Biallelic Loss-of-Function NDUFA12 Variants Cause a Wide Phenotypic Spectrum from Leigh/Leigh-Like Syndrome to Isolated Optic Atrophy

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Abstract: Background: Biallelic loss-of-function NDUFA12 variants have hitherto been linked to mitochondrial complex I deficiency presenting with heterogeneous clinical and radiological features in nine cases only.

Objectives: To fully characterize, both phenotypically and genotypically, NDUFA12-related mitochondrial disease.

Methods: We collected data from cases identified by screening genetic databases of several laboratories worldwide and systematically reviewed the literature.

Results: Nine unreported NDUFA12 cases from six pedigrees were identified, with presentation ranging from movement disorder phenotypes (dystonia and/or spasticity) to isolated optic atrophy. MRI showed basal ganglia abnormalities (n = 6), optic atrophy (n = 2), or was unremarkable (n = 1). All carried homozygous truncating NDUFA12 variants, three of which are novel.

Conclusions: Our case series expands phenotype–genotype correlations in NDUFA12-associated mitochondrial disease, providing evidence of intra- and inter-familial clinical heterogeneity for the same variant. It confirms
NDUFA12 is a nuclear gene encoding the supernumerary subunit A12 of mitochondrial complex I (CI; NADH:ubiquinone oxidoreductase), the foremost multimeric enzyme of the respiratory chain which contributes ~40% of the proton driving force for ATP synthesis. Subunit A12 is proposed to act in assembling and stabilizing the extramembrane arm of CI.2

The first reported case of NDUFA12-related mitochondrial disease was a Pakistani child with Leigh syndrome (LS) carrying a homozygous nonsense variant. Few NDUFA12 cases have been described since then, with clinical manifestations ranging from complex neurological syndromes with prominent dystonia/spasticity and MRI evidence of basal ganglia (BG) changes to isolated optic atrophy (OA) in one case.3-4

We report nine additional cases from six kindreds (Fig. 1A), all carrying biallelic NDUFA12 variants, three of which are novel, and review cases previously reported.

Methods

To fully characterize the clinical spectrum and course of NDUFA12-related mitochondrial disease, we collected phenotypic and genetic data from cases identified by retrieving databases of several diagnostic and research genetic laboratories worldwide. Variants were prioritized according to the following criteria: (1) variant in NDUFA12 coding regions or at exon-intron boundaries; (2) gnomAD v3.1 frequency < 0.001; (3) no phenotype restriction. Among resulting variants, we selected pathogenic and likely pathogenic variants according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines,5 in particular for variants with unequivocal or highly predicted loss-of-function effect. A systematic literature review of NDUFA12 cases previously reported was performed by consulting PubMed® and Google Scholar using “NDUFA12” as search term on 31/05/2021. Predetermined clinical and genetic features were extracted and tabulated. Finally, genes associated with both dystonia and optic neuropathy were identified through Genomics England PanelApp (https://panelapp.genomicsengland.co.uk/) and searched on PubMed® using the gene name as search term on the same date. PubMed® results were filtered for article type “review” and/or “systematic review”. “Mutation” and “patient” were occasionally used as additional search terms to rule out non-clinical studies. Phenotypes associated with the above-mentioned genes were outlined to delineate the differential diagnosis of NDUFA12-associated mitochondrial disease.

