

# BIOTINIDASE DEFICIENCY



## **BIOTINIDASE DEFICIENCY**

Biotinidase deficiency is an inherited metabolic disorder that results from the inability to recycle biotin, leading to carboxylase deficiencies. Complete or partial enzyme deficiency causes a variety of symptoms. Early diagnosis and treatment can prevent or reverse many or all of the clinical manifestations.

### **Clinical Features in Children with Untreated Biotinidase Deficiency**

Children with less than 10% normal biotinidase activity often have seizures and hypotonia. Additional early symptoms can include breathing problems, skin rashes, and hair loss. Later problems include developmental delays, speech problems, vision and hearing loss, and ataxia.

### **Causes of Biotinidase Deficiency**

Mutations in the BTD gene cause biotinidase deficiency. The BTD gene provides instructions for making an enzyme called biotinidase. This enzyme helps the body reuse biotin, a B vitamin found in foods such as liver, egg yolks and milk. Biotinidase also recycles biotin from enzymes involved in metabolism. A lack of biotin inhibits carboxylases from processing fats, proteins or carbohydrates.

### **Laboratory Screening Tests**

Biotinidase deficiency is detected by the Wolfe colorimetric method. Results are reported either as Normal or Abnormal. Normal specimens show that they have adequate enzyme activity. Abnormal specimens show no biotinidase enzyme and are deficient of the biotinidase enzyme and need further testing and consultation.

### **Confirmatory Testing**

When the infant's primary care provider is notified that the screening results show an absence of biotinidase activity, a referral to a metabolic specialist should be made. The specialist should examine the baby for symptoms and may repeat the newborn screening test or decide to perform confirmatory testing. The confirmatory testing is performed by either Mayo Clinic or the University of MD - Biochemical Genetics Laboratory.

### **Treatment**

Treatment of biotinidase deficiency is life long and consists of daily biotin therapy in the form of oral biotin. No dietary restrictions are needed. The prognosis for individuals with biotinidase deficiency is very good, particularly if they are treated before symptoms appear.

### **Screening Practice Considerations**

Since the laboratory test looks for enzymatic activity, it is important that the newborn screening card not be exposed to high temperatures during drying or transport, as that may inactivate the enzyme and cause a false positive result. Pre-term infants and delay in submission of the screening card may also cause a false positive result. False negatives can occur if the infant has had a blood

transfusion or if the infant has been on sulfonamides. A repeat screen should be performed 90 days post-transfusion.

### **Medical Consultant for Children with Biotinidase Deficiency**

A medical consultant is available to provide consultation for the follow-up, evaluation and long-term management of children with biotinidase deficiency through the State of Kansas. Please contact:

Dr. Majed Dasouki  
KU Medical Center  
Kansas City, KS  
Office: 913-588-6326  
FAX: 913-588-6288

## Overview of Follow-up Procedure Abnormal Newborn Screening for Biotinidase Deficiency (BIOT)

- 1) Newborn Screening follow-up team reviews the laboratory reports that are faxed overnight from the lab or records the information provided per telephone call from the laboratory on a white phone information sheet.
- 2) If the Biotinidase result is "Present", the result is considered **normal**.
  - a) Follow-up team does not receive results.
  - b) Lab will fax or mail the results to the healthcare provider listed on the NBS card.
- 3) If the Biotinidase result is "Absent" the result is considered **presumptive**.
  - a) Lab will contact follow-up team via phone with baby's information and test results. Follow-up team will document information on white phone slip.
  - b) Follow-up team will print out baby's information from DHEL database on a green sheet of paper, attach the white phone slip and write "BIOT" and the result on green sheet.
  - c) Follow-up team will enter data into Access database under BIOT.
  - d) Follow-up team will call healthcare provider listed on report and:
    - i) Verify that they are seeing the baby.
    - ii) Inform them of results.
    - iii) Ask them to notify parents and arrange appointment with specialist.
    - iv) Confirm doctor's fax number.
    - v) Inform them that a letter will be faxed to their office with the results and instructions.
  - e) Follow-up team will print BIOT presumptive letter and BIOT physician report form and fax (or mail, if no fax) to healthcare provider.
  - f) Follow-up team will print BIOT parent letter and BIOT parent information sheet and mail to baby's parents to inform them that their child has an abnormal result. NOTE: If infant is in the NICU, no parent letter is sent.
  - g) Follow-up team will enter data into Excel spreadsheet "Presumptive Totals" located on the "H" drive.
  - h) Lab will fax or mail results to doctor listed on NBS card.
  - i) Lab will fax results to follow-up team. Report is attached to green sheet.
  - j) Follow-up team will enter lab information into WebIZ and set a follow-up reminder for 2 weeks from date of letter. NOTE: Name changes are documented on the lab report. Surname changes are also documented in WebIZ as an alias.
  - k) When complete, paperwork is filed by infant's date of birth.



