食餌摂取量が関係していると推測し、コントロールマウスとして用いたmGPDH-KOマウスのAIN-93M摂取量を制限し摂食量を測定した（実験5）。

（倫理面への配慮）

この研究は、鹿児島大学にて、動物実験倫理委員会、遺伝子組換え実験安全委員会の承認を得ている。倫理に最大限の配慮がなされている。

C.研究結果

実験1.4種類のマウスに20%ショ糖液と水を自由摂取させ、飲水量を比較した。ほかのgenotypeのマウスはショ糖液を好んで飲むが、double-KOマウスはほとんど飲まないことがわかった（図3）。ショ糖の濃度が変化しても、double-KOマウスだけが5%以上のショ糖液を好んで飲むことはなかった。

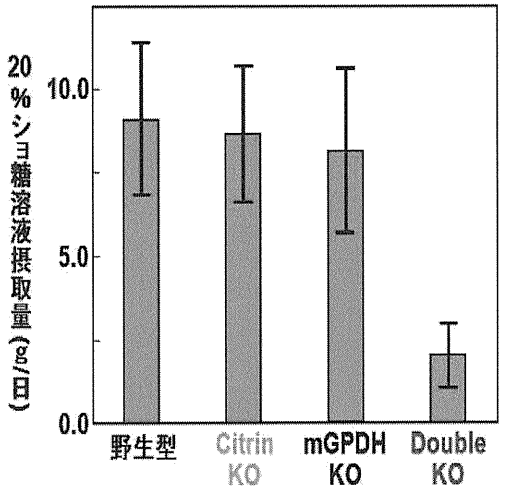

図3. 20%ショ糖溶液の1日摂取量の比較

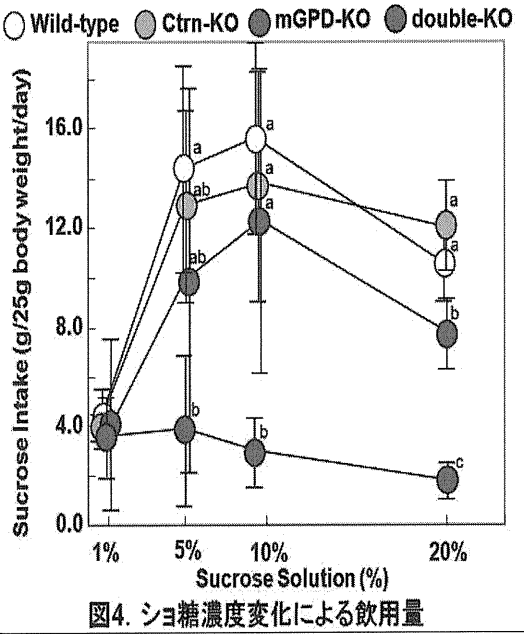

図4. ショ糖濃度変化による飲用量

実験2.ショ糖液にカゼインの水解物であるトリプトンを加えたところ、double-KOマウスの飲水量が増えた（図5）。

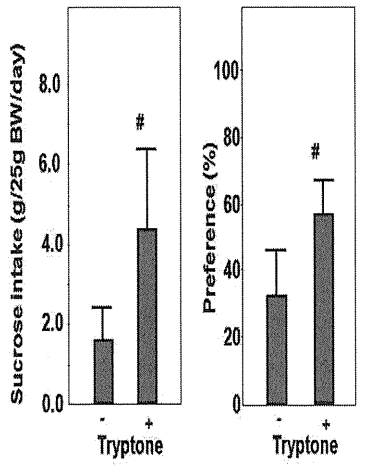

図5. Double-KOマウスのショ糖摂取量と嗜好度に対するトリプトンの効果

Preference = (Sucrose Intake)/(Sucrose + Water Intake)x100

実験3.20%ショ糖溶液に添加したアミノ酸の飲用量への効果を比較したところ、アラニンなどにショ糖摂取量を増加させる効果があった（図6,7）。

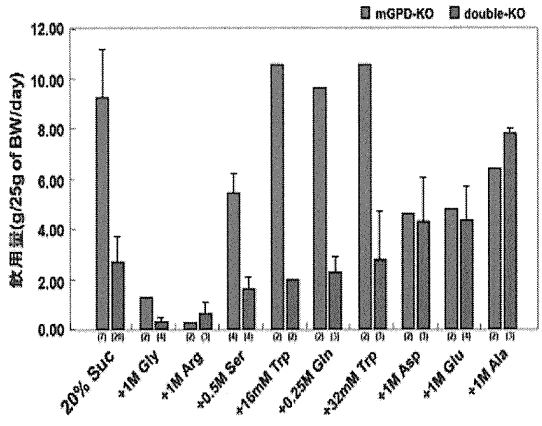

図6. 20%ショ糖溶液に添加したアミノ酸の飲用量への効果

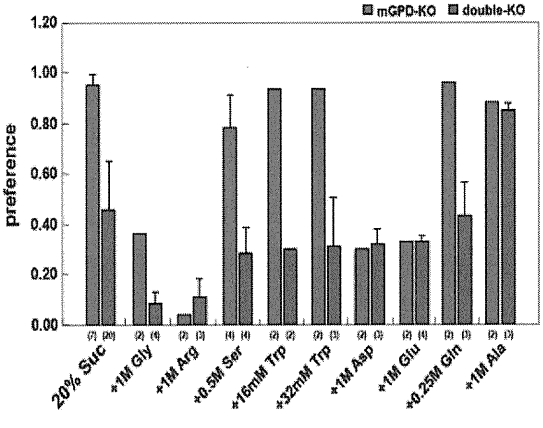

図7. 20%ショ糖溶液に添加したアミノ酸のpreferenceへの効果

実験4.CE-2(タンパク質25%)では、4種のマウス間の摂取量にあまり差はなかった。しかし、AIN-93M（タンパク質14%）では、double-KOマウスは摂取量が少なく、体重が減少した（図8）。

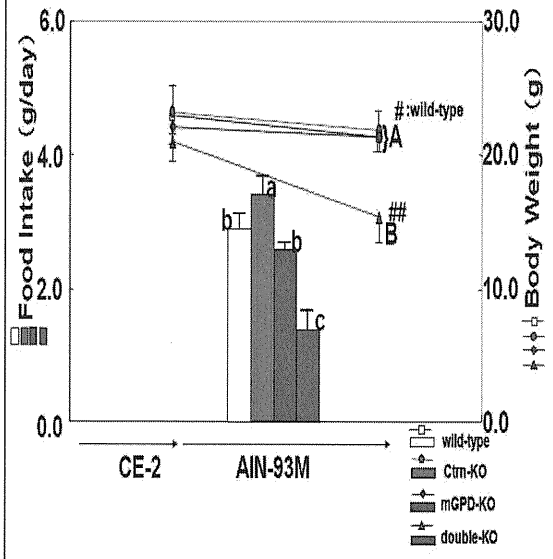

図8. 4種類のマウスにおける食餌摂取量と体重変化

実験5. Double-KOマウスの平均摂食量は1.4g/日であった。AIN-93MをmGPDH-KOマウスに約2g/日摂取させた結果、mGPDH-KOマウスの体重は有意に減少した。（CE-2;20.5±1.0,AIN-93M;16.3±1.3　体重(g)±SD　$p<0.01$（CE-2投与後体重との比較）

D.考察

1.アラニンにショ糖の摂取を増加させる効果があったので、臨床応用できる可能性が示された。

2.コントロールマウスとして用いたmGPDH-KOマウスのAIN-93Mの食餌摂取量を制限した結果、double-KOマウスと同様に体重が減少したことから、double-KOマウスの体重減少には、食餌摂取量が関係している可能性が考えられた。

