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RRM2B Mitochondrial DNA Maintenance Defects

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Summary

Clinical characteristics

Four phenotypes comprise the *RRM2B* mitochondrial DNA maintenance defects (*RRM2B*-MDMDs):

- ***RRM2B* encephalomyopathic MDMD,** the most severe phenotype, usually manifesting shortly after birth as hypotonia, poor feeding, and faltering growth requiring hospitalization. Subsequent assessments are likely to reveal multisystem involvement including sensorineural hearing loss, renal tubulopathy, and respiratory failure.
- **Autosomal dominant progressive external ophthalmoplegia (adPEO),** typically adult onset; other manifestations can include ptosis, bulbar dysfunction, fatigue, and muscle weakness.
- ***RRM2B* autosomal recessive progressive external ophthalmoplegia (arPEO),** a typically childhood-onset predominantly myopathic phenotype of PEO, ptosis, proximal muscle weakness, and bulbar dysfunction
- ***RRM2B* mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like,** characterized by progressive ptosis, ophthalmoplegia, gastrointestinal dysmotility, cachexia, and peripheral neuropathy.

To date, 78 individuals from 52 families with a molecularly confirmed *RRM2B*-MDMD have been reported.

Diagnosis/testing

The diagnosis of an *RRM2B*-MDMD is established in a proband with suggestive findings and either biallelic *RRM2B* pathogenic variants or a heterozygous *RRM2B* pathogenic variant identified by molecular genetic testing.

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Management

Treatment of manifestations: To date, there are no known cures and few effective treatments for any forms of mitochondrial disease, including the *RRM2B*-MDMDs. Treatment modalities focusing on symptomatic management and supportive care are best implemented by a multidisciplinary team.

Surveillance: Because most infants and young children with the encephalomyopathic phenotype are severely affected and are hospitalized for prolonged periods, monitoring typically occurs regularly by senior clinical specialists. Individuals with the other phenotypes warrant routine monitoring based on their clinical findings, rate of disease progression, and response to interventions.

Agents/circumstances to avoid: Valproic acid should be used only in exceptional circumstances. Use of prescription drugs should always take into consideration the specific needs of and potential risks for the affected individual.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of at-risk relatives of an affected family member so that those with the *RRM2B* pathogenic variant(s) can undergo timely routine surveillance for disease complications and avoid possible precipitating factors.

Genetic counseling

With the exception of autosomal dominant progressive external ophthalmoplegia, *RRM2B* mitochondrial DNA maintenance defects – *RRM2B* encephalomyopathic MDMD, *RRM2B* MNGIE-like, and *RRM2B*-arPEO – are inherited in an autosomal recessive manner.

- **Autosomal recessive inheritance.** If both parents are known to be heterozygous for an *RRM2B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *RRM2B* pathogenic variants and being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *RRM2B* pathogenic variants.
- **Autosomal dominant inheritance.** If a parent of the proband is affected and/or is known to have the *RRM2B* pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%.

Once the *RRM2B* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for *RRM2B*-MDMD are possible.

GeneReview Scope

***RRM2B* Mitochondrial DNA Maintenance Defects (MDMD): Included Phenotypes**

Relative Prevalence [1]	Disorder	Disease Pathogenesis
Common	*RRM2B* encephalomyopathic MDMD [2]	Mitochondrial DNA depletion
	RRM2B autosomal dominant progressive external ophthalmoplegia (adPEO)	Accumulation of clonally expanded (multiple) mtDNA deletions causes tissue-specific COX deficiency.

RRM2B Mitochondrial DNA continued from previous page.

Relative Prevalence [1]	Disorder	Disease Pathogenesis
Rare	*RRM2B* autosomal recessive progressive external ophthalmoplegia (arPEO)	Accumulation of clonally expanded (multiple) mtDNA deletions causes tissue-specific COX deficiency.
	RRM2B mitochondrial neurogastrointestinal encephalopathy (MNGIE) [3]	Mitochondrial DNA depletion

COX = cytochrome *c* oxidase; mtDNA = mitochondrial DNA

1. No true epidemiologic study is available to assess the exact prevalence for each of these disorders.

2. Previously referred to as mtDNA depletion syndrome 8A (encephalomyopathic type with renal tubulopathy) or *RRM2B*-MDS (with renal tubulopathy)

3. Previously referred to as mtDNA depletion syndrome 8B

Diagnosis

Suggestive Findings

RRM2B mitochondrial DNA maintenance defects should be suspected in individuals with suggestive findings of the two common phenotypes and considered in those with suggestive findings of the two rare phenotypes; the diagnosis should be informed by family history.

Note: While muscle biopsy is not required to consider this diagnosis, muscle biopsy findings – in the event that one was obtained for other reasons – may include cytochrome *c* oxidase (COX)-deficient fibers and subsarcolemmal mitochondrial accumulation (classic "ragged-red" fibers).

Common Phenotypes

***RRM2B* encephalomyopathic mitochondrial DNA maintenance defect (MDMD)** should be suspected in children with combinations of the following clinical and laboratory findings and family history:

- **Clinical findings**
  - Myopathy manifesting as muscle hypotonia and weakness, often associated with respiratory insufficiency/failure
  - CNS findings including seizures, developmental delay, microcephaly, faltering growth
  - Sensorineural hearing loss
  - Proximal renal tubulopathy with nephrocalcinosis
  - Gastrointestinal disturbance manifesting as dysmotility or feeding difficulties
- **Laboratory findings.** Lactic acidemia
- **Family history** consistent with autosomal recessive inheritance (e.g., affected sibs). The possibility of consanguinity should be explored if the family history is consistent with autosomal recessive inheritance, especially if the proband has severe, early onset disease. However, absence of a known family history does not preclude the diagnosis.

***RRM2B* autosomal dominant progressive external ophthalmoplegia (adPEO)** should be suspected in adults with combinations of the following clinical findings and family history:

- **Clinical findings**
  - Progressive external ophthalmoplegia
  - Ptosis of variable severity
  - Sensorineural hearing loss
  - Proximal muscle weakness and fatigue

- Bulbar dysfunction
- Gastrointestinal issues, including irritable bowel syndrome-like symptoms and low body mass index, cachexia
- CNS findings either absent or minimal (including ataxia, cognitive dysfunction, and mood disturbance)
- Sensory axonal peripheral neuropathy
- Endocrinopathy (including hypothyroidism, hypoparathyroidism, diabetes mellitus, and hypogonadism)

- **Family history** consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations)

  Note: Absence of a known family history does not preclude the diagnosis.

Rare Phenotypes

***RRM2B* autosomal recessive progressive external ophthalmoplegia (arPEO),** typically presenting with multisystem involvement and more severe phenotypes than adPEO, should be suspected in individuals with a Kearns-Sayre-like syndrome when inheritance appears to follow a mendelian pattern and/or examination of muscle tissue reveals evidence of multiple mtDNA deletions.

***RRM2B* mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like**, a rarer phenotype that mimics other mitochondrial syndromes, should be suspected when plasma thymidine concentration is normal (<3 µmol/L), plasma deoxyuridine concentration is normal (<5 µmol/L), thymidine phosphorylase enzyme activity in leukocytes is normal (>10% of the control mean), and molecular genetic testing does not identify biallelic pathogenic variants in *TYMP,* the gene encoding thymidine phosphorylase.

Establishing the Diagnosis

The diagnosis of an *RRM2B* mitochondrial DNA maintenance defect (*RRM2B*-MDMD) **is established** in a proband with suggestive findings and either biallelic *RRM2B* pathogenic (or likely pathogenic) variants or a heterozygous *RRM2B* pathogenic (or likely pathogenic) variant identified by molecular genetic testing (see Table 1). Note: 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.

- The identification of biallelic *RRM2B* variants of uncertain significance * (or of one known *RRM2B* pathogenic variant and one *RRM2B* variant of uncertain significance) does not establish or rule out the diagnosis of an autosomal recessive *RRM2B*-MDMD.
- The identification of a heterozygous *RRM2B* variant of uncertain significance * does not establish or rule out the diagnosis of an autosomal dominant *RRM2B*-MDMD.

* Note: The authors of this chapter have offered to review *RRM2B* variants of uncertain significance with clinicians; see Chapter Notes.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing).

Note: Single-gene testing (sequence analysis of *RRM2B*, followed by gene-targeted deletion/duplication analysis) is now rarely recommended with regard to establishing a genetic diagnosis of mitochondrial disease. Overlapping phenotypes with common clinical features demand a much broader approach employing, for example, use of a mitochondrial multigene panel analysis or exome sequencing.

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 in whom the diagnosis of *RRM2B*-MDMD has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A multigene panel that includes *RRM2B* 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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used, although **genome sequencing** is becoming more widely available.

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 *RRM2B* Mitochondrial DNA Maintenance Defects

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
RRM2B	Sequence analysis [3]	~97% [4]
	Gene-targeted deletion/duplication analysis [5]	~3% [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 [2017], Keshavan et al [2020]
5. 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

RRM2B mitochondrial DNA maintenance defects (*RRM2B*-MDMD) are an important cause of both childhood- and adult-onset mitochondrial disease. To date, 78 individuals from 52 families with molecularly confirmed *RRM2B*-MDMD have been reported. In general, the clinical manifestations are similar in males and females.

RRM2B-MDMD can, for the most part, be broadly categorized into two main groups: mtDNA depletion and multiple mtDNA deletions; and further characterized by phenotype, mode of inheritance, and disease pathogenesis (Table 2).

The two common forms of *RRM2B*-MDMD are *RRM2B* encephalomyopathic MDMD (the most severe form) and RRM2B autosomal dominant progressive external ophthalmoplegia (adPEO) (typically adult onset).

The two rare phenotypes – *RRM2B* mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like and autosomal recessive progressive external ophthalmoplegia (arPEO) – are described briefly in this section. See Rare Forms.

Table 2. Phenotypic Spectrum of *RRM2B* Mitochondrial DNA Maintenance Defects

Relative Prevalence	Phenotype	MOI	Onset	Comments	Disease Pathogenesis
Common	*RRM2B* encephalomyopathic MDMD	AR	Infancy	Severe multisystem disease often fatal in early life	mtDNA depletion
	adPEO [1]	AD	Adulthood	Milder & often tissue-specific	Clonally expanded (multiple) mtDNA deletions [2]
Rare	MNGIE [3]	AR	Childhood or adulthood	GI dysmotility, PEO, ptosis, peripheral neuropathy & leukoencephalopathy	mtDNA depletion
	arPEO [1]	AR	Early childhood or adulthood	Multisystem involvement & Kearns-Sayre syndrome-like [4]	Clonally expanded (multiple) mtDNA deletions [2]

AD = autosomal dominant; AR = autosomal recessive; GI = gastrointestinal; MDMD = mitochondrial DNA maintenance defects; MOI = mode of inheritance; MNGIE = mitochondrial neurogastrointestinal encephalopathy; PEO = progressive external ophthalmoplegia

1. For review of the adPEO and arPEO phenotypes, see *POLG*-Related Disorders.

2. Accumulation of clonally expanded (multiple) mtDNA deletions causes tissue-specific cytochrome *c* oxidase (COX) deficiency.

3. For review of the MNGIE phenotype, see Mitochondrial Neurogastrointestinal Encephalopathy Disease.

4. For review of the Kearns-Sayre syndrome phenotype, see Mitochondrial DNA Deletion Syndromes.

RRM2B Encephalomyopathic MDMD

RRM2B encephalomyopathic MDMD, reported in 31 children, is the most severe form of *RRM2B*-MDMD, manifesting shortly after birth as hypotonia, poor feeding, and faltering growth (previously known as failure to thrive) requiring hospitalization. Subsequent assessments are likely to reveal multisystem involvement including sensorineural hearing loss, renal tubulopathy, and respiratory failure (see Table 3) [Bourdon et al 2007, Bornstein et al 2008, Acham-Roschitz et al 2009, Kollberg et al 2009, Shaibani et al 2009, Spinazzola et al 2009, Stojanovic et al 2013, Pronicka et al 2016, Iwanicka-Pronicka et al 2019, Penque et al 2019, Keshavan et al 2020].

Table 3. Select Clinical Features of *RRM2B* Encephalomyopathic MDMD

Feature	# of Children [1] w/Feature (%)	Comment
Neuromuscular	31 (100%)	Truncal hypotonia (almost universally present) gross motor delay, feeding difficulties, poor head control, generalized weakness, areflexia, ptosis, PEO, discoordinated swallow, exercise intolerance

Table 3. continued from previous page.

