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AUTONOMIC DYSFUNCTION (L.H. WEIMER, SECTION EDITOR)

Hereditary Sensory and Autonomic Neuropathies: Adding More to the Classification

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Abstract

Purpose of Review Hereditary sensory and autonomic neuropathies (HSANs) are a clinically heterogeneous group of inherited neuropathies featuring prominent sensory and autonomic involvement. Classification of HSAN is based on mode of inheritance, genetic mutation, and phenotype. In this review, we discuss the recent additions to this classification and the important updates on management with a special focus on the recently investigated disease-modifying agents.

Recent Findings In this past decade, three more HSAN types were added to the classification creating even more diversity in the genotype–phenotype. Clinical trials are underway for disease-modifying and symptomatic therapeutics, targeting mainly HSAN type III.

Summary Obtaining genetic testing leads to accurate diagnosis and guides focused management in the setting of such a diverse and continuously growing phenotype. It also increases the wealth of knowledge on HSAN pathophysiologies which paves the way toward development of targeted genetic treatments in the era of precision medicine.

Keywords Congenital insensitivity to pain · Familial dysautonomia · Hereditary sensory and autonomic neuropathies · *IKBKAP/ELP1* · L-Serine

Introduction

The hereditary sensory and autonomic neuropathies (HSANs) are a group of heterogeneous genetic disorders that predominantly feature slowly progressive loss of multimodal sensation and autonomic dysfunction. In general, the main pathology is variable involvement of the unmyelinated and small more than large myelinated peripheral nerve fibers resulting in diverse phenotypes. The first reports of HSANs date back to the mid-nineteenth century with familial neurotrophic plantar ulcerations presenting between the second and fifth decades of life as described by Nelaton [1]. By the 1970s, sensory deficits in distal lower limbs with painless ulcerations and fractures were described as presenting earlier in life in additional kinships [2]. This prompted further investigations into the underlying etiologies of the variable phenotypes, including genetic causes, guiding a classification system that initially recognized these neuropathies as hereditary sensory neuropathies (HSNs). The term evolved into HSANs as our understanding of the role of small nerve fibers in autonomic functions has developed [3]. The classification is based on the involved genetic mutation, inheritance pattern, and predominant clinical features [3, 4]. This now encompasses eight phenotypically diverse HSAN types (Table 1), of which three were added in this past decade. In this review, we provide detailed descriptions of these types with a special focus on diagnosis and management of such a heterogeneous disease.

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Classification, Genotypes, and Phenotypes

HSAN Type I

HSAN-I is considered the most common category of HSAN, with an autosomal dominant (AD) pattern of inheritance, exhibiting signs and symptoms classically in the second to fourth decades of life [5].

Table 1 Hereditary sensory and autonomic neuropathies (HSANs)

HSAN types and other names	Inheritance	Onset decade	Locus	Gene	Phenotype	Diagnostic abnormalities (NCS, QST, HT, autonomic testing)	Nerve and skin punch biopsy
HSAN-IA/HSN1	AD	2nd–4th	9q22.2	*SPTLC1*	Loss of pain/temperature sensation; lancinating pain; self-mutilation; ± sweat disturbance; distal weakness	Reduced CMAP and SNAP amplitudes; abnormal temperature threshold on QST; absent axon flare on HT; cardiovagal and cardiosympathetic impairment, absent distal QSART response; absent SSR	Distal small un/myelinated greater than proximal large fibers loss; absent or reduced epidermal nerve fibers in the distal with relative preservation in the thigh
HSAN-IB	AD	2nd	3p22–p24		+ GERD; cough		
HSAN-IC	AD	2nd	14q24.3	*SPTLC2*			
HSAN-ID	AD	2nd	14q22.1	*ATL1*	+ Trophic skin/nails; variable UMN		
HSAN-IE	AD	2nd	19p13.2	*DNMT1*	+ SNHL; early dementia		
HSAN-IF	AD	2nd	11q13.1	*ATL3*			
HSAN-IIA	AR	1st	12p13.3	*WNK1*	Loss of pressure/vibration > pain/temperature; impotence; impaired bladder function; areflexia	Absent SNAP; normal to reduced CMAP amplitudes; abnormal vibration and temperature thresholds on QST; mild axon flare on HT	Absent large myelinated fibers; mild loss of small un/myelinated fibers
HSAN-IIB	AR	Birth	5p15.1	*FAM134B*			
HSAN-IIC	AR	Birth	2q37	*KIF1A*			
HSAN-IID/CIP1	AR	Birth	2q24.3	*SCN9A*			
HSAN-III, familial dysautonomia, Riley–Day syndrome	AR	Birth	9q31	*IKBKAP/ELP1*	Loss of pain/temperature more than pressure/vibration; dysautonomia, vomiting crisis; absent lingual fungiform papillae; alacrima; absent reflexes; postural hypotension; hyperhidrosis	Reduced amplitudes of SNAPs; abnormal temperature and vibration QST; absent axon flare on HT; cardiovagal and cardiosympathetic impairment; orthostatic hypotension	Similar to HSAN-I
HSAN-IV, CIPA	AR	Birth	1q23.1	*NTRK1*	Global anhidrosis; hyperpyrexia; ID; insensitivity to pain; self-mutilation	Similar to HSAN-I	Similar to HSAN-I
HSAN-V	AR	Birth	1p13.2	*NGFβ*	Impaired deep pain and loss of pain/temperature > touch/vibration	Similar to HSAN-I with mixed axon flare on HT	Similar to HSAN-I
HSAN-VI	AR	Birth	6p12.1	*DST*	Severe dysautonomia; impaired pain/temperature > touch/vibration; self-mutilation; distal contractures	Similar to HSAN-I	Similar to HSAN-I
HSAN-VII, CIP2	AD	Birth	3p22.2	*SCN11A*	Hyperhidrosis; pruritis; self-mutilation, GI dysmotility	Similar to HSAN-I	None
HSAN-VIII, CIP3	AR	Birth	9q34.12	*PRDM12*	Loss of pain/temperature sensation; hypohidrosis; fevers; self-mutilation	Similar to HSAN-I with normal autonomic testing	Similar to HSAN-I

