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MERRF

Synonym: Myoclonic Epilepsy Associated with Ragged Red Fibers

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Summary

Clinical characteristics

MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) is a multisystem disorder characterized by myoclonus (often the first symptom) followed by generalized epilepsy, ataxia, weakness, exercise intolerance, and dementia. Onset can occur from childhood to adulthood, occurring after normal early development. Common findings are ptosis, hearing loss, short stature, optic atrophy, cardiomyopathy, cardiac dysrhythmias such as Wolff-Parkinson-White syndrome, and peripheral neuropathy. Pigmentary retinopathy, optic neuropathy, diabetes mellitus, and lipomatosis have been observed.

Diagnosis/testing

A clinical diagnosis of MERRF can be established in a proband with the following four "canonic" features: myoclonus, generalized epilepsy, ataxia, and ragged red fibers (RRF) in the muscle biopsy. A molecular diagnosis is established in a proband with suggestive findings and a pathogenic variant in one of the genes associated with MERRF. The m.8344A>G pathogenic variant in the mitochondrial gene *MT-TK* is present in more than 80% of affected individuals with typical findings. Pathogenic variants in *MT-TF*, *MT-TH*, *MT-TI*, *MT-TL1*, *MT-TP*, *MT-TS1*, and *MT-TS2* have also been described in a subset of individuals with MERRF.

Management

Treatment of manifestations: Ubiquinol, carnitine, alpha lipoic acid, vitamin E, vitamin B complex, and creatine may be of benefit to some individuals; traditional anticonvulsant therapy per neurologist for seizures; levetiracetam or clonazepam for myoclonus; physical therapy to improve any impaired motor function; aerobic exercise; standard pharmacologic therapy for cardiac symptoms; hearing aids or cochlear implants for hearing loss; diabetes mellitus treatment per endocrinologist.

Prevention of primary manifestations: Coenzyme Q_{10} (50-200 mg 2-3x/day), L-carnitine (1000 mg 2-3x/day), alpha lipoic acid, vitamin E, vitamin B supplements, and creatine, often used to improve mitochondrial function, have been of modest benefit in some individuals. Doses for children should be adjusted appropriately.

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Surveillance: Routine evaluations every six to 12 months initially; annual neurologic, ophthalmologic, cardiology (electrocardiogram and echocardiogram), and endocrinologic evaluations (fasting blood sugar and TSH); audiology evaluations every two to three years.

Agents/circumstances to avoid: Mitochondrial toxins (e.g., aminoglycoside antibiotics, linezolid, cigarettes, alcohol); valproic acid should be avoided in the treatment of seizures.

Pregnancy management: During pregnancy, affected or at-risk women should be monitored for diabetes mellitus and respiratory insufficiency, which may require therapeutic interventions.

Genetic counseling

MERRF is caused by pathogenic variants in mtDNA and is transmitted by maternal inheritance. The father of a proband is not at risk of having the mtDNA pathogenic variant. The mother of a proband usually has the mtDNA pathogenic variant and may or may not have symptoms. A male with a mtDNA pathogenic variant cannot transmit the pathogenic variant to any of his offspring. A female with a mtDNA pathogenic variant (whether symptomatic or asymptomatic) transmits the pathogenic variant to all of her offspring. Prenatal testing and preimplantation genetic testing for MERRF are possible if a mtDNA pathogenic variant has been detected in the mother. However, because the mutational load in embryonic and fetal tissues sampled (i.e., amniocytes and chorionic villi) may not correspond to that of all fetal tissues and because the mutational load in tissues sampled prenatally may shift in utero or after birth as a result of random mitotic segregation, prediction of the phenotype from prenatal studies is not possible.

Diagnosis

Clinical diagnostic criteria for MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) have been published [Finsterer et al 2018] (see Establishing the Diagnosis).

Suggestive Findings

MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) **should be suspected** in individuals with the following features.

Clinical features

- Myoclonus
- Generalized epilepsy
- Ataxia
- Myopathy
- Exercise intolerance
- Dementia
- Ptosis
- Sensorineural hearing loss
- Short stature
- Optic atrophy
- Peripheral neuropathy

Less common clinical signs (seen in <50% of affected individuals) include the following:

- Cardiomyopathy
- Pigmentary retinopathy
- Pyramidal signs
- Ophthalmoparesis

- Multiple lipomas

Laboratory features

- **Lactic acidosis both in blood and in the CSF.** In individuals with MERRF, the concentrations of lactate and pyruvate are commonly elevated at rest and increase excessively after moderate activity.

