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Prenatal genetic testing for NDUFV1 gene-related mitochondrial complex I deficiency in a Kazakhstani family

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Abstract

Introduction. Mitochondrial diseases (MDs) are clinically heterogeneous disorders caused by mutations across a wide spectrum of genes encoded by the nuclear or mitochondrial genome, and have complex inheritance patterns, including X-linked or autosomal inheritance for mutations in nDNA genes, and maternal inheritance for mtDNA mutations. Mitochondrial complex I (MCI) is the largest and most complicated component of the respiratory chain. The NDUFV1 gene encodes an essential core subunit of the electron-input (N) module of mitochondrial complex I within the oxidative phosphorylation (OXPHOS) system.

Methods. Recruitment of the family took place at the Corporate Fund «University Medical Center» (UMC). Blood from the pregnant woman and her partner was collected into a blood collection tube. Chorionic villus sampling (CVS) was performed according to the standard operating procedure (SOP). DNA was isolated using commercially available kits. Variant verification was performed by Sanger sequencing. Sequencing data analyzed using Data Collection Software.
Results. A Kazakhstani family with a history of mitochondrial complex I deficiency (MCID), nuclear type 4, autosomal recessive inheritance pattern (OMIM: 618225) was recruited on the basis of the UMC. The parents were verified by Sanger sequencing and are obligate heterozygous carriers of genetic variants in the NDUFV1 gene at the following points: mother – NM_007103.4: c.289C>T (p.Leu97Phe), father – NM_007103.4: c.357G>C (p.Glu119Asp). Prenatal testing detected both heterozygous mutations in points NM_007103.4: c.262C>T (p.Arg88Cys) and NM_007103.4 c.357G>C (p.Glu119Asp) in the fetus. It was recommended to observe by a pediatrician with no specific treatment. Also, medical and genetic counseling of the couple when planning the next pregnancy was recommended.
Conclusion. NDUFV1-related MCID can lead to a broad spectrum of clinical outcomes and complications and may progress rapidly. Therefore, early recognition is essential to ensure timely diagnosis and appropriate management. Our findings highlight the importance of early prenatal genetic testing for NDUFV1-associated MCID, which can facilitate early detection and support informed decision-making during pregnancy.

Key words: mitochondrial diseases, prenatal genetic testing, NDUFV1, mitochondrial complex I deficiency.

1. Introduction

Mitochondria play a central role in cellular bioenergetics and the regulation of apoptosis, thereby maintaining normal cell function and influencing the activation of cell death pathways [1]. The majority of mitochondrial proteins are encoded by nuclear DNA (nDNA), while only a small proportion is encoded by mitochondrial DNA (mtDNA). Variants in mtDNA or in nuclear genes that regulate mitochondrial structure and function may lead to mitochondrial impairment and dysfunction [2]. Mitochondrial diseases (MDs) are clinically heterogeneous disorders caused by mutations across a wide spectrum of genes encoded by the nuclear or mitochondrial genome [3]. MDs comprise a heterogeneous group of inherited disorders characterized by impaired mitochondrial respiratory chain function, leading to disrupted cellular energy production [4]. The most common MDs are shown in Table 1.

Table 1 - Common mitochondrial syndromes

Syndrome	Main features	Genetic cause
Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke-like episodes (MELAS)	Stroke-like episodes, seizures, lactic acidosis	mtDNA mutations (MT-TL1)
Myoclonic Epilepsy with Ragged-Red Fibers (MERRF)	Myoclonic epilepsy, muscle weakness	mtDNA mutations
Leigh syndrome	Neurodegeneration in infancy	mtDNA or nuclear DNA
Leber hereditary optic neuropathy (LHON)	Optic neuropathy, vision loss	mtDNA mutations
Kearns–Sayre syndrome	Ophthalmoplegia, retinopathy	mtDNA deletions

MDs have complex inheritance patterns, including X-linked or autosomal inheritance for mutations in nDNA genes, and maternal inheritance for mtDNA mutations [5]. The occurrence frequency of

mtDNA mutations is much higher than that of nDNAs, since histones do not protect mtDNA, it is not efficiently repaired, and is more prone to mutations [6]. This led to an increase in reports of *de novo* mutations [7].