## KANSAS DEPARTMENT OF HEALTH AND ENVIRONMENT

# NEWBORN SCREENING ACT SHEET

**SCREEN FOR:** ABSENT BIOTINIDASE ACTIVITY

**CONDITION:** BIOTINIDASE DEFICIENCY (BIOT)

**DIFFERENTIAL DIAGNOSIS:** Biotinidase deficiency

**METABOLIC DESCRIPTION:** *Biotinidase deficiency results from defective activity of the biotinidase enzyme.*

### ACTION TO BE TAKEN **IMMEDIATELY:**

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, lethargy, hypotonia).
- See and evaluate infant.
- Consultation/referral to a metabolic specialist to determine appropriate follow-up.
- If infant can not be seen immediately at metabolic specialist, undertake confirmatory testing in consultation with metabolic specialist.
- Emergency treatment if symptomatic.
- Report findings to newborn screening program.

**CONFIRMATION OF DIAGNOSIS:** Enzyme assay for biotinidase reveals low or absent activity. Plasma acylcarnitine analysis may show normal or increased 3-hydroxyisovaleric acid and 3-methylcrotonyl-glycine. C5-OH acylcarnitine may be high but lack of an abnormal acylcarnitine profile does not rule out biotinidase deficiency.

**CLINICAL EXPECTATIONS:** The neonate is usually asymptomatic but episodic hypoglycemia, lethargy, hypotonia and mild developmental delay can occur at any time from the neonatal period through childhood. Untreated biotinidase deficiency leads to developmental delay, seizures, alopecia, and hearing deficits. Biotin treatment is available and highly effective.

**REPORTING:** Report diagnostic result to family and Kansas NBS program.

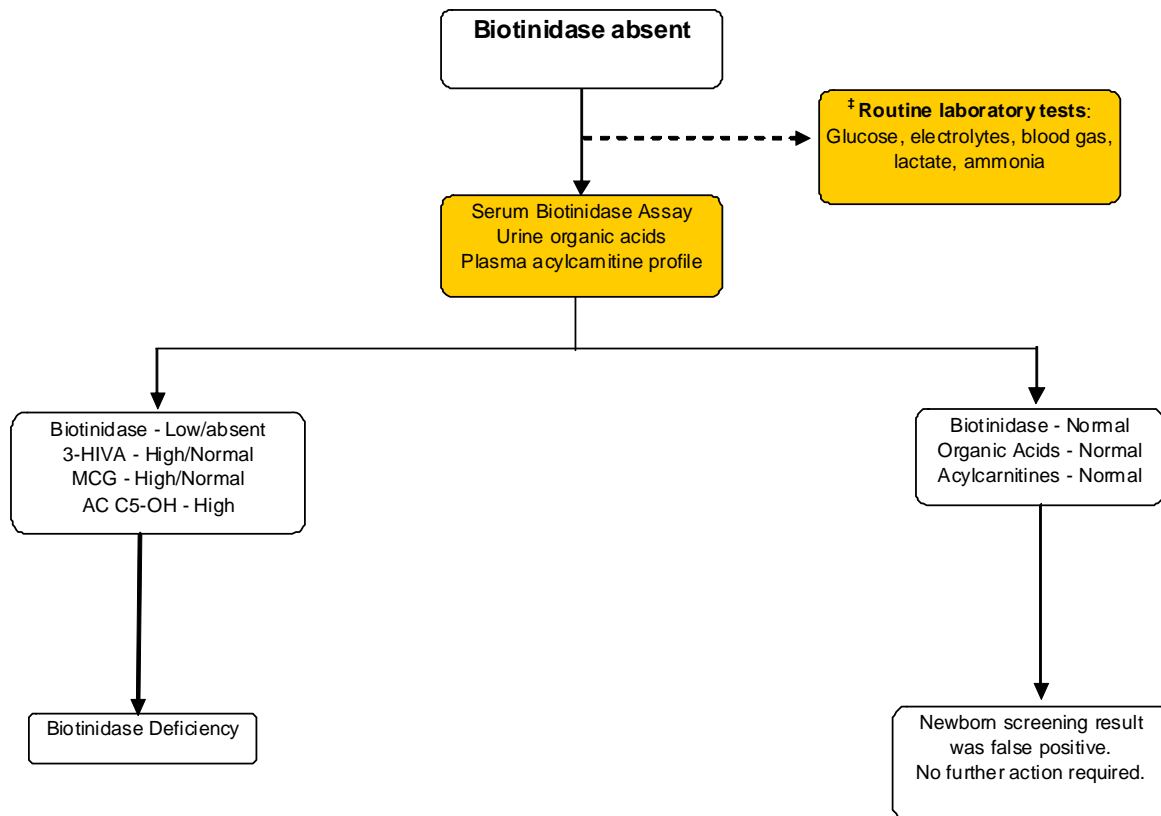
### **SPECIALIST:**

Dr. Majed Dasouki  
KU Medical Center  
Kansas City, KS  
Office: 913-588-6326  
FAX: 913-588-6288

