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MPV17-Related Mitochondrial DNA Maintenance Defect

Synonyms: Mitochondrial DNA Depletion Syndrome 6 (MTDPS6), Hepatocerebral Type; MPV17 Deficiency; *MPV17* Hepatocerebral Mitochondrial DNA Depletion Syndrome

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Summary

Clinical characteristics

MPV17-related mitochondrial DNA (mtDNA) maintenance defect presents in the vast majority of affected individuals as an early-onset encephalohepatopathic (hepatocerebral) disease that is typically associated with mtDNA depletion, particularly in the liver. A later-onset neuromyopathic disease characterized by myopathy and neuropathy, and associated with multiple mtDNA deletions in muscle, has also rarely been described. *MPV17*-related mtDNA maintenance defect, encephalohepatopathic form is characterized by:

- Hepatic manifestations (liver dysfunction that typically progresses to liver failure, cholestasis, hepatomegaly, and steatosis);
- Neurologic involvement (developmental delay, hypotonia, microcephaly, and motor and sensory peripheral neuropathy);
- Gastrointestinal manifestations (gastrointestinal dysmotility, feeding difficulties, and failure to thrive); and
- Metabolic derangements (lactic acidosis and hypoglycemia).

Less frequent manifestations include renal tubulopathy, nephrocalcinosis, and hypoparathyroidism. Progressive liver disease often leads to death in infancy or early childhood. Hepatocellular carcinoma has been reported.

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Diagnosis/testing

The diagnosis of *MPV17*-related mtDNA maintenance defect is established in a proband by the identification of biallelic pathogenic variants in *MPV17* by molecular genetic testing.

Management

Treatment of manifestations: Ideally management is by a multidisciplinary team including specialists in hepatology, neurology, nutrition, clinical genetics, and child development. Nutritional support should be provided by a dietitian experienced in managing children with liver diseases; prevention of hypoglycemia requires frequent feeds and uncooked cornstarch (1-2 g/kg/dose). Although liver transplantation remains the only treatment option for liver failure, it is controversial because of the multisystem involvement in this disorder.

Prevention of secondary complications: Prevent nutritional deficiencies (e.g., of fat-soluble vitamins) by ensuring adequate intake.

Surveillance: Monitor:

- Liver function to assess progression of liver disease;
- Serum alpha fetoprotein (AFP) concentration and hepatic ultrasound examination for evidence of hepatocellular carcinoma;
- Development, neurologic status, and nutritional status.

Agents/circumstances to avoid: Prolonged fasting.

Genetic counseling

MPV17-related mtDNA maintenance defect is inherited in an autosomal recessive manner. Each sib of an affected individual has 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. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family are known.

GeneReview Scope

MPV17-Related Mitochondrial DNA Maintenance Defect: Included Phenotypes [1]
• *MPV17*-related encephalohepatopathy, including Navajo neurohepatopathy [2] • *MPV17*-related neuromyopathy

1. For other genetic causes of these phenotypes see Differential Diagnosis.
2. See also Nomenclature.

Diagnosis

Suggestive Findings

MPV17-related mitochondrial DNA (mtDNA) maintenance defect **should be suspected** in individuals with the following clinical features, brain MRI findings, and supportive laboratory findings.

Clinical features

- Hepatic
  - Liver dysfunction or failure
  - Cholestasis and steatosis
  - Hepatomegaly

- Neurologic
  - Developmental delay
  - Hypotonia
  - Microcephaly
  - Motor and sensory peripheral neuropathy
- Gastrointestinal
  - Gastrointestinal dysmotility
  - Feeding difficulties
  - Failure to thrive

Brain MRI findings

- White matter abnormalities
- Brain stem signal abnormalities
- Basal ganglia signal abnormalities

Supportive laboratory findings

- Serum testing
  - Elevated hepatic transaminases and hyperbilirubinemia
  - Lactic acidosis
  - Hypoglycemia
- Liver histology
  - Steatosis
  - Cirrhosis
- Mitochondrial DNA analysis in liver and muscle [El-Hattab et al 2018]
  - Mitochondrial DNA content:
    - Is typically reduced in liver tissue (<20% of that found in tissue- and age-matched controls);
    - Can also be reduced in muscle tissue (typically <30% of that found in tissue- and age-matched controls).
  - Multiple mtDNA deletions have been occasionally described in muscle and liver.
- Electron transport chain (ETC) assays in liver and muscle tissue of affected individuals typically show decreased activity of multiple complexes with complex I having reduced activity in 80% of affected individuals [El-Hattab et al 2018].