Mitochondrial complex I (MCI) is the largest and most complicated component of the respiratory chain, which consists of 44 subunits and is encoded by seven mitochondrial and 37 nuclear genes. Out of 44 genes, 14 code proteins of the core subunits and are conserved in most species [8]. The list of genes that encode the structural constituents of mammalian MCI is presented in Table 2.

Table 2 - Genes which encode the structural constituents of mammalian MCI

Nuclear genes	Mitochondrial genes	Genes involved in assembly
NDUFV1*, NDUFV2*, NDUFV3	ND1*	NDUFAF1 (CIA30)
NDUFS1*, NDUFS2*, NDUFS3*, NDUFS4, NDUFS5, NDUFS6, NDUFS7*, NDUFS8*	ND2*	NDUFA12L (B17.2L)
NDUFA1, NDUFA2, NDUFA3, NDUFA4, NDUFA5, NDUFA6, NDUFA7, NDUFA8, NDUFA9, NDUFA10, NDUFA11, NDUFA12, NDUFA13	ND3*	AIF
NDUFB1, NDUFB2, NDUFB3, NDUFB4, NDUFB5, NDUFB6, NDUFB7, NDUFB8, NDUFB9, NDUFB10, NDUFB11	ND4*	NDUFS4
NDUFAB1	ND4L*	Ecsit
NDUFC1	ND5*	C6ORF66
NDUFC2	ND6*	

** - genes coding core subunits*

Mitochondrial complex I deficiency (MCID) is the most frequent mitochondrial disorder presenting in childhood, accounting for up to one-third of cases. Like most MDs, MCID has a significant clinical and genetic variability, which poses substantial diagnostic difficulties, particularly due to the dual contribution of the nuclear and mitochondrial genomes. The most common clinical manifestations include Leigh syndrome, leukoencephalopathy, and other early-onset neurodegenerative conditions, as well as fatal infantile lactic acidosis, hypertrophic cardiomyopathy, and exercise intolerance. To date, pathogenic variants have been identified in 26 of these genes, including all seven mtDNA-encoded complex I subunits and 21 nuclear-encoded genes [9].

The *NDUFV1* gene encodes an essential core subunit of the electron-input (N) module of mitochondrial complex I within the oxidative phosphorylation (OXPHOS) system. It produces a 51-kDa flavoprotein subunit of NADH-ubiquinone oxidoreductase that catalyzes NADH oxidation and contributes to reactive oxygen species generation. Pathogenic variants in this gene are associated with diverse clinical phenotypes, most commonly fatal infantile lactic acidosis, Leigh syndrome, leukoencephalopathy and cardiomyopathy, optic neuropathy, cavitating leukodystrophy pattern, etc. [9-11].

Genetic testing and confirmation of a molecular diagnosis are crucial for affected individuals and their families, as they offer important insights into disease prognosis and therapeutic options, while facilitating appropriate genetic counselling and informed reproductive planning [12]. However, establishing a precise diagnosis of mitochondrial disorders remains complex because of their marked genetic and phenotypic diversity, broad spectrum of clinical manifestations, and the involvement of over 300 associated genes. Technological progress has enabled the development of a wide range of genetic diagnostic methods, spanning from single-nucleotide polymorphism (SNP) analysis to comprehensive next-generation sequencing (NGS) [13].

In this study, we report a case of prenatal genetic testing for *NDUFV1*-associated mitochondrial complex I deficiency, emphasizing the critical role of prenatal diagnostics in improving disease prognostication, guiding potential management strategies, facilitating appropriate genetic counselling, and supporting informed reproductive decision-making.

