

Disease Name:

CLASSIC CITRULLINEMIA
(CITRULLINEMIA, TYPE I; CTLN1; ARGININOSUCCINATE SYNTHETASE DEFICIENCY; ASS DEFICIENCY)

Classification: Urea cycle defect

Genetic Information:

Inheritance: Autosomal recessive

Population Incidence: 1:57,000

Ethnic Incidence: No known population at increased risk

Gene & Location: ASS- 9q34

Common Mutation: No known common mutations

OMIM # #215700

Disease Information:

Symptom Onset: Two forms, one with neonatal onset and the other with infantile onset.

Symptoms: This defect produces hyperammonemia, encephalopathy and respiratory alkalosis. Infants are generally well for the first 24-72 hours but then demonstrate lethargy, poor feeding, vomiting, grunting respirations, tachypnea, hypothermia, progressing to opisthotonus, seizures, cerebral edema, coma, apnea and death if not treated. Milder variants, asymptomatic individuals and intra-family variability have been reported.

Physical Findings: Patients with pili torti have been described, probably due to nutritional deficiency. Otherwise no dysmorphisms.

Treatment: Rescue of an infant from hyperammonemic encephalopathy may be possible with aggressive hemodialysis and specialized care. Maintenance treatment consists of a protein-restricted diet, ammonia disposal drugs, arginine supplementation and aggressive intervention for recurrent bouts of hyperammonemia.

Natural History without treatment: Progressive encephalopathy proceeding to coma and death if untreated. However, there are milder variants and reports of asymptomatic patients.

Natural History with treatment: None of the infants with peak ammonias over 480umol/l had a normal neurological outcome. Otherwise outcome depends on amount of neurological damage and metabolic control, but theoretically normal.

Metabolic Information:

Missing Enzyme & Location:

Argininosuccinate synthetase, which catalyses the conversion of citrulline and aspartate to argininosuccinate as a rate limiting step in the urea cycle.

MS/MS profile:

Citrulline- very elevated
Arginine – low/ undetectable

Prenatal testing:

Enzyme assay on amniocytes or CVS is possible.

Miscellaneous Information:

Prepared for the NW Regional Newborn Screening Program by Sara Copeland MD, Judith Tuerck RN MS and Lorinda Paradise at OHSU in Portland, OR.

References:

1. Brusilow SW, Horwich AL. Urea Cycle Enzymes In: C. Scriver, A.L. Beaudet, W. Sly and D. Valle, Editors, *The Metabolic and Molecular Basis of Inherited Disease* (eighth ed.), McGraw-Hill, New York (2001), MMBID Online (genetics.accessmedicine.com)
2. Sauduray JM, Touati G, Delonlay P, Jouvet P, Narcy C, Laurent J, Rabier D, Kamoun P, Jan D, Revillon Y. Liver transplantation in urea cycle disorders. *Eur J Pediatr* 1999 158 [Suppl 2]:S55-S59.
3. Fletcher JM, Couper R, Moore D, Coxon R, Dorney S. Liver transplantation for citrullinaemia improves intellectual function. *J Inher Metab Dis* 1999 22: 581-586.
4. Bachmann C. Outcome and survival of 88 patients with urea cycle disorders: a retrospective evaluation. *Eur J Pediatr*. 2003 Jun;162(6):410-416.
5. Lee B, Goss J. Long-term correction of urea cycle disorders. *J Pediatr* 2001 138:1 S62-S71.
6. Ban K, Sugiyama N, Sugiyama K, Wada Y, Suzuki T, Hashimoto T, Kobayashi K. A pediatric patient with classical citrullinemia who underwent living-related partial liver transplantation. *Transplantation* 2001 71:10 1495-1497.
7. Chadifaux-Vekemans B, Rabier D, Chabli A, Blanc A, Aupetit J, Bardet J, Kamoun P. Improving the prenatal diagnosis of citrullinemia using citrulline/ornithine + arginine in amniotic fluid. *Prenat Diagn* 2002; 22: 456-458.
8. Kayler LK, Merion RM, Lee S, Sung RS, Punch JD, Rudich SM, Turcotte JG, Campbell DA Jr, Holmes R, Mcgee JC. Long-term survival after liver transplantation in children with metabolic disorders. *Pediatr Transplantation* 2002 6: 295-300.
9. Kasahara N, Ohwada S, Takeichi T, Kaneko H, Tomohasa T, Morikawa A, Yonemura K, Asonuma K, Tanaka K, Kobayashi K, Saheki T, Takeyoshi I, Morishita Y. *Transplantation* 2001 71:10 1495-7.
10. Fletcher JM, Couper R, Moore D, Coxon R, Dorney S. Liver transplantation for citrullinaemia improves intellectual function. *J Inher Metab Dis* 1999 22: 581-586.
11. Vilaseca MA, Kobayashi K, Briones P, Lambruschini N, Campistol J, Tabata A, Alomar A, Rodes M, Lluch M, Saheke T. Phenotype and genotype heterogeneity in Mediterranean citrullinemia. *Molecular Genetics and Metabolism* 2001 74: 396-398.
12. Bennett MJ, Dear PRF, McGinlay JM, Gray RGF. Acute neonatal citrullinaemia. *J Inher Metab Dis* 1984 7:85.