Results

Clinicogenetic Characterization of New Cases

Pedigree A

Case 1: This 10-year-old Pakistani female, born to healthy consanguineous parents, was delivered at 37 weeks following labor induction due to intrauterine growth restriction (birth weight: 1.9 kg). She had unremarkable developmental milestones. She experienced a febrile seizure at age 4 and developed progressive gait and posture impairment as well as left arm weakness since age 6.5, when brain MRI revealed symmetrical T2-hyperintensity of the posterior putamen (Fig. 1B), with lesions demonstrating a mixed pattern of chronic gliosis and more acute features of cytotoxic oedema. She experienced an episode of status dystonicus at age 8. One year later, she was admitted to the hospital due to an episode of prolonged lethargy which was ultimately attributed to accidental baclofen overdosing. Paired lactate values in CSF and blood were normal. Repetitive nerve conduction studies (NCS)/electromyography (EMG) were unremarkable. Muscle biopsy revealed non-specific mild predominance of slow fibers and mild myopathic features, whereas assessment of respiratory chain enzymes (RCE) showed low CI activity (0.034; normal: 0.104–0.268) and normal activity of complexes II, III, and IV. Genetic testing for common mitochondrial and nuclear genes associated with Leigh syndrome came back to be normal. She was started on coenzyme Q10, thiamine, biotin, and anticholinergics and lost to follow-up between the age of 7 and 10 years. On examination at age 10, she was wheelchair bound with scoliosis and truncal hypotonia, limb fl exor spasticity and dystonic posturing of the extremities. Her cognitive functions were unremarkable. Due to recent deterioration of her visual function in the absence of any identifiable traumatic, inflammatory, or infectious trigger, the patient underwent an ophthalmological assessment and was diagnosed with significant visual deficit and severe OA. An extensive next-generation sequencing panel for nuclear mitochondrial genes revealed a homozygous NM_018838.5(NDUFA12):c.178C > T (p.Arg60*) variant.

Pedigree B

Case 2: This 21-year-old Turkish male, product of a third-degree consanguineous marriage, developed progressive kyphoscoliosis and gait diffl culty with left foot in-turning since age 7. Dystonia did not respond to levodopa or anticholinergics and became generalized over 2 years. The patient was wheelchair bound at age 11 and...
experienced intractable focal seizures since age 12. Although there was no history of intellectual disability, he showed cognitive deterioration with disease progression. On examination, he showed generalized dystonia, with dysarthria and feeding difficulty due to oromandibular involvement, kyphoscoliosis, left hand clenching, lower-limb hyperreflexia, and diffuse muscle atrophy (Fig. 1C; Video 1). There was no visual impairment.

Case 3: Case 2’s 25-year-old brother had a 15-year history of tiptoe walking on the left foot, with eversion aggravated by...
walking (Video 1). Lower-limb hyperreflexia and kyphoscoliosis were also detected. His cognitive functions were normal, and he graduated from university.

Both siblings had no visual impairment nor sensory deficits suggesting peripheral neuropathy. Metabolic work-up, including blood lactate and pyruvate, ammonia, urinary organic acids, serum and urine amino acids, and very long chain fatty acids, was unremarkable in both brothers. Their brain MRI showed symmetrical T2-hyperintensity and atrophy of lentiform nuclei (Fig. 1B), with diminished N-acetylaspartate peak and normal lactate peak on magnetic resonance spectroscopy (MRS). Whole-exome sequencing (WES) revealed a homozygous NM_018838.5(NDUFA12):c.121dupG (p.Glu41Glyfs*10) variant.

**Pedigree C**

**Case 4:** This 9-year-old Egyptian male, born to first cousins, had normal development until age 2, when he started walking on his tiptoes and falling. Achilles tenotomy surgery provided transient improvement. After age 4, he developed right hand tremor, scoliosis, and progressive stiffness in his lower limbs, with loss of independent walking. He was reported having school problems, but he had never undergone intelligence testing nor shown any deterioration of his cognitive function on follow-up. On examination, he showed kyphoscoliosis, acral dystonia with dystonic hand tremor, and lower-limb spasticity (Fig. 1C; Video 1). His visual function was unremarkable. Serum ceruloplasmin, creatine kinase, and amino acids and acylcarnitines were normal. He had increased urine lactate. Brain MRI revealed T2/FLAIR-hyperintensity and T1-hypointensity with cystic areas in the BG (Fig. 1B).

**Case 5:** One of Case 4’s elder sisters developed right hand grip weakness since age 16. Her past medical history was otherwise unremarkable, including absence of cognitive and visual issues. Brain MRI showed bilateral T2/FLAIR-hyperintensity of globi pallidi.