Feature		# of Children [1] w/Feature (%)	Comment
Nervous system	**Central**	1-15 (3%-48%)	Encephalopathy: gross motor delay, seizures, focal &/or generalized UMN signs, microcephaly, neurologic regression, dystonia. MRI shows central hypomyelination, cerebral atrophy
	Peripheral	2 (6%)	Demyelinating peripheral neuropathy
Respiratory		18 (58%)	Respiratory distress, respiratory failure. In some cases artificial ventilation may prolong life span.
Renal		17 (55%)	Tubulopathy (proximal), nephrocalcinosis, aminoaciduria, glycosuria, lactic acidemia, hypocalcemia
Faltering growth (previously known as failure to thrive)		16 (52%)	Likely due to multisystem involvement
Hearing loss		11 (35%)	Sensorineural hearing loss may only be identified on formal assessment.
Gastrointestinal		10 (32%)	Recurrent vomiting, feed intolerance, chronic diarrhea, cachexia
Eye		4 (13%)	Ophthalmoparesis, pigmentary retinopathy (rod-cone dystrophy), cataracts, megalocornea, blindness, nystagmus
Cardiovascular		4 (13%)	Left ventricular hypertrophy, cardiomyopathy, ventricular septal defect

Based on Keshavan et al [2020]
PEO = progressive external ophthalmoplegia; UMN = upper motor neuron
1. n = 31

Onset is typically in the first few months of life; affected children succumb in early childhood. Disease characteristics include myopathy manifesting as hypotonia, weakness associated with respiratory insufficiency, faltering growth (failure to thrive), and proximal renal tubulopathy.

Central nervous system (CNS) features can include encephalopathy (15 affected individuals), gross motor delay (15), feeding difficulties (14), seizures (12), and sensorineural hearing loss (11). Other less frequently reported CNS manifestations include cerebral atrophy, and generalized central hypomyelination.

Given the multisystem involvement, most infants with the encephalomyopathic phenotype have faltering growth and a poor prognosis.

RRM2B Autosomal Dominant Progressive External Ophthalmoplegia

RRM2B autosomal dominant progressive external ophthalmoplegia (adPEO) is characterized by a slowly progressive loss of function of the muscles that move the eye and retract the eyelid. The phenotype is a mild myopathy with proximal muscle weakness, bulbar dysfunction, and fatigue (see Table 4) [Shaibani et al 2009, Fratter et al 2011, Pitceathly et al 2012, Sommerville et al 2014]. Mean age of disease onset is 46 years.

Table 4. Select Features of *RRM2B* Autosomal Dominant Progressive External Ophthalmoplegia

Feature		# of Persons [1] w/Feature (%)
Ophthalmologic	**PEO**	42 (100%)
	Ptosis	40 (95%)
Neuromuscular	**Myopathy**	37 (88%)
	Exercise intolerance	33 (79%)

Table 4. continued from previous page.

Feature		# of Persons [1] w/Feature (%)
Central nervous system	**Cerebellar ataxia**	35 (83%)
	Sensorineural hearing loss	26 (62%)
	Cognitive dysfunction	24 (57%)
	Bulbar dysfunction	9 (21%)
Mood disturbance		20 (48%)
Low body mass index		9 (21%)
Gastrointestinal dysmotility		6 (14%)

Based on Pitceathly et al [2012] and Sommerville et al [2014]
PEO = progressive external ophthalmoplegia
1. n = 42

The first individuals reported were from two large, unrelated families with autosomal dominant PEO [Tyynismaa et al 2009]. From published cases, the cardinal features of *RRM2B* adPEO are PEO and ptosis. Other commonly reported findings include myopathy, exercise intolerance, cerebellar ataxia, sensorineural hearing loss, cognitive dysfunction, mood disturbance, bulbar dysfunction and low body mass index. These features may have variable age of onset and severity.

Rare Forms of *RRM2B*-MDMD

***RRM2B* autosomal recessive progressive external ophthalmoplegia (arPEO).** Disease onset was at a mean age of seven years in reported cases. The predominantly myopathic phenotype of PEO, ptosis, proximal muscle weakness, and bulbar dysfunction was more severe than the multisystem disorder observed in individuals with a heterozygous *RRM2B* pathogenic variant [Pitceathly et al 2012].

A homozygous missense pathogenic variant in *RRM2B* in a man age 43 years who presented at age 16 years was associated with progressive hearing loss followed by the insidious onset of PEO, muscle weakness, retinopathy, and a major depressive disorder – findings that further extend the phenotype [Takata et al 2011].

Kearns-Sayre-like syndrome (KSS) was reported in two individuals with onset before age 20 years of PEO-plus / Kearns-Sayre syndrome (PEO, pigmentary retinopathy, sensorineural hearing loss, and increased CSF protein documented in one and renal tubulopathy in the other, similar to single mtDNA deletion disorders) [Pitceathly et al 2011, Wilichowski et al 2013]. See Mitochondrial DNA Deletion Syndromes, which includes KSS.

***RRM2B* mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like** was reported in a woman age 42 years with *RRM2B* biallelic missense pathogenic variants and mtDNA depletion in clinically relevant tissues [Shaibani et al 2009]. She had a 12-year history of progressive ptosis, ophthalmoplegia, gastrointestinal dysmotility, cachexia, peripheral neuropathy, and brain magnetic resonance imaging changes. For more information about this phenotype, see Mitochondrial DNA Maintenance Defects Overview, which includes MNGIE.

Genotype-Phenotype Correlations

Defining the genotype-phenotype correlations in *RRM2B*-MDMD remains challenging as the same *RRM2B* pathogenic variants are associated with varied phenotypic severity depending on whether they are biallelic or heterozygous. See Figure 1.