13. Ruitenbeek W, Kobayashi K, Iijima M, Smeitink JAM et al. Moderate citrullinaemia without hyperammonaemia in a child with mutated and deficient argininosuccinate synthetase. *Annals of Clinical Biochemistry* 2003 40:1 102-111.
14. Haberle J, Pauli S Linnebank M, Kleijer WJ, Bakker HD, Wanders RJA, Harms E, Koch HG. Structure of the human argininosuccinate synthetase gene and an improved system for molecular diagnostics in patients with classical and mild citrullinemia. *Hum Genet* 2002 110:327-333.
15. Kakinoki H, Kobayashi K, Terazono H, Nagata Y Saheki T. Mutations and DNA diagnoses of classical citrullinemia. *Human Mutation* 1997 9:250-259.
16. Albayram S, Murphy J, Gailloud P, Moghekar A, Brunberg A. CT findings in the infantile form of citrullinemia. *Am J Neuroradiol* 2002 23:334-336.
17. Wilson CJ, Lee PJ, Leonard JV. Plasma glutamine and ammonia concentrations in ornithine carbamoyltransferase deficiency and citrullinaemia. *J Inher Metab Dis.* 2001 24:691-695.
18. Li CM, Chao HK, Liu YF, Su TS. A nonsense mutation is responsible for the RNA-negative phenotype in human citrullinaemia. *European J Hum Genetics* 2001 9:685-689.
19. Choi CG, Yoo HW. Localized proton MR spectroscopy in infants with urea cycle defect. *Am J Neuroradiol* 2001 22:834-837.
20. Ye X, Whiteman B, Jerebtsova M, Batshaw ML. Correction of argininosuccinate synthetase (AS) deficiency in a murine model of citrullinemia with recombinant adenovirus carrying human AS cDNA. *Gene Therapy* 2000 7: 1777-1782.
21. Sass JO, Skladal D. Plasma concentrations and renal clearance of orotic acid in argininosuccinic acid synthetase deficiency. *Pediatr Nephrol* 1999 13:912-916.
22. Sander J, Janzen N, Sander S, Steuerwald U, Das AM, Scholl, Trefz FK, Koch HG, Haberle J, Korall H, Marquardt I, Korenke C. *Eur J Pediatr* 2003 162:6; 417-20.
23. Tuchman M, Yudkoff M. Blood levels of ammonia and nitrogen scavenging amino acids in patients with inherited hyperammonemia. *Molecular Genetics and Metabolism* 1999 66: 10-15.
24. Patejunas G, Lee B, Dennis JA, Healy PJ, Reeds PJ, Yu H, Frazer M, Mull B, Warman AW, Beaudet AL, O'Brien WE. Evaluation of gene therapy for citrullinaemia using murine and bovine models. *J Inher Metab Dis* 1998 21(Suppl 1) 138-150.
25. Zamora SA, Pinto A, Scott RB, Parsons HG. Mitochondrial abnormalities of liver in two children with citrullinaemia. *J Inher Metab Dis* 1997 20: 509-516.
26. Yazaki M, Ikeda S, Takei Y, Yanagisawa N, Matsunami H, Hashikura Y, Kawasaaki S, Makuuchi M, Kobayashi K, Saheki T.. Complete neurological recovery of an adult patient with type II citrullinemia after living related partial liver transplantation. *Transplantation* 1996 62:11 1679-1681.
27. Kawamoto S, Strong R, Kerlin P, Lynch SV, Steadman C, Kobayashi K, Nakagawa S, Matunami H, Akatsu T, Saheki T. Orthotopic liver transplantation for adult-onset type II citrullinaemia. *Clin Transplant* 1997 11:5 453-458.
28. 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. *Nature Genetics* 1999 22: 159-163.
29. Yasuda T, Yamaguchi N, Kobayashi K, Nishi I, Horinouchi H, Jalil A, Li MX, Ushikai M, Iijima M, Kondo I, Saheki T. Identification of two novel mutations in the SLC25A13 gene and detection of seven mutations in 102 patients with adult-onset type II citrullinemia. *Hum Genet* 2000 107:537-545.
30. 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 71:1 157-159.

