Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is MERRF

Definition

Myoclonic Epilepsy with Ragged Red Fibers (MERRF) is a multisystem mitochondrial disease.¹

- MERRF typically presents with myoclonus (brief, involuntary twitching of a muscle or a group of muscles), followed by generalized epilepsy, ataxia (lack of coordination of muscle movements), weakness, and dementia.¹ Ragged red fibers (RRF) are identified on muscle biopsy pathology.¹

  - Other common findings include hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White syndrome (a syndrome in which there is extra electrical connection in the heart at birth causing rapid heartbeat). Occasionally pigmentary retinopathy and lipomatosis are observed.¹

  - Most cases present in childhood after normal early development.¹

- MERRF is caused by mutations in the mitochondrial DNA (mtDNA) and follows maternal inheritance. This means that a female who carries the mtDNA point mutation will pass it on to all of her children. A male who carries the mtDNA mutation cannot pass it on to his children.¹,²

- For all mtDNA mutations, clinical expressivity depends on the three following factors:
  - The relative abundance of mutant mtDNA, or mutational load (heteroplasmy)
  - The organs and tissues in which the mutant mtDNA is found (tissue distribution), and
The vulnerability of each tissue to impaired oxidative metabolism (threshold effect).

- The estimated prevalence of MERRF is approximately 0.25-1.5/100,000 individuals.¹
- Management is usually palliative. Certain antiepileptic drugs, such as valproic acid, should be avoided as they may cause secondary carnitine deficiency or can be used with L-carnitine supplementation.¹
- At-risk individuals may also benefit from clinical assessment to initiate baseline evaluations (neurology, cardiology, ophthalmology, and audiology) and potential intervention prior to exhibiting clinical manifestations.¹

Test information

- The investigation and diagnosis of patients with mitochondrial disease often necessitates a combination of techniques including muscle histocytochemistry, biochemical assessment and molecular genetic studies along with clinical assessment. Any molecular genetic test for a mtDNA mutation should ideally be directed by the clinical phenotype and results of these other investigations.³
- MERRF Mutation Panel: Heteroplasmic mutations in the mtDNA genes, MT-TK, MT-TL1, MT-TF, MT-TI, and MT-TP cause MERRF. Mutations in the mtDNA genes MT-TH, MT-TS1, MT-TS2, cause MELAS/MERRF overlap syndrome.
  - Approximately 90% of cases of MERRF are due to MT-TK mutations. 80% of MERRF cases are the result of a specific genetic change, m.8344A>G (formerly A8344G) in MT-TK.¹²⁴
  - Three additional MT-TK mutations, m.8356T>C, m.8363G>A, and m.8361G>A, are present in an additional 10% of affected individuals. These three mutations can also be associated with other mitochondrial or genetic conditions.¹
  - Detection rate of the four-mutation panel is about 90%.¹
  - “Sequence analysis / scanning for pathogenic variants is used to detect pathogenic variants throughout mtDNA and is not specific for MERRF. The overall variant detection rate for MERRF by scanning/sequence analysis of mtDNA is 90%-95%.”¹
- Due to its ability to simultaneously sequence the entire mtDNA and measure heteroplasmy at each position, next generation sequencing (NGS) is an option for assessing MERRF and overlapping syndromes. However, certain targeted mutation analyses can also estimate heteroplasmy. Typically, Sanger sequence analysis will miss heteroplasmy below 20%.
- If genetic testing is negative in a blood sample in a person with symptoms of MERRF, testing can be done on other specimens. Typically this is done when the
phenotype is highly suggestive of presence of a MERRF mutation or when there is a need to assess reproductive risk.

- Muscle may be considered as a secondary tissue since it is clinically involved as evidenced by Ragged Red Fibers. Muscle biopsy allows enzymatic analysis of the electron transport chain, light and ultra structural microscopy, and mtDNA copy number analysis—all of which may provide highly useful information. However, the invasiveness and procedural costs associated with a muscle biopsy are factors to consider.

- Genetic testing can also be done on skin fibroblasts, urinary sediment, saliva, or buccal mucosa. If cultured fibroblasts are used, measures such as limited passaging and uridine supplementation should be taken to reduce selection against mutant genotypes that may lead to skewed heteroplasmcy.

### Guidelines and evidence

- No specific evidence-based U.S. testing guidelines were identified.
- Case reports and a limited number of case series are the primary evidence base available for the diagnosis of mitochondrial disease.\(^5\text{-}^7\)
- The Mitochondrial Medicine Society developed consensus recommendations using the Delphi method and published them in 2015.\(^8\)

**Recommendations for DNA testing**

- “Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.”

- “Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmcy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling.”

- “Heteroplasmcy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m.3243 A>G mutation.”

- “When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease gene is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no mutation is identified via known NGS panels, then whole exome sequencing should be considered.”
• The European Federation of Neurological Sciences (2009) provided molecular diagnostic consensus-based guidelines based on literature reviews: “If the phenotype suggests syndromic mitochondrial disease due to mtDNA point mutations (MELAS, MERRF, NARP, LHON) DNA-microarrays using allele-specific oligonucleotide hybridization, real-time-PCR or single-gene sequencing are indicated.”

• The clinical utility of genetic testing for MERRF was described by a workshop of the National Institute of Neurological Disorders and Stroke (2008):
  o “The diagnosis of mitochondrial diseases is complicated by their heterogeneous presentations and by the lack of screening procedures or diagnostic biomarkers that are both sensitive and specific. The workshop panelists explained that diagnosis is often a lengthy process beginning with a general clinical evaluation followed by metabolic screening and imaging and finally by genetic tests and more invasive biochemical and histological analyses. The identification of known mitochondrial mutations in tissue has greatly aided diagnosis. However, even when clinical features and family history strongly suggest mitochondrial disease, the underlying genetic mutation can elude detection, and there is no current screening procedure that would be practical for all cases of suspected mitochondrial disease.”
  o Initial screening includes testing lactate and CSF protein levels, muscle biopsy, EEG, ECG, and MRI. “It is important to note that biochemical abnormalities may not be present during periods when the mitochondrial disease is quiescent/dormant.”

• The Clinical Molecular Genetics Society of UK (2008) provided practice-based guidelines for the molecular diagnosis of mitochondrial disease: “In cases with strong clinical evidence, testing should begin with checking for the common mutation, m.8344A>G. Subsequent testing for other mutations, such as m.8356T>C, may be indicated in cases with a strong clinical indication of MERRF.”

Criteria

Known MERRF Familial Mutation Testing

• Genetic Counseling
  o Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing
  o No previous genetic testing in the individual for MERRF,** and
  o MERRF pathogenic variant identified in matrilineal relative, AND
• Predictive Testing for Asymptomatic Individual:
  o 18 years of age or older, or
  o Under the age of 18 years, and
    ▪ Presymptomatic screening for Wolff-Parkinson-White is being considered, OR
• Diagnostic Testing for Symptomatic Individual:
  o Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a diagnosis of MERRF, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy

**MERRF Targeted Mutation Analysis**

• Genetic Counseling
  o Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Testing:
  o No previous genetic testing for MERRF,** and
  o No known MERRF pathogenic variants in the family, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Clinical exam and/or biochemical testing suggestive, but not confirmatory, of a diagnosis of MERRF, and
  o Genetic testing is needed to confirm the diagnosis, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy

**Whole mtDNA Sequencing**

• Genetic Counseling
  o Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Criteria for MERRF targeted mutation analysis is met, AND
• No pathogenic variants identified in the MERRF targeted mutation analysis, AND
• Paternal transmission has been ruled out

**Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.**
References