  Note: Neither mtDNA analysis nor ETC assays are required to make the diagnosis of *MPV17*-related mtDNA maintenance defect.

Establishing the Diagnosis

The diagnosis of *MPV17*-related mtDNA maintenance defect **is established** in a proband with biallelic pathogenic (or likely pathogenic) variants in *MPV17* by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *MPV17* variants of uncertain significance (or of one known *MPV17* pathogenic variant and one *MPV17* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of *MPV17*-related mtDNA maintenance defect is indistinguishable from many other inherited disorders with encephalohepatopathy, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *MPV17*, followed by gene-targeted deletion/duplication analysis) is rarely useful.

- **A multigene panel** that includes *MPV17* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  Exome array (when clinically available) may be considered if exome sequencing is not diagnostic, particularly when evidence supports autosomal dominant inheritance.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *MPV17*-Related mtDNA Maintenance Defect

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
MPV17	Sequence analysis [3]	94/98 (96%) [4, 5]
	Gene-targeted deletion/duplication analysis [6]	4/98 (4%) [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. El-Hattab et al [2018]
5. Affected individuals of Navajo descent are commonly homozygotes for the p.Arg50Gln pathogenic variant [Karadimas et al 2006].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

MPV17-related mtDNA maintenance defect has been reported in 100 individuals [Karadimas et al 2006, Spinazzola et al 2006, Wong et al 2007, Navarro-Sastre et al 2008, Spinazzola et al 2008, Kaji et al 2009, Parini et al 2009, El-Hattab et al 2010, Al-Jasmi et al 2011, AlSaman et al 2012, Blakely et al 2012, Garone et al 2012,

Merkle et al 2012, Nogueira et al 2012, Al-Hussaini et al 2014, Bijarnia-Mahay et al 2014, Mendelsohn et al 2014, Piekutowska-Abramczuk et al 2014, Sarkhy et al 2014, Uusimaa et al 2014, Vilarinho et al 2014, Choi et al 2015, Bitting & Hanson 2016, Kim et al 2016, McKiernan et al 2016, El-Hattab et al 2018].

The vast majority of affected individuals (96/100) presented with an early-onset encephalohepatopathic (hepatocerebral) disease affecting mainly the nervous system and liver; mtDNA depletion is typically identified, particularly in liver. A later-onset neuromyopathic disease characterized by myopathy and neuropathy and associated with multiple mtDNA deletions in muscles has also rarely been described (4/100 affected individuals) [El-Hattab et al 2018].

***MPV17*-related mtDNA maintenance defect, encephalohepatopathy form** is typically an early-onset disease that presents during the neonatal period (36 out of 96; 38%) or infancy (56 out of 96; 58%). Childhood onset (2-18 years) has been reported on rare occasions (4 out of 96; 4%) [El-Hattab et al 2018].

Clinical manifestations include hepatic and neurologic findings summarized in Table 2.

Table 2. Clinical Manifestations of *MPV17*-Related Encephalohepatopathy

Clinical Manifestations		Frequency
Hepatic	Liver dysfunction [1]	96/96 (100%)
	Liver failure [2]	87/96 (91%)
	Cholestasis	70/96 (73%)
	Hepatomegaly	60/96 (63%)
	Steatosis	49/96 (51%)
	Liver cirrhosis	20/96 (21%)
	Hepatocellular cancer [3]	3/96 (3%)
Neurologic [4]	Developmental delay [5]	75/91 (82%)
	Hypotonia	67/91 (74%)
	Microcephaly	21/91 (23%)
	Peripheral neuropathy [6]	17/91 (19%)
	Seizures	9/91 (10%)
	Dystonia	4/91 (4%)
	Ataxia	3/91 (3%)
Abnormalities on brain MRI	White matter [7]	27/71 (38%)
	Brain stem signal	6/71 (8%)
	Basal ganglia signal	6/71 (8%)
Gastrointestinal	Failure to thrive [8]	82/91 (90%)
	Gastrointestinal dysmotility [9]	30/91 (33%)
	Feeding difficulties	28/91 (31%)
Metabolic	Lactic acidosis [10]	72/91 (79%)
	Hypoglycemia [11]	55/91 (60%)

Table 2. continued from previous page.