WES identified a homozygous NM_018838.5(NDUFA12):c.178C > T (p.Arg60*) variant in both siblings.

**Pedigree D**

**Case 6:** This 16-year-old Saudi male, son of first cousins, experienced motor developmental delay and progressive gait unsteadiness with frequent falls since age 2. He developed fixed flexion of the right hand which progressed to right hemiplegia, and severe visual impairment. He was reported with mild attention deficit disorder, but there was no history of intellectual disability nor cognitive deterioration. Brain MRI detected symmetrical T2-hyperintensity of the BG, with cystic degeneration on the left. Neurological examination revealed dysarthria and limb spasticity. Ophthalmological assessment revealed OA. Plasma lactate was normal on two occasions, whereas plasma pyruvate was increased (3.07 mg/dl; normal: 0.3–0.7).

**Case 7:** Case 6’s 12-year-old brother had a history of severe global neurodevelopmental delay, balance difficulties and falls since age 6. There was no history of intellectual disability nor cognitive impairment. On examination, he was dysarthric and wheelchair bound due to spastic quadriplegia. Brain MRI detected symmetrical T2-hyperintensity of the BG. Plasma lactate was 4.9 mmol/L (normal: 0.5–1).

WES revealed a homozygous NM_018838.5(NDUFA12):c.4G > T (p.Glu2*) variant in both siblings. Segregation analysis revealed that their younger sister, who was asymptomatic and did not present any neurological or ocular manifestations on examination at age 9, was homozygote for the same mutant allele.
| Pedigree Case | Sex/AE (y) | Ethnicity | Consanguinity | Perinatal FH history/NDM | AO (y) Symptoms(s) at onset | Clinical manifestations | Brain MRI | Findings from other investigations | NDUFA12 variant (NM_018838.5) | Ref |
|---------------|------------|-----------|---------------|--------------------------|-----------------------------|------------------------|----------|-----------------------------------|--------------------------------|-----|
| A             | F/10       | Pakistani | Yes           | No                       | 6.5 Gait abnormality and left arm weakness | Tunk hypotonia; dytonic posturing; episode of status dystonicus. | Visual impairment | Febrile convulsion; scoliosis | T2 hyperintenstities of the posterior putamen bilaterally (chronic gliotic scarring and acute cytotoxic edema). | Hom c.178C > T (p.Arg60§§) | -   |
| B1            | M/21       | Turkish   | Yes           | Yes                      | Normal birth.               | Normal NDM.               | None      | Kyphoscoliosis | Atrophy and T2 hyperintensity of lentiform nucleus | Hom c.121dupG (p.Glu41Gly§§10) | -   |
| B2            | M/25       | Turkish   | Yes           | Yes                      | Normal birth.               | Normal NDM.               | None      | Kyphoscoliosis | Atrophy and T2 hyperintensity of lentiform nucleus bilaterally | Hom c.121dupG (p.Glu41Gly§§10) | -   |
| C             | M/9        | Egyptian  | Yes           | Yes                      | Unilateral tip-toe walking, recurrent falls | Right hand tremor; generalized dystonia lower limbs Muscle weakness | None      | Kyphoscoliosis | T2/FLAIR hyperintenstities and T1 hypointensity of BG, with some cystic areas | Hom c.178C > T (p.Arg60§§) | -   |
| C             | F/20       | Egyptian  | Yes           | Yes                      | Chamness and tremor of the right hand | Muscle weakness right hand | None      | - | T2 hypointenstity of GP | Hom c.178C > T (p.Arg60§§) | -   |
| D             | M/16       | Saudi     | Yes           | Yes                      | Gait unsteady-dyskinesia and falls | Right hand dystonia | Visual impairment | - | Bilateral symmetrical T2 hyperintensity of BG along with left BG encephalomalacia | Hom c.4G > T (p.Glu2§§) | -   |
| E             | M/16       | Syrian    | Yes           | No                       | Subacute visual loss | Absent direct and consensual papillary light reflexes | Visual impairment | Depression | Normal | V.A. 20/1600 bilaterally. Optic atrophy. Normal plasma lactate. Seordogy for HIV, syphilis, HTLV: negative. Autoimmune screening: negative. CSF: mildly elevated proteins (63.9 mg/dL; r.i. <45 mg/dL). | Hom c.253G > T (p.Glu2§§) | -   |

