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A.K. Gabdulkayum[1], Zh.Zh. Mirmanova[1], T.B. Kadenova[1], M.F. Bayanova[2], L.K. Nazarova[2], A.K. Bolatov[2], A. Yerezhepov[3], A.M. Aitkulova[1], A.R. Akilzhanova[1], D.A. Yerezhepov[1*]

[1]PI "National Laboratory Astana", Astana, Kazakhstan
[2]Corporate Found "University Medical Center", Astana, Kazakhstan
[3]NJSC «Al-Farabi Kazakh National University», Almaty, Kazakhstan
*e-mail: dauren.yerezhepov@nu.edu.kz

PRENATAL GENETIC TESTING FOR MULTIPLE MITOCHONDRIAL DYSFUNCTION SYNDROME CAUSED BY IBA57 GENE MUTATION KAZAKHSTANI FAMILY: A CASE REPORT

Mitochondria, commonly known as the cell's power generator, carry out their primary function through oxidative phosphorylation (OXPHOS), a process that produces ATP, the main energy source of the cell and the only cell organelles with their own mitochondrial DNA. Any genetic alterations in DNA sequences that encode mitochondrial structural or functional proteins may cause mitochondrial disorders. Multiple mitochondrial dysfunction syndrome type 3 (MMDS3) is a rare autosomal recessive mitochondrial disorder caused by homozygous or biallelic pathogenic variants in the IBA57 gene. In the current study, we present a case report on prenatal genetic testing for multiple mitochondrial dysfunction syndrome (MMDS) type 3 caused by the IBA57 gene to highlight the importance of prenatal diagnostics for disease prognosis and treatment, appropriate genetic counselling, and informed reproductive decision-making. We recruited a 27-year-old G2P1001 at 22 weeks' gestation with MMDS3 in family history, confirmed by whole exome sequencing (WES) and also verified by Sanger sequencing in the IBA57 gene c.286T>C (NM_001010867.4, p.Tyr96His) and c.667C>G (NM_001010867.4, p.Arg223Gly) in the proband and parents. The ccfDNA genetic test revealed the absence of the heterozygous IBA57 gene variant at position c.286T>C (NM_001010867.4, p.Tyr96His), but the heterozygous IBA57 gene variant at position c.667C>G (NM_001010867.4, p.Arg223Gly) was detected. The child is a heterozygous carrier of the genetic variant of the IBA57 gene at position c.667C>G (NM_001010867.4, p.Arg223Gly). No specific treatment is required; observation by a pediatrician and medical and genetic counseling of the couple when planning the next pregnancy are recommended. The IBA57 gene-related MMDS3 can have a wide range of outcomes and consequences and may progress rapidly. Early awareness is crucial to prompt and proper administration. Our study reveals the importance of early prenatal genetic testing for IBA57-related MMDS3 for early diagnostics and consent decision-making.

Keywords: multiple mitochondrial dysfunction syndrome 3; prenatal genetic testing; IBA57; genetic counseling; consent decision-making.

А.Қ. Ғабдулкаюм[1], Ж.Ж. Мирманова[1], Т.Б. Каденова[1], М.Ф. Баянова[2], Л.К. Назарова[2], А.К. Болатов[2], А. Ережепов[3], А.М. Айткулова[1], А.Р. Акильжанова[1], Д.А. Ережепов[1*]

[1]«Астана Ұлттық зертханасы» ЖМ, Астана, Қазақстан
[2]«Университеттік медициналық орталық» КҚ, Астана, Қазақстан
[3]«Әл-Фараби атындағы Қазақ ұлттық университеті» КеАҚ, Алматы, Қазақстан
*e-mail: dauren.yerezhepov@nu.edu.kz

Қазақстандық отбасын IBA57 генінің мутациясынан туындаған көптік митохондриялық дисфункция синдромына пренаталдық генетикалық тестілеу: клиникалық жағдай

Митохондриялар жасушаның «энергия генераторы» ретінде белгілі және өздерінің негізгі қызметін тотығу фосфорлануы (oxidative phosphorylation, OXPHOS) арқылы жүзеге асырады. Митохондриялар өздерінің жеке митохондриялық ДНҚ-сына ие болатын жалғыз жасушалық органеллалар болып табылады. Митохондриялық құрылымдық немесе функционалдық ақуыздарды кодтайтын ДНҚ тізбектеріндегі кез келген генетикалық өзгерістер митохондриялық ауруларға әкелуі мүмкін. Көптік митохондриялық дисфункция синдромы 3-типі (Multiple

