GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

MERRF

[*Myoclonic Epilepsy Associated with Ragged-Red Fibers*]

Salvatore DiMauro, MD
MDA/ALS Center
Neurological Institute of New York
sd12@columbia.edu

Michio Hirano, MD
Department of Neurology
Columbia University

Initial Posting: June 3, 2003.
Last Update: September 27, 2005.

Summary

Disease characteristics. MERRF (**M**yoclonic **E**pilepsy associated 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, and dementia. Onset is usually in childhood, occurring after normal early development. Common findings are hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White (WPW) syndrome. Occasionally pigmentary retinopathy and lipomatosis are observed.

Diagnosis/testing. The clinical diagnosis of MERRF is based on the following four "canonical" features: myoclonus, generalized epilepsy, ataxia, and ragged-red fibers (RRF) in the muscle biopsy. The most common mutation, present in over 80% of affected individuals with typical findings, is an A-to-G transition at nucleotide-8344 in the mitochondrial DNA gene *MT-TK*, which encodes $tRNA^{Lys}$. Mutations are usually present in all tissues and are conveniently detected in mtDNA from blood leukocytes. However, the occurrence of "heteroplasmy" in disorders of mtDNA can result in varying tissue distribution of mutated mtDNA. Hence, in individuals having few symptoms consistent with MERRF or in asymptomatic maternal relatives of an affected individual, the pathogenic mutation may be undetectable in mtDNA from leukocytes and may only be detected in other tissues, such as cultured skin fibroblasts, urinary sediment, oral mucosa (from mouthwash), hair follicles, or, most reliably, skeletal muscle.

Management. The seizure disorder can be treated with conventional anticonvulsant therapy. No controlled studies have compared the efficacy of different anticonvulsants. Coenzyme Q10 (100 mg three times a day) and L-carnitine (1000 mg three times a day) are often used in hopes of improving mitochondrial function.

Genetic counseling. MERRF is caused by mutations in mtDNA and is transmitted by maternal inheritance. The father of a proband is not at risk for having the disease-causing mtDNA mutation. The mother of a proband usually has the mtDNA mutation and may or may not have symptoms. A male with an mtDNA mutation cannot transmit the mutation to any of his offspring. A female with the mutation (whether affected or unaffected) transmits the mutation to all of her offspring. Prenatal diagnosis for MERRF is available if an mtDNA mutation has been detected in the mother. However, because the mutational load in the mother's tissues and in the fetal tissues sampled (i.e., amniocytes and chorionic villi) may not correspond to that of other fetal tissues and because the mutational load in tissues sampled prenatally may shift in

utero or after birth because of random mitotic segregation, prediction of the phenotype from prenatal studies is not possible.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of MERRF (**M**yoclonic **E**pilepsy associated with **R**agged **R**ed **F**ibers) is based on the following four "canonical" features [Fukuhara et al 1980]:

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

Additional frequent manifestations include the following [Hirano & DiMauro 1996]:

- Sensorineural hearing loss
- Peripheral neuropathy
- Dementia
- Short stature
- Exercise intolerance
- Optic atrophy

Less common clinical signs (seen in <50% of affected individuals) include the following [Hirano & DiMauro 1996]:

- Cardiomyopathy
- Pigmentary retinopathy
- Pyramidal signs
- Ophthalmoparesis
- Multiple lipomas

Testing

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

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

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

Electroencephalogram (EEG) usually shows generalized spike and wave discharges with background slowing, but focal epileptiform discharges may also be seen.

Electrocardiogram often shows pre-excitation, but heart block has not been described.

Electromyogram and nerve conduction velocity studies are consistent with a myopathy, but neuropathy may coexist.

Brain MRI often shows brain atrophy and basal ganglia calcification.

Muscle biopsy typically shows ragged-red fibers (RRF) with the modified Gomori trichrome stain and hyperactive fibers with the succinate dehydrogenase (SDH) stain. Both RRF and some non-RRF fail to stain with the histochemical reaction for cytochrome c oxidase (COX).

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.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene

- The mitochondrial DNA (mtDNA) gene *MT-TK* encoding $tRNA^{Lys}$ is the gene most commonly associated with MERRF.
- Mutations in the *MT-ND5* gene can cause overlap syndromes that include MERRF features [Crimi et al 2003, Naini et al 2005, DiMauro & Davidzon 2005, Table 3].
- One individual with the MERRF phenotype had a mutation in the gene *MT-TK* encoding $tRNA^{Phe}$ [Mancuso et al 2004].