  Note: Other situations (unrelated to the diagnosis of MERRF or other mitochondrial diseases) in which lactate and pyruvate can be elevated are acute neurologic events such as seizure or stroke.

- **Elevated CSF protein concentration.** The concentration of CSF protein may be increased but rarely surpasses 100 mg/dL.

- **Respiratory chain studies.** Biochemical analysis of respiratory chain enzymes in muscle extracts usually shows decreased activity of respiratory chain complexes containing mtDNA-encoded subunits, especially COX deficiency. However, biochemical studies may also be normal.

Histopathologic features on muscle biopsy. Ragged red fibers (RRF) are seen with the modified Gomori trichrome stain and hyperactive fibers with the succinate dehydrogenase stain. Both RRF and some non-RRF fail to stain with the histochemical reaction for cytochrome *c* oxidase. Occasionally, RRF may not be observed [Mancuso et al 2007].

Electrophysiologic features

- **Electroencephalogram** usually shows generalized spike and wave discharges with background slowing, but focal epileptiform discharges may also be seen.
- **Electrocardiogram** often shows pre-excitation; heart block has not been described.
- **Electromyogram** and **nerve conduction velocity** studies are consistent with a myopathy, but neuropathy may coexist.

Brain imaging. Brain MRI often shows brain atrophy and basal ganglia lesions. Bilateral putaminal necrosis and atrophy of the brain stem and cerebellum have been reported [Orcesi et al 2006, Ito et al 2008].

Establishing the Diagnosis

The clinical diagnosis of MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) **can be established** in a proband based on clinical diagnostic criteria [Finsterer et al 2018] or the molecular diagnosis can be established in a proband with suggestive findings and a pathogenic variant in one of the genes listed in Table 1, identified by molecular genetic testing.

Clinical diagnosis. The clinical diagnosis is based on the following four "canonic" features:

- Myoclonus
- Generalized epilepsy
- Ataxia
- Ragged red fibers (RRF) in the muscle biopsy

Molecular diagnosis. The diagnosis of MERRF **is established** in a proband with suggestive findings and a pathogenic variant in one of the genes listed in Table 1.

Note: Pathogenic variants can usually be detected in mtDNA from leukocytes in individuals with typical MERRF; however, the occurrence of "heteroplasmy" in disorders of mtDNA can result in varying tissue distribution of mutated mtDNA. Hence, the pathogenic variant may be undetectable in mtDNA from leukocytes and may be detected only in other tissues, such as buccal mucosa, cultured skin fibroblasts, hair follicles, urinary sediment, or (most reliably) skeletal muscle.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, concurrent or serial single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with seizures and weakness are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Serial single-gene testing can be considered if (1) mutation of a particular gene accounts for a large proportion of the condition **or** (2) clinical findings, laboratory findings, ancestry, or other factors indicate that mutation of a particular gene is most likely.

Targeted analysis. Typically, blood leukocyte DNA is initially screened for pathogenic variants in *MT-TK* using targeted analysis for the m.8344A>G pathogenic variant, which is present in more than 80% of individuals with typical clinical findings. Note: If no pathogenic variant is found, consider targeted analysis for this pathogenic variant on DNA from buccal mucosa, muscle, or urine sediment.

Entire mitochondrial genome sequencing that includes the genes in Table 1 and other mtDNA genes of interest (Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.

A multigene panel that includes the genes in Table 1 and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included and the sensitivity of multigene panels 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by seizures and weakness, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Many laboratories require that the clinician specify if the mitochondrial genome should be included as part of the comprehensive genomic testing.