3.今後は、なぜ糖の摂取ができないのかについて、脳内ペプチドの遺伝子発現のレベルから解析する予定である。

E.結論

Double-KOマウスに、タンパク質含量の少ないAIN-93Mを与えると食事摂取量、体重がともに減少した。また、アラニンにピルビン酸ナトリウムよりもショ糖の摂取を増加させる効果があることが認められ、治療に応用できる可能性が示唆された。

G.研究発表

1.　論文発表
　該当なし

2.　学会発表
　該当なし

H.知的財産権の出願・登録状況
　該当なし

〔III〕　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
大浦敏博	シトリン欠損症	五十嵐隆	小児科臨床ピクシス23	中山書店	東京	2010	252-253
Kobayashi K, Saheki T, Song Y-Z	Citrin deficiency	Pagon RA, Bird TD, Dolan CR et al.	Gene Reviews		Seatlle	2011	

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kobayashi K, Okano Y, Hohashi N	Reliability and validity of the PedsQLTM Multidimensional Fatigue Scale in Japan	Qual Life Res	20(7)	1091-1102	2011
Saheki T, Inoue K, Tushima A, Mutoh K, Kobayashi K.	Citrin deficiency and current treatment concepts.	Mol Genet Metab	100 (Suppl 1)	S59-S64	2010
Saheki T, Inoue K, Ono H, Tushima A, Katsura N, Yokogawa M, Yoshidumi Y, Kuhara T, Ohse M, Eto K, Kadowaki T, Sinasac DS, Kobayashi K.	Metabolomic analysis reveals hepatic metabolite perturbations in citrin/mitochondrial glycerol-3-phosphate dehydrogenase double-knockout mice, a model of human citrin deficiency.	Mol Genet Metab.	104(4)	492-500	2011
Ushikai M, Horiuchi M, Kobayashi K, Matuda S, Inui A, Takeuchi T, Saheki T.	Induction of PDK4 in the heart muscle of JVS mice, an ani-mal model of systemic carnitine deficiency, does not appear to reduce glucose utilization by the heart.	Mol Genet Metabol 1	102(3)	349-355	2011
Nakamura M, Yazaki M, Kobayashi Y, Fukushima K, Ikeda S, Kobayashi K, Saheki T, Nakaya Y	The characteristics of food intake in patients with type II citrullinemia.	J Nutr Sci Vitaminol	57(3)	239-245	2011
Contreras L, Urbieta	Low levels of citrin (SLC25	J Neurosci	85(5)	1009-10	2010

A, Kobayashi K, Saheki T, Satrústegui J.	A13) expression in adult mouse brain restricted to neuronal clusters.	Res.		16	
Pardo B, Rodrigues TB, Contreras L, Garzón M, Llorente-Folch I, Kobayashi K, Saheki T, Cerdan S, Satrústegui J,	Brain glutamine synthesis requires neuronal-born aspartate as amino donor for glial glutamate formation,	J Cereb Blood Flow Metab.	31(1)	90-101	2011
Ramos M, Pardo B, Llorente-Folch I, Saheki T, Del Arco A, Satrústegui J.	Deficiency of the mitochondrial transporter of aspartate/glutamate aralar/AGC1 causes hypomyelination and neuronal defects unrelated to myelin deficits in mouse brain.	J Neurosci Res.	89(12)	2008-2017	2011
Song YZ, Deng M, Chen FP, Wen F, Guo L, Cao SL, Gong J, Xu H, Jiang GY, Zhong L, Kobayashi K, Saheki T, Wang ZN.	Genotypic and phenotypic features of citrin deficien-cy: five-year experience in a Chinese pediatric center.	Int J Mol Med.	28(1)	33-40	2011
Kikuchi A, Arai-Ichinoi N, Sakamoto O, Matsubara Y, Saheki T, Kobayashi K, Ohura T, Kure S.	Simple and rapid genetic testing for citrin deficiency by screening 11 prevalent mutations in SLC25A13.	Mol Genet Metab.			in press
Fu HY, Zhang SR, Wang XH, Saheki T, Kobayashi K, Wang JS.	The mutation spectrum of the SLC25A13 gene in Chinese infants with intrahepatic cholestasis and aminoacidemia.	J Gastroenterol	46(4)	510-518	2011
Chew HB, Ngu LH, Zabedah MY, Keng WT, Balasubramaniam S, Hanifah MJ, Kobayashi K.	Neonatal intrahepatic cholestasis associated with citrin deficiency (NICCD): a case series of 11 Malaysian patients.	J Inherit Metab Dis			in press
Guo L, Li BX, Deng M, Wen F, Jiang JH, Tan YQ, Song YZ, Liu ZH, Zhang CH, Kobayashi K, Wang ZN.	Etiological analysis of neurodevelopmental disabilities: single-center eight-year clinical experience in south China.	J Biomed Biotechnol			in press

Kawatani M, Tsukahara H, Mayumi M	Evaluation of oxidative stress status in children with pervasive developmental disorder and attentior deficit hyperactivity disorder using urinary-specific biomarkers	Redox Rep	16 (1)	45-46	2011
Nagasaka H, Yorifuji T, Takatani T, Okano Y, Tsukahara H, et al.	CD36 deficiency predisposing young children to fasting hypoglycemia	Metabolism	60 (6)	881-887	2011
Sanayama Y, Nagasaka H, Takayanagi M, Ohura T, Sakamoto O, et al.	Experimental evidence that phenylalanine is strongly associated to oxidative stress in adolescents and adults with phenylketonuria	Mol Genet Metab	103 (3)	220-225	2011
Nagasaka H, Tsukahara H, Takatani T, Sanayama Y, Takayanagi M, et al.	Cross-sectional study of bone metabolism with nutrition in adult classical phenylketonuric patients diagnosed by neonatal screening	J Bone Miner Metab	29 (6)	737-743	2011
Tsukahara H, Fujii Y, Hayashi Y, Morishima T	Multiple biomarkers for oxidative stress in patients with brain disorders	J Neurol Sci	313 (1-2)	196	2012
矢崎正英、 池田修一、小林圭子、佐伯武頼.	成人型シトルリン血症の治療—低炭水化物食と経口ピルビン酸投与の有効性	臨床神経学	50	844-847	2010
大浦敏博、呉繁夫、菊地敦生、坂本修、重松陽介、岡野善行、小林圭子、佐伯武頼.	シトリン欠損症マス・スクリーニングの可能性.	日本先天代謝異常学会雑誌	27巻	42-45	2011
岡野善行	ガラクトース血症マス・スクリーニングの現状と課題	日本先天代謝異常学会雑誌	27巻	46-51	2011

〔IV〕　研究成果の刊行物・別刷

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-.

Bookshelf ID: NBK1181 PMID: 20301360

Citrin Deficiency

Includes: Citrullinemia Type II, Failure to Thrive and Dyslipidemia Caused by Citrin Deficiency, Neonatal Intrahepatic Cholestasis Caused by Citrin Deficiency

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Summary

Disease characteristics. Citrin deficiency can manifest in newborns as neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD), in older children as failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD), and in adults as recurrent hyperammonemia with neuropsychiatric symptoms in citrullinemia type II (CTLN2). Often citrin deficiency is characterized by fondness for protein-rich and/or lipid-rich foods and aversion to carbohydrate-rich foods.

NICCD: Children younger than age one year have growth retardation with transient intrahepatic cholestasis, hepatomegaly, diffuse fatty liver and parenchymal cellular infiltration associated with hepatic fibrosis, variable liver dysfunction, hypoproteinemia, decreased coagulation factors, hemolytic anemia, and/or hypoglycemia. Although NICCD is generally not severe and symptoms often resolve by age one year with appropriate treatment, some infants succumb to infection and liver cirrhosis and others require liver transplantation.

FTTDCD: Around age one to two years, many children with citrin deficiency develop the food preferences mentioned. Some have growth retardation, hypoglycemia, and fatigue as well as hyperlipidemia, pancreatitis, fatty liver, and hepatoma. One or more decades later, some individuals with NICCD or FTTDCD develop CTLN2.

