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Narcolepsy is a common phenotype in HSAN IE and ADCA-DN

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We report on the extensive phenotypic characterization of five Italian patients from four unrelated families carrying dominant heterozygous *DNMT1* mutations linked to two distinct autosomal dominant diseases: hereditary sensory and autonomic neuropathy with dementia and hearing loss type IE (HSAN IE) and autosomal dominant cerebellar ataxia, deafness and narcolepsy (ADCA-DN). Patients underwent genetic analysis of *DNMT1* gene, neurophysiological tests investigating sleep, auditory functions and peripheral nervous system, ophthalmological studies including optical coherence tomography, lymphoscintigraphy, brain magnetic resonance and nuclear imaging, cerebrospinal fluid hypocretin-1, total tau, phosphorylated tau, amyloid-β_{1-42} and 14-3-3 proteins measurement, skin, muscular and sural nerve biopsies. Exome and direct sequencing studies disclosed two different point mutations affecting exon 21 of *DNMT1* gene in patients with ADCA-DN, a novel heterozygous point mutation in exon 20 in two affected HSAN IE siblings, and a trinucleotide deletion in exon 20 in the latter patient with HSAN IE. Phenotypic characterization pinpoints that ADCA-DN and HSAN IE represent two discrete clinical entities belonging to the same disease spectrum, with variable degree of overlap. Remarkably, narcolepsy with or without cataplexy with low/intermediate or normal

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cerebrospinal fluid hypocretin-1 is present in both diseases. The human leukocyte antigen DQB1*06:02 was absent in all patients. Other common symptoms and features observed in our cases, involving the central and peripheral nervous system, include deafness, optic neuropathy-previously not reported in HSAN IE-large and small fibres polyneuropathy and lower limbs oedema. Overall, the two syndromes share more characteristics than previously recognized and narcolepsy is common to both. HSAN IE and ADCA-DN are two extreme phenotypic manifestations of a DNMT1 methylopathy.

Keywords: ADCA-DN; HSAN IE; DNMT1; narcolepsy; cataplexy; neurodegeneration

Abbreviations: ADCA-DN autosomal dominant cerebellar ataxia, deafness and narcolepsy; HSAN IE = hereditary sensory and autonomic neuropathy with dementia and hearing loss type IE

Introduction

Mutations affecting the DNA methyl-transferase type 1 (*DNMT1*) gene, which encodes a DNA methyltranferase involved in maintenance of DNA methylation patterns, have been associated with two distinct autosomal dominant diseases: hereditary sensory and autonomic neuropathy with dementia and hearing loss type IE (HSAN IE, OMIM 614116) and autosomal dominant cerebellar ataxia, deafness and narcolepsy (ADCA-DN, OMIM 604121) (Klein *et al.*, 2011; Winkelmann *et al.*, 2012).

HSAN IE is characterized by hearing loss, severe sensory and autonomic polyneuropathy, and early-onset dementia. Motor polyneuropathy and psychiatric manifestations were also reported in some patients (Wright and Dyck, 1995; Hojo *et al.*, 1999; Klein *et al.*, 2011, 2013; Yuan *et al.*, 2013).

ADCA-DN is peculiar for the prevalent occurrence of narcolepsy with and without cataplexy, often appearing years before the onset of hearing loss and cerebellar ataxia. Other clinical manifestations of ADCA-DN include sensorimotor polyneuropathy, optic atrophy, extrapyramidal, pyramidal and dysautonomic signs, psychiatric disturbances, dementia and diabetes mellitus (Melberg *et al.*, 1995, 1999, 2001; Pedroso *et al*., 2013).

Although overlapping in their symptomatology, the two methylopathies have been considered to date as distinct clinical entities (Klein *et al.*, 2013). Indeed, major symptoms of narcolepsy with cataplexy, namely excessive daytime sleepiness with sleep onset REM periods, cataplexy, nocturnal sleep disruption, dissociated REM sleep features such as hypnagogic hallucinations, sleep paralysis, and REM sleep behaviour disorder (American Academy of Sleep Medicine, 2005), have been reported only in the ADCA-DN phenotype. However, studies with sleep recordings in HSAN IE have not been reported to date, thus narcolepsy could have been overlooked (Klein *et al.*, 2013; Yuan *et al.*, 2013). Furthermore, although pyramidal and extrapyramidal signs have only been described in ADCA-DN, cerebellar signs have been recently observed also in HSAN IE (Klein *et al.*, 2011), suggesting overlap of clinical features between the two diseases. In addition, genotype–phenotype correlations indicated that mutations in exon 20 of *DNMT1* have been associated with HSAN IE, whereas mutations in exon 21 have been found in all cases of ADCA-DN, with the exception of a single family presenting with HSAN IE but with a novel mutation in exon 21 (Yuan *et al.*, 2013).

Current data suggest an immune-mediated pathophysiology for sporadic narcolepsy with cataplexy based on a strong association with human leukocyte antigen (HLA) DQB1*06:02 haplotype and genome-wide association studies. As the condition is due to a loss of hypothalamic hypocretin cells, it is postulated that these are the targets of the autoimmune process (Mahlios *et al.*, 2013). Not surprisingly, symptomatic narcolepsy with cataplexy —i.e. occurring during the course of other neurological condition— has also been described, mainly in the context of CNS lesions affecting the posterior hypothalamus (Nishino and Kanbayashi, 2005; Kanbayashi *et al.*, 2011). A few inherited disorders, such as Prader-Willi syndrome, Niemann-Pick type C disease and myotonic dystrophy, can also show typical symptoms of narcolepsy with and without cataplexy (Nishino and Kanbayashi, 2005; Kanbayashi *et al.*, 2011). Only a few multiplex families, in which narcolepsy with cataplexy appears to be an inherited disease, have been reported in the literature (Mignot, 1998; Dauvilliers *et al.*, 2004), and two pathogenic mutations potentially found, one in the hypocretin gene, the other in *MOG* (Peyron *et al.*, 2000; Hor *et al.*, 2011).

We here report on the extensive phenotypic characterization of five Italian patients from four unrelated families carrying dominant heterozygous *DNMT1* mutations, two with patients displaying the hallmark features of ADCA-DN and two those of HSAN IE. Our study demonstrates that a spectrum of clinical manifestations, in particular narcolepsy that is present in all pedigrees, is common to both disorders.

Materials and methods

Families and case reports

Phenotypic characterization was carried out in two probands from two ADCA-DN Italian kindred in comparison with three patients with HSAN IE from two Italian kindred (Winkelmann *et al.*, 2012). Clinical features of affected members from each kindred are summarized in Table 1, and the pedigrees are shown in Fig. 1. The clinical history of all probands is reported below.

