Published in final edited form as:
J Pediatr. 2013 October ; 163(4): 942–948. doi:10.1016/j.jpeds.2013.05.036.

Mitochondrial Hepatopathies: Advances in Genetics, Therapeutic Approaches, and Outcomes

Way Seah Lee, MD[1,2] and **Ronald J. Sokol, MD**[3]

[1]Department of Pediatrics, University of Malaya Medical Center, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO

[2]Pediatrics and Child Health Research Group, University of Malaya, Kuala Lumpur, Malaysia, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO

[3]Section of Pediatric Gastroenterology, Hepatology, and Nutrition and the Digestive Health Institute, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO

Cellular mitochondria play important roles in the production of energy required by human cells, thermogenesis, calcium and iron homeostasis, innate immune responses, production of reactive oxygen species, and programmed cell death (apoptosis).[1] Approximately 1000 nuclear genes encoding mitochondrial proteins have been identified to date. A mutation in any of these genes has the potential to give rise to monogenic or primary mitochondrial disorders.[2] Mitochondrial dysfunction is also associated with many common human conditions, including cardiac disease,[3] diabetes,[4] cancer,[5] epilepsy,[6] obesity,[7] and degenerative diseases such as Parkinson and Alzheimer's diseases.[8,9]

A unique feature of mitochondria in mammalian cells is the presence of a separate genome, mitochondrial DNA (mtDNA), which is distinct from nuclear genes.[1] The respiratory chain peptide components are encoded by both nuclear and mtDNA genes.[1] Thirteen essential polypeptides are synthesized from the small (16.5-kb), circular, double-stranded mtDNA, and nuclear genes encode more than 70 respiratory chain subunits and an array of enzymes and cofactors required to maintain mtDNA.[1]

Mitochondrial hepatopathies, disorders in which dysfunction of hepatocyte mitochondria plays a key role in the pathogenesis of liver injury or failure,[10-12] are divided into primary and secondary disorders.[10,11] Mitochondrial hepatopathies as a whole have been characterized only relatively recently,[10] and the identification of more types is anticipated. Primary mitochondrial hepatopathies occur when a mitochondrial protein, transfer RNA, or ribosomal RNA is miscoded by a mutation in either a nuclear gene or an mtDNA gene. Secondary mitochondrial hepatopathies are conditions in which mitochondria are the targets of endogenous or exogenous toxins. Examples include Reye syndrome, copper and iron overload conditions, drugs (eg, salicylates, reverse-transcriptase inhibitors, antimycin A) and toxins (eg, ethanol, cyanide), cholestasis, nonalcoholic steatohepatitis, and α-1 antitrypsin deficiency. [10,11]

In primary mitochondrial hepatopahies, liver involvement is often part of multiorgan manifestations (Table I).[1,10,12] Much of our current knowledge about mitochondria has

Reprint requests: Ronald J. Sokol, MD, University of Colorado School of Medicine, Box B290, Children's Hospital Colorado, 13123 E 16th Ave, Aurora, CO 80045. Ronald.Sokol@childrenscolorado.org.

The authors declare no conflicts of interest.

come from studying patients with respiratory chain disorders, which compose a growing number of individually rare syndromes, each presenting in a unique and often devastating way.[12]

Prevalence of Mitochondrial Hepatopathies

Epidemiologic studies from northern Europe and Australia have shown a population prevalence of all mitochondrial diseases ranging from 1.6 to 6.57/100 000.[13-17] Estimating the population prevalence of mitochondrial hepatopathies is difficult, however. In the Australian childhood mitochondrial population prevalence study, 3 of the 107 patients (2.8%) had jaundice.[17] In a retrospective, single-center French study, 13 of the 57 patients (22.8%) with neonatal mitochondrial cytopathies had hepatic manifestations,[18] consistent with previous studies indicating liver involvement in approximately 20% of patients with mitochondrial cytopathy.

Mitochondrial hepatopathies are important causes of acute liver failure (ALF) in childhood, particularly in infancy.[19-21] A retrospective French review of infants (aged ≤12 months) with ALF identified mitochondrial disease in 22.5% (17 of 80).[19] In a British retrospective review, 8 of 39 infants aged ≤12 months with ALF (20.5%) had a mitochondrial disorder.[20] In a prospective pediatric ALF study in North America and the United Kingdom, 5.4% (8 of 148) of infants aged <90 days had mitochondrial disease identified as the cause of ALF.[21]

