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DNMT1-Related Dementia, Deafness, and Sensory Neuropathy

Synonyms: Hereditary Sensory and Autonomic Neuropathy Type 1 with Dementia and Hearing Loss, Hereditary Sensory Neuropathy Type IE, HSNIE

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Summary

Disease characteristics. *DNMT1*-related dementia, deafness, and sensory neuropathy (HSAN IE) is a degenerative disorder of the central and peripheral nervous systems characterized by sensory impairment of the distal lower extremities, loss of sweating (sudomotor function) on the distal aspects of the upper and lower limbs, sensorineural hearing loss, and dementia. Affected persons are normal in their youth but begin to manifest progressive sensory neuropathy and moderate to severe progressive sensorineural deafness by age 20 to 35 years. The sensory alterations result in gait unsteadiness from sensory ataxia and mutilating ulcers and/or amputations of distal extremities in approximately 50% of affected persons. Dementia usually manifests by the fourth decade.

Diagnosis/testing. The diagnosis is based on clinical findings and molecular genetic testing of *DNMT1*, the only gene in which mutations are known to cause HSAN IE.

Management. *Treatment of manifestations:* Injury prevention when sensory impairment is significant; use of hearing aids and/or assistive communication methods as needed. Sedative or antipsychotic drugs help to reduce the extreme restlessness, roaming behavior, delusions, and hallucinations associated with dementia. Behavioral changes and the loss of insight and judgment are often a considerable burden for partners / caregivers, who need information about the disease and psychological support.

Prevention of secondary complications: To prevent injury to extremities with decreased sensation protect the skin with appropriate socks and shoes and avoid exposure of feet to hot water.

Surveillance: Daily: examine feet for evidence of skin injury. Annually: (1) audiogram and (2) clinical testing for dementia by observation of behavior and use of tools such as Mini Mental State Exam (MMSE)

Agents/circumstances to avoid: Sharp objects and hot water, which may damage skin.

Genetic counseling. HSAN IE is inherited in an autosomal dominant manner. The proportion of HSAN IE caused by *de novo* mutations is unknown. Each child of an individual with HSAN IE has a 50% chance of inheriting the disease-causing mutation. If the disease-causing mutation has been identified in an affected family member, prenatal testing for at-risk pregnancies is possible through laboratories offering either prenatal testing for the gene of interest or custom testing.

Diagnosis

Clinical Diagnosis

The diagnosis of *DNMT1*-related dementia, deafness, and sensory neuropathy (HSAN IE) is established in individuals with the following:

- **Sensory impairment,** which is predominantly loss of feeling to touch, pain, temperature, and proprioception of the feet and legs, with less severe loss in the hands. Pain tends to be minimal but can be lancinating or burning; some have described parathesias. The face and trunk are characteristically spared.
- **Autonomic dysfunction,** manifest as loss of sweating (sudomotor abnormalities). Laboratory-based tests such as tilt table testing for postural hypotension, quantitative sudomotor axon reflex testing (QSART), and thermoregulatory sweat testing (TST) can help to identify postganglionic sudomotor abnormalities that spare cardiovagal and adrenergic autonomic functions.

Special quantitative sensory testing and histopathologic preparations can assist in studying the

sensory fibers implicated in autonomic involvement. The HSAN IE pan sensory neuropathy affects large proprioceptive and vibratory sensing fibers as well as small heat-, pain-, and temperature-sensing fibers.

- **Dementia.** Progressive decline in cognition and behavior is usually the first manifestations of dementia.

  Wechsler Adult Intelligence and Memory Scales as well as Boston naming test and the Mini Mental State Exam (MMSE) can be used to identify diffuse cortical dementia.

  Brain imaging of affected persons can also help to determine the existence of global atrophy without intraparenchymal signal change.

- **Moderate to severe sensorineural hearing loss** (i.e., 70- to 80-db loss at 4000 Hz) beginning in the teens or early 20s

Molecular Genetic Testing

Gene. *DNMT1* is the only gene in which mutations are known to cause *DNMT1*-related dementia, deafness, and sensory neuropathy.