(continues)
| Pedigree Case Sex/ | AE (y) | Ethnicity | Consanguinity FH | Perinatal History/NDM AO (y) | Symptom(s) at onset | Neurological | Ophthalmological | Other | Brain MRI | Findings from other investigations | NDUFA12 variant (NM_018838.5) | Ref |
|-------------------|--------|-----------|------------------|-----------------------------|---------------------|--------------|----------------|-------|-----------|-------------------------------|---------------------------|-----|
| **F** 9 M/33      | Turkish | Yes       | Normal birth.    | Normal NDM.                 | Acute visual loss   | None         | Visual impairment | -     | Optic chiasm atrophy          | V.A. 20/200 (age 30).          | Hom c.83del (p.Phe28Serfs^{11}) |     |
| **F** 10 F/21     | Pakistani | Yes       | Normal birth.    | Normal NDM.                 | Regression of motor abilities | Genommati dyssomina | Severe muscle atrophy | Scoliosis (surgery at age 18) | T2 hyperintensity of GP | MB type 1 fiber atrophy and fiber type disproportion. | Hom c.178C>T (p.Arg60^{2}) | 1   |
| **H** 11 F/Birth  | Mennonite | No        | Symmetric intrauterine growth restriction | Both | Facial dysmorphism, short limbs, persistent thrombocytopenia, direct hyperbilirubinemia, and poor feeding | Facial dysmorphism | Long philtrum, small mouth with prominent alveolar ridge, epicanthal folds, short upper and lower extremities with bowing of the tibia and fibula, kyphoscoliosis, supinated ankles, and mild generalized hypotonia. | Elevated AIP: low serum vitamin D 25-OH, direct hyperbilirubinemia. US abdomen: normal. | - | Pale optic discs. | Hom c.178C>T (p.Arg60^{2}) | 4   |