Patient K1 II-1 ADCA-DN

The proband is a 57-year-old male, without any remarkable family history, who presented at age 42 years with excessive daytime sleepiness, partial and generalized cataplectic attacks and deafness. He subsequently developed cerebellar ataxia, lower limb oedema, pyramidal, extrapyramidal (rest and postural tremor, rigidity) and autonomic (erectile dysfunction and urinary urge/incontinence) signs and

Table 1 Patient demographics

Phenotype	ADCA-DN			HSAN IE			
Patient	**K1 II-1**	**K2 II-2†**	**K2 III-1**	**K3 II-1†**	**K3 III-1**	**K3 III-2**	**K4 I-1**
DNMT1 mutation	p.Ala570Val	NA	p.Gly605Ala	NA	p.Pro507Asn	p.Pro507Asn	p.Lys521del
Age at time of study	57	45	47	38	36	33	59
Life span		52		41			
Sex	M	M	M	M	F	M	M
Excessive daytime sleepiness	42	Y	43	N	Y	Y	43
Cataplexy	42	Y	43	NA	N	N	58
Hypnagogic hallucinations	N	NA	Y	NA	N	N	N
Sleep paralysis	N	NA	N	NA	N	N	N
REM sleep behaviour disorder	49	NA	46	NA	N	N	58
Hearing loss	43	Y	43	30	26	31	33
Cerebellar ataxia	46	Y	47	NA	Y	N	Y
Optic atrophy (age of detection)	55	NA	47	NA	36	33	59
Altered glucose metabolism	57	N	N	N	N	N	45
Lower limbs oedema	45	NA	47	NA	N	N	Y
Sensory neuropathy	47	NA	47	36	30	32	34
Ulcers	N	N	N	36	N	N	35
Depression	48	Y	N	NA	N	N	N
Dementia	N	NA	N	38	N	N	44
Pyramidal signs	53	Y	N	N	N	N	N
Extrapyramidal signs	56	N	N	N	N	N	N
Autonomic dysfunctions	52	NA	N	NA	N	N	50
Epilepsy	N	N	N	Y	N	N	N

†: deceased.
Age at onset (where available) of symptoms and signs is reported.
NA = not available; N = not present; Y = present.

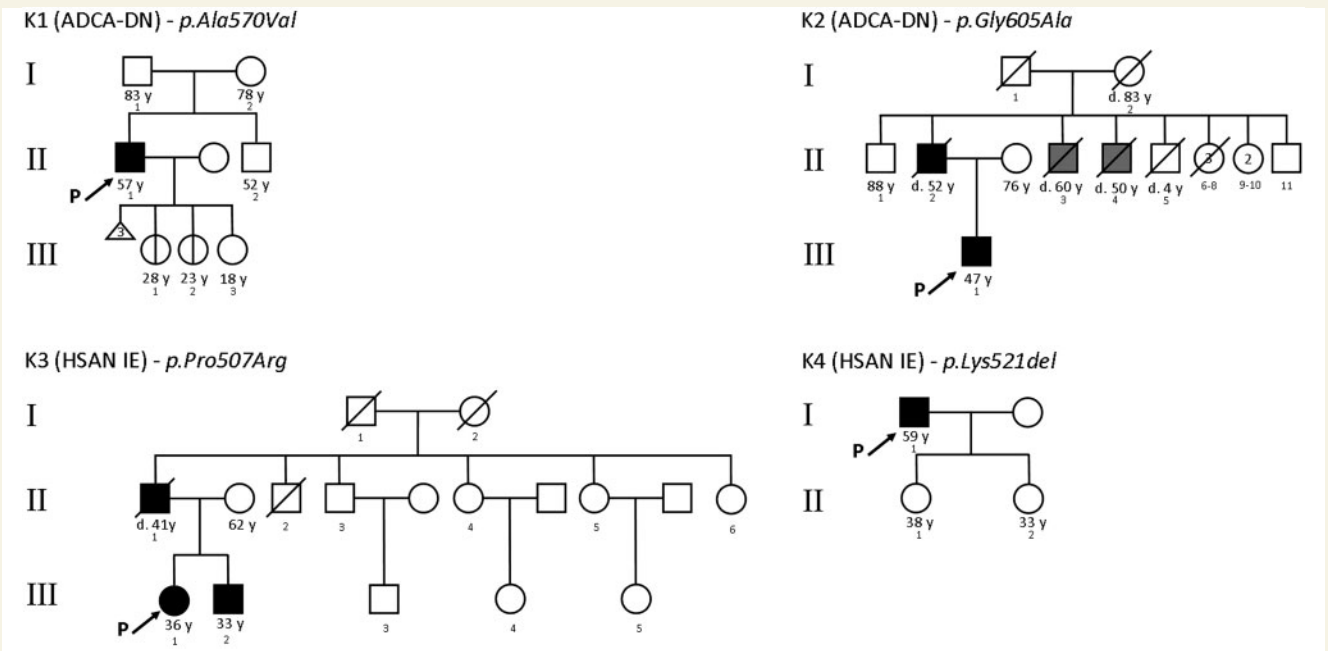

Figure 1 Pedigrees. Age at the time of the study is reported next to each symbol. Black symbol indicates affected individuals, grey symbol indicates the state of presumed affected, split symbols indicate asymptomatic carriers. P = proband.

symptoms. He also complained of slight subjective memory and attentive deficits, and depressed mood. At age 48, narcolepsy with cataplexy was diagnosed and the patient was treated with methylphenidate, modafinil, venlafaxine, clomipramine, and sodium oxybate in various combinations without significant improvement of excessive daytime sleepiness and cataplexy. At age 57, clinical and neurological examination showed severe hearing loss, pyramidal, extrapyramidal and cerebellar signs, sporadic postural myoclonus, reduced distal algaesthesia and pallaesthesia with abolished deep tendon reflexes at lower limbs, globally altered thermoesthesia, remarkable lower limbs oedema (Fig. 2), ataxic gait, and primitive reflexes (Supplementary Video 1). He also presented seldom 'cataplectic status' episodes with waxing and waning deep tendon reflexes lasting up to 2 days in association with infections (i.e. pneumonia) (Supplementary Video 2). Lower limbs Doppler ultrasound, echocardiography and neuropsychological evaluation were normal. Blood exams showed impaired glucose tolerance; serum lactate was normal at age 55, but abnormally elevated after exercise and after recovery at age 57.

Patient K2 III-1 ADCA-DN

The proband is a 47-year-old male who presented with excessive daytime sleepiness, cataplexy and hearing loss since age 43 years. Clinical and neurological examination disclosed emotionally triggered and spontaneous cataplectic attacks, mainly involving the cranial district (Supplementary Video 3), severe hearing loss, mild cerebellar syndrome, absent ankle reflexes, lower limbs hypopallesthesia and oedema (Fig. 2). Lower limbs Doppler ultrasound, cardiac ultrasound evaluations, and cognitive functions were normal. The patient reported a significant improvement of excessive daytime sleepiness and cataplexy after modafinil administration. Lactate values were abnormally elevated after exercise and after recovery. Clinical data of the proband's father, who was similarly affected and died at the age of 52 years, are provided in Table 1.

