U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Kurth I. Hereditary Sensory and Autonomic Neuropathy Type II. 2010 Nov 23 [Updated 2021 Apr 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Hereditary Sensory and Autonomic Neuropathy Type II

Synonyms: Hereditary Sensory and Autonomic Neuropathy Type 2 (HSAN2), HSANII

Ingo Kurth, MD[1]

Created: November 23, 2010; Updated: April 1, 2021.

Summary

Clinical characteristics

Hereditary sensory and autonomic neuropathy type II (HSAN2) is characterized by progressively reduced sensation to pain, temperature, and touch. Onset can be at birth and is often before puberty. The sensory deficit is predominantly distal with the lower limbs more severely affected than the upper limbs. Over time sensory function becomes severely reduced. Unnoticed injuries and neuropathic skin promote ulcerations and infections that result in spontaneous amputation of digits or the need for surgical amputation. Osteomyelitis is common. Painless fractures can complicate the disease. Autonomic disturbances are variable and can include hyperhidrosis, tonic pupils, and urinary incontinence in those with more advanced disease.

Diagnosis/testing

The diagnosis of HSAN2 is established in a proband with suggestive clinical and electrophysiologic findings and biallelic pathogenic variants in one of four genes: *KIF1A, RETREG1* (*FAM134B*), *SCN9A*, or *WNK1*.

Management

Treatment of manifestations: Treatment is symptomatic and often involves a team including neurologists, orthopedic surgeons, and physiotherapists. Training in the care of the sensory-impaired limb, often in a diabetic foot care clinic, is important and includes self-examination – especially of the feet – for any signs of trauma. To prevent osteomyelitis, and hence the need for amputation, wounds require cleaning and protection along with antiseptic treatment. To prevent callous formation, the skin of neuropathic limbs requires hydration and lipid-based unguents. Appropriate shoes and socks are recommended.

Surveillance: The feet should be inspected daily for injuries or sources of wear. Annual follow up in centers with comprehensive care of diabetics and/or persons with Charcot-Marie-Tooth neuropathy is recommended.

Author Affiliation: 1 Institute of Human Genetics, Uniklinik RWTH Aachen, Aachen, Germany; Email: ikurth@ukaachen.de.

Agents/circumstances to avoid: Ill-fitting shoes or other sources of trauma to the feet or hands (e.g., use protective gloves when handling hot items when cooking.)

Genetic counseling

HSAN2 is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an HSAN2-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the HSAN2-causing pathogenic variants in the family are known, carrier testing of at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

Hereditary Sensory and Autonomic Neuropathy Type II (HSAN2): Included Phenotypes [1]
• *KIF1A*-related HSAN2 (HSAN2C) • *RETREG1*-related HSAN2 (HSAN2B) • *SCN9A*-related HSAN2 (HSAN2D) • *WNK1*-related HSAN2 (HSAN2A)

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

Diagnosis

No consensus clinical diagnostic criteria for hereditary sensory and autonomic neuropathy type II (HSAN2) have been published.

Suggestive Findings

Hereditary sensory and autonomic neuropathy type II (HSAN2) **should be suspected** in individuals with the following clinical and electrophysiologic findings and family history.

Clinical findings

- Congenital or early-onset (1st to 2nd decade) sensory deficit
- Sensory loss affecting all modalities
- Ulcerations of hands/feet often requiring amputation
- Acral mutilations
- Painless fractures and neuropathic arthropathy in some
- Varying degree of autonomic involvement: hyperhidrosis, urinary incontinence, and slow pupillary reaction to light

Electrophysiologic findings

- Reduced/absent sensory nerve action potentials
- Preserved or reduced motor nerve conduction velocities (NCV)
- Variably reduced compound muscle action potentials (CMAP)

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of HSAN2 is established in a proband with suggestive clinical and electrophysiologic findings and biallelic pathogenic variants in one of four genes: *KIF1A, RETREG1* (*FAM134B*), *SCN9A*, or *WNK1*. (See Table 1.)

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (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. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of a pure sensory neuropathy has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and electrophysiologic findings suggest the diagnosis of HSAN2, the molecular genetic testing approach is use of a **multigene panel**.