Clinical Manifestations		Frequency
Other	Renal tubulopathy	9/91 (10%)
	Nephrocalcinosis	7/91 (8%)
	Hypoparathyroidism	4/91 (4%)
	Retinopathy	7/91 (8%)
	Nystagmus	6/91 (7%)
	Corneal anesthesia & ulcers	4/91 (4%)

1. Liver dysfunction typically presents as elevated transaminases, jaundice, hyperbilirubinemia, and coagulopathy.
2. Liver disease progresses to liver failure typically during infancy and early childhood.
3. Identified between ages seven and 11 years [Karadimas et al 2006, El-Hattab et al 2010, Vilarinho et al 2014]
4. The neurologic manifestations can be overlooked or underestimated in children with early onset of severe hepatic involvement.
5. Some affected individuals present with psychomotor delays during early infancy, while others have normal development early in life followed by loss of motor and cognitive abilities later in infancy or early childhood.
6. Peripheral neuropathy typically manifests in early childhood with muscle weakness and wasting, decreased reflexes, and loss of sensation in the hands and feet.
7. Diffuse white matter abnormalities may resemble leukodystrophy or hypomyelination.
8. Some children have normal growth, especially early in the course of the disease.
9. May present as gastroesophageal reflux, recurrent vomiting, and/or diarrhea.
10. Lactic acidosis is a biochemical finding with mild to moderate elevation of lactate (3-9 mmol/L).
11. Hypoglycemia typically presents during the first six months of life and can be associated with lethargy, apnea, and/or seizures.

Prognosis. *MPV17*-related encephalohepatopathy typically has a poor prognosis due to early liver failure. Liver transplantation has been performed in some affected individuals, with high rates of post-transplantation death.

Table 3. Outcome of Children with *MPV17*-Related Encephalohepatopathy

Liver Transplant?	Outcome	Frequency
Yes (17/96; 18%)	Death [1]	10/17 (59%)
	Survival	7/17 (41%)
No (79/96; 82%)	Death from liver failure [2]	65/79 (82%)
	Survival [3]	14/79 (18%)

1. Death most commonly occurred in the post-transplantation period due to sepsis, respiratory failure, or multiorgan failure.
2. The majority died during infancy (52/65; 80%); some died during early childhood (1-5 years) (10/65; 15%), adolescence (2/65; 3%), or early adulthood (1/65; 2%).
3. The oldest reported affected individual is 25 years old [El-Hattab et al 2018]. Note: This does NOT mean that survival past 25 years is not possible.

***MPV17*-related mtDNA maintenance defect, neuromyopathy form** is a rare emerging phenotype described in four out of 100 (4%) affected individuals. Onset of symptoms is typically later and characterized by myopathy and neuropathy.

- One individual presented during childhood, two during adolescence, and one during adulthood.
- All four individuals had myopathy and peripheral neuropathy.
- Liver manifestations were absent in two individuals, while the other two had milder liver involvement but without liver failure.
- Development was normal in all affected individuals.
- One individual had ptosis and ophthalmoplegia.
- Mitochondrial DNA was assessed in muscle tissue in two individuals and showed normal mtDNA content with multiple mtDNA deletions [Blakely et al 2012, Garone et al 2012, Choi et al 2015].

Genotype-Phenotype Correlations

No clear genotype-phenotype correlation exists. However, a trend for longer survival can be observed in individuals with biallelic pathogenic missense variants compared to individuals with biallelic null (nonsense, frameshift, deletions, and splice site) variants or individuals compound heterozygous for missense and null variants. In particular, individuals homozygous for p.Arg50Gln, p.Pro98Leu, or p.Arg41Gln may carry a relatively better prognosis [El-Hattab et al 2018].

Nomenclature

Navajo neurohepatopathy (NNH) was originally described as a distinct condition among Navajo children in the southwestern United States, but it is now clear that NNH is part of the *MPV17*-related mtDNA maintenance defect spectrum, falling under the encephalohepatopathy phenotype.