Patients K3 III-1 and K3 III-2 HSAN IE

A 36-year-old female (Patient K3 III-1) and her 33-year-old brother (Patient K3 III-2) complained of hearing loss since age 26 and 31 years, respectively, and subsequently developed a sensory polyneuropathy. Both patients reported post-prandial drowsiness and sleep episodes, and sleepiness in the early evening, although this was not a primary complaint. At neurological examination, both patients showed deafness, lower limbs distal hypoesthesia and hypopallesthesia, weak deep tendon reflexes and ataxic gait. Isolated deficits in verbal, attention or logical tasks were detectable. Behavioural therapy (planned naps) improved daytime sleepiness. Serum lactate values at rest and after standardized exercise revealed abnormal values after exercise and after recovery in Patient K3 III-2, whereas they were normal in Patient K3 III-1. Their father was similarly affected and died at the age of 41, his data are provided in Table 1.

Patient K4 I-1 HSAN IE

A 59-year-old male presented since age 33 with sensorineural deafness and severe sensory polyneuropathy with spontaneous bones fractures, foot ulcers, diffuse arthropathy and sensory ataxia. Ten years later, he developed a slowly progressive global cognitive impairment, erectile dysfunction and excessive daytime sleepiness, with irresistible sleep attacks, dream enactment during sleep and occasional sudden knees weakness with falls triggered by the 'fear of falling'. Neurological examination showed severe hearing loss, limb ataxia, sporadic postural and action myoclonus, reduced distal thermoesthesia and algaesthesia, apallesthesia with abolished deep tendon reflexes at lower limbs, Romberg sign, ataxic gait, primitive reflexes, lower limbs oedema and distal limb joints deformities (Fig. 2 and Supplementary Video 4). Neuropsychological testing showed global cognitive impairment with predominant involvement of verbal and visuospatial functions. Excessive daytime sleepiness improved with modafinil administration. Blood exams showed impaired glucose tolerance.

Procedures

All patients underwent exome and direct sequencing of exons 20 and 21 of the *DNMT1* gene, neurophysiological tests investigating sleep

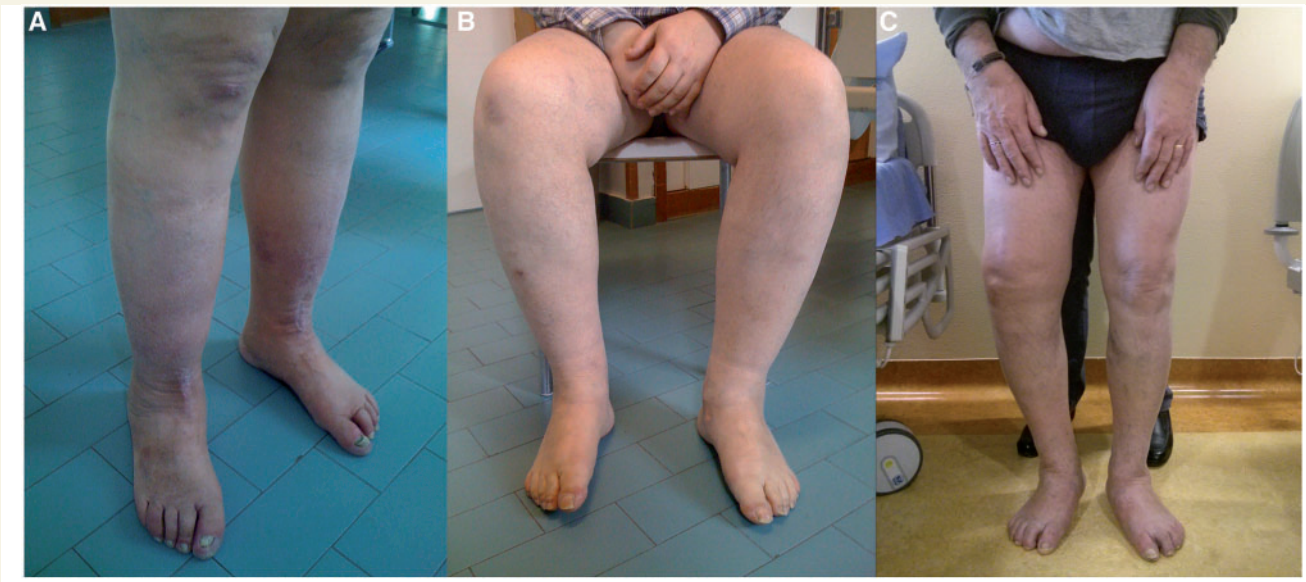

Figure 2 Pictures of patients' limbs. (**A**) Patient K1 II-1; (**B**) Patient K2 III-1; (**C**) Patient K4 I-1.

(i.e. 48-h continuous video-polysomnography followed by a multiple sleep latency test) auditory functions, PNS and CNS (i.e. electroneurography and motor evoked potentials), ophthalmological studies including fundus eye examination, pattern and flash visual evoked potentials and retinal optical coherence tomography scan, brain MRI, CSF hypocretin 1, total tau, phosphorylated tau, amyloid-β_{1-42} and 14-3-3 proteins measurement, and skin biopsy. Muscular and sural nerve biopsies, microneurography, lymphoscintigraphy, cerebral ^{123}I-FP CIT SPECT and 99mTc-ECD SPECT were performed only in some of the patients, depending on clinical opportunity and availability. The study was approved by local Institutional Review Board, and all patients signed a written informed consent.

Further details can be found in the online Supplementary material.

Results

Genetic studies

ADCA-DN

The results of exome sequencing studies performed in Patient K1 II-1 and his healthy parents were previously reported (Winkelman *et al.*, 2012). In brief, we found a *de novo* point mutation in Patient K1 II-1 leading to the amino acid change p.Ala570Val (RefSeq NM_001130823.1: c.1709G.A) affecting exon 21 of the *DNMT1* gene located on 19p13.3-p13.2. Direct Sanger sequencing allowed to identify a different point mutation in the same region of the gene in Patient K2 III-1 leading to the amino acid change p.Gly605Ala (RefSeq NM_001130823.1: c.1814C.G). HLA DQB1*06:02 and DQA1*01:02 haplotypes were excluded in both subjects.

Previous genetic investigation in Patient K1 II-1 excluded spinocerebellar ataxia type 1, 2, 3 and 6 and no mutations were found in the *OPA1* gene.

HSAN IE

Direct Sanger sequencing of exons 20 and 21 of the *DNMT1* gene was performed in Patients K3 III-1, K3 III-2 and K4 I-1. Sibling Patients K3 III-1 and K3 III-2 carried a novel heterozygous point mutation in exon 20, leading to the amino acid change p.Pro507Arg (RefSeq NM_001130823.1; c.C1520G), located within a domain previously involved by a triple nucleotide change in a HSAN IE kindred (Pro491 in Klein *et al.*, 2011). Previous genetic investigations excluded pathogenic mutations in the *GJB2*, *GJB6*, *HSN2* and *MPZ* genes, as well as mitochondrial DNA A3243G, A1555G and A7445G mutations associated with deafness (MITOMAP, 2013).