Dysfunction Syndrome type 3, MMDS3) IBA57 геніндегі гомозиготалы немесе екіаллельді патогенді нұсқалардан туындайтын сирек кездесетін аутосомды-рецессивті митохондриялық ауру. Осы зерттеуде біз IBA57 генімен байланысты MMDS3-ке пренаталдық генетикалық тестілеуіне арналған клиникалық жағдайды ұсынамыз. Зерттеудің мақсаты аурудың болжамын және емдеу тактикасын анықтауда, сондай-ақ дұрыс генетикалық кеңес беру мен саналы репродуктивті шешім қабылдауда пренаталдық диагностиканың маңыздылығын көрсету. Зерттеуге MMDS3 бойынша отбасылық анамнезі бар, жүктіліктің 22 аптасында тұрған 27 жастағы әйел (G2P1001) рекрутталды. Диагноз толық экзомдық секвенирлеу (WES) әдісімен расталды және кейіннен Сэнгер бойынша секвенирлеу арқылы IBA57 геніндегі c.286T>C (NM_001010867.4, p.Tyr96His) және c.667C>G (NM_001010867.4, p.Arg223Gly) нұсқалары пробандта және ата-анасында тексерілді. Циркуляциядағы клеткадан тыс ДНҚ (ccfDNA) бойынша генетикалық талдау нәтижесінде IBA57 генінің c.286T>C (NM_001010867.4, p.Tyr96His) позициясындағы гетерозиготалы нұсқасы анықталмады, алайда c.667C>G (NM_001010867.4, p.Arg223Gly) позициясындағы гетерозиготалы нұсқасы анықталды. Осылайша, бала IBA57 генінің c.667C>G (NM_001010867.4, p.Arg223Gly) нұсқасының гетерозиготалы тасымалдаушысы. Бұл жағдайда арнайы емдеу қажет емес. Баланы педиатрдың бақылауында ұстау және келесі жүктілікті жоспарлау кезінде ерлі-зайыптыларға медициналық-генетикалық кеңес беру ұсынылады. IBA57 генімен байланысты MMDS3 клиникалық көріністерінің спектрі кең болуы мүмкін және ауру кейбір жағдайларда жылдам үдеуі ықтимал. Сондықтан ерте анықтау уақтылы диагностика жүргізуге, дұрыс медициналық басқару тактикасын таңдауға және саналы репродуктивті шешім қабылдауға мүмкіндік береді.

Түйін сөздер: көптік митохондриялық дисфункция синдромы 3; пренаталдық генетикалық тестілеу; IBA57; генетикалық кеңес беру; репродуктивті шешім қабылдау.

А.Қ. Ғабдулкаюм[1], Ж.Ж. Мирманова[1], Т.Б. Каденова[1], М.Ф. Баянова[2], Л.К. Назарова[2], А.К. Болатов[2], А. Ережепов[3], А.М. Айткулова[1], А.Р. Акильжанова[1], Д.А. Ережепов[1*]

[1]ЧУ «National Laboratory Astana», Астана, Казахстан
[2]КФ «University Medical Center», Астана, Казахстан
[3]НАО «Казахский национальный университет имени аль-Фараби», Алматы, Казахстан
*e-mail: dauren.yerezhepov@nu.edu.kz

Пренатальное генетическое тестирование синдрома множественной митохондриальной дисфункции, вызванного мутацией гена IBA57, в казахстанской семье: клинический случай

Митохондрии, широко известные как «энергетические станции» клетки, выполняют свою основную функцию посредством окислительного фосфорилирования (oxidative phosphorylation, OXPHOS) – процесса, в ходе которого синтезируется АТФ, являющийся главным источником энергии клетки. Кроме того, митохондрии являются единственными клеточными органеллами, обладающими собственной митохондриальной ДНК. Любые генетические изменения в последовательностях ДНК, кодирующих структурные или функциональные белки митохондрий, могут приводить к развитию митохондриальных заболеваний. Синдром множественной митохондриальной дисфункции типа 3 (Multiple Mitochondrial Dysfunction Syndrome type 3, MMDS3) – редкое аутосомно-рецессивное митохондриальное заболевание, обусловленное гомозиготными или биаллельными патогенными вариантами в гене IBA57. В настоящем исследовании представлен клинический случай пренатального генетического тестирования на синдром множественной митохондриальной дисфункции (MMDS) типа 3, вызванный мутациями в гене IBA57, с целью подчеркнуть важность пренатальной диагностики для прогноза заболевания и выбора тактики лечения, проведения адекватного генетического консультирования и принятия информированных репродуктивных решений. В исследование была включена 27-летняя беременная женщина (G2P1001) на сроке гестации 22 недели, имеющая семейный анамнез MMDS3. Диагноз был подтвержден методом полного экзомного секвенирования (whole exome sequencing, WES), а также верифицирован методом секвенирования по Сэнгеру для вариантов гена IBA57 c.286T>C (NM_001010867.4, p.Tyr96His) и c.667C>G (NM_001010867.4, p.Arg223Gly) у пробанда и его родителей. Генетическое исследование циркулирующей свободной ДНК плода (ccfDNA) выявило отсутствие гетерозиготного варианта гена IBA57 в позиции c.286T>C (NM_001010867.4, p.Tyr96His), однако был обнаружен гетерозиготный вариант в позиции c.667C>G (NM_001010867.4, p.Arg223Gly). Таким образом, ребенок является гетерозиготным носителем генетического варианта гена IBA57 c.667C>G (NM_001010867.4, p.Arg223Gly). Специфическое лечение в данном случае не требуется. Рекомендуется наблюдение ребенка у педиатра, а также проведение медико-генетического консультирования супругов при планировании последующей беременности. Синдром MMDS3, связанный с мутациями гена IBA57, может характеризоваться широким спектром клинических

проявлений и в ряде случаев прогрессировать достаточно быстро. Ранняя диагностика играет ключевую роль для своевременного медицинского вмешательства, правильного генетического консультирования и принятия информированных репродуктивных решений.