A hereditary sensory and autonomic neuropathy multigene panel that includes some or all of the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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*. (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

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 Hereditary Sensory and Autonomic Neuropathy Type II (HSAN2)

Gene [1, 2]	Proportion of HSAN2 Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
KIF1A	Too few case reports for conclusive assessment	100% [6]	None reported [6]
RETREG1 (FAM134B)		100% [6]	None reported [6]
SCN9A		>90% [6]	A few cases [6, 7]
WNK1		>90% [6]	Whole-gene deletion in 1 family [8]; intragenic deletion [9]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. 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.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
7. And Author, unpublished data
8. Wang et al [2019]
9. Author, unpublished data

Clinical Characteristics

Clinical Description

The published clinical descriptions of hereditary sensory and autonomic neuropathy type II (HSAN2) are inconsistent, possibly in part as a result of reports that lack molecular genetic confirmation of the diagnosis. Clinically, *WNK1*-related HSAN2 (HSAN2A), *RETREG1* (*FAM134B*)-related HSAN2 (HSAN2B), and *KIF1A*-related HSAN2 (HSAN2C) appear to be very similar.

Autonomic dysfunction may be more pronounced in *RETREG1*-related neuropathy, and individuals with *KIF1A*-related HSAN2 also showed distal muscle weakness. *SCN9A*-related HSAN2 was reported in two families [Yuan et al 2013].

Table 2. Hereditary Sensory and Autonomic Neuropathy Type II (HSAN2): Gene-Phenotype Correlations

Feature	Associated Gene (HSAN2 Subtype)			
	WNK1 (HSAN2A)	*RETREG1* (HSAN2B)	*KIF1A* (HSAN2C)	*SCN9A* (HSAN2D)
Sensory deficit	+++	+++	+++	+++
Autonomic dysfunction	++	+++	++	+
Distal motor involvement	+	+	++	-

+ ++= most common; ++= less common; += rare; -= not observed

In molecularly confirmed HSAN2, onset is typically in the first two decades (often before puberty). It is characterized by progressive numbness of the hands and feet, together with reduced sensation to pain, temperature, and touch. The sensory deficit is predominantly distal with the lower limbs more severely affected than the upper limbs. Over time, sensory function becomes severely reduced.

Neuropathic skin tends to produce excessive keratin and hyperkeratosis that may be forced down into the deeper layers of soft tissue and/or may crack, promoting ulcerations and infections that result in spontaneous amputation of digits or the need for surgical amputation. Osteomyelitis is common.

Secondary muscle atrophy and Charcot joints may occur. Painless fractures can complicate the disease.

Intellectual development is usually normal but can be impaired, especially in *KIF1A*-related HSAN2.

Sweating and tearing are usually normal but hyperhidrosis is present in some cases. Tonic pupils are observed. With progression of the disease urinary incontinence is reported.

Histopathology. Sural nerve biopsy shows signs of an axonal sensory neuropathy, pronounced absence of (small) myelinated fibers, and decreased unmyelinated fibers. Additionally, loss of large myelinated fibers may be seen in those with HSAN2D.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known. Inter- and intrafamilial phenotypic variability is reported.

Nomenclature

HSAN2 has also been reported as the following:

- Morvan's disease
- Congenital sensory neuropathy
- Neurogenic acroosteolysis
- Hereditary sensory radicular neuropathy

Dyck originally proposed five different HSAN types on the basis of clinical manifestations and nerve biopsy specimens [Dyck 1993]. More recently, genetic and additional phenotypic heterogeneity has been described [Verhoeven et al 2006], suggesting a need for a detailed classification based on the underlying gene defects [Rotthier et al 2012, Schwartzlow & Kazamel 2019].

Prevalence

The worldwide prevalence of HSAN2 is unknown. Several hundred affected individuals have been reported.

For comparison, the overall prevalence of the closely related hereditary motor and sensory neuropathies (HMSN or Charcot-Marie-Tooth neuropathy) is about 30:100,000, and hereditary sensory and autonomic neuropathies (HSAN) occur with markedly lower frequency.

See Table 5 for *WNK1* founder variants identified in eastern Canada [Roddier et al 2005] and Japan [Yuan et al 2017].

