GENEReviews

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# Biotinidase Deficiency

[*Late-Onset Biotin-Responsive Multiple Carboxylase Deficiency, Late-Onset Multiple Carboxylase Deficiency*]

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## Summary

**Disease characteristics.** In the untreated state, profound biotinidase deficiency is usually characterized initially by seizures, hypotonia, ataxia, developmental delay, vision problems, hearing loss, and cutaneous abnormalities such as alopecia, skin rash, and candidiasis. With age, motor limb weakness, spastic paresis, and decreased visual acuity occur. Individuals with partial biotinidase deficiency may have hypotonia, skin rash, and hair loss, particularly during times of stress. Once vision problems, hearing loss, and developmental delay occur, they are usually irreversible even with biotin therapy.

**Diagnosis/testing.** Individuals with profound biotinidase deficiency have lower than 10% of mean normal serum biotinidase activity. Individuals with partial biotinidase deficiency have 10%-30% of mean normal serum biotinidase activity. Both profound and partial biotinidase deficiency are usually identified by newborn screening in states where such screening is offered. Targeted mutation analysis of the *BTD* gene, the only gene known to be associated with biotinidase deficiency, is clinically available for a panel of common *BTD* mutations and detects about 60% of cases; sequence analysis of the entire gene is available clinically.

**Management.** Children with biotinidase deficiency identified by newborn screening remain asymptomatic if biotin therapy is instituted early and maintained continuously. All symptomatic children 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. Management of irreversible features includes low vision aids, hearing aids or cochlear implants for hearing loss, and appropriate interventions for developmental deficits. Testing of asymptomatic sibs of an individual with biotinidase deficiency ensures that biotin therapy can be instituted in a timely manner.

**Genetic counseling.** 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. Sibs of an individual with biotinidase deficiency should be tested for the deficiency even if they do not exhibit symptoms. Carrier testing for at-risk family members by targeted mutation analysis using the panel of common *BTD* mutations is available on a clinical basis if the mutations identified in the proband are included in this panel. Prenatal testing for pregnancies at 25% risk is available through measurement of biotinidase activity in cultured amniotic fluid cells. Prenatal diagnosis by molecular genetic testing may be available from laboratories offering custom prenatal genetic testing.

## Diagnosis

### Clinical Diagnosis

Biotinidase deficiency is suspected in the presence of the following characteristic symptoms and is confirmed by enzymatic testing.

Children with **untreated profound biotinidase deficiency** usually exhibit one or more of the following features, which are also observed in children with many other inherited metablic disorders:

- Seizures
- Hypotonia
- Respiratory problems such as hyperventilation, laryngeal stridor, and apnea
- Developmental delay

More specific features of profound biotinidase deficiency include the following:

- Eczematoid skin rash
- Alopecia
- Conjunctivitis
- Candidiasis
- Ataxia

Older children and adolescents may exhibit limb weakness, paresis, and scotomata.

Children with **untreated partial biotinidase deficiency** (10%-30% of mean normal serum biotinidase activity) may exhibit any of the above symptoms, but usually the symptoms are mild and occur only when the child is stressed, such as with a prolonged infection.

### Testing

**Newborn screening.** Biotinidase deficiency can be detected in virtually 100% of infants if the newborn screening panel for the state in which they are born includes biotinidase deficiency testing [see National Newborn Screening Status Report (pdf)]. Newborn screening utilizes a small amount of blood obtained from a heel prick for a colorimetric test for biotinidase activity [Heard et al 1984; Wolf, Heard, Jefferson et al 1985; Heard et al 1986; Wolf 1991].

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

**Biotinidase enzyme activity.** For laboratories offering biochemical testing, see 

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Biotinidase activity in serum is most commonly determined by measuring the release of *p*-aminobenzoate from *N*-biotinyl-*p*-aminobenzoate, a biocytin analogue [Wolf, Grier, Allen, Goodman, & Kien 1983]. Deficient biotinidase activity has also been shown in extracts of leukocytes and fibroblasts [Wolf & Secor McVoy 1983]. (Other assays for biotinidase activity in serum and tissues measure the hydrolysis of biocytin or other biotinyl derivatives.)