Patient K4 I-1 carried a trinucleotide deletion leading to the loss of the single amino acid p.Lys521del (RefSeq NM_001130823.1; c.1562-1564delAGA) in exon 20, leaving the remaining protein sequence in frame. Previous genetic testing excluded mutations in the *GDAP1*, *MPZ*, *HSP22/27*, *NF-L*, *MFN2*, *LMNA*, *POLG1* and *SPTLC1* genes.

Testing for the HLA DQB1*06:02 haplotype was negative in all three patients.

Neurophysiological studies

ADCA-DN

Both ADCA-DN probands displayed narcolepsy features clinically and at sleep recordings: spontaneous multiple sleep onset REM sleep periods during daytime and nocturnal sleep at 48-h continuous polysomnography, REM sleep behaviour disorder (also with violent behaviours), and multiple sleep onset REM periods during the five nap opportunity multiple sleep latency test. Patients also presented periodic limb movements during sleep (periodic limb movement index ranging from 41 to 144).

Severe sensorineural deafness was confirmed by audiograms and by absent responses at brainstem auditory evoked potentials in both ADCA-DN probands.

Electroneurography showed a moderate axonal sensory polyneuropathy in both probands. In Patient K1 II-1 motor evoked potentials were normal at 55 years of age (Table 2).

HSAN IE

Ad libitum 48-h continuous polysomnography disclosed diurnal sleep onset REM periods in all three patients with HSAN IE, and periodic limb movements during sleep in two of them. Patient K4 I-1 also presented with REM sleep behaviour disorder, and all subjects had multiple sleep onset REM periods with reduced sleep latency at the multiple sleep latency test. Audiogram showed bilateral sensorineural deafness in all patients with HSAN IE.

Electroneurography documented a severe axonal sensory polyneuropathy in all three patients. Motor evoked potentials were normal in all patients (Table 2).

Microneurography revealed normal skin sympathetic nerve activity and the absence of muscle sympathetic nerve activity in Patient K3 III-1 at 30 years of age, whereas skin and muscle activity where within normal values in Patient K4 I-1.

Ophthalmological studies

ADCA-DN

Visual acuity was 10/10 in both probands, but fundus examination disclosed temporal pallor and excavated optic disc in Patient K1 II-1 and diffuse pallor with optic disc excavation in Patient K2 III-1. Retinal nerve fibre layer thickness evaluation at optical coherence tomography showed reduction of retinal nerve fibre layer thickness more evident in temporal than in superior and inferior quadrants with nasal sparing in Patient K1 II-1, whereas Patient K2 III-1 had a diffuse and severe reduction of retinal nerve fibre layer thickness with nasal sparing. Macular ganglion cell layer (GCL) analysis disclosed diffuse atrophy in both probands, more severe in Patient K2 III-1 (Fig. 3). Pattern visual evoked potentials were abnormal in both probands, showing increased latency and decreased amplitude of cortical responses (Table 2).

HSAN IE

Visual acuity was 10/10 in all subjects investigated (Patients K3 III-1, K3 III-2 and K4 I-1). Fundus examination showed a

Table 2 Instrumental findings

Phenotype	ADCA-DN		HSAN IE		
Patient	**K1 II-1**	**K2 III-1**	**K3 III-1**	**K3 III-2**	**K4 I-1**
DNMT1 mutation	p.Ala570Val	p.Gly605Ala	p.Pro507Asn	p.Pro507Asn	p.Lys521del
HLA-DQB1*0602 haplotype	Negative	Negative	Negative	Negative	Negative
vPSG - TST (min)	366	308	444	408	401
vPSG - SE (%)	68	71	96	93	79
vPSG - REM latency (min)	3	1	74	4	2
vPSG - PLMI	144	41	1	19	17
vPSG - RBD	Yes	Yes	No	No	Yes
MSLT - SL (min)	6.6	11.3	5.6	4.4	3.5
MSLT - SOREMPs	4	4	3	5	5
Audiometry	Bilateral sensorineural deafness	Bilateral sensorineural deafness	Bilateral sensorineural deafness	Bilateral sensorineural deafness	Bilateral sensorineural deafness
Auditory evoked potentials	Absent	Absent	NA	NA	NA
Pattern visual evoked potentials	Altered	Altered	Normal	Normal	Normal
Electroneurography	Moderate axonal sensory polyneuropathy	Moderate axonal sensory polyneuropathy	Severe axonal sensory neuropathy	Severe axonal sensory neuropathy	Severe axonal sensory neuropathy
Motor evoked potentials	Normal	NA	Normal	Normal	Normal
Skin biopsy	Somatic and autonomic neuropathy	Somatic and autonomic neuropathy	Severe somatic and autonomic neuropathy	Severe somatic and autonomic neuropathy	Severe somatic and autonomic neuropathy
CSF hypocretin 1 (pg/ml)	123	93	339	251	296
CSF total-tau (pg/ml) [NV 141 ± 127]	539	301	468	391	517
CSF phosphorylated tau (pg/ml) [NV 25–65]	113	46	54	54	77
CSF amyloid-β_{42} (pg/ml) [NV 560–1150]	1120	947	833	800	1131
Neuropsychological testing	Normal	Normal	Subtle alterations	Subtle alterations	Global cognitive decline
Brain ^{123}I-FP CIT SPECT	Altered	Normal	NA	NA	NA
Brain 99mTc-ECD SPECT	Altered	NA	Normal	NA	Altered

vPSG = video-polysomnography; TST = total sleep time; SE = sleep efficiency; REM = rapid eye movements sleep; PLMI = periodic limb movements index; RBD = REM sleep behaviour disorder; MSLT = multiple sleep latency test; SL = sleep latency; SOREMPs = sleep onset REM periods; NA = not available; NV = normal values.