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *KIF1A*, *SCN9A*, and *WNK1* are summarized in Table 3.

Table 3. Allelic Disorders to Consider in the Differential Diagnosis of Hereditary Sensory and Autonomic Neuropathy Type II (HSAN2)

Gene	Disorder	MOI	Comment / Reference
KIF1A	Hereditary spastic paraplegia 30 (OMIM 610357)	AR AD	See Hereditary Spastic Paraplegia Overview. An entire *KIF1A* deletion was reported in 1 person [Pennings et al 2020].
	NESCAV syndrome (OMIM 614255)	AD	Neurodegeneration & spasticity ± cerebellar atrophy or cortical visual impairment
	Early onset or congenital ataxia	AD	Nicita et al [2020]
SCN9A	Congenital insensitivity to pain	AR	See Differential Diagnosis.
	SCN9A neuropathic pain syndromes	AD	Incl erythromelalgia, paroxysmal extreme pain disorder, & small fiber neuropathy
	Generalized epilepsy febrile seizures plus; simple febrile seizures (OMIM 613863)	AD	
WNK1	Pseudohypoaldosteronism type II (PHA2C)	AD	Hypertension, hyperkalemia, & renal tubular acidosis. HSAN2-causing *WNK1* variants are apparent LOF variants & are not assoc w/PHA2C (see Molecular Genetics).

AD = autosomal dominant; AR = autosomal recessive; LOF = loss of function; MOI = mode of inheritance

RETREG1. No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *RETREG1*.

Differential Diagnosis

HSAN is a heterogeneous group of disorders in which pathogenic variants in other genes lead to overlapping clinical phenotypes. The distinction between HSAN and clinically similar congenital insensitivity to pain (CIP) is inconsistent. A list of genes implicated in other types of HSAN and/or CIP is provided in Table 4.

Table 4. Disorders of Interest in the Differential Diagnosis of Hereditary Sensory and Autonomic Neuropathy Type II (HSAN2)

Gene	HSAN Classification	MOI	Typical Age at Onset	Clinical (Distinguishing) Features	Reference
ATL1	HSAN1	AD	Adulthood	Painless ulcers, fractures; involvement of upper motor neurons described	See HSN1D or allelic Spastic Paraplegia 3A.
ATL3	HSAN1	AD	Adulthood	Painless ulcers, fractures; spasticity in some persons; severely delayed wound healing; multiple fractures of foot skeleton	OMIM 615632
CLTCL1	Not classified	AR	Congenital	CIP, inability to feel touch, ID	OMIM 601273
DNMT1	HSAN1	AD	Adulthood	Loss of pain, ulcers; sensorineural hearing loss, progressive dementia, sensory ataxia	*DNMT1*-Related Disorder
DST	HSAN6	AR	Congenital	Autonomic involvement; alacrimia, feeding difficulties, contractures, hypomimia, severeDD/ID	OMIM 614653
ELP1	HSAN3	AR	Congenital	Predominant autonomic neuropathy; alacrimia, gastrointestinal dysfunction, vomiting, cardiovascular instability, blood pressure fluctuations, autonomic crises, scoliosis	Familial Dysautonomia

Table 4. continued from previous page.

Gene	HSAN Classification	MOI	Typical Age at Onset	Clinical (Distinguishing) Features	Reference
FAAHP1 (*FAAH-OUT*)	CIP	AD AR	Congenital	Pain insensitivity & impaired anxiety	OMIM 618377
FLVCR1		AR	Congenital	Painless injuries, psychomotor delay, anemia	Chiabrando et al [2016]
NGF	HSAN5	AR	Congenital	See phenotype of HSAN4.	Congenital Insensitivity to Pain Overview
NTRK1	HSAN4	AR	Congenital	CIP w/anhidrosis, self-mutilations (biting the tongue, biting of fingertips), fever episodes (lack of sweat gland innervation), painless fractures, variable degree of ID, corneal lesions	*NTRK1* Congenital Insensitivity to Pain with Anhidrosis
PRDM12	HSAN8	AR	Congenital	Pain insensitivity, facial injuries, sweating usually preserved, ID less common	Congenital Insensitivity to Pain Overview
RAB7A		AD	Adulthood	Strong motor involvement, also classified as CMT2B	Charcot-Marie-Tooth Hereditary Neuropathy Overview
SCN11A	CIP/HSAN7	AD	Congenital	Predilection for skin ulcers to cervical region, pruritus, intestinal dysmotility, delayed motor development, joint hypermobility	Congenital Insensitivity to Pain Overview
SPTLC1	HSAN1	AD	Adulthood	Loss of pain (may be assoc w/ lancinating pain); ulcerations, mutilations, mild motor involvement (may be pronounced in some persons)	*SPTLC1*-Related Hereditary Sensory Neuropathy
SPTLC2	HSAN1	AD	Adulthood	Similar to *SPTLC1*-HSN	OMIM 613640
ZFHX2	CIP	AD	Childhood	Hyposensitivity to painful thermal & capsaicin stimulation & painless injuries	Congenital Insensitivity to Pain Overview