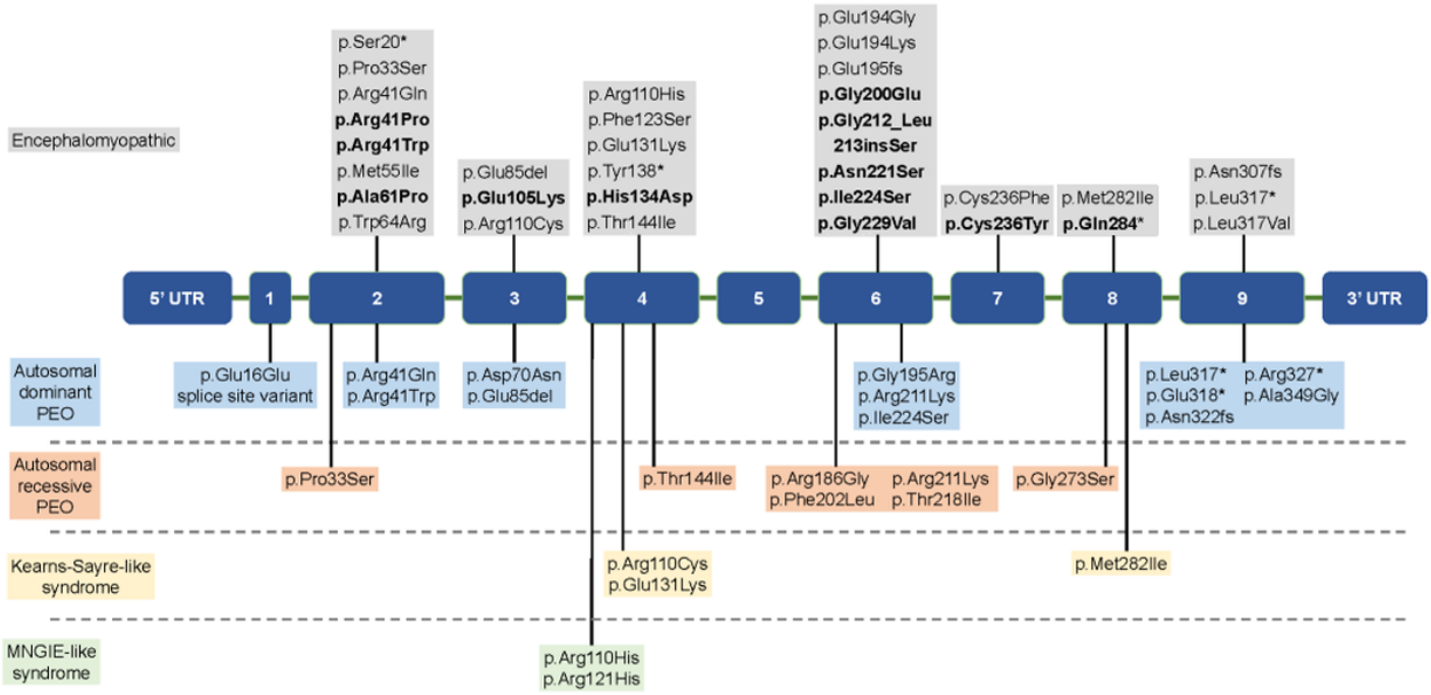

Figure 1. Schematic representation of the *RRM2B* gene structure (NM_015713.5) illustrating reported pathogenic variants. Coding exons are numbered 1 to 9. *RRM2B* variants associated with encephalomyopathic phenotype are highlighted in grey, autosomal dominant PEO are highlighted in light blue, autosomal recessive PEO are highlighted in pink, Kearns-Sayre-like syndrome are highlighted in light yellow, and MNGIE-like syndrome are highlighted in light green. The variants in bold associated with an encephalomyopathic phenotype have been reported as homozygous changes. Some variants are reported across different phenotypes.

Prevalence

The prevalence of *RRM2B*-MDMD is unknown.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *RRM2B*.

Differential Diagnosis

To date, pathogenic variants in 20 nuclear genes are known to be associated with mtDNA maintenance defects (see Mitochondrial DNA Maintenance Defects Overview). These genes and their primary presenting features are organized in Table 5 by the category of the defect: mtDNA synthesis, mitochondrial nucleotide salvage pathway, cytosolic nucleotide metabolism, mitochondrial nucleotide import, and mitochondrial fusion.

Note: As is apparent in Table 5, mitochondrial disease phenotypes are associated with significant locus heterogeneity (i.e., multiple genes can be associated with the same clinical features). For this reason, single-gene testing is rarely useful; use of multigene panels that target all nuclear genes known to be associated with mitochondrial disorders is recommended to establish a molecular diagnosis of mitochondrial disease.

Table 5. Categories of mtDNA Maintenance Defects: Genes and Primary Presenting Features

Category of Defect	Gene	Primary Presenting Features							
		Encephalo-hepatopathy	Encephalo-myopathy	Encephalo-neuropathy	Neurogastro-intestinal encephalopathy (MNGIE)-like	Myopathy	Ophthal-moplegia [1]	Optic atrophy	Neuropathy
MtDNA synthesis	*POLG*	X	X	X	X	X	X		
	POLG2					X			
	TWNK	X		X			X		
	TFAM	X							
	RNASEH1		X						
	MGME1					X			
	DNA2					X			
Mt nucleotide salvage pathway	*TK2*					X	X		
	DGUOK	X				X			
	SUCLA2		X						
	SUCLG1		X						
	ABAT		X						
Cytosolic nucleotide metabolism	*TYMP*				X				
	RRM2B		**X**		**X**		**X**		
Mt nucleotide import	*SLC25A4*					X	X		
	AGK					X			
	MPV17	X							X
Mt fusion	*OPA1*		X	X				X	
	MFN2							X	X
	FBXL4		X						

MNGIE = mitochondrial neurogastrointestinal encephalopathy; Mt = Mitochondrial

1. RRM2B pathogenic variants are the third largest cause of adult-onset CPEO after pathogenic variants in *POLG* and *TWNK* [Sommerville et al 2014].

Kearns-Sayre syndrome (KSS) associated with a mitochondrial DNA deletion (see Mitochondrial DNA Deletion Syndromes). KSS, a progressive multisystem disorder defined by onset before age 20 years, pigmentary retinopathy, and progressive external ophthalmoplegia, is caused by a single large-scale deletion in the mtDNA genome ranging in size from 1.1 to 10 kb. Large-scale mtDNA deletion is a common cause of mitochondrial disease and occurs in simplex cases (i.e., a single affected family member) with very rare exceptions.

Management

No clinical guidelines specific to *RRM2B* mitochondrial DNA maintenance defects (*RRM2B*-MDMD) are available; however, detailed evaluations are outlined in the Wellcome Centre for Mitochondrial Research Clinical Guidelines.

The management of the two common phenotypes, *RRM2B*-MDMD encephalomyopathic form and *RRM2B* autosomal dominant progressive external ophthalmoplegia (adPEO), is discussed below.

For management of the two rare phenotypes, mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like disease and Kearns-Sayre syndrome-like, see Mitochondrial DNA Maintenance Defects Overview and Mitochondrial DNA Deletion Syndromes, respectively.