AD, autosomal dominant; AR, autosomal recessive; *ATL1*, Atlastin GTPase 1; CIP, congenital insensitivity to pain; CIPA, congenital insensitivity to pain with anhidrosis; CMAP, compound muscle action potential; *DNMT1*, DNA methyltransferase 1; *DST*, dystonin; *ELP1*, elongator complex protein 1; HT, histamine test; GERD, gastroesophageal reflux; GI, gastrointestinal; HSN, hereditary sensory neuropathy; ID, intellectual disability; *IKBKAP*, inhibitor of kappa light polypeptide enhancer in B cells–kinase complex associated protein; *KIF1A*, kinesin family member 1A; NCS, nerve conduction studies; *NGFβ*, nerve growth factor β; *NTRK1*, neurotrophic tyrosine kinase receptor type 1; QST, quantitative sensory testing; *RAB7*, RAS-associated protein RAB7; *SCN9A*, sodium voltage-gated channel alpha subunit 9; SNAP, sensory nerve action potential; SNHL, sensorineural hearing loss; *SPTLC1,* serine palmitoyletransferase long-chain base unit 1; SSR, sympathetic skin response; UMN, upper motor neuron; *WNK1*, With-No lysine kinase or lysine-deficient protein kinase

HSAN-IA

The first discovered genetic mutations were in the *SPTLC1* gene in four large Australian kindreds [6]. These matched phenotypes of the first mid-nineteenth century kinships described in French literature with painless, symmetric, distal ulcerations, and mutilating arthropathies due to loss of pain and temperature sensation, mixed with lancinating and burning pains [7–9]. There is only minimal, if any, distal motor, vibration, or proprioception involvement [7]. These clinical findings are due to reduced activity of serine palmitoyltransferase, a key enzyme in a rate-limiting step in sphingolipid synthesis. This causes neurotoxins (like deoxysphinganine) accumulation, sensory neuronal apoptosis, and subsequent loss of sensation [10]. This also leads to pupillary abnormalities, loss of corneal reflex and abrasions, deafness, restless legs, cramps, absent reflexes, Charcot joints, and a propensity to painless injuries of the tongue and limbs. Serious complications are progression to osteomyelitis, limb amputation, and death secondary to sepsis [11, 12].

Other HSAN-Is

Identification of subtle differences within and across kinships, along with further genetic studies and linkage analyses, led to sub-classification within HSAN-I. All are phenotypically similar to the prototypical HSAN-I, some with prominent additional unique characteristics. With knowing that mutations in *SPTLC1* led to the clinical phenotype of HSAN-IA, mutations in other serine palmitoyltransferase subunits were investigated [13]. Mutations in *SPTLC2*, a second subunit involved in sphingolipid synthesis, was identified as HSAN-IC, noted to have a clinically indistinguishable phenotype from HSAN-IA [13]. At the same time, no disease-associated sequences were identified in *SPTLC3* [13]. HSAN-IB has been characterized in two Australian families with strong history of chronic cough and gastroesophageal reflux disease (GERD) and localizes to chromosome 3p22–p24, with no culprit gene identified yet [14]. Mutations of *ATL1*, coding endoplasmic reticulum (ER) and axonal proteins, accounts for HSAN-ID, feature additional findings of trophic skin, nail changes, and variable upper motor neuron signs, primarily brisk reflexes [15]. Like *ATL1*, mutations in *ATL3* gene, essential in ER formation, result in a phenotype similar to HSAN-I without additional clear distinguishing features. It was studied in families of German and Spanish decent, and now is designated as HSAN-IF [16]. HSAN-IE is associated with mutations in *DNMT1*, coding a DNA methylation proteins, and exhibits prominent sensorineural hearing loss (SNHL) with early dementia initially noted on exome sequencing in American, Japanese, and European kindreds [17, 18].

HSAN Type II

Clinical Presentation

First described in Canadian population in 1973, patients presented at birth or early childhood with an autosomal recessive (AR) inheritance pattern [2]. In general, patients experience profound loss of pressure, proprioception and vibration sensation, areflexia, decreased corneal reflexes, and generalized hypotonia. This results in development of Charcot joints, scoliosis, bone dysplasia, corneal ulcers, delayed milestones, and painless injuries complicated by osteomyelitis and amputation [2]. Neonates commonly present with difficulty swallowing and feeding, weak gag reflex, and frequent apnea [19]. Taste is diminished due to hypotrophic lingual fungiform papillae [20]. Autonomic dysfunction is limited to episodic and patchy hyperhidrosis, delayed overflow tearing, and exaggerated response to parasympathomimetic agents [20]. Additionally, patients have variable intellectual disability, aphasia, and SNHL. Muscle strength remains relatively normal [19].

