RRM2B Gene Mutations Causing Mitochondrial DNA Depletion Syndrome: Clinical Features and Genetic Analysis of Two Cases, Types 8A and 8B (Postprint)

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Abstract

Diseases associated with RRM2B gene mutations can be classified into four types based on inheritance patterns and clinical phenotypes: mitochondrial DNA depletion syndrome type 8A (MTDPS8A), mitochondrial DNA depletion syndrome type 8B (MTDPS8B), cone-rod dystrophy, sensorineural deafness, and Fanconi-type renal dysfunction (RCDFRD), and autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions type 5 (PEOA5). Among these, both MTDPS8A and MTDPS8B belong to mitochondrial DNA depletion syndrome, share the same inheritance pattern, and exhibit complex and heterogeneous clinical phenotypes in the early stages of the disease, making them difficult to differentiate. This article systematically reviews and analyzes the clinical features, genetic testing results, diagnosis and treatment courses, and other case data of two pediatric patients diagnosed with MTDPS8A and MTDPS8B, respectively, and revisits relevant literature to summarize the genetic characteristics of these two types, providing diagnostic approaches for future suspected cases, further improving the clinical diagnostic rate of RRM2B gene mutation-related mitochondrial encephalomyopathy, and also facilitating prognostic assessment.

Full Text

Mitochondrial DNA Depletion Syndrome Caused by RRM2B Gene Mutation: Clinical Characteristics and Genetic Analysis of Two Cases with Different Types (8A and 8B)

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Abstract

RRM2B gene mutation-related diseases can be classified into four types based on genetic pattern and clinical phenotype: mitochondrial DNA depletion syndrome type 8A (MTDPS8A), mitochondrial DNA depletion syndrome type 8B (MTDPS8B), rod-cone dystrophy with sensorineural deafness and Fanconi-type renal dysfunction (RCDFRD), and autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions type 5 (PEOA5). Among these, MTDPS8A and MTDPS8B are both mitochondrial DNA depletion syndromes with identical inheritance patterns, and their clinical phenotypes are complex and heterogeneous in the early disease stage, making differential diagnosis challenging. This article systematically reviews and analyzes the clinical characteristics, genetic testing results, diagnosis, treatment, and other case data of two children diagnosed with MTDPS8A and MTDPS8B, respectively, and summarizes the genetic features of these two types through literature review. The aim is to provide diagnostic insights for future suspected cases, further improve the clinical diagnostic rate of RRM2B mutation-related mitochondrial encephalomyopathy, and facilitate prognosis assessment.

Keywords: RRM2B gene; Mitochondrial DNA depletion syndrome 8A; Mitochondrial DNA depletion syndrome 8B; Genetic testing; Whole-exome sequencing

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Introduction

RRM2B gene mutations can cause various inherited mitochondrial diseases. Currently reported disease types include mitochondrial DNA depletion syndrome type 8A (MTDPS8A), mitochondrial DNA depletion syndrome type 8B (MTDPS8B), rod-cone dystrophy with sensorineural deafness and Fanconi-type renal dysfunction (RCDFRD), and autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions type 5 (PEOA5) [1-2]. Among

RRM2B gene mutation-related syndromes, MTDPS8A, MTDPS8B, and RCD-FRD follow autosomal recessive inheritance, while PEOA5 follows autosomal dominant inheritance, allowing preliminary differentiation based on inheritance patterns [3]. This article describes the clinical data of two cases carrying the same pathogenic RRM2B gene but presenting with two different clinical phenotypes—mitochondrial DNA depletion syndrome types 8A and 8B—to analyze the genotype-phenotype correlation and improve clinicians' understanding of the genetics and diagnosis of different RRM2B-related disease subtypes.

