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LETTER TO THE EDITOR

Novel de novo *DNMT1* gene mutation associated with hereditary sensory and autonomic neuropathy 1E (HSAN1E)

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Dear Sirs,

Hereditary sensory autonomic neuropathy with dementia and hearing loss (HSAN1E) is an adult onset, autosomal-dominant neurodegenerative disorder caused by heterozygous pathogenic mutations in the DNA methyltransferase 1 (*DNMT1*) gene [1]. Cohort studies have shown a frequently stereotypic progression of the disease, starting with hearing loss, followed by a pan-sensory neuropathy (unmyelinated and myelinated axons) with its complications (arthropathy and ulcerations), whereas cognitive decline of varied severity dominates its later phase [2]. Herein, we describe a patient of Greek-Cypriot origin with HSAN1E resulting from a novel, de novo occurring, *DNMT1* mutation.

Case report

A 33-year-old female was evaluated at the Cyprus Institute of Neurology and Genetics due to sensory loss, in particular, insensibility to pain, combined with neuralgic symptoms in her feet starting at least 5 years ago. She had recently suffered a fracture in the first metacarpal bone without noticing much pain. The patient also complained of mild memory difficulties and sleep problems with frequent acting out her dreams. Otherwise, her personal and family medical history was unremarkable.

On examination, she had generalized areflexia, very severe impairment of pinprick and vibration sensation in the lower more than upper limbs in a stocking/glove distribution without muscle weakness or atrophy (Table 1). On bedside testing, she was also found to have hearing deficits, attributed to high-frequency peripheral hearing loss by subsequent audiogram and brainstem auditory evoked potentials.

Nerve conduction studies were consistent with a severe, predominantly sensory, axonal neuropathy. In particular, the median, ulnar, radial and sural sensory responses were severely reduced on first evaluation at age 33 years and were unobtainable on repeat evaluation at the age of 35, whereas all motor nerve responses were normal initially and on repeat testing the tibial and peroneal motor responses showed mildly reduced amplitudes with normal conduction velocities (Table 2). Needle electromyography revealed mild chronic denervation in leg muscles.

Blood tests were unremarkable, including complete blood count, sedimentation rate, glycosylated haemoglobin, thyroid function, vitamin B12 and homocysteine levels and autoimmunity screening (anti-nuclear, anti-double-stranded DNA, anti-neutrophil cytoplasmic antibodies, ENA, angiotensin-converting enzyme). Serology for HIV 1/2, hepatitis B/C and syphilis and screening for heavy metals were negative.

Further investigations for acquired causes of her neuropathy, including antiganglioside and paraneoplastic autoantibodies, MAG antibodies, gliadin and transglutaminase antibodies, and SSA and SSB antibodies, were also unrevealing. Serum protein electrophoresis revealed no paraprotein. An MRI of the brain was unremarkable.

Subsequently, targeted genetic testing for TTR V30M and MFN2 mutations proved negative. A custom panel of genes associated with inherited peripheral neuropathies (using the Illumina NextSeq 550 system) allowed the detection of a novel heterozygous variant in exon 21 of DNMT1

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Table 1 Clinical features observed in HSAN1E patient at 2 different time points

Age (years)	CMTNSv2 (Rasch)	Distal weakness UL	Distal weakness LL	Vibration UL	Vibration LL	Foot deformity	DTRs UL (biceps, triceps)	DTRs LL (patellar, Achilles)	Positive sensory symptoms
33	12	No	No	Reduced to the wrist	Absent to knee	None	Absent	Absent	Feet
35	13	No	No	Reduced to the elbow	Absent to knee	None	Absent	Absent	Feet

CMTNSv2 CMT neuropathy score version 2, *LL* lower limb, *ND* no data, *UL* upper limb

