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A typical phenotypes due to NDUFV1 mutations

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ABSTRACT

Mitochondria have a critical role in energy metabolism, generating and scavenging of free radicals, intracellular Ca2+ regulation, and cell mitophagy. Dysfunction of the mitochondrial oxidative phosphorylation complex is the most frequent inborn errors of metabolism. Mitochondrial diseases are highly diverse in etiology, age of the disease onset, involvement of multiple organ systems, and genetic causes. NDUFV1 is a core subunit of mitochondrial Complex I (CI), and mutations cause CI deficiency. Clinically, CI deficiency is associated with severe infantile lactic acidosis, cardiomyopathy, encephalomyopathy, leukoencephalopathy, and Leigh syndrome. The cellular biology and molecular mechanisms of mitochondrial diseases are still elusive due to the heterogeneous genetic background and lack of phenotype-genotype correlation. Neurological abnormalities are the second most frequent presentations of mitochondrial diseases, including white matter abnormalities, psychomotor regression, and mental disability. The defects in myelin sheath or glial cells cause leukodystrophy which is a progressive genetical syndrome. To date, no therapy is available to cure mitochondrial diseases; exploration of the phenotype and molecular background are crucial for disease diagnosis, supportive treatments, proper genetic counselling, prenatal diagnosis, and experimental treatments. This article underscores the atypical clinical presentations of NDUFV1 mutations and the importance of a multidisciplinary approach to correlate phenotypes, biochemical, radiological, and molecular diagnosis. Implementation of multidisciplinary approach will enhance the possibility of discovering the therapeutic targets to treat mitochondrial disorders and ensure prenatal diagnosis to prevent inherited diseases.

Key Words: NDUFV1, leukoencephalopathy, leigh syndrome, LBSL, phenotype

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Introduction

Mitochondrial Oxidative Phosphorylation (OxPhos) defects are a group of heterogeneous diseases of metabolism. Mutations in Mitochondrial-DNA encoded (mt-DNA) genes and nuclear-DNA encoded genes cause OxPhos dysfunction. The OxPhos subunit Complex I (CI) is the largest of the five complexes, and NDUFV1 is a core subunit of CI that transfers electrons from NADH to iron-sulfur cluster [1]. Pathogenic NDUFV1 variants may cause Leigh Syndrome (LS), Leigh-Like syndrome (LL), leukoencephalopathy with or without cavitation, and episodic leukoencephalopathy [2-4].

NDUFV1 gene expression is higher in the brain, intestine, and lung and neurodegenerative diseases are common among NDUFV1 patients. LS and

leukoencephalopathies are frequently found in NDUFV1 patients. Leigh syndrome (MIM# 256000) is a common neurodegenerative disease caused by the involvement of multiple genes [5]. The patients with NDUFV1 loss-of-function mutations usually show developmental regression, epilepsy, hypotonia, spasticity, dystonia, ophthalmoplegia, strabismus, and nystagmus [3].

The mitochondrial translation machinery required mt-DNA encoded RNAs (two rRNAs and 22 tRNAs) and nuclear genome encoded ribosomal proteins, tRNA modifying enzymes, translation factors, aminoacyl-tRNA synthetases (mt-aaRSs) for translation [6]. Mutations in mt-aaRSs enzymes predominantly cause pathologies in the Central Nervous System (CNS), like LBSL, sporadic bilateral optic neuropathy, mitochondrial myopathy, myoclonic epilepsy, and psychomotor regression [7]. Leukodystrophies are chronic progressive glial cell or myelin sheath abnormalities of the CNS, highly variable in clinical findings, pathogenic mechanisms, and genetic backgrounds. Early-onset leukodystrophies are incurable and cause premature death. In addition, Leukoencephalopathies are the white matter diseases of the CNS as a secondary consequence of metabolic diseases, toxic injuries, infectious white matter damage, and acquired vascular insults. Heritable white matter abnormalities are considered genetic leukoencephalopathies [8].

Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate (LBSL, MIM#611105)) is a form of mitochondrial disease that causes slowly progressive pyramidal and cerebellar white matter abnormalities, lateral corticospinal tracts, and dorsal column dysfunction [9]. Neuroimaging shows characteristic abnormalities in the cerebral white matter, and selective involvement of the certain brainstem and spinal cord tracts, with or without lactate elevation. The Aspartyl-TRNA Synthetase 2, Mitochondrial (DARS2) is the first-ever gene identified to cause LBSL [10]. Subsequently, pathogenic variants in Mitochondrial Iron-Sulfur Cluster Assembly 2 (ISCA2) [11] and NADH: Ubiquinone Oxidoreductase Core Subunit V1 (NDUFV1) [12] were found to be associated with LBSL. The involvement of the NDUFV1 compound heterozygous mutations with LBSL is a rare presentation with a mild clinical course [12].

Diagnosis of mitochondrial diseases is complex due to monogenic, digenic, or polygenic involvement with a wide range of phenotypes. A single gene may cause several disease phenotypes, or multiple genes may have a single disease phenotype. This review highlights the atypical presentation of mitochondrial diseases due to NDUFV1 mutations and the importance of knowledge about the diversity of phenotypes to diagnose heritable diseases precisely.

Literature review

To provide an overview of the clinical characteristics of NDUFV1, we searched the ClinVar database and included the variants (Table 1) with clinical significance of pathogenic or likely pathogenic, and PubMed database for published articles associated with NDUFV1, DARS2, and AARS2 genes. We enlisted new NDUFV1 variants (Table 1) based on published articles to date. Some of those variants have not been submitted to ClinVar yet, and some variants have uncertain significance status on ClinVar.

Table 1. NDUFV1 variants described to date based on clinvar significance (pathogenic/likely pathogenic) and published articles.

Genomic position (GRCh38), Chr:11	Transcript variant (NM_007103.4)	Protein change (NP_009034.2)	Diagnosis	ClinVar significance
67607055-67607056	c.53_54del TG	p.Val18fs*20	Optic nerve atrophy	Pathogenic
67608439	c.116A>G	p.Asp39Gly	NP	LP
67608479	c.155+1G>A	p.(=)	Leukoencephalopathy (cystic)	LP
67608554	c.158T>C	p.Leu53Pro	Leukoencephalopathy, seizure, optic nerve atrophy	NR
67608562	c.166T>C	p.Ser56Pro	Leukoencephalopathy, MCID	LP/US
67608571	c.175C>T	p.Arg59Ter	MCID, LS, Encephalomyopathy (progressive)	Pathogenic

67608644	c.248C>T	p.Ser83Leu	MCID	LP
67608658	c.262C>G	p.Arg88Gly	LS	US
67609474	c.349G>A	p.Ala117Thr	NP	Pathogenic
67609490	c.365C>T	p.Pro122Leu	Leukoencephalopathy, epileptic seizure, optic nerve atrophy	Pathogenic/LP
67609508	c.383G>A	p.Arg128Gln	MCID	LP
67609604	c.479G>A	p.Gly160Glu	NP	LP
67610399	c.529dupT	p.Tyr177Leufs*2	LS	NR
67610465	c.595C>T	p.Arg199Cys	NP	LP
67610466	c.596G>C	p.Arg199Pro	LS	NR
67610481	c.611A>G;	p.Tyr204Cys	Ophthalmoplegia, LLS	NR
67610486	c.616T>G;	p.Cys206Gly	Ophthalmoplegia, LLS	NR
67610487	c.617G>A	p.Cys206Tyr	NP	Pathogenic
67610502	c.632T> C	p.Ala211Val	Leukoencephalopathy	NR
67610510	c.640G>A	p.Glu214Lys	MCID, IBSN, leukoencephalopathy, LS, MR	LP
67610522	c.652G>T	p.Gly218Cys	Leukoencephalopathy	NR
67611027	c.733G>A	p.Val245Met	LS	NR
67611047	c.753delCCCC	p.Ser251Serfs*44	LS	US
67611050	c.756delC	p.Thr253Glnfs*44	LS/LBSL	NR
67611064	c.770G>A	p.Arg257Gln	White matter abnormality	US
67611403-67611436	c.914-8G_947del		Leukoencephalopathy (diffuse)	NR
67611479-67611480	c.990delTG		MCID, IBSN, leukoencephalopathy	NR
67611511	c.1022C>T	p.Ala341Val	Leukoencephalopathy, macrocephaly	US
67611559	c.1070T>C	p.Met357Thr	NP	LP
67611569	c.1080G > A	p.Ser360=	LS	LP/US
67611933	c.1117T>C	p.Phe373Leu	White matter abnormality	NR
67611934	c.1118T>C	p.Phe373Ser	MCID	Pathogenic
67611945	c.1129G>T	p.Glu377Ter	LS, LIMD	LP
67611948	c.1132A>C	p.Ser378Arg	NP	Pathogenic
67611971	c.1155C>T	p.Arg386Cys	White matter abnormality, developmental regression	NR
67611972	c.1156C>T	p.Arg386Cys	MCID, LS, brain lesions, LS/LBSL	Pathogenic/LP
67611972	c.1156G>A	p.Arg386His	LS, leukoencephalopathy	NR
67611982	c.1162+4A>C		MCID, optic nerve atrophy	Pathogenic/LP
67612153	c.1192+4A>C		Brain atrophy, White matter abnormality, cerebellar ataxia, seizure, psychomotor regression	NR
67612158-67612159	c.1207dup	p.Asp403fs	LS	Pathogenic
67612210-67612213	c.1256_1259del	p.Ile419fs*19	NP	Pathogenic
67612225	c.1268C>T	p.Thr423Met	MCID, cerebellar atrophy	Pathogenic/LP
67612251	c.1294G>C	p.Ala432Pro	LS	NR
67612375	c.1312C>A	p.Leu438Met	MCID	LP
67612627	c.1564C>A	p.Gln522Lys	Leukoencephalopathy (diffuse, no cavitation)	NR

