Genetics inMedicine | ORIGINAL RESEARCH ARTICLE



# Successful outcomes of older adolescents and adults with profound biotinidase deficiency identified by newborn screening

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**Purpose:** We began screening newborns for biotinidase deficiency disorder in 1984, and now all states in the United States and many countries perform this screening. The purpose of this study was to determine the outcomes of older adolescent and adult individuals with the disorder identified by newborn screening.

**Subjects and methods:** We located and surveyed, by questionnaire and telephone interviews, 44 individuals with profound biotinidase deficiency identified by newborn screening with a mean age of 23.1 years.

**Results:** All individuals had successfully completed high school, and many were attending or had completed college or graduate school. Compliance in using biotin has been excellent. Several individuals developed a variety of symptoms when they discontinued biotin for days or weeks. These features readily resolved when biotin was resumed. In addition, five treated women had nine uneventful pregnancies and deliveries.

**Conclusions:** Newborn screening for profound biotinidase deficiency and early treatment with biotin result in excellent outcomes for older adolescents and adults with the disorder. In addition, mothers with profound biotinidase deficiency who were treated with biotin had pregnancies with good outcomes. These outcome results indicate that newborn screening for biotinidase deficiency is one of the most successful newborn screening programs.

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**Key Words:** biotinidase; biotinidase deficiency; newborn screening; outcomes; pregnancy in metabolic disease

## INTRODUCTION

Biotinidase deficiency is the primary enzymatic defect in biotin-responsive, late-onset multiple carboxylase deficiency.[1,2] If untreated, symptomatic individuals with the disorder usually exhibit neurological and cutaneous findings that may progress to coma or death. Fortunately, symptomatic individuals markedly improve after treatment with pharmacological doses of the vitamin biotin.[3] In addition, symptoms can be prevented in asymptomatic enzyme-deficient individuals. However, even if symptomatic individuals are treated, optic atrophy, hearing loss, and/or developmental delays are usually irreversible. Because the disorder met the criteria for inclusion in newborn metabolic screening program,[4] we began screening newborns for the disorder in Virginia in 1984.[5] Since then, all states and many countries have incorporated testing for the disorder in their newborn screening programs.[6]

We recently reviewed the outcomes of individuals with profound biotinidase deficiency (less than 5–10% of mean normal serum activity) identified by newborn screening during a 25-year period in Michigan.[7] Although the outcomes were excellent, we noted that the study population was definitely skewed to younger children with a mean age of 8.3 years. Contact had been lost with many of the older individuals with the disorder. Although there are a number of reasons why these older individuals are no longer being seen in genetic and metabolic clinics, we wanted to determine the outcomes of adolescents older than 15 years of age and adults with profound biotinidase deficiency identified by newborn screening.

## MATERIALS AND METHODS

My laboratory discovered biotinidase deficiency in 1982.[2] It was one of the few laboratories in the world that performed quantitative enzymatic testing of symptomatic children, because confirmatory testing used an enzymatic substrate that had to be synthesized and was not commercially available. We developed a method of newborn screening for the disorder[4] and piloted a newborn screening program.[5,8] Early records of those tested in my laboratory have enabled us to search for and find many of the older individuals with profound biotinidase deficiency identified by newborn screening. In addition, because we were the first to characterize the biotinidase gene (*BTD*),[9,10] our laboratory performed mutation analysis of most of these individuals.[11]

We were able to contact 44 older individuals, and in some cases their parents, by e-mail or telephone. All the individuals

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contacted agreed to participate in accordance with the approved institutional review board protocol (no. 9340) at Henry Ford Hospital in Detroit. They were given a questionnaire inquiring about their medical, educational, and compliance experiences (available as **Supplementary Material** online). Some aspects of their responses were discussed in more detail during telephone interviews.

Biotinidase activities and mutation analyses were determined as described below and were not obtained from questionnaire responses. Biotinidase activity was measured in serum using the artificial substrate of biocytin, *N*-biotinyl-*p*-aminobenzoate.[2] Mean normal serum activity is 7.2 nmol/min/ml (range 4.4 to 11.0). Nearly all of the enzymatic activity assays reported here were performed to confirm the diagnosis soon after the child had been identified by newborn screening in my laboratories at the Medical College of Virginia at Virginia Commonwealth University in Richmond, Virginia, and at the University of Connecticut School of Medicine in Farmington, Connecticut. The remaining assays were performed at the Biochemical Genetics Laboratories at Children's Hospital of Michigan and at several other laboratories where the infants' samples were sent.

