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Intra- and inter-familial phenotypic heterogeneity of the m.7510T>C variant

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Abstract

In a recent article Kytövuori et al. reported a Finnish family with phenotypically variable multiorgan disease manifesting in the brain, ears, and endocrine organs, due to the variant m.7510T>C in the MT-TS1 (tRNA(Ser)) gene with high heteroplasmy. We have the following comments and concerns.

Keywords: Mitochondrial; mtDNA; Phenotype; Genotype; Epilepsy; Heterogeneity; Multisystem

Introduction

Though the mutation m.7510T>C has been previously reported (Table 1) [1-5], the pathogenicity of this variant is not well supported. Currently it is recommended to assess the pathogenicity of tRNA variants according to the modified Yarham score [6]. According to this tool the variant m.7510T>C scores 9 (>1 independent report: 2, heteroplasmy: 2, segregation with variant: 2, biochemical defect in CI, CIII, or CIV: 0, variant segregation with biochemical defect on single fiber studies: 0, mutant mt-tRNA steady state level studies or evidence of pathogenicity in *trans*-mitochondrial cybrid studies: 0, evidence of normality in trans-mitochondrial cybrid studies: 0, evolutionary conservation of nucleotide: 2, histopathology: 1), indicating that the variant is only "possibly pathogenic" [6].

The index patient had epilepsy with onset at age 9 years [1]. Why was valproate (VPA) initially chosen? It is well established that VPA, together with carbamazepine, phenytoin, and phenobarbital, is mitochondrion-toxic [7] and a pediatric patient with hearing impairment and epilepsy is highly suspicious of a mitochondrial disorder (MID). Were antiepileptic drugs other than valproic acid and levetiracetam prescribed? Were seizures well controlled with levetiracetam?

Discussion

Which was the cause of the reduced tendon reflexes? Myopathy or neuropathy? Was there also wasting, hypotonia, or fasciculations? Which were the results of nerve conduction studies and the needle electromyography? Were biochemical or single fiber studies carried out with the muscle biopsy? Which were the results? Was creatine-kinase elevated? mtDNA mutations usually cause multisystem disease

Variables	Kytövuori (2017)				Komlosi (2013)			Labay (2008)	Castillo (2002)	Hutchin (2000)		
Phenotype	I/2	II/1	III/1	III/2	II/3	III/2	IV/1	n=11	n=26	III/9	IV/6	IV/7
Sex	f	f	m	f	f	f	m	f=5, m=6	f=16, m=10	f	m	f
Age	70 y	46 y	21 y	17 y	nr	nr	7 y	np	9-70 y	np	np	np
Onset	np	ES	20 y	6 y	20 y	30 y	4.5 y	5-20 y	np	np	15 m	5 y
Short stature	np	np	np	yes	nr	no	nr	nr	no	np	np	np
Hypoacusis	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Epilepsy	no	no	no	yes	no	no	no	no	no	np	np	np
Ataxia	yes	yes	no	yes	no	no	no	no	no	np	np	np
Tremor	yes	no	no	no	no	no	no	no	no	np	np	np
Cognitive impairment	no	no	no	yes	no	no	no	no	no	np	np	np
RLS	yes	no	no	no	no	no	no	no	no	np	np	np
HP (blood), %	90	99	99	99	homoplasmic			homoplasmic	no	>95	>95	>95
HP (muscle), %	np	np	np	99	np	np	np	np	no	np	np	np
HP (buccal mucosa), %	np	99	np	np	np	np	np	np	no	np	np	np
Haplotype	H13a1a1d1				H variant			H	H1	np	--	--
RLS: Restless Leg Syndrome, HP: Heteroplasmy, Np: Not Provided, ES: During Elementary School												

Table 1: Intra- and inter-familial phenotypic heterogeneity of the m.7510T>C variants.

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either already at onset of the abnormalities or during the natural course of the disease. Thus, affection of organs can be mild or even subclinical at an early stage of the disease. However, since affection of multiple organs may strongly influence the outcome and prognosis of these patients, it is essential that they are prospectively investigated for multisystem involvement. Particularly important is the thorough investigation of the heart since patients with a mitochondrial disorder and cardiac involvement are prone to develop, cardiomyopathy, conduction defects, and arrhythmias, including sudden cardiac death (SCD). Which were the results of the routine ECG, long-term ECGs, and echocardiography? It is also important to screen MID patients for endocrine abnormalities, hypopituitarism, diabetes, hypo- /hyperthyroidism, hypoaldosteronism, Addison's disease, and hypogonadism, for renal disease, for hematological abnormalities, and for gastrointestinal involvement.

Conclusion

Overall, this interesting report requires confirmation of the pathogenicity of the variant proposed to be causative, prospective clinical and instrumental investigations for mild or subclinical involvement of organs other than the brain, muscle, and ears, and discussion of possibly mechanisms for the extensive intra- and inter-familial phenotypic heterogeneity of the m.7510T>C variant.

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