficiency, the following evaluations are recommended:

- History of seizures, balance problems, feeding problems, breathing problems, loss of hair, fungal infections, skin rash, conjunctivitis
- Physical examination for hypotonia, ataxia, eye findings such as optic atrophy, eczematous skin rash, alopecia, conjunctivitis, breathing abnormalities such as stridor, thrush, and/or candidiasis
- Evaluation for psychomotor deficits
- Evaluation for sensorineural hearing loss
- Ophthalmologic examination
- Identification of cellular immunologic abnormalities because of the increased risk of recurrent viral or fungal infections caused by immunologic dysfunction
- Consultation with a metabolic specialist or clinical geneticist

To establish the extent of disease and needs in infants or children diagnosed with biotinidase deficiency following newborn screening, the following evaluations are recommended:

- Physical examination for neurologic findings (e.g., hypotonia, ataxia), eye findings (e.g., conjunctivitis), skin findings (eczematous rash, alopecia), breathing abnormalities (e.g., stridor) and fungal infections caused by immunologic dysfunction (thrush and/or candidiasis).
- Evaluation for psychomotor deficits
- Evaluation for sensorineural hearing loss
- Ophthalmologic examination (for finding such as optic atrophy)
- Consultation with a metabolic specialist or clinical geneticist

Treatment of Manifestations

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. These children may become metabolically compromised and require hydration, occasionally bicarbonate for acidosis, and procedures to ameliorate hyperammonemia. Once it is
recognized that the child has a multiple carboxylase deficiency, administration of biotin – or a multivitamin "cocktail" containing biotin – can rapidly resolve the metabolic derangement and improve many of the clinical symptoms within hours to days.

Compliance with biotin therapy (see Prevention of Primary Manifestations) improves symptoms in symptomatic individuals.

Some features such as optic atrophy, hearing loss, or developmental delay may not be reversible; they should be addressed with ophthalmologic evaluations and intervention, hearing aids or cochlear implants, and appropriate interventions for developmental deficits.

**Prevention of Primary Manifestations**

All individuals with profound biotinidase deficiency (<10% mean normal enzyme activity), even those who have some residual biotinidase enzyme activity, should be treated with biotin independent of their genotype [Wolf 2003]. Note: Although Möslinger et al [2003] stated that children with greater than 1% to 10% biotinidase activity may not need treatment, a child with 1% to 10% biotinidase activity may be just as likely to develop symptoms as one with total loss of enzyme activity [Wolf 2002]. It is therefore strongly recommended that all
children with profound biotinidase deficiency, regardless of the residual biotinidase enzyme activity, be treated with biotin.

Note: 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.

Biotinidase deficiency is treated by supplementation with oral biotin in free form as opposed to the bound form. Children with biotinidase deficiency identified by newborn screening will remain asymptomatic with compliance to biotin therapy.

All symptomatic children with biotinidase deficiency have improved after treatment with 5-10 mg oral biotin per 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). 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. Note that 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.

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. The liquid preparations usually do not provide a consistent dose and should not be added to milk in a bottle.

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.

Only a few anecdotal reports exist regarding symptoms in children with partial biotinidase deficiency who were not treated with biotin. Because there is no known toxicity for biotin, children with partial deficiency are usually treated with 1-10 mg oral biotin per day.

Biotin therapy is lifelong. There are no known adverse side effects from pharmacologic doses of biotin. In fact, the major problem is the lack of treatment or non-compliance with prescribed treatment.

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. Anecdotally, two girls with profound biotinidase deficiency developed hair loss during adolescence that resolved following increase of their biotin dosages from 10 mg per day to 15 or 20 mg per day.

A protein-restricted diet is not necessary.

**Surveillance**

For all children with biotinidase deficiency:

- Yearly ophthalmologic examination and auditory testing for individuals with profound deficiency and every two years for those with partial deficiency
- Regularly scheduled appointments with primary care physicians or as needed
- Yearly evaluation by a clinical geneticist or metabolic specialist for individuals with profound deficiency and every two years for those with partial deficiency
Symptomatic children with residual clinical problems should be seen as directed by the appropriate subspecialists:

- Evaluation of urinary organic acids if return of symptoms with biotin therapy (most commonly the result of non-compliance)
  
  Note: Measurement of biotin concentrations in blood or urine is not useful except to determine compliance with 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. (Thoroughly cooked eggs present no problem because heating inactivates avidin, rendering it incapable of binding biotin.)

**Evaluation of Relatives at Risk**

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.

The genetic status of any relative with symptoms consistent 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.

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

**Pregnancy Management**

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 of the mother. An optimal prenatal dose has not been determined.

**Therapies Under Investigation**

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://www.clinicaltrialsregister.eu) 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, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —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 obligate heterozygotes (i.e., carriers of one BTD pathogenic variant).
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

**Sibs of a proband**
- At conception, each sib of an individual with biotinidase deficiency has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Sibs of an individual with biotinidase deficiency should be tested for the deficiency even if they do not exhibit symptoms.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband**
- All offspring of an individual with biotinidase deficiency are obligate heterozygotes (carriers) for a BTD pathogenic variant.
- The risk of biotinidase deficiency occurring in the offspring of an individual with biotinidase deficiency is essentially zero if the reproductive partner is not heterozygous for a BTD pathogenic variant.
- Based on a carrier frequency of approximately one in 120 in the general population \(\text{[Wolf 1991]}\), the empiric risk to an individual with biotinidase deficiency of having a child with the disorder is one in 240.