Note: 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]. 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].

- Individuals with profound biotinidase deficiency have lower than 10% mean normal serum enzyme activity.
- Individuals with partial biotinidase deficiency have 10%-30% of mean normal serum biotinidase activity.

Note: Individuals with either profound biotinidase deficiency or partial biotinidase deficiency are usually identified by newborn screening in states in which it is offered [McVoy et al 1990, Suormala et al 1990].

**Plasma biotin concentration.** Plasma biotin concentrations may be decreased or in the low normal range in individuals with profound biotinidase deficiency.

**Other.** Most individuals with biotinidase deficiency exhibit metabolic ketolactic acidosis, organic aciduria, and mild hyperammonemia. However, the absence of organic aciduria or metabolic ketoacidosis does not exclude the diagnosis of biotinidase deficiency in a symptomatic child.

**Carrier detection.** Carriers (heterozygotes) usually have serum enzyme activity levels intermediate between those of affected and those of normal individuals [Wolf, Grier, Allen, Goodman, & Kien 1983]. Heterozygosity can be diagnosed with about 95% accuracy [Weissbecker et al 1991].

## Molecular Genetic Testing

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

**Molecular Genetic Testing—Gene.** *BTD* is the only gene known to be associated with biotinidase deficiency.

### Clinical use

- Carrier testing

### Clinical testing

- **Targeted mutation analysis.** Real-time PCR of DNA from the blood spot of a newborn screen card can be used to identify a panel of common *BTD* mutations (G98del3ins, p.Gln456His, p.Arg538Cys, p.Asp444His, and the double mutation p.Ala171Thr:p.Asp444His) [Dobrowolski et al 2003]. These five mutations that cause profound biotinidase deficiency comprise approximately 60% of the abnormal alleles found in symptomatic individuals and in children identified by newborn screening [Pomponio et al 1997, Norrgard et al 1999].
  - Two mutations, G98del3ins and 1612C>T (p.Arg538Cys), occurred in both symptomatic individuals and children identified by newborn screening, but occurred in symptomatic individuals at a significantly greater frequency.

- The other common mutations, 1368A>C (p.Gln456His) and the double mutation 511G>A:1330G>C (p.Ala171Thr:p.Asp444His), occurred only in the newborn screening group in this study.

- **Sequence analysis.** Direct sequencing of *BTD* and its intron/exon junctions is available clinically [Hymes et al 2001, Wolf 2003].
- Almost all individuals with partial biotinidase deficiency have the mutation 1330G>C (p.Asp444His) in one allele of *BTD* in combination with a mutation for profound deficiency in the other allele [Swango et al 1998].

Table 1 summarizes molecular genetic testing for this disorder. **Note:** Because genotype/phenotype correlations in biotinidase deficiency are not well established, decisions regarding treatment should be based on the results of enzyme activity only. Genotyping is most useful when the results of enzymatic testing are ambiguous, such as in differentiating profound biotinidase deficiency from partial biotinidase deficiency and in differentiating heterozygosity for profound biotinidase deficiency from partial biotinidase deficiency.

Table 1. Molecular Genetic Testing Used in Biotinidase Deficiency

| Test Method | Mutations Detected | Mutation Detection Frequency [1] | Test Availability |
|---|---|---|---|
| Targeted mutation analysis | G98del3ins, p.Gln456His, p.Arg538Cys, p.Asp444His, and p.Ala171Thr:p.Asp444His | ~60% | Clinical Testing |
| Sequence analysis | All mutations in *BTD* and intron/exon junctions | ~99% | |

1. Proportion of affected individuals with a mutation(s) as classified by test method

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

### Testing Strategy

A child with clinical features suggestive of biotinidase deficiency or whose biochemical findings are indicative of multiple carboxylase deficiency should have biotinidase enzyme activity determined in serum/plasma. With appropriate controls, this testing is definitive for confirming the diagnosis.