Case Reports

Case 1 A 6-month-old female infant was admitted to Sanya Maternal and Child Health Hospital on December 25, 2022, with hypotonia, poor head control, and severe pneumonia. Following an infection, the patient developed limb hypotonia, poor head control, respiratory distress, lethargy, poor feeding, and decreased mental responsiveness. She was the second child of a non-consanguineous marriage, born at full term via normal delivery without asphyxia or birth trauma, and had been healthy with normal growth and development before 6 months of age. She had an older brother who was diagnosed with congenital heart disease (ventricular septal defect) at 5 months of age and underwent ventricular septal defect closure surgery. Postoperatively, the brother's condition deteriorated with recurrent infections, skeletal muscle and respiratory muscle weakness, persistently elevated blood lactate levels, and continuous hospitalization until death at 1 year and 9 months due to respiratory and heart failure. Whole-exome sequencing performed during his hospitalization did not identify any gene variants highly associated with the clinical phenotype with sufficient pathogenic evidence, but among other variants, the brother was found to have compound heterozygous variants c.125T>G and c.175G>C in the RRM2B gene on chromosome 8, though their clinical significance was unclear. Both parents were healthy, non-consanguineous, and the mother had no abnormal conditions during pregnancy.

Physical examination revealed lethargy, fatigue, irritability, uniform emaciation, severe malnutrition, thin subcutaneous fat, poor skin elasticity, weak crying, slight eyeball depression, normal eye movements in all directions, equal-sized round pupils with sensitive light reflex, no skull deformities, no jaundice of skin or mucous membranes, soft neck without resistance, scaphoid abdomen, soft abdomen without gastrointestinal patterns or peristaltic waves, no tenderness or rebound tenderness throughout the abdomen, liver and spleen not palpable below the ribs, bowel sounds 6-8 times per minute, limb muscle strength grade IV, and decreased muscle tone.

Auxiliary examinations: Blood gas analysis showed lactate 4.0 mmol/L; electrolytes showed sodium 125 mmol/L (reference range: 137-147 mmol/L) and potassium 3.3 mmol/L (reference range: 3.5-5.3 mmol/L); chest CT and X-ray both indicated pneumonia; blood tandem mass spectrometry, urine organic acid analysis, stool routine, stool culture and smear, rotavirus, liver and kidney func-

tion, myocardial enzyme profile, blood lipids, autoantibodies, rheumatoid factor, abdominal ultrasound, and abdominal CT showed no abnormalities. Whole-exome sequencing revealed two heterozygous mutations in the RRM2B gene on chromosome 8: c.125T>G and c.175G>C, forming a compound heterozygous variant. Sanger sequencing confirmed that the two heterozygous mutations were inherited from the patient's parents, respectively. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, c.125T>G was classified as a likely pathogenic variant, while c.175G>C was of uncertain significance. The patient was diagnosed with mitochondrial DNA depletion syndrome type 8A.

Initially, the patient received continuous non-invasive ventilator support, cyclophosphamide adenosine for myocardial nutrition, combined with multiple anti-heart failure drugs to reduce myocardial oxygen consumption, compound coenzyme and B vitamin supplementation for energy, and anti-infection symptomatic treatment for over half a month. Respiratory and cardiac function showed no significant improvement. The family requested transfer to a higher-level hospital for further treatment. Follow-up until March 15, 2023, revealed that after 1 month of tracheostomy mechanical ventilation, the patient's respiratory distress improved, and she was switched to non-invasive continuous positive airway pressure (CPAP) ventilation. After multidisciplinary consultations in Canada and the United States, mononucleotide therapy was added to regulate cellular metabolism. Her condition remained relatively stable but still required ventilator support.

Case 2 A 10-month-old male infant was admitted to the Capital Institute of Pediatrics Affiliated Children's Hospital on July 28, 2020, with intermittent diarrhea and vomiting for over 5 months and cough for 3 months. The patient developed diarrhea with yellow loose stools 6-8 times per day, accompanied by vomiting 3-5 times per day and poor appetite; cough with throat phlegm and occasional respiratory distress appeared in the past 3 months. He lost 1 kg of body weight within 1 month. He was the first child of a non-consanguineous marriage, born at full term via normal delivery. He began complementary feeding at 6 months but could not crawl at 8 months, with growth and motor development lagging behind peers. He denied postnatal hypoxic asphyxia history, and no similar disease was found in the family. History of drug or food poisoning was denied.

Physical examination revealed poor mental responsiveness, soft neck, tachypnea, positive three-concave sign, rough breath sounds in both lungs with moist rales, irregular heart rhythm, strong heart sounds without pathological murmurs, grade III limb muscle strength, and hypotonia. Other abdominal and neurological examinations showed no abnormalities.

