

Disease Name:

GLUTARIC ACIDEMIA TYPE II

(GLUTARIC ACIDURIA TYPE II; GA II; ETHYLMALONIC-ADIPIC ACIDURIA;
ELECTRON TRANSFER FLAVOPROTEIN DEHYDROGENASE DEFICIENCY;
ETF/ETF QO DEFICIENCY)

Classification: Fatty Acid Oxidation

Genetic

Inheritance: Autosomal recessive

Information:

Population Incidence: Not a rare disease but incidence is unknown

Ethnic Incidence: No known population at increased risk

Gene & Location: ETF alpha subunit: 15q23-25
ETF beta subunit 19q13.3

Common Mutation: No known common mutations

OMIM # *231680; *130410; *231675; #231680

Disease

Symptom Onset: Newborn to adult

Information:

Symptoms: Three different phenotypes that stay consistent within families:
Neonatal onset with congenital anomalies: Infants often premature, present during the first 24-48 hrs of life with hypotonia, hepatomegaly, hypoglycemia, metabolic acidosis, sweaty feet odor, kidneys are often palpably enlarged and cystic, facial dysmorphisms, rocker-bottom feet, muscular defects of the anterior abdominal wall and anomalies of the external genitalia (hypospadias and chordee). Virtually all die within the first week of life.
Neonatal onset without anomalies: Infants develop problems within the first few days of life with hypotonia, tachypnea, metabolic acidosis, hepatomegaly, hypoglycemia, and sweaty feet odor. The few who have survived beyond the first week of life have died within a few months usually with severe cardiomyopathy. A few others have been hypoglycemic as newborns and later developed typical episodes of Reye syndrome-like illness and have survived somewhat longer.
Mild or late onset is extremely variable in its course and age at presentation, but typically include episodes of hypoketotic hypoglycemia and hepatic dysfunction. There is progressive lipid storage myopathy and carnitine deficiency and few had progressive extrapyramidal movement disorders similar to GAI. There are reports of asymptomatic adults.

Physical Findings: In the congenital form the above described dysmorphisms.

Treatment: Treatment of the severe neonatal presentations is not effective. Mainstay therapies include avoidance of fasting, a diet low in fat and protein and high in carbohydrate. Riboflavin supplementation in the milder cases has been curative in some cases. Additional supplements of glycine and L-carnitine have been used.

Natural History without treatment: Variable, depending on age at presentation and severity of symptoms.

Natural History with treatment: Treatment may not help infants with congenital or early onset, especially if there is cardiomyopathy. For individuals with the milder late onset type, therapy may prevent some of the neurological findings and the carnitine deficiency. One infant diagnosed at birth through newborn screening was alive and well at 4 years of age.

Metabolic Information:

Missing Enzyme & Location: Electron Transfer Flavoprotein (ETF) or ETF-ubiquinone oxidoreductase- a branch of the electron transport system

MS/MS profile: C4; C5; C6; C8; C10- multiple elevations
C6 hexanoyl carnitine- mild elevations
C8 octanoyl carnitine- elevated
C16; C18:1- multiple elevations

Prenatal testing: Yes- analyte analysis of amniotic fluid or enzyme analysis of amniocytes.

Miscellaneous Information:

Urine organic acids may only be abnormal during acute episodes. The finding of 2-OH glutaric aciduria is useful diagnostic point as it distinguishes between GA I and GA II. Been implicated as a cause of SIDS
Mothers have been reported with HELLP syndrome.

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. Abdenur JE, Chamoles NA, Schenone AB, Jorge L, Guinle A, Bernard C, Levandovskiy V, Fusta M, Lavorgna S. "Multiple acyl-CoA-dehydrogenase deficiency (MADD): use of acylcarnitines and fatty acids to monitor the response to dietary treatment", *Pediatr Res*. 2001 Jul;50(1):61-6.
2. al-Essa MA, Rashed MS, Bakheet SM, Patay ZJ, Ozand PT. "Glutaric aciduria type II: observations in seven patients with neonatal- and late-onset disease", *J Perinatol*. 2000 Mar;20(2):120-8.

