CASE REPORT

A novel *DNMT1* mutation associated with early onset hereditary sensory and autonomic neuropathy, cataplexy, cerebellar atrophy, scleroderma, endocrinopathy, and common variable immune deficiency

Robin Fox[1], John Ealing[1], Helen Murphy[2], David P. Gow[3], and David Gosal[1]

[1] *Department of Neurology, Salford Royal NHS Foundation Trust, Manchester, UK;* [2] *Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester, UK; and* [3] *Department of Neurology, Dunedin Public Hospital, Dunedin, New Zealand*

Abstract DNA methyltransferase 1 (*DNMT1*) is an enzyme which has a role in methylation of DNA, gene regulation, and chromatin stability. Missense mutations in the *DNMT1* gene have been previously associated with two neurological syndromes: hereditary sensory and autonomic neuropathy type 1 with dementia and deafness (HSAN1E) and autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN). We report a case showing overlap of both of these syndromes plus associated clinical features of common variable immune deficiency, scleroderma, and endocrinopathy that could also be mutation associated. Our patient was found to be heterozygous for a previously unreported frameshift mutation, c.1635_1637delCAA p.(Asn545del) in the *DNMT1* gene exon 20. This case displays both the first frameshift mutation described in the literature which is associated with a phenotype with a high degree of overlap between HSAN1E and ADCA-DN and early age of onset (c. 8 years). Our case is also of interest as the patient displays a number of new non-neurological features, which could also be *DNMT1* mutation related.

Key words: autosomal dominant cerebellar atrophy, cataplexy, cerebellar atrophy, deafness and narcolepsy (ADCA-DN), genetics, hereditary sensory and autonomic neuropathy

A 20-year-old man presented with sensory symptoms. From age 8 years, he had complained of intermittent, sudden, lancinating pains in his feet with associated reflex spasms. An electroencephalogram (EEG) was said to show polyspike activity and a diagnosis of primary generalized epilepsy was given, and sodium valproate prescribed without resolution of his symptoms.

Prior to this he had been diagnosed with common variable immune deficiency (CVID) on the basis of repeated infections with low immunoglobulin levels for which subcutaneous immunoglobulin therapy was commenced. His early childhood development had been otherwise normal, and there was no relevant family history.

He now experienced worsening of his pre-existing sensory symptoms with new burning discomfort involving hands and feet. He noted worsening of his symptoms in the cold with Raynaud's phenomenon.

On neurological examination, there were signs of a sensory (small fiber predominant) and motor neuropathy with distal muscle wasting, oedema of his feet, and pes cavus. There were distal skin changes with 'mechanic's hands', sclerodactyly,

Address correspondence to: Robin Fox, Department of Neurology, Salford Royal NHS Foundation Trust, Manchester, UK. Tel: +44161 789 7373; E-mail: robinfox@doctors.org.uk

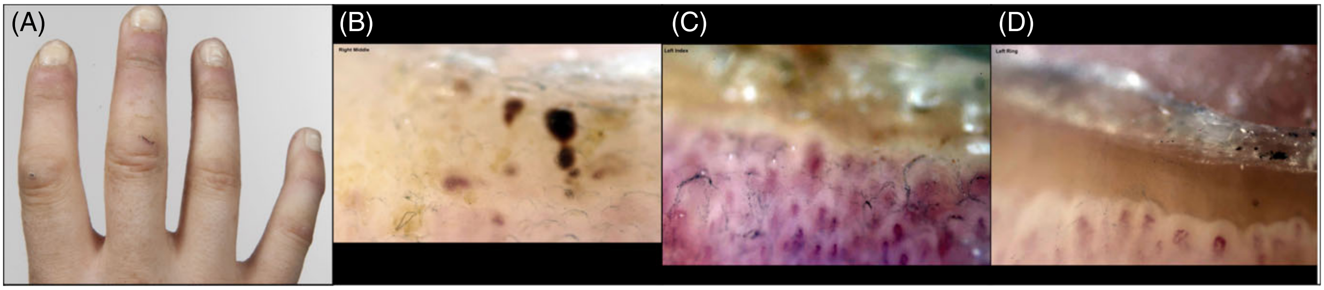

Figure 1. (A) Photograph of patient's hands showing distal skin changes with 'mechanic's hands', sclerodactyly, and evidence of old healed ulceration at the fingertips. (B–D) Nail fold capillaroscopy – it is not possible to see distal row of capillaries clearly in any finger, where visible capillaries are widened. (B) Right middle finger (showing giant capillary and areas of hemorrhage), (C) left index finger, (D) left ring finger.

Table 1. Nerve conduction studies from patient showing length-dependent axonal neuropathy - with attenuated lower limb motor responses.

Motor	Latency	Amplitude	CV	F
R Median				
Wrist-APB	3.4	5.0	50	30
Elbow–Wrist	8.8	4.3		
R Ulnar				
Wrist–ADM	2.1	6.5		31.2
B Elbow–Wrist	7.1	4.1	51	
A Elbow–B Elbow	8.6	4.0	53	
R Tibial				
Ankle	–	–		
R Peroneal				
Ankle–EDB	–	–		
PopFoss–Ank	–	–		

APB, abductor pollicis brevis; ADM, abductor digiti minimi; EDB, extensor digitorum brevis.

and evidence of healed ulceration at the fingertips (see Fig. 1).

Nerve conduction studies showed globally absent sensory responses and attenuated lower limb motor responses (Table 1). His syndrome was most consistent with hereditary sensory neuropathy type 1. Screening for a *SPLTC-1* mutation was negative.

The pain and involuntary movements initially responded well to Pregabalin. A repeat EEG showed no abnormality, and sodium valproate was withdrawn.