CTLN2: Onset is sudden and usually between ages 11 and 79 years. Manifestations are recurrent hyperammonemia with neuropsychiatric symptoms including nocturnal delirium, aggression, irritability, hyperactivity, delusions, disorientation, restlessness, drowsiness, loss of memory, flapping tremor, convulsive seizures, and coma; death can result from brain edema. Symptoms are often provoked by alcohol and sugar intake, medication, and/or surgery. Affected individuals may or may not have a prior history of NICCD or FTTDCD.

Diagnosis/testing. The diagnosis of citrin deficiency is suspected from clinical and biochemical findings (in general, increased blood or plasma concentration of ammonia, plasma or serum concentration of citrulline and arginine, plasma or serum threonine-to-serine ratio, and serum concentration of pancreatic secretory trypsin inhibitor [PSTI]). Identification of biallelic mutations in *SLC25A13*, the only gene in which mutations are known to cause citrin deficiency, confirms the diagnosis.

Management. *Treatment of manifestations:* NICCD: Supplement diet with fat-soluble vitamins and use of lactose-free formula (in those with galactosemia) or formulas containing medium-chain triglycerides. FTTDCD: In addition to dietary treatment, administration of sodium pyruvate may improve growth. CTLN2: Liver transplantation prevents hyperammonemic crises, corrects metabolic disturbances, and eliminates preferences for protein-rich foods; arginine decreases blood ammonia concentration and lessens hypertriglyceridemia by reducing calorie/carbohydrate intake and increasing protein intake. Arginine and sodium pyruvate may effectively treat hyperammonemia and fatty liver, thereby delaying the need for liver transplantation.

Prevention of primary manifestations: Lipid and protein-rich low-carbohydrate diet.

Surveillance: Periodic measurement of plasma concentration ammonia and citrulline, PSTI for all phenotypes associated with citrin deficiency. Follow up of children who have had NICCD for the laboratory and physical findings of FTTDCD.

Agents/circumstances to avoid: Low-protein high-carbohydrate diets; glycerol and fructose infusions for brain edema; alcohol; acetaminophen and rabeprozole.

Evaluation of relatives at risk: It is appropriate to identify affected sibs of a proband so that appropriate dietary management can be instituted before symptoms occur.

Genetic counseling. Citrin deficiency is inherited in an autosomal recessive manner. When both parents are carriers, each sib of an affected individual has, at conception, a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. When one parent is a carrier and the other parent has two mutated *SLC25A13* alleles, each sib of an affected individual has, at conception, a 50% chance of being affected and a 50% chance of being an asymptomatic carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the disease-causing mutations in the family are known.

Diagnosis

Clinical Diagnosis

Citrin deficiency has two distinct well-recognized phenotypes: neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) and citrullinemia type II (CTLN2) (see Figure 1) [Saheki & Kobayashi 2002, Yamaguchi et al 2002, Kobayashi & Saheki 2004, Saheki & Kobayashi 2005, Kobayashi et al 2006]. Failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD was recently proposed as a novel intermediate phenotype [Song et al 2011].

- **Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD)** characterized by transient neonatal cholestasis and variable hepatic dysfunction
- **Failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD)** characterized by post-NICCD growth retardation before CTLN2 onset and abnormalities of serum lipid concentrations, including triglycerides, total cholesterol, and HDL-cholesterol. Clinical diagnosis of citrin deficiency during this stage is difficult in the absence of a history of unique food preferences or without molecular testing.
- **Citrullinemia type II (CTLN2)** characterized by childhood- to adult-onset, recurring episodes of hyperammonemia and associated neuropsychiatric symptoms

Testing

Table 1. Biochemical Findings in Citrin Deficiency by Phenotype

Phenotype (Age)	Blood or Plasma Concentration of Ammonia (µmol/L)	Plasma or Serum Concentration of Citrulline (C) [1]	Plasma or Serum Concentration of Arginine (A) (µmol/L)	Plasma or Serum Threonine-to-Serine Ratio	Serum Concentration of Pancreatic Secretory Trypsin Inhibitor (PSTI) [2] (ng/mL)
Control	18-47 [3]	17-43 [3]	54-130 [3]	1.10	4.6-20 [3]
NICCD (0-6 months)	60	300	205	2.29	30
FTTDCD (>1 to 11 years)	Normal, or slightly elevated	Normal, or slightly elevated	Usually normal	Unknown	Unknown
CTLN2 (11-79 years)	152	418	198	2.32	71

Kobayashi et al [2006]

1. Citrullinemia, which can be detected on newborn screening, is the earliest identifiable biochemical abnormality of NICCD [Tamamori et al 2004].

2. Because the serum PSTI concentration is high in some individuals with NICCD [Tamamori et al 2002] and also in individuals before the onset of CTLN2 [Tsuboi et al 2001], the measurement of serum PSTI concentration may be useful in presymptomatic diagnosis of CTLN2.

3. Range

In addition to the findings in Table 1, the following are observed in citrin deficiency:

NICCD

- **Plasma concentration of galactose, methionine, and/or phenylalanine** is elevated in newborn screening blood spots in approximately 40% of children with NICCD [Ohura et al 2003, Ohura et al 2007].

- **Plasma concentrations of threonine, methionine, and tyrosine** are elevated (see Table 2).

Table 2. Plasma Concentrations of Threonine, Methionine, and Tyrosine at Age 0-6 Months in NICCD

Amino Acid	Median (25%-75% Range) (µmol/L)	Control Range (µmol/L)
Threonine	496 (291-741)	67-190
Methionine	124 (53-337)	19-40
Tyrosine	178 (99-275)	40-90

Kobayashi et al [2006]

- **Plasma concentration of bilirubin, bile acids, and alpha-fetoprotein** are elevated (see Table 3).

Table 3. Measurements of Hepatic Cell Function at Age 0-6 Months in NICCD

Assayed Item	Median (25%-75% range) (mg/dL)	Control Range (mg/dL)
TB in NICCD	4.9 (2.8-8.0)	0.2-1.0
TB in CTLN2	0.8 (0.52-1.1)	
DB in NICCD	2.5 (1.5-3.7)	0-0.4
DB in CTLN2	0.3 (0.2-0.4)	
TB/DB ratio in NICCD	0.55 (0.41-0.66)	—
TBA	239 (172-293)	5-25
AFP	91,900 (33,200-174,700)	260-6,400 [1, 2] 2-55 [2, 3]

Kobayashi et al [2006]

TB= total bilirubin

DB= direct bilirubin

TBA= total bile acids

AFP= α-fetoprotein

1. 0-1 month

2. Tamamori et al [2002]

3. >1 month

FTTDCD

- **Dyslipidemia** manifests as abnormal levels of triglyceride and cholesterol (including total-, HDL- and LDL-cholesterol) [Song et al 2009a, Song et al 2011].
- **Other abnormal laboratory findings** include increased lactate to pyruvate ratio, elevated cholesterol, and higher levels of urinary oxidative stress markers [Kobayashi & Saheki 2004, Saheki & Kobayashi 2005, Kobayashi et al 2006, Nagasaka et al 2009, Lee et al 2010].

CTLN2

- **Pancreatic secretory trypsin inhibitor (PSTI)** concentration is increased in the liver [Kobayashi et al 1997] (see Table 1). Note: PSTI mRNA is increased 30-140 fold in the liver of individuals with CTLN2
- **Fischer ratio** (branched-chain amino acids [BCAAs] Val+Leu+Ile / aromatic amino acids [AAAs] Tyr+Phe) in the plasma or serum is decreased from ~3.4 to ~2 as a result of decreased BCAA.
- **Liver-specific argininosuccinate synthetase (ASS) enzyme activity** is decreased to approximately 10% that of controls (secondary effect of mutations) [Yasuda et al 2000].
- **Plasma α-fetoprotein concentration** is normal in almost all individuals with CTLN2 [Kobayashi et al 1997], except some individuals with CTLN2 associated with hepatoma [Hagiwara et al 2003].