Genetics

The four identified mutations were reported in *WNK1*, *KIF1A*, *FAM134B*, and *SCN9A* genes. HSAN-IIA is caused by loss-of-function mutations of *WNK1* gene which is involved in regulating sodium and chloride ions fluxes and cell membrane excitability. It also regulates the expression of TRpV4, a cation channel involved in nociception, thus acting as a primary regulator of pain threshold in free nerve endings [21]. HSAN-IIB is due to mutations of *FAM134B* gene, which downregulates autophagy in the Golgi apparatus, leading to decreased survival of sensory and autonomic neurons [22]. Mutations in *FAM134B* also feature increased reflexes and mild non-progressive spastic paraplegia [22]. A third gene, *KIF1A* is involved in HSAN-IIC and its mutations cause disruption of axonal transport, and also present with spastic paraparesis [23]. Finally HSAN-IID, congenital insensitivity to pain type 1 (CIP1), is associated with loss-of-function mutations of *SCN9A*. This results in loss of Nav1.7, a voltage-gated sodium channel found in nociceptive networks and olfactory nerves, accounting for inability to perceive pain as well as hyposmia that was first reported in Japanese patients [24].

HSAN Type III

HSAN-III (Riley–Day syndrome), which is also termed familial dysautonomia (FD), was first reported by Riley and colleagues in 1949 in families from Ashkenazi Jewish ancestry following AR inheritance pattern [25, 26]. The founder population was estimated to be as little as 350 individuals who

migrated from the Pale of Settle region, between Poland, Byelorussia, and the Black and Baltic Seas in the 1500s [27]. HSAN-III is the most extensively studied HSAN. It often presents at birth with gradual onset and progressive course of loss of pain and temperature more than pressure and vibration sensations. Like other HSANs, there is considerable phenotypic variability. This has led to the generation of a set of common clinical criteria including pupillary hypersensitivity to parasympathomimetic agents with absence of emotional overflow tears (alacrima), lingual fungiform papillae, flare with intradermal histamine, and reflexes in an individual of Ashkenazi Jewish descent [19].

Epidemiology and Genetics

Before DNA diagnosis was available, carrier rate in Ashkenazi Jewish population was estimated to be 1 in 32, with incidence of 1:3600 live births [28]. The underlying biologic basis of HSAN-III was first identified in 2001 as a mutation of the *IKBKAP* or *ELP1* gene. The coded protein, IKK complex-associated protein (IKAP) or elongator complex protein 1 (ELP1), is involved in transcription and truncation of other proteins instrumental in the migration and motility of neural crest cells, preferentially affecting sensory and autonomic neurons [29, 30]. Approximately 99% of HSAN-III patients have been identified as homozygous for a particular splice-site mutation of intron 20, indicating a strong founder effect [26, 31]. The second missense mutation, affecting phosphorylation of IKAP/ELP1, has been identified in four unrelated patients with heterozygous major splice mutations. Another non-Jewish proline to leucine missense mutation in exon 26 was also identified in a heterozygous state [26, 31]. Today, many families with no known Jewish ancestry, including those who live in Central Mexico, only to be recognized through whole-exome sequencing show homozygous copies of the founder mutation [32]. Using molecular diagnosis, carrier rates have been cited from 1 in 25 to 1 in 42 with highest number of patients in North America (54%) and Israel (34%), but also South Africa, Argentina, Australia, Brazil, and Britain [33, 34]. To date, the population appears to be stable averaging three new recorded cases annually [32].

Pathology

The main pathological finding is loss of the non- and thinly myelinated peripheral nerve fibers that can be observed in peripheral nerve and skin punch biopsies. The dorsal root ganglia (DRG), spinal cord lateral root entry zones, and Lissauer's tracts are depleted of axons. Involvement of dorsal column myelinated axons occur with advancing age [35, 36]. Sympathetic ganglia and spinal cord preganglionic neurons are reduced in number [37]. Despite the decrease in sympathetic neurons, staining for dopamine precursor, tyrosine hydroxylase, is enhanced in the sympathetic ganglia [38]. Peripheral blood vessels demonstrate absent autonomic axons underscoring postural hypotension and exaggerated response to sympathomimetic agents [39, 40]. The neuronal populations in the parasympathetic nervous system show variable decrease, as can be seen in the ciliary ganglia [41]. Decreased neurons in the sphenopalatine ganglia explain alacrima and hypersensitivity of the lacrimal glands to methacholine [41, 42]. Central neuropathology shows compromised myelination with decrease in optic radiation and middle cerebral peduncle fractional anisotropy and decreased prefrontal cortex volume, consistent with the visual, gait, and neuropsychiatric impairments, respectively [43]. The current Natural History of Familial Dysautonomia study focuses on tracking the clinical and electrophysiological parameters of visual and gait impairment.