(Continues)
| Pedigree Case | Sex/ Age [y] | Ethnicity | Consanguinity | Perinatal history/ NDM | AO [y] | Symptom(s) at onset | Clinical manifestations | Neurological Findings | Ophthalmological Findings | Other Findings | Brain MRI Findings | NDUFA12 variants | Ref |
|--------------|-------------|-----------|---------------|------------------------|--------|---------------------|------------------------|------------------------|------------------------|--------------|----------------|----------------|-----|
| 1            | M/9         | Italian   | Yes           | No Birth: poor sucking, hypotonia. Mild global delay of NDM. | 12     | Sudden-onset convergent strabismus | Strabismus, nystagmus, minimal ptosis in the left eye | Age 5: T2 hyperintensity of the brainstem (red nucleus) and tegmental tract | None | None | None | Brain MRS: normal. VEP: increased latency in both eyes. BAEPs: normal. ECG/Ecocardiography: normal. Plasma lactate: 2.85 mmol/L (r.i. 0.5–3.2) on one occasion only. RCE (muscle homogenate): low complex I, normal complexes II-III-IV. | Hom c.86G > A (p.Arg29Lys) | 3 |
| L            | F/15        | Italian   | Yes           | Birth: respiratory distress. Normal NDM. | 13     | Dyssania right arm | Generalized dystonia, Spastic-dysmetric gait evolving to spastic- dystonic tetraparesis, Oromandibular dystonia | Typical Leigh syndrome pattern. Follow-up MRI: lesions in the BG (putamen), partial agenesis of septum pellucidum, and mild enhancement of left optic nerve after gadolinium. | None | None | Scoliosis | Brain MRS: normal. VEP: abnormal in amplitude in both eyes. Cardiological evaluation: normal. Plasma lactate: 3.62 mmol/L (r.i. 0.5–2.2). Urine lactate: >400 mmol/L creatinine (r.i. <200). Plasma amino acids: increased alanine (1120 mmol/L; r.i. 50–400). RCE (muscle homogenate): low complex I, normal complexes II-III-IV. | Hom c.395delA (p.Lys132-Argfs50) | 3 |
| M            | F/13        | Moroccan  | Yes           | Birth: respiratory distress. Normal NDM. | 14     | Sudden-onset nystagmus, right hemiparesis | Generalized dystonia, Tunk hypotonia, Extrapyramidal syndrome, Peripheral neuropathy | T2 hyperintensity of lentiform nucleus and brainstem | None | None | None | Brain MRS: lactate peak. Plasma lactate: 2.4 mmol/L (r.i. 0.5–1.9). CSF lactate: 2.8 mmol/L (r.i. 1–3.9). NCS: peripheral neuropathy. RCE (muscle homogenate): low complex I, normal complexes II-III-IV. | Hom c.224G > A (p.Trp75§) | 3 |
| M            | F/9         | Moroccan  | Yes           | Normal NDM. | 15     | Sudden-onset visual impairment | Extrapyramidal syndrome | T2 hyperintensity of lentiform nucleus | None | None | None | Hyperlactatorachia (lactate 2.8 mmol/L; r.i. 1–1.9). With normal plasma lactate | Hom c.224G > A (p.Trp75§) | 3 |
| M            | F/7         | Moroccan  | Yes           | Normal NDM. | 16     | Visual impairment | None | None | None | Optic atrophy. Hyperlactatorachia (2.4 mmol/L; r.i. 1–1.9). | Hom c.224G > A (p.Trp75§) | 3 |
| N³           | M/11        | Syrian    | Yes           | Normal NDM. | 17     | Limb dystonia | Limb dystonia | T2/T2-FLAIR hyperintensity of lentiform nucleus and red nucleus | FO, VEP, ERG, BAEPs normal. Serum lactate: 26 mmol/L (r.i. 0.5–2.2). | Brain MRS: normal. | Hom c.253G > T (p.Glu85§) | 3 |

(Continues)
Pedigree E

Case 8: This 16-year-old Syrian male, product of consanguineous parents, had a one-year history of progressive bilateral visual loss without any identifiable trigger. He had an asymptomatic sibling. On examination, visual acuity (VA) was 20/1600 bilaterally, with normal intraocular pressure and anterior segment US biomicroscopy. Direct and consensual pupillary light reflexes were absent. Fundoscopy disclosed mild optic disc pallor bilaterally, with cup-to-disc ratios 0.2 (right eye) and 0.4 (left eye), narrow temporal rim of the left optic disc, and retinal arterial tortuosity bilaterally. Fundus autofluorescence was normal (Fig. 1D). His neurological assessment was otherwise unremarkable, his cognitive functions were normal, and his mood was low. Serum lactate was normal. Serological testing for HIV, syphilis and HTLV was negative. Paraneoplastic antibodies and rheumatological workup including serum anti-AQP4, anti-MOG, and anti-CRMP5 antibodies were unremarkable, as well as serum thiamin, cyanocobalamin, and folate levels. He had normal brain and orbit MRI, and slightly increased CSF protein levels (63.9 mg/dL; normal: <45). WES revealed a homozygous NM_018838.5(NDUFA12): c.253G > T (p.Glu85*) variant.