Both NICCD and CTLN2

- **Western blot analysis** using anti-human citrin antibody specific for the amino-terminal half detects little or no cross-reactive immune material in liver, cultured fibroblasts, or lymphocytes from individuals with *SLC25A13* mutations [Yasuda et al 2000, Takahashi et al 2006, Dimmock et al 2007, Tokuhara et al 2007, Fu et al 2011].

For laboratories offering biochemical testing for CTLN2, see Testing.

Molecular Genetic Testing

Gene. *SLC25A13* is the only gene in which mutations are known to cause citrin deficiency.

Table 4. Summary of Molecular Genetic Testing Used in Citrin Deficiency

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]	Test Availability
SLC25A13	Sequence analysis	Sequence variants [2]	>95% [3]	Clinical Testing
	Deletion / duplication analysis [4]	Exonic and whole-gene deletions	Unknown [5]	

Test Availability refers to availability in the GeneTests™ Laboratory Directory. *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.

1. Because the criteria for clinical and biochemical diagnosis of citrin deficiency other than CTLN2 are not yet established, it is difficult to calculate the mutation detection frequency.

2. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations.

3. Kobayashi et al [1999], Yasuda et al [2000], Ben-Shalom et al [2002], Yamaguchi et al [2002], Saheki et al [2004], Lu et al [2005], Takaya et al [2005], Ko et al [2007a], Song et al [2008], Tabata et al [2008], Song et al [2009b], Xing et al [2010], Fu et al [2011], Song et al [2011], Wen et al [2011]

4. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; a variety of methods including quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), or targeted chromosomal microarray analysis (gene/segment-specific) may be used. A full chromosomal microarray analysis that detects deletions/duplications across the genome may also include this gene/segment. See array GH.

5. Takaya et al [2005], Wong et al [2008]

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

Testing Strategy

Confirming/establishing the diagnosis of citrin deficiency in a proband (see Figure 2 and Figure 3)

The following testing strategy (see **Order of testing**) should be considered for:

- Infants who have had a positive newborn screening test for:
  - Citrullinemia and/or prolonged jaundice; or
  - Galactosemia, hypermethionemia or hyperphenylalanemia, who on follow-up diagnostic testing were found not to have one of these disorders.
- Children beyond age one year who present with failure to thrive and dyslipidemia;
- Older children and adults with hepatic encephalopathy with hyperammonemia, especially those with aversion to carbohydrate and fondness for protein- and lipid-rich foods;
- Children and adults with unexplained recurrent pancreatitis, hyperlipidemia, fatty liver or hepatoma.

Order of testing

- Perform quantitative plasma amino acid analysis (children age 1-4 months).
- Measure blood ammonia, plasma amino acids, PSTI, liver enzymes (when CTLN2 is suspected).
- Perform dietary assessment, including food preferences (particularly important if FFTDCD or CTLN2 is suspected).
- Perform molecular genetic testing:

Sequence analysis of *SLC25A13*, followed by deletion/duplication analysis if neither or only one disease-causing mutation is identified.

- Note: Western blotting for citrin protein is considered if no or only one disease-causing mutation is identified by molecular genetic testing.

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

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

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutations in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Note: It is the policy of *GeneReviews* to include in *GeneReviews*™ chapters any clinical uses of testing available from laboratories listed in the GeneTests™ Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Genetically Related (Allelic) Disorders

CTLN2, NICCD, and FTTDCD are the only phenotypes currently known to be associated with mutations in *SLC25A13*.

Clinical Description

Natural History

Citrin deficiency can manifest in newborns as neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD), in older children as failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD), and in adults as recurrent hyperammonemia with neuropsychiatric symptoms in citrullinemia type II (CTLN2). Often FTTDCD and CTLN2 are characterized by fondness for protein-rich and/or lipid-rich foods and aversion to carbohydrate-rich foods. Individuals with CTLN2 may or may not have a prior history of NICCD or FTTDCD. The proportion of persons with NICCD or FTTDCD that evolves into CTLN2 is unknown.

Neonatal Intrahepatic Cholestasis Caused by Citrin Deficiency (NICCD)

Children under age one year with NICCD have transient intrahepatic cholestasis. Other findings include diffuse fatty liver with hepatomegaly and parenchymal cellular infiltration associated with hepatic fibrosis, low birth weight, growth retardation, hypoproteinemia, decreased coagulation factors, hemolytic anemia, variable (mainly mild) liver dysfunction, and/or hypoglycemia.

NICCD is generally not severe, although liver transplantation has been required in rare cases [Tamamori et al 2002, Kobayashi et al 2006]. Symptoms typically resolve by age one year with treatment, including fat-soluble vitamin supplementation and use of lactose-free formulas (for those with galactosemia) or formulas containing medium-chain triglycerides [Ohura et al 2003, Song et al 2010].

Starting around age one to two years, children show a strong preference for protein-rich and lipid-rich foods and an aversion to sugar-rich and carbohydrate-rich foods [Hachisu et al 2005, Saheki & Kobayashi 2005, Saheki et al 2008].

In the second or later decades, some individuals with citrin deficiency develop severe CTLN2 with neuropsychiatric symptoms [Saheki & Kobayashi 2002]. Typically the transition from the adaptation (and/or compensation) stage following NICCD to the onset of CTLN2 is gradual.

Failure to Thrive and Dyslipidemia Caused by Citrin Deficiency (FTTDCD)

FTTDCD has recently been proposed as a novel post-NICCD phenotype before the onset of CTLN2 [Song et al 2011]. The clinical and laboratory features of FTTDCD are still being elucidated. During this period (traditionally assumed to be an "apparently healthy" stage before CTLN2 onset) some children were found to have laboratory abnormalities (see Diagnosis) and/or clinical abnormalities including fatigue, growth retardation, hypoglycemia, and pancreatitis.

Citrullinemia Type II (CTLN2)

CTLN2 is characterized by recurring episodes of hyperammonemia and neurologic and psychotic symptoms that closely resemble those of hepatic encephalopathy or genetic urea cycle disorders, including nocturnal delirium, aberrant behaviors (aggression, irritability, and hyperactivity), delusions, disorientation, restlessness, drowsiness, loss of memory, flapping tremor, convulsive seizures, and coma. Brain CT is normal, and EEG shows diffuse slow waves.

Onset is sudden and usually between ages 20 and 50 years (range: 11-79 years; mean age: 34.4 ±12.8 years; n=103) [Yasuda et al 2000].

Many individuals with CTLN2 have a strong preference for protein-rich and/or lipid-rich foods (e.g., beans, peanuts, eggs, milk, cheese, fish, meat) and an aversion to carbohydrate-rich foods including rice, juice, and sweets. Symptoms are often provoked by alcohol and sugar intake, medication, and/or surgery.

Most individuals are thin. More than 90% have a body mass index lower than 20 and approximately 40% have a body mass index lower than 17 (range: 15.6-19.1; n=110) [Kobayashi et al 2006] (range in healthy Japanese individuals: 20-24 in males; 19-23 in females).

The following complications occur in more than 10% of individuals with CTLN2 [Kobayashi et al 2000]. Studies regarding these complications are ongoing.

