Juvenile-onset generalized dystonia in Leigh syndrome caused by a novel *NDUFA10* variant: a case report.

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1. Background

Leigh syndrome (LS) is an inherited neurometabolic disorder due to **mitochondrial dysfunction** affecting predominantly the **central nervous system** (CNS).

The **onset** of LS occurs before the age of **2 years** in the 80% of cases. Generally, LS patients do not survive past mid-childhood or adolescence.

Motor disorders represent the most prevalent clinical presentation of LS. They include hypotonia, dystonia, spasticity, ataxia, and chorea-athetosis. LS patients may present also with feeding difficulties, epileptic seizures, respiratory dysfunction, intellectual disability, optic atrophy, oculomotor abnormalities, ptosis, cardiac problems, and gastro-intestinal dysfunction. Life

The neuroradiological hallmark of LS is the presence of symmetrical hyperintense lesions in **basal ganglia**, **thalamus**, **brainstem**, cerebellum, optic nerves and/or spinal cord on T2-weighted MRI sequences. An increase of **lactic acid** and lactate/pyruvate ratio in serum and cerebrospinal fluid (CSF) samples are common findings of LS.

Several **mitochondrial and nuclear genes** have been etiologically linked to LS (Table 1). Genetic mutations affecting the function of the OXPHOS complex I represent the most common biochemical defect identified in LS.

In this context, biallelic mutations of NADH:ubiquinone oxidoreductase subunit A10 (*NDUFA10*) are an extremely rare cause of LS. Three *NDUFA10*-mutated patients with neonatal or early-infantile onset LS were described so far. Here we report a novel case of LS with onset at the age of 6 and characterized by a severe generalized dystonia, carrying an extremely rare *NDUFA10* pathogenic variant.

2. Methods and materials

A **clinical examination** was performed on a patient with generalized dystonia and tetraparesis by movement disorders expert neurologists.

A LS diagnosis was performed following to **laboratoristic**, **neuroelectrophysiological** and **neuroradiologic** tests.

The DNA of the proband was extracted by a peripheral blood sample and a **Whole Exome Sequencing** (WES) was performed. A virtual **gene panel** containing the genes associated with LS (Table 1) was used to filter WES variants. This operation was followed by an additional filtering looking for rare (Allele Frequency <0.001) nonsynonymous variants.

3. Results

The disease **onset** of the proband was **late** (5-6 years) and included bilateral optic atrophy, gait difficulties and ataxia. The proband is now 43 years old, he has a mild intellectual disability and a generalized dystonia with tetraparesis.

The brain MRI showed **bilateral T2-hyperintensity of the striatum**, with greater involvement of the right putaminal nucleus. CSF analysis, wide spectrum screening for neurometabolic disorders and EMG were normal.

The bioinformatical analysis revealed two heterozygous *NDUFA10* (NM_004544.4) variants (Figure 1): **c.296G>A (p.Gly99Glu)** and **c.233_235delCAG (p.Ala78del)**.

While c.296G>A (p.Gly99Glu) is a known pathogenic *NDUFA10* variant already associated with early-onset LS, c.233_235delCAG (p.Ala78del) is a novel genetic cause of LS, is extremely rare (gnomAD AF=0.000004), and is reported as a variant of unknown significance in genetic databases (i.e. ClinVar). It affects a strongly evolutionary-conserved amino acid and is predicted pathogenic by in silico prediction tools.

The presence of this rare deleterious variant in association with a known *NDUFA10* pathogenic mutation in a LS patient strongly supports its pathogenic role.

4. Discussion

We report **the fourth case** of LS due to a mutation of *NDUFA10*.

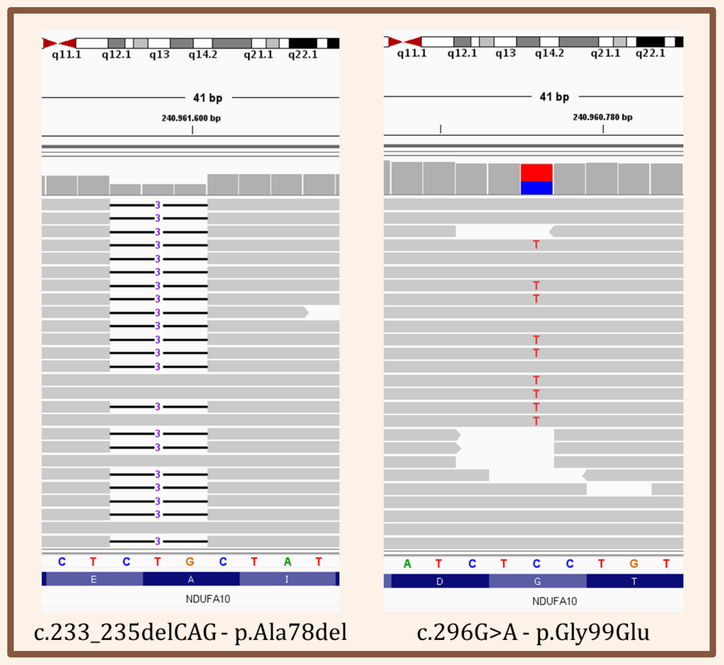
The c.296G>A variant has already been reported in two cases while the c.233_235delCAG variant is extremely rare.