Molecular genetic testing: Clinical uses

- Diagnostic testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis.** Four *MT-TK* mutations (A8344G, T8356C, G8363A, and G8361A) account for about 90% of mutations in individuals with MERRF. Testing for the first three mutations is available as a panel.
  - The most common mutation in MERRF, present in over 80% of affected individuals with typical findings, is A8344G [Shoffner et al 1990].
  - Three additional mutations, T8356C, G8363A, and G8361A, are present in 10% of affected individuals.

Note: (1) Mutations are usually present in all tissues and can be detected in mtDNA from blood 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, in individuals having few symptoms consistent with MERRF or in asymptomatic maternal relatives, the pathogenic mutation may be undetectable in mtDNA from leukocytes and may only be detected in other tissues, such as cultured skin fibroblasts, urinary sediment, oral mucosa (from mouthwash), hair follicles, or, most reliably, skeletal muscle.

- **Mutation scanning/sequence analysis.** The remaining 10% of affected individuals probably have other mutations in *MT-TK*, possibly including the A8296G mutation, single mtDNA deletions, the A3243G mutation most commonly seen in MELAS, the G611A mutation in *MT-TF*, or mutations in *MT-ND5*.

Note: Mutation scanning/sequence analysis is used to detect mutations throughout mtDNA and is not specific for MERRF.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in MERRF

Test Method	*MT-TK* Mutations Detected	Mutation Detection	Test Availability
Targeted mutation analysis	A8344G	>80%	Clinical Testing
	T8356C	~10%	
	G8363A		
	G8361A		
Mutation scanning/sequence analysis	*MT-TK* sequence alterations	<5%	

Interpretation of test results

- For issues to consider in interpretation of sequence analysis results, click here.
- Some of the 10% of individuals without an identifiable *MT-TK* mutation may have single mtDNA deletions, the A3243G mutation in *MT-TL1,* the G611A mutation in *MT-TF* or mutations in *MT-ND5.*

Genetically Related Disorders

A8344G mutation. The A8344G mutation can also be associated with isolated myopathy, resembling limb-girdle muscular dystrophy [Lombes et al 1989], or with multiple lipomas, usually located in the neck and shoulders area (Ekbom syndrome). Other clinical presentations of the A8344G mutation include spinocerebellar degeneration and Leigh syndrome [Howell et al 1996] or isolated Leigh syndrome [Berkovic et al 1991, Hammans et al 1993, Silvestri et al 1993].

T8356C mutation. In two families with the T8356C mutation, some affected individuals had typical MERRF but others also had stroke-like episodes and migraine (MERRF/MELAS overlap) [Zeviani et al 1993].

G8363A mutation. The G8363A mutation has been associated with typical MERRF, but also with cardiomyopathy [Santorelli et al 1996] or Leigh syndrome [Shtilbahns et al 2000].

Clinical Description

Natural History

MERRF is a multisystem disorder characterized by myoclonus, which is often the first symptom, followed by generalized epilepsy, ataxia, weakness, and dementia. Onset is usually in childhood, after a normal early development. Table 2 lists the symptoms and signs seen in 62 affected individuals [Hirano & DiMauro 1996]. About 80% (34 of 42) had a family history compatible with maternal inheritance, but not all maternal relatives were affected and not all those affected had the full MERRF picture. For example, seven oligosymptomatic relatives had "limb-girdle myopathy" as the only manifestation.

Occasionally individuals fulfilling the clinical criteria for MERRF also have strokes (MERRF/MELAS overlap) [Crimi et al 2003, Melone et al 2004, Naini et al 2005] or progressive external ophthalmoplegia and retinopathy, reminiscent of Kearns-Sayre syndrome [Nishigaki et al 2003].

Maternally inherited spinocerebellar degeneration and Leigh syndrome [Howell et al 1996], atypical Charcot-Marie-Tooth disease [Howell et al 1996], and Leigh syndrome [Lombes et al 1989, Berkovic et al 1991, Chomyn et al 1991] have been reported as unusual manifestations in families with individuals diagnosed with MERRF.

Unusual manifestations in individuals with the A8344G mutation include: (1) sudden infant death syndrome (SIDS) in an infant girl, who had an unsuspected cardiomyopathy with the histologic features of histiocytoid cardiomyopathy [Vallance et al 2004]; and (2) spasmodic dysphonia in a 46-year-old woman with otherwise fairly typical personal and family history of MERRF [Peng et al 2003].