Essentially all of the mutation analyses were performed in my laboratory; several were performed in the Molecular Diagnostic Laboratory at Children's Hospital of Michigan. DNA sequencing of the exonic and intron–exon boundaries of the biotinidase gene (BTD) was performed by polymerase chain reaction amplification using primers and conditions described previously.[12,13]

## RESULTS

### Ascertainment and demographics

Forty-four individuals from 40 families agreed to participate in the study. Recruitment was based on my ability to make contact with individuals and their responses. All individuals whom I located and successfully contacted participated in the study. I attempted to contact several other individuals, but they did not respond. This might have been because the contact information was incorrect, they did not receive the information, and/or the individual received the contact information but chose not to respond.

The mean age of the participants was 23.1 years, with a range of 16 to 32 years of age. The subjects are listed by descending age in **Table 1**. We have indicated their level of scholastic attainment as high school, college, graduate school, or advanced education beyond college.

### Enzymatic activity and mutational analysis

The mean activity of the 44 participating individuals is 0.21 nmol/min/ml or 2.7%, with a range of 0.0 to 0.76 nmol/min/ml of serum.

Mutation analysis was performed for 38 of the 44 participating individuals (**Table 1**). The individuals are usually compound heterozygous for common as well as several uncommon mutations,[14] and the mutations span the entire gene. Many of the mutations have been reported in symptomatic individuals.[11,14]

### Initiation of biotin therapy

The individuals and their families in this study were asked when biotin therapy was initiated after diagnosis. The responses varied from "at birth," "shortly after birth," "as a newborn," and "during infancy" to definitive ages. In general, all of the children were treated before 6 weeks of age, with the majority being treated between 2 and 4 weeks of age, with the exception of three—subjects 1, 3, and 36—who did not start using biotin until 4, 3, and 2 months of age, respectively.

### Biotin dosage and preparation

Almost all individuals were initially treated with 10 mg daily, either as a single 10-mg dose or as one 5-mg dose twice daily; a few individuals were treated with only 5 mg daily. Most have continued on this dosage. One individual increased her dose to 15 mg per day when ill but has returned to 10 mg per day. Several individuals increased their dosage to 15 mg or 20 mg per day after puberty.

The individuals reported that they obtain their biotin from a variety of sources often dictated by whether their insurance covers its cost or whether they must purchase it out of pocket. Because there are now multiple commercial preparations available in 5-mg capsules or tablets, their choice of the preparation is usually based on its availability and cost.

### Developmental and educational outcomes

Older adolescents and adults with profound deficiency in this study have also been well clinically and developmentally. Several individuals had older siblings who were symptomatic prior to screening; in one instance, a sibling probably died of the disorder prior to newborn screening.[15]

In general, essentially all individuals have achieved academic success. There was no consistency regarding courses or areas in which they had difficulties or excelled. Multiple individuals indicated that they had no school difficulties and excelled in most areas. Several needed additional help or classes in specific academic areas in high school. Several of the older individuals have completed college and have attended graduate school or had advanced training beyond college.

Two unrelated individuals were diagnosed with dyslexia (subjects 42 and 43) when they started elementary school and attended special schools for this disability, but they completed high school equivalency programs. One of these individuals had speech difficulties, hypotonia, and anxiety, all of which have resolved. A third child, diagnosed with William-Beuren syndrome (subject 38), attended special education classes.

### Clinical outcomes

One child (subject 44) became lethargic and hypotonic at 2 weeks of age, which was likely precipitated by a urinary tract infection. Usually, children with profound biotinidase deficiency do not develop symptoms until several months of age; however, this child was born in a location that was piloting newborn screening and at 1 month of age was diagnosed and treated with biotin. However, upon early audiological testing,