Auxiliary examinations: Blood tandem mass spectrometry showed elevated acetylcarnitine; urine organic acid analysis showed elevated lactate-2, 2-hydroxybutyrate-2, pyruvate-OX-2, 3-hydroxybutyrate-2, and acetoacetate-

OX-2; blood gas analysis showed lactate 3.38 mmol/L (reference range: 1.0-1.4 mmol/L); liver function showed alanine aminotransferase 88.29 U/L (reference range: 9-60 U/L) and aspartate aminotransferase 161.72 U/L (reference range: 15-45 U/L); myocardial enzyme profile showed lactate dehydrogenase 795.16 U/L (reference range: 180-430 U/L), lactate dehydrogenase isoenzyme 331.6 U/L (reference range: $ $90 U/L), creatine kinase 557.81 U/L (reference range: <190 U/L), and creatine kinase-MB isoenzyme 89.83 U/L (reference range: 0-25 U/L); kidney function showed creatinine 19.54 mol/L (reference range: 59-104 mol/L) and uric acid 175.93 mol/L (reference range: 120-330 mol/L). Urine routine, thyroid function five items, perinatal infection five items, respiratory pathogen panel, brain MRI, and cardiac ultrasound showed no abnormalities.

Whole-exome sequencing revealed two heterozygous variants in the RRM2B gene on chromosome 8: c.420G>C and c.321+1G>A. Family validation showed that this compound heterozygous variant was inherited from the parents, respectively. According to ACMG guidelines, c.420G>C was of uncertain significance, while c.321+1G>A was a likely pathogenic variant. The patient was diagnosed with mitochondrial DNA depletion syndrome type 8B.

The child had visited multiple external hospitals where relevant examinations failed to identify the etiology. He was treated with extensively hydrolyzed protein formula feeding and probiotics to regulate intestinal flora disorder, but diarrhea and vomiting persisted with unsatisfactory weight gain. During this hospitalization, active treatment for gastrointestinal symptoms included antidiarrheal therapy, enteral and parenteral nutrition, acid suppression and gastric protection, and maintenance of electrolyte and acid-base balance. Due to respiratory muscle weakness complicated by infection, pneumonia worsened, even progressing to respiratory failure. After more than 20 days of non-invasive ventilator support and anti-infection treatment, pulmonary signs gradually improved. Subsequent genetic sequencing confirmed mitochondrial disease, and treatment with coenzyme Q10, B vitamins, levocarnitine, and other energy cocktails was administered to improve cellular metabolism. After discharge, the patient continued oral energy cocktail therapy. Follow-up until May 6, 2023, showed reduced frequency of diarrhea and vomiting, improved appetite, but still prone to recurrent pulmonary infections, which could be effectively improved with home ventilator during severe episodes. Weight was 9 kg (<-3 SD), with slow growth and development and slightly delayed intellectual and motor development.

Comparison of the Two Cases

Comparison of phenotypes and genotypes in two children with RRM2B gene mutation

Feature	Case 1 (MTDPS8A)	Case 2 (MTDPS8B)
Primary clinical manifestations	Hypotonia, poor head control, severe pneumonia, similar history in older brother	Recurrent diarrhea, vomiting, cachexia
Age at onset	6 months	4 months
Blood lactate	4.0 mmol/L	3.38 mmol/L
RRM2B gene variants	c.125T>G (maternal)/c.175G>C (paternal)	c.420G>C (maternal)/c.321+1G>A (paternal)
Inheritance pattern	Autosomal recessive	Autosomal recessive
Pathogenic evidence (ACMG)	PM2+PP3	PVS1+PM2
Preliminary pathogenicity level	Likely pathogenic/Uncertain significance	Uncertain significance/Likely pathogenic
Diagnosis	Mitochondrial DNA depletion syndrome type 8A	Mitochondrial DNA depletion syndrome type 8B
Prognosis	Poor, still requires ventilator support	Symptoms improved compared with before

Note: ACMG = American College of Medical Genetics and Genomics.