Clinical Presentation

Early in life, there is motor incoordination, hypotonia, feeding difficulties, increased secretions, vomiting, inappropriate temperature control, breath-holding spells, and insensitivity to hypoxemia. These result in delayed motor development, failure to thrive, gastroesophageal reflux, esophageal and intestinal dysmotility, recurrent aspiration pneumonia, and chronic lung disease [20, 44, 45].

Sensory neuropathy affects lower more than upper limbs sparing palms, soles, and genital areas [46]. The preferential involvement of small nerve fibers results in unrecognized burns, fractures, and inadvertent trauma to joints, causing Charcot joints and aseptic necrosis [47]. At the same time, sensitivity to visceral pain is preserved and can play a role in precipitating dysautonomic crisis [20]. Tendon reflexes are decreased to absent while vibration and proprioception eventually become abnormal leading to progressive sensory ataxia and imbalance [48]. Cranial nerve-wise, there is notable diminished corneal reflex, alacrima with subsequent corneal ulceration, optic atrophy, impaired saccades, and decreased sweet taste perception due to the lack of tongue fungiform papillae (Fig. 1) [20].

Another key feature of HSAN-III is the profound dysautonomia presenting as orthostatic hypotension with lack of compensatory tachycardia, supine hypertension, and dysautonomic crisis [20, 44]. The profound cardiovascular effects also include labile blood pressure (BP), bradyarrhythmia, and syncope [20, 44, 45]. Labile BP is due to baroreflex failure leading to failure to modulate sympathetic activity [49]. Cardiovascular instability and labile BP worsen with time leading to renal failure that is compounded by deficient vascular innervation and subsequent glomerulosclerosis [19].

Dysautonomic crisis is the most debilitating aspect of autonomic dysfunction. The underlying mechanism is likely

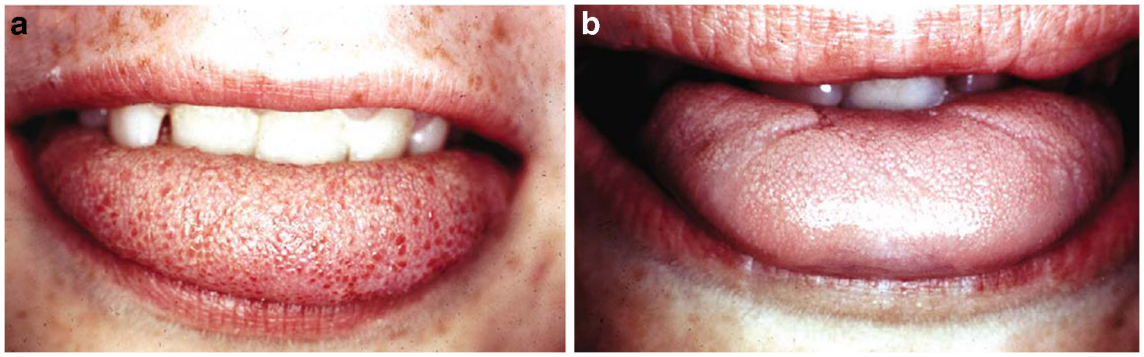

Fig. 1 (**a**) Normal tongue with highly vascularized fungiform papillae. (**b**) HSAN-III patient's tongue with absent fungiform papillae (reproduced from Axelrod and Gold-von Simson, *Orphanet Journal of Rare Diseases*, 2007, 2:39; https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-2-39) [20]

increased circulating levels of dopamine [46, 50, 51]. This leads to nausea, vomiting, hypertension, tachycardia, hyperhidrosis, skin blotching, and increased pulmonary and gastrointestinal secretions [19, 20, 44]. Crisis can occur daily with morning arousal, enteral feeds, and physical or emotional stress [20, 52].

Additional features of HSAN-III involve growth and development. Common physical appearance features micrognathia, flattening of the upper lip, and kyphoscoliosis which contributes to short stature and impacts ventilation capacity. The abnormal posture also contributes to the propensity to develop ulcers [20]. Hypotonia and autonomic instability delay developmental milestones and cause negativism, social withdrawal, and extreme irritability [19, 20, 44]. Intelligence generally falls within low normal ranges and learning disabilities are common [53]. Executive planning and organizational skills tend to be poor and hampered by anxiety, obsessive behavior, and concrete thinking [44, 53]. Sexual maturation is also often delayed, yet there is still normal reproductive functions [46].

HSAN Type IV

Congenital insensitivity to pain with anhidrosis (CIPA), or HSAN-IV, has an AR inheritance pattern manifesting at birth or early childhood. It presents with insensitivity to pain, self-mutilation, intellectual disability, and anhidrosis [47]. Hyperactivity and emotional lability are also common psychological manifestations [54]. Anhidrosis results in additional complications, including dystrophic hair and nails, hyperpyrexia, and febrile seizures [47]. Motor strength and reflexes are typically normal. Patients do not show signs of gastrointestinal or respiratory involvement [20].

HSAN-IV is due to over 40 loss-of-function mutations in the *NTRK1* gene, a kinase necessary for the autophosphorylation pathway which is instrumental in growth and survival of sympathetic, nociceptive sensory, and cholinergic neurons [20, 54]. In addition, it plays a role in immune system development and thus, loss of function leads to slow healing [54, 55].