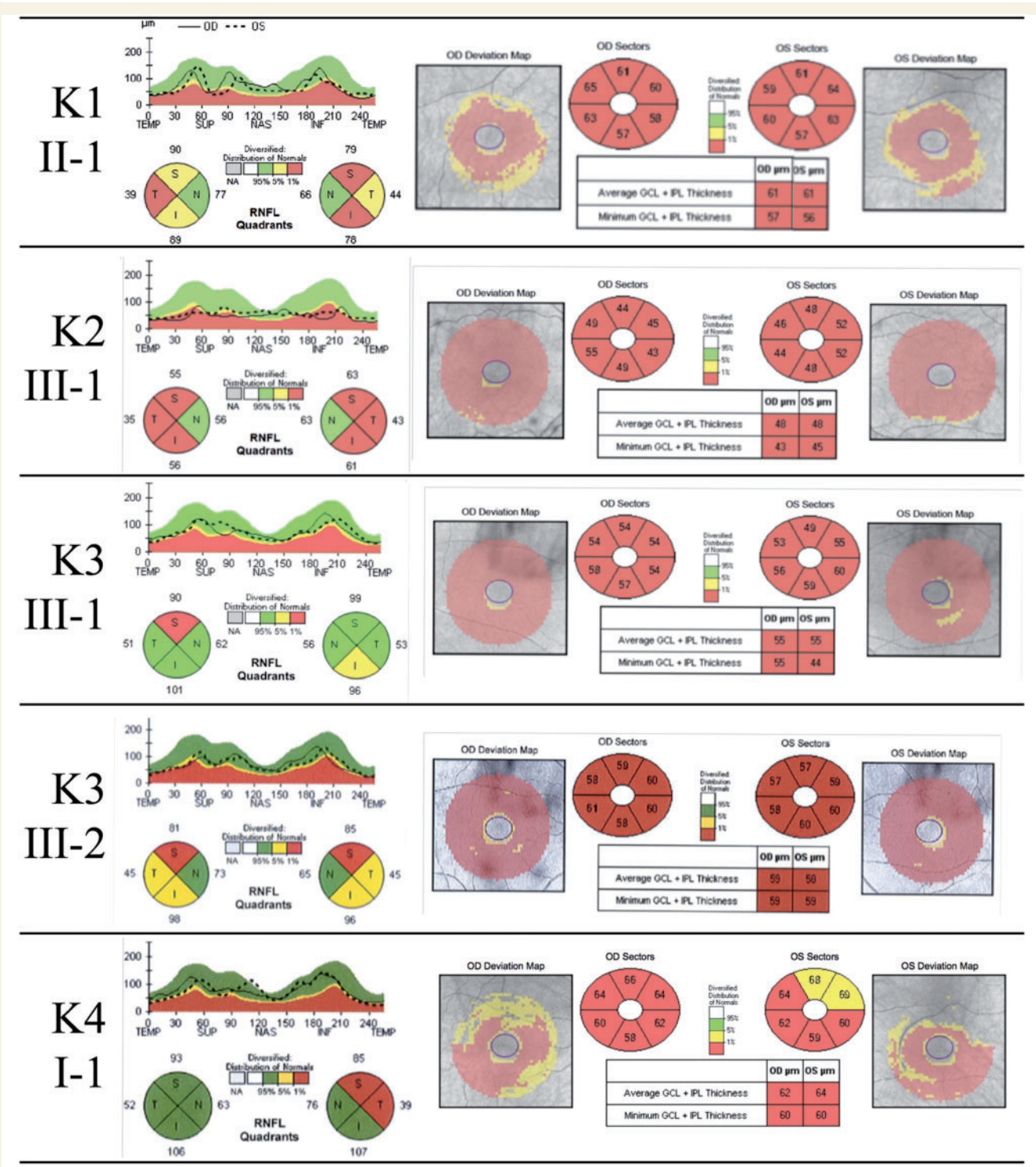

Figure 3 Optical coherence tomography retinal nerve fibre layer thickness (RNFL; *left*) and macular ganglion cell layer analysis (*right*) in Patients K1 II-1, K2 III-1, K3 III-1, K3 III-2 and K4 I-1. GCL = ganglion cell layer; IPL = inner plexiform layer.

mild temporal pallor of the optic disc in all three subjects. Retinal nerve fibre layer evaluation at optical coherence tomography showed a diffuse reduction of retinal nerve fibre layer thickness in Patient K3 III-1, a diffuse reduction with nasal sparing in Patient K3 III-2, and temporal and less evident superior/inferior quadrants thinning in Patient K4 I-1. Macular ganglion cell layer analysis disclosed diffuse thinning in all three subjects, less evident in Patient K4 I-1 (Fig. 3). Pattern visual evoked potential testing gave normal results in Patients K3 and K4 I-1 (Table 2).

Neuroimaging

ADCA-DN

MRI (Fig. 4, Table 3 and Supplementary material) showed in both ADCA-DN probands a similar distribution of brain atrophy, more severe in the older patient (Patient K1 II-1). In particular, both patients showed a global cerebral cortical atrophy, more marked in the parietal region, enlargement of the third ventricle, thinning of the corpus callosum, atrophy of the basal ganglia, cerebellum and mesencephalic tegmentum. Only Patient K1 II-1 presented mild atrophy of the hypothalamus and hippocampi. Long repetition time sequences showed reduced signal intensity of the lentiform nuclei in both patients, consistent with iron deposition secondary to neurodegeneration. All the reported brain MRI alterations showed a progressive worsening in the follow-up exams on Patient K1 II-1.

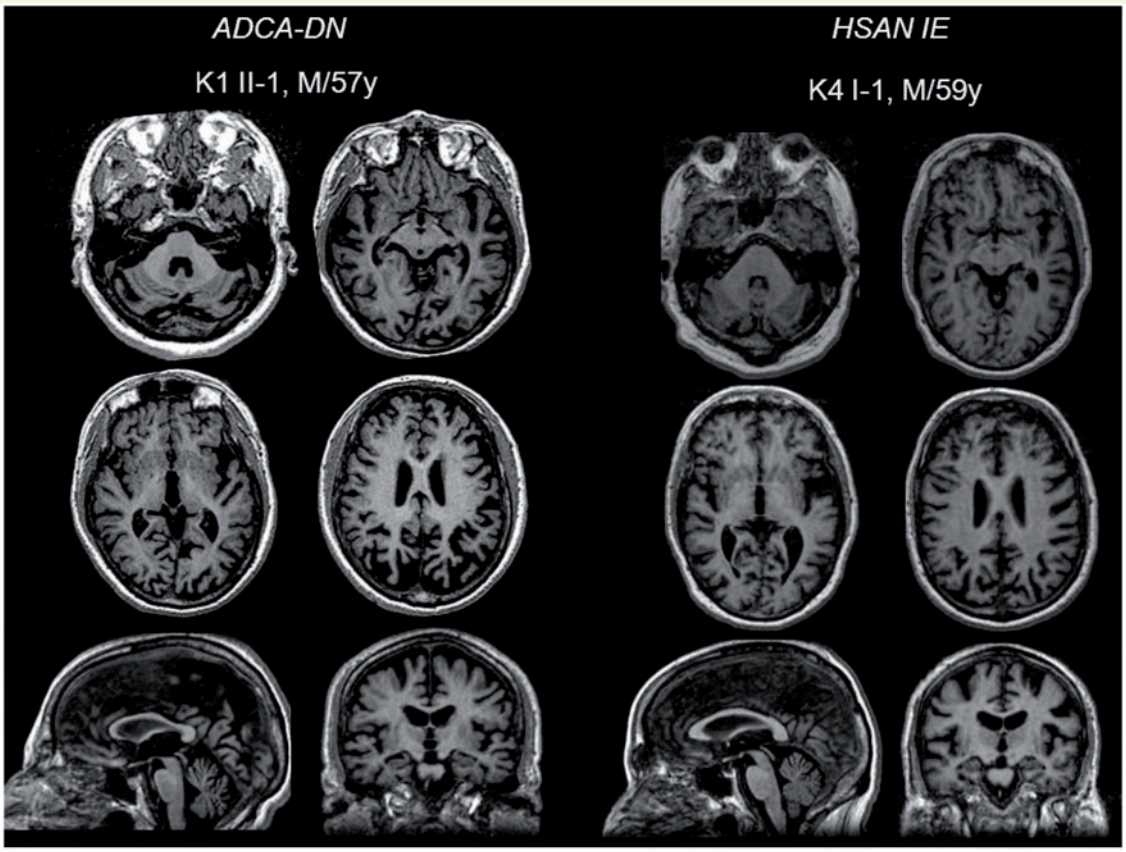

Figure 4 Brain MRI. Axial, sagittal and coronal reconstructions of volumetric high resolution FSPGR T_1 images of one patient with ADCA-DN and one with HSAN-IE showing sovra- and infra-tentorial atrophy, that was quantified semi-quantitatively, as reported in Table 3.