A child who is identified as a putative positive for biotinidase deficiency by newborn screening should have confirmational testing of biotinidase enzyme activity in serum/plasma.

**Carrier testing for at-risk relatives** requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

### Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in the *BTD* gene.

## Clinical Description

### Natural History

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. Neurologic problems occur only in those individuals with biotinidase deficiency who have recurrent symptoms and metabolic compromise prior to biotin treatment.

**Profound biotinidase deficiency.** Symptoms of untreated profound biotinidase deficiency usually appear between the ages of one week and ten years, with a mean age of three and one-half months [Wolf, Heard, Weissbecker et al 1985].

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

The most common neurologic features of individuals with untreated, profound biotinidase deficiency are seizures and hypotonia [Wolf, Grier, Allen, Goodman, Kien et al 1983; Wolf, Heard, Weissbecker et al 1985; Wastell et al 1988; Wolf 1995]. The seizures are usually myoclonic, but may be grand mal and focal; some individuals have infantile seizures [Salbert, Pellock et al 1993]. Older affected children often have ataxia and developmental delay.

Neurosensory hearing loss and eye problems, such as optic atrophy, have also been described in untreated children [Wolf, Grier, & Heard 1983; Taitz et al 1985; Salbert, Astruc et al 1993; Weber et al 2004]. About 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, Spencer et al 2002].

Many symptomatic children with biotinidase deficiency exhibit a variety of central nervous system abnormalities on MRI or CT of the brain [Wolf et al 1983, Wastell & Bartlett 1988, Salbert et al 1993, Lott et al 1993, Grunewald et al 2004]. These findings may improve or become normal after biotin treatment.

Cutaneous symptoms include skin rash, alopecia, and recurrent viral or fungal infections caused by immunologic dysfunction. Respiratory problems, such as 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].

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, Ramaekers et al 1993, Lott et al 1993]. After several months of biotin therapy, the eye findings resolved and the spastic paraparesis improved. In addition, other individuals with enzyme deficiency have had the occurrence of paresis and eye problems during early adolescence [Tokatli et al 1997, Wolf et al 1998]. Two adults with profound biotinidase deficiency, both of whom are parents of children with profound biotinidase deficiency identified by newborn screening, have never had symptoms [Wolf et al 1997].

**Partial biotinidase deficiency.** 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 about six months of age. When treated with biotin, the symptoms resolved. Individuals with partial biotinidase deficiency may develop symptoms only when stressed, such as during infection.

**Outcome with biotin treatment.** An outcome study of children with biotinidase deficiency indicates that biotin treatment is effective in preventing symptoms [Moslinger et al 2001]. Moslinger et al suggested that children with profound deficiency who have less than 1% biotinidase activity should be treated with biotin, but those 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.

## Genotype-Phenotype Correlations

Genotype/phenotype correlations are not well established. Deletions, insertions, or nonsense mutations usually result in complete absence of biotinidase enzyme activity, whereas missense mutations 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 of earlier onset of symptoms. Regardless of their molecular genetic test results, all individuals with deficient biotinidase activity require biotin treatment.