A six-year-old boy with the G8631A mutation developed seizures and myoclonus, followed by ataxia, cognitive impairment, and sensorineural hearing loss. Maternal relatives were oligosymptomatic [Rossmanith et al 2003].

An individual with the G611A mutation had mild truncal and proximal limb weakness, cerebellar ataxia, bilateral Babinski sign, and frequent myoclonic jerks [Mancuso et al 2004].

Table 2. Signs & Symptoms Seen in 62 Individuals with MERRF

Sign / Symptom	Present / Evaluated	Percentage
Myoclonus	62/62	100
Epilepsy	62/62	100
Normal early development	17/17	100
RRF (ragged red fibers)	47/51	92
Hearing loss	41/45	91
Lactic acidosis	24/29	83
Family history	34/42	81
Exercise intolerance	8/10	80
Dementia	39/52	75
Neuropathy	17/27	63
Short stature	4/7	57
Impaired sensation	9/18	50
Optic atrophy	14/36	39
Cardiomyopathy	2/6	33
W-P-W syndrome [1]	2/9	22
Pigmentary retinopathy	4/26	15
Pyramidal signs	8/60	13
Ophthalmoparesis	3/28	11
Lipomatosis	2/60	3

Hirano & DiMauro 1996

1. Wolff-Parkinson-White

Genotype-Phenotype Correlations

No clear correlation has been identified between genotype and clinical phenotype for affected individuals, nor is it clear why typical MERRF is associated with mutations in the *MT-TK* gene of mtDNA.

For all mtDNA mutations, clinical expression depends on three factors:

- **Heteroplasmy.** The relative abundance of mutant mtDNAs
- **Tissue distribution** of mutant 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.

The selective vulnerability of the dentate nucleus of the cerebellum and the olivary nucleus of the medulla is unexplained. Also unexplained is the pathogenesis of the multiple lipomas characteristically associated with mutations in the *MT-TK* gene.

Penetrance

See Genotype-Phenotype Correlations.

Anticipation

No evidence of anticipation has been found, but knowledge of the molecular defect may favor earlier diagnosis in subsequent generations.

Nomenclature

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

Prevalence

Three epidemiologic studies of mtDNA-related diseases in northern Europe gave concordantly low estimates for the prevalence of the A8344G mutation: 0-1.5/100,000 in the adult population of northern Finland [Remes et al 2005], 0.25/100,000 in the adult population of northern England [Chinnery et al 2000], and 0-0.25/100,000 in a pediatric population of western Sweden [Darin et al 2001]. See Mitochondrial Disorders Overview for general prevalence information.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Neurologic findings. The differential diagnosis includes syndromes characterized by ataxia (such as DRPLA) (see also Hereditary Ataxia Overview) and myoclonus epilepsy, such as Unverricht-Lundborg disease, Lafora disease, neuronal lipofuscinosis, and sialidosis [Zupanc & Legros 2004]. The multisystem involvement, lactic acidosis, evidence of maternal inheritance, and the muscle biopsy with RRF (ragged red fibers) distinguish MERRF from other conditions.

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

Management

Evaluations at Initial Diagnosis

- Measurement of height and weight to assess growth
- Audiologic evaluation
- Ophthalmologic evaluation
- Assessment of cognitive abilities
- Physical therapy assessment
- Neurologic evaluation, including MRI, MRS, and EEG if seizures are suspected
- Cardiac evaluation

Treatment of Manifestations

The seizure disorder can be treated with conventional anticonvulsant therapy. No controlled studies have compared the efficacy of different anticonvulsants.

The myoclonus improved substantially in two of three indivdudals treated with levetiracetam [Crest et al 2004].

Physical therapy is helpful for any impaired motor abilities.

Aerobic exercise is helpful in MERRF and other mitochondrial diseases [Taivassalo & Haller 2004].

Standard pharmacologic therapy is used to treat cardiac symptoms.

Prevention of Primary Manifestations

No treatment for the genetic defect is currently available.

Coenzyme Q10 (100 mg three times a day) and L-carnitine (1000 mg three times a day) are often used in hopes of improving mitochondrial function.

Therapies Under Investigation

Search Clinical Trials.gov 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

MERRF is caused by mutations in mtDNA and is transmitted by maternal inheritance.

Risk to Family Members

Parents of a proband

- The father of a proband is not at risk of having the disease-causing mtDNA mutation.
- The mother of a proband (usually) has the mtDNA mutation and may or may not have symptoms.
- Alternatively, the proband may have a *de novo* (somatic) mitochondrial mutation.