2. Materials and Methods

Recruitment of patients and ethics. Recruitment is conducted at the Corporate Fund "University Medical Center" (UMC). Patient selection is performed according to predefined inclusion and exclusion criteria approved by the local bioethics committee. Inclusion criteria were the first trimester pregnancy, registration at antenatal clinics, and a confirmed or suspected risk of hereditary neurogenetic conditions in the family anamnesis. Indications for prenatal testing include the presence of a child in the family affected by a monogenic disorder (such as epilepsy, spinal muscular atrophy, or multiple mitochondrial dysfunction syndrome), or previously identified parental genotypes, including carrier status in clinically unaffected 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. The family attended individualized information sessions and prenatal genetic counselling at the UMC. Each counselling session included a comprehensive oral explanation of the genetic testing procedure, potential outcomes, methodological limitations, and ethical considerations related to participation. A clinical geneticist provided a standardized written conclusion and recommendations, which were subsequently recorded in the medical information system (MIS). The woman and her partner were allowed to ask questions, discuss the possible implications of different test results, and make an informed decision regarding participation. This approach is consistent with the principle of "informed choice" outlined in international prenatal counselling guidelines. After confirming their willingness to proceed, written informed consent was obtained. The consent form included dedicated sections describing the nature of the test, storage of biological samples and genetic data, and the participant's right to withdraw consent at any stage. All procedures were documented in the project's research database, and a unique identification code was assigned to each participant to ensure confidentiality. This structured framework promoted a high level of trust between healthcare professionals and participants and ensured adherence to international bioethical standards for genetic research involving pregnant women and their families. An individual clinical record was created for each participant, containing demographic information (age, ethnicity, place of residence), medical and obstetric history, family history of hereditary disorders, and results of relevant laboratory and instrumental investigations.

Biomaterial sampling, DNA isolation, and quality control. Following a medical genetic consultation and informed consent, biological material was collected from each participant. Blood from the pregnant woman and her partner 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). For invasive prenatal diagnosis, fetal tissue samples were selected depending on the gestational age. Thus, chorionic villus (CV) sampling was performed between 9 and 11 weeks of pregnancy, and placentocentesis (PC) between 14 and 18 weeks of pregnancy.

DNA of pregnant woman and her 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. DNA from CVS was extracted by DNeasy Blood & Tissue Kit (Qiagen, Germany), according to the manufacturer's instructions. 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 Assay Kit (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).

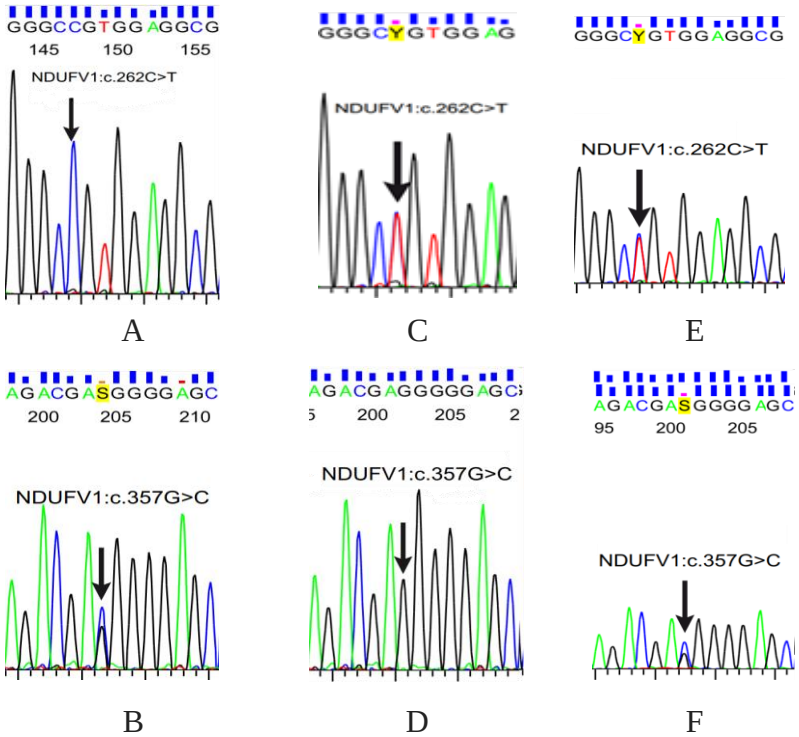
Confirmatory DNA sequencing. The variants identified by next-generation sequencing were confirmed by Sanger sequencing. PCR mixture in a final volume of 20 μL, consisted of 50 ng/μL of the gDNA, 10 pmol of the forward and reverse primers, 4 μL of 5× buffer 2.5 mM dNTP (Fermentas, Lithuania, Vilnius), and 0.2 U 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 epy 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). Finally, sequencing analysis was conducted using the Genetic DNA Analyzer (Applied Biosystems, Foster City, CA, USA). The sequencing analysis was conducted using the Data Collection Software (Applied Biosystems, Foster City, CA, USA).