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

- Most mutations in *BTD* cause complete loss or nearly complete loss of biotinidase activity. These alleles are considered profound biotinidase deficiency alleles; a combination of two such alleles, whether homozygous or compound heterozygous, results in the individual having profound biotinidase deficiency. Such individuals are likely to develop symptoms if not treated with biotin.
- Individuals with one profound biotinidase deficiency allele and a normal allele are heterozygotes or carriers of profound biotinidase deficiency. Parents of children with profound biotinidase deficiency are in this group. No parents of children with profound or partial biotinidase deficiency have ever exhibited symptoms [B Wolf, personal observation]. Such individuals do not need biotin therapy.
- Individuals who are compound heterozygotes for the p.Asp444His mutation and a mutation that results in profound biotinidase deficiency are expected to have about 20%-25% of mean normal serum biotinidase activity or partial biotinidase deficiency [Swango et al 1998]. Individuals in this group are routinely treated with biotin [McVoy et al 1990].
- The p.Asp444His mutation in cis configuration with the p.Ala171Thr mutation (double mutation) results in an allele causing profound biotinidase deficiency. An individual with an allele having these two mutations in cis configuration combined with another allele with a mutation for profound biotinidase deficiency has profound biotinidase deficiency and requires biotin therapy [Norrgard et al 1998].
- Individuals who are homozygous or have two alleles for the p.Asp444His mutation are expected to have about 45%-50% of mean normal serum biotinidase activity. This is similar to the activity of heterozygotes for profound biotinidase deficiency. Such individuals do not need biotin therapy.
- Several adults with profound biotinidase deficiency have never had symptoms and have never been treated [Wolf et al 1997], while some children with the same mutations have been symptomatic. Therefore, it has been speculated that some children with profound biotinidase deficiency may exhibit mild or no symptoms if left untreated. However, it is recommended that these children be treated [Moslinger et al 2003].

## Penetrance

All children with profound biotinidase deficiency become symptomatic or are at risk of becoming symptomatic if not treated. Several adults with profound biotinidase deficiency identified through family studies have never exhibited symptoms. 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 are the accepted nomenclature for this disorder. Individuals with this disorder were previously described as having late-onset or juvenile multiple or combined carboxylase deficiency.

Biotinidase deficiency should not be confused with holocarboxylase synthetase deficiency, previously called 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; and one in 61,067 for the combined incidence of profound and partial biotinidase deficiency. Carrier frequency in the general population is about one in 120.

## Differential Diagnosis

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

Clinical features, such as 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, such as isolated carboxylase deficiency, before they are correctly identified [Suormala et al 1985, Wolf 1992]. 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.

**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, but it is important to know the method used for determining the biotin concentration. 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, isolated beta-methylcrotonyl-CoA carboxylase deficiency, 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.

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.** Both biotinidase deficiency and holocarboxylase synthetase deficiency are multiple carboxylase deficiencies. Both are biotin responsive.

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 three months of age, whereas biotinidase deficiency usually occurs after three months of age; 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 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.

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.

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

**Ataxia (see Hereditary Ataxia Overview).** Ataxia has multiple causes. Biotinidase deficiency can be excluded as a cause by determining enzymatic activity in serum. The test should be performed especially on children with ataxia who are exhibiting other clinical features consistent with biotinidase deficiency.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an 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, eczematoid skin rash, alopecia, conjunctivitis, breathing abnormalities such as stridor, thrush, and/or candidiasis
- Evaluation for sensorineural hearing loss and psychomotor deficits
- Identification of biochemical abnormalities such as metabolic ketolactic acidosis, hyperammonemia, and organic aciduria
- Identification of cellular immunologic abnormalities
- Quantitative determination of biotinidase activity in serum/plasma

### Treatment of Manifestations

Compliance with biotin therapy improves symptoms in symptomatic individuals.

Some features, such as optic atropy, 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, even those who have some residual enzymatic activity, should be treated with biotin independent of their genotype [Wolf 2003].

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 of oral biotin per day.

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 of oral biotin per day.

Biotin therapy is lifelong.

More data are required to determine the dosage of biotin that is necessary for older children with both profound and 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.

It is not necessary to treat individuals with protein-restricted diets.

### Surveillance

For all children with biotinidase deficiency:

- Yearly ophthalmologic examination and auditory testing
- Regular scheduled appointments with primary care physicians or as needed
- Yearly evaluation by the geneticist or metabolic specialist

Symptomatic children with residual clinical problems should be seen as directed by the appropriate sub-specialists:

- 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 as they contain avidin, an egg-white protein that binds biotin, thus decreasing its bioavailability (Thoroughly cooked eggs present no problem, as heating inactivates avidin, making it incapable of binding biotin.)

### Testing of Relatives at Risk

Sibs who have never been tested, even if asymptomatic, should have enzymatic testing.