Thermography confirmed Raynaud's phenomenon. Nail fold capillaroscopy (Fig. 1) showed areas of hemorrhage in several capillary loops. Autoantibody screen was negative. There were no joint, sicca or gastrointestinal symptoms. There was no history of thromboembolic disease or rash. An echocardiogram and ECG were normal, and pulmonary function tests (PFTs) showed a moderate obstructive defect. A rheumatology consult diagnosed a systemic sclerosis spectrum disorder.

At 21 years he began to experience depression with suicidal ideation, treatment with duloxetine resulted in confusion and visual hallucinations. The hallucinations subsided following the withdrawal of duloxetine. At 22 years, impotence was reported along with episodes of orthostatic hypotension.

At 23 years he began to suffer from tinnitus and hearing loss with sudden episodes of atonia associated with excitement, attacks strongly suggestive of cataplexy. There were no additional features of narcolepsy. The cataleptic episodes responded to clomipramine.

At 24 years despite ongoing subcutaneous immunoglobulin therapy the patient experienced episodes of systemic infection associated with acute encephalopathy which resolved following antimicrobial treatment. He was found to be in urinary retention, catheterisation revealing a residual urine volume of 2.4 l. Following this there was progressive loss of bladder function with development of a neurogenic bladder requiring intermittent self-catheterisation. Further autonomic dysfunction developed affecting his bowel, causing chronic constipation.

A magnetic resonance (MR) brain showed cerebellar atrophy. Endocrinological testing revealed Addison's disease and low serum testosterone. Formal cognitive testing revealed no significant impairments.

Our patient was found to be heterozygous for a novel small in-frame deletion mutation, c.1635_1637delCAA p.(Asn545del) in the *DNMT1* gene exon 20. Confirmatory testing was performed by direct sequencing of *DNMT1* exon 20 (Sanger sequencing using BigDye v3.1, see Fig. 2). Testing of both parents revealed no similar mutations, suggesting a *de novo* occurrence. This is the first in-frame deletion mutation in *DNMT1* discovered to our knowledge, with all previous mutations reported being missense mutations. This in-frame deletion is absent in the ExAC database (http://exac.broadinstitute.org/).

Figure 2. Sanger sequencing of DNMT1 exon 20 in our patient showing forward and reverse sequences (reverse complemented) using Mutation Surveyor.

Discussion

Our patient displays features of both of the described *DNMT1* mutation syndromes, plus several new features such as scleroderma spectrum disorder, endocrinopathy, and CVID.

DNMT1 mutations have been previously associated with two distinct phenotypes depending on the position of the mutation, an Hereditary Sensory, and Autonomic neuropathy (HSAN), termed HSAN1E, usually associated with exon 20 mutations, or Autosomal Dominant Cerebellar Ataxia with deafness and narcolepsy (ADCA-DN) with mutations in exon 21. There is growing evidence however that this distinction is less clear.

Several reports have found considerable overlap between the two phenotypes. Narcolepsy with or without cataplexy, optic neuropathy, deafness, large and small fiber polyneuropathy and lower limb oedema are common to both forms *(Moghadam et al., 2014)*. Dementia is found in both phenotypes but is more prominent in HSAN1E *(Klein et al., 2013)*. There has also been a report of HSAN1E phenotype associated with an exon 21 mutation *(Yuan et al., 2013)*, suggesting phenotype/genotype heterogeneity.

Our patient has a novel *de novo* mutation in the exon 20 region, and phenotypically is more consistent with HSAN1E, but showing a high degree of overlap between the two phenotypes with features such as cerebellar atrophy and psychiatric symptoms including severe depression, which were very prominent in Winklemann *et al.'s (2012)* series of ADCA-DN patients. This case reinforces recent work *(Moghadam et al., 2014; Baets et al., 2015)* suggesting that *DNMT1* mutations cause a spectrum of disease with ADCA-DN and HSAN1E at the polar ends, rather than two distinct syndromes.

Our patient's symptoms began earlier than commonly reported; the mean onset of HSAN1E in *Baets et al.'s (2015)* cohort (45 subjects) was 37.7 years, with mean survival to 53.6 years. The earliest reported symptom was hearing loss at age 18. In our patient the sensory symptoms at age 8 were not diagnosed as a neuropathy, although they are of interest in light of the subsequent development of a clear sensory and autonomic neuropathy. The mutation in our patient is the first in-frame deletion mutation described in *DNMT1*, and it is possible this causes a more profound dysfunction in *DNMT1* structure and function than the previously described missense mutations, leading to an earlier onset.

Non-neurological features

In addition to the recognized neurological features, our patient has immunological features including a scleroderma spectrum disorder, CVID, and an endocrinopathy. Given the patient's young age we do not think that they are independent occurrences. Patients with CVID are prone to autoimmunity in general, as many as 20–29% of patients with CVID in three large studies *(Wehr et al., 2008; Resnick et al., 2012; Gathmann et al., 2014)* had evidence of auto-immune disease, but adrenal insufficiency or scleroderma have not been described before to our knowledge.

It is possible that these features represent a downstream effect of *DNMT1* mutation on transcription. In patients with myotonic dystrophy, a trinucleotide repeat disorder that results in the production of toxic mRNA species, multiple downstream effects including non-neurological conditions occur, such as diabetes, low IgG levels *(Kaminsky et al., 2011)* and an association with autoimmunity *(Tieleman et al., 2009)*.

Winklemann *et al. (2012)* noted that HSAN1E patients are often susceptible to infection and postulated that as *DNMT1* is highly expressed in immune cells, and required for the maturation and differentiation of CD4+ into T-regulatory lymphocytes, *DNMT1* dysfunction may link with autoimmunity and immunodeficiency, thus supporting our argument of a causal association.

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