Encephalohepatopathic *MPV17*-related mtDNA maintenance defect may also be referred to as infantile hepatocerebral mtDNA depletion syndrome.

Prevalence

The prevalence of *MPV17*-related mtDNA maintenance defect is unknown but likely to be very low; only 100 affected individuals have been reported to date.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are associated with pathogenic variants in *MPV17*.

Differential Diagnosis

Encephalohepatopathic form of *MPV17*-related mtDNA maintenance defect needs to be differentiated from other mtDNA maintenance defects that present with encephalohepatopathy (summarized in Table 4a). (See Mitochondrial DNA Maintenance Defects Overview.)

Table 4a. Mitochondrial DNA Maintenance Defects Presenting with Encephalohepatopathy

Gene	Disorder / Phenotype	MOI	mtDNA Maintenance Defect	Usual Age of Onset	Common Clinical Manifestations
MPV17	Subject of this *GeneReview*	AR	Depletion	Neonatal period or infancy	• DD • Hypotonia • Liver dysfunction/failure • FTT • Lactic acidosis
DGUOK	Deoxyguanosine kinase deficiency	AR	Depletion	Neonatal period	• DD • Hypotonia • Nystagmus • Liver dysfunction/failure • Lactic acidosis
POLG	Alpers-Huttenlocher syndrome	AR	Depletion	Early childhood	• DD • Psychomotor regression • Epilepsy • Liver dysfunction/failure • Hearing impairment

Table 4a. continued from previous page.

Gene	Disorder / Phenotype	MOI	mtDNA Maintenance Defect	Usual Age of Onset	Common Clinical Manifestations
TFAM	Encephalohepatopathy (OMIM 617156)	AR	Depletion	Neonatal period	• IUGR • Hypoglycemia • Liver dysfunction/failure
TWNK	Encephalohepatopathy (OMIM 271245)	AR	Depletion	Neonatal period or infancy	• DD • Hypotonia • Liver dysfunction/failure • Lactic acidosis

AR = autosomal recessive; DD = developmental delay; FTT = failure to thrive; IUGR = intrauterine growth restriction; MOI = mode of inheritance

In addition, pathogenic variants in *BCS1L* (encoding a mitochondrial protein involved in complex III assembly) and *SCO1* (encoding a mitochondrial protein involved in complex IV assembly) have been associated with encephalopathy and hepatic dysfunction (OMIM 124000, 220110).

Infantile liver failure is also a feature of the disorders caused by pathogenic variants in *TRMU* (encoding mitochondria tRNA-specific 2-thiouridylase 1) and *GFM1* (encoding mitochondrial elongation factor G); mtDNA depletion is not a feature in these disorders (see TRMU Deficiency and OMIM 609060).

Neuromyopathic form of *MPV17*-related mtDNA maintenance defect needs to be differentiated from other mtDNA maintenance defects that present with myopathy (summarized in Table 4b). (See Mitochondrial DNA Maintenance Defects Overview.)

Table 4b. Mitochondrial DNA Maintenance Defects Presenting with Myopathy

Gene	Disorder	MOI	mtDNA Maintenance Defect	Usual Age of Onset	Common Clinical Manifestations in Addition to Muscle Weakness
AGK	Sengers syndrome (OMIM 212350)	AR	Depletion	Neonatal period	• Hypotonia • HCM • Cataracts
DGUOK	Deoxyguanosine kinase deficiency	AR	Multiple deletions	Early or mid-adulthood	• Ptosis • Ophthalmoplegia
DNA2	Myopathy (OMIM 615156)	AD	Multiple deletions	Childhood or early adulthood	• Ptosis • Ophthalmoplegia
MGME1	Myopathy (OMIM 615084)	AR	Depletion & multiple deletions	Childhood or early adulthood	• Ptosis • Ophthalmoplegia
POLG2	Myopathy (See *POLG*-Related Disorders.)	AD	Multiple deletions	Infancy to adulthood	• Ptosis • Ophthalmoplegia
SLC25A4	Cardiomyopathy (OMIM 615418)	AR	Multiple deletions	Childhood	• Exercise intolerance / easy fatigability • HCM
	Cardiomyopathy (OMIM 617184)	AD	Depletion	Birth	• Hypotonia • HCM
TK2	Mitochondrial DNA depletion syndromes	AR	Depletion	Infancy or childhood	• Hypotonia • Loss of acquired motor skills