Table 3 Brain MRI

	Cortical atrophy	Pattern of cortical atrophy	Corpus callosum thinning	Basal ganglia and thalami atrophy	Hippocampi atrophy	Hypothalamus atrophy	Cerebellar/ vermian atrophy	Brainstem atrophy
ADCA-DN								
K1 II-1	+ + + +	P > F O T	+ +	+ + +	+	+	+ +	+ mesencephalon
K2 III-1	+ + +	P > F O T	+ + +	+ thalamus	–	–	+	+ + + mesencephalon
HSAN IE								
K3 III-1	+	–	–	–	–	–	+	–
K3 III-2	+	–	–	–	–	–	+	–
K4 I-1	+ +	F P > O T	–	+	–	–	+	–

Semi-quantitative evaluation of brain atrophy on volumetric fast spoiled gradient echo T_1 high resolution images in patients with ADCA-DN and HSAN IE. In none of the patients specific signal intensity changes were detected in both T_1- and T_2-weighted images.
– = absent, + = mild, + + = moderate, + + + = severe, + + + + = very severe.
F = frontal; P = parietal; O = occipital; T = temporal.

Brain ^{123}I-FP CIT SPECT was normal in Patient K2 III-1, whereas it showed a diffused and symmetrical reduction of tracer uptake, homogeneous on both caudate and putamen nuclei, in Patient K1 II-1.

Cerebral 99mTc-ECD SPECT performed at 49 years showed a mild left temporal and parietal hypoperfusion in Patient K1 II-1.

HSAN IE

Brain MRI (Fig. 4, Table 3 and Supplementary material) of patients with HSAN IE showed milder atrophy than patients with ADCA-DN, but with a similar distribution. In all HSAN IE patients, cortical atrophy (which was moderate in Patient K4 I-1 and mild in Patients K3 III-1 and K3 III-2) and a mild cerebellar atrophy were found. Only Patient K4 I-1 showed a mild atrophy of the basal ganglia and long repetition time sequences showed reduced signal intensity of the lentiform nuclei in all patients.

Cerebral 99mTc-ECD SPECT was normal in Patient K3 III-1, whereas showed in Patient K4 I-1 multiple areas of reduced cerebral perfusion on temporal, fronto-parietal and parieto-occipital lobes, bilaterally.

Cerebrospinal fluid evaluation

ADCA-DN

CSF examination showed a normal profile of routine parameters (e.g. cell count, protein and glucose concentration). Total tau concentrations were increased and 14-3-3 absent in both patients, with one also showing increased phosporylated tau levels, whereas the levels of amyloid-β_{1-42} were normal and 14-3-3 absent in both subjects; hypocretin 1 was in the low (Patient K2 III-1) and intermediate (Patient K1 II-1) range (Table 2) (Mignot *et al.*, 2002).

HSAN IE

All affected subjects showed normal routine CSF parameters. All three patients had increased total tau concentrations, and one also showed increased levels of phosphorylated-tau (Table 2). None of the patients had abnormal levels of amyloid-β_{1-42} nor of 14-3-3 in the CSF. Hypocretin 1 was within normal values in all three patients (Table 2).

Other findings

ADCA-DN

Muscular biopsy performed at 55 years in Patient K1 II-1 was essentially normal. Skin biopsy displayed a somatic and autonomic peripheral small fibres neuropathy in both patients. Patient K2 III-1 underwent lower limb lymphoscintigraphy, which showed a normal pattern on the right limb, whereas a definite delay in tracer progression was found on the left limb.

HSAN IE

Muscular biopsy, performed in Patient K3 III-1 showed moderate neurogenic changes, whereas in Patient K4 I-1 it displayed non-specific abnormalities. Sural nerve biopsy was remarkable for severe chronic axonal neuropathy in both Patients K3 III-1 and K4 I-1. Skin biopsy showed a severe somatic and autonomic small fibres neuropathy in all three patients.

Discussion

This study reveals that ADCA-DN and HSAN IE, both caused by *DNMT1* mutations, represent two discrete phenotypes belonging to the same disease spectrum, involving the CNS and PNS, with variable degree of overlap in symptoms and signs. Most remarkably, we found that narcolepsy with or without cataplexy is a key feature of both phenotypes. Excessive daytime sleepiness, sleep onset REM periods and cataplexy are heralding features in ADCA-DN, and sleep onset REM periods have also been reported in young presymptomatic ADCA-DN mutation carriers (Moghadam *et al.*, 2014) but, although sleepiness was reported in some patients (Hojo *et al.*, 1999), narcoleptic features were never clearly documented previously in HSAN IE (Klein *et al.*, 2013). Other common aspects observed in our cases include subclinical optic neuropathy, previously not documented in HSAN IE, deafness, cerebellar ataxia and large and small fibres neuropathy, all of them displaying different levels of clinical severities. Overall, the two syndromes share more characteristics than previously recognized.

To date, only six ADCA-DN and seven HSAN IE kindreds with *DNMT1* mutations have been reported (Melberg *et al.*, 1995; Wright and Dyck, 1995; Hojo *et al.*, 1999; Klein *et al.*, 2011, 2013; Winkelmann *et al.*, 2012; Pedroso *et al.*, 2013; Yuan *et al.*, 2013). Clinical data of all reported cases are summarized in Table 4. We performed an extensive clinical assessment on available members of two previously reported ADCA-DN kindred and two further HSAN IE kindred carrying new *DNMT1* mutations in exon 20, comparing our findings to previously described patients (Table 4 and Supplementary Table 1).