HSAN Type V

HSAN-V follows an AR inheritance pattern with milder heterozygote phenotype variations and age of onset ranging from birth to as late as adulthood. It was initially identified in Swedish, and subsequently found in Arab and Japanese kinships with different mutations [39, 56–59]. HSAN-V is associated with *NGFβ* gene mutations. The gene binds with the *NTRK1* gene involved in HSAN-IV and is also involved with signaling apoptosis of nociceptive sensory neurons [57]. HSAN-V patients resemble HSAN-IV phenotype with loss of pain and thermal perception, Charcot joints, painless fractures, scoliosis, mouth lesions, and absent corneal reflexes. However, HSAN-V phenotype has less propensity to progress to auto-amputation, variable degrees of hyper- and hypohidrosis, and milder hyperactivity and cognitive delay [59, 60]. Patients have normal vision, taste, smell, motor strength, reflexes, autonomic function, light touch, proprioception, and vibration sensations. It is suggested that patients have a lack of deep pain from bones and joints which result in the lack of protective reflexes [57–59].

HSAN Type VI

Initially described in 2012 in an Ashkenazi Jewish family, HSAN-VI presented in three infants with severe autonomic dysfunction, psychomotor retardation, distal contractures, and early death. This was clinically suspected as being HSAN-III until it was found to be associated with a mutation of *DST* gene [61]. Additionally, infants in this family with homozygous truncating mutation showed absent tearing, blotched skin, feeding difficulties with gastrointestinal dysfunction, apnea, abnormal sweating, hyperpyrexia, and labile BP and heart rate [61]. On examination, these infants, and subsequently milder phenotypes with heterozygote missense mutations,

were noted to have absent fungiform papilla, corneal reflexes, and tendon reflexes with diminished pain and temperature more than touch and vibration sensations, self-mutilation, auto-amputation, hypotonia, distal contractures, and intrinsic foot muscle weakness [61, 62•].

DST is inherited in AR fashion and encodes dystonin which has neuronal, muscle, and skin isoforms, all of which contribute to cytoskeletal function [24]. *DST* knockout mouse showed prominent disorganization in the large myelinated sensory axons of dorsal columns and DRG, autonomic dysfunction with decreased size of sympathetic and ciliary ganglia, decreased fungiform papillae, and progressive limb contractures [63]. Given the potential for large variability in mutations of *DST* with multiple protein isoforms, additional studies are still needed to further understand difference and similarities between HSAN-III and HSAN-VI, which to date has shown striking overlap.

HSAN Type VII

HSAN-VII, another congenital insensitivity to pain (CIP2), was identified in 2013 with an AD inheritance pattern, like HSAN-I; however, patients presented at birth or early childhood and found to be due to gain-of-function mutations in the *SCN11A* gene [64]. *SCN11A* codes for a voltage-gated sodium channel 1.9 (NaV1.9) expressed in enteric plexus, nociceptive, and temperature sensory neurons [65]. The few patients and mouse models reported to date show notable decreased pain and temperature sensations, hyperhidrosis, significant pruritis, self-mutilation, delayed healing, Charcot joints, scoliosis, hypotonia, delayed motor development, and failure-to-thrive due to intestinal dysmotility and diarrhea [64, 66, 67••]. Patients also report exaggerated abdominal, perianal, or rectal paroxysmal pains that were reported with defecation or urination which have also been observed with *SCN9A* mutations in HSAN-IID [66]. On examination, pin prick caused mild pain but more pruritis, while cognition, cranial nerves, motor strength, reflexes, proprioception, vibration, and temperature sensations were intact [64, 67••].

HSAN Type VIII

HSAN-VIII is yet another AR congenital insensitivity to pain (CIP3) presenting at birth or early childhood in association with *PRDM12* gene mutations, involved in sensory nociceptor neurogenesis [68, 69•]. Again, the phenotype across mutations is consistent with loss of pain and temperature sensations, painless injuries, self-mutilation, dental trauma, osteomyelitis, anhidrosis, hyperpyrexia, absent corneal reflexes, and alacrima. Vibration, proprioception, and cognition are normal. Autonomic functions are mostly preserved [68].

Differential Diagnosis

It is important to consider more common and uncommon causes of severe sensory neuropathy especially if associated with foot ulcers when no clear family history is established. These include diabetic neuropathy, leprosy, and tabes dorsalis. Other non-neuropathic conditions like peripheral vascular disease and syringomyelia (featuring dissociated sensory loss) should be included in the differential diagnosis. These acquired disorders can be considered in sporadic cases and older patients. HSAN is also sometimes hard to differentiate from other neuropathies with known inheritance pattern posing an important indication of genetic testing. Except for the absence of lancinating pain, CMT-IIB due to *RAB7* mutation is clinically indistinguishable from HSAN-IA [70]. HSAN-I also needs to be differentiated from erythromelalgia, which is an AD disorder caused by gain-of-function mutations of *SCN9A* and enhanced activity of NaV1.7 channels leading to episodic attacks of symmetric distal burning pain, erythema, warmth, and swelling, precipitated by heat and exercise and relieved by rest, elevation, and cooling [71]. Fabry's disease is X-linked alpha-galactosidase-A deficiency affecting males as well as most female carriers. The lower abdominal angiokeratomas, corneal dystrophy, and indeed the renal and cerebrovascular involvement help differentiate it from HSAN. Hereditary transthyretin amyloidosis (hATTR) is an AD disorder often presenting in adulthood with a more progressive neuropathy. It is often accompanied by cardiac, renal, gastrointestinal, ocular manifestations, and cachexia. Differentiating HSAN from the last two conditions through genetic testing is imperative as we now have genetic-based treatments for these other disorders.