Table 1. Summary of Molecular Genetic Testing Used in *DNMT1*-Related Dementia, Deafness, and Sensory Neuropathy

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]	Test Availability
DNMT1	Targeted mutation analysis	c. 1484A>G c.1470_1472delTCCinsATA c.1483T>C	100% for the targeted variant [2]	Research only
	Sequence analysis	Sequence variants including the 3 known pathologic variants above [3]	100%	Clinical

1. The ability of the test method used to detect a mutation that is present in the indicated gene

2. In 6/6 families identified to date, all affected family members had a heterozygous mutation in the targeting sequence domain of *DNMT1*. See Molecular Genetics.

3. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations; typically, exonic or whole gene deletions/duplications are not detected.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Information on specific allelic variants may be available in Molecular Genetics (Table A. Genes and Databases and/or **Pathologic allelic variants**).

Testing Strategy

To confirm/establish the diagnosis in a proband

- Perform targeted mutation analysis if clinical examination reveals:
  - Young adult-onset hearing loss
  - Foot ulcers
  - Loss of sensation in the feet
  - Depressed tendon reflexes in the lower limbs
  - Signs of memory loss or abnormal behavior
- If no mutation is detected, sequence analysis of the coding region and related intron junctions of *DNMT1* may be performed.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutation in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *DNMT1*.

Clinical Description

Natural History

DNMT1-related dementia, deafness, and sensory neuropathy (HSAN IE) is a degenerative disorder of the central and peripheral nervous systems characterized by sensory impairment, sudomotor dysfunction (loss of sweating), dementia, and sensorineural hearing loss [Klein et al 2011]. Affected persons are normal in their youth but begin to manifest progressive sensorineural deafness and sensory neuropathy by age 20 to 35 years.

Winkelmann et al [2012] have reported four families with mutations in *DNMT1* associated with early onset (18-44 years) of a narcolepsy/cataplexy syndrome followed by ataxia, deafness, sensory neuropathy and memory loss. The ataxia appeared to be cerebellar in nature.

Sensory impairment can manifest as early as the second decade of life, starting with loss of sensation leading to painless extremity injuries, and is associated with hyporeflexia. The disease predominantly affects the distal lower extremities with minimal to no motor involvement. The sensory alterations are associated with gait unsteadiness from sensory ataxia and mutilating acropathy with ulcers and/or amputations of distal extremities in approximately 50% of affected persons.

Autonomic dysfunction that is limited to loss of sweating (sudomotor) on the distal aspects of the upper and lower limbs.

Dementia manifests as progressive cognitive, executive function and behavioral decline usually by the fourth decade. Behavior changes including anger and change in personality may precede decline in memory. Memory loss, apathy, indifference, inattention, and somnolence have all been described [Wright & Dyck 1995, Hojo et al 1999]. Irritability, delusions, and delirium are also reported.

Moderate to severe sensorineural hearing loss (i.e., 70- to 80-db loss at 4000 Hz) typically begins in the teens or early 20s.

Gait ataxia is common and is usually the result of sensory loss in the feet, but rarely may be cerebellar ataxia.

Electrophysiologic testing shows:

- Length-dependent sensory axonal loss including both small fiber loss (drC and Aσ) and large fiber proprioceptive Aβ loss;
- Absent or reduced sensory nerve action potentials with normal motor nerve conduction velocities.

PET and SPECT imaging have been used to show medial frontal and thalamic hypometabolism.

Sural nerve biopsy shows marked loss of myelinated fibers without onion bulb change.

Brain neuropathology at autopsy has shown diffuse neuronal loss without distinctive histologic features and no amyloid, tau, or α-synuclein inclusions [Klein et al 2011].

Genotype-Phenotype Correlations

Three mutations in exon 21 of *DNMT1* have been associated with narcolepsy / cataplexy (p.Ala570Val, p.Gly605Ala, and p.Val606Phe).

Penetrance

Penetrance is high in the few reported families.

Nomenclature

DNMT1-related dementia, deafness, and sensory neuropathy, also known as hereditary sensory and autonomic neuropathy type IE (HSAN IE), is considered a sensory-predominant neuropathy.

