Deep pheno-genotyping of NDUFV1-related mitochondrial disorder

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Background:

The NDUFV1 gene encodes a 51-kDa flavin-binding core subunit of mitochondrial complex I (NADH: ubiquinone oxidoreductase), the major multiprotein enzyme of the mitochondrial respiratory chain. Our aim is to expand the phenotypic and genotypic spectrum of this NDUFV1-related mitochondrial disease.

Results:

We identified 28 new patients (16 males) from 22 families of Indian, Pakistani, Iranian, Malaysian and Egyptian ancestry and 61 cases previously reported. Parental consanguinity was reported in 27 cases. Age at onset ranged from birth to 10 years, with gait impairment and seizures as the most common initial symptoms. Core clinical features included intellectual disability, gait abnormalities, muscle weakness, poor speech and axial hypotonia, often progressing to spasticity. Minor features included orofacial or limb dystonia, myoclonus, hyperreflexia and cerebellar signs. (*Fig.1)*

In all patients who underwent MRI, the scan was abnormal, showing periventricular white matter and corpus callosum involvement, often with cystic degeneration and basal ganglia changes.

We identified 27 homozygotes and 1 compound heterozygote. Among six identified variants, two were novel. The most frequent was NM_007103.4:c.1156C>T, found in 78% of patients, followed by NM_007103.4:c.1268C>T (10%). *(Fig.2)* Haplotype analysis revealed distinct haplotypes surrounding the NDUFV1 locus. *(Fig.3)*

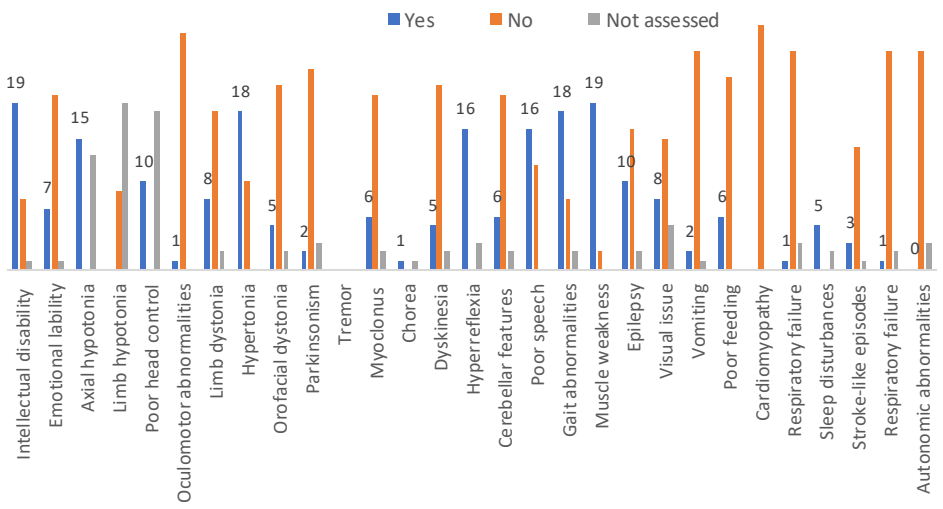

Fig. 1: clinical features of the 28 patients of our cohort

Materials and Method:

We screened large-scale next-generation sequencing datasets worldwide for biallelic NDUFV1 variants using a genotype-first approach. Variants were prioritized according to the following criteria: variant in NDUFV1 coding regions or at exon- intron boundaries; GnomAD v4.1 frequency < 0.001; 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. Detailed phenotypic information was collected for new cases identified.

Haplotype analysis was performed on raw exome sequencing data from probands carrying recurrent variants.

A systematic literature review was performed on February 2025 using PubMed, with «NDUFV1» as keyword. Predetermined data on genetic variants, neuroimaging findings, and clinical features were extracted.

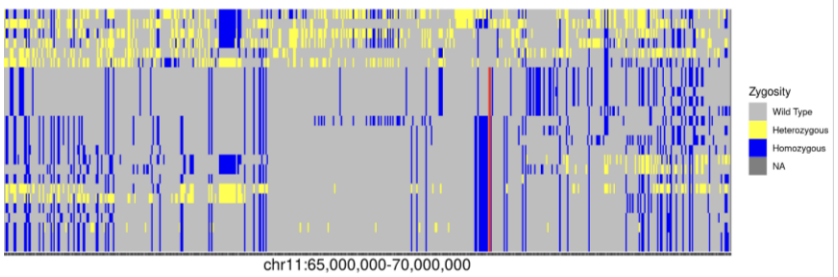

Fig 3: Haplotype analysis on exome files performed in Pakistani patients carrying the NM_007103.4:c.1156C>T variant

Discussion:

Our cohort, the largest reported to date, expands the known age at onset of NDUFV1-related disorders, extending the upper limit by one year. Clinically, we also document orofacial dystonia, previously underemphasized, and sleep disturbances as newly associated features. Oculomotor abnormalities (nystagmus and strabismus), frequently reported in the literature (29% and 22% of cases, respectively), were rare in our cohort (3% each). Respiratory insufficiency, very common in previously reported cases (16%), was also rare in our cohort (3%).

We report two novel variants: NM_007103.4:c.597delC p.(Ala201LeufsTer25) and NM_007103.4:c.466A>G p.(Ile156Val). Although c.1156C>T was found recurrently in individuals from neighbouring Asian regions, haplotype analysis showed distinct genetic backgrounds, supporting the view that it is not a founder effect.

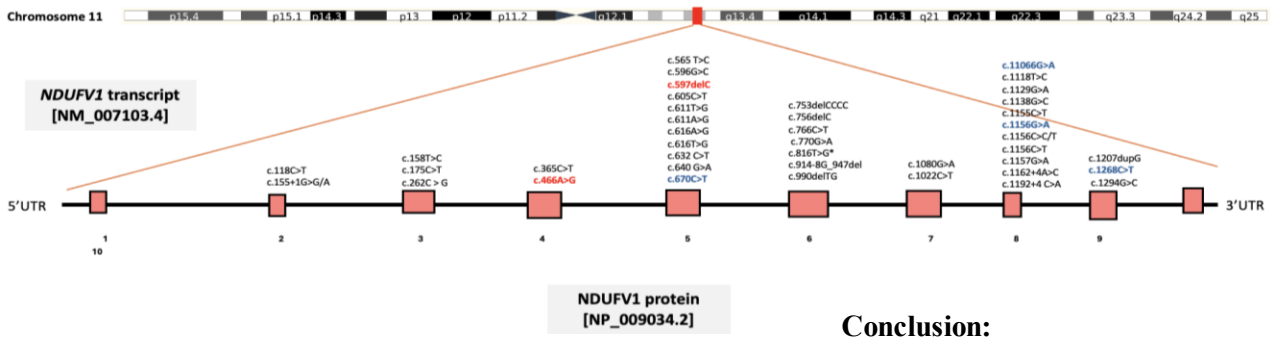

Fig.2: NDUFV1 gene schematic with introns to scale; literature variants in black, known variants in our cohort in blue, novel variants in our cohort in red.

Conclusion:

Our study expands the phenotypic spectrum of NDUFV1-related mitochondrial disorder by highlighting wider age range of onset, the presence of orofacial dystonia and the occurrence of sleep disturbances. Additionally, it expands the genotypic landscape by identifying two novel variants.

24-28 Ottobre 2025
Padova Congress
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