Clinical Features

A striking feature of mitochondrial disorders is their clinical heterogeneity, ranging from single-organ disease to multiorgan involvement (Table II).[1,22] Generally, the clinical presentations in mitochondrial hepatopathies can be divided into neonatal liver failure, later-onset disease (eg, Alpers-Huttenlocher disease), and variable later presentations, which may include hepatic enlargement with elevated liver enzyme concentrations, hepatic steatosis, liver failure, and cholestasis.[23] Initial clinical signs of mitochondrial liver dysfunction may be subtle and undetected.[23]

Neonatal Liver Failure

In previous studies, this presentation was noted in 13 of 57 infants (22.8%) with neonatal mitochondrial cytopathies with hepatic manifestation,[18] and in 8 of 32 infants (25.0%) with mitochondrial oxidative phosphorylation disorders with neonatal presentation.[24] Approximately 12% of the affected infants were born preterm, and another 30% had intrauterine growth retardation.[24] Onset may occur within the first weeks to months of life, and may manifest as mild hepatic dysfunction that progresses to liver failure, vomiting, poor feeding, hypotonia, seizures, and lethargy.[10-12] In these patients, laboratory investigations generally reveal an elevated serum lactate level (>2.5 mmol/L), increased lactate/pyruvate molar ratio (>25 mol/mol), hypoglycemia, prolonged prothrombin time, hyperammonemia, and variably elevated aminotransferase and bilirubin concentrations.[11]

Alpers-Huttenlocher Disease

The inheritance of Alpers-Huttenlocher disease is autosomal recessive, although clinically more males are affected than females.[25] Symptom onset occurs between age 3 months and 8 years (Table II).[26] The typical clinical course includes intractable seizures and liver failure after a period of developmental regression. In some children, seizures may be the initial manifestation.[25,26] The disease is usually fatal within 3 years of onset; however, some patients survive into their teens and even early adulthood. Genetic heterogeneity and exposure to environmental factors (including medications) may explain the wide variation in

clinical presentation. Assays of respiratory chain complex concentrations reveal complex 1 deficiency,[27] and genotyping shows 2 pathologic mutations in the *POLG* gene.[25,27]

Variable Later Presentations

Clinical presentations include failure to thrive with elevated aminotransferase levels, lactic acidosis, hepatic steatosis, portal hypertension and cirrhosis, acute (or recurrent) liver failure presenting at any age, and intestinal pseudo-obstruction.[23,24,28] Any of the foregoing features can present at any age, not infrequently in combination with neurologic, muscular, renal, pancreatic, cardiac, hearing, visual, and other involvement.[23,24,29]

Genetics of Mitochondrial Hepatopathies

More than 1000 nuclear genes and 37 mtDNA genes encode mitochondrial proteins, ribosomal RNA, and transfer RNA.[1,28] To date, mutations in more than 228 protein-encoding nuclear DNA genes and 13 mtDNA have been identified as human mitochondrial disease-causing genes.[1] Mitochondrial hepatopathies result more frequently from autosomal recessive mutations in nuclear genes than from mutations in the mtDNA genome.[12] At least 14 nuclear gene defects have been linked to primary mitochondrial hepatopathies; these can be classified into several categories: mtDNA depletion syndrome, nuclear assembly factors —respiratory chain complex, and nuclear translation factor genes (Table II).

mtDNA Depletion Syndrome

In this syndrome, nuclear gene mutations responsible for mtDNA replication and maintenance lead to impaired synthesis of mtDNA or reduced capacity of salvaging activity of deoxyridbonucleotide triphosphate, resulting in abnormally low amounts of mtDNA relative to the normal levels of nuclear DNA.[11,12] This results in marked impairment of respiratory chain complexes I, III, and IV, increased oxidative stress, and adenosine triphosphate depletion. The clinical presentation is diverse, but generally 3 clinical forms are recognized: myopathic, encephalomyopathic, and hepatocerebral.[12] Mutations in various genes have been implicated,[28] including *DGUOK*,[29] *MPV17*,[30] *SUCLG1*,[31] *POLG1*,[25] and *C10ORF2/Twinkle*[32] (Table II).

Depletion of mtDNA also can result from large deletions of mtDNA, affecting the production of several respiratory chain components, such as in the Pearson marrow-pancreas syndrome.[1] Clinical presentation depends on the length of mtDNA deletions.[33] More recently, multiple mtDNA deletions also have been shown in *MPV17* mutations, causing an adult-onset multisystemic disorder with steatohepatopathy (Table II).[34]

Nuclear Assembly Factors—Respiratory Chain Complex

Nuclear genes coding for respiratory chain assembly factors can cause hepatopathy. Lactic acidosis, liver involvement, and Fanconi type renal tubulopathy are common when the complex III assembly factor gene *BCS1L* harbors mutations. The most severe form is the GRACILE syndrome (growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death).[35] Mutations in *SCO1* cause complex IV deficiency with severe acidosis, hypotonia, hypoglycemia, enlarged liver, and liver failure with hepatic steatosis.[36]

Nuclear Translation Factor Genes

Mutations in nuclear translation factor genes (*TRMU*, *EFG1*, and *EFTu*) of the respiratory chain enzyme complexes have been linked to neonatal liver failure or dysfunction and chronic liver disease.[37-39]

Common Forms of mtDNA Depletion Syndrome

The most common genetic causes of mtDNA depletion are discussed below. Details of other genetic causes of mitochondrial hepatopathies are presented in the references cited in Table II.

DGUOK Deficiency

The most common form of hepatocerebral mtDNA depletion, *DGUOK* deficiency can present as neonatal liver failure along with elevated serum transferrin saturation and serum ferritin and alpha-fetoprotein levels, resembling neonatal hemochromatosis.[39] Death due to liver failure generally occurs at age 2-18 months[40]; however, there have been reports of spontaneous survival in the absence of significant neurologic involvement.[41] Hepatocellular carcinoma has been reported in survivors; thus, surveillance is required for survivors with native liver.[41]

POLG1 Deficiency

The enzyme DNA polymerase γ is essential for mtDNA (but not nuclear DNA) replication and repair. *POLG1* mutations are a common cause of mtDNA depletion,[15] resulting in low concentrations of respiratory chain complexes I, III, and IV[15] and presenting as Alpers-Huttenlocher syndrome or neonatal liver failure.[42] Liver transplantation (LT) is generally contraindicated because of its systemic nature and the inevitable progression of severe central nervous system lesions and symptoms despite LT.[10] Treatment of complex seizures in patients with Alpers-Huttenlocher syndrome with valproic acid may precipitate ALF.[43] In these patients, the respiratory chain enzyme activities and mtDNA content in skeletal muscle may be normal; thus, liver tissue analysis or genotyping is necessary to establish the diagnosis.[43]

A prospective study of Drug-Induced Liver Injury Network data over a 5-year period identified 17 patients (including 10 adults) with valproate hepatic toxicity.[44] Eight of the 14 patients with probable valproate hepatotoxicity had a heterozygous POLG mutation, and 1 patient was homozygous.[44] It is currently recommended that POLG genotying be considered before administering valproate as an anticonvulsant in children under age 2 years.[44] The success rate of LT after sodium valproate-induced liver failure is dismal.[45] According to the Organ Procurement and Transplantation Network data on pediatric LT in the US, the 1-year survival rate post-LT in patients with valproate-induced ALF was 18%, compared with 69% in those with non–valproate-induced ALF.[45] Thus, LT is not indicated in patients with Alpers-Huttenlocher syndrome with valproate-induced liver failure.

MPV17 Disease

Originally described in 4 infants with fatal liver failure and hypotonia, autosomal recessive mutations in *MPV17* were subsequently linked to Navajo neurohepatopathy, a mtDNA depletion syndrome comprising sensorimotor neuropathy associated with neonatal cholestasis, hepatic steatosis, cirrhosis, or ALF in full-blooded Native Americans of the Navajo tribe.[30] *MPV17* disease also has been described as isolated hepatic involvement in infants. Extrahepatic manifestations can be severe and terminal and do not respond to LT. Hepatocellular carcinoma has been reported in a young Caucasian child with a *MPV17* mutation.[30] More recently, a fatal hepatocerebral form of mitochondrial hepatopathy caused by a *MPV17* mutation was described in a Brazilian child.[46]

Medical Therapy for Mitochondrial Hepatopathies

Currently, no curative therapy for mitochondrial hepatopathies is available.[1,47] The greatest challenge to performing randomized controlled trials in the affected population is the

heterogeneity of mitochondrial disorders. In neonatal ALF, supportive therapy includes prevention of hypoglycemia and correction of acidosis and hyperammonemia.[10] In children with chronic liver disease, management includes feeding a formula enriched with medium-chain triglycerides, providing a diet with 30%-40% of energy as fat, preventing hypoglycemia, and providing adequate fat-soluble vitamin supplementation.[10]

Various pharmacologic therapies have been advocated for mitochondrial disorders. However, a recent Cochrane systemic review examining the efficacies of coenzyme Q10, dichloroacetate, creatine monohydrate, and a whey-based, dietary supplement failed to show any clear evidence supporting their use in treating mitochondrial disorders.[48] Nonetheless, some disorders appear to respond to treatment, such as coenzyme Q deficiency.[49] Clearly, future research should identify novel agents for testing in homogenous study populations with clinically relevant endpoints.[48]

Potential future therapies for mitochondrial disorders include genetic therapy, enzyme replacement therapy, small-molecule therapy, bypass of electron transport complexes, nutritional therapies, and for myopathies, exercise and conditioning.[1] Recently, interest has focused on the potential of small molecules, a novel class of small peptide molecules that selectively target the inner mitochondrial membrane and protect mitochondrial function, as a mitochondrial protective agent.[50]

LT for Mitochondrial Hepatopathies

Long-term outcomes of patients with primary mitochondrial hepatopathies are very poor.[19,51] In the study of Cormier-Daire et al[51] of 22 patients with mitochondrial hepatopathies, the mortality rate was higher in those with the neonatal-onset form compared with those with the delayed-onset form (66% vs 38%). Another French study reported a mortality rate of 94%.[19] In patients with *DGUOK* mutations, survival into childhood may occur in the absence of neurologic features.[41]

The role of LT in treating mitochondrial hepatopathies remains controversial.[10] In many mitochondrial diseases, post-LT progression of neuromuscular, cardiac, or other symptomatology may prove fatal despite excellent results of the LT procedure, and thus the outcomes after LT have not been encouraging (Table III).[30,40,49-52] In the 54 patients with respiratory chain disease who underwent LT reported in the literature to date (many of whom did not have obvious extrahepatic involvement before LT), the overall survival rate was only 30% (Table III). However, there is a subset of patients who do not exhibit progression of respiratory chain dysfunction in other organs after LT. It is hoped that with vigilant pre-LT evaluation and selection to exclude neurologic and extrahepatic involvement, post-LT deterioration and death can be avoided in most, if not all, patients. However, it should be emphasized that in young patients with ALF and some forms of mitochondrial hepatopathy, even thorough evaluation might not detect extrahepatic involvement.

Indications for LT include patients with ALF and respiratory chain involvement limited to the liver only. Significant involvement of the central nervous system, heart, skeletal muscle, retina, and/or intestines usually is predictive of poor outcome and thus are considered contraindications to transplantation. Outcome of LT in patients with *DGUOK* disease without significant neurologic involvement may be better than that in patients with other forms of mitochondrial hepatopathy.[40] LT is usually contraindicated in patients with mitochondrial disease caused by mutations in *POLG* and *MPV17*.[30,52] Family members should be counseled about the possibility of other organ involvement after LT that may be potentially devastating and fatal. The most difficult cases are those in which a young infant

presents in ALF without definable extrahepatic involvement and with a previously normal history. Ideally, a thorough evaluation with magnetic resonance imaging/magnetic resonance spectroscopy (and possibly electroencephalography) of the brain, echocardiography, retinal examination, cerebrospinal fluid analysis, respiratory chain testing of muscle and/or liver, and genotyping for the likely genetic defects should be performed if time permits.

Summary

An ever-increasing number of nuclear gene mutations have been identified as responsible for mitochondrial hepatopathies. A diagnosis of such a hepatopathy is suggested by lactic acidosis, hepatic steatosis, liver failure without markedly increased aminotransferase levels, and features of extrahepatic involvement. At present, genotyping is available for many of the mutations identified. Although medical therapy is currently inadequate, selective LT may be life-saving in carefully selected cases, with special caution regarding the presence of extrahepatic disease.