Sibs of a proband

- The risk to the sibs depends upon the genetic status of the mother.
- If the mother has the mtDNA mutation, all sibs of a proband will inherit the disease-causing mtDNA mutation and may or may not have symptoms.

Offspring of a proband

- All offspring of females with an mtDNA mutation will inherit the mutation.
- Offspring of males with an mtDNA mutation are not at risk of inheriting the mutation.

Other family members of a proband

- The risk to other family members depends upon the genetic status of the proband's mother.
- If the mother has an mtDNA mutation, her sibs and mother are also at risk.

Related Genetic Counseling Issues

Phenotypic variability. The phenotype of an individual with an mtDNA mutation results from a combination of factors including the severity of the mutation, the percentage of mutant mitochondria (mutational load), and the organs and tissues in which they are found (tissue distribution). Different family members often inherit different percentages of mutant mtDNA and therefore 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.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Although results of prenatal diagnosis for MERRF cannot provide additional information, it is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The specific mtDNA mutation in the mother must be identified before prenatal diagnosis can be performed.

Interpretation of prenatal diagnostic results is complex 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.
- Prediction of phenotype, age of onset, severity, or rate of progression is not possible.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of MERRF

Gene Symbol	Chromosomal Locus	Protein Name
MT-TK	Mitochondrial	Mitochondrial tRNA lysine

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for MERRF

545000	MYOCLONIC EPILEPSY ASSOCIATED WITH RAGGED-RED FIBERS; MERRF
590060	TRANSFER RNA, MITOCHONDRIAL, LYSINE; MTTK

Table C. Genomic Databases for MERRF

Gene Symbol	HGMD
MT-TK	MT-TK

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

The origin of mtDNA mutations is uncertain. It is also unclear how the mtDNA point mutations cause MERRF. Using rho^0 cell lines (permanent human cell lines emptied of their mtDNA by exposure to ethydium bromide [King & Attardi 1989] repopulated with mitochondria harboring the A8344G mutation, 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 mutation, suggesting that the *MT-TK* mutation directly inhibits protein synthesis. Similarly, cultured myotubes containing more than 85% mutant mtDNA showed decreased translation, especially of proteins containing large numbers of lysine residues [Boulet et al 1992]. Cells harboring the A8344G mutation contained decreased levels of $tRNA^{Lys}$ and aminoacylated $tRNA^{Lys}$ [Enriquez et al 1995]. Also, the A8344G mutation blocked a modification of the $tRNA^{Lys}$, resulting in impaired protein synthesis [Yasukawa et al 2001]. The mutation 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 A8344G or the T8356C mutation, and identified aberrant mitochondrial protein in both cell lines, which they attributed to ribosomal frame-shifting. Studies of engineered in vitro transcribed $tRNA^{Lys}$ mutants showed that the mutations associated with MERRF had no effect on lysylation efficiency whereas the

two mutations associated with encephalomyopathies without typical MERRF features (G8313A and G8328A) severely impaired lysylation [Sissler et al 2004].

Normal allelic variants: *MT-TK* is the only mtDNA gene that encodes $tRNA^{Lys}$, which is indispensable for proper lysylation of proteins.

Pathologic allelic variants: A8344G, T8356C, G8363A, G8361A, G611A, A13084T, and G13042A

Normal gene product: The normal gene product, $tRNA^{Lys}$, is indispensable for the lysylation of nascent mitochondrial proteins.

Abnormal gene product: See Molecular Genetic Pathogenesis.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

United Mitochondrial Disease Foundation
8085 Saltsburg Road, Suite 201
Pittsburg, PA 15239
Phone: 412-793-8077
Fax: 412-793-6477
Email: info@umdf.org
www.umdf.org

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson, AZ 85718-3208
Phone: 800-572-1717; 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Berkovic S, Shoubridge E, Andermann F, Carpenter S. Clinical spectrum of mitochondrial DNA mutations at base pair 8344. Lancet. 1991;338:457. [PubMed: 1678125]

Boulet L, Karpati G, Shoubridge EA. Distribution and threshold expression of the tRNA(Lys) mutation in skeletal muscle of patients with myoclonic epilepsy and ragged-red fibers (MERRF). Am J Hum Genet. 1992;51:1187–200. [PubMed: 1334369]