Table 2 Sequential electrophysiological findings

Year (age)	Nerve	Latency (ms)	Amplitude	Conduction velocity (m/s)
2019 (33)	Right median motor	2.54	17.9 mV	60.6
	Right ulnar motor	1.94	12.1 mV	51.1
	Right peroneal motor	3.73	6.0 mV	58.0
	Right tibial motor	3.27	18.3 mV	51.1
	Right median sensory	3.35	0.77 µV	51.6
	Right ulnar sensory	2.48	0.52 µV	53.3
	Right radial sensory	2.43	3.1 µV	54.6
	Right sural sensory	Unobtainable		
2021 (35)	Right median motor	2.42	16.9 mV	59.0
	Right ulnar motor	1.75	7.8 mV	64.7
	Right peroneal motor	3.73	4.0 mV	48.0
	Right tibial motor	3.27	4.3 mV	52.0
	Right median sensory	Unobtainable		
	Right ulnar sensory	Unobtainable		
	Right radial sensory	Unobtainable		
	Right sural sensory	Unobtainable		

(NM_001130823.1, c.1697 T > A; p.Leu566His). Additionally, Sanger sequencing confirmed the presence of this variant in the proband, whereas her unaffected parents and sister were negative.

Discussion

HSAN1E is an allelic disorder to autosomal-dominant cerebellar ataxia, deafness and narcolepsy (ADCA-DN) [2, 3]. The latter is characterized by adult onset prominent narcolepsy/cataplexy, sensorineural hearing loss and cerebellar ataxia, whereas cognitive impairment and peripheral neuropathy may also occur in the course of the disease. Based on the marked phenotypic overlap, Baets et al. proposed the unifying term DNMT1-complex disorder to incorporate both entities [2].

Pathogenic variants located within exon 20 of the *DNMT1* gene are associated with HSAN1E, while in exon 21 with the ADCA-DN [2]. With one notable exception, all *DNMT1* pathogenic variants reside within the replication focus targeting sequence (RFTS) domain, which is essential in mediating DNA substrate binding to the DNMT1 catalytic region [4]. Cellular expression studies revealed these mutations alter proper DNMT1 folding and produce global genome hypomethylation leading to impaired epigenetic regulation [2, 5].

In our patient, the nucleotide change c.1697 T > A is located in close vicinity to the variants reported by Yuan et al. (c.1706A > G) and Coelho et al. (c.1700 T > C) within exon 21 [6, 7]. It affects a highly conserved across species leucine residue at position 566. Multiple lines of computational evidence support a deleterious effect on the gene or gene product. More specifically, a pathogenic computational verdict is based on eleven pathogenic predictions from DEOGEN2 (score: 0.95), EIGEN (score: 0.718), FATHMM-MKL (score: 0.9719), LRT (score: 0), M-CAP (score: 0.6291), MutPred (score: 0.643), PrimateAI (score: 0.8302), PROVEAN (score: 6.31), Polyphen2 HDIV (score: 1.000), SIFT (score: 0) and SIFT4G

Table 3 Predicted scores of pathogenicity for the identified *DNMT1* c.1697 T > A missense variant

Prediction tool	Score	Supporting benign score range	Supporting pathogenic score range
DEOGEN2	0.95	≤ 0.402	≥ 0.795
EIGEN	0.718	≤ 0.189	≥ 0.683
FATHMM-MKL	0.9719	≤ 0.758	≥ 0.969
LRT	0	≤ 0.000435	≥ 0
M-CAP	0.6291	≤ 0.0854	≥ 0.29
MutPred	0.643	≤ 0.403	≥ 0.614
PrimateAI	0.8302	≤ 0.519	≥ 0.789
PROVEAN	6.31	≤ 2.29	≥ 4.38
Polyphen2 HDIV	1.000	≤ 0.768	≥ 1
SIFT	0	≤ − 0.03	≥ − 0.001
SIFT4G	0	≤ − 0.063	≥ − 0.002
FATHMM	− 1.27	≤ 0.46	≥ 4.4

(score: 0), versus one benign prediction from FATHMM (score: − 1.27) (Table 3).

Interestingly, in our case as well as the reports by Yuan et al. and Coelho et al., a classical HSAN1E phenotype emerged on a background of exon 21 variants, indicating the diversity and genotype–phenotype correlation intricacy of DNMT1-complex disorder. This finding, combined with the recent expansion of its phenotypic spectrum and the conceivable identification of novel *DNMT1* mutations, would lead to a better understanding of this rare disorder [4].

Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval None.

Conflict of interest The authors declare no competing interests.

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