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

**Carrier (Heterozygote) 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 those of normal individuals \(\text{[Wolf et al 1983a]}\). Using serum enzyme activity, heterozygosity can be diagnosed with approximately 95% accuracy \(\text{[Weissbecker et al 1991]}\). However, if the BTD pathogenic variants in the family have been identified, molecular testing is preferred.

**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, clarification of carrier status, and discussion of the availability of prenatal 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.

**DNA banking** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.
Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the BTD pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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 available and preferred.

Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- Biotinidase Deficiency Family Support Group
  biotinidasedeficiency.20m.com

- My46 Trait Profile
  Biotinidase deficiency

- National Library of Medicine Genetics Home Reference
  Biotinidase deficiency

- Save Babies Through Screening Foundation, Inc.
  P. O. Box 42197
  Cincinnati OH 45242
  Phone: 888-454-3383
  Email: email@savebabies.org
  www.savebabies.org

- Association for Neuro-Metabolic Disorders (ANMD)
  5223 Brookfield Lane
  Sylvania OH 43560-1809
  Phone: 419-885-1809; 419-885-1497
  Email: volk4olks@aol.com

- Medical Home Portal
  The Parents & Families section of the Medical Home Portal provides information and resources to help families learn how to better care for a child with chronic and complex conditions and to become more effective partners in their child's care.
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

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<tr>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Protein</th>
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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)

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</tbody>
</table>

Gene structure. BTD consists of four exons [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. For a detailed summary of gene and protein information, see Table A, Gene.

Pathogenic variants. Nearly 200 pathogenic variants have been described in symptomatic children with profound biotinidase deficiency.

A continually updated database of current pathogenic variants has been established [Procter et al 2013]. See www.arup.utah.edu.
Table 2. Selected BTD Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change (Alias 1)</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.98_104delinsTCC (G98del3ins)</td>
<td>p.Cys33PhefsTer36</td>
<td>NM_000060.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_000051.1</td>
</tr>
<tr>
<td>c.511G&gt;A</td>
<td>p.Ala171Thr</td>
<td></td>
</tr>
<tr>
<td>c.1330G&gt;C</td>
<td>p.Asp444His</td>
<td></td>
</tr>
<tr>
<td>c.1368A&gt;C</td>
<td>p.Gln456His</td>
<td></td>
</tr>
<tr>
<td>c.1612C&gt;T</td>
<td>p.Arg538Cys</td>
<td></td>
</tr>
</tbody>
</table>

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.

1. Variant designation that does not conform to current naming conventions.

Normal gene product. Biotinidase is essential for the recycling of the vitamin biotin [Wolf et al 1985a]. Biotinidase has been shown to have biotinyl-hydrolase and biotinyl-transferase activities (see Abnormal gene product) [Hymes & Wolf 1996].

The BTD cDNA has two possible ATG initiation codons and an open reading frame of 1629 bp, relative to the first ATG codon [Cole et al 1994]. The cDNA encodes for a mature protein of 543 amino acids with a molecular mass of 56,771 d. The amino terminus of the mature serum biotinidase is in the same reading frame with both of the ATG codons, consistent with the two putative signal peptides. BTD is expressed in human lung, liver, skeletal muscle, kidney, pancreas, heart, brain, and placenta. The enzyme is a monomeric sialylated glycoprotein with multiple isoforms resulting from differences in the degree of sialylation [Hart et al 1991].

Abnormal gene product. Loss of biotinidase activity is associated with disease [Hymes & Wolf 1996].

References

Published Guidelines / Consensus Statements


Literature Cited


Wolf B. Biotinidase deficiency: "if you have to have an inherited metabolic disease, this is the one to have. Genet Med. 2012;14:565–75. PubMed PMID: 22241090.


Chapter Notes

Author Notes

The author’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. They currently confirm the diagnosis of the enzyme deficiency in a majority of children in the United States and collaborate with laboratories in the US and around the world in determining the mutations that cause profound and partial biotinidase deficiency. Dr Wolf’s laboratory accepts DNA from children with biotinidase deficiency for molecular genetic testing on an experimental basis. He is also currently studying the outcomes of children with biotinidase deficiency identified by newborn screening.

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

Revision History

- 9 June 2016 (bp) Comprehensive update posted live
- 5 December 2013 (me) Comprehensive update posted live
- 15 March 2011 Comprehensive update posted live
- 25 September 2008 (me) Comprehensive update posted live
- 2 March 2006 (me) Comprehensive update posted live
- 10 February 2005 (bw,cd) Revision: targeted mutation analysis clinically available
- 26 November 2003 (me) Comprehensive update posted live
- 27 September 2001 (me) Comprehensive update posted live
- 24 March 2000 (pb) Review posted live
- December 1999 (bw) Original submission

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