AD = autosomal dominant; AR = autosomal recessive; HCM = hypertrophic cardiomyopathy; MOI = mode of inheritance

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *MPV17*-related mtDNA maintenance defect, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *MPV17*-Related mtDNA Maintenance Defect

System/Concern	Evaluation	Comment
Gastrointestinal (liver)	Liver function tests	Liver transaminases (ALT & AST), GGT, albumin, total & direct bilirubin, & coagulation profile (PT & PTT)
	Liver ultrasound	To assess liver size, liver texture, & for presence of masses
	Alpha fetoprotein level	To screen for hepatocellular carcinoma
	Hepatology / liver transplantation consultations	
	Nutrition eval	
	Consultation w/gastroenterologist	If dysmotility is suspected
Neurologic	Consultation w/neurologist	
	Developmental eval	By developmental pediatrician
	Brain MRI	To establish degree of CNS involvement; as a baseline for monitoring progression of neurologic disease
	Nerve conduction velocity	To establish degree of peripheral nervous system involvement; as a baseline for monitoring progression of neurologic disease
	Electroencephalogram	If seizures are suspected
Metabolic	Plasma glucose & lactate concentrations	To assess lactic acidosis & hypoglycemia
Renal	Urinalysis & urine amino acids	To assess for renal tubulopathy
Ocular	Ophthalmologic exam	To assess corneal sensation & possible corneal ulcers/ scarring
Other	Consultation w/clinical geneticist &/or genetic counselor	

CNS = central nervous system

Treatment of Manifestations

Management should involve a multidisciplinary team including specialists in hepatology, neurology, nutrition, clinical genetics, and child development.

Table 6. Treatment of Manifestations in Individuals with *MPV17*-Related mtDNA Maintenance Defect

Manifestation/Concern	Treatment
Liver failure	Consideration of liver transplantation [1]
Hepatocellular carcinoma	Standard treatment
Failure to thrive	Support from a dietitian experienced in managing children w/liver disease
Hypoglycemia	Frequent feeds & avoidance of fasting; uncooked cornstarch (1-2 g/kg/dose) [2]

Table 6. continued from previous page.

Manifestation/Concern	Treatment
Feeding difficulties	Consideration of nasogastric or gastrostomy tube feeding
Gastrointestinal dysmotility	Standard treatment per gastroenterologist
Seizures	Standard treatment per neurologist
Renal tubulopathy	Standard treatment per nephrologist
Hypoparathyroidism	Standard treatment per endocrinologist
Corneal ulcers	Standard treatment per ophthalmologist

1. Note: Liver transplantation is controversial (see Clinical Description).
2. Cornstarch may slow but not stop the progression of liver disease [Spinazzola et al 2008, Parini et al 2009].

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy, typically from an occupational or speech therapist, is recommended for affected individuals who have difficulty feeding as a result of poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

Prevention of Secondary Complications

Nutritional deficiencies (e.g., of fat-soluble vitamins) can be prevented by ensuring adequate intake and frequent assessment by a dietitian experienced in managing children with liver disease.

Surveillance

No clinical guidelines for surveillance are available.

The following evaluations are suggested, with frequency varying according to the severity of the condition:

Table 7. Recommended Surveillance for Individuals with *MPV17*-Related mtDNA Maintenance Defect

System/Concern	Evaluation	Frequency
Gastrointestinal (liver)	Liver function tests [1]	Depending on clinical severity
	Hepatic ultrasound	
	Serum AFP level	
	Nutritional assessment	At each visit
Neurologic	Neurologic assessment	
	Developmental assessment	
	Brain MRI, NCV, & EEG	Based on clinical symptoms
Metabolic	Glucose level	Depending on clinical severity
Renal	Urinalysis & urine amino acids to screen for renal tubulopathy	
Ocular	Ophthalmology eval	

EEG = electroencephalogram; MRI = magnetic resonance imaging; NCV = nerve conduction velocity
1. Liver transaminases (ALT and AST), GGT, albumin, total and direct bilirubin, and coagulation profile (PT and PTT)