References

1. Koopman WJH, Willems PHGM, Smeitink JAM. Monogenic mitochondrial disorders. New Engl J Med. 2012; 366:1132–41. [PubMed: 22435372]
2. Calvo SE, Mootha VK. The mitochondrial proteome and human disease. Annu Rev Genomics Hum Genet. 2010; 11:25–44.
3. Chen L, Knowlton AA. Mitochondrial dynamics in heart failure. Congest Heart Fail. 2011; 17:257–61.
4. Supale S, Li N, Brun T, Maechler P. Mitochondrial dysfunction in pancreatic β cells. Trends Endocrinol Metab. 2012; 23:477–87. [PubMed: 22766318]
5. Wallace DC. Mitochondria and cancer. Nat Rev Cancer. 2012; 12:685–98. [PubMed: 23001348]
6. Bindoff LA, Engelsen BA. Mitochondrial diseases and epilepsy. Epilepsia. 2012; 53(Suppl 4):92–7.
7. Hu F, Liu F. Mitochondrial stress: a bridge between mitochondrial dysfunction and metabolic diseases? Cell Signal. 2011; 23:1528–33.
8. Exner N, Lutz AK, Haass C, Winklhofer KF. Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. EMBO J. 2012; 31:3038–62.
9. Silva DF, Selfridge JE, Lu J, E L, Cardoso SM, Swerdlow RH. Mitochondrial abnormalities in Alzheimer's disease: possible targets for therapeutic intervention. Adv Pharmacol. 2012; 64:83–126.
10. Lee WS, Sokol RJ. Mitochondrial hepatopathies: advances in genetics and pathogenesis. Hepatology. 2007; 45:1555–65.
11. Lee WS, Sokol RJ. Liver disease in mitochondrial disorders. Semin Liver Dis. 2007; 27:259–73. [PubMed: 17682973]
12. Fellman V, Kotarsky H. Mitochondrial hepatopathies in the newborn period. Sem Fetal Neonate Med. 2011; 16:222–8.
13. Majamaa K, Moilanen JS, Uimonen S, Remes AM, Salmela PI, Karppa M, et al. Epidemiology of A3243G, the mutation for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes: prevalence of the mutation in an adult population. Am J Hum Genet. 1998; 63:447–54.
14. Chinnery PF, Johnson MA, Wardell TM, Singh-Kler R, Hayes C, Brown DT, et al. The epidemiology of pathogenic mitochondrial DNA mutations. Ann Neurol. 2000; 48:188–93.
15. Darin N, Oldfors A, Moslemi AR, Holme E, Tulinius M. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities. Ann Neurol. 2001; 49:377–83.
16. Remes AM, Majamaa-Voltti K, Kärppä M, Moilanen JS, Uimonen S, Helander H, et al. Prevalence of large-scale mitochondrial DNA deletions in an adult Finnish population. Neurology. 2005; 64:976–81.
17. Skladal D, Halliday J, Thorburn DR. Minimum birth prevalence of mitochondrial respiratory chain disorders in children. Brain. 2003; 126(Pt 8):1905–12.

18. Garcìa-Cazorla A, De Lonlay P, Nassogne MC, Rustin P, Touati G, Saudubray JM. Long-term follow-up of neonatal mitochondrial cytopathies: a study of 57 patients. Pediatrics. 2005; 116:1170–7. [PubMed: 16264005]
19. Durand P, Debray D, Mandel R, Baujard C, Branchereau S, Gauthier F, et al. Acute liver failure in infancy: a 14-year experience of a pediatric liver transplant center. J Pediatr. 2001; 139:871–6.
20. Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United Kingdom. J Pediatr Gastroenterol Nutr. 2005; 40:575–81.
21. Sundaram SS, Alonso EM, Narkewicz MR, Zhang S, Squires RH. Pediatric Acute Liver Failure Study Group. Characterization and outcomes of young infants with acute liver failure. J Pediatr. 2011; 159:813–8.
22. Vafai SB, Mootha VK. Mitochondrial disorders as windows into an ancient organelle. Nature. 2012; 491:374–83.
23. Garcìa-Cazorla A, De Lonlay PD, Rustin P, Chretien D, Touati G, Rabier D, et al. Mitochondrial respiratory chain deficiencies expressing the enzymatic deficiency in the hepatic tissue: a study of 31 patients. J Pediatr. 2006; 149:401–5.
24. Gibson K, Halliday JL, Kirby DM, Yaplito-Lee J, Thorburn DR, Boneh A. Mitochondrial oxidative phosphorylation disorders presenting in neonates: clinical manifestations and enzymatic and molecular diagnoses. Pediatrics. 2008; 122:1003–8.
25. Davidzon G, Mancuso M, Ferraris S, Quinzii C, Hirano M, Peters HL, et al. *POLG* mutations and Alpers syndrome. Ann Neurol. 2005; 57:921–3.
26. Narkewicz MR, Sokol RJ, Beckwith B, Sondheimer J, Silverman A. Liver involvement in Alpers disease. J Pediatr. 1991; 119:260–7.
27. Saneto RP, Cohen BH, Copeland WC, Naviaux RK. Alpers-Huttenlocher syndrome. Pediatr Neurol. 2013; 48:167–78.
28. Suomalainen A, Isohanni P. Mitochondrial DNA depletion syndromes: many genes, common mechanisms. Neuromuscular Disord. 2010; 20:429–37.
29. Mandel H, Szargel R, Labay V, Elpeleg O, Saada A, Shalata A, et al. The deoxyguanosine kinase gene is mutated in individuals with depleted hepatocerebral mitochondrial DNA. Nat Genet. 2001; 29:337–41. [PubMed: 11687800]
30. El-Hattab AW, Li FY, Schmitt E, Zhang S, Craigen WJ, Wong LJC. MPV17-associated hepatocerebral mitochondrial DNA depletion syndrome: new patients and novel mutations. Mol Genet Metab. 2010; 99:300–8.
31. Van Hove JL, Saenz MS, Thomas JA, Gallagher RC, Lovell MA, Fenton LZ, et al. Succinyl-CoA ligase deficiency: a mitochondrial hepatoencephalopathy. Pediatr Res. 2010; 69:159–64.
32. Goh V, Helbling D, Biank V, Jarzembowski J, Dimmock D. Next-generation sequencing facilitates the diagnosis in a child with twinkle mutations causing cholestatic liver failure. J Pediatr Gastroenterol Nutr. 2012; 54:291–4.
33. Jacobs LJ, Jongbloed RJ, Wijburg FA, de Klerk JB, Geraedts JP, Nijland JG, et al. Pearson syndrome and the role of deletion dimers and duplications in the mtDNA. J Inherit Metab Dis. 2004; 27:47–55.
34. Garone C, Rubio JC, Calvo SE, Naini A, Tanji K, DiMauro S, et al. *MPV17* mutations causing adult-onset multisystemic disorder with multiple mitochondrial DNA deletions. Arch Neurol. 2012; 69:1648–51.
35. De Lonlay PD, Valnot I, Barrientos A, Garbatyuk M, Tzagoloff A, Taanman JW, et al. A mutant mitochondrial respiratory chain assembly chain protein causes complex III deficiency in patients with tubulopathy, encephalopathy and liver failure. Nat Genet. 2001; 29:57–60. [PubMed: 11528392]
36. Valnot I, Osmond S, Gigarel N, Mehaye B, Amiel J, Cormier-Daire V, et al. Mutations of the *SCO1* gene in mitochondrial cytochrome c oxidase deficiency with neonatal-onset hepatic failure and encephalopathy. Am J Human Genet. 2000; 67:1104–9.
37. Schara U, von Kleist-Retzow JC, Lainka E, Gerner P, Pyle A, Smith PM, et al. Acute liver failure with subsequent cirrhosis as the primary manifestation of *TRMU* mutations. J Inherit Metab Dis. 2011; 34:197–201.