Any relative with symptoms consistent with biotinidase deficiency should have enzymatic testing.

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

### Therapies Under Investigation

Search ClinicalTrials.gov 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.

### Other

**Genetics clinics** are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

**Support groups** have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed*

*medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the* GeneTests Clinic Directory.

## Mode of Inheritance

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.
- Heterozygotes are asymptomatic.

**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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

**Offspring of a proband**

- All offspring of an individual with biotinidase deficiency are obligate carriers.
- The risk of biotinidase deficiency occurring in the offspring of an individual with biotinidase deficiency is essentially zero if the partner is not heterozygous for the enzyme deficiency.
- Based on a carrier frequency of about one in 120 in the general population, 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 Detection

- Carrier testing is possible by measuring serum biotinidase activity and is about 95% accurate.
- Carrier testing for at-risk family members by targeted mutation analysis using the panel of common *BTD* mutations or by sequence analysis is available on a clinical basis if the mutations identified in the proband are included in this panel.

## Related Genetic Counseling Issues

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

**DNA banking.** DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our

understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

### Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible through measurement of biotinidase activity in cultured amniotic fluid cells and in amniotic fluid obtained by amniocentesis usually performed at about 15-18 weeks' gestation [Secor McVoy et al 1984, Chalmers et al 1994].

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

Although prenatal diagnosis is possible by mutation analysis [Pomponio et al 1998], no laboratories offering molecular genetic testing for prenatal diagnosis of biotinidase deficiency are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research laboratory. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as biotinidase deficiency that do not affect intellect and for which treatment is available are not common. 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

**Preimplantation genetic diagnosis (PGD)** may be available for families in which the disease-causing mutations have been identified in an affected family member. However, because immediate biotin treatment of a newborn child with biotinidase deficiency apparently prevents all symptoms, requests for PGD for biotinidase deficiency will likely be very uncommon. For laboratories offering PGD, see Testing.

## Molecular Genetics

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

Table A. Molecular Genetics of Biotinidase Deficiency

| Gene Symbol | Chromosomal Locus | Protein Name |
|---|---|---|
| *BTD* | 3p25 | Biotinidase |

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

Table B. OMIM Entries for Biotinidase Deficiency

| | |
|---|---|
| 253260 | BIOTINIDASE DEFICIENCY |
| 609019 | BIOTINIDASE; BTD |

Table C. Genomic Databases for Biotinidase Deficiency

| Gene Symbol | Entrez Gene | HGMD |
|---|---|---|
| *BTD* | 686 (MIM No. 253260) | BTD |

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

**Note:** HGMD requires registration.

**Normal allelic variants:** The human biotinidase gene consists of four exons, designated 1-4, with sizes of 79 bp, 265 bp, 150 bp, and 1502 bp, respectively [Knight et al 1998]. Intron 1, separating exons 1 and 2, is at least 12.5 kb; intron 2 is 6.2 kb, and intron 3 is 0.7 kb. Two putative translation initiation codons exist in the gene; the first 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.

The nucleotide sequence upstream of exons 1 and 2 has been examined for putative promoter elements. Promoter features identified from –600 to +400 are consistent with the ubiquitous expression of biotinidase with characteristics of a CpG island, lack of a TATA element, six consensus methylation sites, and three initiator (Inr) sequences, which are thought to be important in transcription initiation of TATA-less promoters. A consensus sequence for the liver-specific transcription factor HNF-5 is present at –352. The nucleotide sequence 5' of exon 2, which contains the second putative ATG initiator codon, has features associated with housekeeping genes, but does contain a consensus sequence for the liver-specific transcription factor C/EBP within 300 bp of the 5' end of exon 2.

Polymorphisms have been found among individuals with normal biotinidase activity.

The cDNA for human biotinidase from a human cDNA hepatic library has two possible ATG initiator 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.

Northern blot analysis, using a 2000-bp probe consisting of the cDNA sequence, revealed that the biotinidase message is present in human lung, liver, skeletal muscle, kidney, pancreas, heart, brain, and placenta under the hybridization conditions used.

