MEDICAL SCIENCES

OPEN ACCESS

CLINICAL, BIOCHEMICAL, AND GENETIC DISTINCTIONS IN PATIENTS WITH MITOCHONDRIAL INVOLVEMENT VERSUS OTHER GENETIC DISORDERS

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https://doi.org/10.38045/ohrm.2026.1.05 CZU: 616-056.7:[575.224:576.311.347]

ABSTRACT

Introduction Mitochondrial diseases are clinically and genetically heterogeneous disorders characterized by respiratory chain dysfunction, often mimicking other multisystem genetic conditions, necessitating an integrated clinical, biochemical, and molecular diagnosis. This study aims to compare the clinical, biochemical, and genetic profiles of patients with mitochondrial involvement and those with other inherited genetic disorders.

Material and methods We analyzed 81 patients with suspected mitochondrial disease (Nijmegen Mitochondrial Disease Score ≥3), categorized into Group 1 (mitochondrial involvement) and Group 2 (other inherited disorders). Clinical, biochemical, instrumental, and molecular evaluations were performed using qPCR-HRM and Sanger sequencing, with data analyzed through descriptive statistics and non-parametric tests.

Results Group 1 showed significantly higher rates of severe neuromuscular impairment, skill regression, ocular abnormalities, elevated plasma lactate and alanine, and characteristic neuroimaging findings, including basal ganglia abnormalities and cerebral-cerebellar atrophy. Genetic analysis identified phenotype-associated mutations in 32 patients, primarily affecting Complex I and V subunits and mitochondrial RNA genes, often involving multiple respiratory chain sites. Group 2 comprised a range of genetically confirmed non-mitochondrial disorders, identified through targeted genomic testing.

Conclusions This study highlights the crucial role of integrated clinical, biochemical, and genomic approaches, emphasizing the importance of comprehensive molecular testing and multidisciplinary evaluation in addressing the diagnostic complexities of overlapping genetic disorders.

Keywords Mitochondrial diseases, mitochondrial DNA, Sanger sequencing, qPCR-HRM.

CARACTERISTICI CLINICE, BIOCHIMICE ȘI GENETICE DISTINCTIVE LA PACIENȚII CU AFECTARE MITOCONDRIALĂ COMPARATIV CU ALTE AFECȚIUNI GENETICE EREDITARE

Introducere Bolile mitocondriale reprezintă tulburări clinice și genetice eterogene, caracterizate prin disfuncția lanțului respirator, frecvent mimând alte afecțiuni genetice multisistemice, ceea ce impune un diagnostic integrat clinic, biochimic și molecular. Acest studiu își propune să compare profilurile clinice, biochimice și genetice ale pacienților cu afectare mitocondrială și ale celor diagnosticați cu alte boli genetice ereditare.

Material și metode Au fost analizați 81 de pacienți cu suspiciune de boală mitocondrială (Scor clinic Nijmegen ≥3), împărțiți în două grupuri-țintă: grupul 1 (afectare mitocondrială) și grupul 2 (alte afecțiuni ereditare). Evaluările clinice, biochimice, instrumentale și moleculare au inclus qPCR-HRM și secvențierea Sanger, iar datele au fost analizate prin statistica descriptivă și teste neparametrice.

Rezultate Grupul 1 a prezentat rate semnificativ mai mari de afectare neuromusculară severă: pierderea achizițiilor motorii, anomalii oculare, lactat și alanină plasmatică crescute, precum și modificări neuroimagistice caracteristice (afectarea ganglionilor bazali, atrofie cerebrală și cerebeloasă). Testele genetice au identificat mutații asociate fenotipului la 32 dintre pacienți, predominant în subunitățile Complexelor I și V și genele ARN mitocondrial, adesea cu implicare concomitentă a mai multor complexe respiratorii. Grupul 2 a inclus o varietate de afecțiuni genetice non-mitocondriale, confirmate prin teste genomice țintite.

Concluzii Studiul subliniază rolul esențial al abordării integrate clinic, biochimic și genomic, accentuând testarea moleculară completă și evaluarea multidisciplinară pentru a depăși complexitatea diagnosticului în afecțiunile genetice suprapuse.

Cuvinte-cheie Boli mitocondriale, ADN mitocondrial, secvențiere Sanger, qPCR-HRM.

INTRODUCTION

Mitochondrial diseases represent a clinically and genetically heterogeneous group of disorders caused by dysfunction of the mitochondrial respiratory chain, predominantly affecting tissues with high energy demands. With an estimated prevalence of approximately 1 in 4,300 individuals, they are among the most common inherited metabolic disorders (1). However, establishing a definitive diagnosis remains challenging due to the nonspecific and overlapping nature of clinical manifestations, which often mimic those of other multisystem genetic conditions (2, 3).