3. Bennett MJ, Curnock DA, Engel PC, Shaw L, Gray RG, Hull D, Patrick AD, Pollitt RJ. "Glutaric aciduria type II: biochemical investigation and treatment of a child diagnosed prenatally", *J Inherit Metab Dis*. 1984; 7(2): 57-61.
4. Bernstein J, Chandra M, Creswell J, Kahn E, Malouf NN, McVicar M, Weinberg AG, Wybel RE. "Renal-hepatic-pancreatic dysplasia: a syndrome reconsidered", *Am J Med Genet*. 1987 Feb;26(2):391-403.
5. Bohm N, Uy J, Kiessling M, Lehnert W. "Multiple acyl-CoA dehydrogenation deficiency (glutaric aciduria type II), congenital polycystic kidneys, and symmetric warty dysplasia of the cerebral cortex in two newborn brothers. II. Morphology and pathogenesis", *Eur J Pediatr*. 1982 Sep;139(1):60-5.
6. Brivet M, Tardieu M, Khellaf A, Boutron A, Rocchiccioli F, Haengeli CA, Lemonnier A. "Riboflavin responsive ethylmalonic-adipic aciduria in a 9-month-old boy with liver cirrhosis, myopathy and encephalopathy", *J Inherit Metab Dis*. 1991;14(3):333-7.
7. Burlina AB, Dionisi-Vici C, Bennett MJ, Gibson KM, Servidei S, Bertini E, Hale DE, Schmidt-Sommerfeld E, Sabetta G, Zacchello F, et al. "A new syndrome with ethylmalonic aciduria and normal fatty acid oxidation in fibroblasts", *J Pediatr*. 1994 Jan;124(1):79-86.
8. Burns SP, Holmes HC, Chalmers RA, Johnson A, Iles RA. "Proton NMR spectroscopic analysis of multiple acyl-CoA dehydrogenase deficiency--capacity of the choline oxidation pathway for methylation in vivo", *Biochim Biophys Acta*. 1998 Apr 28;1406(3):274-82.
9. Chisholm CA, Vavelidis F, Lovell MA, Sweetman L, Roe CR, Roe DS, Frerman FE, Wilson WG. "Prenatal diagnosis of multiple acyl-CoA dehydrogenase deficiency: association with elevated alpha-fetoprotein and cystic renal changes", *Prenat Diagn*. 2001 Oct;21(10):856-9.
10. Christensen E. "Glutaryl-CoA dehydrogenase activity determined with intact electron-transport chain: application to glutaric aciduria type II", *J Inherit Metab Dis*. 1984;7 Suppl 2:103-4.
11. Curcoy A, Olsen RK, Ribes A, Trenchs V, Vilaseca MA, Campistol J, Osorio JH, Andresen BS, Gregersen N. "Late-onset form of beta-electron transfer flavoprotein deficiency", *Mol Genet Metab*. 2003 Apr;78(4):247-9.
12. de Visser M, Scholte HR, Schutgens RB, Bolhuis PA, Luyt-Houwen IE, Vaandrager-Verduin MH, Veder HA, Oey PL. "Riboflavin-responsive lipid-storage myopathy and glutaric aciduria type II of early adult onset", *Neurology*. 1986 Mar;36(3):367-72.
13. Elias E, Gray RG, Poulton K, Green A. "Ethylmalonic adipic aciduria--a treatable hepatomuscular disorder in two adult brothers", *J Hepatol*. 1997 Feb;26(2):433-6.
14. Farag E, Argalious M, Narouze S, DeBoer GE, Tome J. "The anesthetic management of ventricular septal defect (VSD) repair in a child with mitochondrial cytopathy", *Can J Anaesth*. 2002 Nov;49(9):958-62.