Ключевые слова: синдром множественной митохондриальной дисфункции 3, пренатальное генетическое тестирование, IBA57, генетическое консультирование, информированное репродуктивное решение.

Introduction

Mitochondria, commonly known as the cell's power generator, carry out their primary function through oxidative phosphorylation (OXPHOS), a process that produces ATP, the main energy source of the cell (Mitchell, 1961). Despite most cellular activity being regulated by nuclear DNA (nDNA), mitochondria are an exception. Mitochondria are the only cell organelles with their own mitochondrial DNA (mtDNA), which consists of light (L) and heavy (H) chains. The mtDNA genome includes 37 structural genes, most of which (22) encode transport RNA, 13 encode subunits of OXPHOS complexes, and 2 encode the large subunit of ribosomes (Xu et al., 2016). Any genetic alterations in DNA sequences involved in mitochondrial function or that encode mitochondrial structural or functional proteins may cause mitochondrial disorders (Schapira, 2012).

Mitochondrial disorders are a group of genetic conditions characterized by dysfunctional mitochondria. Since mitochondrial diseases are caused by genetic mutations in nDNA and/or mtDNA, it has complex inheritance patterns, including autosomal and X-linked inheritance for nDNA mutations and maternal inheritance for mtDNA mutations. Additionally, due to mtDNA's lower mutational resistance, many de novo mutations are being reported (Gorman et al., 2016). Mitochondrial diseases are clinically heterogeneous, can occur at any age and in any organ or tissue, usually affecting aerobic-metabolism-dependent cells and tissues, such as neurons, muscle fibers, and cardiomyocytes, and can manifest with a wide range of clinical symptoms (McFarland et al., 2010).

Multiple mitochondrial dysfunction syndrome (MMDS) refers to a group of rare autosomal recessive disorders caused by impaired energy metabolism, which results in abnormal neurological development, muscle weakness, lactic acidosis, and respiratory insufficiency and is typically associated with premature death. MMDS can be classified into 9 types (types 1-9B, OMIM#: 605711, 614299, 615330, 616370, 617613, 617954, 620423, 251900, 620887) based on pathogenic variants in 9 genes: NFU1, BOLA3, IBA57, ISCA2, ISCA1, PMPCB, GCSH, FDX2, and FDXR (Bargagna et al., 2024).

Multiple mitochondrial dysfunction syndrome type 3 (MMDS3) (OMIM#: 615330) is a rare autosomal recessive mitochondrial disorder caused by homozygous or biallelic pathogenic variants in the IBA57 gene. The IBA57 gene product is a nuclear-encoded mitochondrial protein that plays an important role in the maturation of [4Fe-4S] cluster-binding proteins (Mandigers et al., 2023). To date, more than 30 pathogenic variants in the IBA57 gene have been reported, mostly causing psychomotor regression, progressive spasticity, and visual impairment (Camponeschi et al., 2022).

Accurate genetic testing and confirmation of a genetic diagnosis are essential for patients and their families, as they provide critical information on prognosis and treatment and enable appropriate genetic counselling and informed reproductive decision-making (Mavraki et al., 2023). Accurate diagnosis of mitochondrial diseases remains challenging due to their genetic and phenotypic heterogeneity, the wide range of clinical symptoms, and the involvement of more than 300 genes. Advances in technology have led to the development of various genetic diagnostic approaches and techniques, ranging from single-nucleotide polymorphism (SNP) detection to whole-genome sequencing (WGS) (Belousova et al., 2025), resulting in an increase in diagnostic success from under 20% to over 60% (Gorman et al., 2016).

In the current study, we present a case report on prenatal genetic testing for multiple mitochondrial dysfunction syndrome (MMDS) type 3 caused by the IBA57 gene to highlight the importance of prenatal diagnostics for disease prognosis and treatment, appropriate genetic counselling, and informed reproductive decision-making.

Materials and methods

Recruitment of patients and ethics. Patients for prenatal diagnosis are recruited among pregnant women registered at antenatal clinics, as well as

families with a confirmed or suspected risk of hereditary diseases such as epilepsy, neuromuscular disorders, and other neurogenetic pathologies. Recruitment was performed on the basis of the National Scientific Center for Maternal and Child Health, University Medical Center (Astana, Kazakhstan). Selection is conducted in accordance with established inclusion and exclusion criteria agreed upon with the local bioethics committee. Indications for prenatal diagnosis were: the presence of a child with a monogenic pathology in the family (epilepsy, spinal muscular atrophy, multiple mitochondrial dysfunction syndrome) or known genotypes (unaffected carriers) of the parents.