3. Results

Clinical report. A 26-year-old G3P1101 at 10+2 weeks' gestation was recruited. Partner is a 31-year-old man. Marriage is non-consanguineous. Labor 1: Caesarean section, the child died at 4 months. According to the parents, the diagnosis was not established. Labor 2: girl, Caesarean section, diagnosed with mitochondrial complex I deficiency (MCID), nuclear type 4, autosomal recessive inheritance pattern (OMIM: 618225). A mutation was detected in the *NDUFV1* gene, at points NM_007103.4: c.262C>T (p.Arg88Cys) and NM_007103.4 c.357G>C (p.Glu119Asp), variant of uncertain significance (VUS), compound heterozygous. The parents were verified by Sanger sequencing and are obligate heterozygous carriers of genetic variants in the *NDUFV1* gene at the following points: mother – NM_007103.4: c.289C>T (p.Leu97Phe), father – NM_007103.4: c.357G>C (p.Glu119Asp). Genetic counselling recommended the IVF with PGT-M for known genetic variants. However, gestation occurred naturally. Non-invasive prenatal testing was performed, as well as invasive prenatal diagnostics at 10 weeks of pregnancy for Sanger sequencing of both variants in the *NDUFV1* gene. Prenatal testing detected both heterozygous mutations in points NM_007103.4: c.262C>T (p.Arg88Cys) and NM_007103.4 c.357G>C (p.Glu119Asp). The results of Sanger sequencing are presented in Figure 1.

Conclusion: The child is a heterozygous carrier of the *NDUFV1* c.289C>T variant (NM_007103.4, p.Leu97Phe) and *NDUFV1* c.357G>C variant (NM_007103.4, p.Glu119Asp). No specific treatment is required; observation by a pediatrician and medical and genetic counseling of the couple when planning the next pregnancy are recommended.



A, B – Father; C, D – Mother; E, F – Fetus.

Figure 1 – The results of Sanger sequencing

4. Discussion

Over the past three decades, mitochondrial dysfunction has been implicated in a broad spectrum of human disorders, including seizures, ataxia, cortical blindness, dystonia, exercise intolerance, ophthalmoplegia, optic atrophy, cataracts, diabetes mellitus, short stature, cardiomyopathy, sensorineural hearing loss, renal failure, and Alzheimer's Disease (AD) pathogenesis [14,15]. Among mitochondrial diseases, isolated MCID is the most common biochemical defect. It has been associated with pathogenic variants in genes encoding complex I structural subunits as well as its assembly factors.

Since Hatefi et al. isolated complex I from bovine heart mitochondria in 1962 [16], genes encoding all 44 subunits of the MCI and their functions were discovered. Out of 14 core subunits, 7 are coded by mtDNA, the other half by nDNA. Genetic variations in genes encoding core subunits are crucial ones.

To date, the ClinVar database of the National Center for Biotechnology Information (NCBI) contains 578 entries for NM_007103.4 (NDUFV1), of which 84 are pathogenic/likely pathogenic, 265 are benign/likely benign, and 177 are VUS [17].