15. Fontaine M, Briand G, Vallee L, Ricart G, Degand P, Divry P, Vianey-Saban C, Vamecq J. "Acylcarnitine removal in a patient with acyl-CoA beta-oxidation deficiency disorder: effect of L-carnitine therapy and starvation", *Clin Chim Acta*. 1996 Aug 30;252(2):109-22.
16. Frerman FE, Goodman SI. Defects of Electron Transfer Flavoprotein and Electron Transfer Flavoprotein-Ubiquinone Oxidoreductase: Glutaric Acidemia Type II 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), www.genetics.accessmedicine.com
17. Galloway JH, Cartwright IJ, Bennett MJ. "Abnormal myocardial lipid composition in an infant with type II glutaric aciduria", *J Lipid Res*. 1987 Mar;28(3):279-84.
18. Goodman SI. "Prenatal diagnosis of glutaric acidemias", *Prenat Diagn* 2001; 21: 1167-1168.
19. Goodman SI, Binard RJ, Woontner MR, Frerman FE. "Glutaric acidemia type II: gene structure and mutations of the electron transfer flavoprotein:ubiquinone oxidoreductase (ETF:QO) gene", *Mol Genet Metab*. 2002 Sep-Oct;77(1-2):86-90.
20. Goodman SI, Frerman FE. "Glutaric acidaemia type II (multiple acyl-CoA dehydrogenation deficiency)", *J Inherit Metab Dis*. 1984;7 Suppl 1:33-7.
21. Green A, Preece MA, de Sousa C, Pollitt RJ. "Possible deleterious effect of L-carnitine supplementation in a patient with mild multiple acyl-CoA dehydrogenation deficiency (ethylmalonic-adipic aciduria)." *J Inherit Metab Dis*. 1991;14(5):691-7.
22. Gregersen N, Christensen MF, Kolvraa S. "Metabolic effects of carnitine medication in a patient with multiple acyl-CoA dehydrogenation deficiency", *J Inherit Metab Dis*. 1985;8 Suppl 2:139-40.
23. Grice AS, Peck TE. "Multiple acyl-CoA dehydrogenase deficiency: a rare cause of acidosis with an increased anion gap", *Br J Anaesth*. 2001 Mar;86(3):437-41.
24. Harkin JC, Gill WL, Shapira E. "Glutaric acidemia type II. Phenotypic findings and ultrastructural studies of brain and kidney", *Arch Pathol Lab Med*. 1986 May;110(5):399-401.
25. Harpey JP, Charpentier C, Coude M. "Methylene-blue for riboflavin-unresponsive glutaricaciduria type II", *Lancet*. 1986 Feb 15;1(8477):391.
26. Harpey JP, Charpentier C, Goodman SI, Darbois Y, Lefebvre G, Sebbah J. "Multiple acyl-CoA dehydrogenase deficiency occurring in pregnancy and caused by a defect in riboflavin metabolism in the mother. Study of a kindred with seven deaths in infancy: Value of riboflavin therapy in preventing this syndrome", *J Pediatr*. 1983 Sep;103(3):394-8.
27. Hirose S, Hamamoto K, Yoshida I, Inokuchi T, Kogo T, Mitsudome A. "Late-onset type II glutaric aciduria with massive pericardial effusion associated with severe fatty liver", *Acta Paediatr*. 2000 Jul;89(7):887-8.

28. Hostetler MA, Arnold GL, Mooney R, Bennett MJ, Rinaldo P, Roe CR. "Hypoketotic hypoglycemic coma in a 21-month-old child", *Ann Emerg Med.* 1999 Sep;34(3):394-8.
29. Koeberl DD, "Diagnosis and management of new inborn errors of metabolism identified through tandem mass spectroscopy", SIMD National Conference, March 3, 2004.
30. Loehr JP, Goodman SI, Frerman FE. "Glutaric acidemia type II: heterogeneity of clinical and biochemical phenotypes", *Pediatr Res.* 1990 Mar;27(3):311-5.
31. Mandel H, Africk D, Blitzer M, Shapira E. "The importance of recognizing secondary carnitine deficiency in organic acidemias: case report in glutaric acidemia type II", *J Inherit Metab Dis.* 1988;11(4):397-402.
32. Manning NJ, Bonham JR, Downing M, Edwards RG, Olpin SE, Pollitt RJ, Pourfarzam M, Sharrard MJ, Tanner MS. "Normal acylcarnitines in maternal urine during a pregnancy affected by glutaric aciduria type II", *J Inherit Metab Dis.* 1999 Feb;22(1):88-9.
33. Millington DS. "Interpretation and follow-up of abnormal newborn screening results from MS/MS", 2004 Newborn Screening & Genetics Testing Symposium, May 3, 2004, Atlanta, GA
34. Mooy PD, Giesberts MA, van Gelderen HH, Scholte HR, Luyt-Houwen IE, Przyrembel H, Blom W. "Glutaric aciduria type II: multiple defects in isolated muscle mitochondria and deficient beta-oxidation in fibroblasts", *J Inherit Metab Dis.* 1984;7 Suppl 2:101-2.
35. Mooy PD, Przyrembel H, Giesberts MA, Scholte HR, Blom W, van Gelderen HH. "Glutaric aciduria type II: treatment with riboflavin, carnitine and insulin", *Eur J Pediatr.* 1984 Dec;143(2):92-5.
36. Morris AA, Leonard JV. "Early recognition of metabolic decompensation", *Arch Dis Child.* 1997 Jun;76(6):555-6.
37. Morris AA, Olpin SE, Van't Hoff WG, Johnson AW, Leonard JV. "Renal tubular dysfunction in multiple acyl-CoA dehydrogenase deficiency", *J Inherit Metab Dis.* 1997 Aug;20(4):604-5.
38. Morris AA, Turnbull DM. "Fatty acid oxidation defects in muscle", *Curr Opin Neurol.* 1998 Oct;11(5):485-90.
39. OMIM- Online Mendelian Inheritance in Man; GLUTARICACIDURIA IIA ELECTRON TRANSFER FLAVOPROTEIN, ALPHA POLYPEPTIDE, INCLUDED; ETFA, INCLUDED-*231680
40. OMIM- Online Mendelian Inheritance in Man; ELECTRON TRANSFER FLAVOPROTEIN, BETA POLYPEPTIDE; ETFB GLUTARICACIDURIA IIB, INCLUDED- *130410
41. OMIM- Online Mendelian Inheritance in Man; GLUTARICACIDURIA IIC ELECTRON TRANSFER FLAVOPROTEIN DEHYDROGENASE, INCLUDED; ETFDH, INCLUDED- *231675