This study was approved by the Local Ethics Committee of the National Laboratory Astana (No. 03-2024 from October 2, 2024), and the Local Ethics Committee at the Corporate Fund University Medical Center (No. 3/2025/ПЭ from April 28, 2025). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Interview and clinical data acquisition. All families underwent the information sessions or prenatal genetic counseling individually at the University Medical Center. Each genetic counseling session included an oral explanation of the genetic testing procedure, possible results, the method's limitations, and the ethical implications of participation. A genetic counseling specialist provides a conclusion and recommendations in a standard format, which are registered in the medical information system (MIS). Women and their partners were given the opportunity to ask questions, discuss the potential consequences of various test results, and make an informed decision about participation. This format complies with the principles of "informed choice" outlined in international guidelines for prenatal counseling. Following the discussion and confirmation of willingness to participate, written informed consent was issued, including separate sections on the nature of the test, data and biomaterial storage, and the right to withdraw consent. The process was documented in the project's research database, with a unique identifier assigned to the participant. This organization of work ensured a high level of trust between specialists and participants, as well as compliance with international bioethical principles when conducting genetic research among pregnant women and their families. An individual clinical record was created for each participant, including demographic data (age, ethnicity, place of residence), medical and obstetric history, family history of hereditary diseases, and results of laboratory and instrumental studies.

Biomaterial sampling, DNA isolation, and quality control. Following a medical genetic consultation and informed consent, biological material was collected from each participant. Blood from pregnant women (and their partners when needed) was collected into a blood collection tube containing K2EDTA (BD, Franklin Lakes, NJ, USA). For non-invasive prenatal testing (to isolate the placental fragments and circulating cell-free DNA), the blood was drawn into a commercially available blood collection system (Cell-Free DNA BCT, Streck, USA).

DNA of the pregnant woman and partner was extracted from 300 µL of whole blood using the Illustra Blood Genomic Prep Spin Kit (Cytivia, Marlborough, MA, USA), according to the manufacturer's instructions, and stored at −20°C. ccfDNA was isolated from 2 mL of plasma using QIAamp MinElute ccfDNA Kit (Qiagen, Germany), according to the manufacturer's instructions.

The quality and quantity of extracted DNA were assessed using the spectrophotometric method with the NanoDrop 2000 UV spectrophotometer (ThermoFisher Scientific, Waltham, MA, USA) and the fluorometric assay with the Qubit BR and HS Assay Kits (ThermoFisher Scientific, Waltham, MA, USA) on a Qubit v4.0 fluorometer. Additionally, fragment size distribution and the integrity of ccfDNA were evaluated using the High Sensitivity DNA reagents Kit (Agilent Technologies, USA) on an Agilent 2100 Bioanalyzer (Agilent Technologies, USA).

Confirmatory DNA sequencing. To confirm the variants identified by next-generation sequencing, Sanger sequencing was performed on gDNA obtained from family members' blood samples. Amplified PCR was performed in a final volume of 20 µL, containing 50 ng/µL of the gDNA, 10 pmol of the forward and reverse primers, 4 µL of 5× buffer 2.5 mM dNTP (Fermentas, Lithuania, Vilnius), and 0.2U of PhusionTM High-Fidelity DNA Polymerase (ThermoFisher, Cleveland, OH, USA). The thermal cycling conditions for PCR included initial denaturation for 5 min at 96 ◦C, followed by 35 cycles of denaturation at 94 ◦C for 30 s, annealing at 58 ◦C for 45 s, elongation at 72 ◦C for 45 s, and a final extension for 10 min at 72 ◦C. The PCR products were run on 1% agarose gel to detect DNA amplicon size. After verification, PCR products were purified using the ExoSAP-IT Express PCR Product Cleanup (Thermo Fisher Scientific, Wilmington, Germany). DNA sequencing of the PCR products was performed using the BigDye Terminator Cycle