In the absence of universally reliable biomarkers, the diagnostic evaluation of patients with suspected mitochondrial involvement often relies on integrative clinical scores, such as the Nijmegen Mitochondrial Disease Score (NMDS) (4). These tools incorporate clinical symptoms, biochemical findings, and instrumental investigations to guide further testing. However, their utility in distinguishing mitochondrial involvement from other genetic disorders remains limited, particularly in the absence of molecular confirmation.

In this context, targeted molecular screening approaches, such as High-Resolution Melting qPCR (qPCR-HRM) for common mitochondrial DNA mutations, followed by Sanger sequencing of coding mitochondrial genes in high-scoring patients, can enhance diagnostic accuracy. Importantly, a substantial proportion of individuals referred for suspected mitochondrial disease are ultimately found to harbor pathogenic variants associated with non-mitochondrial genetic syndromes, many of which present with phenotypes that closely resemble mitochondrial disorders.

This study aims to conduct a comparative analysis of the clinical, biochemical, and genetic features of patients with mitochondrial involvement, defined by the presence of mitochondrial DNA mutations consistent with the individual phenotype, and those diagnosed with other inherited genetic disorders.

MATERIALS AND METHODS

This research was designed as an observational, prospective study and was conducted between March 2021 and November 2024 at the National Center for Reproductive Health and Medical Genetics, Institute of Mother and Child, Republic of Moldova.

Patient Selection and Cohort Overview

Patient selection was based on clinical suspicion of mitochondrial disease, assessed using the Nijmegen Mitochondrial Disease Score (NMDS), a validated, domain-based diagnostic tool that integrates clinical manifestations, metabolic and biochemical abnormalities, neuroimaging findings, and, in its original form, muscle biopsy and respiratory chain enzymology (4). In the original scoring system, NMDS values of 0–1 indicate that mitochondrial disease is unlikely; scores of 2–4 suggest possible mitochondrial disease; 5–7 indicate probable disease; and scores of 8 or higher are consistent with definite mitochondrial involvement.

In this study, a modified version of the NMDS was implemented to accommodate local diagnostic constraints. The entire biopsy and enzymatic domain (Section IV of the original NMDS), which includes histopathological features such as ragged-red fibers, cytochrome c oxidase–negative fibers, and respiratory chain complex deficiencies, was omitted due to the limited availability of

muscle biopsy and enzymatic testing in our setting. The modified NMDS was therefore calculated using only the remaining domains: clinical, biochemical/metabolic, and neuroimaging criteria. Importantly, the internal scoring within each retained category remained unchanged; as a result, while the maximum attainable score was reduced, the relative weight and discriminative structure of the scale were preserved.

Given that the modification reduced the maximum attainable score, a threshold of ≥3 points was retained to preserve diagnostic sensitivity. This decision was supported by two considerations: first, published NMDS classifications indicate that scores of 3 or higher already correspond to the "possible mitochondrial disease" category, capturing early or partially expressed phenotypes; second, preliminary assessment of our dataset showed that maintaining this threshold ensured adequate inclusion of patients who were later found to carry pathogenic mitochondrial variants, whereas increasing it would have excluded clinically relevant cases. The resulting modified NMDS thus represents a pragmatic and context-adapted approach that preserves the scale's discriminatory structure in the absence of biopsy data.

Written informed consent was obtained from all patients or their legal guardians prior to inclusion, ensuring voluntary participation and compliance with ethical research standards.

A total of 240 patients with a modified NMDS ≥3 were initially enrolled. From this cohort, 81 patients for whom a molecular genetic result suggestive of a specific diagnosis had been received were selected for comparative analysis:

- Group 1 (n = 37): Patients with mitochondrial involvement, defined by the presence of mitochondrial DNA variants, identified via qPCR-HRM or Sanger sequencing, that correlated with the patient's clinical phenotype, as well as five patients with variants in nuclear genes related to mitochondrial function, identified through next-generation sequencing or targeted Sanger analysis.
- Group 2 (n = 44): Patients with other inherited genetic disorders, diagnosed through targeted gene panels, clinical exome sequencing, or other molecular approaches.

Clinical and Laboratory Assessment

All patients included in the study underwent a detailed clinical assessment, including both medical history and neurological examination. Standard laboratory testing comprised hematological parameters, kidney and liver function, serum electrolytes, blood gas analysis, lactate, creatine kinase, and uric acid. In addition, ammonia levels, urinary organic acid analysis, acylcarnitine profile, and plasma amino acid profiles were included, when available, as part of the extended metabolic assessment. Complementary instrumental evaluations, such as electromyography, electroencephalography, electrocardiography, audiometry, and cerebral imaging (MRI or CT) were performed based on symptomatology to evaluate multisystemic or neurological involvement.