Villain et al. reported of p.Arg386His variant in siblings with brainstem lesions and Leigh syndrome. The mutation, p.Arg386His (c.G1156A), affects a highly conserved residue, contiguous to a cysteine residue known to coordinate the Fe ion [18]. Marin et al. reported an association between Leigh syndrome and a novel mutation in the NDUFV1 and NDUFS2 genes. They found R386C, R88G, and R199P mutations in the NDUFV1 gene [19]. Wadhwa et al. reported a compound heterozygous missense pathogenic variant in exon 8 of the NDUFV1 gene [c.1156C>C/T (p.Arg386Cys)] and possibly a novel splice site variation in intron 2 of the NDUFV1 gene (c.155 + 1G > G/A) in a one-year-old boy with cystic leucoencephalopathy [20]. Srivastava et al. presented a case report on 2 children born to third-degree consanguineous parents. They found the novel homozygous missense c.1118T > C [p.(Phe373Ser)] and the biallelic c.1156C > T [p.(Arg386Cys)] NDUFV1 variants. They also concluded that this c.1156C>T [p.(Arg386Cys)]. The NDUFV1 variant is specific to South Asian populations, and it must be considered during diagnostic procedures [21]. Incecik et al. reported a homozygous mutation, p.Thr423Met, in the NDUFV1 gene in a 10-year-old boy with late-onset Leigh syndrome [22].

In the current study, we report on prenatal genetic testing results in a family with MCID history. Testing detected both heterozygous mutations in points NM_007103.4: c.262C>T (p.Arg88Cys) and NM_007103.4 c.357G>C (p.Glu119Asp) in the fetus. Both variants belong to an extremely low frequency in the gnomAD v4.0.0 dataset (total allele frequency: <0.001%). In silico tool predictions suggest a damaging effect of the variants on the gene or gene product [REVEL: 0.84 (>=0.6, sensitivity 0.68 and specificity 0.92)]. Since both variants of the NDUFV1 gene found in the fetus are VUS, it was recommended to prolong the pregnancy. Observation by a pediatrician of newborn and after-birth follow-up will increase our understanding of MCID pathology and benefit the medical and genetic counseling.

5. Conclusion

NDUFV1-related MCID can lead to a broad spectrum of clinical outcomes and complications and may progress rapidly. Therefore, early recognition is essential to ensure timely diagnosis and appropriate management. Our findings highlight the importance of early prenatal genetic testing for *NDUFV1*-associated MCID, which can facilitate early detection and support informed decision-making during pregnancy.

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Қазақстандық отбасында NDUFV1 генімен байланысты митохондриялық кешен I жеткіліксіздігіне пренаталдық генетикалық тестілеу

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Түйіндеме

Кіріспе. Митохондриялық аурулар (МД) – ядролық немесе митохондриялық геномнен кодталған гендердің кең спектріндегі мутациялардан туындаған клиникалық тұрғыдан гетерогенді бұзылулар. Олар ядролық ДНҚ (яДНҚ) гендеріндегі мутациялардың Х-байланысты немесе аутосомды тұқым қуалау және митохондриялық ДНҚ (мтДНҚ) мутацияларының аналық жағынан тұқым қуалау сияқты күрделі тұқым қуалаушылық қасиеттеріне ие болады. Митохондриялық кешен I (МКІ) – тыныс алу тізбегінің ең үлкен және ең күрделі компоненті. NDUFV1 гені тотығу фосфорлану (OXPHOS) жүйесіндегі митохондриялық I кешенінің электронды кіріс (N) модулінің маңызды негізгі суббірлігін кодтайды.

Әдістер. Отбасын іріктеу «University Medical Center» корпоративтік қорында (UMC) өтті. Жүкті әйел мен оның серіктесінің қан үлгілері қан алу түтікшелеріне жиналды. Хорионбүрлерінің сынамасын алустандартты операциялық процедураға (СОП) сәйкес жүргізілді. ДНҚ коммерциялық қолжетімді жинақтарды пайдаланып бөлініп алынды. Вариантты тексеру Сэнгердің секвенирлеу әдісінің көмегімен іске асырылды. Секвенирлеу деректері Data Collection Software бағдарламалық жасақтамасының көмегіен талданды.