31. Ito T, Shiraki K, Sekoguchi K, Yamanaka T, Sugimoto K, Takase K, Tameda Y, Nakano T. Hepatocellular carcinoma associated with adult-type citrullinemia. *Digestive Disease and Sciences* 2000 45:11 2203-2206.
32. Hwu WL, Kobayashi K, Hu YH, Yamaguchi N, Saheki T, Chow SP, Wang JH. A Chinese adult onset type II citrullinaemia patient with 851del4/1638ins23 mutations in the SLC25A13 gene. *J Med Genet* 2001 38e23.
33. Palmieri L, Pardo B, Lasorsa FM, del Arco A, Kobayashi K, Iijima M, Runswick MJ, Walker JE, Saheki T, Satrustegui J, Palmieri F. Citrin and aralar1 are Ca²⁺-stimulated aspartate/glutamate transporters in mitochondria. *The EMBO Journal* 2001 20:18 5060-5069.
34. Chen YF, Huang YC, Liu HM, Hwu WL. MRI in a case of adult-onset citrullinemia. *Neuroradiology* 2001 43: 845-847.
35. Maruyama H, Ogawa M, Nishio T, Kobayashi K, Saheki T, Sunohara N. Citrullinemia type II in a 64-year-old man with fluctuating serum citrulline levels: mutations in the SLC25A13 gene. *J of Neurological Sciences* 2001 193:63.
36. Oshiro S, Kochinda T, Tana T, Yamazato M, Kobayashi K, Komine Y, Muratani H, Saheki T, Iseki K, Takishita, S. A patient with adult-onset type II citrullinemia on long-term hemodialysis: reversal of clinical symptoms and brain MRI findings. *Am J Kidney Dis* 2002 39:189-92.
37. Yamaguchi N, Kobayashi K, Yasuda T, Nishi I, Iijima M, Nakagawa M, Osame M, Kondo I, Saheki T. Screening of SLC25a13 mutations in early and late onset patients with citrin deficiency in the Japanese population: identification of two novel mutations and establishment of multiple DNA diagnosis methods for nine mutations. *Human Mutation* 2002 19:122-130.
38. Saheki T, Kobayashi K, Iijima M, Nishi I, Yasuda T, Yamaguchi N, Gao HZ, Jalil MA, Begum L, Li MX. Pathogenesis and pathophysiology of citrin (a mitochondrial aspartate glutamate carrier) deficiency. *Metabolic Brain Disease* 2002 17:4 335-346.
39. Au WL, Lim TCC, Seow CC, Koh PL, Loh NK, Lim MSF, Tan IK, Yee WC. Serial diffusion-weighted magnetic resonance imaging in adult-onset citrullinaemia. *J Neurological Sciences* 2003 209:101-104.
40. 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 71:663-670.
41. Okeda R, Tanaka M, Kawahara Y, Tokushige J, Imai T, Kameya K. Adult-type citrullinemia. *Acta Neuropathol* 1989 78:96-100.
42. Tazawa Y, Kobayashi K, Ohura T, Abukawa D, Nishinomiya F, Hosoda Y, Yamshita M, Nagata I, Kono Y, Yasuda T, Yamaguchi N, Saheki T. Infantile cholestatic jaundice associated with adult-onset type II citrullinemia. *J of Pediatrics* 138:5 735-740.
43. Naito E, Ito M, Matsuura S, Yokota I, Saijo T, Ogawa Y, Kitamura S, Kobayashi K, Saheki T, Nishimura Y, Sakura N, Kuroda Y. Type II citrullinaemia (citrin deficiency) in a neonate with hypergalactosaemia detected by mass screening. *J Inherit Metab Dis* 2002 25:71-76.
44. Ohura T, Kobayashi K, Abukawa D, Tazawa Y, Aikawa J, Sakamoto O, Saheki T, Iinuma K. A novel inborn error of metabolism detected by elevated methionine and/or Galactose in newborn screening: neonatal intrahepatic cholestasis caused by citrin deficiency. *Eur J Pediatr* 2003 162:317-322.
45. Tamamori A, Okano Y, Ozaki H, Fujimoto A, Kajiwara M, Fukuda K, Kobayashi K, Saheki T, Tagami Y, Yamano T. Neonatal intrahepatic cholestasis caused by citrin deficiency: severe hepatic dysfunction in an infant requiring liver transplantation. *Eur J Pediatr* 2002 161:609-613.
46. 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. *Molecular Genetics and Metabolism* 2002 77:202-208.