Evaluations Following Initial Diagnosis

RRM2B-MDMD, Encephalomyopathic Form

To establish the extent of disease and needs in an individual diagnosed with *RRM2B*-MDMD encephalomyopathic form, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis of *RRM2B*-MDMD, Encephalomyopathic Form

System/Concern	Evaluation	Comment
Constitutional	Measure length, weight, head circumference.	Plot measurements serially on growth charts.
Neuromuscular	By pediatric neurologist	• Assess functional neurologic status. • EEG & brain imaging if seizures suspected
	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Need for adaptive devices
	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Respiratory	Referral to pediatric pulmonologist for children w/evidence of ↓ respiratory function	Assessment may incl consideration of tracheostomy & artificial ventilation. (See **Ethics consultation**.)
Renal	Referral to pediatric nephrologist	To evaluate for proximal renal tubulopathy
GI/Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval for gastrointestinal dysmotility, aspiration risk & nutritional status • Consider eval for gastric tube placement in persons w/dysphagia &/or aspiration risk.
Hearing	Audiologic eval	For sensorineural hearing loss
Eyes	• Bedside fundoscopy • Visual acuity testing • Ptosis & CPEO assessment	• Early ophthalmology involvement • Clinical photographs for comparison of ptosis
Cardiovascular	Basic EKG if any clinical evidence of cardiac disease	Routine echocardiography not clinically indicated

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Genetic Counseling	By healthcare practitioner w/experience in both genetic counseling & mitochondrial disease	To inform family re nature, MOI & implications of *RRM2B*-MDMD in order to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community resources & support/advocacy organizations (e.g., Parent to Parent); • Social work involvement for parental support; • Home nursing referral.
Ethics consultation	Clinical ethics services	• Assess healthcare decisions in the context of the best interest of the child & values & preferences of the family. • For difficult life-prolonging decisions or for clarification of treatment options, consider further consultation w/independent clinical teams. [1]

MOI = mode of inheritance
1. Linney et al [2019]

RRM2B-MDMD Progressive External Ophthalmoplegia

To establish the extent of disease and needs in an individual diagnosed with *RRM2B*-MDMD progressive external ophthalmoplegia, the evaluations summarized in Table 7 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 7. Recommended Evaluations Following Initial Diagnosis of *RRM2B*-MDMD Progressive External Ophthalmoplegia

System/Concern	Evaluation	Comment
Eyes	Complete ophthalmologic exam	• Assess best corrected visual acuity; nystagmus, saccades & smooth pursuit; vertical & horizontal gaze limitation; ptosis. • Consider need for corrective measures incl prisms &/or surgery
Neurologic	Neurologist: assess for cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades & smooth pursuit).	Use standardized scale to establish baseline for ataxia (SARA, ICARS, or BARS). [1]
	Assess for myopathy (weakness, sensory loss)	
Speech	For those w/dysarthria: speech/language eval	Consider referral to speech & language pathologist.
Bulbar dysfunction	For those w/frequent choking or severe dysphagia, assess: • Nutritional status; • Aspiration risk.	Consider involving a gastroenterology/nutrition/feeding team, incl formal swallowing eval.

Table 7. continued from previous page.

System/Concern	Evaluation	Comment
Mobility/ADL	Orthopedics / physical medicine & rehab / PT eval	To incl assessment of: • Muscle tone; joint range of motion; posture; mobility; strength, coordination & endurance; pain; bedsores • Need for adaptive devices • Footwear needs • PT needs
	OT	To assess • Small motor function (e.g., hands, feet, face, fingers, toes) • ADL
Cognitive/ Psychiatric	Assess for cognitive dysfunction assoc w/ cerebellar cognitive affective syndrome (executive function, language processing, visuospatial/visuoconstructional skills, emotion regulation)	Consider use of: • CCAS Scale to evaluate cognitive & emotional involvement; • Psychiatrist, psychologist, neuropsychologist if needed.
Gastrointestinal dysmotility	Gastroenterology follow up	• Measure height & weight. • Calculate BMI. • Serial weight measurement
Sensorineural hearing loss	Complete audiologic exam incl hearing test, BAEP	Consider hearing aids, cochlear implant
Speech & language	Eval by speech & language pathologist	
Endocrinopathy	Eval by endocrinologist	For diabetes mellitus, hypothyroidism, hypoparathyroidism, hypogonadism
Genetic Counseling	By healthcare practitioner w/experience in both genetic counseling & mitochondrial disease	To inform affected persons & their family re nature, MOI, & implications of *RRM2B*-MDMD to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community resources & support/advocacy organizations; • Social work involvement for parental support; • Home nursing referral.

ADL = activities of daily living; BAEP = brain stem auditory evoked potentials; BARS = Brief Ataxia Rating Scale; BMI = body mass index; CCAS = cerebellar cognitive affective syndrome; ICARS = International Co-operative Ataxia Rating Scale; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia
1. Bürk & Sival [2018]

Treatment of Manifestations

To date, there are no known cures and few effective treatments for any forms of mitochondrial disease, including *RRM2B*-MDMD. Treatment modalities currently focus on symptomatic management and supportive care and are best implemented by a multidisciplinary team.

RRM2B-MDMD, Encephalomyopathic Form

Table 8. Treatment of Manifestations of *RRM2B*-MDMD, Encephalomyopathic Form

Manifestation/ Concern	Treatment	Considerations/Other
Nutrition/ Feeding	By feeding team incl nutritionist, gastroenterologist	Nasogastric tube, gastrostomy
Renal tubulopathy	Per treating nephrologist	
Respiratory insufficiency	Per treating pulmonologist	May incl consideration of tracheostomy & artificial ventilation
Neuromuscular	Physical therapy	• To maintain muscle strength & mobility; prevent contractures • Consider need for adaptive positioning devices.
Seizures	Standard treatment w/ASM by experienced neurologist based on seizure semiology	• Certain ASMs require monitoring of levels. • Education of parents/caregivers [1]
Sensorineural hearing loss	By hearing loss specialists	To determine the best habilitation options [2]
Other	Aggressive management of fever & infection	
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing

ASM = anti-seizure medication

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

2. See Hereditary Hearing Loss and Deafness.

RRM2B-MDMD Progressive External Ophthalmoplegia

Table 9. Treatment of Manifestations of *RRM2B*-MDMD Progressive External Ophthalmoplegia

Manifestation/Concern		Treatment	Considerations/Other
Ptosis/PEO		Ptosis surgery for cosmesis &/or symptomatic relief	In persons w/good residual orbicularis oculi muscle strength
Neuro-logic	**Myopathy**	PT & OT	
	Bulbar dysfunction	• Speech & language therapy • Parenteral feeding to avoid aspiration	
	Ataxia	PT & OT	
	Exercise intolerance		
Psycho-logical	**Cognitive dysfunction**	Psychologist input	
	Mood disturbance	Severe mood disturbance may necessitate psychiatrist input & medications.	