**Table 1** Clinical, biochemical, and molecular characteristics of older adolescent and adult individuals with profound biotinidase deficiency identified by newborn screening

| Subject | Age | Gender | Biotinidase activity[a] | Mutation 1 | Mutation 2 | High school | Attends or completed college | Graduate education | Dose of biotin | Medical problems | Hearing loss or vision problem | Children |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 32 | F | 0.3 | c.511G>A;1330G>C; p.A171T; D444H | c.755A>G; p.D252G | X | | | 10 mg | Depression | Unilateral SNHL | 1 Boys/1 Girl |
| 2 | 31 | M | 0.23 | ND | ND | X | X | | 10 mg | | | |
| 3 | 30 | M | 0 | c.511G>A;1330G>C; p.A171T; D444H | c.470G>A; p.R157H | X | X | | 10 mg | Single seizure | | |
| 4 | 29 | M | 0.06 | c.755A>G; p.D252G | c.755A>G; p.D252G | X | | | 10 mg | | | |
| 5 | 29 | F | 0 | c.511G>A;1330G>C; p.A171T; D444H | c.470G>A; p.R157H | X | X | | 5-10 mg | ADHD | Unilateral conductive HL | 2 Boys |
| 6 | 28 | F | 0.1 | c.755A>G; p.D252G | c.933delT; p.S311fs | X | X | | 10 mg | Eczema | Refraction | |
| 7 | 28 | F | 0.4 | c.511G>A;1330G>C; p.A171T; D444H | c.933delT; p.S311fs | X | X | | 20 mg | | Astigmatism | 1 Boy |
| 8 | 28 | M | 0.1 | c.1612C>T; p.R538C | c.755A>G; p.D252G | X | X | X | 15 mg | Anxiety/depression/ eczema | | |
| 9 | 27 | F | 0.35 | ND | ND | X | X | | 10 mg | Anxiety | Refraction | |
| 10 | 27 | F | 0.1 | c.100G>A; p.G34S | c.485C>T; p.A162V | X | | | 10 mg | | | 3 Girls |
| 11 | 26 | F | 0 | c.755A>G; p.D252G | c.1595C>T; p.T532M | X | X | | 10 mg | | | |
| 12 | 26 | F | 0 | ND | ND | X | X | X | 10 mg | | | |
| 13 | 25 | F | 0.2 | c.511G>A;1330G>C; p.A171T; D444H | c.511G>A;1330G>C; p.A171T; D444H | X | X | | 10 mg | | Unilateral conductive HL/tinnitus | 1 Boy |
| 14 | 25 | F | 0.2 | c.1368A>C; p.Q456H | c.98_104delinsTCC; p.C33fs | X | X | X | 10 mg | Eczema | | |
| 15 | 25 | M | 0.64 | ND | ND | X | | | 10 mg | | Refraction | |
| 16 | 25 | M | 0.06 | c.98_104delinsTCC; p.C33fs | c.511G>A;1330G>C; p.A171T; D444H | X | X | | 10 mg | | | |
| 17 | 25 | F | 0 | c.1368A>C; p.Q456H | c.1158G>A; p.W386X | X | X | | 10 mg | | | |
| 18 | 24 | M | 0.48 | c.1368A>C; p.Q456H | c.133G>A; 865G>C; p.G45R; A289P | X | X | | 10 mg | | | |
| 19 | 24 | M | 0.53 | c.511G>A;1330G>C; p.A171T; D444H | c.1368A>C; p.Q456H | X | | | 10-20 mg | | Refraction | |
| 20 | 23 | M | 0.09 | c.98_104delinsTCC; p.C33fs | c.1267T>C p.C423R | X | | | 10 mg | | Unilateral HL | 1 Boy |
| 21 | 23 | F | 0.16 | c.1368A>C; p.Q456H | c.933delT; p.S311fs | X | X | X | 10 mg | | | |
| 22 | 23 | F | 0 | c.184G>T; p.V62L | c.1617ins1fs | X | X | | 5-10 mg | Eczema | Refraction | |

ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; HL, hearing loss; ND, not determined; SNHL, sensorineural hearing loss.

[a]Nmols of *N*-biotinyl-*p*-aminobenzoate formed/min/ml of serum.