Diagnostic Tests

Although there are phenotypic variabilities across HSAN types, there are key unifying characteristics which set them apart from other disease processes and led to the underlying classification system. A predominant feature is early loss of pain and temperature sensations. This can be more objectively demonstrated by quantitative sensory testing (QST) with abnormalities in temperature and pain more than vibration and touch thresholds [57, 58, 62•]. However, the test is not available in the majority of medical centers and is still not reimbursable. Intradermal histamine administration fails to elicit a normal axon flare response. This is due to inability to mediate arteriolar dilation because of the antidromic conduction failure associated with small nerve fiber loss, and is characteristic of all HSANs except HSAN-V which may show mixed results [19, 58, 61]. There is a less prominent, or a later onset, loss of large myelinated fibers' function. This is highlighted in electrodiagnostic studies, typically showing minimal abnormalities, although significant heterogeneity has been noted

[12, 62•, 72]. Nerve conduction studies (NCSs) can demonstrate a length-dependent axonal, sensorimotor polyneuropathy with distal greater than proximal reduction in sensory nerve action potential (SNAP) more than compound motor action potential (CMAP) amplitudes, normal distal latencies, and conduction velocities [12, 62•, 72].

Autonomic involvement is most prominent in HSAN-I, III, IV, and VI [39, 49, 73, 74]. Autonomic testing will detect autonomic involvement by looking at heart rate responses to deep breathing and Valsalva maneuver, BP response to Valsalva maneuver, tilt-table testing, quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test (TST), and sympathetic skin response (SSR) [74]. QSART can demonstrate postganglionic sympathetic cholinergic dysfunction. In a cohort of 25 families with HSAN-I, abnormalities in autonomic testing were found in 18 of the 20 index patients who underwent formal autonomic testing. The most common abnormality was reduced sweat output in QSART (13 patients), which was distal in 10 patients [73]. TST often shows distal anhidrosis or hypohidrosis, but also can be patchy or diffuse [73–75]. Sympathetic adrenergic impairment is typically mild and presents with absent late phase II of the BP response to Valsalva maneuver due to deficient vasoconstrictor response. Cardiovagal impairment manifests with decreased heart rate responses to deep breathing, and less often, to Valsalva maneuver. Postural hypotension on routine vital signs or tilt-table testing is relatively common in HSAN-III cases. There is often decreased to absent SSR [49, 73, 74].

Skin punch biopsy of the distal leg is also supportive of small fiber neuropathy showing reduced ankle epidermal nerve fiber density (ENFD) with its relative preservation in the thigh, except with the non-length dependence noted in HSAN-III [62•]. HSAN-VI skin punch biopsy also showed low numbers of Meissner corpuscles and absent nerve fibers adjacent to sweat glands [62•]. Sural nerve biopsy shows loss of unmyelinated and small myelinated more than large myelinated fibers, with axonal degeneration, and regeneration clusters [12, 62•, 76].

There are some additional exceptions to the above findings. HSAN-II is unique in that there is a primary loss of pressure and vibration more than pain and temperature sensations [2, 76], leading to abnormalities in vibration rather than heat thresholds in QST [3]. NCS demonstrate absent SNAPs and normal to reduced CMAP amplitudes [2, 76]. Sural nerve biopsy shows a marked decrease in large and small myelinated fibers, and mild loss of unmyelinated fibers [3]. HSAN-V cases show normal NCS, autonomic testing, and SSR, otherwise demonstrate similar findings, notable for more severe reduction of unmyelinated and small myelinated nerve fibers in sural nerve biopsy [57, 58, 77]. Sural nerve biopsy did not show any abnormalities in HSAN-VII as reported in a limited number of studies [64]. Although the aforementioned findings sometimes help raise the clinical suspicion of HSAN or even one of its types, definitive diagnosis through DNA analysis remains essential as most HSANs are indistinguishable both clinically and electrodiagnostically [20].

Treatment

Symptomatic Management

Treatment remains primarily supportive at this point across all HSANs [19, 78–80]. Neuropathic pain medications like pregabalin or gabapentin can improve burning, lancinating pains, and symptoms of restless legs syndrome. Carbidopa, an inhibitor of DOPA-decarboxylase, blocks dopamine synthesis outside the brain and is effective in dysautonomic crisis [51, 81]. In a randomized, double-blind, placebo-controlled study, it was proven to be superior to benzodiazepines, central sympatholytic agents, and other dopamine antagonist antiemetics, like metoclopramide which cause sedation [51]. Further studies are needed to identify optimal dosing and further understand the interaction with norepinephrine synthesis and the antihypertensive effect with increasing dose [78]. A current double-blind randomized clinical trial is addressing these three aims in HSAN-III patients with unstable BP. For now, the hypertension seen with dysautonomic crisis can be treated with α_2-adrenergic agonists like clonidine and intranasal dexmedetomidine or diazepam [82, 83, 84•].