Adapted from Cox et al [2020], Table 1.
AD = autosomal dominant; AR = autosomal recessive; CIP = congenital insensitivity to pain; CMT = Charcot-Marie-Tooth hereditary neuropathy; DD = developmental delay; HSAN = hereditary sensory and autonomic neuropathy; HSN = hereditary sensory neuropathy; ID = intellectual disability; MOI = mode of inheritance

Other genetic disorders to consider. Disorders accompanied by self-mutilating behavior resemble some aspects of the congenital forms of HSAN including Lesch-Nyhan disease (see *HPRT1* Disorders) or untreated phenylketonuria.

Management

No clinical practice guidelines for hereditary sensory and autonomic neuropathy type II (HSAN2) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hereditary sensory and autonomic neuropathy type II (HSAN2), 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 extent of sensory loss and involvement of autonomic and motor nervous system
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of HSAN2 in order to facilitate medical and personal decision making

Treatment of Manifestations

Treatment is symptomatic and often involves a multidisciplinary team including neurologists, orthopedic surgeons, and physiotherapists.

Training in the care of the sensory-impaired limb is important and includes self-examination – especially of the feet – for any signs of trauma. A diabetic clinic is a good source of advice. Appropriate shoes and socks are recommended.

It is best to prevent callous formation in neuropathic skin; once present, calluses should be treated with hydration and lipid-based unguents to prevent cracking and may require medical consultation.

Cleaning and protection of wounds on neuropathic limbs in combination with antiseptic treatment to eradicate infections helps prevent osteomyelitis and the possible future need to amputate a limb.

Surveillance

The feet should be inspected daily for injuries and sources of wear.

Affected individuals should be followed annually by centers with comprehensive care, such as those for diabetic foot care and/or Charcot-Marie-Tooth neuropathy, also known as hereditary motor and sensory neuropathy.

Agents/Circumstances to Avoid

Avoid ill-fitting shoes or other sources of trauma to the feet or hands (e.g., use protective gloves when handling hot items when cooking).

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk sibs in order to identify those who will develop sensory loss and would benefit from measures to prevent injury to limbs and/or self-mutilation.

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 access to 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

Hereditary sensory and autonomic neuropathy type II (HSAN2) is an autosomal recessive disorder caused by biallelic *KIF1A* (HSAN2C), *RETREG1* (HSAN2B), *SCN9A* (HSAN2D), or *WNK1* (HSAN2A) pathogenic variants.

Risk to Family Members

Parents of a proband

- In most families, both parents of an affected child are carriers (i.e., heterozygotes) for a *KIF1A*, *RETREG1* (*FAM134B*), *SCN9A*, *or WNK1* pathogenic variant.
- In rare families, only one parent is heterozygous for a pathogenic variant and the child has HSAN2 as the result of uniparental isodisomy and consequent homozygosity for the HSAN2-causing pathogenic variant from the carrier parent. (Uniparental isodisomy has been reported in a child with *RETREG1*-related HSAN2 [Park et al 2019].)
- Accurate recurrence risk counseling relies on carrier testing of both parents to determine if both are heterozygous for an HSAN2-causing pathogenic variant. If carrier testing detects the pathogenic variant in only one parent:
  - And the child appears to have homozygous HSAN2-causing pathogenic variants, possible explanations include a large deletion on one allele (if not previously tested for) and uniparental isodisomy [Park et al 2019]);
  - And the child has compound heterozygous HSAN2-causing pathogenic variants, the child may theoretically have one inherited pathogenic variant and one *de novo* pathogenic variant. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic except for the report of increased sensitivity to thermal stimuli in individuals who are heterozygous for an HSAN2-related *WNK1* pathogenic variant [Loggia et al 2009].

Sibs of a proband

- If both parents are known to be heterozygous for an HSAN2-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.
- Significant clinical variability between affected sibs can be observed.
- If the proband has HSAN2 as the result of uniparental isodisomy, if only one parent is heterozygous for an HSAN2-causing pathogenic variant, and if neither parent has a chromosome rearrangement, each sib of an affected individual has at conception a 50% chance of being a carrier and an approximately 50% chance of being unaffected and not a carrier. (The risk to sibs of a proband of being affected is unknown but is presumed to be <1%.)
- Heterozygotes (carriers) are typically asymptomatic (see exception in **Parents of a proband**).

Offspring of a proband. Unless an individual with HSAN2 has children with an affected individual or a carrier (see Prevalence), his/her offspring will be obligate heterozygotes (carriers) for an HSAN2-causing pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an HSAN2-causing pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the HSAN2-causing pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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, are carriers, or are at risk of being carriers.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the HSAN2-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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.

- **MedlinePlus**
  Hereditary sensory and autonomic neuropathy type II
- **European Network on Inherited Sensory Neuropathies and Insensitivity to Pain (ENISNIP)**
  Email: contact@enisnip.org
  www.enisnip.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. Hereditary Sensory and Autonomic Neuropathy Type II: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KIF1A	2q37.3	Kinesin-like protein KIF1A	KIF1A @ LOVD	KIF1A	KIF1A
RETREG1	5p15.1	Reticulophagy regulator 1	FAM134B homepage - Leiden Muscular Dystrophy pages	RETREG1	RETREG1
SCN9A	2q24.3	Sodium channel protein type 9 subunit alpha	SCN9A database	SCN9A	SCN9A
WNK1	12p13.33	Serine/threonine-protein kinase WNK1	WNK1 @ LOVD WNK1 homepage - Leiden Muscular Dystrophy pages	WNK1	WNK1

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 Hereditary Sensory and Autonomic Neuropathy Type II (View All in OMIM)

201300	NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, TYPE IIA; HSAN2A
243000	INDIFFERENCE TO PAIN, CONGENITAL, AUTOSOMAL RECESSIVE; CIP
601255	KINESIN FAMILY MEMBER 1A; KIF1A
603415	SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 9; SCN9A
605232	PROTEIN KINASE, LYSINE-DEFICIENT 1; WNK1
613114	RETICULOPHAGY REGULATOR 1; RETREG1
613115	NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, TYPE IIB; HSAN2B
614213	NEUROPATHY, HEREDITARY SENSORY, TYPE IIC; HSN2C

Molecular Pathogenesis

Mechanism of disease causation for all genes. Given the spectrum of pathogenic variant types in the HSAN2-related genes (nonsense variants, frameshift variants, and splice-site variants are part of the mutation spectrum), biallelic loss of function can be assumed.

Gene-specific laboratory technical considerations. Alternate splicing of *WNK1* results in the inclusion of exon 10 ("*HSN2*" exon). *HSN2* was first reported as a single-exon gene located in intron 8 of *WNK1*, with both genes transcribed from the same strand [Lafreniere et al 2004]. Subsequently, *HSN2* was found to be an alternatively spliced exon present in a nervous system-specific isoform of *WNK1* [Shekarabi et al 2008]. The majority of HSAN2-causing variants in *WNK1* reported to date are frameshift or nonsense variants in exon 10. Because pathogenic variants in other exons of *WNK1* may also contribute to the HSAN2A phenotype, sequence analysis of all known exons from genomic DNA may be necessary if only one pathogenic variant is found in exon 10. Note: Homozygous or compound heterozygous null alleles affecting all *WNK1* isoforms are thought to be embryonically lethal.