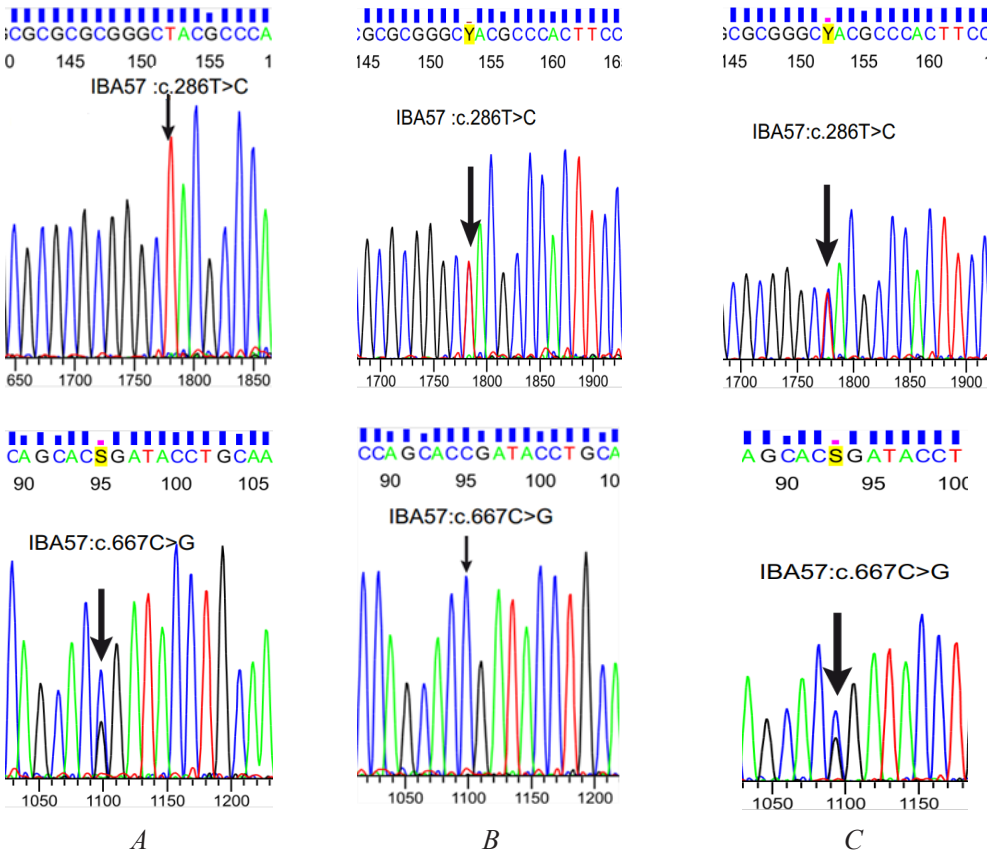
Sequencing v.3.1 kit (Applied Biosystems, Foster City, CA, USA) on the 3730 xL Genetic DNA Analyzer (Applied Biosystems, Foster City, CA, USA). Finally, sequencing analysis was conducted using the Data Collection Software (Applied Biosystems, Foster City, CA, USA).

Results and discussion

A 27-year-old G2P1001 at 22 weeks' gestation was recruited. Partner is a 32-year-old man, marriage is non-consanguineous. The medical history includes a child MMDS3 (OMIM 615330), an autosomal recessive inheritance, confirmed by whole exome sequencing (WES) and also verified by Sanger sequencing in the IBA57 gene c.286T>C (NM_001010867.4, p.Tyr96His) and c.667C>G (NM_001010867.4, p.Arg223Gly) in the proband and parents (Figure 1).

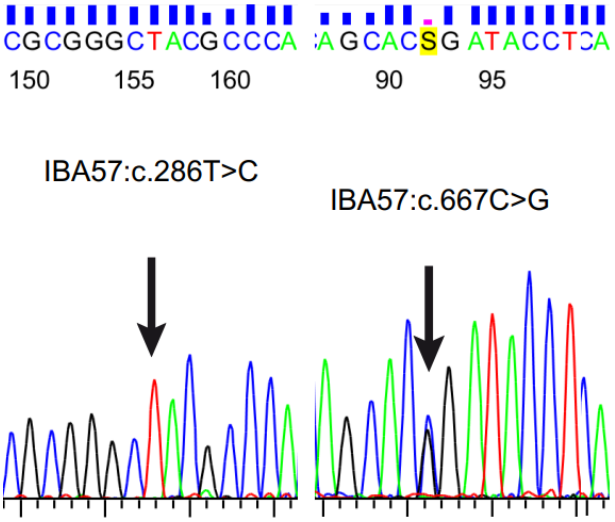
Proband has both heterozygous mutations in the IBA57 gene (c.286T>C and c.667C>G). Parents are obligate heterozygous carriers of the genetic variant in the IBA57 gene c.286T>C (mother) and c.667C>G (father). Given the 22 weeks' gestation, invasive prenatal testing was not possible due to high risk. A ccfDNA test for these genetic variants in the fetus is recommended, as is genetic examination of the newborn and postnatal genetic testing. Results of the ccfDNA genetic test (fetus) are shown in Figure 2.

Figure 1
Sequencing analysis of a family (father, mother, and proband)



A – Father, B – Mother, C – Proband

Figure 2
Sequencing analysis of a fetus



The ccfDNA genetic test revealed the absence of the heterozygous IBA57 gene variant at position c.286T>C (NM_001010867.4, p.Tyr96His), but the heterozygous IBA57 gene variant at position c.667C>G (NM_001010867.4, p.Arg223Gly) was detected. The labor was spontaneous, resulting in the birth of a male infant. Genetic counseling was provided. Confirmatory Sanger sequencing of the IBA57 variants c.286T>C and c.667C>G was recommended in accordance with ACMG guidelines. In the analyzed neonatal sample, previous results were confirmed.