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 MERRF

Gene [1, 2]	% of MERRF Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Sequence Analysis [4]
MT-TK	>90% [5]	100%
MT-TF	<5%	100%
MT-TH		
MT-TI		
MT-TL1		
MT-TP		
MT-TS1		
MT-TS2		
Unknown [6]	NA	

1. Genes are listed from most frequent to least frequent genetic cause of MERRF.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on pathogenic allelic variants detected.
4. 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, partial-, whole-, or multigene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Four *MT-TK* pathogenic variants (m.8344A>G, m.8356T>C, m.8363G>A, and m.8361G>A) account for approximately 90% of pathogenic variants in individuals with MERRF.
6. One child with MERRF was found to have two mtDNA deletions in a buccal swab, suggesting an autosomal disorder with multiple mtDNA deletions; however, the causative nuclear gene was not identified [Yorns et al 2012].

Clinical Characteristics

Clinical Description

MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) is a multisystem disorder characterized by myoclonus, which is often the first symptom, followed by generalized epilepsy, ataxia, weakness, exercise intolerance, and dementia. Onset can occur from childhood to adulthood, after normal early development. Table 2 lists the most frequent signs and symptoms reported [Hirano & DiMauro 1996, Mancuso et al 2013].

Table 2. MERRF: Frequency of Select Features

Feature	% of 62 Persons w/Feature [1]	% of 34 Persons w/Feature [2]	% of 321 Persons w/Feature [3]
Myoclonus	100%	24%	61%
Epilepsy	100%	35%	43%
Normal early development	100%		
Ragged red fibers	92%	96%	
Hearing loss	91%	35%	39%
Lactic acidosis	83%	65%	
Family history of MERRF	81%		
Exercise intolerance	80%	44%	
Dementia	75%		25%
Neuropathy	63%	15%	24%
Short stature	57%		

Table 2. continued from previous page.

Feature	% of 62 Persons w/Feature [1]	% of 34 Persons w/Feature [2]	% of 321 Persons w/Feature [3]
Impaired sensation	50%		
Optic atrophy	39%		
Cardiomyopathy	33%	12%	
Arrhythmia	22%	18%	
Pigmentary retinopathy	15%		
Pyramidal signs	13%		
Ophthalmoparesis	11%	6%	6%
Lipomatosis	3%	32%	8%
Diabetes mellitus		12%	3%

1. Hirano & DiMauro [1996]
2. Mancuso et al [2013]
3. Reviewed from the literature by Mancuso et al [2013]

Neurologic manifestations

- **Myopathy.** The most common features are exercise intolerance, muscle weakness, and elevated blood creatine kinase level.
- **Epilepsy.** Generalized myoclonic seizures are the most frequent seizure type in individuals with MERRF. Other reported types of seizures include focal myoclonic, focal atonic, focal clonic, generalized tonic-clonic, generalized atonic, generalized myoclonic-atonic, typical absences, myoclonic absences, or tonic-clonic seizures of unknown onset [Finsterer & Zarrouk-Mahjoubb 2017].
- **Migrainous headaches**. Migraines are common in individuals with MERRF and can be present at the onset of symptoms. Vollono et al [2018] reported seven individuals with MERRF and migraines and found that migraines can present with or without aura. The frequency of migraine episodes in most individuals was every two months.
- **Hearing impairment**. Hearing loss is typically sensorineural and occurs in 35%-91% of individuals.
- **Peripheral neuropathy**. It has been reported that either sensory axonal neuropathy or sensory motor axonal neuropathy can be present.
- **Early psychomotor development**. Early development is typically normal in individuals with MERRF.
- **Psychiatric illnesses.** Although psychiatric illness is not a prominent feature in this disorder, several individuals with depressive mood disorders have been reported.

Cardiac involvement. Cardiomyopathy can be observed. Both hypertrophic and dilated cardiomyopathy have been described. Arrhythmias are common in individuals with MERRF and can accompany the cardiomyopathy or be an isolated cardiac finding.

Lipomatosis can be seen in adulthood in individuals with MERRF, with an average age of onset of 45.2 years [Chong et al 2003]. Lipomas can be infiltrative, progressive, and massive in size [Gilson & Osswald 2018]. The most common location of lipomas is the cervical region.

Phenotype Correlations by Gene

No phenotype correlations by gene have been identified.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

For all mtDNA pathogenic variants, clinical expression depends on three factors:

- **Heteroplasmy.** The relative abundance of mutated mtDNAs
- **Tissue distribution** of mutated mtDNAs
- **Threshold effect.** The vulnerability of each tissue to impaired oxidative metabolism

The tissue vulnerability threshold probably does not vary substantially among individuals, but variable mutational load and tissue distribution may account for the clinical diversity of individuals with MERRF.