Table 5. Notable *WNK1* Pathogenic Variants

Gene	Reference Sequences	DNA Nucleotide Change [1] (Alias [2])	Predicted Protein Change [1] (Alias [2])	Comment [Reference]
WNK1	NM_213655.5 NP_998820.3	c.2952delA (594delA)	p.Glu984AspfsTer10 (Glu198AspfsTer10)	French Canadian founder variants [Roddier et al 2005]
		c.3276dupA (918_919insA)	p.Ser1093IlefsTer13 (Ser307IlefsTer13)	
		c.3301C>T (943C>T)	p.Gln1101Ter (Gln315Ter)	
		c.3492dupT	p.Asp1165Ter	Japanese founder variant [Yuan et al 2017]

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

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

1. Nucleotide and amino acid nomenclature is based on the reference sequences for *WNK1* isoform wnk1tv3. In this transcript, the "*HSN2*" exon is number 10. All of the pathogenic variants in this table are in exon 10 (see **Gene-specific laboratory technical considerations**).

2. The alias nucleotide and amino acid changes are derived from Lafreniere et al [2004] based on the original identification and numbering of the purported gene *HSN2* (UCSC *HSN2* uc001qiq.2 protein sequence). The first codon of the *HSN2* exon of *WNK1* is located 12 amino acids 3′ of the initially supposed Met start-codon of the single-exon HSN2 transcript; pathogenic variants in parentheses in Table 5 and in Lafreniere et al [2004] are numbered accordingly.

Chapter Notes

Author Notes

Website: www.ukaachen.de/en/clinics-institutes/institute-of-human-genetics

The Institute of Human Genetics offers HSAN testing on a research basis via the ENISNIP consortium. For further information regarding massive parallel sequencing of HSAN-relevant genes, please contact ikurth@ukaachen.de.

Revision History

- 1 April 2021 (bp) Comprehensive update posted live
- 19 February 2015 (me) Comprehensive update posted live
- 3 November 2011 (ik) Revision: added HSAN2C, caused by *KIF1A* pathogenic variants
- 23 November 2010 (me) Review posted live
- 14 July 2010 (ik) Original submission

References

Literature Cited

Chiabrando D, Castori M, di Rocco M, Ungelenk M, Gießelmann S, Di Capua M, Madeo A, Grammatico P, Bartsch S, Hübner CA, Altruda F, Silengo L, Tolosano E, Kurth I. Mutations in the heme exporter FLVCR1 cause sensory neurodegeneration with loss of pain perception. PLoS Genet. 2016;12:e1006461. PubMed PMID: 27923065.

Cox JJ, Woods CG, Kurth I. Peripheral sensory neuropathies – pain loss vs. pain gain. Med Genet. 2020;32:233–41.

Dyck P. Neuronal atrophy and degeneration predominantly affecting peripheral sensory and autonomic neurons. In: Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF, eds. *Peripheral Neuropathy*. 3 ed. Philadelphia, PA: WB Saunders Company; 1993:1065-93.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Lafreniere RG, MacDonald ML, Dube MP, MacFarlane J, O'Driscoll M, Brais B, Meilleur S, Brinkman RR, Dadivas O, Pape T, Platon C, Radomski C, Risler J, Thompson J, Guerra-Escobio AM, Davar G, Breakefield XO, Pimstone SN, Green R, Pryse-Phillips W, Goldberg YP, Younghusband HB, Hayden MR, Sherrington R, Rouleau GA, Samuels ME; Study of Canadian Genetic Isolates. Identification of a novel gene (HSN2) causing hereditary sensory and autonomic neuropathy type II through the Study of Canadian Genetic Isolates. Am J Hum Genet. 2004;74:1064–73. PubMed PMID: 15060842.

Loggia ML, Bushnell MC, Tétreault M, Thiffault I, Bhérer C, Mohammed NK, Kuchinad AA, Laferrière A, Dicaire MJ, Loisel L, Mogil JS, Brais B. Carriers of recessive WNK1/HSN2 mutations for hereditary sensory and autonomic neuropathy type 2 (HSAN2) are more sensitive to thermal stimuli. J Neurosci. 2009;29:2162–6. PubMed PMID: 19228968.