Prevalence

To date, only six families have been identified with HSAN IE.

Differential Diagnosis

Autosomal dominant hereditary sensory and autonomic neuropathies are genetically heterogeneous, but hereditary sensory and autonomic neuropathy type IE (HSAN IE) that includes dementia and hearing loss represents a unique phenotype. See Table 2.

Table 2. Hereditary Sensory and Autonomic Neuropathies (HSAN)

HSAN Type	Phenotype	Phenotype OMIM Number	Gene Symbol	Gene OMIM Number
HSANIA	HSAN IA	162400	*SPTLC1*	605712
HSNIB	HSN IB	608088	NA	608088
HSANIC	HSAN IC	613640	*SPTLC2*	605713
HSNID	HSN ID	613708	*ATL1*	606439
HSNIE	HSAN IE	614116	*DNMT1*	126375
HSANIIA		201300	*WNK1*	605232
HSANIIB	HSAN II	613115	*FAM134B*	613114
HSNIIC		614213	*KIF1A*	601255
HSANIII	Familial dysautonomia	223900	*IKBKAP*	603722
HSANIV	HSAN IV	256800	*NTRK1*	191315
HSANV	HSAN V	608654	*NGF*	162030

HSAN = hereditary sensory and autonomic neuropathy

NA= not applicable

Data from www.omim.org/phenotypicSeries/162400

The combination of neuropathy with hearing loss can be confused with some forms of Charcot-Marie-Tooth (CMT) and the dementia is similar to that found in frontotemporal dementia (FTD) or, more commonly, global cognitive disorder. However, if it is recognized that the neuropathy, hearing loss, and dementia represent a single syndrome, the diagnosis should be clear when it occurs in persons younger than age 50 years.

Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, go to **SimulConsult®**, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *DNMT1*-related dementia, deafness, and sensory neuropathy (HSAN IE), the following evaluations are recommended:

- Neurologic examination to determine the extent of sensory involvement, including sensory testing and observation for skin ulceration
- Past medical history to determine extent of autonomic involvement
- Evaluation of central nervous system involvement, using tests of cognitive function and brain imaging
- Audiologic examination to determine if hearing loss is present and, if present, its type and severity
- Medical genetics consultation

Treatment of Manifestations

Currently no effective treatment exists for any type of HSAN.

The emphasis of management is to help parents and affected individuals understand the sudomotor defect and injury prevention when sensory impairment is significant.

Because hearing loss may be severe, initial use of hearing aids and/or assistive communication methods may be needed.

Sedative or antipsychotic drugs help to reduce extreme restlessness, roaming behavior, delusions, and hallucinations associated with dementia.

Because behavioral changes and the loss of insight and judgment in individuals often present a considerable burden for partners or other caregivers, information about the disease and psychological support for partners or other caregivers are essential.

Prevention of Secondary Complications

To prevent injury to extremities with decreased sensation, protect the skin with appropriate socks and shoes and avoid exposure of feet to hot water.

Surveillance

Sensory impairment. Examine feet on a daily basis to screen for skin injury.

Dementia. Perform annual routine clinical testing for dementia:

- Observation of behavior
- Use of tools such as the Mini Mental State Exam (MMSE)

Hearing loss. Perform annual audiogram.

Agents/Circumstances to Avoid

Avoid sharp objects and hot water, which may damage skin.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

DNMT1-related dementia, deafness, and sensory neuropathy (HSAN IE) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, all individuals diagnosed with HSAN IE have had an affected parent.
- A proband with HSAN IE may have the disorder as the result of a new mutation. Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the mutation was *de novo*, the proportion of HSAN IE caused by *de novo* mutations is unknown.
- If the disease-causing mutation found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include clinical evaluation of parents and molecular genetic testing if the mutation has been identified in the proband. Such evaluations may determine that one is affected but has escaped previous diagnosis because of failure to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until

appropriate evaluations have been performed.

Note: Although all affected individuals in six of six families reported with HSAN IE have an affected parent, the family history, in other families, may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- The sibs of a proband with clinically unaffected parents are still at increased risk for HSAN IE because of the possibility of reduced penetrance in a parent.
- If the disease-causing mutation found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with HSAN IE has a 50% chance of inheriting the mutation.