Table 9. continued from previous page.

Manifestation/Concern		Treatment	Considerations/Other
Sensorineural hearing loss		• Hearing aids • Cochlear implants	• Consider regular assessments for insidious onset. • Require ENT surgeon for cochlear implant.
Gastrointestinal dysmotility		• Dietary modifications to improve bowel movements • Laxatives • PEG/PEJ insertion (if clinically indicated) • TPN (very rare)	Regular weight measurement
Low BMI		Dietary supplementation	• Regular BMI measurement • Ensure appropriate growth based on centiles of children.
Endocrin-opathy	**Diabetes mellitus**	• Correction of blood sugar w/oral medication or insulin • Targeted treatment based on clinical features & blood results	Standard treatment as recommended by endocrinologist or diabetologist
	Hypothyroidism		
	Hypoparathyroidism		
	Hypogonadism		
Other		Aggressive management of fever & infection	

BMI = body mass index; OT = occupational therapy; PEG/J = percutaneous endoscopic gastrostomy/jejunostomy; PEO = progressive external ophthalmoplegia; PT = physical therapy; TPN = total parenteral nutrition

Surveillance

RRM2B-MDMD, Encephalomyopathic Form

Because most infants and young children with the encephalomyopathic form are severely affected and are hospitalized for prolonged periods from the onset of disease manifestations, they should be reviewed regularly by senior clinical specialists if they are hospitalized. The recommendations regarding frequency in Table 10 pertain to outpatient surveillance only.

Table 10. Recommended Surveillance of *RRM2B*-MDMD, Encephalomyopathic Form

System/Concern	Evaluation	Suggested Frequency of Outpatient Surveillance After Initial Assessment (per treating clinician)
Neurologic status incl possible seizures / subclinical status epilepticus	By pediatric neurologist; to incl EEG & video EEG monitoring	• Quarterly • W/o seizure correlates, routine EEG is not indicated.
	Assess for new manifestations (e.g., seizures, changes in tone, movement disorders).	Quarterly
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, need for adaptive devises	
Development	Monitor developmental progress & educational needs.	
Gastrointestinal	• Assessment of feeding • Monitor stool frequency. • Dietary assessment to maintain adequate nutrition & growth	
Growth	Assessment of nutritional status, height, weight, & BMI	Quarterly, then biannually if growth trajectory is satisfactory
Renal function	Eval by pediatric nephrologist	Quarterly if blood tests of renal function are abnormal
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	Quarterly
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit to hospital

BMI = body mass index; OT = occupational therapy; PT = physical therapy

RRM2B-MDMD Progressive External Ophthalmoplegia

Table 11. Recommended Surveillance of *RRM2B*-MDMD Progressive External Ophthalmoplegia

System/Concern	Evaluation	Suggested Frequency (per treating clinician)
Ptosis/PEO	Examine eye movements & degree of ptosis obscuring the pupils.	Annually
Neurologic	Comprehensive neurology consultation & clinical exam incl measures of functional neurologic status	Biannually
	Imaging & diagnostic procedures incl EEG & brain MRI	As indicated by clinical findings & rate of disease progression
Mobility/ADL	OT & PT assessments	Biannually
Psychologic	Consider formal psychological assessment for cognition and mood disturbances if indicated	Annually
Pulmonary function	Assessment of blood gases to monitor for early respiratory compromise	Biannually
Sensorineural hearing loss	Formal audiology	Annually
GI dysmotility	Bedside exam of GI systems	Biannually
Low body mass index	Nutritional status, weight gain, BMI	

Table 11. continued from previous page.

System/Concern	Evaluation	Suggested Frequency (per treating clinician)
Endocrinopathy	Screen for abnormalities in routine blood tests	Annually

ADL = activities of daily living; BMI = body mass index; GI = gastrointestinal; OT = occupational therapy; PEO = progressive external ophthalmoplegia; PT = physical therapy

Agents/Circumstances to Avoid

Valproic acid should be used only in exceptional circumstances.

Decisions related to drug prescribing should always be tailored to the affected individual's specific needs and risks [De Vries et al 2020]. All drugs where clear evidence in vivo of mitochondrial toxicity is absent or poor can be used with careful monitoring in the first few days of treatment for potential side effects and measurement of blood lactate.

It is safe to use metformin in primary mitochondrial disease.

If indicated, linezolid could be used in mitochondrial disease with careful lactate monitoring, particularly in children and other individuals with preexisting lactic acidemia.

Although historically there have been largely theoretic concerns regarding general anesthetic use in individuals with mitochondrial disease, adverse events are exceptionally rare. Catabolism should be prevented by minimizing preoperative fasting and administering intravenous glucose perioperatively during prolonged anesthesia, unless the individual is on a ketogenic diet.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk relatives of an affected family member so that those with the *RRM2B* pathogenic variant(s) can (1) undergo timely routine surveillance for disease complications and (2) avoid possible precipitating factors.

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

With the exception of autosomal dominant progressive external ophthalmoplegia (adPEO), *RRM2B* mitochondrial DNA maintenance defects (MDMDs) – *RRM2B* encephalomyopathic MDMD, *RRM2B*

mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like, and *RRM2B* autosomal recessive progressive external ophthalmoplegia (arPEO) – are inherited in an autosomal recessive manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *RRM2B* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *RRM2B* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) for autosomal recessive *RRM2B* pathogenic variant associated with arPEO, encephalomyopathic MDMD, or MNGIE-like disease are asymptomatic and are not expected to develop manifestations of an *RRM2B*-MDMD.

Sibs of a proband

- If both parents are known to be heterozygous for an *RRM2B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *RRM2B* pathogenic variants and being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *RRM2B* pathogenic variants.
- A wide range of intrafamilial variability in symptomatology, age of onset, and severity is observed among sibs who inherit biallelic *RRM2B* pathogenic variants.
- Heterozygotes (carriers) for autosomal recessive *RRM2B* pathogenic variant associated with arPEO, encephalomyopathic MDMD, or MNGIE-like disease are asymptomatic and are not expected to develop manifestations of an *RRM2B*-MDMD.