Molecular and Genetic Profiling

All patients first underwent molecular prescreening at the Scientific Laboratory of Human Molecular Genetics, Institute of Mother and Child, using a high-resolution melting (qPCR-HRM) assay targeting seven recurrent mitochondrial DNA point mutations (m.3243A>G, m.8344A>G, m.8993T>G/C, m.13513G>A, m.3460G>A, m.11778G>A, and m.14484T>C). The assay was specifically optimized for the detection of these canonical pathogenic variants, with its analytical performance validated using synthetic oligonucleotide

controls encompassing both wild-type and mutant sequences, thereby providing internal reference standards for melting-curve profiling and calibration. Given the intrinsic limitations of HRM in reliably detecting variants at low heteroplasmic levels, the workflow was systematically complemented by PCR-RFLP analysis, with fragment ratios quantified in ImageJ to obtain a semi-quantitative estimation of heteroplasmy. Importantly, all cases with positive, borderline, or otherwise inconclusive HRM signatures were advanced to confirmatory Sanger sequencing of the corresponding mitochondrial regions, ensuring definitive molecular characterization and mitigating the risk of false-positive or unresolved findings.

Patients with a modified Nijmegen score of ≥6, as well as those exhibiting suggestive or ambiguous findings on the initial screening assay, were referred for targeted mitochondrial genome sequencing using Sanger sequencing by capillary electrophoresis. This analysis encompassed all 13 protein-coding mitochondrial genes, along with the adjacent mitochondrial rRNA and tRNA regions, ensuring coverage of genomic loci with established relevance to primary mitochondrial pathology. All detected variants were systematically evaluated and classified according to the American College of Medical Genetics and Genomics (ACMG) criteria, using curated reference databases and established interpretation frameworks.

For individuals assigned to Group 2, comprehensive genomic analyses, including whole-exome sequencing (WES), whole-genome sequencing (WGS), targeted multigene panels, and, in rare cases, array comparative genomic hybridization (aCGH), were performed in ISO 15189-accredited laboratories, ensuring methodological rigor, reproducibility, and full compliance with international quality standards. WES was conducted using commercially available exome capture kits such as Agilent SureSelect or IDT xGen, and sequenced on high-throughput instruments to achieve a mean coverage of ≥100× across coding regions, with over 98% of bases covered at ≥20×. Targeted NGS panels encompassing 50–480 genes were sequenced on benchtop or mid-throughput platforms with average coverage exceeding 150× and >99% of targeted regions covered at ≥30×. WGS was performed with PCR-free library preparation to attain an average genome-wide depth of approximately 30×. All sequencing datasets were processed through standardized bioinformatic pipelines, including alignment to the human reference genome, variant calling, annotation, and, when indicated, copy-number assessment using dedicated computational tools. Detected variants were rigorously interpreted following ACMG-AMP 2015 guidelines and classified as pathogenic, likely pathogenic, or variants of uncertain significance, providing a consistent and clinically meaningful framework for molecular diagnosis.

Statistical Analysis

Descriptive statistics were used to summarize clinical, laboratory, and instrumental findings. The normality of continuous variables was assessed using the Shapiro-Wilk test, confirming approximately normal distributions. Accordingly, comparisons of continuous variables were performed using independent samples t-test or one-way ANOVA, while categorical variables were analyzed with the Chi-square test. All statistical analyses were conducted in IBM SPSS Statistics (version 27.0), with significance set at $p < 0.05$.

RESULTS

Analysis of the molecular findings alongside clinical and biochemical data revealed significant differences between patients exhibiting mitochondrial DNA variants correlated with their phenotype and those diagnosed with alternative genetic conditions.

Clinically, both groups exhibited overlapping features such as developmental delay, hypotonia, and seizures; however, several manifestations were significantly more prevalent among patients with mitochondrial involvement. Severe neuromuscular impairment ($\chi^2 = 6.16$, $p = 0.013$) and regression of previously acquired skills ($\chi^2 = 4.52$, $p = 0.033$) were more frequently observed in Group 1, reflecting the progressive and multisystemic nature characteristic of mitochondrial dysfunction. In addition, ocular abnormalities, particularly ophthalmoplegia ($\chi^2 = 7.70$, $p = 0.006$) and optic nerve atrophy ($\chi^2 = 4.94$, $p = 0.026$), were significantly associated with this group. In contrast, dysmorphic features ($\chi^2 = 4.30$, $p = 0.038$) and intellectual disability ($\chi^2 = 3.92$, $p = 0.048$) were more commonly reported among patients in Group 2. An overview of the clinical signs and symptoms observed in both groups, including the percentage of affected patients and the corresponding p-values for features reaching statistical significance, is presented in Figure 1.