Our findings in patients with ADCA-DN are in line with previous descriptions. In both patients with ADCA-DN excessive daytime sleepiness and cataplexy were the first clinically relevant problems leading to medical (i.e. a sleep specialist) consultation and to a diagnosis of narcolepsy with cataplexy (Melberg *et al.*, 1995; Pedroso *et al.*, 2013). Cataplexy can also present with 'cataplectic status' episodes. Together with narcolepsy, severe hearing loss was another early and consistent symptom (Melberg *et al.*, 1995). The full-blown clinical picture subsequently develops in the fourth decade, leading to death in the fifth decade (Melberg *et al.*, 1995). Cerebellar ataxia slowly progresses over years leading to a severe motor impairment. Optic atrophy was present in both of our patients, even if without subjective complaints. Axonal sensory or sensorimotor polyneuropathy and a small fibre neuropathy were also present, although patients did not report any symptom until very late in the disease evolution. Over time, the clinical picture worsened and extrapyramidal, pyramidal and dysautonomic abnormalities appeared in different combinations. Dementia, that was reported in all patients in the seminal description of the syndrome (Melberg *et al.*, 1995), was not present in either of our patients, neither at baseline evaluation nor during a 9-year follow-up (Patient K1 II-1). One of our patients with ADCA-DN presented with impaired glucose tolerance, confirming

Table 4 Clinical features of ADCA-DN and HSAN IE patients based on published data

	ADCA-DN					HSAN IE								
Kindred origin	**Swedish**	**American**	**Brazilian/Italian descendant**	**Italian**	**Italian**	**American**	**European**	**American**	**Japanese**	**Norwegian**	**Scottish**	**Japanese**	**Italian**	**Italian**
Reference	**Melberg *et al.*, 1995, 1999; Winkelmann *et al.*, 2012**	**Winkelmann *et al.*, 2012**	**Pedroso *et al.*, 2013**	**Winkelmann *et al.*, 2012; Moghadam *et al.*, 2014**			**Klein *et al.*, 2011**		**Hojo *et al.*, 1999; Klein *et al.*, 2011;**	**Klein *et al.*, 2013**		**Yuan *et al.*, 2013**	**Moghadam *et al.*, 2014**	
***DNMT1* mutation**	**Val606Phe**	**Ala570Val**	**Cys596Arg**	**Ala570Val**	**Gly605Ala**	**Tyr511His***	**Asp506_ Pro507delinsGluTyr***	**Tyr511Cys***	**Tyr511Cys***	**Tyr511His***	**Tyr511Cys***	**His569Arg**	**Pro507Asn**	**Lys521del**
DNMT1 mutation location (exon)	21	21	21	21	21	20	20	20	20	20	20	21	20	20
Patients	5	1	1	1	1	11	3	3	4	3	3	1	2	1
Sex	3 F	M	F	M	M	6 F	2F	2F	1 F	1 F	3 F	M	1F	M
Mean age at evaluation	40	58	31	57	47	38	36	42	49	53	47 (1 patient)	41	35	56
Excessive daytime sleepiness	5/5	Y	Y	Y	Y				3/3			N	2/2	Y
Cataplexy	4/5	Y	N	Y	Y							N	0/2	Y
Sleep paralysis	2/3	N	N	N	N								0/2	N
Hypnagogic hallucinations	2/3	N	N	N	Y								0/2	N
REM sleep behaviour disorder	2/2	Y		Y	Y								0/2	Y
Deafness	5/5	Y	Y	Y	Y	11/11	3/3	3/3	4/4	3/3	3/3	Y	2/2	Y
Cerebellar ataxia	5/5	Y	Y	Y	Y	0/11	2/3	2/3	0/3			N	1/2	Y
Neuropathy symptoms/ sensation tested	1/4		Y	Y	Y	11/11 (two patients also motor)	3/3	3/3	4/4	3/3 (one patient also motor)	2/2	Y	2/2	Y
Neuropathy objectived	1/1	Y		Y	Y	6/6	3/3	1/1	1/1	1/1	2/2	Y	2/2	Y
Dementia	3/4	Y	N	N	N	11/11	3/3	3/3	4/4	1 patient	1 MCI, 2 'cognitive problems'	Mild mental retardation	0/2	Y
Pyramidal signs	3/4		N	Y	N								0/2	N
Extrapyramidal signs	3/4		N	Y	N								0/2	N
Dysautonomic signs	3/4		N	Y	N				0/2				0/2	Y
Optic atrophy	4/5	Y	N	Y	Y								2/2	Y
Psychiatric features	3/5	Y	N	Y	N				1/1		1 patient		0/2	N
Lower limb oedema	1/5	N	N	Y	Y								0/2	Y
Foot ulcers	0		N	N	N	4/11	3/3	2/3	3/4		1 patient	Y	0/2	Y
Diabetes	2/5	Y		Altered glucose metabolism	N								0/2	Altered glucose metabolism
Cardiomyopathy	1/5		N	N	N								0/2	N
Epilepsy	1/5			N	N					1 patient			0/2	N
Life Span (years)	52 (3 patients, range 49–56)					51 (4 patients, range 46–61)	46 (1 patient)	49 (3 patients, range 44–55)	50 (1 patient)	61 (1 patient)				
CSF hypocretin-1 (pg/ml)	62 (1 patient)		191	123	93								339 and 251	296
HLA-DQB1*0602	Negative (1 patient)	Negative	Positive	Negative	Negative								Negative (2 patients)	Negative

All mutations are here referred to RefSeq NM_001130823.1, the ones marked with an asterisk were previously reported referring to NM_001379 (where Tyr495 corresponds to Tyr511, Asp490 to Asp506 and Pro491 to Pro507).

a higher risk for diabetes (Melberg *et al.*, 1995; Winkelmann *et al.*, 2012). Although a chance association cannot be excluded, diabetes may be part of the clinical picture of ADCA-DN, or of the frequent metabolic alterations often reported in narcolepsy (Honda *et al.*, 1986; Poli *et al.*, 2009). Interestingly, both our ADCA-DN probands, and HSAN IE Patient K4 I-1 developed a lower limb oedema. This finding, apparently not due to venous or cardiac alterations, was previously reported in a patient with ADCA-DN (Melberg *et al.*, 1995) and suggested to be secondary to a concurrent cardiomyopathy, an abnormality clearly absent in our cases. Rather, altered lymphoscintigraphy in our patient (Patient K2 III-1) suggests that the lower limb oedema was due to a defective lymphatic circulation, possibly caused by a primitive lymphatic tissue alteration or by a degeneration of autonomic fibres regulating lymphatic vessels functions (Howarth *et al.*, 1999; Davis *et al.*, 2008). An autonomic involvement was indeed demonstrated by skin biopsy.

Similar to other previously reported patients with HSAN IE (Wright and Dyck, 1995; Hojo *et al.*, 1999; Klein *et al.*, 2011, 2013; Yuan *et al.*, 2013), our patients developed hearing loss and a severe polyneuropathy in adulthood, the latter leading to trophic skin and joint lesions in Patient K4 I-1. This patient also developed cognitive decline and complained of excessive daytime sleepiness with sudden sleep attacks, REM sleep behaviour disorder and cataplexy evoked exclusively by a negative emotion, an uncommon finding in sporadic narcolepsy with cataplexy (Poli *et al.*, 2013). Sleepiness was also reported in both affected siblings of pedigree K3 (Patients III-1 and III-2), although partially masked by lifestyle changes (daytime scheduled naps). However, multiple sleep latency test data showed both short sleep latencies and multiple sleep onset REM periods, confirming the diagnosis of narcolepsy without cataplexy with normal CSF hypocretin 1 level. Although occasional or situational somnolence was described as an accessory symptom in three patients from a Japanese kindred (Hojo *et al.*, 1999), narcolepsy was previously ruled out in HSAN IE (Klein *et al.*, 2013; Yuan *et al.*, 2013). In these prior studies, however, sleep studies had not been performed to formally exclude narcolepsy, thus we believe that the condition was overlooked, perhaps because it is less severe than in the ADCA-DN phenotype. A similar situation was found for optic atrophy, which was never described in HSAN IE, but revealed by optic nerve and macular retinal ganglion cell investigations disclosing a subclinical optic nerve involvement in all of our cases. We suggest that narcolepsy should be systematically explored in both ADCA-DN and HSAN IE, as its treatment may improve the quality of life of these patients.