Discussion

MTDPS8A is a severe encephalomyopathic form of mitochondrial DNA depletion syndrome caused by homozygous or compound heterozygous mutations in the RRM2B gene [4]. The disease typically manifests in infancy, progresses rapidly, and has high mortality. Clinical features include feeding difficulties, growth and developmental delay, respiratory failure, and renal tubular disease [6]. Central nervous system involvement may present as psychomotor retardation, cognitive impairment, seizures, hearing loss, intellectual disability, and gait ataxia, usually appearing later in the disease course. Respiratory failure often requires mechanical ventilation for relief. Kollberg et al. [7] described two brothers with MTDPS8A syndrome who were related and had severe phenotypes, dying at 3 and 5 months of age, respectively. Both presented with feeding difficulties, developmental delay, severe hypotonia, and hyperlactatemia; the older brother also developed renal tubular disease. Based on disease severity, differential diagnosis can be made from MTDPS8B, which has similar clinical phenotypes. MTDPS8B patients exhibit higher clinical heterogeneity but generally milder symptoms and longer disease course than MTDPS8A patients; some may even have adult onset, with specific manifestations including gastrointestinal dysmotility, external ophthalmoplegia and/or ptosis, and peripheral

neuropathy [8]. Unlike classic MNGIE syndrome caused by TYMP gene mutations, MTDPS8B patients often show no diffuse cerebral white matter lesions on brain MRI, instead presenting with patchy white matter lesions or normal findings [9]. Shaibani et al. [5] reported a 42-year-old female with MNGIE-like phenotype in 2009, who developed recurrent nausea, vomiting, and weight loss at age 30, followed by limited eye movement, ocular muscle weakness, and gait instability at age 37. Genetic sequencing eventually identified compound heterozygous RRM2B variants c.329G>A and c.362G>A. Patients with early-stage MTDPS8B with atypical symptoms are easily misdiagnosed with acute gastroenteritis, food protein allergy-associated proctocolitis, anorexia nervosa, or irritable bowel syndrome, leading to delayed diagnosis and treatment.

In Case 1, the two related siblings developed the disease sequentially with similar clinical courses. The younger sister developed hypotonia, poor head control, feeding difficulties, severe pneumonia, and respiratory failure at 6 months of age, with elevated serum creatine kinase, lactate, and acylcarnitine, and increased urinary organic acids including lactate, pyruvate, tricarboxylic acid cycle, and fatty acid β-oxidation intermediates, as well as abnormal liver and cardiac function indicators, suggesting mitochondrial dysfunction. Comparing with the brother's history, he developed the disease after surgical trauma and infection at 5 months of age, presenting with muscle weakness, hypotonia, lactic acidosis, and recurrent pulmonary infections. He died at 1 year and 9 months due to severe complications despite symptomatic treatment for over one year. Both siblings developed the disease in infancy, with severe outbreaks following muscle weakness, suggesting that clinicians should actively provide respiratory and nutritional support early after diagnosis or when muscle weakness appears to delay disease progression. Since both siblings developed symptoms early, central nervous system development could not be fully assessed. As the younger sister grows, she may develop new clinical manifestations such as renal tubular disease, seizures, ophthalmoplegia, or hearing loss, requiring regular follow-up. Based on the clinical presentation of both siblings, they met the typical manifestations of MTDPS8A. However, if new abnormal phenotypes suggesting other syndromes appear during follow-up, re-evaluation of the diagnosis may be necessary. In Case 2, the patient developed symptoms at 4 months of age, starting with diarrhea and vomiting that progressed to malnutrition and cachexia. Abdominal imaging showed no abnormalities, but the patient had obvious chronic progressive gastrointestinal dysmotility that could not be explained by infectious or organic gastrointestinal diseases alone. Combined with severe malnutrition, low BMI, hypotonia, and muscle weakness, mitochondrial disease could be an important cause of refractory diarrhea. Due to the young age, the main manifestations were gastrointestinal and respiratory symptoms, lacking ophthalmoplegia or peripheral neuropathy symptoms, and muscle biopsy and brain MRI were not performed. Besides genetic testing, long-term follow-up is needed for further diagnostic evidence. After discharge, the patient received long-term mitochondrial cocktail therapy with satisfactory results, strongly supporting the diagnosis of MTDPS8B.