Other family members. The risk to other family members depends on the status of the proband's parents. If a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has clinical evidence of the disorder it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

If the disease-causing mutation has been identified in an affected family member, prenatal testing for at-risk pregnancies is possible through laboratories offering either prenatal testing for the gene of interest or custom testing.

Preimplantation genetic diagnosis (PGD) may be an option for some families in which the disease-causing mutation has been identified.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

No specific resources for *DNMT1*-Related Dementia, Deafness, and Sensory Neuropathy have been identified by *GeneReviews* staff.

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. DNMT1-Related Dementia, Deafness, and Sensory Neuropathy: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
DNMT1	19p13.2	DNA (cytosine-5)-methyltransferase 1	DNMT1 @ LOVD	DNMT1

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

Table B. OMIM Entries for DNMT1-Related Dementia, Deafness, and Sensory Neuropathy (View All in OMIM)

126375 DNA METHYLTRANSFERASE 1; DNMT1

614116 NEUROPATHY, HEREDITARY SENSORY, TYPE IE; HSN1E

Molecular Genetic Pathogenesis

DNMT1 maintains patterns of methylated cytosine residues in the mammalian genome. Studies of individuals with *DNMT1*-related dementia, deafness, and sensory neuropathy (HSAN IE) have provided a direct link between *DNMT1* defects and a neurodegenerative disorder affecting both the central and peripheral nervous systems, and suggest that *DNMT1* participates in a precise mechanism of dynamic regulation of neuronal survival [Klein et al 2011].

Normal allelic variants. Two transcript variants encoding different isoforms have been found for this gene [provided by RefSeq, Aug 2008]. The transcript variant NM_001379.2 (Table 3) comprises 40 coding exons, numbered 1-41 but without exon 5.

Pathologic allelic variants. In 6/6 families identified to date, all affected family members had a heterozygous mutation in the targeting sequence domain of *DNMT1*. The mutations identified are listed in Table 3.

Table 3. Selected *DNMT1* Pathologic Allelic Variants

DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change (Alias [1])	Reference Sequences
c.1484A>G	p.Tyr495Cys	
c.1470_1472delTCCinsATA (1470TCC-1472ATA)	p.Asp490_Pro491delinsGluTyr (D490E-P491Y)	NM_001379.2 NP_001370.1
c.1483T>C	p.Tyr495His	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

Normal gene product. NP_001370.1 encodes a DNA (cytosine-5)-methyltransferase 1 with 1616 amino acids. This isoform has the same N- and C-termini but is shorter than the isoform NP_001124295.1, which has 1632 amino acids. The mutations occurred in the targeting-sequence domain of the protein, the N-terminal regulatory region shown to be an important factor for the structure, function, and localization of DNA (cytosine-5)-methyltransferase 1 required for enzymatic function; see Klein et al [2011] for domain structure.

Abnormal gene product. Expression of either mutated *DNMT1* expressing p.Tyr495Cys or p.Asp490_Pro491delinsGluTyr showed misfolded DNA (cytosine-5)-methyltransferase 1 and resulted in premature protein degradation, reduced methyltransferase activity, and impaired heterochromatin binding during the G_2 cell cycle phase. The pathogenic mechanism of mutant *DNMT1* is potentially complex and provides a new direction for the study of neurodegeneration. *DNMT1* is highly expressed in postmitotic neurons and the adult central nervous system. It interacts with a series of important cell cycle-regulating proteins and is likely involved in neuronal differentiation and migration and neural connection [Spada et al 2006]. It remains to be determined how DNMT1 participates in a precise mechanism of dynamic regulation of the nervous system.

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed

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Chapter Notes

Revision History

- 17 May 2012 (cd) Revision: sequence analysis of *DNMT1* available clinically
- 8 March 2012 (cd) Revision: four families with mutations in *DNMT1* associated with early onset of a narcolepsy / cataplexy syndrome followed by ataxia, deafness, sensory neuropathy, and memory loss [Winkelmann et al 2012]
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