**Table 1** Continued on next page

**Table 1** Continued

| Subject | Age | Gender | Biotinidase activity[a] | Mutation 1 | Mutation 2 | High school | Attends or completed college | Graduate education | Dose of biotin | Medical problems | Hearing loss or vision problem | Children |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | 23 | M | 0.49 | c.1368A>C; p.Q456H | c.1368A>C; p.Q456H | X | X | X | 10 mg | Single seizure as child | | |
| 24 | 22 | F | 0.76 | c.701C>T; p.T234I | c.701C.T; p.T234I | X | X | X | 15 mg | | Refraction | |
| 25 | 22 | M | 0.25 | c.1368A>C; p.Q456H | c.98_104delinsTCC; p.C33fs | X | X | | 10 mg | | Refraction | |
| 26 | 22 | F | 0.12 | c.511G>A;1330G>C; p.A171T; D444H | c.1368A>C; p.Q456H | X | X | | 5-10 mg | Seizure after car accident/eczema/ hair loss | Tinnitus/refraction | |
| 27 | 21 | F | 0.1 | c.755A>G; p.D252G | c.933delT; p.S311fs | X | X | | 10 mg | | Refraction | |
| 28 | 21 | M | 0.68 | c.511G>A;1330G>C; p.A171T; D444H | c.1368A>C; p.Q456H | X | X | | 10 mg | ADD/depression | | |
| 29 | 21 | F | 0 | c.1368A>C; p.Q456H | c.933delT; p.S311fs | X | X | | 10 mg | | Refraction | |
| 30 | 21 | F | 0? | c.511G>A;1330G>C; p.A171T; D444H | c.1368A>C; p.Q456H | X | X | | 10-20 mg | | Refraction | |
| 31 | 20 | M | 0 | c.755A>G; p.D252G | c.1368A>C; p.Q456H | X | X | | 5 mg | Migraines/rash | | |
| 32 | 20 | M | 0.12 | c.511G>A;1330G>C; p.A171T; D444H | c.1368A>C; p.Q456H | X | X | | 10.mg | | | |
| 33 | 20 | M | 0.25 | c.1368A>C; p.Q456H | c.1368A>C; p.Q456H | X | X | | 5 mg | | | |
| 34 | 20 | M | 0.35 | c.511G>A;1330G>C; p.A171T; D444H | c.933delT; p.S311fs | X | | | 20 mg | | | |
| 35 | 20 | M | 0.1 | c.511G>A;1330G>C; p.A171T; D444H | c.1595C>T; p.T532M | X | X | | 10 mg | | HL?/tinnitus | |
| 36 | 19 | F | 0 | ND | ND | X | X | | 10 mg | | | |
| 37 | 19 | M | 0.64 | c.98_104delinsTCC; p.C33fs | c.470G>A; p.R157H | X | | | | | | |
| 38 | 19 | M | 0.2 | c.1368A>C; p.Q456H | c.98_104delinsTCC; p.C33fs | | | | 10 mg | William Beuren syndrome | | |
| 39 | 19 | F | 0.28 | c.1368A>C; p.Q456H | c.511G>A;1330G>C; p.A171T; D444H | X | X | | 10 mg | | | |
| 40 | 18 | F | 0 | ND | ND | X | | | 10 mg | | Refraction | |
| 41 | 17 | M | 0 | c.1368A>C; p.Q456H | c.470G>A; p.R157H | X | | | 10 mg | Sepsis at age 2 years | | |
| 42 | 17 | M | 0 | c.755A>G; p.D252G | c.1368A>C; p.Q456H | X | X | | 5 mg | Dyslexia | | |
| 43 | 17 | M | 0.68 | c.511G>A;1330G>C; p.A171T; D444H | c.1368A>C; p.Q456H | X | | | 10 mg | Dyslexia | | |
| 44 | 16 | M | 0.06 | c.341G>T; p.G114V | c.701C.T; p.T234I | X | | | 10-20 mg | | Sensorineural HL | |

ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; HL, hearing loss; ND, not determined; SNHL, sensorineural hearing loss.

[a]Nmols of *N*-biotinyl-*p*-aminobenzoate formed/min/ml of serum.

he was found to have bilateral sensorineural hearing loss. He used hearing aids as an infant and continues to wear them. He has normal cognition, speech, and development.

An unscreened older sibling of a child identified by newborn screening (subject 40) had frequent periods of vomiting and developed a rash. Once the younger brother was found to have profound biotinidase deficiency, his older sibling was tested and was also found to have the disorder. Both were treated and today both are clinically and developmentally normal.