Penetrance

See Genotype-Phenotype Correlations.

Nomenclature

Ramsay Hunt [1921] described six individuals with a disorder characterized by ataxia, myoclonus, and epilepsy, which he called "dyssynergia cerebellaris myoclonica." Individuals with the diagnosis of Ramsay Hunt syndrome should be investigated for MERRF.

Prevalence

Four epidemiologic studies of mtDNA-related diseases in northern Europe gave concordantly low estimates for the prevalence of the m.8344A>G pathogenic variant:

- 0-1.5:100,000 in the adult population of northern Finland [Remes et al 2005]
- 0.39:100,000 in the adult population of northern England [Schaefer et al 2008]
- 0-0.25:100,000 in a pediatric population of western Sweden [Darin et al 2001]
- 0.7:100,000 in a large population-based study in northeast England [Gorman et al 2015]

See Mitochondrial Disorders Overview for general prevalence information.

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *MT-TF*, *MT-TH*, *MT-TI*, *MT-TK*, and *MT-TL1* are summarized in Table 3.

Table 3. Selected Allelic Disorders

Gene	Phenotype
MT-TF	• MELAS
MT-TH	• MELAS • Cardiomyopathy (OMIM 590040) • Pigmentary retinopathy (OMIM 590040) • Deafness
MT-TI	• Mitochondrial DNA-associated Leigh syndrome • Neonatal weakness, lactic acidosis, hypoglycemia, cardiopulmonary arrest, & early fatality in one individual [1]
MT-TK	• Multiple symmetric lipomatosis [Perera et al 2018] • MELAS • MERRF/MELAS overlap [2, 3] (See also Differential Diagnosis.) • Mitochondrial DNA-associated Leigh syndrome

Table 3. continued from previous page.

Gene	Phenotype
MT-TL1	• Cardiomyopathy (OMIM 590050) • Maternally inherited diabetes mellitus w/ or w/o deafness (OMIM 590050) • MERRF/MELAS overlap (See also Differential Diagnosis.) • MELAS • MERRF/Kearns-Sayre syndrome (See Mitochondrial DNA Deletion Syndromes.) [3, 4] • Mitochondrial nonsyndromic hearing loss and deafness • Progressive external ophthalmoplegia (See Mitochondrial DNA Deletion Syndromes.)
MT-TS1	• MELAS • Mitochondrial nonsyndromic hearing impairment
MT-TS2	• MELAS • Cerebellar ataxia, cataract, and diabetes mellitus (OMIM 590085)

1. Yoon et al [1993]
2. In three families with the *MT-TK* m.8356T>C pathogenic variant, some affected individuals had typical MERRF but others also had stroke-like episodes and migraine (MERRF/MELAS overlap). See also Differential Diagnosis.
3. One affected individual with MERRF/MELAS overlap syndrome had two pathogenic variants: the *MT-TL1* variant m.3243A>G (the most frequent cause of MELAS) and the *MT-TK* variant m.8356T>C (a rare cause of MERRF) [Nakamura et al 2010].
4. A MERRF/Kearns-Sayre syndrome overlap syndrome has been reported to be caused by the pathogenic variant m.3255G>A in *MT-TL1* (reported in 2 individuals [Nishigaki et al 2003, Fujioka et al 2014]) and by the pathogenic variant m.3291T>C in *MT-TL1* (reported in 1 individual [Emmanuele et al 2011]).

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *MT-TP*.

Differential Diagnosis

Neurologic findings. The differential diagnosis includes other mitochondrial disorders (see Mitochondrial Disorders Overview), syndromes characterized by ataxia (see Hereditary Ataxia Overview) and myoclonus epilepsy (e.g., Unverricht-Lundborg disease, Lafora type progressive myoclonus epilepsy, neuronal ceroid lipofuscinosis, and sialidosis [Kälviäinen 2015]), and the disorders summarized in Table 4.

The multisystem involvement, lactic acidosis, evidence of maternal inheritance, and muscle biopsy with RRF (ragged red fibers) distinguish MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) from other conditions.

