

Genetic Testing for Neuropathy: Hereditary Sensory and Autonomic Neuropathy Panel Sequencing and Exon-Level Deletion/Duplication Analysis of 14 Genes

Disorder also known as: HSAN, Hereditary Sensory Neuropathy (HSN)

Panel Gene List: *ATL1, DNMT1, IKBKAP, KIF1A, NGF, NTRK1, PRDM12, RAB7A, RETREG1, SCN9A, SCN11A, SPTLC1, SPTLC2, WNK1**

* (exon 10 "HSAN exon" only)

Clinical Features:

The hereditary sensory and autonomic neuropathies (HSAN) are a phenotypically diverse group of disorders. Some individuals only have sensory symptoms, others have a combination of sensory, autonomic and motor abnormalities, while others have purely autonomic findings.¹ Typically patients experience distal sensory loss, particularly related to pain and temperature, leading to chronic ulcerations of the hands and feet, soft tissue infections, osteomyelitis. Some individuals also have skin and nail changes. Autonomic features can include: anhidrosis, fever, fluctuations in blood pressure, and gastrointestinal issues.¹ Axonal nerve damage is most frequently observed in patients with HSAN; however, some patients also have demyelinating features.¹

Subtypes of HSAN are broken down based on age of onset, mode of inheritance, and main clinical findings.^{1,2} HSAN I is characterized by autosomal dominant inheritance, a predominance of sensory symptoms, and onset of symptoms in childhood or adulthood. It is caused by pathogenic variants in the *SPTLC1, SPTLC2, RAB7A, DNMT1, and ATL1* genes.^{1,2} HSAN II-V and HSAN VIII are characterized by autosomal recessive inheritance, congenital or early childhood onset of symptoms, and are caused by pathogenic variants in *WNK1, RETREG1, KIF1A, IKBKAP, NTRK1, SCN9A, PRDM12, and NGF*.^{1,2,3,4} These subtypes tend to have primarily autonomic involvement without motor symptoms. Due to severe autonomic involvement and increased risk of sepsis associated with HSAN III and HSAN IV, life expectancy of these patients is lower than in the other types.¹ HSAN VII is an autosomal dominant disorder caused by pathogenic variants in the *SCN11A* gene. HSAN VII is characterized by congenital inability to experience pain, delayed motor development, mild weakness, hyperhidrosis, and gastrointestinal dysfunction.⁵ Episodic pain syndrome type 3 is also associated with pathogenic variants in the *SCN11A* gene and is characterized by early childhood onset of episodic, intense pain, most commonly of the distal lower extremities, co-occurring with sweating.⁶ Small fiber neuropathy is typically an adult-onset disorder

characterized by neuropathic pain and autonomic symptoms, and has been associated with pathogenic variants in *SCN9A* and *SCN11A*.^{7,8}

Genetics:

A genetic diagnosis is identified in approximately 20-33% of individuals with HSAN.^{1:9} The complete list of genes included on the Hereditary Sensory and Autonomic Neuropathy panel is included in the table below. The hereditary sensory and autonomic neuropathies show a great deal of genetic and phenotypic heterogeneity, and can be inherited in an autosomal dominant or autosomal recessive manner.

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). For the *WNK1* gene, only exon 10 in the neuronal specific transcript associated with hereditary sensory neuropathy type II (NM_213655) is analyzed. The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Sequencing and deletion/duplication analysis of the remaining genes on the Hereditary Neuropathy Panel is available as a reflex test if the HSAN panel is negative.