- **Pancreatitis.** Juvenile-onset chronic pancreatitis and hepatocellular carcinoma without cirrhosis can precede the appearance of CTLN2 [Ikeda et al 2004].
- **Hyperlipidemia.** Hypertrigyceridemia is frequently observed if high carbohydrate meals are provided to individuals with citrin deficiency [Imamura et al 2003].
- **Fatty liver.** Most individuals with NICCD and CTLN2 have fatty liver, which is histologically identical to NASH (non-alcoholic steatohepatitis) [Takagi et al 2006, Fukumoto et al 2008, Komatsu et al 2008]. Mild fibrosis can also be seen [Kobayashi et al 2000].
- **Hepatoma** may be present, even before the diagnosis of CTLN2 is made [Tanaka et al 2002, Hagiwara et al 2003, Tsai et al 2006, Soeda et al 2008]

Intrahepatic cholestasis is rare; however, some individuals are noted in retrospect to have had signs of NICCD in early childhood [Kobayashi & Saheki 2004, Saheki & Kobayashi 2005]. For example, a 16-year-old with CTLN2 undergoing liver transplantation [Kasahara et al 2001] had had transient hypoproteinemia and jaundice in early infancy [Tomomasa et al 2001].

Pathologic findings include fatty infiltration and mild fibrosis of the liver despite little or no liver dysfunction.

Genotype-Phenotype Correlations

No significant correlation between *SLC25A13* mutation types and decreased level of hepatic enzyme ASS activity/protein or age of onset in individuals with CTLN2 is observed [Yasuda et al 2000].

Penetrance

The male-to-female ratio in NICCD is roughly equal (73:80) [Kobayashi & Saheki 2004].

The male-to-female ratio in CTLN2 is 2.4 to 1 (120:50) [Kobayashi & Saheki 2004].

The unequal male-to-female ratio in CTLN2 suggests that for unknown reasons, homozygous females are more resistant to the CTLN2 phenotype than males.

Nomenclature

NICCD. NICCD was known as "idiopathic neonatal hepatitis with fatty liver of unknown origin" [Ohura et al 1997] before molecular genetic testing confirmed the presence of *SLC25A13* mutations.

CTLN2. Miyakoshi et al [1968] reported that blood citrulline concentrations were increased in individuals with hyperammonemia and a unique chronic recurrent hepatocerebral degeneration. This hepatocerebral degeneration came to be known as "pseudo-ulegyric hepatocerebral disease" on the basis of pathologic brain changes, and "nutritional hepatocerebral disease" on the basis of metabolic disturbance resulting from a highly unbalanced diet or developmental disturbance caused by endocrine abnormalities.

Saheki et al [1981] reported this hepatocerebral disease as a type of citrullinemia with a qualitative and liver-specific decrease of the arginosuccinate synthetase activity/protein, and later Saheki et al [1985] named it "adult-onset type II citrullinemia."

Prevalence

In Japan, the frequency of homozygotes or compound heterozygotes for *SLC25A13* mutations is calculated to be 1:17,000 based on the carrier or heterozygote rate of 1:65 [Saheki & Kobayashi 2002, Tabata et al 2008]. This is similar to the observed prevalence of NICCD [Shigematsu et al 2002], but different from the observed prevalence of CTLN2 (1:100,000-1:230,000) [Kobayashi et al 2006]. Based on their observations, the authors believe that most homozygotes of Japanese heritage have NICCD.

Until recently, citrin deficiency was thought to be restricted to Japan; citrin deficiency is now recognized to be pan ethnic [Dimmock et al 2009]. Individuals with novel *SLC25A13* mutations have been identified in Israel, Pakistan, the US, the United Kingdom, China, and the Czech Republic [Ben-Shalom et al 2002, Hutchin et al 2006, Luder et al 2006, Dimmock et al 2007, Fiermonte et al 2008, Song et al 2008, Tabata et al 2008, Song et al 2009b, Song et al 2011].

The carrier frequency is also high in China (1/65), especially southern China including Taiwan (1/48), and in Korea (1/112) [Lu et al 2005, Lee et al 2011].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory

Directory. —ED.

Plasma concentration of citrulline is increased in citrin deficiency as well as in the following disorders:

- **Citrullinemia type 1 (CTLN1; ASS deficiency).** CTLN1 presents as a wide spectrum of overlapping phenotypes: an acute neonatal form (the "classic" form), a milder late-onset form, a form without symptoms and/or hyperammonemia, and a form in which women have onset of severe symptoms during pregnancy or post partum [Gao et al 2003]. Shortly after birth, infants with the acute neonatal form develop hyperammonemia and its complications, from which they die without prompt intervention. Those who are treated promptly may survive for an indeterminate period of time, but usually with significant neurologic deficit. In the late-onset form, the episodes of hyperammonemia are similar to those seen in the acute neonatal form, but the initial neurologic findings may be more subtle.

  CTLN1 results from deficiency of the enzyme ASS, the third step in the urea cycle, in which citrulline is condensed with aspartate to form argininosuccinic acid. Untreated individuals with the severe form of CTLN1 have hyperammonemia, increased plasma concentration of citrulline, and decreased plasma concentration of arginine. Inheritance is autosomal recessive.

  In CTLN2, the liver-specific deficiency of the ASS protein is secondary by unknown mechanisms [Yasuda et al 2000] as no abnormalities are present in hepatic ASS mRNA or *ASS1*.
- **Argininosuccinic aciduria (argininosuccinate lyase [ASL] deficiency)** (see Urea Cycle Disorders Overview)
- **Lysinuric protein intolerance (LPI)**
- **Pyruvate carboxylase (PC) deficiency**
- **Renal insufficiency**
- **Galactosemia**. In one neonate, classic galactosemia presented as citrin deficiency [Feillet et al 2008].

Hyperammonemia occurs in citrin deficiency as well as in the urea cycle disorders, which result from defects in the metabolism of the nitrogen produced by the breakdown of protein and other nitrogen-containing molecules (see Urea Cycle Disorders Overview). Severe deficiency or total absence of activity of any of the first four enzymes (CPSI, OTC, ASS, ASL) in the urea cycle, the ornithine transporter, or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life in most affected individuals.

Neonatal/infantile cholestasis occurs in citrin deficiency as well as the following disorders:

- **Idiopathic neonatal hepatitis (INH) and extrahepatic biliary atresia (EBA).** In comparison with INH and EBA, NICCD is associated with lower levels of serum direct bilirubin or ALT and higher levels of serum total bile acids and alkaline phosphatase. NICCD also has higher levels of serum γ-GTP and lower levels of serum AST activity than are seen in INH [Tazawa et al 2005].
- **Progressive familial intrahepatic cholestasis (PFIC, Byler disease).** The high-serum γ-GTP levels of NICCD may distinguish it from other intrahepatic cholestasis disorders with low-normal γ-GTP levels including PFIC and benign recurrent intrahepatic cholestasis (BRIC). PFIC is caused by mutations in *ATP8B1* (*FIC1*) or *ABCB11* (*BSEP*). Some cases of BRIC are caused by mutations in *ATP8B1.*

Hereditary jaundice and hyperbilirubinemia result from defects in the metabolism of bilirubin. These include disorders resulting in predominantly unconjugated (indirect) hyperbilirubinemia (UDP-glucuronosyltransferase 1-1 deficiency) and those resulting in predominantly conjugated (direct) hyperbilirubinemia (deficiency in canalicular ATP-dependent transporters: ABCC2 [MRP2], ABCB11, or ATP8B1).

Other

- Portal-systemic shunts can be excluded by angiography.
- More than 30% of individuals with CTLN2 have been misdiagnosed initially as having epileptic seizures and/or a psychological disorder (e.g., depression, schizophrenia); others may be diagnosed as having diseases such as hepatoma, pancreatitis, and hyperlipidemia.

Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, go to SimulConsult®, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

- CTLN2
- NICCD

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with citrin deficiency the following are recommended by phenotype:

NICCD

- Assess the size of the liver and spleen.
- Seek evidence of fatty liver by abdominal US, CT, or MRI.
- Investigate feeding pattern.

FTTDCD

- Perform detailed anthropometric examination and evaluation using age- and gender-matched growth standards.
- Investigate feeding pattern.

CTLN2

- Investigate carbohydrate, protein, and lipid composition of the diet.