38. Smits P, Antonicka H, van Hasselt PM, Weraarpachai W, Haller W, Schreurs M, et al. Mutation in subdomain G′ of mitochondrial elongation factor G1 is associated with combined OX-PHOS deficiency in fibroblasts but not in muscle. Eur J Hum Genet. 2011; 19:275–9.
39. Valente L, Tiranti V, Marsano RM, Malfatti E, Fernandez-Vizarra E, Donnini C, et al. Infantile encephalopathy and defective mitochondrial DNA translation in patients with mutations of mitochondrial elongation factors EFG1 and EFTu. Am J Hum Genet. 2007; 80:44–58.
40. Nobre, S.; Grazina, M.; Silva, F.; Pinto, C.; Gonéalves, I.; Diogo, L. Neonatal liver failure due to deoxyguanosine kinase deficiency. BMJ Case Rep. 2012. http://dx.doi.org/10.1136/bcr.12.2011.5317
41. Dimmock DP, Dunn JK, Feigenbaum A, Rupar A, Horvath R, Freisinger P, et al. Abnormal neurological features predict poor survival and should preclude liver transplantation in patients with deoxyguanisine kinase deficiency. Liver Transpl. 2008; 14:1480–5.
42. Sofou K, Moslemi AR, Kollberg G, Bjarnadottir I, Oldfors A, Nennesmo I, et al. Phenotypic and genotypic variability of Alpers syndrome. Eur J Paediatr Neurol. 2012; 16:379–89. [PubMed: 22237560]
43. Isohanni P, Hakonen AH, Euro L, Paetau I, Linnankivi T, Wallden T, et al. POLG1 manifestations in childhood. Neurology. 2011; 76:811–5.
44. Stewart JD, Horvath R, Baruffini E, Ferrero I, Bulst S, Watkins PB, et al. Polymerase γ gene *POLG* determines the risk of sodium valproate-induced liver toxicity. Hepatology. 2010; 52:1791–6. [PubMed: 21038416]
45. Nogueira C, de Souza CFM, Derks TGJ, Santorelli FM, Vilarinho L. MPV17: fatal hepatocerebral presentation in a Brazilian infant [letter]. Mol Gen Metab. 2012; 107:764.
46. Mindikoglu AL, King D, Magder LS, Ozolek JA, Mazariegos GV, Shneider BL. Valproic acid–associated acute liver failure in children: case report and analysis of liver transplantation outcomes in the United States. J Pediatr. 2011; 158:802–7.
47. Suomalainen A. Therapy for mitochondrial disorders: little proof, high research activity, some promise. Semin Fetal Neonatal Med. 2011; 16:236–40.
48. Pfeffer G, Majamaa K, Turnbull DM, Thornburn D, Chinnery PF. Treatment for mitochondrial disorders. Cochrane Database Syst Rev. 2012; 18:CD004426.
49. Hirano M, Garone C, Quinzii CM. CoQ10 deficiencies and MNGIE: two treatable mitochondrial disorders. Biochim Biophysica Acta. 2012; 1820:625–31.
50. Szeto HH, Schiller PW. Novel therapies targeting inner mitochondrial membrane: from discovery to clinical development. Pharm Res. 2011; 28:2669–79.
51. Cormier-Daire V, Chretien D, Rustin P, Röotig A, Dubuisson C, Jacquemin E, et al. Neonatal and delayed-onset liver involvement in disorders of oxidative phosphorylation. J Pediatr. 1997; 130:817–22. [PubMed: 9152294]
52. Sokal EM, Sokol R, Cormier V, Lacaille F, McKeirnan PJ, Van Spronsen FJ, et al. Liver transplantation in mitochondrial respiratory chain disorders. Eur J Pediatr. 1999; 158(Suppl 2):S81–4. [PubMed: 10603105]
53. Dubern B, Broue P, Dubuisson C, Cormier-Daire V, Habes D, Chardot C, et al. Orthotopic liver transplantation for mitochondrial respirator chain disorders: a study of 5 children. Transplantation. 2001; 71:596–8. [PubMed: 11292286]
54. Rabinowitz SS, Gelfond D, Chen CK, Gloster ES, Whitington WF, Sacloni S, et al. Hepatocerebral mitochondrial DNA depletion syndrome: clinical and morphological features of a nuclear gene mutation. J Pediatr Gastroenterol Nutr. 2004; 38:216–20. [PubMed: 14734888]
55. Iwama I, Baba Y, Kagimoto S, Kishimoto H, Kasahara M, Murayama K, et al. Case report of a successful liver transplantation for acute liver failure due to mitochondrial respiratory chain complex III deficiency. Transplant Proc. 2011; 43:4025–8. [PubMed: 22172894]