Conclusion: The child is a heterozygous carrier of the genetic variant of the IBA57 gene at position c.667C>G (NM_001010867.4, p.Arg223Gly). No specific treatment is required; observation by a pediatrician and medical and genetic counseling of the couple when planning the next pregnancy are recommended.

Multiple mitochondrial dysfunctions syndrome-3 (MMDS3) is a severe autosomal recessive neurodegenerative disorder characterized by loss of previously acquired developmental milestones in the first months or years of life, caused by homozygous or compound heterozygous mutations in the IBA57 gene (Online Mendelian Inheritance in Man, 2026). Currently, more than 30 pathogenic variants of IBA57 have been reported, with a broad phenotypic spectrum ranging from severe intellectual disability to adolescent-onset spastic paraplegia (Camponeschi et al., 2022). The homozygous c.706C>T (Pro236Ser) mutation was associated with leukodystrophy and variable clinical phenotypes (Torraco et al., 2017), and the heterozygous Tyr219Cys mutation was associated with mitochondrial leukoencephalopathies in children (Bindu et al, 2018). Ajit Bolar et al. reported 2 sibs, born of consanguineous Moroccan parents, with a lethal encephalomyopathy and myopathy resulting from mitochondrial dysfunction (Ajit Bolar et al., 2013). Debray et al. reported a male infant born to consanguineous Moroccan parents with MMDS3. The newborn had progressive hypotonia, motor regression, and loss of previously acquired skills, including sitting, babbling, and visual tracking, and he died at age 17 months. WES detected a homozygous c.436C>T (p.Arg146Trp) variant in the IBA57 gene (Debray et al., 2015). Lang et al. reported the IBA57 c.310G>T (p.Gly104Cys) in a 2-month-old infant of Cuban descent with progressive hypotonia, weakness, and episodes of upgaze deviation (Lang et al., 2022). Sato et al. reported the same mutation but with a compound heterozygous genotype (c.49_67dup (p.Leu23fs) (Sato et al., 2021). Xu et al. reported compound heterozygous variants in the IBA57 gene: c.395_400dup (p.V132_Q133dup) and c.832delC (p.R278Afs*23). Both variants may alter the protein structure and stability, potentially resulting in partial or complete impairment of its activity and function (Xu et al., 2026).

In this report, we describe a heterozygous variant in the IBA57 gene at positions c.286T>C (NM_001010867.4, p.Tyr96His) and c.667C>G (NM_001010867.4, p.Arg223Gly). The Tyr96His mutation of IBA57 was found in a high number of patients, in heterozygosity with several missense (Gly63Asp, Thr106Ala, Gly252Cys) and non-missense (c.697C > T, Arg223*; p.307C > T, Gln103*; c.22C>T, Arg8*; c.522_523del, Leu175Alafs; c.589_590del, Arg197Alafs; c.1053G>A, Trp351*; c.589_590del, Arg197Alafs) mutations (Liu et al., 2018; Zhang et al., 2019; Hu et al., 2020)). Jiang et al. identified the IBA57 c.286T>C mutation as a hotspot mutation in Chinese patients with a stable natural history. Of 61 patients, 46 presented with MMDS3; 58.7% were of Chinese origin, and 85.2% had the c.286T>C mutation (Jiang et al., 2025). Xu et al. presented a case report on a child, aged 1 year and 2 months, who had motor decline, was unable to sit alone, had limited right arm movement, hypotonia, hyperreflexia of both knees, and Babinski sign positivity on the right side, accompanied by nystagmus. WES detected two heterozygous mutations in the IBA57 gene, c.286T>C (p.Y96H) (likely pathogenic, LP) and c.992T>A (p.L331Q) (variant of uncertain

significance, VUS) (Xu et al., 2024). Wu et al. presented a case report of two MMDS3 twin girls having compound heterozygous variants of the IBA57 gene, namely c.286T>C (p.Tyr96His) and c.307C>T (p.Gln103Ter). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, both variants were classified as pathogenic. However, after treatment with vitamins, levocarnitine, ATP, coenzyme Q10, and other medications and supplements, both children showed partial recovery of neurodevelopmental regression and improvement in motor, language, and cognitive development (Wu et al., 2025).

We did not identify homo- nor heterozygous mutation at position c.286T>C in the fetus sample, which, according to the ACMG guidelines, is considered as PM3_VeryStrong (highly pathogenic). However, we found a heterozygous variant in the IBA57 gene at position c.667C>G (NM_001010867.4, p.Arg223Gly). Currently, there are no reports on the pathogenicity of this variant; it is considered a VUS and has a single submission in the ClinVar database (ClinVar, 2026). Detection of a compound heterozygous variant in a proband diagnosed with MMDS3, likely the first such identification.