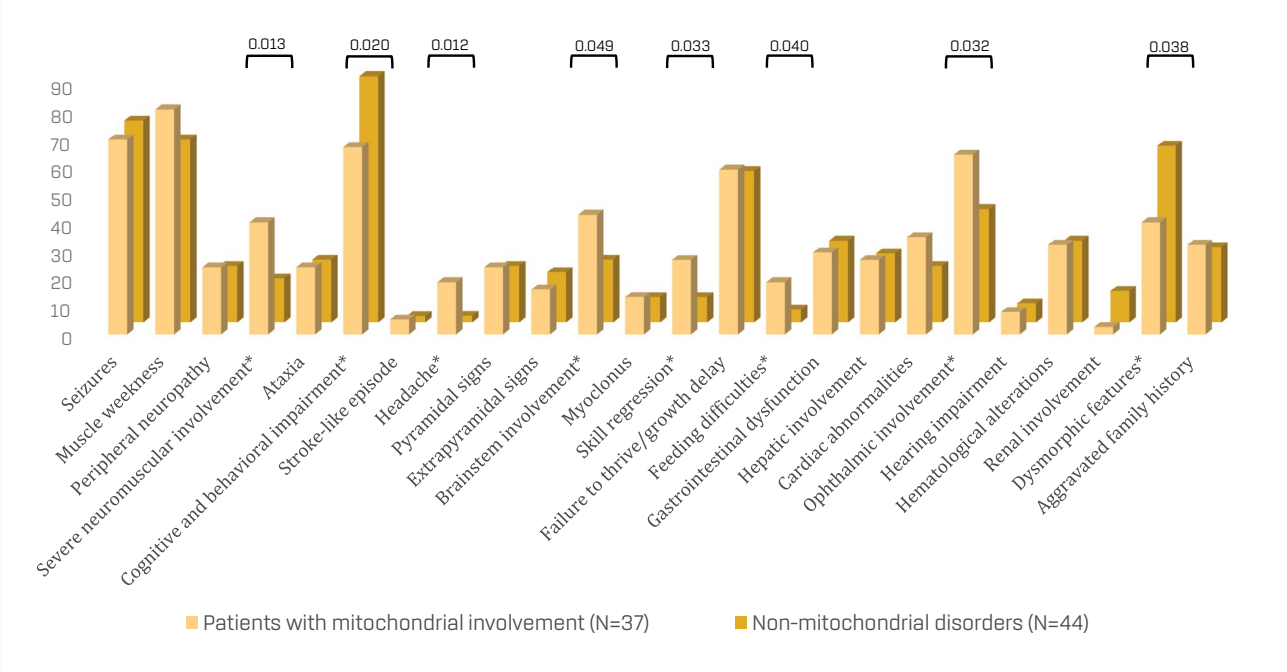

Figure 1. Prevalence of clinical features in patients with mitochondrial and other genetic disorders (p-values indicate intergroup significance).

Biochemically, plasma lactate levels were significantly higher in the mitochondrial group compared to the non-mitochondrial group (mean 3.6 mmol/L vs. 2.2 mmol/L), with one-way ANOVA revealing a robust group effect ($F(1, 74) = 9.74$, $p = 0.003$). This suggests that elevated lactate may serve as a relevant indicator in the context of mitochondrial involvement. Additionally, plasma alanine levels were significantly higher in patients with mitochondrial involvement (mean ± SD: 441 ± 45 µmol/L) compared to those with other genetic disorders (262 ± 22 µmol/L; $p < 0.001$), as revealed by independent samples t-test, thereby reinforcing the potential utility of amino acid profiling in the biochemical evaluation of suspected mitochondrial dysfunction.

Mean values of several biochemical markers, including creatine kinase (CK: 281 ± 66 U/L vs. 210 ± 32 U/L), lactate dehydrogenase (LDH: 541 ± 175 U/L vs. 395 ± 3 U/L), alanine aminotransferase (ALT: 93 ± 49 U/L vs. 49 ± 8 U/L), and aspartate aminotransferase (AST: 247 ± 193 U/L vs. 68 ± 12 U/L), were higher in the mitochondrial group compared to the non-mitochondrial group. However, none of these differences reached statistical significance, limiting their individual diagnostic utility in distinguishing between the two conditions. Other specialized metabolic investigations, such as ammonia levels, urinary organic acid analysis, and acylcarnitine profiling, did not reveal statistically significant differences between groups, but remain essential components of a comprehensive diagnostic workup given their potential to uncover subtle metabolic abnormalities.