The individual with William-Beuren syndrome exhibited hypotonia, balance problems, attention issues, bilateral inguinal hernias, and developmental delays. Because this individual has been continually treated with biotin, the clinical findings and developmental delays in this individual are probably attributable to William-Beuren syndrome.

Two individuals (subjects 3 and 23) had a single seizure as children, and another (subject 26) developed seizures immediately after being in an automobile accident. Several had attention deficit disorder or attention deficit hyperactivity disorder. One had migraines and several reported having emotional issues, particularly anxiety and mild depression.

Untreated individuals with biotinidase deficiency usually have bilateral sensorineural hearing loss, and periodic auditory evaluations are recommended;[16] however, few of the study's individuals had continued these evaluations unless they exhibited overt hearing problems. Subject 1 was found to have undergone abnormal auditory-evoked potential studies at 4 months of age. She was started on biotin and the auditory study results normalized after several months of therapy. However, she reported that she may have some residual unilateral hearing loss.

Three individuals have unilateral hearing loss (subjects 5, 13, and 20). In the first two individuals, the hearing loss is conductive and does not require hearing aids; both have normal cognition, speech, and development. The third has mild, possibly sensorineural, hearing loss and receives no treatment. A fourth individual subjectively thinks he has hearing loss, but it had not been confirmed as of the study. Several other individuals indicated that they had episodes of tinnitus.

Although periodic ophthalmological examinations were recommended, few subjects had undergone evaluations on a regular basis. None reported major vision problems. Several reported refractive abnormalities corrected by glasses or contact lenses.

Several of the individuals had episodes of rashes or eczema; however, the rashes occurred even when on biotin and did not resolve by increasing the dose of biotin. The eczema was usually successfully treated with medications for eczema.

### Compliance

Compliance in using the biotin was exceptionally good in our survey population. Several individuals related what happened when they did not take biotin for varying periods.

Subject 2 had been routinely using his biotin; however, when he stopped taking his biotin for several weeks to a month, he developed hand tremors, gastrointestinal problems, memory issues, muscle pain, and trouble breathing. Essentially all the symptoms resolved when he resumed taking the biotin. His older sister, who identified as also being enzyme-deficient, developed similar symptoms when she stopped taking biotin at 14 years of age. She resumed taking her biotin, and the clinical abnormalities resolved. In fact, both individuals have since increased their dose from 10 mg to 20 mg per day.

One individual (subject 26) was not administered biotin at age 13 years because the family could no longer afford the vitamin and the insurance company would not cover its cost. Over several months, the patient developed emesis and lethargy, began losing hair, could not concentrate, and had vision problems requiring glasses. The biotin was reinstituted and the symptoms resolved. Similarly, this individual's two enzyme-deficient older siblings reported becoming fatigued or lethargic when they stopped taking the vitamin. Their symptoms resolved when biotin was restarted.

One individual (subject 34) said that she developed lethargy and cloudy thinking and was moody when she did not take her biotin for a short period.

Subject 16 said that he did not take pharmacological doses of biotin for approximately 20 years, but he was given a multivitamin containing 75 to 150 μg of biotin per day for most of his early childhood. He has now recently begun to take biotin on a regular basis because he learned that an individual can initially develop symptoms even as an adolescent or adult.

### Children of women with profound biotinidase deficiency

Six individuals—five females and one male—have had 10 children (**Table 1**). The five females (subjects 1, 5, 7, 10, and 13) had nine children (five boys and four girls). All of these mothers used biotin throughout their pregnancies. Three of the mothers used 10 mg of biotin daily and one used 20 mg of biotin daily. One of these women was also treated with carnitine during her pregnancy because she was found to be deficient. However, when she was not pregnant, her carnitine concentrations were normal and she did not take the supplement.

There were no problems that could be attributed to the biotinidase deficiency during any of the pregnancies All of these children are developmentally normal; the oldest is 7 years old. All five mothers discussed the implications of the children having biotinidase deficiency with their obstetrician and/or a geneticist. They all understood the inheritance of the disorder and its implications for their pregnancies. None of the spouses underwent carrier status testing. None of the couples considered prenatal diagnosis. Two children were treated prophylactically with biotin until enzymatic results for the children indicated that they were not affected. All but two children had quantitative serum enzymatic testing at birth in addition to newborn screening; none was affected.