Glossary

ALF	Acute liver failure
LT	Liver transplantation

mtDNA	Mitochondrial DNA

Table I
Phenotypic classification of primary mitochondrial hepatopathies

RC (electron transport) defects (OXPHOS)
Neonatal liver failure
Complex I deficiency
Complex IV deficiency (*SCO1* mutations)
Complex III deficiency (*BCS1L* mutations)
Co-enzyme Q deficiency
Multiple complex deficiencies (transfer and elongation factor mutations)
mtDNA depletion syndrome (*DUGOK, MPV17, POLG, SUCLG1, C10orf2/Twinkle* mutations)
Later-onset liver dysfunction or failure
Alpers-Huttenlocher disease (*POLG* mutations)
Pearson's marrow pancreas syndrome (mtDNA deletion)
Mitochondrial neurogastrointestinal encephalopathy (*TYMP* mutations)
NNH (*MPV17* mutations)
Fatty acid oxidation defects
Long-chain 3 hydroxyacyl-coenzyme A dehydrogenase
Carnitine palmitoyltransferase I and II deficiencies
Carnitine-acylcarnitinetranslocase deficiency
Urea cycle enzyme deficiencies
Electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase deficiencies
Phosphoenol pyruvate carboxykinase (mitochondrial) deficiency; nonketotic hyperglycemia
Citrin deficiency; neonatal intrahepatic cholestasis caused by citrin deficiency (*SLC25A13* mutations)

OXPHOS, oxidative phosphorylation; *NNH*, Navajo neurohepatopathy; *RC*, respiratory chain. Adapted with permission.[10]

Table II

Genotypic classification of primary mitochondrial hepatopathies and organ involvement