**Pathologic allelic variants:** About 100 mutations have been described in symptomatic children with profound biotinidase deficiency [Pomponio, Hymes et al 1997; Muhl et al 2001; Wolf, Jensen et al 2002]:

- A seven-base deletion/three-base insertion (G98del3ins) that occurs in at least one allele of the biotinidase gene in about 50% of symptomatic children [Pomponio et al 1995]
- A missense mutation, 1612C>T (p.Arg538Cys), the second most common cause of profound biotinidase deficiency in symptomatic children [Pomponio, Norrgard et al 1997]

Multiple mutations have been reported in children with profound biotinidase deficiency who were identified by newborn screening [Norrgard et al 1999]. Of this group, two mutations occurred most commonly:

- A 1368A>C (p.Gln456His) missense mutation

- A double mutation, 511G>A:1330G>C (p.Ala171Thr:p.Asp444His) [Norrgard et al 1997, Norrgard et al 1998]
  - This double mutation (p.Asp444His in cis configuration with the p.Ala171Thr mutation) results in a profound biotinidase deficiency allele.
  - An allele with the double mutation combined with a second allele for profound biotinidase deficiency causes profound biotinidase deficiency.
  - Individuals who are compound heterozygous for the p.Asp444His mutation and a mutation that results in profound biotinidase deficiency are expected to have about 20%-25% of mean normal serum biotinidase activity (i.e., partial biotinidase deficiency) [Swango et al 1998].
  - Individuals who are homozygous for the p.Asp444His mutation are expected to have about 50% of mean normal serum biotinidase deficiency. This is similar to the activity of heterozygotes for profound biotinidase defiency.

Several of these pathologic allelic variants are included in OMIM 253260 (see tables above).

**Normal gene product:** Human biotinidase has been purified to homogeneity from plasma and serum by the author and by several others [Wolf et al 1987, Craft et al 1985, Chauhan & Dakshinamurti 1986]. The enzyme is a monomeric sialylated glycoprotein with a molecular weight of 76-77 kd. Normal serum or plasma biotinidase has at least nine isoforms (four major and five minor isoforms) between pH 4.15 and 4.35 observed by isoelectric focusing [Hart et al 1991].

There are six potential N-linked glycosylation sites (N-X-T/S) in the deduced amino acid sequence. Glycosylation of the protein could increase its mass by 13 to 19 kd; the molecular mass of the glycosylated enzyme is thus estimated at between 70 and 76 kd, which is consistent with that of the glycosylated serum enzyme reported by the author's laboratory and other investigators [Craft et al 1985, Chauhan & Dakshinamurti 1986, Wolf et al 1987, Oizumi et al 1989]. Most of the microheterogeneity observed on isoelectric focusing results from differences in the degree of sialylation.

Biotinidase is a thiol enzyme that migrates to the α1-region on agarose electrophoresis. The serum enzyme has a pH optimum of 5-6 when biocytin or biotinyl-p-aminobenzoate (artificial substrate) is the substrate [Pispa 1965, Craft et al 1985, Chauhan & Dakshinamurti 1986]. Biocytin is cleaved more readily than larger biotinyl-peptides [Craft et al 1985]. Biotinidase apparently does not cleave biotin from intact holocarboxylases at acid pH. The biotinyl-binding site of biotinidase is specific for the ureido group of the biotinyl moiety of various substrates [Knappe et al 1963, Chauhan & Dakshinamurti 1986]. Biotinidase plays a role in the processing of dietary protein-bound biotin [Heard et al 1984; Wolf, Grier et al 1985] and has recently been shown to transfer biotin from biocytin to nucleophiles, such as histones [Hymes et al 1995], but the physiologic significance of the latter activity is not known.

**Abnormal gene product:** Biotinidase is essential for the recycling of the vitamin biotin [Wolf, Grier et al 1985]. Biotinidase has been shown to have biotinyl-hydrolase and biotinyl-transferase activities [Hymes & Wolf 1996].