**DISCLAIMER:** These standards and guidelines were adapted from the American College of Medical Genetics ACT sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines



# BIOTINIDASE DEFICIENCY



**Abbreviations/Key**

3-HIVA = 3-OH-isovaleric acid

AC = Acylcarnitine

AC C5-OH = C5-hydroxyacylcarnitine

MCG = 3-methylcrotonylglycine

Action steps are shown in gold (shaded) boxes; results are in plain boxes.

Dash lines indicate optional steps

‡ = When the positive predictive values of screening are sufficiently high and the risk to the baby is high, some initiate diagnostic studies at the same time as confirmation of screening result is done.

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EXAMPLE OF PRESUMPTIVE BIOTINIDASE DEFICIENCY (BIOT) PHYSICIAN LETTER



Mark Parkinson, Governor  
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH  
AND ENVIRONMENT

www.kdheks.gov

**Absent Biotinidase Activity (BIOT) Lab Report  
Kansas Newborn Screening Program**

Date

Doctor's Name  
Address Line 1  
Address Line 2

RE: Baby's Name  
DOB: xx/xx/xxxx

MOTHER'S NAME: Mother's Name  
MOTHER'S PHONE: xxx-xxx-xxxx

Specimen date: xx/xx/xxxx

**Biotinidase activity:** Result  
Expected result: Present

The absence of biotinidase activity is highly suggestive of a biotinidase deficiency. Untreated biotinidase deficiency leads to developmental delay, seizures, alopecia, skin rash, visual and hearing deficits.

The final newborn screening lab report will be sent when all testing is completed.

**RECOMMENDATION:**

Immediate consultation with the consultant listed below is essential for diagnostic testing. Please call to arrange an immediate appointment.

***In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.***

For consultation, please contact:

Dr. Majed Dasouki  
KU Medical Center  
Kansas City, KS  
Office: 913-588-6326  
FAX: 913-588-6288

**\*\*PLEASE COMPLETE AND RETURN THE ENCLOSED PHYSICIAN REPORTING FORM WHEN FOLLOW UP IS COMPLETE\*\***

Additional information is available on the Kansas Newborn Screening Website at:  
[http://www.kdheks.gov/newborn\\_screening/info\\_professionals.htm](http://www.kdheks.gov/newborn_screening/info_professionals.htm).

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF BIOTINIDASE DEFICIENCY (BIOT) PHYSICIAN'S REPORT FORM



Mark Parkinson, Governor  
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH  
AND ENVIRONMENT

www.kdheks.gov

**BIOTINIDASE (BIOT) NEWBORN SCREENING  
PHYSICIAN REPORTING FORM**

**\*\*Return this form When Follow-Up is Complete \*\***

Date

Doctor's Name  
Address Line 1  
Address Line 2

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**If this infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.**

RE: Baby's Name  
DOB: xx/xx/xxxx

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**Baby's name if different than listed**

**DIAGNOSIS EXCLUDED:** Date Excluded: \_\_\_\_\_

Baby does **NOT** have Biotinidase deficiency

**DIAGNOSIS CONFIRMED:** Date Diagnosis Confirmed: \_\_\_\_\_

Baby has Biotinidase deficiency

Lab Results: (please fill in and attach copy of specialist's report)

Serum biotinidase activity: \_\_\_\_\_ Plasma acylcarnitine profile: \_\_\_\_\_

Urine organic acids: \_\_\_\_\_ Additional labs: \_\_\_\_\_

Date treatment began: \_\_\_\_\_

Baby referred to specialist (please attach copy of specialist's report)

Name of specialist: \_\_\_\_\_

**FORM CONTINUES ON BACK**





## **Biotinidase Deficiency Information for Healthcare Professionals**

Biotinidase deficiency is an inherited metabolic disorder that results from the inability to recycle biotin, leading to multiple carboxylase deficiencies. Complete or partial enzyme deficiency causes a variety of neurological and cutaneous symptoms. **Early diagnosis and treatment can prevent or reverse many or all of the clinical manifestations.**

### **✓ Clinical Symptoms**

The signs and symptoms of biotinidase deficiency typically appear within the first few months of life, but the age of onset varies. Children with profound biotinidase deficiency (less than 10% of normal biotinidase activity), often have seizures and hypotonia. Additional early symptoms can include breathing problems, skin rashes, and hair loss. Later problems that may occur include developmental delays, speech problems, vision and hearing loss, and ataxia.