Pedigree F

Case 9: This 33-year-old Turkish male born to consanguineous parents presented at age 28 with sudden bilateral painless visual loss (VA 20/40), which slowly progressed over the following years. No triggers were identified at symptom onset. There was a history of mild intellectual disability. His VA was 20/200 bilaterally at age 30 and remained relatively stable ever since. Perimetry revealed central scotomas spanning most of the central 30 degrees of the visual field bilaterally, more pronounced in the left eye. Intraocular pressure was normal, and anterior segment US biomicroscopy was unremarkable aside from mild cataract. Pupils were isochoric, with the left one showing relative afferent deficit. Fundoscopy revealed pale optic discs with cup-to-disc ratios 0.7 (right eye) and 0.8 (left eye), whereas macula, peripheral retina, and vessels were unremarkable. Bilateral optical coherence tomography detected markedly reduced thickness of the peripapillary retinal nerve fiber layer and microcystic macular edema (left>right; Fig. 1E). Neurological assessment was otherwise unremarkable, with cognitive functions being unchanged since early childhood. Serum lactate levels were not tested. MRI brain orbits detected optic chiasm atrophy. Screening for cardiovascular risk factors, including sleep apnea, was unremarkable. An NGS panel for nuclear and mitochondrial OA-associated genes detected a heterozygous ENST00000304511.2(TMEM126A):c.314G > A (p.Arg105Gln) variant, whose causal relationship was excluded based on high frequency in population databases and in silico prediction tools. Whole-genome sequencing revealed a homozygous variant NM_018838.5(NDUFA12): c.83del (p.Phe28Serfs*11).
Phenotype–Genotype Characterization of all Reported Cases

Including our series, 18 NDUFA12 cases (nine males) from 11 pedigrees of Arabian, North African and European ancestry have hitherto been reported (Table 1).1,3,4 Perinatal issues were reported in 5/18 (27.8%) patients3,4 (one with coexistent mucolipidosis type II).4 Neurodevelopmental milestones were delayed in 5/18 (27.8%) cases,1,3 Age of symptom onset ranged from birth to 28 years, with acute or subacute gait (10/18 cases, 55.6%) or visual (4/18, 22.2%) impairment being the most frequent presenting features.1,3 Main clinical manifestations (Fig. 1F) encompassed dystonia (11/18 cases, 61.1%), pyramidal features (8/18, 44.4%), and visual impairment (7/18, 38.9%), either isolated or combined. (Kypho)Scoliosis (6/18 cases, 33.3%), muscle weakness/atrophy (5/18, 27.8%), sporadic seizures (2/18, 11.1%), and peripheral neuropathy (1/18, 5.6%)3 represented minor phenotypic features. Brain MRI was unremarkable in two patients with isolated visual impairment and revealed BG T2-hyperintensity, BG atrophy/cystic degeneration, and optic chiasm atrophy in 13/18 (72.2%), 9/18 (50.0%), and 1/18 (5.6%) cases, respectively. Lactate was increased in blood, urine, or CSF in 10/13 (76.9%). NCS documented peripheral neuropathy in one out of two cases where available.3 Muscle biopsy, whose details were available in two cases, showed only subtle myopathic features. In five cases, low CI activity was documented on assessment of RCE.5 Parental consanguinity was reported in 17/18 (94.4%) cases, with 11/18 (61.1%) having at least one affected sibling. Eight homozygous NDUFA12 pathogenic variants have been hitherto reported, including three novel variants described here (p.Glu2*, p.Phe28Serfs*11, p.Glu41Glyfs*10). These are scattered throughout NDUFA12 exons, all but one being truncating variants (4 nonsense, 3 frameshift; Fig. 1G). Intriguingly, the asymptomatic sibling of two affected individuals (Pedigree D) carried the mutant allele in the homozygous state, thus suggesting either incomplete penetrance or further intra-familial variability with respect to age at symptom onset.6

