# Childhood-Onset Generalized Dystonia Due to *NDUFA9* Gene Mutation: An Expansion of Mutations Causing Leigh's Syndrome

Dear Sir,

Leigh syndrome (LS) causes focal, necrotizing lesions of the basal ganglia, diencephalon, cerebellum, or brainstem and clinical presentations include psychomotor retardation, seizures, nystagmus, ophthalmoparesis, optic atrophy, ataxia, dystonia, or respiratory failure, and lactacidosis of the blood, cerebrospinal fluid, or urine. Leigh-like syndrome refers to the presentation of neurologic abnormalities which is atypical for, but highly suggestive of, LS. The respiratory chain (particularly of complexes I, II, IV, or V), coenzyme Q, or the pyruvate dehydrogenase complex deficits are responsible for LS or Leigh-like syndrome. Nicotinamide adenine dinucleotide (NADH) – ubiquinone oxidoreductase or NADH dehydrogenase (complex I) transfers electrons from NADH molecules to ubiquinone and pumps protons across the inner mitochondrial membrane. Complex I have 44 subunits – 37 encoded by nuclear deoxyribonucleic acid (DNA) and 7 by mitochondrial DNA. It contains three functional modules: the Q-module (ubiquinone reduction), the N-module (NADH dehydrogenase), and the P-module (proton translocation).[1] NDUFA9, a component of the Q-module, is essential for complex I assembly or stability. There are very few reports of neurological symptoms associated with a mutation in the *NDUFA9* gene.[2,3] Hereby, we report a 26-year-old female patient with childhood-onset generalized dystonia with bilateral striatal signal changes on magnetic resonance imaging (MRI) of the brain. Whole exome sequencing showed a homozygous missense variant in the *NDUFA9* gene.

A 26-year-old lady born out of consanguineous parentage, an only child with normal birth and developmental history presented with the history of dystonic posturing of head and neck followed by both upper and lower limbs since the age of 9 years. She had developed slurring of speech in the form of strained quality of voice from the age of 10 years. Symptoms progressed slowly over the next 4–5 years, and thereafter it had been relatively static for the past 10 years. There was no diurnal variation in the dystonia. Her scholastic performance was poor since early childhood. The patient was the only child of her parents. There was no family history of similar complaints. Systemic examination was unremarkable. Neurological examination showed normal fundus, normal saccades, and pursuits, dysarthria in the form of strained quality of voice suggestive of adductor laryngeal dystonia, upper and facial dystonia in the form of frontalis contraction, blepharospasm, perioral and lingual dystonia, cervical dystonia in the form of intermittent left rotational torticollis, left laterocollis and anterocaput, bilateral finger, and toes dystonia suggestive of generalized dystonia [Video 1]. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) score was 59/120. Motor and sensory examination was normal. There were no cerebellar signs. A clinical diagnosis of childhood-onset craniocervical onset generalized isolated dystonia was made. Plasma and cerebrospinal fluid lactate level was normal. Brain MRI showed bilateral symmetrical hyperintensities on T2/fluid-attenuated inversion recovery in caudate, putamen with bilateral putaminal atrophy [Figure 1], isointensities in T1-weighted imaging with no blooming on gradient-echo sequence, no contrast enhancement, and no brainstem involvement. Magnetic resonance spectroscopy did not reveal abnormal peaks of brain metabolites. A radiological possibility of LS was considered. Muscle biopsy did not reveal ragged red fibers, and complex 1 activity was 20%. Whole exome sequencing showed a homozygous missense mutation in the *NDUFA9* gene (NM_005002.5:c.727G >A (p.Val243Ile)). The clinical phenotype of the proband matched with that of the disorder caused by pathogenic variants in the NDUFA9 gene. She was started on trihexyphenidyl (maximum tolerated dose 12 mg/day) and clonazepam (1 mg/day) for dystonia. She was treated with carnitine, coenzyme Q10, riboflavin, thiamine, vitamin E, and biotin. The BFMDRS score was 37/120 with 20% improvement in dystonia at 1-year follow-up.