Partial biotinidase deficiency (10-30% of normal biotinidase activity), is a milder form of this condition. Symptoms in these individuals may only appear during times of metabolic stress including infection, illness, and fasting.

### **✓ Incidence**

Profound or partial biotinidase deficiency occurs in approximately 1 in 75,000 newborns.

### **✓ Genetics of biotinidase deficiency**

Mutations in the BTBD9 gene cause biotinidase deficiency. The BTBD9 gene encodes an enzyme called biotinidase. This enzyme helps the body release biotin, a B vitamin found in foods such as liver, egg yolks, and milk. Biotinidase also recycles biotin from enzymes involved in metabolism. Biotin deficiency then inhibits several carboxylases that are responsible for processing fats, proteins, or carbohydrates.

### **✓ Inheritance Patterns**

Biotinidase deficiency is inherited in an autosomal recessive pattern. Typically, parents of a child diagnosed with biotinidase deficiency are unaffected. These individuals are carriers of the condition and have one normal BTBD9 gene and one abnormal BTBD9 gene. Each pregnancy between carrier parents has a 25% chance of producing a child affected with biotinidase deficiency, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier. In some families, asymptomatic parents and siblings were found to have either partial or complete BTBD9 deficiency.

### **✓ Treatment**

Treatment is life long and consists of daily biotin therapy in the form of oral biotin. No dietary restrictions are necessary. The prognosis for individuals is very good, particularly if they are treated before symptoms appear.

## ✓ **Screening Methodology**

Testing methodology used in newborn screening to detect biotinidase deficiency is a colorimetric assay. A positive newborn screen indicates absent biotinidase enzyme activity.

False positives are possible and may occur if the specimen is drawn from pre-term infants, submission is delayed, or if the specimen has been exposed to heat. False negatives can result if an infant has had a blood transfusion. The newborn screen should be performed 90 days post-transfusion. In such babies, if clinically indicated, DNA analysis can help confirm biotinidase deficiency.

## ✓ **What to do After Receiving Presumptive Biotinidase Deficiency Screening Results**

- 1) **Clinical Evaluation: Common findings include seizures, hypotonia, and skin rashes.**
- 2) **Immediately consult a metabolic specialist.**
- 3) **Laboratory: Order enzymatic testing for biotinidase activity unless told otherwise by metabolic specialist.**
- 4) **Call KS Newborn Screening Program at 785-291-3363 with questions about results.**
- 5) **Report Clinical Findings to Newborn Screening Program at 785-291-3363.**

## ✓ **Communication of Results to Parents**

**If a baby has a presumptive biotinidase deficiency newborn screening result, additional testing needs to be performed to confirm a diagnosis.** In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with biotinidase deficiency, the following points should be conveyed to parents:

- ***Treatment is life-long. While very effective, it does not prevent all medical problems.***
- ***Compliance with treatment is necessary for the best outcome.***
- ***Parents who have a child with biotinidase deficiency have a 25% chance with each pregnancy of having another affected child.***
- ***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.***

For consultation, contact:

Dr. Majed Dasouki  
KU Medical Center  
Kansas City, KS  
913-588-6326

11/24/08

EXAMPLE OF PARENT LETTER FOR BIOTINIDASE DEFICIENCY (BIOT)



Mark Parkinson, Governor  
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH  
AND ENVIRONMENT

[www.kdheks.gov](http://www.kdheks.gov)

Date

Mother's Name  
Address Line 1  
Address Line 2

RE: Baby's Name                      DOB: xx/xx/xxxx

Dear Parent:

Best wishes on the birth of your baby! Shortly after your baby was born, a small blood sample was taken for a test called the Newborn Screen. This test helps parents find out if their baby has certain health problems. A baby can look healthy, but may have a harmful illness that can be found by doing this blood test.

The result of your baby's blood test shows that more testing needs to be done for biotinidase deficiency. ***This does not necessarily mean your child is ill.***

**THIS IS WHAT YOU NEED TO DO NOW:**

1. Call your baby's doctor. Say that you have received a letter stating that your baby's Newborn Screen test was not normal. Set up a time for your baby to have a second test done as soon as you can.
2. We have < Doctor's Name > listed as your baby's doctor, and we have notified him/her of your baby's test result. If this is NOT your baby's doctor, please call the Newborn Screening Program at 785-296-0109 so we can contact the right doctor.