DNMT1, a methyltranferase involved in the maintenance of DNA methylation, influences gene transcription, genomic imprinting and genome stability and is fundamental for the function and survival of various tissues, including CNS neurons (Fan *et al.*, 2001). The fact that symptoms are overlapping in these conditions is not surprising, considering that both exon 20 and 21 mutations affect the same regulatory domain, the Replication Foci Targeting Sequence (RFTS), in DNMT1 (22894906). The RFTS domain is known to target DNMT1 to replication foci and also mediates dimerization of DNMT1. It effectively blocks the catalytic core and prevents the enzyme from needlessly methylating the genome *de novo*. In a previous study, Klein *et al*. (2011) found that *DNMT1* mutations alter the DNA methylation pattern producing global hypomethylation and local hypermethylation. Subtypes of *DNMT1* mutations might lead to slightly different tissue-specific disruptions in methylation patterns, over- or under-expressing proteins involved in survival of different neuronal or glial cell populations, and this could account for the different clinical expressivity of diseases related to *DNMT1* mutations.

Distinct methylation patterns have also been observed in conditions such as Parkinson's and Alzheimer's diseases (Di Francesco *et al*., 2013; Masliah *et al.*, 2013), suggesting the importance of epigenetic modifications in neurodegenerative disorders in general. In this view, the finding of neurodegeneration caused by *DNMT1* mutations, such in ADCA-DN and HSAN IE, is not surprising and requires in-depth investigations on genome expression in these conditions.

A remarkable finding of the present study is that all patients, whether with the ADCA-DN or the HSAN IE phenotypes, displayed narcolepsy. DNMT1 is highly expressed in immune cells and is required for lymphocyte differentiation (Josefowicz *et al.*, 2009). Altered DNMT1 activity may lead to dysregulation of the immune system, facilitating an autoimmune attack to hypocretin neurons. However, the HLA-DQB1*06:02 negativity in all of our patients seems to lower a possible role of a common immune-mediated pathophysiology for sporadic narcolepsy and narcolepsy in DNMT1-related disorders. Another possibility is that *DNMT1* mutations influence hypocretin gene expression or hypocretin cell death leading to the development of narcolepsy. Interestingly, a recent genome-wide association study in patients with sporadic narcolepsy with cataplexy identified narcolepsy-associated polymorphisms in a region including the *DNMT1* gene, and its expression was found to be lower as compared to control subjects (Kornum *et al.*, 2011). This, together with the finding of narcolepsy in DNMT1-related diseases, suggests that impaired *DNMT1* activity could influence hypocretin expression, which is regulated by epigenetic factors influenced by metabolic intermediates in mice (Hayakawa *et al.*, 2013). Interestingly, however, only cases with ADCA-DN presented with low/intermediate hypocretin 1 levels, suggesting more severe alteration of hypocretin physiology in ADCA-DN, also likely explaining why cataplexy is observed more clearly in ADCA-DN than HSAN IE. Importantly, however, considering the pleiotropic effects of these mutations, it is likely that *DNMT1* mutations also affect other neuronal systems regulating sleep and REM sleep. To rule out that *DNMT1* pathogenic mutations may also lead to sporadic cases of narcolepsy, we screened by standard Sanger sequencing of *DNMT1* (all exons 1–41) a total of 95 narcoleptic patients with typical and atypical clinical, serological and CSF features, failing to identify any mutation (data not shown).

Another interesting aspect of these conditions is the resemblance of the phenotype with mitochondrial encephalomyopathies, including the combination of sensorineural deafness, optic atrophy, cerebellar involvement and peripheral neuropathy. The nasal sparing of retinal nerve fibre layer thickness in the more severe cases with ADCA-DN and the prevalent involvement of the temporal sector in the less severe cases with HSAN IE are both reminiscent of mitochondrial optic neuropathies (Carelli *et al.*, 2004). In the seminal description of ADCA-DN mitochondrial dysfunction was suggested in muscle (Melberg *et al.*, 1995),

also evidenced here by an occasional increase of lactic acid observed in our patients after exercise. We hypothesize that defect in DNMT1 may lead to mitochondrial dysfunction through two pathways. First, defective methylation of nuclear DNA is predicted to impinge on the nuclear encoded set of mitochondrial proteins (Takasugi *et al.*, 2010), composed of over 1000 genes (Calvo and Mootha, 2010). Second, recent studies indicate that DNMT1 also expresses a mitochondrial-targeted isoform that may directly regulate mitochondrial DNA methylation (Shock *et al.*, 2011; Bellizzi *et al.*, 2013).

Another hint on the mechanism of neurodegeneration in both DNMT1-related disorders comes from our finding of increased CSF total tau, associated with a raise in phosporylated tau in the two subjects with the highest total tau concentrations and normal amyloid-β_{42} levels. CSF tau and amyloid-β isoforms are increasingly explored as biomarkers of neurodegeneration. Current evidences indicate that an isolated increase in total tau (i.e. not associated with a raise in phosporylated tau) usually reflects the release of the protein into the CSF as a result of neuronal damage or death. In contrast, a CSF profile characterized by a concomitant increase in total tau and phosporylated tau is most commonly associated with neurodegenerative conditions characterized by tau pathology, namely Alzheimer's disease (Blennow *et al.*, 2010) and some other cerebral proteinopaties (Goodall *et al.*, 2006; Giaccone *et al.*, 2008). Given the normal amyloid-β_{42} levels that exclude an amyloid-β-related cerebral amyloidosis, the tau abnormalities in our patients suggest that a tau pathology involving its post-translational modifications, may also be part of the pathophysiology of both ADCA-DN and HSAN IE.

In conclusion, until recently, ADCA-DN and HSAN IE were considered as two distinct clinical entities with different mutations in exon 20 for HSAN IE and exon 21 for ADCA-DN, respectively. More recently, however, a novel missense mutation in exon 21 (p.His569Arg) was found to generate a HSAN IE-like phenotype in a Japanese patient, breaking the genotype–phenotype correlation (Yuan *et al.*, 2013). Our study further demonstrates that excessive daytime sleepiness and sleep onset REM periods, the hallmarks of narcolepsy, and optic nerve pathology may also occur in HSAN IE phenotype and that peripheral neuropathic involvement is frequent in ADCA-DN, whereas unambiguous cataplexy and low/intermediate CSF hypocretin 1 deficiency are specific to ADCA-DN. Overall, we suggest that screening for *DNMT1* mutations is needed in any patient with narcolepsy with cataplexy showing additional neurologic manifestations.

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Supplementary material

Supplementary material is available at *Brain* online.

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