Нәтижелер. UMC негізінде митохондриялық кешен I жетіспеушілігі (MCID), ядролық типті 4, аутосомды-рецессивті тұқым қуалау үлгісінің (OMIM: 618225) тарихы бар қазақстандық отбасы іріктелді. Ата-аналар Сангер секвенирлеуімен тексерілді және келесі нүктелерде NDUFV1 геніндегі нұсқалардың облигатты гетерозиготалы тасымалдаушылары болатыны анықталды: анасы – NM_007103.4: c.289C>T (p.Leu97Phe), әкесі – NM_007103.4: c.357G>C (p.Glu119Asp). Пренаталды тестілеу ұрықта NM_007103.4: c.262C>T (p.Arg88Cys) және

NM_007103.4 c.357G>C (p.Glu119Asp) нүктелерінде гетерозиготалы мутацияларды анықтады. Арнайы ем шаралары қажет емес, педиатрдың бақылауында болу ұсынылды. Сондай-ақ, келесі жүктілікті жоспарлау кезінде жұпқа медициналық және генетикалық кеңес беру ұсынылды.

Қорытынды. NDUFV1 геніне байланысты MCID клиникалық нәтижелер мен асқынулардың кең ауқымды түрлеріне әкелуі. Сондықтан, уақтылы диагноз қоюды және тиісті емдеуді қамтамасыз ету үшін генетикалық негізді ерте анықтау өте маңызды. Біздің зерттеу нәтижелері NDUFV1 геніне байланысты MCID үшін ерте пренаталды генетикалық тестілеудің маңыздылығын көрсетеді, бұл ерте анықтауды жеңілдетеді және жүктілік кезінде ақпараттандырылған шешім қабылдауға көмектеседі.

Түйін сөздер: митохондриялық аурулар, пренатальды генетикалық тестілеу, NDUFV1, митохондриялық I кешенінің жетіспеушілігі.

Пренатальное генетическое тестирование на дефицит митохондриального комплекса I, связанный с геном NDUFV1, в казахстанской семье

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Резюме

Введение. Митохондриальные заболевания (МЗ) — это клинически гетерогенные расстройства, вызванные мутациями в широком спектре генов, кодируемых ядерным или митохондриальным геномом, и имеющие сложные модели наследования, включая Х-сцепленное или аутосомное наследование для мутаций в генах ядерной ДНК и материнское наследование для мутаций митохондриальной ДНК. Митохондриальный комплекс I (МКI) является самым крупным и сложным компонентом дыхательной цепи. Ген NDUFV1 кодирует важную базовую субъединицу модуля ввода электронов (N) митохондриального комплекса I в системе окислительного фосфорилирования (OXPHOS).

Методы. Набор членов семьи проводился в корпоративном фонде «University Medical Center» (UMC). У беременной женщины и ее партнера брали кровь в пробирку. Биопсия ворсинок хориона (БВХ) проводилась в соответствии со стандартной операционной процедурой (СОП). ДНК выделяли с использованием коммерчески доступных наборов. Верификацию вариантов проводили методом секвенирования по Сэнгеру. Данные секвенирования анализировали с помощью программного обеспечения Data Collection Software.

Результаты. В исследование была включена казахстанская семья, рекрутированная на базе UMC, с анамнезом дефицита митохондриального комплекса I (MCID), ядерного типа 4, аутосомно-рецессивного типа наследования (OMIM: 618225). Варианты родителей были подтверждены секвенированием по Сэнгеру. Они

являются облигатными гетерозиготными носителями генетических вариантов в гене NDUFV1 в следующих точках: мать – NM_007103.4: c.289C>T (p.Leu97Phe), отец – NM_007103.4: c.357G>C (p.Glu119Asp). Пренатальное тестирование выявило у плода гетерозиготные мутации в точках NM_007103.4: c.262C>T (p.Arg88Cys) и NM_007103.4 c.357G>C (p.Glu119Asp). Было рекомендовано наблюдение у педиатра, специфического лечения не назначалось. Также было рекомендовано медицинское и генетическое консультирование пары при планировании следующей беременности.

Заключение. Связанные с NDUFV1 MCID могут приводить к широкому спектру клинических исходов и осложнений и могут быстро прогрессировать. Поэтому раннее выявление имеет важное значение для своевременной диагностики и надлежащего лечения. Наши результаты подчеркивают важность раннего пренатального генетического тестирования на минимальные клинические проявления, связанные с NDUFV1, которое может способствовать раннему выявлению и принятию обоснованных решений во время беременности.

Ключевые слова: митохондриальные заболевания, пренатальное генетическое тестирование, NDUFV1, дефицит митохондриального комплекса I.