Electrophysiological studies revealed abnormal electromyography findings in 27% of Group 1 patients compared to 21% in Group 2, while abnormal electroencephalography patterns were observed in 57% and 65%, respectively. These differences were not statistically significant. However, significant deviations on electrocardiograms were more frequently detected in Group 1 (χ^2 = 4.108, p = 0.043), underscoring the cardiovascular involvement associated with mitochondrial dysfunction. Neuroimaging abnormalities were observed in 75.7% of patients with mitochondrial involvement compared to 68.2% in the non-mitochondrial group. Notably, Group 1 exhibited a significantly higher prevalence of basal ganglia alterations (χ^2 = 4.95, p = 0.026) as well as cerebral and cerebellar atrophy (χ^2 = 6.16, p = 0.013), highlighting characteristic neuroanatomical changes associated with mitochondrial pathology. Figure 2 illustrates the percentage of patients in both groups exhibiting biochemical, instrumental, and neuroimaging abnormalities, with p-values indicated for statistically significant differences.

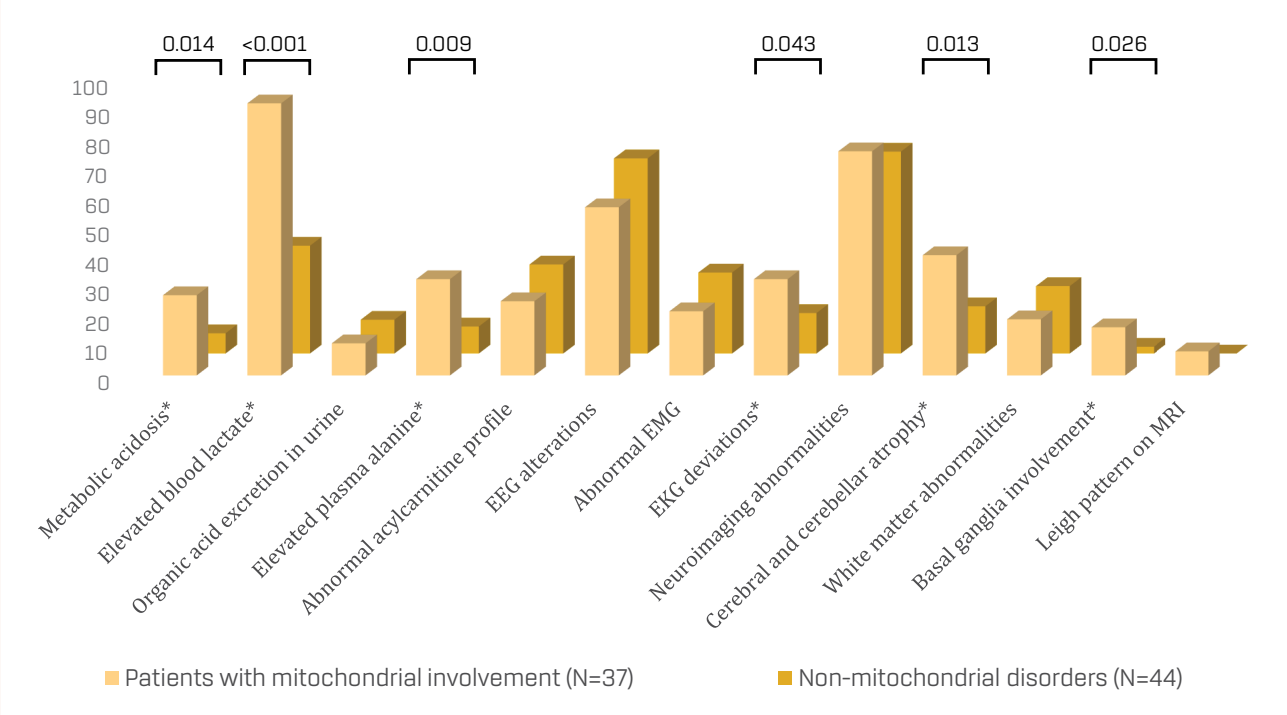

Figure 2. Prevalence of biochemical, instrumental, and neuroimaging abnormalities in patients with mitochondrial and other genetic disorders (p-values indicate intergroup significance).

Legend: EEG – Electroencephalography; EMG – Electromyography; EKG – Electrocardiography; MRI – Magnetic Resonance Imaging.

Genetic investigations further elucidated the molecular basis of the observed clinical and laboratory features. Eight patients were identified with common pathogenic point mutations through qPCR-HRM screening, including m.3243A>G (n=3), m.8993T>G (n=2), m.11778G>A (n=1), and m.3460G>A (n=2). Subsequent Sanger sequencing of the mitochondrial genome, focusing primarily on protein-coding genes, uncovered additional variants.