Treatment of Manifestations

NICCD. The symptoms in most children with NICCD resolve by age 12 months following supplementation with fat-soluble vitamins and use of lactose-free formula (in those with galactosemia) or formulas containing medium-chain triglycerides (MCT) [Ohura et al 2003]. Moreover, the efficacy of lactose-free and/or MCT-enriched therapeutic formulas has also been demonstrated in a Chinese NICCD cohort [Song et al 2010]. Two siblings improved after switching from breast milk to formula, which has higher proline content [Ben-Shalom et al 2002]. Some children with NICCD improve without treatment.

Four infants with NICCD and severe liver dysfunction were diagnosed as having tyrosinemia of unknown cause and underwent liver transplantation at age ten to 12 months [Tamamori et al 2002, Kobayashi et al 2006].

FTTDCD. Few treatment measures have been described for this novel citrin-deficient phenotype.

- A toddler with FTTDCD was fed in accordance with his own food preferences (including aversion to rice and fondness for fish); FTT improved gradually, with weight-for-age recovering beyond the thirrd percentile at age three years. The dyslipidemia also improved gradually [Song et al 2009a].
- In addition to dietary treatment, administration of sodium pyruvate may be effective in correcting growth retardation [Mutoh et al 2008, Saheki et al 2010].

CTLN2. The most successful therapy to date has been liver transplantation [Ikeda et al 2001, Kasahara et al 2001, Yazaki et al 2004, Hirai et al 2008], which prevents episodic hyperammonemic crises, corrects the metabolic disturbances, and eliminates preferences for protein-rich foods [Kobayashi & Saheki 2004]. Nearly all cases of CTLN2 need liver transplantation in the past, but this situation starts to change since introduction of arginine and sodium pyruvate.

- Administration of arginine was reported to be effective in decreasing blood ammonia concentration. Reducing calorie/carbohydrate intake and increasing protein intake ameliorates hypertriglyceridemia [Imamura et al 2003].
- Administration of sodium pyruvate was effective in several cases [Yazaki et al 2005; Mutoh et al 2008; Saheki et al 2010; Yazaki et al 2010; Ohura et al, personal communication; Okano et al, personal communication].

Prevention of Primary Manifestations

To prevent hyperammonemia and resolve failure to thrive, a diet rich in protein and lipids and low in carbohydrates is recommended [Saheki & Kobayashi 2005, Saheki et al 2006, Dimmock et al 2007, Saheki et al 2008, Dimmock et al 2009].

Avoid high-carbohydrate meals and alcohol.

Arginine administration may be effective in preventing hyperammonemic crisis.

Prevention of Secondary Complications

Vitamin D deficiency and zinc deficiency are common complications in NICCD [Song et al, in preparation]. Severe infection and liver cirrhosis have also been reported to be lethal complications in some individuals with NICCD. Therefore, vitamin D and zinc supplements and active infection control are recommended in NICCD.

Surveillance

To monitor for emergence of the FTTDCD phenotype in persons with citrin deficiency older than age one year: close surveillance of anthropometric indices, such as height, weight, and head circumference; serum lipid levels, including triglycerides, total cholesterol, HDL-cholesterol, and LDL-cholesterol.

It is recommended that the following be measured every several months:

- Plasma ammonia concentration (especially in the evening or 2 hours after feeding)
- Plasma citrulline concentration
- Serum PSTI concentration

Increases in plasma citrulline concentration and serum PSTI suggest onset of CTLN2 [Tsuboi et al 2001, Mutoh et al 2008] and should trigger initiation of treatment.

Agents/Circumstances to Avoid

Low-protein/high-caloric (high-carbohydrate) diet. Although a low-protein/high-caloric diet helps prevent hyperammonemia in urea cycle enzyme deficiencies, it is harmful for individuals with all forms of citrin deficiency (i.e., NICCD, FTTDCD, or CTLN2) [Saheki et al 2004, Saheki & Kobayashi 2005, Saheki et al 2006]. A high-carbohydrate diet may increase NADH production, disturb urea synthesis, and stimulate the citrate-malate shuttle, resulting in hyperammonemia, fatty liver, and hypertriglyceridemia [Saheki & Kobayashi 2002, Imamura et al 2003, Saheki et al 2006, Saheki et al 2007].

Infusion of sugars, such as glycerol, fructose, and glucose. Severe brain edema treated with glycerol-containing osmotic agents has resulted in continued deterioration and is contraindicated in those with CTLN2 [Yazaki et al 2005]. Degradation of large amounts of glycerol and fructose generates NADH in the liver, which may disturb liver function and produce toxic substances [Saheki et al 2004, Yazaki et al 2005, Takahashi et al 2006].

Infusion of high-concentration glucose may also exacerbate hyperammonemia [Tamakawa et al 1994, Takahashi et al 2006].

Note: Mannitol infusion appears to be safer [Yazaki et al 2005].

Alcohol. Drinking alcohol can trigger the onset of CTLN2 because alcohol dehydrogenase (ADH) generates NADH in the cytosol of the liver.

Medications. Acetaminophen and rabeprozole may trigger CTLN2 [Shiohama et al 1993, Imamura et al 2003].

Evaluation of Relatives at Risk

It is appropriate to test at-risk asymptomatic sibs of a proband for citrin deficiency so that appropriate dietary management of infants (discontinuation of breast feeding and introduction of lactose-free and/or MCT-enriched formulas) can be instituted before symptoms occur.

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

Glycerol or similar drugs containing glycerol and fructose for brain edema are not only ineffective but also dangerous for persons with citrin deficiency (see Agents/Circumstances to Avoid).

Genetics clinics, staffed by genetics professionals, provide 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.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

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

Citrin deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Occasionally a parent may have two mutated *SLC25A13* alleles without severe symptoms of CTLN2, a finding in two of 48 fathers and one of 54 mothers tested in 163 Japanese families with NICCD [Kobayashi et al 2006].
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- When both parents are carriers, each sib of an affected individual has, at conception, a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- When one parent is a carrier and the other parent has two mutated *SLC25A13* alleles, each sib of an affected individual has, at conception, a 50% chance of inheriting two mutated *SLC25A13* alleles and being affected and a 50% chance of inheriting one mutated *SLC25A13* allele and being an asymptomatic carrier.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with citrin deficiency are obligate heterozygotes (carriers) for a disease-causing mutation in *SLC25A13*.

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 for at-risk family members is possible once the mutations have been identified in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis [Zhao et al 2011] usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing mutations in the family must have been identified before prenatal testing can be performed.

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

Requests for prenatal testing for conditions which (like citrin deficiency) have treatment available are not common. Differences in perspective may exist among medical professionals and within 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, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Note: It is the policy of *GeneReviews* to include in *GeneReviews*™ chapters any clinical uses of testing available from laboratories listed in the GeneTests™ Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Citrin Deficiency: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
SLC25A13	7q21.3	Calcium-binding mitochondrial carrier protein Aralar2	SLC25A13 @ LOVD	SLC25A13

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click here.

Table B. OMIM Entries for Citrin Deficiency (View All in OMIM)

603471	CITRULLINEMIA, TYPE II, ADULT-ONSET; CTLN2
603859	SOLUTE CARRIER FAMILY 25 (CITRIN), MEMBER 13; SLC25A13
605814	CITRULLINEMIA, TYPE II, NEONATAL-ONSET

Normal allelic variants. The normal *SLC25A13* gene comprises 18 exons [Kobayashi et al 1999, Sinasac et al 1999].

Pathologic allelic variants. To date, 59 pathologic allelic variants occurring in exons or introns resulting in missense mutations, predicted truncated forms of citrin, or abnormal mRNA splicing have been reported [Kobayashi et al 1999, Yasuda et al 2000, Ben-Shalom et al 2002, Yamaguchi et al 2002, Lu et al 2005, Takaya et al 2005, Hutchin et al 2006, Ko et al 2007a, Ko et al 2007b, Komatsu et al 2008, Song et al 2008, Tabata et al 2008, Wong et al 2008, Dimmock et al 2009, Hutchin et al 2009, Song et al 2009b, Xing et al 2010, Fu et al 2011, Lin et al 2011, Song et al 2011, Wen et al 2011]. Thirteen novel pathologic variations have been identified by the authors [Song et al, unpublished data].