42. Osorio JH, Lluch M, Ribes A. "Analysis of organic acids after incubation with (16-2H₃)palmitic acid in fibroblasts from patients with mitochondrial beta-oxidation defects", *J Inherit Metab Dis*. 2003;26(8):795-803.
43. Pang CP, Law LK, Mak YT, Shek CC, Cheung KL, Mak TW, Lam CW, Chan AY, Fok TF. "Biochemical investigation of young hospitalized Chinese children: results over a 7-year period", *Am J Med Genet*. 1997 Nov 12;72(4):417-21.
44. Parini R, Vegni C, Martini J, Romeo A, Garavaglia B. "Sudden infant death and multiple acyl-CoA dehydrogenation disorders", *Eur J Pediatr*. 1995 May;154(5):421-2.
45. Peluchetti D, Antozzi C, Roi S, DiDonato S, Cornelio F. "Riboflavin responsive multiple acyl-CoA dehydrogenase deficiency: functional evaluation of recovery after high dose vitamin supplementation", *J Neurol Sci*. 1991 Sep;105(1):93-8.
46. Poplawski NK, Ranieri E, Harrison JR, Fletcher JM. "Multiple acyl-coenzyme A dehydrogenase deficiency: diagnosis by acyl-carnitine analysis of a 12-year-old newborn screening card", *J Pediatr*. 1999 Jun;134(6):764-6.
47. Purejav E, Kimura M, Takusa Y, Ohura T, Tsuchiya M, Hara N, Fukao T, Yamaguchi S. "Molecular study of electron transfer flavoprotein alpha-subunit deficiency in two Japanese children with different phenotypes of glutaric acidemia type II", *Eur J Clin Invest*. 2002 Sep;32(9):707-12.
48. Rinaldo P. "Mitochondrial fatty acid oxidation disorders and cyclic vomiting syndrome", *Dig Dis Sci*. 1999 Aug;44(8 Suppl):97S-102S.
49. Salazar D, Zhang L, deGala GD, Frerman FE. "Expression and characterization of two pathogenic mutations in human electron transfer flavoprotein", *J Biol Chem*. 1997 Oct 17;272(42):26425-33.
50. Santer R, Claass A, Krawinkel M, Schaub J, Ruitenbeek W. "Decreased activity of respiratory-chain enzymes in glutaric aciduria type II", *J Inherit Metab Dis*. 1995;18(1):75-6.
51. Shevell MI, Didomenicantonio G, Sylvain M, Arnold DL, O'Gorman AM, Scriver CR. "Glutaric acidemia type II: neuroimaging and spectroscopy evidence for developmental encephalomyopathy", *Pediatr Neurol*. 1995 May;12(4):350-3.
52. Sills MR, Zinkham WH. "Methylene blue-induced Heinz body hemolytic anemia", *Arch Pediatr Adolesc Med*. 1994 Mar;148(3):306-10.
53. Sovik O. "Inborn errors of amino acid and fatty acid metabolism with hypoglycemia as a major clinical manifestation", *Acta Paediatr Scand*. 1989 Mar;78(2):161-70.
54. Spector EB, Seltzer WK, Goodman SI. "Assignment of electron transfer flavoprotein-ubiquinone oxidoreductase (ETF-QO) to human chromosome 4q33 by fluorescence in situ hybridization and somatic cell hybridization", *Mol Genet Metab*. 1999 Aug;67(4):364-7.