**DO NOT DELAY. YOUR BABY'S HEALTH DEPENDS ON YOU.**

If your baby does not have a doctor, or if you have questions about this letter, please call Kansas Newborn Screening at 785-296-0109.

Sincerely,

A handwritten signature in black ink that reads "Jamey Kendall".

Jamey Kendall BSN, RN  
Kansas Newborn Screening  
Follow-up Coordinator

A handwritten signature in black ink that reads "Linda A. Williams".

Linda A. Williams, MT(ASCP)  
Kansas Newborn Screening  
Follow-up Coordinator



## **Biotinidase Deficiency Information for Parents**

### **➤ Overview**

Biotinidase deficiency is a rare condition that affects the way a person's body uses the vitamin biotin. Individuals with biotinidase deficiency can not use the biotin that is normally found in foods. Treatment is very effective for these individuals, and can prevent most symptoms from occurring.

### **➤ What is biotinidase deficiency?**

Biotin is found in many foods and is important for proper growth and development. Normally, an enzyme in our body called biotinidase helps separate biotin from the food we eat so our body can use it to help other enzymes in the body do their job. In babies with biotinidase deficiency, the enzyme doesn't work very well so the baby's body doesn't get enough biotin.

### **➤ Why is newborn screening done for biotinidase deficiency?**

Newborn screening is done for biotinidase deficiency so that babies with this condition can be diagnosed quickly. If babies are diagnosed quickly, treatment can begin before any health problems occur.

### **➤ Does a positive result from the Kansas Newborn Screening Lab mean that my baby has biotinidase deficiency?**

No, not necessarily. Newborn screening tests the baby's level of biotinidase enzyme, but additional tests will need to be done to determine if the baby has biotinidase deficiency or not.

### **➤ How common is biotinidase deficiency?**

About 1 out of every 75,000 babies born has either a partial or complete absence of this enzyme.

### **➤ How is biotinidase deficiency inherited?**

Biotinidase deficiency is inherited in an autosomal recessive pattern. Parents of a child diagnosed with biotinidase deficiency are unaffected. These individuals are carriers of the condition and have one normal BTM gene and one abnormal BTM gene. Each pregnancy between carrier parents has a 25% chance of producing a child affected with biotinidase deficiency, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

### **➤ What are the signs and symptoms of biotinidase deficiency?**

Babies that have biotinidase deficiency will appear normal at birth. Within a few weeks or months after birth, symptoms will develop if the individual is untreated. The number of symptoms that a baby will develop, as well as how severe the symptoms will be, varies from baby to baby.

Some common early signs include:

- seizures
- low muscle tone (floppiness)
- hair loss
- skin rash

Some common later signs include:

- hearing loss
- vision loss
- delayed development
- ataxia (poor coordination)
- possibly coma and death

Once treatment begins, most of the symptoms will disappear. Some symptoms, such as hearing loss, developmental delay, and vision loss, may not be fully corrected with treatment, but usually won't get worse. If babies are diagnosed early and treatment is started before symptoms appear, they usually don't develop any symptoms.

➤ **How is biotinidase deficiency diagnosed?**

Confirmation of any initial abnormal newborn screening result requires an immediate referral to a metabolic disease specialist.

➤ **Is there a cure for biotinidase deficiency?**

No, there is no cure for biotinidase deficiency. Treatment can ensure that babies grow up healthy and prevent many symptoms of this condition.

➤ **How is biotinidase deficiency treated?**

Children with biotinidase deficiency will need to take extra biotin. Biotin supplements come in pill and liquid forms. They will have to take this supplement throughout their life. Babies should also have regular checkups with a metabolic specialist and their pediatrician.

➤ **Where can I get additional information?**

Parents may find beneficial support groups that give them the opportunity to talk with parents of other children with biotinidase deficiency. For more information about newborn screening in general and about biotinidase deficiency specifically, contact the National Newborn Screening and Genetics Resource Center, 1912 W. Anderson Lane, Suite 210, Austin, TX 78757; telephone 512-454-6419; fax 512-454-6509.

GeneTests at [www.genetests.org](http://www.genetests.org)

Biotinidase Family Support Group at [www.biotinidasedeficiency.20m.com](http://www.biotinidasedeficiency.20m.com)

Biotinidase Deficiency: A Booklet for Families & Professionals  
[www.ccmckids.org/research/Biotinidase/Biotinidase\\_Deficiency\\_Booklet.pdf](http://www.ccmckids.org/research/Biotinidase/Biotinidase_Deficiency_Booklet.pdf)

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