Outside of dysautonomic crisis, fluctuations in BP and orthostatic hypotension require elevation of head of the bed to avoid supine hypertension, while sufficient water and salt intake, compression devices, exercise, and adrenergic agents like midodrine and droxidopa can improve postural hypotension [82, 85]. Counseling is needed to avoid overheating with the use of cold pack, regular rest, and staying in cool areas for those with prominent anhidrosis, especially in HSAN-IV [74].

Multidisciplinary Management

In addition to the neurologist, consultations from podiatrists, dermatologists, physical and occupational therapists, prosthetics, and orthopedic surgeons are needed for optimal skin and limb care. They can provide guidance on foot care including daily examinations and cleaning, protective footwear with well-fitted shoes, splinting, stretching, guided exercise programs, and early treatment of injuries [20, 86, 87]. Gastroenterology can be instrumental in assisting with vomiting, GERD, and dysphagia as this can lead to dehydration and aspiration, and consideration for gastrostomy tube and fundoplication [82, 83]. Recurrent aspiration may lead to chronic lung disease requiring involvement of pulmonology and sleep medicine to evaluate the need to oxygen and/or continuous positive airway pressure [20, 87].

Additional supportive measures should not be overlooked. For those with tongue ulceration, smoothing incisors is preferable to dental extraction [88]. Artificial tears, moisture chamber glasses, scleral lenses, tarsorrhaphy, and cautery of tear ducts should be evaluated for by ophthalmologist to protect anesthetic corneas and increase baseline moisture [74]. Those with early cognitive impairment may benefit from early special education school programs and treatment of underlying anxiety and depression [89]. Genetics are an invaluable resource for identifying the underlying genetic mutation, providing guidance for future implications of the diagnosis, and family planning [20].

Clinical Trials of Disease-Modifying Agents

HSAN-III is the first HSAN for which promising interventions are on the horizon. It is speculated that therapeutic agents could be developed to raise the wild-type protein expression of the mutated gene, thus slowing progression and improving symptoms [90]. Tocotrienol, epigallocatechin gallate, phosphatidylserine, and kinetin have been shown to modify genetic expression in vitro [80, 90–93]. The initial tocotrienol study reported increased *IKBKAP/ELP1* expression [90]; however, this was not replicated in subsequent studies [91, 94]. Phosphatidylserine is an over-the-counter compound that was also shown to increase *IKBKAP/ELP1* expression. However, the clinical correlates of elevated IKAP/ELP1 levels are still unknown and a placebo-controlled trial is still underway [32, 93]. Epigallocatechin gallate and kinetin modify mRNA splicing; however, effectiveness of epigallocatechin gallate was only modest compared to kinetin [80, 90, 91]. Kinetin demonstrated the ability to both correct splicing defect in olfactory stem cells from HSAN-III subjects and raise wild-type mRNA *IKBKAP/ELP1*in peripheral leukocytes [95–97]. A clinical trial of kinetin is underway; however, small sample size, lack of control group, and subject drop-out due to nausea are expected obstacles [32].

On the HSAN-I front, mutations are known to reduce the affinity of serine palmitoyltransferase for L-serine. This results in formation of toxic lipid metabolites, including deoxysphinganine, that accumulate in peripheral nerves and affect neurite growth in the DRG [98]. High dose L-serine was found to reduce these toxic metabolites in human and mice which paralleled clinical improvement in motor function and increased myelinated fibers [99]. A randomized, placebo-controlled trial of high-dose oral L-serine supplementation with an open-label extension showed that high-dose L-serine was safe. It was also associated with reduction in the CMT Neuropathy Score and increase in the ankle site ENFD. These two outcomes significantly correlated with the reduction in deoxysphinganine levels [100••].

Conclusion

Although currently supportive therapies are still the mainstay of treatment, performing genetic testing helps establish the accurate diagnosis of such a heterogeneous and continuously expanding phenotype. It also helps differentiate HSANs from other treatable hereditary neuropathies with prominent sensory and autonomic features like those encountered in Fabry's disease and hATTR amyloidosis. This will allow appropriate genetic counseling and focused therapeutic interventions to decrease morbidity and mortality. In the era of precision medicine, compiling wealth of knowledge on the genetics and pathophysiologies of different HSANs paves the way toward development of disease-modifying treatments. These treatments can be simply an oral supplement as in the case of L-serine in HSAN-1.