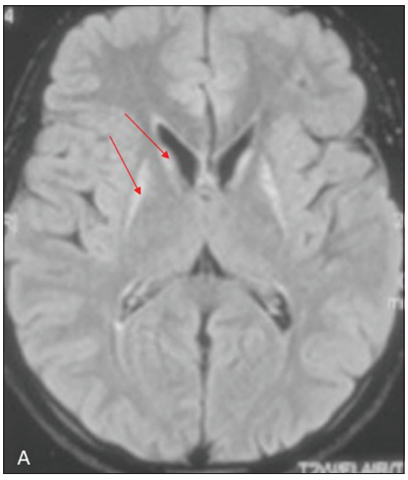


**Figure 1:** Brain MRI fluid-attenuated inversion recovery axial images (A) showing bilateral symmetrical caudate and putaminal hyperintense signal (red arrow) with caudate atrophy

LS was first described by Denis Archibald Leigh in 1951. It is a progressive neurodegenerative condition that can manifest during infancy, childhood, or adolescence. The neurological manifestations include psychomotor delay or regression, hypotonia, dystonia, ataxia, spasticity, seizures, and brainstem dysfunction. There are over 75 nuclear genes that are implicated in LS. Complex 1 deficiency accounts for approximately 35 to 50% of LS patients. The nuclear genes causing complex 1 deficiency and LS are *NDUFA1, NDUFA2, NDUFA9, NDUFA10, NDUFA12, NDUFS1, NDUFS2, NDUFS3, NDUFB8, NDUFS4, NDUFS7, NDUFS8, NDUFV1, NDUFV2*, *NDUFAF2, NDUFAF4, NDUFAF5, NDUFAF6, C17ORF89, FOXRED1,* and *NUBPL*. *NDUFA9*, a component of the Q-module, is essential for complex I assembly or stability.[4,5]

The first report of the complex I deficiency due to the pathogenic *NDUFA9* mutation was described by Van den Bosch *et al*. (2012).[2] The affected patient was a neonate who developed lactic acidosis with isolated complex I deficiency demonstrated in the muscle and fibroblasts (2% of control panel activity). The pathogenic *NDUFA9* gene mutation resulted in changing a highly conserved arginine at position 321 to proline (c.962G>C.; p. (Arg321Pro)). Baertling *et al.* (2018)[3] reported one patient with a novel *NDUFA9* gene mutation with an expanded clinical phenotype. The patient developed dystonia of the upper limb at the age of 7 years and became generalized by 10 years with sensorimotor peripheral neuropathy at 28 years of age. His MRI brain showed bilateral putaminal signal change. Whole exome sequencing showed a homozygous missense variant in the *NDUFA9*

**Table 1: Brief summary of reported cases of NDUFA9 gene mutation**

| Author | Phenotype | Brain imaging | Genotype |
|---|---|---|---|
| van den Bosch *et al*. (2012)[2] | Neonate with profound hearing loss, apnoeas associated with brainstem abnormalities, and retinitis pigmentosa and lactic acidosis | Diffuse loss of supratentorial white matter and brain stem volume with T2 hyperintensities of the basal nuclei (thalamus and putamen) | Missense mutation p. (Arg321Pro) |
| Baertling *et al*. (2018)[3] | Childhood-onset generalized dystonia with dysarthria and peripheral neuropathy | Bilateral putaminal signal change seen | Homozygous missense mutation p. (Arg360Cys) |
| Present case | Childhood-onset generalized dystonia with dysarthria | Bilateral caudate and putamen signal changes seen | homozygous missense mutation p. (Val243Ile) |

gene (NM_005002.4): c. 1078C>T; p. (Arg360Cys). There was no lactate peak detectable by magnetic resonance spectroscopy. The reduced complex I activity in fibroblast was 17% of control activity [Table 1]. Our patient had a similar phenotypic presentation of childhood-onset generalized dystonia as reported by Baertling *et al.* (2018) with bilateral striatal signal changes of LS. We found a homozygous missense mutation in the *NDUFA9* gene (NM_005002.5:c.727G >A (p. Val243Ile)). The muscle biopsy showed lower than normal (20%) complex 1 activity.

LS due to NDUFA9 deficiency is rarely reported, and the neurological manifestations range from neonatal-onset lactic acidosis, retinitis pigmentosa, and fatal respiratory failure to childhood-onset progressive dystonia.[4,5] We report a rare case of LS due to a novel mutation in the *NDUFA9* gene with a phenotypic presentation of childhood-onset progressive dystonia.

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## Conflicts of interest
There are no conflicts of interest.

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