One Variant, Two Genes: Mitochondrial Disease Caused By a Single Nucleotide Change Leading to Two Different Missense Variants in Mitochondrial DNA

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INTRODUCTION

Mitochondriopathies, in which mitochondrial function is disrupted, have a broad phenotypic variability and can occur at any age. ATP synthase/Complex V (CV) is the terminal enzyme of the mitochondrial oxidative phosphorylation chain and is responsible for most of ATP synthesis. The complex is composed of 18 subunits, 2 of which are encoded by the mtDNA, more specifically the *MT-ATP6* and *MT-ATP8* genes.[1] Pathogenic variants in these genes frequently affect the CNS, muscles, eyes and/or heart, presenting a wide phenotypic variability. Classically, *MT-ATP6* variants are associated with a neurodegenerative spectrum, ranging from Neuropathy, Ataxia, and Retinitis Pigmentosa Syndrome (NARP) to Leigh Syndrome (MILS). MILS is associated with heteroplasmy levels >90%, while NARP presents in adulthood with 70%-90% heteroplasmy.[1-5]

Interestingly, there is a 46-base pair region between positions m.8527 and m.8572, where part of the 5' portion of *MT-ATP6* partially overlaps with the 3' portion of *MT-ATP8*, in different reading frames. As a result, a single base change can affect both proteins simultaneously. Cases in which variants altered amino acids in both proteins are extremely rare and predominantly associated with cardiomyopathy. However, variants in the m.8561 position have been associated with MILS[2-8]

We report an adult-onset NARP syndrome case resulting from a C>T base change at the 8561 position of the mtDNA.

Figure 1.

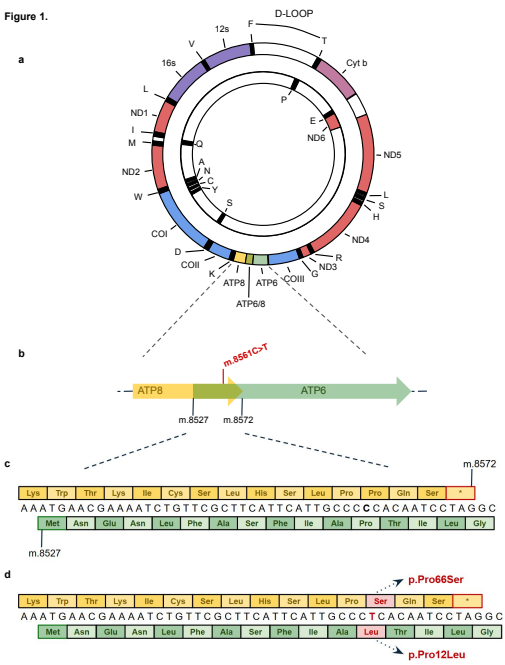

Figure 1. a) The human mtDNA, **b)** *MT-ATP6 (green)* and *MT-ATP8 (yellow)* genes. Our patient's variant (red) **c)** 46-base pair region between positions m.8527 and m.8572, where part of the 5' portion of *MT-ATP6* partially overlaps with the 3' portion of *MT-ATP8*, in different reading frames. **d)** In red: Our patient's single base change and the resulting amino acid changes in *MT-ATP6* and *MT-ATP8*.

CASE REPORT

Our patient is a 42 year old male, born to non-consanguineous parents, who presented with progressive bilateral visual loss at age 30. Initial ophthalmological examination showed retinal dystrophy with macular atrophy. At age 32, the patient developed gait ataxia, dysarthria and motor incoordination. He also presented acute confusional paroxysms during infectious episodes, returning to baseline status after the infections resolved, with no cognitive, behavioral, epileptic, swallowing, or hearing impairments. At age 39, progressively worsening symptoms prompted him to see a neurologist, who identified cerebellar atrophy on a brain MRI and subsequently referred him to the neurogenetics department for investigation.

During the investigation, electromyography revealed mild axonal sensorimotor polyneuropathy (predominantly sensory) associated with an intermediate-pattern neuropathy (axonal) distally in the left fibular nerve. Cardiac workup including EKG, echo, and Holter was negative. Whole exome sequencing revealed the m.8561C>T mtDNA variant with 89% heteroplasmy in buccal swab, confirming a mitochondriopathy due to CV deficiency.

DISCUSSION

The single nucleotide change m.8561C>T is located on the *MT-ATP6/8* overlapping region, leading to two different missense variants: p.Pro66Ser in *MT-ATP8* and p.Pro12Leu in *MT-ATP6*. This variant is extremely rare, with only one previous report in a Leigh syndrome patient who had 96% heteroplasmy in blood and muscle.[7] Notably, a different pathogenic variant at this same position (m.8561C>G) was identified in two siblings with an intermediate Leigh syndrome phenotype (ataxia with neuropathy, diabetes and hypogonadism) and 99% muscle heteroplasmy. [8]

Our patient's 89% heteroplasmy level, in turn, places him on the NARP/Leigh threshold, explaining his later, more attenuated phenotype in contrast to the previously reported Leigh cases, who had heteroplasmy levels exceeding 90%.

These cases' neurological phenotype, however, contrasts to the cardiomyopathic phenotype associated with variants in the same *MT-ATP6/8* overlap region. We hypothesize that this may be due to different tissue levels of heteroplasmy within a single individual, impacting tissues with higher heteroplasmy more severely, and that the specific simultaneous alteration to both ATP6 and ATP8 proteins caused by this variant's position may lead to a CV dysfunction that is more deleterious to neuronal tissues.

FINAL REMARKS

To elucidate the precise physiopathological mechanism of our patient's variant and other *MT-ATP6/8* overlap variants, further investigation is required. Multiple tissues assessment is necessary to correlate heteroplasmy levels with clinical presentation, while cellular and molecular functional studies will determine how variants with different combined protein changes compromise tissues differently.

REFERENCES: