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DNMT1-Related Disorder

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Summary

Clinical characteristics

DNMT1-related disorder is a degenerative disorder of the central and peripheral nervous systems comprising a phenotypic spectrum that includes hereditary sensory and autonomic neuropathy type 1E (HSAN1E) and autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN). *DNMT1* disorder is often characterized by moderate-to-severe sensorineural hearing loss beginning in the teens or early 20s, sensory impairment, sudomotor dysfunction (loss of sweating), and dementia usually beginning in the mid-40s. In some affected individuals, narcolepsy/cataplexy syndrome and ataxia are predominant findings.

Diagnosis/testing

The diagnosis of *DNMT1* disorder is established by identification of a heterozygous pathogenic variant in *DNMT1* by molecular genetic testing.

Management

Treatment of manifestations: No cure for *DNMT1* disorder currently exists. The emphasis of management is to help affected individuals and their caregivers 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 often present a considerable burden for partners or other caregivers, information about the disorder and psychological support for partners or other caregivers are essential.

Surveillance: Examination of feet daily for evidence of skin injury; annual routine clinical testing for dementia and audiogram to monitor hearing loss.

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

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Genetic counseling

DNMT1 disorder is inherited in an autosomal dominant manner. Most affected individuals have an affected parent; the proportion of affected individuals with a *de novo DNMT1* pathogenic variant is unknown.

Each child of an individual with *DNMT1* disorder has a 50% chance of inheriting the pathogenic variant. Once the *DNMT1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

DNMT1-Related Disorder: Included Phenotypes [1]
• Hereditary sensory and autonomic neuropathy type 1E (HSAN1E) • Autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN)

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

The phenotype of *DNMT1*-related disorder is a continuum ranging from hereditary sensory and autonomic neuropathy type 1E (HSAN1E) to autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN).

Suggestive Findings

DNMT1 disorder **should be suspected** in individuals with the following clinical, electrophysiologic, and neuroimaging findings and family history.

Clinical findings

- **Sensory neuropathy** that 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. Tendon reflexes tend to be depressed in the lower limbs. The face and trunk are characteristically spared. Age of onset ranges from early 20s to late 40s.
- **Autonomic neuropathy,** manifest as loss of sweating (sudomotor abnormalities). Significant symptoms of autonomic neuropathy usually do not occur until the late 40s.

  Laboratory-based tests such as tilt table testing for postural hypotension, quantitative sudomotor axon reflex testing, and thermoregulatory sweat testing 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 pan sensory neuropathy affects large proprioceptive and vibratory sensing fibers as well as small heat-, pain-, and temperature-sensing fibers.
- **Cerebellar ataxia** manifest as impaired coordination, loss of balance, unsteady gait, difficulty performing fine motor tasks, and changes in speech. Age of onset ranges from the late 30s to late 40s.
- **Dementia** that typically first manifests as progressive decline in cognition and behavior. 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. Dementia usually starts in the mid-40s.
- **Moderate to severe progressive sensorineural hearing loss** (i.e., 70- to 80-db loss at 4,000 Hz) beginning in the teens or early 20s

- **Early- or late-onset narcolepsy/cataplexy syndrome.** Narcolepsy is a chronic sleep disorder characterized by overwhelming daytime drowsiness and sudden attacks of sleep. Cataplexy refers to a sudden loss of muscle tone. Age of onset ranges from early 20s to late 40s.

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.

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

Family history is consistent with autosomal dominant inheritance, including simplex cases (i.e., a single occurrence in a family) caused by a *de novo* pathogenic variant.

Establishing the Diagnosis

The diagnosis of *DNMT1* disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *DNMT1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *DNMT1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *DNMT1*-related disorder is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with progressive sensorineural hearing loss, pure sensory neuropathy, and/or cognitive decline are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *DNMT1*-related disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *DNMT1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, heterozygous exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is identified, gene-targeted deletion/duplication analysis can be considered to detect intragenic deletions or duplications; however, to date such variants have not been identified as a cause of *DNMT1*-related disorder.
- **A multigene panel** that includes *DNMT1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated

with the condition discussed in this *GeneReview*. Of note, given the rarity of *DNMT1*-related disorder, some panels for hearing loss and/or dementia may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by sensory neuropathy, and/or hearing loss, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been identified as a cause of *DNMT1*-related disorder.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *DNMT1*-Related Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DNMT1	Sequence analysis [3]	100% of variants reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Klein et al [2011], Winkelmann et al [2012], Baets et al [2015]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