Nicita F, Ginevrino M, Travaglini L, D'Arrigo S, Zorzi G, Borgatti R, Terrone G, Catteruccia M, Vasco G, Brankovic V, Siliquini S, Romano S, Veredice C, Pedemonte M, Armando M, Lettori D, Stregapede F, Bosco L, Sferra A, Tessarollo V, Romaniello R, Ristori G, Bertini E, Valente EM, Zanni G. Heterozygous KIF1A variants underlie a wide spectrum of neurodevelopmental and neurodegenerative disorders. J Med Genet. 2020. Epub ahead of print. PubMed PMID: 32737135.

Park GY, Jang DH, Lee DW, Jang JH, Joo J. Hereditary Sensory and Autonomic Neuropathy 2B Caused by a Novel RETREG1 Mutation (c.765dupT) and Paternal Uniparental Isodisomy of Chromosome 5. Front Genet. 2019;10:1085. PubMed PMID: 31737055.

Pennings M, Schouten MI, van Gaalen J, Meijer RPP, de Bot ST, Kriek M, Saris CGJ, van den Berg LH, van Es MA, Zuidgeest DMH, Elting MW, van de Kamp JM, van Spaendonck-Zwarts KY, Die-Smulders C, Brilstra EH, Verschuuren CC, de Vries BBA, Bruijn J, Sofou K, Duijkers FA, Jaeger B, Schieving JH, van de Warrenburg BP, Kamsteeg EJ. KIF1A variants are a frequent cause of autosomal dominant hereditary spastic paraplegia. Eur J Hum Genet. 2020;28:40–9. PubMed PMID: 31488895.

Roddier K, Thomas T, Marleau G, Gagnon AM, Dicaire MJ, St-Denis A, Gosselin I, Sarrazin AM, Larbrisseau A, Lambert M, Vanasse M, Gaudet D, Rouleau GA, Brais B. Two mutations in the HSN2 gene explain the high prevalence of HSAN2 in French Canadians. Neurology. 2005;64:1762–7. PubMed PMID: 15911806.

Rotthier A, Baets J, Timmerman V, Janssens K. Mechanisms of disease in hereditary sensory and autonomic neuropathies. Nat Rev Neurol. 2012;8:73–85. PubMed PMID: 22270030.

Shekarabi M, Girard N, Rivière JB, Dion P, Houle M, Toulouse A, Lafrenière RG, Vercauteren F, Hince P, Laganiere J, Rochefort D, Faivre L, Samuels M, Rouleau GA. Mutations in the nervous system--specific HSN2 exon of WNK1 cause hereditary sensory neuropathy type II. J Clin Invest. 2008;118:2496–505. PubMed PMID: 18521183.

Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665–77. PubMed PMID: 28349240.

Schwartzlow C, Kazamel M. Hereditary sensory and autonomic neuropathies: adding more to the classification. Curr Neurol Neurosci Rep. 2019;19:52. PubMed PMID: 31222456.

Verhoeven K, Timmerman V, Mauko B, Pieber TR, De Jonghe P, Auer-Grumbach M. Recent advances in hereditary sensory and autonomic neuropathies. Curr Opin Neurol. 2006;19:474–80. PubMed PMID: 16969157.

Wang JJ, Yu B, Li Z. The coexistence of a novel WNK1 variant and a copy number variation causes hereditary sensory and autonomic neuropathy type IIA. BMC Med Genet. 2019;20:91. PubMed PMID: 31132985.

Yuan J, Matsuura E, Higuchi Y, Hashiguchi A, Nakamura T, Nozuma S, Sakiyama Y, Yoshimura A, Izumo S, Takashima H. Hereditary sensory and autonomic neuropathy type IID cause by an SCN9A mutation. Neurology. 2013;80:1641–9. PubMed PMID: 23596073.

Yuan JH, Hashiguchi A, Yoshimura A, Sakai N, Takahashi MP, Ueda T, Taniguchi A, Okamoto S, Kanazawa N, Yamamoto Y, Saigoh K, Kusunoki S, Ando M, Hiramatsu Y, Okamoto Y, Takashima H. WNK1/HSN2 founder mutation in patients with hereditary sensory and autonomic neuropathy: a Japanese cohort study. Clin Genet. 2017;92:659–63. PubMed PMID: 28422281.

License