Table 4. Genes of Interest in the Differential Diagnosis of MERRF

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	Distinguishing Features
CARS2	Combined oxidative phosphorylation deficiency 27 (OMIM 616672)	AR	Juvenile-onset MERRF-like severe myoclonus epilepsy w/ataxia, spastic tetraparesis, vision loss, hearing loss, & cognitive decline	AR inheritance
MT-ND5 *MT-TC*	MERRF/MELAS overlap syndrome	Mat	May initially resemble MERRF [1]	Stroke-like episodes
MT-TL2	*MT-TL2* disorder	Mat	Features of MERRF & NARP in 1 person [2]	Retinitis pigmentosa

Table 4. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	Distinguishing Features
POLG	*POLG*-related disorders	AR	Myoclonus, epilepsy, ataxia, peripheral neuropathy	Absence of RRF in *POLG* phenotype

AR = autosomal recessive; DiffDx = differential diagnosis; Mat = maternal; MOI = mode of inheritance; NARP = neuropathy-ataxia-retinitis pigmentosa; RRF = ragged red fibers
1. Crimi et al [2003], DiMauro & Davidzon [2005], Naini et al [2005], Herrero-Martín et al [2010]
2. Martín-Jiménez et al [2012]

Lipomas. Other syndromes that cause multiple lipomas (e.g., multiple symmetric lipomatosis [OMIM 151800]) need to be considered.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers), 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 MERRF

System/Concern	Evaluation	Comment
Growth	Measurement of height & weight	To evaluate for short stature
Neurologic	Neurologic eval	To assess for neurologic deficits
	Head MRI w/MRS	To evaluate for pathologic changes at baseline
	EEG	If seizures are suspected
	Neuropsychiatric testing	To assess cognitive abilities & evidence of dementia
Ears	Audiologic eval	To detect hearing loss
Eyes	Ophthalmologic eval	To screen for ptosis, optic atrophy, pigmentary retinopathy, ophthalmoplegia, vision deficits
Musculoskeletal	PT/OT assessment	For persons w/neurologic deficits
Cardiovascular	Cardiac eval incl echocardiogram	To evaluate for cardiomyopathy & cardiac defects
	Electrocardiogram	To screen for conduction abnormalities
Endocrinologic	• Fasting serum glucose • Glucose tolerance test	To screen for diabetes mellitus
Genetic counseling	By genetics professionals [1]	To inform patients & their families re nature, MOI, & implications of MERRF to facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	

MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with MERRF

Manifestation/Concern	Treatment	Considerations/Other
Overall disease process	Ubiquinol, carnitine, alpha lipoic acid, vitamin E, vitamin B complex, creatine	May be of benefit to some persons
Seizures	Traditional anticonvulsant therapy per neurologist	Avoid valproic acid (see Agents/Circumstances to Avoid).
Myoclonus	Levetiracetam or clonazepam	Crest et al [2004], Mancuso et al [2007]
Impaired motor abilities	• PT • Aerobic exercise	Taivassalo & Haller [2004]
Cardiomyopathy	Standard pharmacologic therapy per cardiologist	
Cardiac conduction defects		
Hearing loss	Hearing aids, cochlear implants	
Diabetes mellitus	Treatment per endocrinologist	Metformin can aggravate lactic acidosis.

PT = physical therapy

Prevention of Primary Manifestations

The administration of coenzyme Q_{10} (CoQ_{10}) (50-200 mg 2-3x/day) and L-carnitine (1000 mg 2-3x/day) has been of some benefit to some individuals. In a small randomized double-blind placebo-controlled study of affected individuals with heterogeneous mitochondrial diseases, CoQ_{10} combined with creatine and lipoic acid produced modest benefits including slowing progression of ankle weakness and lower resting plasma lactate concentration [Rodriguez et al 2007].

The Mitochondrial Medicine Society published a consensus statement which recommends that CoQ_{10}, alpha lipoic acid, and riboflavin should be offered to individuals with mitochondrial disease. Folinic acid should be considered in those with central nervous system involvement. L-carnitine should be supplemented in those with documented deficiency and levels should continue to be monitored [Parikh et al 2015]. Despite the empiric rationale to administer these vitamins and supplements, there is limited clinical trial evidence supporting their use [Rodriguez et al 2007].

Surveillance

Affected individuals and their at-risk relatives should be followed at regular intervals (e.g., every 6-12 months initially) to monitor progression of disease and the appearance of new symptoms.