Chinnery PF, Johnson MA, Wardell TM, Singh-Kler R, Hayes C, Brown DT, Taylor RW, Bindoff LA, Turnbull DM. The epidemiology of pathogenic mitochondrial DNA mutations. Ann Neurol. 2000;48:188–93. [PubMed: 10939569]

Chomyn A, Meola G, Bresolin N, Lai ST, Scarlato G, Attardi G. In vitro genetic transfer of protein synthesis and respiration defects to mitochondrial DNA-less cells with myopathy-patient mitochondria. Mol Cell Biol. 1991;11:2236–44. [PubMed: 1848674]

Crest C, Dupont S, Leguern E, Adam C, Baulac M. Levetiracetam in progressive myoclonic epilepsy: an exploratory study in 9 patients. Neurology. 2004;62:640–3. [PubMed: 14981187]

Crimi M, Galbiati S, Moroni I, Bordoni A, Perini MP, Lamantea E, Sciacco M, Zeviani M, Biunno I, Moggio M, Scarlato G, Comi GP. A missense mutation in the mitochondrial ND5 gene associated with a Leigh-MELAS overlap syndrome. Neurology. 2003;60:1857–61. [PubMed: 12796552]

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. [PubMed: 11261513]

Dimauro S, Davidzon G. Mitochondrial DNA and disease. Ann Med. 2005;37:222–32. [PubMed: 16019721]

Enriquez JA, Chomyn A, Attardi G. MtDNA mutation in MERRF syndrome causes defective aminoacylation of tRNA(Lys) and premature translation termination. Nat Genet. 1995;10:47–55. [PubMed: 7647790]

Fukuhara N, Tokiguchi S, Shirakawa K, Tsubaki T. Myoclonus epilepsy associated with ragged-red fibres (mitochondrial abnormalities): disease entity or a syndrome? Light-and electron-microscopic studies of two cases and review of literature. J Neurol Sci. 1980;47:117–33. [PubMed: 6774061]

Hammans SR, Sweeney MG, Brockington M, Lennox GG, Lawton NF, Kennedy CR, Morgan-Hughes JA, Harding AE. The mitochondrial DNA transfer RNA(Lys)A-->G(8344) mutation and the syndrome of myoclonic epilepsy with ragged red fibres (MERRF). Relationship of clinical phenotype to proportion of mutant mitochondrial DNA. Brain 116 (Pt. 1993;3):617–32. [PubMed: 8513395]

Hirano M, DiMauro S. Clinical features of mitochondrial myopathies and encephalomyopathies. In: Lane RJM (ed) Handbook of Muscle Disease, Vol 1. Marcel Dekker Inc, New York, pp 479-504. 1996

Howell N, Kubacka I, Smith R, Frerman F, Parks JK, Parker WD Jr. Association of the mitochondrial 8344 MERRF mutation with maternally inherited spinocerebellar degeneration and Leigh disease. Neurology. 1996;46:219–22. [PubMed: 8559379]

Hunt J. Dyssynergia cerebellaris myoclonia-primary atrophy of the dentate system: a contribution to the pathology and symptomatology of the cerebellum. Brain. 1921;44:490–538.

King MP, Attardi G. Human cells lacking mtDNA: repopulation with exogenous mitochondria by complementation. Science. 1989;246:500–3. [PubMed: 2814477]

Lombes A, Mendell JR, Nakase H, Barohn RJ, Bonilla E, Zeviani M, Yates AJ, Omerza J, Gales TL, Nakahara K, et al. Myoclonic epilepsy and ragged-red fibers with cytochrome oxidase deficiency: neuropathology, biochemistry, and molecular genetics. Ann Neurol. 1989;26:20–33. [PubMed: 2549843]

Mancuso M, Filosto M, Mootha VK, Rocchi A, Pistolesi S, Murri L, DiMauro S, Siciliano G. A novel mitochondrial tRNAPhe mutation causes MERRF syndrome. Neurology. 2004;62:2119–21. [PubMed: 15184630]

Masucci JP, Davidson M, Koga Y, Schon EA, King MP. In vitro analysis of mutations causing myoclonus epilepsy with ragged-red fibers in the mitochondrial tRNA(Lys)gene: two genotypes produce similar phenotypes. Mol Cell Biol. 1995;15:2872–81. [PubMed: 7739567]

Melone MA, Tessa A, Petrini S, Lus G, Sampaolo S, di Fede G, Santorelli FM, Cotrufo R. Revelation of a new mitochondrial DNA mutation (G12147A) in a MELAS/MERFF phenotype. Arch Neurol. 2004;61:269–72. [PubMed: 14967777]