The identified variants predominantly involved genes encoding subunits of Complex I (*MT-ND* genes), representing 25.0% of cases, followed by mitochondrial RNA genes at 21.9%, Complex V subunits (*MT-ATP* genes) at 15.6%, and genes associated with Complex III (*MT-CYB*) and Complex IV (*MT-CO2*), each accounting for 3.1%. A notable proportion of patients (31.3%) harbored mutations affecting multiple respiratory chain complexes, suggesting broader mitochondrial dysfunction. However, the presence of combined complex involvement did not correlate significantly with increased clinical severity ($p = 0.064$). Figure 3 presents the gene-level distribution of variants detected in patients with mitochondrial involvement, highlighting the most frequently affected genes within this group.

Among the subset of patients who underwent partial mitochondrial genome sequencing, 19 individuals (59.4%) were found to carry pathogenic or likely pathogenic variants, while 13 (40.6%) harbored variants of uncertain significance (VUS). However, when considering the entire group of patients with mitochondrial involvement, including those harboring pathogenic variants in nuclear genes implicated in mitochondrial dysfunction, approximately 65% carried pathogenic or potentially pathogenic variants, and around 35% had VUS. Most of these uncertain variants were located in genes encoding Complex I subunits (34.1%), followed by Complex V (29.2%) and Complex IV (17.0%). Notably, individuals with pathogenic or likely pathogenic variants exhibited significantly higher NMDS scores compared to those with VUS ($\chi^2 = 6.82$, $p = 0.033$), suggesting a greater clinical impact in genetically confirmed cases.

Within the subgroup of patients carrying nuclear gene mutations associated with mitochondrial dysfunction, pathogenic variants were identified in genes involved in key aspects of mitochondrial maintenance and metabolism. These included *POLG* (n = 2), which encodes the mitochondrial DNA polymerase essential for mtDNA replication and repair; *TWNK* (n = 1) and *DGUOK* (n = 1), both critical for mitochondrial DNA maintenance; *ETHE1* (n = 1), implicated in sulfide detoxification within the mitochondrial matrix; and *OPA1* (n = 1), a gene involved in mitochondrial inner membrane fusion and cristae remodeling. Notably, the patient with the *OPA1* mutation also carried the common pathogenic mtDNA variant m.3243A>G, suggesting a potential synergistic effect in disease expression.

Figure 3 presents the gene-level distribution of variants detected in patients with mitochondrial involvement, highlighting the most frequently affected genes within this group.

In contrast, Group 2 encompassed a heterogeneous array of inherited disorders that phenotypically overlapped with mitochondrial disease. These included syndromic or multisystemic genetic conditions (36.4%), neurometabolic disorders (27.3%), ion channelopathies and epileptic encephalopathies (18.2%), neuromuscular disorders (11.3%), and chromosomal microdeletion syndromes (6.8%). The gene-specific distribution of variants identified in Group 2 is presented in Figure 4, highlighting the relative frequency of each affected gene within the spectrum of non-mitochondrial genetic disorders. Diagnostic confirmation in this group was achieved through targeted next-generation sequencing (NGS) panels, clinical exome sequencing, or array comparative genomic hybridization (aCGH), depending on the clinical suspicion. In

several cases, functional studies such as neurotransmitter metabolite profiling or advanced neuroimaging (including MR spectroscopy) were essential to support the genetic findings and to delineate the pathophysiological mechanism.