Discussion

CI deficiency is the commonest biochemical defect in children with mitochondrial diseases, including LS/Leigh-like syndrome (LLS).7–9 Diagnosis of LS requires progressive neurological deterioration with clinical evidence of BG and/or brainstem dysfunction, developmental delay, and elevated serum or CSF lactate, along with neuroradiological or neuropathological evidence of BG and/or brainstem lesions.8 When these stringent criteria are not fulfilled (e.g., atypical neuroimaging, normal lactate levels), a diagnosis of LLS can be considered.8 Six cases in our series fulfilled the diagnostic criteria for LS/LLS, thus providing further evidence that biallelic loss-of-function NDUFA12 variants are a rare cause of these phenotypes.1,3

Dystonia, either isolated or combined with pyramidal features, emerges as the most common motor feature in NDUFA12-related LS/LLS. As dystonia was always associated with MRI evidence of BG damage in our series and previous cases, a secondary etiology (structural damage caused by mitochondrial dysfunction) most likely explains its occurrence in NDUFA12-related LS/LLS.10 By contrast, we confirmed that biallelic NDUFA12 variants are associated with isolated OA, even in the absence of MRI findings, as previously reported in one case.3 In the original case reported by Ostergaard et al.,1 and Case 1, visual impairment occurred some years after disease onset, thus suggesting visual function should be assessed on follow-up of patients harboring biallelic NDUFA12 variants with pure motor presentations. Overall, this adds to the observation that the best-established nuclear genes linked to OA (Table S1) are involved in mitochondrial pathways, as are pathogenic variants in mitochondrial DNA accounting for Leber hereditary optic neuropathy.11 An overview of genes associated with both dystonia and OA is provided in Table S1. Unlike several of these genes, which are recognized with both dominant and recessive inheritance, NDUFA12 is more likely associated with recessive inheritance only since the observed/expected ratio for both missense and loss-of-function variants is close to 1 according to gnomAD. Finally, we highlight that increased lactate levels were detected in only two out eight cases of our new cohort when this testing was performed, whereas plasma pyruvate level was increased in one case with normal plasma lactate. This proportion is lower than in previously reported cases, which is in keeping with a higher prevalence of LLS phenotype in our series.8

Our series expands the age of onset of NDUFA12-related mitochondrial disease to as late as 28 years. Furthermore, it demonstrates significant intra-familial variability (e.g., Cases 2–3, 4–5, 6–7) and occurrence of the same NDUFA12 variant in patients/kindreds with different phenotypes (inter-familial heterogeneity, e.g., p.Glu85* associated with OA in Case 8 and LS in Pedigree N). This suggests that yet undetermined genetic, epigenetic, and environmental factors modulate the variable expression of mutant NDUFA12 alleles at the phenotypic level.6

In conclusion, our case series expands the phenotype–genotype spectrum of NDUFA12-associated mitochondrial disease and provides evidence of inter- and intra-familial clinical heterogeneity associated with the same variant. It supports the inclusion of NDUFA12 variants in the diagnostic workup of not only LS/LLS, particularly when dystonia is the prominent motor manifestation, but also isolated OA.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

FM: 1A, 1B, 1C, 2B, 3A;
EC: 1B, 1C, 3A;
VLB: 1C, 3B;
UY: 1C, 3B;
HT: 1C, 3B;
HS: 1C, 3B;
JR: 1C, 3B;
CK: 1C, 3B;
FMRF: 1C, 3B;
OGPB: 1C, 3B;
RWT: 1C, 3B;
EO: 1C, 3B;
AT: 1C, 3B;
KS: 1C, 3B;
JMFS: 1C, 3B;
MSZ: 1C, 3B;
FK: 1C, 3B;
KPB: 1C, 3B;
BW: 1C, 3B;
KS: 1C, 3B;
TH: 1C, 3B;
RH: 1C, 3B;
SH: 1C, 3B;
FSA: 1C, 3B;
HH: 1C, 3B;
JLP: 1C, 3B;
RM: 1A, 1B, 1C, 3B.

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work. We confirm that we have obtained the patient consent for genetic testing on a research basis as well as for video acquisition and publication.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1 Overview of disease genes associated with dystonia and optic atrophy which are of interest in the differential diagnosis of NDUFA12-associated mitochondrial disease.