Naini AB, Lu J, Kaufmann P, Bernstein RA, Mancuso M, Bonilla E, Hirano M, DiMauro S. Novel mitochondrial DNA ND5 mutation in a patient with clinical features of MELAS and MERRF. Arch Neurol. 2005;62:473–6. [PubMed: 15767514]

Nishigaki Y, Tadesse S, Bonilla E, Shungu D, Hersh S, Keats BJ, Berlin CI, Goldberg MF, Vockley J, DiMauro S, Hirano M. A novel mitochondrial tRNA(Leu(UUR)) mutation in a patient with features

of MERRF and Kearns-Sayre syndrome. Neuromuscul Disord. 2003;13:334–40. [PubMed: 12868503]

Peng Y, Crumley R, Ringman JM. Spasmodic dysphonia in a patient with the A to G transition at nucleotide 8344 in mitochondrial DNA. Mov Disord. 2003;18:716–8. [PubMed: 12784281]

Remes AM, Majamaa-Voltti K, Karppa M, Moilanen JS, Uimonen S, Helander H, Rusanen H, Salmela PI, Sorri M, Hassinen IE, Majamaa K. Prevalence of large-scale mitochondrial DNA deletions in an adult Finnish population. Neurology. 2005;64:976–81. [PubMed: 15781811]

Rossmanith W, Raffelsberger T, Roka J, Kornek B, Feucht M, Bittner RE. The expanding mutational spectrum of MERRF substitution G8361A in the mitochondrial tRNALys gene. Ann Neurol. 2003;54:820–3. [PubMed: 14681892]

Santorelli FM, Mak SC, El-Schahawi M, Casali C, Shanske S, Baram TZ, Madrid RE, DiMauro S. Maternally inherited cardiomyopathy and hearing loss associated with a novel mutation in the mitochondrial tRNA(Lys) gene (G8363A). Am J Hum Genet. 1996;58:933–9. [PubMed: 8651277]

Shoffner JM, Lott MT, Lezza AM, Seibel P, Ballinger SW, Wallace DC. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA(Lys) mutation. Cell. 1990;61:931–7. [PubMed: 2112427]

Shtilbans A, Shanske S, Goodman S, Sue CM, Bruno C, Johnson TL, Lava NS, Waheed N, DiMauro S. G8363A mutation in the mitochondrial DNA transfer ribonucleic acidLys gene: another cause of Leigh syndrome. J Child Neurol. 2000;15:759–61. [PubMed: 11108511]

Silvestri G, Ciafaloni E, Santorelli FM, Shanske S, Servidei S, Graf WD, Sumi M, DiMauro S. Clinical features associated with the A-->G transition at nucleotide 8344 of mtDNA ("MERRF mutation"). Neurology. 1993;43:1200–6. [PubMed: 8170567]

Sissler M, Helm M, Frugier M, Giege R, Florentz C. Aminoacylation properties of pathology-related human mitochondrial tRNA(Lys) variants. RNA. 2004;10:841–53. [PubMed: 15100439]

Taivassalo T, Haller RG. Implications of exercise training in mtDNA defects--use it or lose it? Biochim Biophys Acta. 2004;1659:221–31. [PubMed: 15576055]

Vallance HD, Jeven G, Wallace DC, Brown MD. A case of sporadic infantile histiocytoid cardiomyopathy caused by the A8344G (MERRF) mitochondrial DNA mutation. Pediatr Cardiol. 2004;25:538–40. [PubMed: 15164143]

Yasukawa T, Suzuki T, Ishii N, Ohta S, Watanabe K. Wobble modification defect in tRNA disturbs codon-anticodon interaction in a mitochondrial disease. EMBO J. 2001;20:4794–802. [PubMed: 11532943]

Zeviani M, Muntoni F, Savarese N, Serra G, Tiranti V, Carrara F, Mariotti C, DiDonato S. A MERRF/MELAS overlap syndrome associated with a new point mutation in the mitochondrial DNA tRNA (Lys) gene. Eur J Hum Genet. 1993;1:80–7. [PubMed: 8069654]

Zupanc ML, Legros B. Progressive myoclonic epilepsy. Cerebellum. 2004;3:156–71. [PubMed: 15543806]

Chapter Notes

Revision History

- 27 September 2005 (me) Comprehensive update posted to live Web site
- 3 June 2003 (ca) Review posted to live Web site
- 8 May 2003 (sdm) Original submission