55. Sperl W, Geiger R, Lehnert W, Rhead W. "Stridor as the major presenting symptom in riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency", *Eur J Pediatr*. 1997 Oct;156(10):800-2.
56. Stockler S, Radner H, Karpf EF, Hauer A, Ebner F. "Symmetric hypoplasia of the temporal cerebral lobes in an infant with glutaric aciduria type II (multiple acyl-coenzyme A dehydrogenase deficiency)", *J Pediatr*. 1994 Apr;124(4):601-4.
57. Takanashi J, Fujii K, Sugita K, Kohno Y. "Neuroradiologic findings in glutaric aciduria type II", *Pediatr Neurol*. 1999 Feb;20(2):142-5.
58. Tang NL, Hui J, Law LK, To KF, Mak TW, Cheung KL, Vreken P, Wanders RJ, Fok TF. "Overview of common inherited metabolic diseases in a Southern Chinese population of Hong Kong", *Clin Chim Acta*. 2001 Nov;313(1-2):195-201.
59. Triggs WJ, Roe CR, Rhead WJ, Hanson SK, Lin SN, Willmore LJ. "Neuropsychiatric manifestations of defect in mitochondrial beta oxidation response to riboflavin", *J Neurol Neurosurg Psychiatry*. 1992 Mar;55(3):209-11.
60. Uziel G, Garavaglia B, Ciceri E, Moroni I, Rimoldi M. "Riboflavin-responsive glutaric aciduria type II presenting as a leukodystrophy", *Pediatr Neurol*. 1995 Nov;13(4):333-5.
61. Vallee L, Fontaine M, Nuyts JP, Ricart G, Krivosic I, Divry P, Vianey-Saban C, Lhermitte M, Vamecq J. "Stroke, hemiparesis and deficient mitochondrial beta-oxidation", *Eur J Pediatr*. 1994 Aug;153(8):598-603.
62. Van Hove JL, Grunewald S, Jaeken J, Demaerel P, Declercq PE, Bourdoux P, Niezen-Koning K, Deanfeld JE, Leonard JV. "D,L-3-hydroxybutyrate treatment of multiple acyl-CoA dehydrogenase deficiency (MADD)", *Lancet*. 2003 Apr 26;361(9367):1433-5.
63. Vergani L, Barile M, Angelini C, Burlina AB, Nijtmans L, Freda MP, Brizio C, Zerbetto E, Dabbeni-Sala F. "Riboflavin therapy. Biochemical heterogeneity in two adult lipid storage myopathies", *Brain*. 1999 Dec;122 (Pt 12):2401-11.
64. Verjee ZH, Sherwood WG. "Multiple acyl-CoA dehydrogenase deficiency: a neonatal onset case responsive to treatment", *J Inherit Metab Dis*. 1985;8 Suppl 2:137-8.
65. Vianey-Saban C, Bouvier R, Cochat P, Buenerd A, Divry P, Dumoulin R, Cordier MP. "Antenatal expression of multiple acyl-CoA dehydrogenase deficiency", *J Inherit Metab Dis*. 2000 Jun;23(4):345-8.
66. Watanabe H, Yamaguchi S, Saiki K, Shimizu N, Fukao T, Kondo N, Orii T. "Identification of the D-enantiomer of 2-hydroxyglutaric acid in glutaric aciduria type II", *Clin Chim Acta*. 1995 Jul 14;238(2):115-24.

67. White RA, Dowler LL, Angeloni SV, Koeller DM. "Assignment of Etf_{dh}, Etf_b, and Etf_a to chromosomes 3, 7, and 13: the mouse homologs of genes responsible for glutaric acidemia type II in human", *Genomics*. 1996 Apr 1;33(1):131-4.
68. Yamaguchi S, Orii T, Maeda K, Oshima M, Hashimoto T. "A new variant of glutaric aciduria type II: deficiency of beta-subunit of electron transfer flavoprotein", *J Inherit Metab Dis*. 1990;13(5):783-6.