MTDPS8B is currently extremely rare, with only two genotypes reported worldwide—compound heterozygous variants c.329G>A and c.362G>A, and homozygous c.420G>C mutation [5,11]. The patient in Case 2 had compound heterozygous variants c.420G>C and c.321+1G>A. The c.420G>C variant involves a nucleotide change from guanine G to cytosine C at position 420, causing the amino acid at position 140 to change from leucine to phenylalanine. This variant has not been reported in normal population databases, is predicted to be deleterious by REVEL software, and follows a recessive inheritance pattern, being in trans with another likely pathogenic variant. Combined with "moderate pathogenic evidence PM2 + moderate pathogenic evidence PM3 + supporting pathogenic evidence PP3," it was preliminarily classified as a variant of uncertain significance (VUS). Wang et al. [11] established a cellular model of the homozygous RRM2B c.420G>C mutation and found that mutant cells had downregulated RRM2B protein expression and significantly decreased mitochondrial DNA content, proving that this mutation impairs RRM2B gene function and satisfying "strong pathogenic evidence PS3," thus upgrading the pathogenicity to likely pathogenic (LP). The c.321+1G>A variant involves a nucleotide change from guanine G to adenine A at position 321+1, causing a 5' splice site variation. This variant has also not been reported in normal population databases. As c.321+1G>A represents a classic splice site variation in a gene with loss-of-function (LOF) pathogenic mechanism, combined with "very strong pathogenic evidence PVS1 + moderate pathogenic evidence PM2," it can be classified as a likely pathogenic variant (LP). Based on the phenotype-genotype correlation, the diagnosis of MTDPS8B in Case 2 was confirmed.

Four types of pathogenic mutations associated with MTDPS8A have been reported, including missense, nonsense, deletion, and splicing mutations, with missense mutations being most common [10]. All confirmed MTDPS8A patients in China have had compound heterozygous variants, including RRM2B c.16delA and c.175G>C, c.587A>G and c.424G>A, c.231delC and c.806C>G, and c.456-2A>G and c.212T>C mutations. In Case 1, the older brother developed symptoms first, but whole-exome sequencing did not identify any clearly pathogenic variants related to the phenotype, and other variant information was not specifically analyzed, resulting in an unclear diagnosis. Not long after the brother's death, the younger sister also presented with the same phenotype after infection, suggesting by coincidence that the siblings might share the same pathogenic gene. Whole-exome sequencing was performed again on the sister, revealing suspicious variants—compound heterozygous RRM2B variants c.125T>G and c.175G>C—with asymptomatic carrier parents. Subsequent retrospective analysis of the brother's genetic testing results revealed new findings: among non-related pathogenic genes, the same variants as his sister were present. Combined with clinical manifestations, this confirmed that the siblings had the same genetic disease. Both mutation sites were missense mutations. The c.125T>G variant involves a nucleotide change from thymine T to guanine G at position 125, causing the amino acid at position 42 to change from phenylalanine

to cysteine. This variant is located in a mutation hotspot region with unknown frequency in normal population databases. Bioinformatics protein function prediction software including REVEL, SIFT, PolyPhen-2, MutationTaster, and GERP+ all predicted it to be deleterious, satisfying "moderate pathogenic evidence PM1 + moderate pathogenic evidence PM2 + supporting pathogenic evidence PP3," and could be preliminarily judged as a likely pathogenic variant (LP). The c.175G>C variant involves a nucleotide change from guanine G to cytosine C at position 175, causing the amino acid at position 59 to change from alanine to proline. This variant shares the same pathogenic evidence as c.125T>G ("moderate pathogenic evidence PM2 + supporting pathogenic evidence PP3") but lacks moderate pathogenic evidence PM1 because it is not in a hotspot mutation region, resulting in a preliminary classification as a variant of uncertain significance (VUS). Wang et al. [4] identified compound heterozygous pathogenic mutations c.16delA and c.175G>C in a 2-month-old female patient diagnosed with MTDPS8A. Using SWISS-MODEL software to analyze the c.175G>C mutation site, they found that the amino acid change p.Ala59Pro occurs in an α-helical structural domain. After mutation, the proline imino group replacing alanine lacks a hydrogen atom, causing the molecule to lose a central hydrogen bond. As α-helices are protein secondary structures stabilized by hydrogen bonds, and this site is highly conserved during evolution, mutation would affect protein function. Bourdon et al. [10] also established molecular models showing that RRM2B gene mutations disrupt the conserved α-helical region of the protein by altering intramolecular interactions, further validating the destructive nature of this mutation. Through comprehensive analysis, although basic experimental support is currently lacking, protein function prediction suggests that the pathogenicity of c.125T>G and c.175G>C mutations is relatively clear.