- **Biotinyl-hydrolase activity:** We have determined that both our polyclonal and monoclonal antibodies react on immunoblot with biotinidase in extracts of normal fibroblasts and lymphoblasts. These antibodies react with normal serum biotinidase that has been sialylated by treatment with neuraminidase [Hart et al 1992a]. Individuals with profound biotinidase deficiency can be classified into at least nine distinct biochemical phenotypes on the basis of the presence or absence of cross-

reacting material (CRM) to biotinidase, the number of isoforms, and the distribution frequency of the isoforms. All CRM-positive individuals had normal-size serum biotinidase on SDS-immunoblots. None of the individuals with CRM had an abnormal Km of the substrate for the enzyme. No relationship exists between the age of onset or severity of symptoms and the isoform patterns or CRM status of the symptomatic children. The isoform patterns of children identified by newborn screening are not different from those of symptomatic children.

We have performed biochemical and immunologic characterization of biotinidase in sera from children with partial biotinidase deficiency [Hart et al 1992b]. All individuals had CRM in their sera. Individuals with partial biotinidase deficiency can be classified into six distinct biochemical phenotypes on the basis of the number of isoforms and the distribution frequency of the isoforms. Kinetic studies were performed on samples from these individuals and were found to be normal in all cases. The isoform patterns observed in the individuals with partial biotinidase deficiency were not different from those of individuals with profound biotidase deficiency who had CRM.

- **Biotinyl-transferase activity:** Over one hundred children with profound biotinidase deficiency were assessed for biotinyl-transferase activity and the presence of CRM to antibodies prepared against purified serum biotinidase [Hymes et al 1995]. Sera from all of the symptomatic individuals studied (both CRM-negative and CRM-positive) had no biotinyl-transferase activity. Sera from children detected by newborn screening who were CRM-negative had no biotinyl-transferase activity, whereas a large group of the CRM-positive children had varying degrees of transferase activity. Statistically, a significant difference in biotinyl-transferase activity exists between the population of symptomatic enzyme-deficient children and the population of children who were identified by newborn screening. We have previously shown a difference in the biotinyl-hydrolase activity between the symptomatic and newborn screening group [Hart, Barnstein et al 1992]. The significance of these differences is not yet known. These differences may indicate variations in the domains of the enzyme resulting from different mutations. We do not know if all children with profound biotinidase deficiency who are detected by newborn screening will become symptomatic. Transfer of biotin to histones, which may represent a physiologic function, may ultimately be a criterion for determining which children with profound enzyme deficiency are likely to become symptomatic.

## Resources

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

**Biotinidase Deficiency: A Booklet for Families and Professionals**
www.ccmckids.org/research/Biotinidase/Biotinidase_Deficiency_Booklet.pdf

**National Library of Medicine Genetics Home Reference**
Biotinidase deficiency

**Association for Neuro-Metabolic Disorders (ANMD)**
PO Box 0202/L3220
1500 Medical Center Drive

Ann Arbor MI 48109-0202
**Phone:** 313-763-4697
**Fax:** 313-764-7502

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

## References

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

### Published Statements and Policies Regarding Genetic Testing

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

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### Suggested Readings

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## 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 U.S. 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.

**Biotinidase Deficiency: A Booklet for Families and Professionals**, by DL Thibodeau, MS and B Wolf, MD, PhD
Available on request from Barry Wolf
Email: bwolf@ccmckids.org
Updated version available online

### Revision History

- 22 October 2007 (bw,cd) Revision: sequence analysis available clinically
- 2 March 2006 (me) Comprehensive update posted to live Web site
- 10 February 2005 (bw,cd) Revision: targeted mutation analysis clinically available
- 26 November 2003 (me) Comprehensive update posted to live Web site
- 27 September 2001 (me) Comprehensive update posted to live Web site
- 24 March 2000 (pb) Review posted to live Web site
- December 1999 (bw) Original submission