Agents/Circumstances to Avoid

Prolonged fasting can lead to hypoglycemia and should be avoided.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

MPV17-related mtDNA maintenance defect is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *MPV17* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with *MPV17*-related mtDNA maintenance defect are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *MPV17* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *MPV17* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic 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 carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *MPV17* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Liver Foundation**
  Phone: 800-465-4837 (HelpLine)
  www.liverfoundation.org
- **Canadian Liver Foundation**
  Canada
  Phone: 800-563-5483
  Email: clf@liver.ca
  www.liver.ca
- **Childhood Liver Disease Research Network (ChiLDReN)**
  Phone: 720-777-2598
  Email: joan.hines@childrenscolorado.org
  www.childrennetwork.org
- **Children's Liver Disease Foundation**
  United Kingdom
  Phone: +44 (0) 121 212 3839
  Email: info@childliverdisease.org
  www.childliverdisease.org
- **The Charlie Gard Foundation**
  United Kingdom
  Email: hello@thecharliegardfoundation.org
  www.thecharliegardfoundation.org
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

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. MPV17-Related Hepatocerebral Mitochondrial DNA Maintenance Defect: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MPV17	2p23.3	Protein Mpv17	MPV17 database	MPV17	MPV17

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for MPV17-Related Hepatocerebral Mitochondrial DNA Maintenance Defect (View All in OMIM)

137960	MITOCHONDRIAL INNER MEMBRANE PROTEIN MPV17; MPV17
256810	MITOCHONDRIAL DNA DEPLETION SYNDROME 6 (HEPATOCEREBRAL TYPE); MTDPS6

Gene structure. *MPV17* spans 13.6 kb and comprises eight exons. For a detailed summary of gene and protein information, see Table A.

Pathogenic variants. To date, 48 *MPV17* pathogenic variants have been reported in children with *MPV17*-related mtDNA maintenance defect (Table A; Table 8). About half of those variants are missense and the remaining half includes nonsense, frameshift, and splice site variants, in-frame deletions, and large exon/multiexon deletions (summarized in El-Hattab et al [2018]). The majority of the *MPV17* pathogenic variants occur in one or a few families. However, homozygous c.149G>A has been reported in several affected individuals of Navajo ancestry. In addition, homozygous c.278A>C has been found in multiple families of Arab ancestry. Homozygosity and compound heterozygosity for c.293C>T have been described in several affected individuals of various ethnicities [El-Hattab et al 2018].

Table 8. *MPV17* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.122G>A	p.Arg41Gln	NM_002437.4 NP_002428.1
c.149G>A	p.Arg50Gln	
c.278A>C	p.Gln93Pro	
c.293C>T	p.Pro98Leu	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The MPV17 protein is composed of 176 amino acids and is localized in the inner mitochondrial membrane [Spinazzola et al 2006]. Molecular modeling of MPV17 predicted that the protein contains four transmembrane (TM) hydrophobic regions (TM1 from amino acids 18-38, TM2 53-73, TM3 94-114, and TM4 131-151) with five hydrophilic regions including three short linker regions connecting the TM spans and C-terminus and N- terminus at the same side of the membrane. Although C- and N-termini are located on the same side, it is unknown whether these termini are facing the matrix side or the intermembrane space side [Wong et al 2007].

Recently, it was reported that MPV17 loss caused mitochondrial deoxynucleotide insufficiency [Dalla Rosa et al 2016]. This finding, along with the localization of MPV17 in the inner mitochondrial membrane and animal models and cellular studies showing that Mpv17 forms a channel allowing small molecules to pass [Löllgen & Weiher 2015], provide strong evidence that MPV17 functions as an inner mitochondrial membrane channel importing cytosolic nucleotides into the mitochondrion [El-Hattab et al 2018].

Abnormal gene product. *MPV17* pathogenic variants result in dysfunctional MPV17 protein causing mitochondrial deoxynucleotide insufficiency and impaired mtDNA maintenance, leading to mtDNA depletion. Decrease in mtDNA content leads to insufficient production of respiratory chain components, resulting in impaired energy production and organ dysfunction [Spinazzola et al 2006].

Chapter Notes

Revision History

- 17 May 2018 (ma) Comprehensive update posted live
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