The RRM2B gene is a nuclear gene located at chromosome 8q22.3, encoding the p53-inducible small subunit (p53R2) of ribonucleotide reductase (RNR) [12] and the R2 subunit. RNR is a heterotetrameric enzyme composed of a homodimeric large subunit R1 (encoded by the RRM1 gene) that binds substrates and has allosteric effects, and a homodimeric small subunit R2 or p53R2 containing highly conserved tyrosine residues [13]. RNR can reduce ribonucleoside diphosphates (NDP) to deoxyribonucleoside diphosphates (dNDP), catalyzing the terminal step of de novo synthesis of deoxyribonucleoside triphosphates (dNTP), which are ultimately localized to mitochondria and the nucleus to participate in mtDNA synthesis and nDNA damage repair. The p53R2 protein participates in maintaining the mitotic process and supplies dNTPs to meet cellular or organ functional requirements, being particularly crucial for continuously replicating mtDNA [14]. If the RRM2B gene is mutated, p53R2 protein function is impaired, disrupting dNTP pool stability, affecting mtDNA synthesis and repair, and leading to reduced mtDNA copy number or accumulation of multiple mtDNA deletions, thus causing disease. Tanaka et al. [15] proposed that inactivation of p53R2 protein leads to insufficient RNR activity, directly interfering with transcription during DNA damage and preventing normal DNA

repair. Misregulation of p53R2 may also cause dNTP pool imbalance and dysregulation of DNA repair mechanisms, thereby increasing mutation frequency. Kimura et al. [16] cultured mice with RRM2B gene defects that developed normally before weaning but subsequently showed growth retardation and early death, with pathological examination revealing multi-organ failure. These studies demonstrate that the p53R2 subunit encoded by the RRM2B gene plays a critical role in maintaining dNTP levels and repairing DNA damage, helping to clarify the correlation between clinical phenotypes and underlying genetic defects. For different forms of mitochondrial DNA depletion syndrome, supplementation with deoxyribonucleotides to bypass the defective step in nucleoside salvage has been proposed as a potential therapeutic strategy. Researchers established another disease-causing gene TK2-deficient mouse model and concluded that oral supplementation with deoxycytidine monophosphate (dCMP) and deoxythymidine monophosphate (dTMP) could delay disease onset and prolong survival [17]. For RRM2B deficiency treatment, appropriate animal knockout models for in vivo studies are lacking because existing animal models cannot fully recapitulate human disease. Therefore, the efficacy of deoxyribonucleotide supplementation requires further validation through more in-depth molecular biology basic research. Patient 1 has attempted mononucleotide therapy, and its efficacy awaits continued follow-up evaluation.

In summary, RRM2B gene mutation carriers exhibit broad phenotypic and genotypic spectra, and correct classification and comprehensive variant analysis present certain difficulties, with MTDPS8A and MTDPS8B being particularly prone to missed or misdiagnosis. Most MTDPS8A patients have poor prognosis and cannot survive to adulthood, while MTDPS8B has a relatively better prognosis. Currently, there is no specific treatment for RRM2B gene mutation patients in clinical practice. General symptomatic treatments such as energy supplementation and organ function maintenance are given to improve symptoms, but new therapeutic approaches are urgently needed.

Author Contributions

DENG Lin: conceptualization and design of the article, collection of case data and literature, writing and revision of the manuscript; LU Jun: quality control and review, writing guidance, overall responsibility for the article, supervision and management.

Conflict of Interest Statement

The authors declare no conflict of interest.

References

[1] ROBERTS L, JULIUS S, DAWLAT S, et al. Renal dysfunction, rod-cone dystrophy, and sensorineural hearing loss caused by a mutation in RRM2B[J]. Hum Mutat, 2020, 41(11): 1871-1876. DOI: 10.1002/humu.24094.

[2] TAKATA A, KATO M, NAKAMURA M, et al. Exome sequencing identifies a novel missense variant in RRM2B associated with autosomal recessive progressive external ophthalmoplegia[J]. Genome Biol, 2011, 12(9): R92. DOI: 10.1186/gb-2011-12-9-r92.