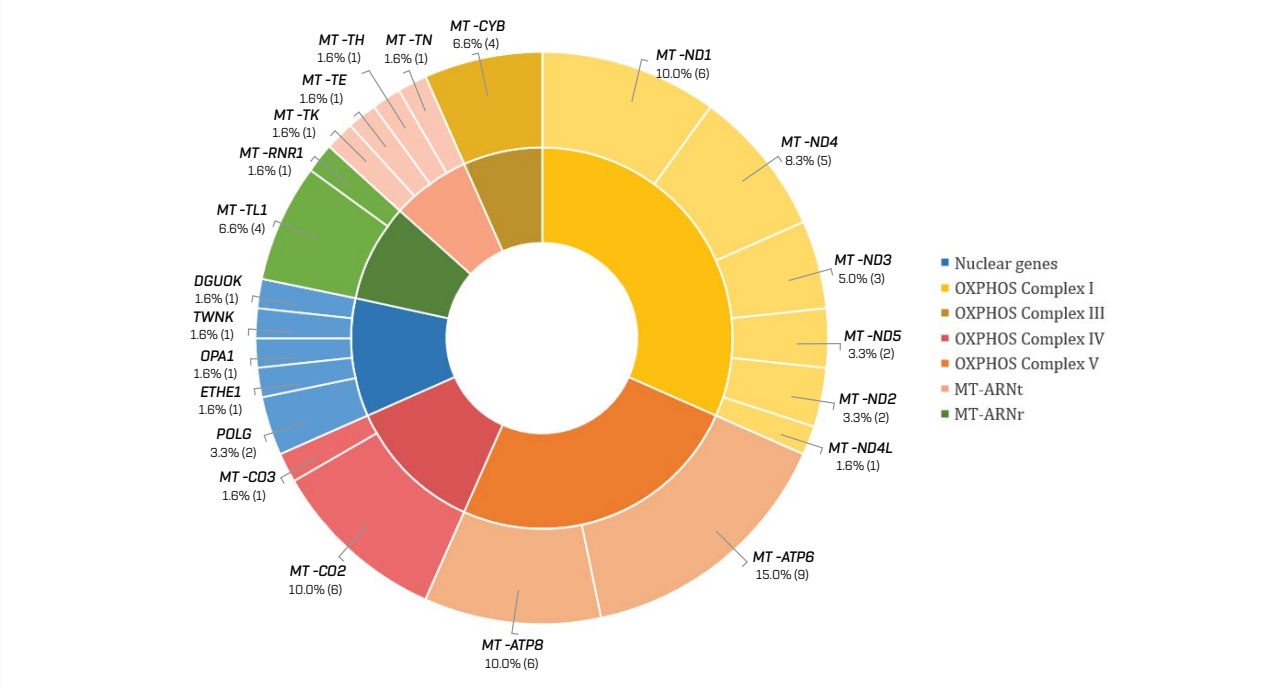

Figure 3. Distribution of identified variants by gene in Group 1, representing patients with mitochondrial involvement.

Legend: OXPHOS – Oxidative Phosphorylation genes; MT-ARNt – Mitochondrial transfer RNA genes; MT-ARNr – Mitochondrial ribosomal RNA genes.

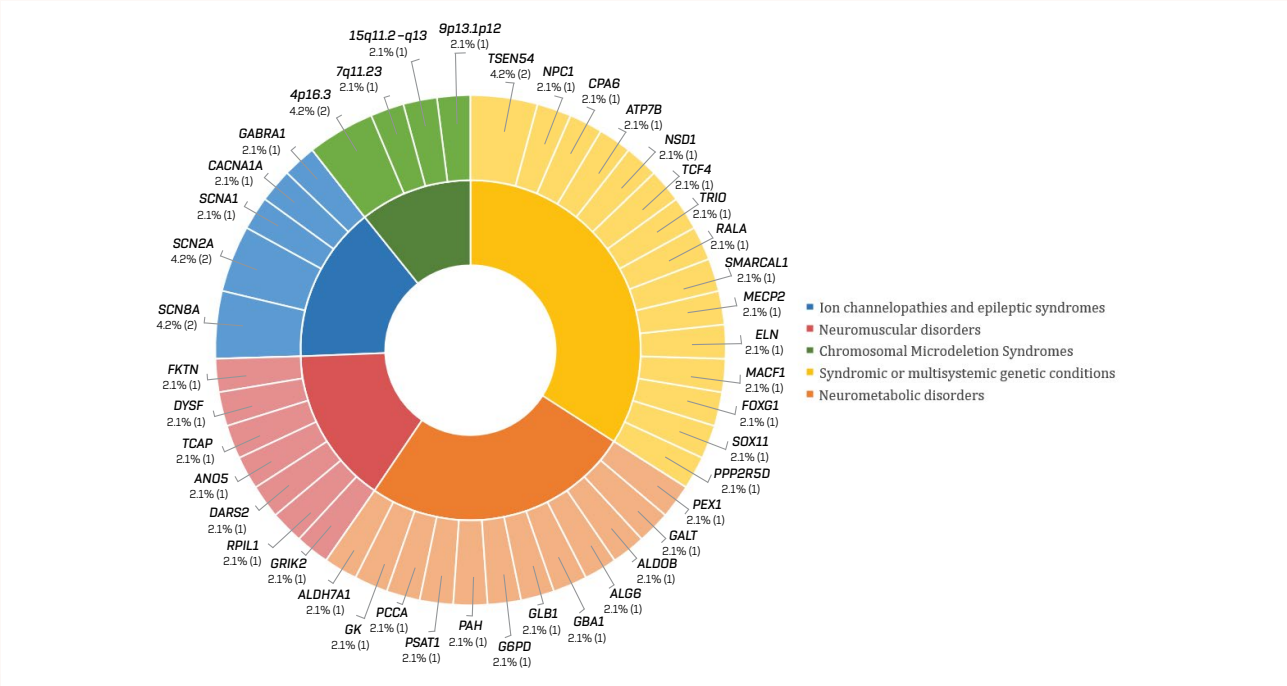

Figure 4. Gene-level distribution of variants identified in Group 2, encompassing patients with other inherited genetic disorders.