The three cases described so far were characterized by a progressive psychomotor delay, hypotonia and mildly increased osteotendinous reflexes. Case 1 also presented a severe hypertrophic cardiomyopathy, while **no myocardial involvement** was reported in cases 2 and 3 (Table 2). The current case presents a milder phenotype, with the prevalence of dystonic features, a **later onset of disease**, and no myocardial involvement.

A possible explanation of the less aggressive features in this patient might be related to the **p.Ala78del variant**, which as **in-frame deletion** could partially retain the NFUDA10 **function**. Besides that, the absence of cardiac involvement in the three cases related to missense or in-frame deletion may indicate that **partially conserved protein** is sufficient for a proper myocardial function, which has relevance for **diagnostic counselling and follow-up** of patients with these pathogenic variants. Further studies will be needed to corroborate these hypotheses.

Table 1: genes involved in mitochondrial functions causing LS.

Metabolic pathway	Genes
OXPHOS Complex I	*FOXRED1, NDUFA1, NDUFA2, NDUFA9,* ***NDUFA10****, NDUFA12, NDUFAF2, NDUFAF5, NDUFAF6, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS7, NDUFS8, NDUFV1, NDUFV2, mtND1, mtND2, mtND3, mtND4, mtND5, mtND6*
OXPHOS Complex II	*SDHA, SDHAF1*
OXPHOS Complex III	*BCS1L, TTC19, UQCRQ*
OXPHOS Complex IV	*COX8A, COX10, COX15, ETHE1, NDUFA4, PET100, SCO2, SURF1, TACO1, mtCO3*
OXPHOS Complex V	*mtATP6*
Mitochondrial transcription and translation	*C12orf65, EARS2, FARS2, GFM1, GFM2, GTPBP3, IARS2, LRPPRC, MRPS34, MRPS39 (PTCD3), MTFMT, NARS2, PNPT1, TRMU, TSFM, mtFMT, mtTI, mtTK, mtTL1, mtTV, mtTW*
RNA-specific adenosine deaminase	*ADAR, RNASEH1*
Mitochondrial DNA maintenance	*FBXL4, MPV17, POLG, POLG2, SLC25A4, SUCLA2, SUCLG1, TWNK*
Mitochondrial dynamics	*DNM1L, MFN2, RRM2B, SLC25A46*
Nuclear translocation system	*RANBP2*
Nuclear pore complex	*NUP62*
Manganese transportation	*SLC39A8*
Pyruvate dehydrogenase complex	*DLAT, DLD, PDHA1, PDHB, PDHX, SLC25A19*
Thiamine deficiency	*SLC19A3, TPK1*
Coenzyme Q10 metabolism	*COQ9, PDSS2*
Lipoic acid	*BOLA3, LIAS, LIPT1*
Amino acid	*ECHS1, HIBCH*
Biotinidase	*BTD*
Membrane phosphocomponents	*SERAC1*
Others	*ADAR, AIFM1, CLPB, GYG2, SPG7*



c.233_235delCAG - p.Ala78del c.296G>A - p.Gly99Glu

Figure 1: Integrative Genomics Viewer shows the two heterozygous variants on the proband's DNA.

Table 2: phenotypes of LS cases due to *NDUFA10* mutation.

Case	1 - Hoefs, S. J. G. et al. (2011)	2 - Haack, T. B. et al. (2012)	3 - Minoia, F. et al. (2017)	4 - Proband
Genotype	c.1A>G (p.Met1?) c.425A>G (p.Gln142Arg)	c.296G>A (p.Gly99Glu) c.296G>A (p.Gly99Glu)	c.296G>A (p.Gly99Glu) c.296G>A (p.Gly99Glu)	c.233_235delCAG (p.Ala78del) c.296G>A (p.Gly99Glu)
Birth age and weight	Born at 32 weeks with distress, 2715 g	Non available	Full term, 3460 g	Full term, 2250 g
Onset	10 months	First days of life	2 years, 8 months	**5 years**
Neurological presentation	• Psychomotor retardation • Hypotonia • Increased deep tendinous reflexes	• Psychomotor retardation • Hypotonia • Deglutition impairment	• Psychomotor retardation • Hypotonia • Increased deep tendinous reflexes • Ataxia and nystagmus	• Psychomotor retardation • Generalized dystonia • Tetraparesis
Cardiological presentation	Hypertrophic cardiomyopathy	**Normal**	**Normal**	**Normal**
Death	23 months	14 years	/	/
Laboratory	Elevated serum and CSF lactates	Elevated serum and CSF lactates	Elevated serum lactates	**Elevated p-OH-phenyllactic acid**
Neuroimaging	Symmetrical lesions of basal ganglia and substantia nigra	Symmetrical lesions of basal ganglia and brainstem	Symmetrical lesions of putamina and globi pallidi, asymmetrical lesions of nuclei caudati and cerebral peduncles	**Asymmetrical lesions of putamina and globi pallidi**

5. Bibliography

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