ORPHA: 456318 DO: 0050548

#614116

NEUROPATHY, HEREDITARY SENSORY, TYPE IE; HSN1E

Alternative titles; symbols

HSN IE

NEUROPATHY, HEREDITARY SENSORY, WITH HEARING LOSS AND DEMENTIA

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance (in progress)	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
19p13.2	Neuropathy, hereditary sensory, type IE	614116	AD	3	DNMT1	126375

Clinical Synopsis | Phenotypic Series

TEXT

A number sign (#) is used with this entry because hereditary sensory neuropathy type IE (HSN1E) is caused by heterozygous mutation in the DNMT1 gene (126375) on chromosome 19p13.

Description

Hereditary sensory neuropathy type IE is an autosomal dominant neurodegenerative disorder characterized by adult onset of progressive peripheral sensory loss associated with progressive hearing impairment and early-onset dementia (summary by Klein et al., 2011).

For a discussion of genetic heterogeneity of HSN, see HSAN1A (162400).

Clinical Features

Wright and Dyck (1995}) reported a 7-generation kindred with autosomal dominant inheritance of sensory neuropathy with sensorineural hearing loss and early-onset dementia. The neurologic deficits began between the second and fourth decades and were progressive, with death occurring in the fifth and sixth decades. The proband was a 42-year-old man with onset of distal sensory impairment primarily affecting the lower limbs in his early thirties followed by progressive memory and hearing impairment in his late thirties. There were no autonomic or motor symptoms. Physical studies showed severe peripheral sensorineural neuropathy with absent sensory nerve action potentials and moderate to severe hearing loss; brain imaging showed mild diffuse cerebral atrophy. Sural nerve biopsy showed almost complete absence of myelinated fibers of all sizes, without onion bulb formation or regenerating clusters. There were reduced numbers of unmyelinated fibers. Wright and Dyck (1995}) classified the disorder as a subtype of HSAN type I.

Hojo et al. (1999) reported 3 Japanese sibs with onset of peripheral sensory neuropathy affecting all modalities in young adulthood, followed by hearing loss and progressive frontal dementia in the later thirties and forties. The neuropathy resulted in ulceration of the feet necessitating amputation of the toes in all patients. Two patients reported lancinating pains. Sural nerve biopsy showed almost complete loss of myelinated fibers with moderate loss of unmyelinated fibers. The dementia was characterized by memory loss, irritability, apathy, impulsivity, delusions, somnolence, and decreased speech output. Functional imaging of 2 patients showed frontal and thalamic hypometabolism, and brain imaging of 1 showed frontal atrophy. Their affected mother had died in the fifth decade with painless foot ulcers and dementia. Cerebellar and autonomic dysfunction were not present.

Klein et al. (2011) reported 2 additional families with HSN1E. Affected individuals were healthy in their youth, but developed worsening sensorineural deafness and sensory neuropathy by the age of 20 to 35 years. Progressive cognitive and behavioral declines developed by the fourth decade. Brain imaging of the affected persons showed global atrophy, and there was reduced weight of the autopsied brains. Quantitative sensory testing, nerve conductions, and nerve biopsy were indicative of length-dependent progressive sensory axonal loss. Neuropathologic examination of 1 patient who died at age 48 years showed ascending spinal sensory tract degeneration with myelin and axonal loss involving the gracile fasciculus in the posterior columns at all spinal levels. There was also generalized cerebral atrophy, chronic cerebellar Purkinje cell swelling and axonal loss, and severe neuronal loss and gliosis of the inferior olivary nucleus.

Klein et al. (2013) reported 2 unrelated families of Norwegian and Scottish descent, respectively, with HSN1E. Affected individuals had onset of hearing loss in their forties, followed by sensory neuropathy, sensory ataxia, behavioral abnormalities, and dementia. One patient had seizures, consistent with neurodegeneration. Neuropathologic examination of 1 patient showed frontal lobe atrophy without distinct histopathology; in

particular, no plaques, neurofibrillary tangles, or Lewy bodies were identified, and immunostaining for MAPT (157140), SNCA (163890), and TDP43 (605078) was negative. None of the patients had narcolepsy or cataplexy.

Inheritance

The transmission pattern in the families reported by Wright and Dyck (1995) and Klein et al. (2011) is consistent with autosomal dominant inheritance.

Molecular Genetics

By linkage analysis followed by exome sequencing, Klein et al. (2011) identified 2 different heterozygous mutations in the DNMT1 gene (126375.0001 and 126375.0002) in 4 unrelated families with autosomal dominant inheritance of hereditary sensory neuropathy type IE. Two of the families had been reported by Wright and Dyck (1995) and Hojo et al. (1999). In vitro functional expression studies in E. coli and HeLa cells showed that the mutations affected proper folding of DNMT1 and resulted in premature degradation, reduced methyltransferase activity, and impaired heterochromatin binding during the G2 cell cycle phase, leading to global hypomethylation and site-specific hypermethylation. These changes indicated epigenetic dysregulation. The results provided a direct link between DNMT1 defects and a neurodegenerative disorder affecting both the central and peripheral nervous systems, and suggested that DNMT1 participates in a precise mechanism of dynamic regulation of neuronal survival.

Klein et al. (2013) identified heterozygous mutations affecting the same codon in exon 20 of the DNMT1 gene (Y495C, 126375.0001 and Y495H, 126375.0006) in affected members of 2 unrelated families with HSN1E. DNMT1 mutations were specific to the phenotype of peripheral neuropathy associated with hearing loss and dementia, as mutations were not found in 48 patients with sensory neuropathy without hearing loss or dementia or in 5 kindreds with familial frontotemporal dementia.

REFERENCES

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NEUROPATHY, HEREDITARY SENSORY, TYPE IE; HSN1E

CATEGORY	SUBCATEGORY	FEATURES
Inheritance	-	Autosomal dominant
Head and Neck	Ears	Hearing loss, sensorineural
Skeletal	Feet	Ulceration of the toes Osteomyelitis Amputation
Neurologic	Central Nervous System	Memory impairment, progressive Dementia, frontal lobe Decreased speech Cerebral atrophy Frontal lobe atrophy Hypometabolism of the frontal lobe and thalamic regions
	Peripheral Nervous System	Sensory neuropathy affecting all modalities primarily affecting the lower limbs with some mild upper limb involvement Hyporeflexia Lancinating pains (2 patients) Almost complete loss of myelinated fibers seen on sural nerve biopsy Loss of unmyelinated fibers
	Behavioral Psychiatric Manifestations	Apathy Somnolence Impulsivity Irritability Distractibility Delirium
Miscellaneous	-	Onset of peripheral neuropathy or hearing loss in young adulthood (range 16 to 35 years) Onset of dementia in the thirties or forties Progressive disorder Death in the fifth or sixth decade
Molecular Basis	-	Caused by mutation in the DNA methyltransferase 1 gene (DNMT1, 126375.0001)

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