DISCUSSIONS

This comparative study highlights critical distinctions in clinical, biochemical, and genetic characteristics of patients with confirmed mitochondrial involvement versus those with other inherited genetic disorders presenting with overlapping phenotypes. Our findings underscore the complexity of diagnosing mitochondrial diseases and reinforce the need for integrated, multidisciplinary approaches that combine molecular genetics, biochemical profiling, and detailed clinical assessment. The Nijmegen Mitochondrial Disease Score proved to be a valuable and practical tool in this study, effectively guiding patient selection and supporting the differentiation between mitochondrial and non-mitochondrial genetic disorders. Its integration of clinical, biochemical, and instrumental parameters enhances diagnostic precision, reaffirming its established role as a cornerstone in the initial evaluation and stratification of patients with suspected mitochondrial pathology.

Severe neuromuscular involvement observed in patients with mitochondrial pathology is consistent with well-documented clinical phenotypes extensively described in the literature (5,6). The predominance of multisystemic manifestations, with at least three organ systems affected in most cases, further supports the systemic nature of mitochondrial dysfunction, as previously reported (7). Additionally, the frequent occurrence of ocular abnormalities, including ophthalmoplegia and optic atrophy, aligns with established mitochondrial syndromes, reflecting mitochondrial vulnerability in highly energy-dependent tissues (8).

Biochemically, the significant elevation of plasma lactate and alanine levels reinforces their utility as reliable metabolic biomarkers in suspected mitochondrial disease. The absence of significant differences in other specialized metabolic assays underscores their supportive role rather than a definitive diagnostic capacity within the broader clinical context.

Genetic analyses identified mitochondrial DNA mutations associated with well-characterized syndromes such as Leigh syndrome, Leber Hereditary Optic Neuropathy (LHON), and Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS), alongside nuclear gene mutations linked to Mitochondrial DNA Depletion Syndrome (*OPA1* gene) and Progressive Sclerosing Poliodystrophy (*POLG* gene). However, in certain cases, the detected genetic variants only partially explain the patients' phenotypes or are currently insufficient to definitively establish a diagnosis of a mitochondrial syndrome, highlighting the evolving nature of genotype-phenotype correlations in mitochondrial pathology. Moreover, variants of uncertain significance identified in mitochondrial genes account for a substantial proportion of findings, underscoring the complexity of genetic interpretation and the need for ongoing functional studies and longitudinal clinical correlation to clarify their pathogenic potential and contribution to disease phenotypes.

Despite providing valuable insights, this study has inherent limitations. The partial sequencing approach limited full genomic coverage, potentially overlooking rare or novel variants. The sample size, although robust, may restrict the statistical power for detecting subtle associations. Moreover, the absence of muscle biopsy and enzymatic activity data, due to limited availability, precluded a more integrative pathological correlation. Importantly, this work underscores the critical need for next-generation sequencing (NGS) technologies to improve diagnostic resolution by enabling comprehensive interrogation of mitochondrial and nuclear genomes. NGS has become a widely adopted approach, facilitating precise genotype-phenotype correlations in mitochondrial diseases and their mimics, as increasingly reflected in the current literature (9, 10).

CONCLUSIONS

1. The Nijmegen Mitochondrial Disease Score proved valuable not only as a screening instrument but also as an indicator of disease severity, showing significant correlations with key clinical features and neuroimaging abnormalities. Elevated plasma lactate and alanine levels emerged as robust biochemical markers associated with mitochondrial pathology.
2. Molecular investigations revealed a broad spectrum of mitochondrial DNA and nuclear gene variants, with a notable impact of Complex V subunit mutations on phenotype severity. Pathogenic variants were linked to higher clinical burden, underscoring the importance of comprehensive genomic analysis.
3. Integrating clinical, biochemical, imaging, and genetic data allowed for refined patient stratification, emphasizing the diagnostic value of a sequential molecular testing approach. Collectively, these findings support early, multidisciplinary evaluation, incorporating next-generation sequencing, to improve diagnostic precision and guide personalized clinical management in suspected mitochondrial disorders.

CONFLICT OF INTEREST The authors declare no conflict of interest.

ACKNOWLEDGMENTS This study was supported by the institutional research project “Diagnosis and Monitoring of Genetic Diseases in the Prevention of Maternal and Child Health Disorders” (Project No. 140102, DiMoGEN).

ETHICAL APPROVAL The study was approved by the Research Ethics Committee of the State University of Medicine and Pharmacy “Nicolae Testemițanu” (Decision No. 3, dated 09.09.2020).

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Date of receipt of the manuscript: 26.06.2025

Date of acceptance for publication: 18.12.2025

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