Given the family history of MMDS3 with a compound heterozygous IBA57 mutation in the proband and the genetic finding in fetal DNA, it was decided to prolong the pregnancy; however, confirmatory DNA sequencing after birth was recommended. Since the DNA sequencing results of the fetus and newborn are matched, only observation by a pediatrician was proposed.

Conclusion

The IBA57 gene-related MMDS3 can have a wide range of outcomes and consequences and may progress rapidly. Early awareness is crucial to prompt and proper administration. Our study reveals the importance of early prenatal genetic testing for IBA57-related MMDS3 for early diagnostics and consent decision-making.

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Author contributions

Aidana Gabdulkayum: Conceptualization, Data Curation, Formal Analysis, Investigation, Validation, Writing, Writing – review & Editing; Zhanel Mirmanova: Formal Analysis, Investigation, Validation; Tomiris Kadenova: Formal Analysis, Investigation, Validation; Mirgul Bayanova: Conceptualization, Data Curation, Formal Analysis, Investigation, Validation, Methodology, Resources; Lyazzat Nazarova: Formal Analysis, Investigation, Validation, Resources; Aidos Bolatov: Data Curation, Formal Analysis, Investigation; Adil Yerezhepov: Conceptualization, Data Curation, Methodology, Validation; Akbota Aitkulova: Conceptualization, Data Curation, Formal Analysis; Ainur Akilzhanova: Conceptualization, Data Curation, Formal Analysis; Dauren Yerezhepov: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Resources, Writing, Validation, Writing, Writing – review & Editing.

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Information about authors:

Aidana Kairatkyzy Gabdulkayum – Junior Researcher, Laboratory of Genomic and Personalized Medicine, PI "National Laboratory Astana" (Astana, Kazakhstan, e-mail: aidana.gabdulkayum@nu.edu.kz).

Zhanel Zhanatbekovna Mirmanova – Research Assistant, Laboratory of Genomic and Personalized Medicine, PI "National Laboratory Astana" (Astana, Kazakhstan, e-mail: zhanel.mirmanova@nu.edu.kz).

Tomiris Batyrbekovna Kadenova – Research Assistant, Laboratory of Genomic and Personalized Medicine, PI "National Laboratory Astana" (Astana, Kazakhstan, e-mail: tomiris.kadenova@nu.edu.kz).

Mirgul Faizullinovna Bayanova – Head of the Genetic Unit, Department of Laboratory Medicine, Pathology and Genetics, Corporate Found "University Medical Center" (Astana, Kazakhstan, e-mail: Mirgul.Bayanova@umc.org.kz).

Lyazzat Kenesovna Nazarova – MD, Clinical cytogeneticist, Corporate Found "University Medical Center" (Astana, Kazakhstan, e-mail: layzzat.nazarova@umc.org.kz).

Aidos Kanatovich Bolatov – Researcher, Department of Clinical and Genetic Diagnostics, Corporate Found "University Medical Center" (Astana, Kazakhstan, e-mail: bolatovaidos@gmail.com).

Adil Yerezhepov – Candidate of Biological Sciences, Associate Professor, Department of Biology and Biotechnology, NJSC "Al-Farabi Kazakh National University" (Almaty, Kazakhstan, e-mail: adil.yerezhepov@mail.ru).

Akbota Maratovna Aitkulova – PhD, Senior Researcher, Laboratory of Genomic and Personalized Medicine, PI "National Laboratory Astana" (Astana, Kazakhstan, e-mail: akbota.aitkulova@nu.edu.kz).

Ainur Rakhmetulovna Akilzhanova – Doctor of Medical Sciences, PhD, M.D., Professor, Head of Laboratory of Genomic and Personalized Medicine, PI "National Laboratory Astana" (Astana, Kazakhstan, e-mail: akilzhanova@nu.edu.kz).

Dauren Adilovich Yerezhepov (corresponding author) – PhD, Leading Researcher, Laboratory of Genomic and Personalized Medicine, PI "National Laboratory Astana" (Astana, Kazakhstan, e-mail: dauren.yerezhepov@nu.edu.kz).

Авторлар туралы мәлімет:

Айдана Қайратқызы Ғабдулкаюм – Кіші ғылыми қызметкер, Геномдық және дербес медицина зертханасы, Өмір туралы ғылымдар орталығы, National Laboratory Astana, Назарбаев Университеті (Астана, Қазақстан, e-mail: aidana.gabdulkayum@nu.edu.kz).

Жанель Жанатбековна Мирманова – Зерттеу көмекшісі, Геномдық және дербес медицина зертханасы, Өмір туралы ғылымдар орталығы, National Laboratory Astana, Назарбаев Университеті (Астана, Қазақстан, e-mail: zhanel.mirmanova@nu.edu.kz).

Томирис Батырбековна Каденова – Зерттеу көмекшісі, Геномдық және дербес медицина зертханасы, Өмір туралы ғылымдар орталығы, National Laboratory Astana, Назарбаев Университеті (Астана, Қазақстан, e-mail: tomiris.kadenova@nu.edu.kz).