Table 7. Recommended Surveillance for Individuals with MERRF

System/Concern	Evaluation	Frequency
Neurologic	Neurologic exam	• Annually • If normal for 3 yrs, less frequent evals can be considered.
Eyes	Ophthalmologic exam	
Cardiovascular	• Electrocardiogram • Echocardiogram	
Endocrinologic	• Fasting blood sugar • TSH	
Hearing	Audiologic eval	Every 2-3 yrs

TSH = thyroid stimulating hormone

Agents/Circumstances to Avoid

Individuals with MERRF should avoid mitochondrial toxins such as aminoglycoside antibiotics, linezolid, cigarettes, and alcohol. Valproic acid should be avoided in the treatment of seizures.

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify as early as possible those who would benefit from institution of treatment and preventive measures. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Complete neurologic evaluation, ophthalmologic and audiology evaluations, EKG, echocardiogram, and blood lactate if the pathogenic variant in the family is not known.

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

Pregnancy Management

During pregnancy, affected or at-risk women should be monitored for diabetes mellitus and respiratory insufficiency, which may require therapeutic interventions.

Therapies Under Investigation

Mitochondrial replacement therapy (MRT) – replacement of a woman's abnormal mitochondrial DNA with healthy mitochondrial DNA from a donor [Sharma et al 2020] – has been under investigation as a way to prevent these disorders from continuing in a family. MRT includes three types of techniques: spindle transfer, pronuclear transfer, and polar body transfer. MRT was successfully approved by the United Kingdom Parliament and a clinical trial is underway. To date, these techniques are not approved in the United States.

Genetic therapy through the delivery of mitochondrially targeted zinc finger nucleases delivered by an adeno-associated virus has been studied in mouse models with mitochondrial disorders. The mutational load decreased by 20% in treated animals, and biochemical phenotypes were reversed [Gammage et al 2018].

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.

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

MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) is caused by pathogenic variants in mitochondrial DNA (mtDNA) and transmitted by maternal inheritance.

Risk to Family Members

Parents of a proband

- The father of a proband is not at risk of having the mtDNA pathogenic variant.

- The mother of a proband usually has the mtDNA pathogenic variant and may or may not have clinical manifestations of the disorder. In some mothers, the pathogenic variant may be undetectable in mtDNA from leukocytes and may be detected in other tissues, such as buccal mucosa, cultured skin fibroblasts, hair follicles, urinary sediment, or (most reliably) skeletal muscle.
- Some individuals diagnosed with MERRF have no known family history of the disorder. The explanation for apparently simplex cases may be the absence of a comprehensive and/or reliable family history or, in rare cases, a *de novo* mtDNA pathogenic variant in the proband.

Sibs of a proband

- The risk to the sibs depends on the genetic status of the mother. If the mother has the mtDNA pathogenic variant, all the sibs of a proband will inherit the mtDNA pathogenic variant. Women with higher levels of mutated mtDNA in their blood may have a greater likelihood of having affected offspring [Chinnery et al 1998].
- Clinical expression in sibs depends on the percentage of mutated mitochondria (mutational load) and the organs and tissues in which they are found (tissue distribution and threshold effect). Sibs often inherit different percentages of mutated mtDNA and have a wide range of clinical manifestations (see Genotype-Phenotype Correlations).

Offspring of a proband

- All offspring of females with a mtDNA pathogenic variant will inherit the pathogenic variant.
- Offspring of males with a mtDNA pathogenic variant are not at risk of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's mother: if the mother has a mtDNA pathogenic variant, her sibs and mother are also at risk.

Related Genetic Counseling Issues

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

Phenotypic variability. The phenotype of an individual with a mtDNA pathogenic variant results from a combination of factors including the percentage of mutated mitochondria (mutational load) and the organs and tissues in which they are found (tissue distribution). Family members can have a wide range of clinical symptoms.

Interpretation of testing results of asymptomatic at-risk family members is extremely difficult. Prediction of phenotype based on test results is not possible. Furthermore, absence of the mtDNA pathogenic variant in one tissue (e.g., blood) does not guarantee its absence in other tissues.