- Two mutations (c.1177+1G>A and c.851-854del) account for the majority (~70%) of pathologic alleles in Japanese persons with citrin deficiency.
- In a cohort of 51 persons with citrin deficiency from 50 Chinese families, four mutations (c.851-854del, c.615+5G>A, c.1750+72_1751-4dup17insNM_138459.3: 2667, and c.1638_1660dup23) accounted for 87% of the mutated alleles [Song et al 2011].
- Only one mutation, p.Arg360X, has been found in both Japanese and Northern European populations [Tabata et al 2008].

Some of the 20 mutations identified in Japanese individuals have been found in Chinese, Vietnamese, and Korean individuals with citrin deficiency (NICCD or CTLN2) [Lu et al 2005, Lee et al 2006, Song et al 2006, Tsai et al 2006, Yeh et al 2006, Ko et al 2007a, Ko et al 2007b, Song et al 2008, Tabata et al 2008].

Different mutations were found in Israel, the United States, the United Kingdom, and China [Ben-Shalom et al 2002, Hutchin et al 2006, Luder et al 2006, Dimmock et al 2007, Song et al 2008, Tabata et al 2008, Song et al 2009b, Xing et al 2010, Fu et al 2011, Song et al 2011].

Table 10. Selected *SLC25A13* Pathologic Allelic Variants

DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change	Reference Sequences	Reference
c.15G>A (Ex1-1G>A)	--	NM_014251.2 NP_055066.1	Tabata et al [2008]
c.550C>T	p.Arg184X		Saheki et al [2004]
c.615+5G>A (IVS6+5G>A)	--		
c.615+1G>C (IVS6+1G>C)	--		Lu et al [2005]
c.674C>A	p.Ser225X		Kobayashi et al [1999]
c.851_854del (851del4)	p.Met285ProfsX2		
c.1078C>T	p. Arg360X		Tabata et al [2008]
c.1177+1G>A (IVS11+1G>A)	--		Kobayashi et al [1999]
c.1311+1G>A (IVS13+1G>A)	--		
c.1592G>A	p.Gly531Asp		Tabata et al [2008]
c.1638_1660dup23 (1638ins23)	p.Ala554GlyfsX17		Kobayashi et al [1999]

c.1799dupA (1800_1801insA)	p.Tyr600X		Yasuda et al [2000]
c.1801G>T	p.Glu601X		Yamaguchi et al [2002]
c.1801G>A	p.Glu601Lys		
c.1813C>T	p.Arg605X		Yasuda et al [2000]
c.1750+72_1751-4dup17ins NM_138459.3: 2667 [2] (IVS16ins3kb)	--		Tabata et al [2008]
g.20984997_20985512del516 (Ex16+74_IVS17-32del516)	--	NT_007933.14	Takaya et al [2005]

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

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

2. A complex allele with an insertion of 2667 nucleotides of processed cDNA in antisense orientation of *NUS1* at 6q22.31 (reference sequence NM_138459.3); this insertion is flanked by the 17 nucleotide duplication of intron 16 sequences (NM_014251.2:c.1751-4_-22dup17) [Tabata et al 2008].

Normal gene product. Citrin and its homolog aralar [del Arco & Satrústegui 1998] are members of the SLC25 (solute carrier family 25) protein family. Both proteins are localized in the mitochondrial inner membrane and function as a Ca^{2+}-binding/-stimulated aspartate-glutamate carrier (AGC), a component of the malate-aspartate NADH shuttle [Palmieri et al 2001, Kobayashi & Saheki 2003]. Citrin is expressed in the liver; aralar in the brain and skeletal muscle; both are expressed in the kidney and heart [Kobayashi et al 1999]. Citrin as a liver-type AGC plays a role in various metabolic pathways, including aerobic glycolysis, gluconeogenesis, the urea cycle, and protein and nucleotide syntheses [Saheki & Kobayashi 2002, Saheki et al 2004, Saheki & Kobayashi 2005, Saheki et al 2006].

Abnormal gene product. Most *SLC25A13* mutations cause or predict truncation of the citrin protein or delete a loop between the mitochondrial transmembrane domains. The lack of significant citrin protein was confirmed by Western blot analysis using antibody against the N-terminal half of the human citrin protein, which detected little or no cross-reactive immune material in liver, cultured fibroblasts, and lymphocytes from individuals with *SLC25A13* mutations [Yasuda et al 2000, Takahashi et al 2006, Dimmock et al 2007, Tokuhara et al 2007, Fu et al 2011].

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

References

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

Literature Cited

1. Ben-Shalom E, Kobayashi K, Shaag A, Yasuda T, Gao HZ, Saheki T, Bachmann C, Elpeleg O. Infantile citrullinemia caused by citrin deficiency with increased dibasic amino acids. Mol Genet Metab. 2002;77:202–8. [PubMed: 12409267]
2. del Arco A, Satrústegui J. Molecular cloning of Aralar, a new member of the mitochondrial carrier superfamily that binds calcium and is present in human muscle and brain. J Biol Chem. 1998;273:23327–34. [PubMed: 9722566]
3. Dimmock D, Maranda B, Dionisi-Vici C, Wang J, Kleppe S, Fiermonte G, Bai R, Hainline B, Hamosh A, O'Brien WE, Scaglia F, Wong LJ. Citrin deficiency, a perplexing global disorder. Mol Genet Metab. 2009;96:44–9. [PubMed: 19036621]
4. Dimmock DP, Kobayashi K, Iijima M, Tabata A, Wong LJ, Lee BH, Saheki T, Scaglia F. Citrin deficiency: a novel cause of failure to thrive that responds to a high protein, low carbohydrate diet. Pediatrics. 2007;119:e773–7. [PubMed: 17332192]
5. Feillet F, Merten M, Battaglia-Hsu SF, Rabier D, Kobayashi K, Straczek J, Brivet M, Favre E, Guéant JL. Evidence of cataplerosis in a patient with neonatal classical galactosemia presenting as citrin deficiency. J Hepatol. 2008;48:517–22. [PubMed: 18207281]
6. Fiermonte G, Soon D, Chaudhuri A, Paradies E, Lee PJ, Krywawych S, Palmieri F, Lachmann RH. An adult with type 2 citrullinemia presenting in Europe. N Engl J Med. 2008;358:1408–9. [PubMed: 18367750]
7. Fu HY, Zhang SR, Wang XH, Saheki T, Kobayashi K, Wang JS. The mutation spectrum of the SLC25A13 gene in Chinese infants with intrahepatic cholestasis and aminoacidemia. J Gastroenterol. 2011;46:510–8. [PubMed: 20927635]
8. Fukumoto K, Sumida Y, Yoshida N, Sakai K, Kanemasa K, Itoh Y, Mitsufuji S, Kataoka K, Okanoue T. A case of adult-onset type II citrullinemia having a liver histology of nonalcoholic steatohepatitis (NASH) . Nippon Shokakibyo Gakkai Zasshi. 2008;105:244–51. [PubMed: 18250596]