Миргуль Файзуллиновна Баянова – Медицина ғылымдарының кандидаты, Клиникалық және генетикалық диагностика бөлімінің меңгерушісі, Зертханалық медицина, патология мен генетика департаменті, "University Medical Center" Корпоративті қоры (Астана, Қазақстан, e-mail: Mirgul.Bayanova@umc.org.kz).

Ляззат Кенесовна Назарова – клиникалық цитогенетик, Клиникалық және генетикалық диагностика бөлімі, Зертханалық медицина, патология мен генетика департаменті, "University Medical Center" Корпоративті қоры (Астана, Қазақстан, e-mail: lyazzat.nazarova@umc.org.kz).

Айдос Канатович Болатов – Зерттеуші, Клиникалық және генетикалық диагностика бөлімі, Зертханалық медицина, патология мен генетика департаменті, "University Medical Center" Корпоративті қоры (Астана, Қазақстан, e-mail: bolatovaidos@gmail.com).

Адил Ережепов – биология ғылымдарының кандидаты, доцент, Биология және биотехнология факультеті, «Әл-Фараби атындағы Қазақ ұлттық университеті» КеАҚ (Алматы, Қазақстан, e-mail: adil.yerezhepov@mail.ru).

Акбота Маратовна Айткулова – PhD, Аға ғылыми қызметкер, Геномдық және дербес медицина зертханасы, Өмір туралы ғылымдар орталығы, National Laboratory Astana, Назарбаев Университеті (Астана, Қазақстан, e-mail: akbota.aitkulova@nu.edu.kz).

Айнур Рахметуловна Акильжанова – Медицина ғылымдарының докторы, профессор, Геномдық және дербес медицина зертханасының меңгерушісі, Өмір туралы ғылымдар орталығы, National Laboratory Astana, Назарбаев Университеті (Астана, Қазақстан, e-mail: akilzhanova@nu.edu.kz).

Даурен Адилович Ережепов – PhD, жетекші ғылыми қызметкер, Геномдық және дербес медицина зертханасы, Өмір туралы ғылымдар орталығы, National Laboratory Astana, Назарбаев Университеті (Астана, Қазақстан, e-mail: dauren.yerezhepov@nu.edu.kz).

Сведения об авторах:

Айдана Қайратқызы Ғабдулкаюм – младший научный сотрудник, Лаборатория геномной и персонализированной медицины, National Laboratory Astana, Назарбаев Университет (Астана, Казахстан, e-mail: aidana.gabdulkayum@nu.edu.kz).

Жанел Жанатбековна Мирманова – ассистент исследователя, Лаборатория геномной и персонализированной медицины, National Laboratory Astana, Назарбаев Университет (Астана, Казахстан, e-mail: zhanel.mirmanova@nu.edu.kz).

Томирис Батырбековна Каденова – ассистент исследователя, Лаборатория геномной и персонализированной медицины, National Laboratory Astana, Назарбаев Университет (Астана, Казахстан, e-mail: tomiris.kadenova@nu.edu.kz).

Миргуль Файзуллиновна Баянова – кандидат медицинских наук, заведующая отделением клинико-генетической диагностики, Департамент Лабораторной медицины, патологии и генетики, Корпоративный фонд «University Medical Center» (Астана, Казахстан, e-mail: Mirgul.Bayanova@umc.org.kz).

Ляззат Кенесовна Назарова – врач-цитогенетик, отделение клинико-генетической диагностики, Департамент Лабораторной медицины, патологии и генетики, Корпоративный фонд «University Medical Center» (Астана, Казахстан, e-mail: layzzat.nazarova@umc.org.kz).

Айдос Канатович Болатов – исследователь, отделение клинико-генетической диагностики, Департамент Лабораторной медицины, патологии и генетики, Корпоративный фонд «University Medical Center» (Астана, Казахстан, e-mail: bolatovaidos@gmail.com).

Адил Ережепов – кандидат биологических наук, доцент, факультет биологии и биотехнологии, НАО «Казахский национальный университет имени аль-Фараби» (Алматы, Казахстан, e-mail: adil.yerezhepov@mail.ru).

Акбота Маратовна Айткулова – PhD, старший научный сотрудник, Лаборатория геномной и персонализированной медицины, National Laboratory Astana, Назарбаев Университет (Астана, Казахстан, e-mail: akbota.aitkulova@nu.edu.kz).

Айнур Рахметуловна Акильжанова – доктор медицинских наук, профессор, руководитель Лаборатории геномной и персонализированной медицины, National Laboratory Astana, Назарбаев Университет (Астана, Казахстан, e-mail: akilzhanova@nu.edu.kz).

Даурен Адилович Ережепов – PhD, ведущий научный сотрудник, Лаборатория геномной и персонализированной медицины, National Laboratory Astana, Назарбаев Университет (Астана, Казахстан, e-mail: dauren.yerezhepov@nu.edu.kz).

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