Gene	Respiratory chain complex	Protein	Function	Hepatic histology	Other organs involved	Clinical features
Class 1A: mtDNA genes						
Deletion[33]	Multiple (Pearson)			Steatosis, fibrosis	Kidney, heart, CNS, muscle	Sideroblasticanemia, variable thrombocytopenia and neutropenia, persistent diarrhea
MPV17[34]	I, III, IV	Mitochondrial inner membrane		Steatosis	CNS, muscle, gastrointestinal tract	Adult-onset multisystemic involvement: myopathy, ophthalmoplegia, severe constipation, parkinsonism
Class 1B: nuclear genes mtDNA depletion syndromes						
DGUOK[29]	I, III, IV	dGK, mitochondrial nucleotide salvaging	dGK, with TK2, functions to maintain the supply of dNTPs for mtDNA synthesis	Steatosis, fibrosis	Kidneys, CNS, muscle	Nystagmus, hypotonia, renal Fanconi syndrome, acidosis
MPV17[30]	I, III, IV	Mitochondrial inner membrane	mtDNA maintenance and regulation of OXPHOS; absence or malfunction causes OXPHOS failure and mtDNA depletion	Steatosis, fibrosis	CNS, PNS	Hypotonia
SUCLG1[31]	I, III, IV	α -subunit of succinate coenzyme A ligase	Catalyzes conversion of succinyl coenzyme A and ADP or GDP to succinate and ATP or GTP	Steatosis	Kidneys, CNS, muscle	Myopathy, sensorineural hearing loss, respiratory failure
POLG1[25]	I, III, IV	mtDNA polymerase γ	Polymerase γ activity essential for mtDNA replication and repair	Steatosis, fibrosis	CNS, muscle	Liver failure preceded by neurologic symptoms, intractable seizures, ataxia, psychomotor regression
C10orf2/Twinkle[32]	I, III, IV	Hexameric DNA helicase	Together with single-stranded mtDNA binding protein and polymerase γ, plays a key role in mtDNA replication	Steatosis	CNS, muscle	Infantile-onset spinocerebellar ataxia, loss of skills

Gene	Respiratory chain complex	Protein	Function	Hepatic histology	Other organs involved	Clinical features
Nuclear assembly fact—respiratory complexes						
BCS1L[35]	III (GRACILE)	Assembly protein of complex III (ubiquinol cytochrome c reductase)	Encodes an assembly factor/chaperone that incorporates the Rieske iron sulphur protein into complex III		CNS ±, muscle ±, kidneys	Fanconi type renal tubulopathy
SCO1[36]	IV	Copper chaperone of complex IV (cytochrome c oxidase)	Transfers copper from Cox17p to cyctochrome c oxidase subunits I and II	Steatosis, fibrosis	Muscle	
Nuclear transfer factor genes						
TRMU[37]	I, III, IV	Transfer RNA-modifying enzyme	Enzyme required for the 2-thio modification of 5-taurinomethyl-2-thiouridine transfer RNA-lysine	Steatosis, fibrosis		Infantile liver failure with subsequent recovery
EFG1[38]	I, III, IV	Mitochondrial translation elongation factor	Precise function unknown	Steatosis	CNS	Severe, rapidly progressive encephalopathy
EFTu[39]	I, III, IV	Isoform of α-subunit of elongation factor-1 complex	Responsible for enzymatic delivery of aminoacyl transfer RNAs to the ribosome	Unknown	CNS	Severe lactic acidosis, rapidly fatal encepaphalopathy

CNS, central nervous system; *dGK*, deoxyguanosine kinase; *TK2*, thymidine kinase 2; *PNS*, peripheral nervous system; *ADP*, adenosine diphosphate; *GDP*, gluanosine diphosphate; *ATP*, adenosine triphosphate; *GTP*, gluanosine triphosphate; *GRACILE*, growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death.

Table III

Outcome of LT in mitochondrial hepatopathies secondary to RC disorders

Authors	Number of patients (age)	Presentation	Diagnosis	Survival	Follow-up	Comments
Sokal et al (1999; Europe and US)[52]	11 (1-7 mo)	ALF	RC enzyme assay and clinical	5 of 11	5 mo to 8 y	All 3 with diarrhea and vomiting died
Durand et al (2001; France)[19]	5 (<1 y)	ALF	RC enzyme assay and clinical	2 of 5	3.5 years	No extrahepatic involvement pre-LT
Dubern et al (2001; France)[53]	5 (<1 y)	ALF	RC enzyme assay and clinical	2 of 5	Not specified	No extrahepatic involvement pre-LT
Rabinowitz et al (2004)[54]	1 (neonate)	Liver failure, neurologic symptoms	*DGUOK* genotyping	Died		Died a few months after LT
Dimmock et al (2008; literature)[41]	10 (<10 mo; one 3 y)	Liver failure, neurologic symptoms	*DGUOK* genotyping	2 of 10		No benefit of LT if neurologic features present
El-Hattab etal (2010; literature and US)[30]	10 (infancy)	Liver failure, neurologic symptoms	*MPV17* genotyping	5 of 10; 2 of 3 NNH, 3 of 7 other presentations	4-21 y	Patients with NNH had progression of neurologic features post-LT
Iwama etal (2010; literature)[55]	12 (<10 mo; one 3 y)	Liver failure	RC enzyme assay and clinical	0 of 7	4 mo to 5 y	No benefit of LT if neurologic features present
Total	54			16 (30%)		