Note: NS: Not specified; NP: Not provided; MCID: Mitochondrial Complex I Deficiency; LS: Leigh Syndrome; LLS: Leigh-Like Syndrome; IBSN: Infantile Bilateral Striatal Necrosis; LBSL: Leukoencephalopathy with Brainstem and Spinal Cord Involvement and Elevated Lactate; LIMD: Lethal Infantile Mitochondrial Disease; LP: Likely Pathogenic; US: Uncertain Significance; NR: Not reported in Clinvar.

Discussion

LBSL is often characterized by slowly progressive cerebellar ataxia, spasticity, and dorsal column dysfunction, sometimes with a mild cognitive deficit or decline [9]. Disease severity depends on the age of disease onset; neonatal or early infantile presentation has a severe disease course than childhood or adult-onset [13]. Genome-wide linkage analysis using microsatellite markers in LBSL families uncovered a candidate region on chromosome 1, and sequencing of genes in that specific region found mutations in DARS2 [10]. Most of the LBSL cases have pathogenic compound heterozygous mutations; however, few cases have been reported as homozygous mutations [13,14]. Diagnosis depends on the specific MRI findings, clinical history, and physical examination and is complemented by the targeted biochemical, functional, and molecular analyses. If the MRI does not meet the criteria for LBSL, elevated lactate may be a general indicator of mitochondrial leukoencephalopathy, but not specifically LBSL. A functional assay to identify reduced mitochondrial aspartyl-tRNA synthetase enzyme activity might be helpful to confirm the diagnosis [13]. In addition, the mitochondrial AARS2 gene transfers alanine to the tRNA during mitochondrial translation, and mutations result in infantile mitochondrial cardiomyopathy,(ovario)leukodystrophy, AARS2-related late-onset leukoencephalopathy, and mitochondrial encephalomyopathy [15,16]. The neurological features of motor deterioration, including cerebellar ataxia, pyramidal signs, cognitive decline, and psychiatric symptoms are frequent among AARS2-related patients [16]. Another article reported a 20-year-old man with progressive gait ataxia, lower limbs stiffness, cognitive decline, and abnormal behaviours. Restricted eye movement and nystagmus were also observed. Brain MRI revealed the periventricular white matter, and corpus callosum signal abnormalities; MRI of the spinal cord indicated hyper intensity in the pyramidal tracks at the level of the medulla and from the cervical to the thoracic spinal cord. Whole-Exome Sequencing (WES) identified two novel compound heterozygous variants in the AARS2 gene (c.965G>A, p.Arg322His; c.334G>C, p.Gly112Arg) [17]. This case expands the phenotypic spectrum in the AARS2 gene since spinal cord dystrophy has been reported for the first time. Therefore, it is worthy to combine phenotypes, radiological, biochemical, and molecular diagnosis to describe an inherited disease precisely. Despite the presence of characteristic leukodystrophy on the MRI images, confirmation of the diagnosis requires genetic analysis.