DNMT1-related disorder 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. In some individuals, late-onset narcolepsy/cataplexy syndrome presents as the prominent manifestation along with: ataxia that appears to be cerebellar in nature, deafness, sensory neuropathy, and memory loss [Klein et al 2011, Winkelmann et al 2012]. Affected persons are normal in their youth but begin to manifest progressive findings, such as sensorineural hearing loss, sensory neuropathy, and/or narcolepsy/cataplexy, by their late teens or early 20s.

In a cohort of 45 affected individuals, the average age of onset was estimated to be 37.7 years; the most common initial manifestation was hearing loss (36%), followed by sensory loss, ulcerations and/or arthropathy (33%), cognitive decline (7%), and gait imbalance (7%). It is likely that the range of phenotypes will expand as more affected individuals are identified [Baets et al 2015].

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

Autonomic dysfunction 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 4,000 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.

Narcolepsy/cataplexy syndrome sometimes presents as the prominent manifestation.

Other clinical findings observed on occasion include visual hallucinations, myoclonic seizures, and renal failure.

Other findings

- **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

All pathogenic variants that cause *DNMT1*-related disorder are located in the targeting sequence (TS) domain of the DNMT1 protein (see Molecular Genetics, **Normal gene product**).

- Variants resulting in the HSAN1E phenotype (a predominantly sensory neuropathy) are in the N-terminus or middle part of the TS domain [Baets et al 2015].
- Variants that cause autosomal dominant cerebellar ataxia, deafness and narcolepsy are located in the C-terminus of the TS domain [Baets et al 2015].

Penetrance

The penetrance of *DNMT1* disorder is 100% in both males and females. However, age of onset and rate of progression vary between individuals.

Nomenclature

This *GeneReview*, formerly titled "*DNMT1*-related dementia, deafness, and sensory neuropathy," was renamed "*DMNT1*-related disorder" to reflect the broader phenotypic spectrum now known to be associated with pathogenic variants in *DNMT1*.

Hereditary sensory and autonomic neuropathy type IE (HSAN1E) is considered a sensory-predominant neuropathy.

Prevalence

To date, a total of 21 families with *DNMT1* disorder have been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are associated with heterozygous pathogenic variants in *DNMT1*.

Differential Diagnosis

Autosomal dominant hereditary sensory and autonomic neuropathies are genetically heterogeneous, but hereditary sensory and autonomic neuropathy type IE (HSAN1E) that includes dementia and hearing loss represents a unique phenotype.

The combination of neuropathy with hearing loss can be confused with some forms of Charcot-Marie-Tooth, and the dementia is similar to that found in frontotemporal dementia 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.

See Hereditary Sensory and Autonomic Neuropathy: OMIM Phenotypic Series to view genes associated with HSAN in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *DNMT1*-related disorder, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) 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
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No cure for *DNMT1* disorder currently exists.

The emphasis of management is to help parents and affected individuals understand the sudomotor defect and injury prevention when sensory impairment is significant. To prevent injury to extremities with decreased sensation, protect the skin with appropriate socks and shoes and avoid exposure of feet to hot water.

Because hearing loss may be severe, initial use of hearing aids and/or assistive communication methods may be needed. See also Hereditary Hearing Loss and Deafness Overview.

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.

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 in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

DNMT1-related disorder is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with *DNMT1* disorder have an affected parent.

- A proband with *DNMT1* disorder may have the disorder as the result of a *de novo* pathogenic variant [Baets et al 2015]. The proportion of *DNMT1* disorder caused by a *de novo* pathogenic variant is unknown.
- Clinical evaluation and molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of a proband inheriting a *DNMT1* pathogenic variant from a parent with germline mosaicism have been reported.
- The family history of some individuals diagnosed with *DNMT1* disorder may appear to be negative because of failure to recognize the syndrome and/or a milder phenotypic presentation, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

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 and/or is known to have the *DNMT1* pathogenic variant, the risk to the sibs is 50%.
- If the *DNMT1* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with *DNMT1* disorder has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *DNMT1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

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

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *DNMT1* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.

- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *DNMT1*-related disorder, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DNMT1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **HSAN1E Society**
  www.hsan1esociety.org

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 Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DNMT1	19p13.2	DNA (cytosine-5)-methyltransferase 1	DNMT1 @ LOVD	DNMT1	DNMT1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for DNMT1-Related Disorder (View All in OMIM)

126375	DNA METHYLTRANSFERASE 1; DNMT1
614116	NEUROPATHY, HEREDITARY SENSORY, TYPE IE; HSN1E

Molecular Pathogenesis

DNMT1 is the sole maintenance methyltransferase and an essential component of cellular epigenetic regulation that keeps the fidelity of methylation inheritance starting from embryogenesis and throughout life. The proper allosteric folding of N-terminal regulatory region is required for enzymatic function.

The targeting sequence (TS) domain, where all the pathogenic variants reside to date, is in the N-terminal regulatory region and regulates DNMT1 binding to hemimethylated DNA during S and binding to heterochromatin during G2 phases.

Mechanism of disease causation. *DNMT1* pathogenic variants cause global DNA hypomethylation and site-specific hypermethylation [Klein et al 2011, Sun et al 2014]. The misfolding of the TS domain of DNMT1 mutated proteins could also contribute to the pathogenesis of HSAN1E phenotype through a toxic gain of function [Klein et al 2011, Baets et al 2015].

Specific laboratory considerations [Baets et al 2015]:

- Variants resulting in the HSAN1E phenotype (a predominantly sensory neuropathy) are in the N-terminus or middle part of the TS domain.
- Variants that cause autosomal dominant cerebellar ataxia, deafness, and narcolepsy are located in the C-terminus of the TS domain.

Chapter Notes

Revision History

- 31 January 2019 (bp) Comprehensive update posted live
- 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]
- 16 February 2012 (me) Review posted live
- 24 October 2011 (cjk) Original submission

References

Literature Cited

Baets J, Duan X, Wu Y, Smith G, Seeley WW, Mademan I, McGrath NM, Beadell NC, Khoury J, Botuyan MV, Mer G, Worrell GA, Hojo K, DeLeon J, Laura M, Liu YT, Senderek J, Weis J, Van den Bergh P, Merrill SL, Reilly MM, Houlden H, Grossman M, Scherer SS, De Jonghe P, Dyck PJ, Klein CJ. Defects of mutant DNMT1 are linked to a spectrum of neurological disorders. Brain. 2015;138:845–61. PubMed PMID: 25678562.

Hojo K, Imamura T, Takanashi M, Ishii K, Sasaki M, Imura S, Ozono R, Takatsuki Y, Takauchi S, Mori E. Hereditary sensory neuropathy with deafness and dementia: a clinical and neuroimaging study. Eur J Neurol. 1999;6:357–61. PubMed PMID: 10210919.

Klein CJ, Botuyan MV, Wu Y, Ward CJ, Nicholson GA, Hammans S, Hojo K, Yamanishi H, Karpf AR, Wallace DC, Simon M, Lander C, Boardman LA, Cunningham JM, Smith GE, Litchy WJ, Boes B, Atkinson EJ, Middha S, Dyck PJB, Parisi JE, Mer G, Smith DI, Dyck PJ. Mutations in DNMT1 cause hereditary sensory neuropathy with dementia and hearing loss. Nat Genet. 2011;43:595–600. PubMed PMID: 21532572.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Sun Z, Wu Y, Ordog T, Baheti S, Nie J, Duan X, Hojo K, Kocher JP, Dyck PJ, Klein CJ. Aberrant signature methylome by DNMT1 hot spot mutation in hereditary sensory and autonomic neuropathy 1E. Epigenetics. 2014;9:1184–93. PubMed PMID: 25033457.

Winkelmann J, Lin L, Schormair B, Kornum BR, Faraco J, Plazzi G, Melberg A, Cornelio F, Urban AE, Pizza F, Poli F, Grubert F, Wieland T, Graf E, Hallmayer J, Strom TM, Mignot E. Mutations in DNMT1 cause autosomal dominant cerebellar ataxia, deafness and narcolepsy. Hum Mol Genet. 2012;21:2205–10. PubMed PMID: 22328086.

Wright A, Dyck PJ. Hereditary sensory neuropathy with sensorineural deafness and early-onset dementia. Neurology. 1995;45:560–2. PubMed PMID: 7898717.

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