RRM2B-related mitochondrial DNA depletion syndrome, encephalomyopathic form with renal tubulopathy

*RRM2B*-related mitochondrial DNA depletion syndrome, encephalomyopathic form with renal tubulopathy (*RRM2B*-MDS) is a severe condition that begins in infancy and affects multiple body systems. It is associated with brain dysfunction combined with muscle weakness (encephalomyopathy). Many affected individuals also have a kidney dysfunction known as renal tubulopathy.

Infants with *RRM2B*-MDS have weak muscle tone (hypotonia) and a failure to grow or gain weight at the expected rate (failure to thrive). Many have a smaller-than-normal head size (microcephaly). Due to muscle weakness, affected infants typically have difficulty controlling head movement and may have delayed development of other motor skills, such as rolling over or sitting. Weakness of the muscles used for breathing leads to serious breathing difficulties and can result in life-threatening respiratory failure. Most affected infants have a buildup of a chemical called lactic acid in the body (lactic acidosis), which can also be life-threatening.

Some individuals with *RRM2B*-MDS have a digestion problem known as gastrointestinal dysmotility, in which the muscles and nerves of the digestive system do not move food through the digestive tract efficiently. This disorder may lead to swallowing difficulties, vomiting, and diarrhea and can contribute to a failure to thrive. Less commonly, individuals with *RRM2B*-MDS develop seizures or hearing loss that is caused by nerve damage in the inner ear (sensorineural hearing loss).

Because of the severity of the signs and symptoms, people with *RRM2B*-MDS usually live only into early childhood.

**Frequency**

*RRM2B*-MDS is a rare condition; the exact prevalence is unknown. At least 15 cases have been reported in the medical literature.

**Causes**

As the condition name suggests, mutations in the *RRM2B* gene cause *RRM2B*-MDS. The *RRM2B* gene provides instructions for making one piece, called the p53 inducible small subunit (p53R2), of a protein called ribonucleotide reductase (RNR). RNR helps produce DNA building blocks (nucleotides), which are joined to one another in a particular order to form DNA.

RNRs containing p53R2 make nucleotides that are used for the formation of DNA in specialized cell structures called mitochondria. Although most DNA is packaged in chromosomes within the cell's nucleus (nuclear DNA), mitochondria also have a small
amount of their own DNA (mitochondrial DNA or mtDNA). Mitochondria are the energy-producing centers in cells, and the DNA in these structures contains genes essential for the process of energy production (called oxidative phosphorylation). The production of nucleotides by p53R2 helps maintain a normal amount of mtDNA in cells.

*RRM2B* gene mutations reduce the activity or amount of RNR, which likely impairs production of mtDNA nucleotides. A shortage of nucleotides available for the production of mtDNA molecules leads to a reduction in the amount of mtDNA (known as mtDNA depletion), which impairs mitochondrial function.

It is unclear why mtDNA depletion particularly affects the brain and kidneys in people with *RRM2B*-MDS, but the high energy demands of these tissues may make them especially susceptible to cell death when mtDNA is lost and less energy is produced in cells.

**Inheritance Pattern**

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

**Other Names for This Condition**

- mitochondrial DNA depletion syndrome 8A (encephalomyopathic type with renal tubulopathy)
- MTDPS8A
- RRM2B-MDS

**Diagnosis & Management**

**Genetic Testing Information**

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: RRM2B-related mitochondrial disease

**Other Diagnosis and Management Resources**

- Cincinnati Children’s Hospital: Mitochondrial Disorders Program
  https://www.cincinnatichildrens.org/service/m/mitochondrial-disorders/patients
- GeneReview: RRM2B-Related Mitochondrial Disease
  https://www.ncbi.nlm.nih.gov/books/NBK195854
Additional Information & Resources

Health Information from MedlinePlus

• Health Topic: Mitochondrial Diseases
  https://medlineplus.gov/mitochondrialdiseases.html

Additional NIH Resources

• National Institute of Neurological Disorders and Stroke: Mitochondrial Myopathy Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Mitochondrial-myopathy-Information-Page

Educational Resources

• Cincinnati Children’s Hospital: Mitochondrial Diseases
  https://www.cincinnatichildrens.org/health/m/mitochondrial

• Kennedy Krieger Institute: Mitochondrial Disorders
  https://www.kennedykrieger.org/patient-care/diagnoses-disorders/mitochondrial-disorders

• MalaCards: rrm2b-related mitochondrial dna depletion syndrome, encephalomyopathic form with renal tubulopathy
  http://www.malacards.org/card/rrm2b_related_mitochondrial_dna_depletion_syndrome_encephalomyopathic_form_with_renal_tubulopathy_2

• Mayo Clinic: Mitochondrial Disease Biobank
  https://www.mayo.edu/research/centers-programs/mitochondrial-disease-biobank/overview

• Orphanet: Mitochondrial DNA depletion syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=35698

• Orphanet: Mitochondrial DNA depletion syndrome, encephalomyopathic form with renal tubulopathy
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=255235

Patient Support and Advocacy Resources

• Muscular Dystrophy Association: Mitochondrial Myopathies
  https://www.mda.org/disease/mitochondrial-myopathies

• Muscular Dystrophy Canada: Mitochondrial Myopathies

• Muscular Dystrophy UK: Mitochondrial Myopathies
  https://www.musculardystrophyuk.org/about-muscle-wasting-conditions/mitochondrial-myopathies/
• North American Mitochondrial Disease Consortium
  https://www.rarediseasesnetwork.org/cms/NAMDC

• Resource List from the University of Kansas Medical Center: Mitochondrial Conditions
  http://www.kumc.edu/gec/support/mitochon.html

• United Mitochondrial Disease Foundation
  http://www.umdf.org/

Clinical Information from GeneReviews
• RRM2B-Related Mitochondrial Disease
  https://www.ncbi.nlm.nih.gov/books/NBK195854

Scientific Articles on PubMed
• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28RRM2B-related+mitochondrial+DNA+depletion+syndrome%29+OR+%28%28mitochondrial+DNA+depletion+5BT1AB+5D%29+AND+%28RRM2B%5BTIAB%5D%29%29+AND+english+5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22+AND+5Bdp%5D

Catalog of Genes and Diseases from OMIM
• MITOCHONDRIAL DNA DEPLETION SYNDROME 8A
  (ENCEPHALOMYOPATHIC TYPE WITH RENAL TUBULOPATHY)
  http://omim.org/entry/612075

Sources for This Summary
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3891825/


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