[3] PITCEATHLY R D, SMITH C, FRATTER C, et al. Adults with RRM2B-related mitochondrial disease have distinct clinical and molecular characteristics[J]. Brain, 2012, 135(Pt 11): 3392-3403. DOI: 10.1093/brain/aws231.

[4] 王彦红, 郑璇, 王向蝶, 等. RRM2B 基因复合杂合变异导致的线粒体耗竭综合征家系的临床特征和遗传学分析 [J]. 中华医学遗传学杂志, 2022, 39(1): 26-30. DOI: 10.3760/cma.j.cn511374-20201116-00799.

[5] SHAIBANI A, SHCHELOCHKOV O A, ZHANG S L, et al. Mitochondrial neurogastrointestinal encephalopathy due to mutations in RRM2B[J]. Arch Neurol, 2009, 66(8): 1028-1032. DOI: 10.1001/archneurol.2009.139.

[6] FINSTERER J, ZARROUK-MAHJOUB S. Phenotypic and genotypic heterogeneity of RRM2B variants[J]. Neuropediatrics, 2018, 49(4): 231-237. DOI: 10.1055/s-0037-1609039.

[7] KOLLBERG G, DARIN N, BENAN K, et al. A novel homozygous RRM2B missense mutation in association with severe mtDNA depletion[J]. Neuromuscul Disord, 2009, 19(2): 147-150. DOI: 10.1016/j.nmd.2008.11.014.

[8] KROPACH N, SHKALIM-ZEMER V, ORENSTEIN N, et al. Novel RRM2B mutation and severe mitochondrial DNA depletion: report of 2 cases and review of the literature[J]. Neuropediatrics, 2017, 48(6): 456-462. DOI: 10.1055/s-0037-1601867.

[9] FINSTERER J. Diagnosing mitochondrial neurogastrointestinal leukoencephalopathy requires mutations in TYMP1, POLG1, LIG1, or RRM2B[J]. J Med Case Rep, 2023, 17(1): 162. DOI: 10.1186/s13256-023-03916-y.

[10] BOURDON A, MINAI L, SERRE V, et al. Mutation of RRM2B, encoding p53-controlled ribonucleotide reductase (p53R2), causes severe mitochondrial DNA depletion[J]. Nat Genet, 2007, 39(6): 776-780. DOI: 10.1038/ng2040.

[11] 王建力, 畅雪丽, 张炜, 等. RRM2B 基因 c.420G>C 新突变细胞模型的建立及初步研究[J]. 中西医结合心脑血管病杂志, 2020, 18(9): 1497-1502. DOI: 10.12102/j.issn.1672-1349.2020.09.038.

[12] AIT EL CADI C, KRAMI A M, CHAROUTE H, et al. Prediction of the impact of deleterious nonsynonymous single nucleotide polymorphisms on the human RRM2B gene: a molecular modeling study[J]. Biomed Res Int, 2020, 2020: 7614634. DOI: 10.1155/2020/7614634.

[13] KESHAVAN N, ABDENUR J, ANDERSON G, et al. The natural history of infantile mitochondrial DNA depletion syndrome due to RRM2B deficiency[J]. Genet Med, 2020, 22(1): 199-209. DOI: 10.1038/s41436-019-0613-z.

[14] CHO E C, KUO M L, CHENG J H, et al. RRM2B-mediated regulation of mitochondrial activity and inflammation under oxidative stress[J]. Mediators Inflamm, 2015, 2015: 287345. DOI: 10.1155/2015/287345.

[15] TANAKA H, ARAKAWA H, YAMAGUCHI T, et al. A ribonucleotide reductase gene involved in a p53-dependent cell-cycle checkpoint for DNA damage[J]. Nature, 2000, 404(6773): 42-49. DOI: 10.1038/35003506.

[16] KIMURA T, TAKEDA S, SAGIYA Y, et al. Impaired function of p53R2 in Rrm2b-null mice causes severe renal failure through attenuation of dNTP pools[J]. Nat Genet, 2003, 34(4): 440-445. DOI: 10.1038/ng1212.

[17] GARONE C, GARCIA-DIAZ B, EMMANUELE V, et al. Deoxypyrimidine monophosphate bypass therapy for thymidine kinase 2 deficiency[J]. EMBO Mol Med, 2014, 6(8): 1016-1027. DOI: 10.15252/emmm.201404092.

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Note: Figure translations are in progress. See original paper for figures.