Offspring of a proband

- Individuals with *RRM2B* encephalomyopathic MDMD are not known to reproduce.
- The offspring of individuals with less severe manifestations of an autosomal recessive *RRM2B*-MDMD are obligate heterozygotes for an *RRM2B* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *RRM2B* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *RRM2B* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with an autosomal dominant *RRM2B*-MDMD have an affected parent.
- Some individuals diagnosed with an *RRM2B*-MDMD have the disorder as the result of a *de novo* pathogenic variant; the proportion of individuals with an *RRM2B*-MDMD resulting from a *de novo* pathogenic variant is unknown.

- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with a mtDNA maintenance defect may appear to be negative because of failure to recognize the disorder in family members because of a milder phenotypic presentation, early death of the parent before the onset of manifestations, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *RRM2B* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Intrafamilial variability in symptomatology and age of onset is observed among sibs who are heterozygous for an *RRM2B* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *RRM2B* pathogenic variant but are clinically unaffected, the risk to sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for an *RRM2B*-MDMD because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. The offspring of individuals with an autosomal dominant *RRM2B*-MDMD have a 50% chance of inheriting the *RRM2B* pathogenic variant.

Other family members. The risk to other family members of a proband depends on the genetic status of the proband's parents: if a parent has the *RRM2B* pathogenic variant, members of the parent's family may be 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.

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 discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *RRM2B* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for *RRM2B*-MDMD are possible. In some challenging circumstances, clinicians and/or families should consider seeking opinions from specialist centers with expertise in prenatal testing.

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.

- **Mito Foundation**
  Australia
  Phone: 61-1-300-977-180
  Email: info@mito.org.au
  www.mito.org.au
- **The Charlie Gard Foundation**
  United Kingdom
  Email: hello@thecharliegardfoundation.org
  www.thecharliegardfoundation.org
- **The Lily Foundation**
  United Kingdom
  Email: liz@thelilyfoundation.org.uk
  www.thelilyfoundation.org.uk
- **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. RRM2B Mitochondrial DNA Maintenance Defects: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
RRM2B	8q22.3	Ribonucleoside-diphosphate reductase subunit M2 B	RRM2B	RRM2B

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 RRM2B Mitochondrial DNA Maintenance Defects (View All in OMIM)

604712	RIBONUCLEOTIDE REDUCTASE REGULATORY TP53 INDUCIBLE SUBUNIT M2B; RRM2B
612075	MITOCHONDRIAL DNA DEPLETION SYNDROME 8A (ENCEPHALOMYOPATHIC TYPE WITH RENAL TUBULOPATHY); MTDPS8A
613077	PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL DOMINANT 5; PEOA5

Molecular Pathogenesis

RRM2B encodes ribonucleoside-diphosphate reductase subunit M2 B, the p53-inducible small subunit (p53R2) of ribonucleotide reductase (RNR), a heterotetrameric enzyme that catalyzes *de novo* syntheses of dNTPs. This process supplements the dNTPs produced by the mitochondrial dNTP salvage pathway that is essential for mtDNA synthesis (and in which defects cause many of the mtDNA depletion syndromes) [Rahman & Poulton 2009].

Abnormal p53R2 function results in disruption of mtDNA maintenance (replication and repair), leading to qualitative (accumulation of multiple mtDNA deletions) and/or quantitative (depletion of mtDNA copy number) downstream mitochondrial genomic effects.

Mechanism of disease causation. The majority of reported *RRM2B* pathogenic variants are missense variants. Molecular modeling showed that homozygous pathogenic missense variants disrupt a conserved alpha helix region of the protein by altering intramolecular interactions [Penque et al 2019]. Spliced transcript variants have also been described [Spinazzola et al 2009].

Truncating variants in the last exon in unrelated individuals with familial autosomal dominant PEO result in abnormal mRNA that escapes nonsense-mediated decay and production of a truncated protein. A dominant-negative or gain-of-function effect on the heterotetrameric structure of the RNR enzyme has been suggested [Tyynismaa et al 2009, Fratter et al 2011].

Chapter Notes

Author Notes

The authors of this chapter have offered to review *RRM2B* variants of uncertain significance with clinicians; please contact nuth.mitochondrial.clinical.enquiries@nhs.net or tnu-tr.newcastle-mitochondrial@nhs.net. Websites: www.newcastle-mitochondria.com; www.mitoresearch.org.uk.

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References

Literature Cited

Acham-Roschitz B, Plecko B, Lindbichler F, Bittner R, Mache CJ, Sperl W, Mayr JA. A novel mutation of the RRM2B gene in an infant with early fatal encephalomyopathy, central hypomyelination, and tubulopathy. Mol Genet Metab. 2009;98:300–4. PubMed PMID: 19616983.

Bornstein B, Area E, Flanigan KM, Ganesh J, Jayakar P, Swoboda KJ, Coku J, Naini A, Shanske S, Tanji K, Hirano M, DiMauro S. Mitochondrial DNA depletion syndrome due to mutations in the RRM2B gene. Neuromuscul Disord. 2008;18:453–9. PubMed PMID: 18504129.

Bourdon A, Minai L, Serre V, Jais JP, Sarzi E, Aubert S, Chrétien D, de Lonlay P, Paquis-Flucklinger V, Arakawa H, Nakamura Y, Munnich A, Rötig A. Mutation of RRM2B, encoding p53-controlled ribonucleotide reductase (p53R2), causes severe mitochondrial DNA depletion. Nat Genet. 2007;39:776–80. PubMed PMID: 17486094.

Bürk K, Sival DA. Scales for the clinical evaluation of cerebellar disorders. Handb Clin Neurol. 2018;154:329–39. PubMed PMID: 29903450.

De Vries MC, Brown DA, Allen ME, Bindoff L, Gorman GS, Karaa A, Keshavan N, Lamperti C, McFarland R, Ng YS, O'Callaghan M, Pitceathly RDS, Rahman S, Russel FGM, Varhaug KN, Schirris TJJ, Mancuso M. Safety of drug use in patients with a primary mitochondrial disease: an international Delphi-based consensus. J Inherit Metab Dis. 2020;43:800–18. PubMed PMID: 32030781.