## DISCUSSION

Biotinidase deficiency meets the major criteria for inclusion in newborn screening programs that are currently in effect in

all the states in the United States and in many countries. We recently reviewed the outcomes of children with profound biotinidase deficiency identified by newborn screening for biotinidase deficiency in Michigan;[7] however, we noted that this population was skewed to younger children. Therefore, we wanted to determine the outcomes of older adolescents and adults with profound biotinidase deficiency identified by newborn screening.

Our laboratory was in the unique position to have the knowledge and information about many of the oldest individuals with profound biotinidase deficiency identified by newborn screening. Most of the individuals studied were reported in the first publications of children with profound biotinidase deficiency identified by newborn screening.[11] The study population represents a reasonable ascertainment of the population and includes various ethnic groups, including Hispanic and Asian individuals, although there were no African-American individuals. We have previously reported the disorder in African Americans;[17] however, it is rarer in this population.

Other studies have found successful outcomes for individuals with profound biotinidase deficiency identified by newborn screening, but, again, there was skewing to children and adolescents.[18,19] The findings of this study demonstrate that newborn screening for profound biotinidase deficiency and early treatment with biotin result in excellent outcomes for older adolescents and adults with the disorder. They did not exhibit major neurological abnormalities attributable to the disorder. It appears that biotin supplementation prevents the sensorineural hearing loss and major vision issues usually associated with the untreated disorder. Some individuals had various medical or developmental issues, but they are unlikely related to the biotinidase deficiency. In addition, mothers with profound biotinidase deficiency who were treated with biotin had successful pregnancies and outcomes. There is one other previous report of a successful pregnancy of a mother with profound biotinidase deficiency.[20]

Even in adulthood, 10 mg of biotin daily appears to be an adequate dosage. Compliance is a major issue in the treatment of many metabolic disorders. I am aware of several adolescents who decided to stop taking their biotin, usually questioning their diagnosis and the need for the vitamin, and subsequently developed neurological and/or cutaneous symptoms. The symptoms resolved following reinitiating biotin therapy (unpublished results).

Affected individuals who stopped taking biotin often developed nonspecific problems, including neurological symptoms (e.g., confusion), poor muscle tone, lethargy, and fatigue. Although these are anecdotal scenarios, they are consistent with the clinical problems of other untreated adolescents and adults, and these symptoms readily resolved when biotin was reinstituted.

Some untreated adults, usually parents of affected children with profound biotinidase deficiency, have been asymptomatic.[21–23] In fact, one of the individuals in this study remained asymptomatic without biotin therapy (subject 16). However, we considered that these individuals were still at risk for developing symptoms if exposed to stress, such as an infection. There is a group of individuals who first developed symptoms, including paraparesis or tetraparesis and/or scotoma and other vision problems, during older adolescence or adulthood.[24–26] Their problems usually improved with biotin treatment, but several have had residual symptoms. These reports supported our findings that once an individual with biotinidase deficiency developed optic atrophy, hearing loss, or cognitive disability, these features were probably not reversible. In addition, an untreated individual with profound biotinidase deficiency, even as an adult, can develop symptoms at any time.

Fortunately, biotin has no known toxicity, and the dose of biotin given to these individuals has been empirically determined. Perhaps the pharmacological doses of biotin are not essential for the treatment of biotinidase deficiency in some individuals or there are some epigenetic effects that permit some individuals to metabolize biotin more slowly, although we are unaware of any data to support this premise.

The results of this study support the idea that individuals probably do not need such close surveillance after childhood or adolescence, unlike some other more volatile inherited metabolic diseases. However, the survey revealed that these patients and their parents had many questions about the disorder that needed answers. They often found that their primary-care physicians did not understand the disorder, and these individuals were no longer seeing a genetic or metabolic specialist.

Because the results of our study indicate that individuals with profound biotinidase deficiency identified by newborn screening have responded well to biotin therapy, we assume that individuals with partial biotinidase deficiency (10–30% of mean normal serum activity) will also respond well.

Newborn screening for biotinidase deficiency is an excellent example of preventing symptoms and ensuring successful outcomes with early and continual treatment. These outcomes provide further support that newborn screening for biotinidase deficiency is one of the most successful, if not the most successful, newborn screening programs.

## SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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## DISCLOSURE

The author declares no conflict of interest.

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