Family planning

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

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

Prenatal Testing and Preimplantation Genetic Testing

Once the mtDNA pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MERRF are technically possible. However, prenatal testing for mtDNA pathogenic variants causing MERRF is of uncertain utility for the following reasons:

- The mutational load in the mother's tissues and in fetal tissues sampled (i.e., amniocytes and chorionic villi) may not correspond to that of other fetal tissues.
- The mutational load in tissues sampled prenatally may shift in utero or after birth as a result of random mitotic segregation.
- Prediction of phenotype, age of onset, severity, or rate of progression is not 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.

- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
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- **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. MERRF: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
MT-TF	Mitochondrion	Not applicable	MT-TF
MT-TH	Mitochondrion	Not applicable	MT-TH
MT-TI	Mitochondrion	Not applicable	MT-TI
MT-TK	Mitochondrion	Not applicable	MT-TK
MT-TL1	Mitochondrion	Not applicable	MT-TL1
MT-TP	Mitochondrion	Not applicable	MT-TP
MT-TS1	Mitochondrion	Not applicable	MT-TS1
MT-TS2	Mitochondrion	Not applicable	MT-TS2

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 MERRF (View All in OMIM)

545000	MYOCLONIC EPILEPSY ASSOCIATED WITH RAGGED-RED FIBERS; MERRF
590040	TRANSFER RNA, MITOCHONDRIAL, HISTIDINE; MTTH
590045	TRANSFER RNA, MITOCHONDRIAL, ISOLEUCINE; MTTI
590050	TRANSFER RNA, MITOCHONDRIAL, LEUCINE, 1; MTTL1
590060	TRANSFER RNA, MITOCHONDRIAL, LYSINE; MTTK
590070	TRANSFER RNA, MITOCHONDRIAL, PHENYLALANINE; MTTF
590075	TRANSFER RNA, MITOCHONDRIAL, PROLINE; MTTP
590080	TRANSFER RNA, MITOCHONDRIAL, SERINE, 1; MTTS1
590085	TRANSFER RNA, MITOCHONDRIAL, SERINE, 2; MTTS2

Molecular Pathogenesis

The origin of mtDNA pathogenic variants is uncertain. It is also unclear how the mtDNA single-nucleotide variants cause MERRF. Using rho^0 cell lines (permanent human cell lines emptied of their mtDNA by exposure to ethidium bromide) repopulated with mitochondria harboring the m.8344A>G pathogenic variant, Chomyn et al [1991] found that high mutational loads correlated with decreased protein synthesis, decreased oxygen consumption, and cytochrome *c* oxidase deficiency. The polypeptides containing higher numbers of lysine residues were more severely affected by the pathogenic variant, suggesting that the *MT-TK* pathogenic variant directly inhibits protein synthesis. Similarly, cultured myotubes containing more than 85% mutated mtDNA showed decreased translation, especially of proteins containing large numbers of lysine residues. Cells harboring the m.8344A>G pathogenic variant contained decreased levels of $tRNA^{Lys}$ and aminoacylated $tRNA^{Lys}$. The variant appears to be functionally recessive because only about 15% wild-type mtDNA restores translation and cytochrome *c* oxidase activity to near-normal levels.

Masucci et al [1995] confirmed that protein synthesis and oxygen consumption were decreased in rho^0 cells repopulated with mtDNA harboring either the m.8344A>G or the m.8356T>C pathogenic variant, and identified aberrant mitochondrial protein in both cell lines, which they attributed to ribosomal frameshifting. Studies of engineered in vitro transcribed tRNA^{Lys} mutants showed that the pathogenic variants associated with MERRF had no effect on lysylation efficiency, whereas the two pathogenic variants associated with encephalomyopathies without typical MERRF features (m.8313G>A and m.8328G>A in *MT-TK*) severely impaired lysylation [Sissler et al 2004].

Mechanism of disease causation. Unknown

Table 8. MERRF: Notable *MT-TK* Pathogenic Variants

Mitochondrial DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequence	Comment
m.8344A>G (A8344G)	No protein translated	NC_012920.1	Most common pathogenic variant; identified in >80% of persons w/MERRF
m.8356T>C (T8356C)			Pathogenic variants identified in ~10% of persons w/MERRF
m.8363G>A (G8363A)			
m.8361G>A (G8361A)			

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

Chapter Notes

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