The pathogenic variants of NDUFV1 have been reported to be associated with few rare phenotypes. The homozygous mutation in NDUFV1 (c.640G>A, p.Glu214Lys) presented with Infantile Bilateral Striatal Necrosis (IBSN) in two siblings [18]. IBSN is a heterogeneous group of disorders causing symmetrical degeneration of the caudate nucleus and the putamen. Mutations in mitochondrial ATP6 and ND6, nuclear-encoded Nucleoporin 62 (NUP62) genes, and Solute Carrier Family 25 Member 19 (SLC25A19) have been associated with this syndrome [19]. Two siblings were diagnosed with IBSN, presented with dysarthria, muscular hypertonia with cogwheel rigidity, exaggerated deep tendon reflexes, and bilateral Babinski signs. The brain MRI demonstrated symmetric cystic lesions of the putamen. WES analysis found the homozygous mutation in NDUFV1, expanding the phenotype of NDUFV1 pathogenic variants [18].

Moreover, a patient with late-onset LS due to compound heterozygous NDUFV1 mutations with the overlapping features of LBSL has been reported [12]. In that patient, neurodegeneration was the main clinical presentation. Until seven months, the patient had normal developmental milestones and gradually developed feeding difficulty, irritability, hypotonia, spasticity, myoclonus, nystagmus, and reduced deep tendon reflexes. MRI of the brain revealed periventricular white matter lesions. At three years, the brain MRI showed overlapping radiological features for LS and LBSL. The signal abnormalities were found in the cerebral white matter, medulla oblongata, corpus callosum, internal capsule, and superior cerebellar peduncles, the spinocerebellar tracts, dorsal columns, and lateral corticospinal tracts [12]. MRI of the brain in LS typically shows bilateral symmetrical lesions

within the brainstem and basal ganglia, periaqueductal region, and cerebral peduncles [5]. The patient showed abnormalities in the basal ganglia, thalamus, substantia nigra, cerebral peduncle, and periaqueductal region in the midbrain. These findings resemble LS. WES identified two variants (c.756delC, p.Thr253Glnfs*44) and (c.1156C>T, p.Arg386Cys) in NDUFV1, and pathogenicity was confirmed by functional analysis [12]. This article added one more previously unrelated phenotype with NDUFV1 mutations and extending the list of genes associated with LBSL.

Pathogenic variants may affect the clinical presentations of mitochondrial diseases diversely, and genomic analysis may play a role in analysing the unexplained clinical phenotypes in mitochondrial diseases. Previously unknown phenotypes or rare phenotypes should be considered; otherwise targeted genome sequencing would miss the actual genetic cause. Molecular genetic testing can include a combination of gene-targeted testing (single-gene testing, multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing, exome array) depending on the phenotypes. Increasing clinical use of genetic analysis is uncovering clinically significant genetic variation, interpretation of disease alleles, and underlying biology. The lack of sensitive and specific biomarkers contributed to the complexity of the diagnosis. Mitochondrial diseases diagnosis is essential to offer palliative or experimental therapies and ensure the prenatal diagnosis, reproductive counseling, and family screening of seemingly unaffected individuals.

This review suggests the highly heterogeneous entity of mitochondria-related leukoencephalopathy and explores the lack of a straightforward genotype-phenotype correlation. Moreover, it emphasizes the necessity of knowing the neuroimaging patterns of the brain and spinal cord diseases and comprehensive genetic screening in clinically resembling mitochondrial disorders. Priority should be given to the atypical phenotypes and large-scale sequence analysis to solve the puzzle of unclassified mitochondrial syndromes, and prevent under- or over-diagnosis or missed diagnosis of asymptomatic patients.

Conclusion

Understanding the pathophysiology of the genes and allelic variants and the natural history of the disease process to determine drug regimens are of great importance. Currently, no cure is available for leukodystrophies, and it is essential to arrive at a definitive diagnosis in an individual patient. The diagnosis will end a frequently time-consuming and distressing search for the cause of a child's abnormalities. It may allow the family to focus on palliative care or more aggressively pursue experimental treatments. All in all, the diagnosis can facilitate a more realistic view of the patient's disease course and appropriate family genetic counselling.

Conflicts of interest

None

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