El-Hattab AW, Craigen WJ, Scaglia F. Mitochondrial DNA maintenance defects. Biochim Biophys Acta Mol Basis Dis. 2017;1863:1539–55. PubMed PMID: 28215579.

Fratter C, Raman P, Alston CL, Blakely EL, Craig K, Smith C, Evans J, Seller A, Czermin B, Hanna MG, Poulton J, Brierley C, Staunton TG, Turnpenny PD, Schaefer AM, Chinnery PF, Horvath R, Turnbull DM, Gorman GS, Taylor RW. RRM2B mutations are frequent in familial PEO with multiple mtDNA deletions. Neurology. 2011;76:2032–4. PubMed PMID: 21646632.

Iwanicka-Pronicka K, Ciara E, Piekutowska-Abramczuk D, Halat P, Pajdowska M, Pronicki M. Congenital cochlear deafness in mitochondrial diseases related to RRM2B and SERAC1 gene defects. A study of the mitochondrial patients of the CMHI hospital in Warsaw, Poland. Int J Pediatr Otorhinolaryngol. 2019;121:143–9. PubMed PMID: 30909120.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Keshavan N, Abdenur J, Anderson G, Assouline Z, Barcia G, Bouhikbar L, Chakrapani A, Cleary M, Cohen MC, Feillet F, Fratter C, Hauser N, Jacques T, Lam A, McCullagh H, Phadke R, Rötig A, Sharrard M, Simon M, Smith C, Sommerville EW, Taylor RW, Yue WW, Rahman S. The natural history of infantile mitochondrial DNA depletion syndrome due to RRM2B deficiency. Genet Med. 2020;22:199–209. PubMed PMID: 31462754.

Kollberg G, Darin N, Benan K, Moslemi AR, Lindal S, Tulinius M, Oldfors A, Holme E. A novel homozygous RRM2B missense mutation in association with severe mtDNA depletion. Neuromuscul Disord. 2009;19:147–50. PubMed PMID: 19138848.

Linney M, Hain RDW, Wilkinson D, Fortune PM, Barclay S, Larcher V, Fitzgerald J, Arkell E. Achieving consensus advice for paediatricians and other health professionals: on prevention, recognition and management of conflict in paediatric practice. Arch Dis Child. 2019;104:413–6. PubMed PMID: 31000533.

Penque BA, Su L, Wang J, Ji W, Bale A, Luh F, Fulbright RK, Sarmast U, Sega AG, Konstantino M, Spencer-Manzon M, Pierce R, Yen Y, Lakhani SA. A homozygous variant in RRM2B is associated with severe metabolic acidosis and early neonatal death. Eur J Med Genet. 2019;62:103574. PubMed PMID: 30439532.

Pitceathly RD, Fassone E, Taanman JW, Sadowski M, Fratter C, Mudanohwo EE, Woodward CE, Sweeney MG, Holton JL, Hanna MG, Rahman S. Kearns-Sayre syndrome caused by defective R1/p53R2 assembly. J Med Genet. 2011;48:610–7. PubMed PMID: 21378381.

Pitceathly RD, Smith C, Fratter C, Alston CL, He L, Craig K, Blakely EL, Evans JC, Taylor J, Shabbir Z, Deschauer M, Pohl U, Roberts ME, Jackson MC, Halfpenny CA, Turnpenny PD, Lunt PW, Hanna MG, Schaefer AM, McFarland R, Horvath R, Chinnery PF, Turnbull DM, Poulton J, Taylor RW, Gorman GS. Adults with RRM2B-related mitochondrial disease have distinct clinical and molecular characteristics. Brain. 2012;135:3392–403. PubMed PMID: 23107649.

Pronicka E, Piekutowska-Abramczuk D, Ciara E, Trubicka J, Rokicki D, Karkucińska-Więckowska A, Pajdowska M, Jurkiewicz E, Halat P, Kosińska J, Pollak A, Rydzanicz M, Stawinski P, Pronicki M, Krajewska-Walasek M, Płoski R. New perspective in diagnostics of mitochondrial disorders: two years' experience with whole-exome sequencing at a national paediatric centre. J Transl Med. 2016;14:174. PubMed PMID: 27290639.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Rahman S, Poulton J. Diagnosis of mitochondrial DNA depletion syndromes. Arch Dis Child. 2009;94:3–5. PubMed PMID: 19103785.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Shaibani A, Shchelochkov OA, Zhang S, Katsonis P, Lichtarge O, Wong LJ, Shinawi M. Mitochondrial neurogastrointestinal encephalopathy due to mutations in RRM2B. Arch Neurol. 2009;66:1028–32. PubMed PMID: 19667227.

Sommerville EW, Chinnery PF, Gorman GS, Taylor RW. Adult-onset Mendelian PEO Associated with Mitochondrial Disease. J Neuromuscul Dis. 2014;1:119–33. PubMed PMID: 27858775.

Spinazzola A, Invernizzi F, Carrara F, Lamantea E, Donati A, Dirocco M, Giordano I, Meznaric-Petrusa M, Baruffini E, Ferrero I, Zeviani M. Clinical and molecular features of mitochondrial DNA depletion syndromes. J Inherit Metab Dis. 2009;32:143–58. PubMed PMID: 19125351.

Stojanovic V, Mayr JA, Sperl W, Barišić N, Doronjski A, Milak G. Infantile peripheral neuropathy, deafness, and proximal tubulopathy associated with a novel mutation of the RRM2B gene: case study. Croat Med J. 2013;54:579–84. PubMed PMID: 24382854.

Takata A, Kato M, Nakamura M, Yoshikawa T, Kanba S, Sano A, Kato T. Exome sequencing identifies a novel missense variant in RRM2B associated with autosomal recessive progressive external ophthalmoplegia. Genome Biol. 2011;12:R92. PubMed PMID: 21951382.

Tyynismaa H, Ylikallio E, Patel M, Molnar MJ, Haller RG, Suomalainen A. A heterozygous truncating mutation in RRM2B causes autosomal-dominant progressive external ophthalmoplegia with multiple mtDNA deletions. Am J Hum Genet. 2009;85:290–5. PubMed PMID: 19664747.

Wilichowski E, Horvath R, Mayr J, Gärtner J. Autosomal-recessive Kearns-Sayre syndrome is caused by mutations in the RRM2B gene with altered mitochondrial transcription. Neuropediatrics. 2013;44-FV16_08

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