9. Gao HZ, Kobayashi K, Tabata A, Tsuge H, Iijima M, Yasuda T, Kalkanoglu HS, Dursun A, Tokatli A, Coskun T, Trefz FK, Skladal D, Mandel H, Seidel J, Kodama S, Shirane S, Ichida T, Makino S, Yoshino M, Kang JH, Mizuguchi M, Barshop BA, Fuchinoue S, Seneca S, Zeesman S, Knerr I, Rodes M, Wasant P, Yoshida I, De Meirleir L, Abdul Jalil M, Begum L, Horiuchi M, Katunuma N, Nakagawa S, Saheki T. Identification of 16 novel mutations in the argininosuccinate synthetase gene and genotype-phenotype correlation in 38 classical citrullinemia patients. Hum Mutat. 2003;22:24–34. [PubMed: 12815590]
10. Hachisu M, Oda Y, Goto M, Kobayashi K, Saheki T, Ohura T, Noma S, Kitanaka S. Citrin deficiency presenting with ketotic hypoglycaemia and hepatomegaly in childhood. Eur J Pediatr. 2005;164:109–10. [PubMed: 15592876]
11. Hagiwara N, Sekijima Y, Takei Y, Ikeda S, Kawasaki S, Kobayashi K, Saheki T. Hepatocellular carcinoma in a case of adult-onset type II citrullinemia. Intern Med. 2003;42:978–82. [PubMed: 14606711]
12. Hirai I, Kimura W, Suto K, Fzjimoto H, Watanabe T, Fuse A, Kobayashi K, Iijima M, Saheki T, Nakatsuka T, Sugawara Y, Makuuchi M. Living donor liver transplantation for type II citrullinemia from a heterozygous donor. Hepatogastroenterology. 2008;55:2211–6. [PubMed: 19260507]
13. Hutchin T, Preece MA, Hendriksz C, Chakrapani A, McClelland V, Okumura F, Song YZ, Iijima M, Kobayashi K, Saheki T, McKiernan P, Baumann U. Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) as a cause of liver disease in infants in the UK. J Inherit Metab Dis. 2009 [PubMed: 19517266]
14. Hutchin T, Preece MA, Kobayashi K, Saheki T, Brown R, Kelly DA, McKiernan PJ, Green A, Baumann U. Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) in a European patient. J Inherit Metab Dis. 2006;29 Suppl. 1:112. [PubMed: 16601877]
15. Ikeda S, Kawa S, Takei Y, Yamamoto K, Shimojo H, Tabata K, Kobayashi K, Saheki T. Chronic pancreatitis associated with adult-onset type II citrullinemia: clinical and pathological findings. Ann Intern Med. 2004;141:W109-10. [PubMed: 15466765]
16. Ikeda S, Yazaki M, Takei Y, Ikegami T, Hashikura Y, Kawasaki S, Iwai M, Kobayashi K, Saheki T. Type II (adult onset) citrullinaemia: clinical pictures and the therapeutic effect of liver transplantation. J Neurol Neurosurg Psychiatry. 2001;71:663–70. [PubMed: 11606680]
17. Imamura Y, Kobayashi K, Shibatou T, Aburada S, Tahara K, Kubozono O, Saheki T. Effectiveness of carbohydrate-restricted diet and arginine granules therapy for adult-onset type II citrullinemia: a case report of siblings showing homozygous SLC25A13 mutation with and without the disease. Hepatol Res. 2003;26:68–72. [PubMed: 12787807]
18. Kasahara M, Ohwada S, Takeichi T, Kaneko H, Tomomasa T, Morikawa A, Yonemura K, Asonuma K, Tanaka K, Kobayashi K, Saheki T, Takeyoshi I, Morishita Y. Living-related liver transplantation for type II citrullinemia using a graft from heterozygote donor. Transplantation. 2001;71:157–9. [PubMed: 11211185]
19. Ko JM, Kim GH, Kim JH, Kim JY, Choi JH, Ushikai M, Saheki T, Kobayashi K, Yoo HW. Six cases of citrin deficiency in Korea. Int J Mol Med. 2007a;20:809–15. [PubMed: 17982687]
20. Ko JS, Song JH, Park SS, Seo JK. Neonatal intrahepatic cholestasis caused by citrin deficiency in Korean infants. J Korean Med Sci. 2007b;22:952–6. [PubMed: 18162705]
21. Kobayashi K, Horiuchi M, Saheki T. Pancreatic secretory trypsin inhibitor as a diagnostic marker for adult-onset type II citrullinemia. Hepatology. 1997;25:1160–5. [PubMed: 9141434]
22. Kobayashi K, Iijima M, Ushikai M, Ikeda S, Saheki T. Citrin deficiency. J Jpn Pediatr Soc. 2006;110:1047–59.
23. Kobayashi K, Iijima M, Yasuda T, Sinasac DS, Yamaguchi N, Tsui L-C, Scherer SW, Saheki T. Type II citrullinemia (citrin deficiency): a mysterious disease caused by a defect of calcium-binding mitochondrial carrier protein. In: Pochet R, ed. *Calcium: The Molecular Basis of Calcium Action in Biology and Medicine.* Dordrecht, Netherlands: Kluwer; 2000:565-87.
24. Kobayashi K, Saheki T. Molecular basis of citrin deficiency. Seikagaku. 2004;76:1543–59. [PubMed: 15675368]
25. Kobayashi K, Saheki T. Aspartate glutamate carrier (citrin) deficiency. In: Broer S, Wagner CS, eds. *Membrane Transporter Diseases.* New York, NY: Kluwer Academic/Plenum Publishers; 2003:147-60.
26. Kobayashi K, Sinasac DS, Iijima M, Boright AP, Begum L, Lee JR, Yasuda T, Ikeda S, Hirano R, Terazono H, Crackower MA, Kondo I, Tsui LC, Scherer SW, Saheki T. The gene mutated in adult-onset type II citrullinaemia encodes a putative mitochondrial carrier protein. Nat Genet. 1999;22:159–63. [PubMed: 10369257]
27. Komatsu M, Yazaki M, Tanaka N, Sano K, Hashimoto E, Takei Y, Song YZ, Tanaka E, Kiyosawa K, Saheki T, Aoyama T, Kobayashi K. Citrin deficiency as a cause of chronic liver disorder mimicking non-alcoholic fatty liver disease. J Hepatol. 2008;49:810–20. [PubMed: 18620775]
28. Lee BH, Jin HY, Kim GH, Choi JH, Yoo HW. Nonalcoholic fatty liver disease in 2 siblings with adult-onset type II citrullinemia. J Pediatr Gastroenterol Nutr. 2010;50:682–5. [PubMed: 20400906]
29. Lee HC, Mak CM, Lam CW, Yuen YP, Chan AO, Shek CC, Siu TS, Lai CK, Ching CK, Siu WK, Chen SP, Law CY, Tai HL, Tam S, Chan AY. Analysis of inborn errors of metabolism: disease spectrum for expanded newborn screening in Hong Kong. Chin Med J (Engl). 2011;124:983–9. [PubMed: 21542954]
30. Lee NC, Chien YH, Kobayashi K, Saheki T, Chen H-L, Chiu PC, Ni YH, Chang MH, Hwu WL. Time course of acylcarnitine elevation in neonatal intrahepatic cholestasis caused by citrin deficiency. J Inherit Metab Dis. 2006;29:551–5. [PubMed: 16736097]
31. Lin JT, Hsiao KJ, Chen CY, Wu CC, Lin SJ, Chou YY, Shiesh SC. High resolution melting analysis for the detection of SLC25A13 gene mutations in Taiwan. Clin Chim Acta. 2011;412:460–5. [PubMed: 21134364]
32. Lu YB, Kobayashi K, Ushikai M, Tabata A, Iijima M, Li MX, Lei L, Kawabe K, Taura S, Yang Y, Liu TT, Chiang SH, Hsiao KJ, Lau YL, Tsui LC, Lee DH, Saheki T. Frequency and distribution in East Asia of 12 mutations identified in the SLC25A13 gene of Japanese patients with citrin deficiency. J Hum Genet. 2005;50:338–46. [PubMed: 16059747]
33. Luder AS, Tabata A, Iijima M, Kobayashi K, Mandel H. Citrullinaemia type 2 outside East Asia: Israeli experience. J Inherit Metab Dis. 2006;29 Suppl. 1:59.