47. Saheki T, Kobayashi K. Mitochondrial aspartate glutamate carrier (citrin) deficiency as the cause of adult-onset type II citrullinemia (CTLN2) and idiopathic neonatal hepatitis (NICCD). *J Hum Genet* 2002 47:333-341.
48. Tomomasa T, Kobayashi K, Kaneko H, Shimura H, Fukusato T, Tabata M, Inoue Y, Ohwada S, Kasahara M, Morishita Y, Kimura M, Saheki T, Morikawa A. Possible clinical and histologic manifestations of adult-onset type II citrullinemia in early infancy. *J of Pediatr* 2001 138:5 741-743.
49. Kobayashi K, Horiuchi M, Saheki T. Pancreatic secretory trypsin inhibitor as a diagnostic marker for adult-onset type II citrullinemia. *Hepatology* 1997 25:5 1160-1165.
50. Kobayashi K, Nakata M, Terazono H, Shinsato T, Saheki T. Pancreatic secretory trypsin inhibitor gene is highly expressed in the liver of adult-onset type II citrullinemia. *BEBS Letters* 1995 372:69-73.
51. Tsuboi Y, Fujino Y, Kobayashi K, Saheki T, Yamada T. High serum pancreatic secretory trypsin inhibitor before onset of type II citrullinemia. *Neurology* 2001 57:5 933-935.
52. Tazawa Y, Kobayashi K, Ohura T, Abukawa D, Nishinomiya F, Hosoda Y, Yamashita M, Nagata I, Kono Y, Yasuda T, Yamaguchi N, Saheki T. Infantile cholestatic jaundice associated with adult-onset type II citrullinemia. *J of Pediatr* 2001 138:5 735-740.
53. Ohura T, Kobayashi K, Tazawa Y, Nishi I, Abukawa D, Sakamoto O, Iinuma K, Saheki T. Neonatal presentation of adult-onset type II citrullinemia. *Hum Genet* 2001 108:87-90.
54. Summar M, Tuchman M. "Urea Cycle Disorders Overview", www.geneclinics.org
55. Morris AA, Leonard JV. "Early recognition of metabolic decompensation", *Arch Dis Child*. 1997 Jun;76(6):555-6.
56. Brusilow SW, Maestri NE. "Urea cycle disorders: diagnosis, pathophysiology, and therapy", *Adv Pediatr*. 1996; 43:127-70.
57. Burns SP, Woolf DA, Leonard JV, Iles RA. "Investigation of urea cycle enzyme disorders by 1H-NMR spectroscopy", *Clin Chim Acta*. 1992 Jul 31;209(1-2):47-60.
58. Sander J, Janzen N, Sander S, Steuerwald U, Das AM, Scholl S, Trefz FK, Koch HG, Häberle J, Korall H, Marquardt I, Korenke C. "Neonatal screening for citrullinaemia", *Eur J Pediatr* 2003 162(6):417-20.
59. Bachmann, C. "Outcome and survival of 88 patients with urea cycle disorders: a retrospective evaluation", *Eur J Pediatr* 2003 162(6):410-16.