Test Sensitivity:

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

References:

1. Rotthier et al. (2012) Nature Reviews. Neurology 8 (2):73-85 (PMID: 22270030).
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3. Kurth (Updated February 2015). Hereditary Sensory and Autonomic Neuropathy Type II. . In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010.
4. Chen et al. (2015) Nat. Genet. 47(7):803-8 (PMID: 26005867).
5. Leipold et al. (2013) Nature Genetics 45 (11):1399-404 (PMID: 24036948).
6. Zhang et al. (2013) American Journal Of Human Genetics 93 (5):957-66 (PMID: 24207120)
7. Faber et al. (2012) Annals Of Neurology 71 (1):26-39 (PMID: 21698661).
8. Huang et al. (2014) Brain: A Journal Of Neurology 137 (Pt 6):1627-42 (PMID: 24776970).
9. Murphy et al. (2012) Journal Of Neurology, Neurosurgery, And Psychiatry 83 (7):706-10 (PMID: 22577229)

Disease Associations	Gene	Protein	Inh	Diagnostic Yield in Selected Populations
HSN ID; Spastic paraplegia 3A	<i>ATL1</i>	Atlastin-1	AD	Unknown in HSN1 ¹ ; ~7% of familial and ~4% of sporadic HSP ²
HSAN IE; Autosomal dominant cerebellar ataxia, deafness and narcolepsy	<i>DNMT1</i>	DNA methyltransferase 1	AD	Rare ³
Familial dysautonomia aka HSN III	<i>IKBKAP</i>	Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex-associated protein	AR	Carrier frequency of 1/27-1/32 in Ashkenazi Jewish population ⁴
HSAN IIC (AR); Spastic paraplegia 30 (AR); Syndromic intellectual disability (AD)	<i>KIF1A</i>	Kinesin family member 1A	AD/ AR	Rare ⁵
HSAN V	<i>NGF</i>	Nerve growth factor	AR	Rare in HSN ⁶
Congenital insensitivity to pain with anhidrosis	<i>NTRK1</i>	Neurotrophic tyrosine kinase receptor type 1	AR	Up to 7% of patients with HSN ^{6,7}
HSAN VIII	<i>PRDM12</i>	PR domain-containing protein 12	AR	Rare ⁸
Charcot-Marie-Tooth type 2B	<i>RAB7A</i>	RAS-associated protein	AD	Up to 7% HSN patients ⁷ ; rare in CMT ^{2,9}

HSAN IIB	<i>RETREG1</i> <i>aka</i> <i>FAM134B</i>	Family with sequence similarity 134, member B	AR	<2% of HSAN patients ⁶
Primary erythralgia (AD); Paroxysmal extreme pain disorder (AD); Small fiber neuropathy (AD); HSAN IID (AR); Congenital insensitivity to pain (AR);	<i>SCN9A</i>	Sodium channel, voltage-gated, type IX, alpha subunit	AD/ AR	Unknown in HSAN II ¹⁰ ; ~28% of Dutch Caucasian patients with biopsy confirmed small fiber neuropathy ¹¹
HSAN VII; Familial episodic pain syndrome 3; Small fiber neuropathy	<i>SCN11A</i>	Sodium channel, voltage-gated, type XI, alpha subunit	AD	Rare ^{12,13}
HSAN IA	<i>SPTLC1</i>	Serine palmitoyltransferase, long chain base subunit 1	AD	Up to 12% of patients with HSAN with a founder mutation noted in the United Kingdom ^{6,7}
HSAN IC	<i>SPTLC2</i>	Serine palmitoyltransferase, long chain base subunit 2	AD	<5% of patients with HSAN ¹⁴
HSAN IIA	<i>WNK1</i>	Protein kinase, lysine-deficient 1	AR	<3% of HSAN patients ^{6,7}

Abbreviations:

AD – Autosomal dominant

HSAN – Hereditary Sensory and Autonomic Neuropathy

AR – Autosomal recessive

HSP – Hereditary Spastic Paraplegia

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8. Bird (Updated April 2016). Charcot-Marie-Tooth Neuropathy Type 2. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010.
9. Kurth (Updated February 2015). Hereditary Sensory and Autonomic Neuropathy Type II. . In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010.
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13. Roththier et al. (2010) *Am. J. Hum. Genet.* 87 (4):513-22 (PMID: 20920666).