Compliance with Ethical Standards

Conflict of Interest M.K. reports personal fees from Akcea Therapeutics, outside the submitted work. C.S. declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Nelaton M. Affection singuliere des os du pied. Gaz Hop Civ Milit 1852;4:13–12.
2. Ota M, Ellefson RD, Lambert EH, Dyck PJ. Hereditary sensory neuropathy, type II. Clinical, electrophysiologic, histologic, and biochemical studies of a Quebec kinship. Arch Neurol. 1973;29:23–37.
3. Dyck PJ. Neuronal atrophy and degeneration predominantly affecting peripheral sensory and autonomic neurons. In: Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF, editors. Peripheral neuropathy. 3rd ed. Philadelphia: WB Saunders Co; 1993. p. 1065–93.
4. 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. https://doi.org/10.1097/01.wco.0000245370.82317.f6.
5. Houlden H, Blake J, Reilly MM. Hereditary sensory neuropathies. Curr Opin Neurol. 2004;17:569–77.
6. Nicholson GA, Dawkins JL, Blair IP, Kennerson ML, Gordon MJ, Cherryson AK, et al. The gene for hereditary sensory neuropathy type I (HSN-I) maps to chromosome 9q22.1-q22.3. Nat Genet. 1996;13:101–4. https://doi.org/10.1038/ng0596-101.
7. Denny-Brown D. Hereditary sensory radicular neuropathy. J Neurol Neurosurg Psychiatry. 1951;14:237–52.

8. Leplat M, editor. Dictionnaire de medecine en 30 volumes 1846; Paris.
9. Nelaton M, editor. Affection singuliere des os du pied. Gazette des Hopitaux Civils et Militaires 1852; Paris.
10. Bejaoui K, Uchida Y, Yasuda S, Ho M, Nishijima M, Brown RH Jr, et al. Hereditary sensory neuropathy type 1 mutations confer dominant negative effects on serine palmitoyltransferase, critical for sphingolipid synthesis. J Clin Invest. 2002;110:1301–8. https://doi.org/10.1172/JCI16450.
11. Ho KW, Jerath NU. V144D mutation of *SPTLC1* can present with both painful and painless phenotypes in hereditary sensory and autonomic neuropathies type I. Case Reports in Genetics. 2018;2018:1898151. https://doi.org/10.1155/2018/1898151.
12. Houlden H, King R, Blake J, Groves M, Love S, Woodward C, et al. Clinical, pathological and genetic characterization of hereditary sensory and autonomic neuropathy type 1 (HSAN I). Brain. 2006;129:411–25. https://doi.org/10.1093/brain/awh712.
13. Rotthier A, Auer-Grumbach M, Janssens K, Baets J, Penno A, Almeida-Souza L, et al. Mutations in the *SPTLC2* subunit of serine palmitoyltransferase cause hereditary sensory and autonomic neuropathy type I. Am J Hum Genet. 2010;87:513–22. https://doi.org/10.1016/j.ajhg.2010.09.010.
14. Spring PJ, Kok C, Nicholson GA, Ing AJ, Spies JM, Bassett ML, et al. Autosomal dominant hereditary sensory neuropathy with chronic cough and gastro-oesophageal reflux: clinical features in two families linked to chromosome 3p22-p24. Brain. 2005;128:2797–810. https://doi.org/10.1093/brain/awh653.
15. Guelly C, Zhu PP, Leonardis L, Papic L, Zidar J, Schabhuttl M, et al. Targeted high-throughput sequencing identifies mutations in atlastin-1 as a cause of hereditary sensory neuropathy type I. Am J Hum Genet. 2011;88:99–105. https://doi.org/10.1016/j.ajhg.2010.12.003.
16. Kornak U, Mademan I, Schinke M, Voigt M, Krawitz P, Hecht J, et al. Sensory neuropathy with bone destruction due to a mutation in the membrane-shaping atlastin GTPase 3. Brain. 2014;137:683–92. https://doi.org/10.1093/brain/awt357.
17. Zheng W, Yan Z, He R, Huang Y, Lin A, Huang W, et al. Identification of a novel *DNMT1* mutation in a Chinese patient with hereditary sensory and autonomic neuropathy type IE. BMC Neurol. 2018;18:174. https://doi.org/10.1186/s12883-018-1177-2.
18. Klein CJ, Botuyan MV, Wu Y, Ward CJ, Nicholson GA, Hammans S, et al. Mutations in *DNMT1* cause hereditary sensory neuropathy with dementia and hearing loss. Nat Genet. 2011;43:595–600. https://doi.org/10.1038/ng.830.
19. Axelrod FB. Hereditary sensory and autonomic neuropathies. Familial dysautonomia and other HSANs. Clin Auton Res. 2002;12(Suppl 1):I2–14.
20. Axelrod FB, Gold-von Simson G. Hereditary sensory and autonomic neuropathies: types II, III, and IV. Orphanet J Rare Dis. 2007;2:39. https://doi.org/10.1186/1750-1172-2-39.
21. Shekarabi M, Girard N, Riviere JB, Dion P, Houle M, Toulouse A, et al. Mutations in the nervous system—specific HSN2 exon of *WNK1* cause hereditary sensory neuropathy type II. J Clin Invest. 2008;118:2496–505. https://doi.org/10.1172/JCI34088.
22. Wakil SM, Monies D, Hagos S, Al-Ajlan F, Finsterer J, Al Qahtani A, et al. Exome sequencing: mutilating sensory neuropathy with spastic paraplegia due to a mutation in *FAM134B* gene. Case Reports in Genetics. 2018;2018:9468049. https://doi.org/10.1155/2018/9468049.
23. Erlich Y, Edvardson S, Hodges E, Zenvirt S, Thekkat P, Shaag A, et al. Exome sequencing and disease-network analysis of a single family implicate a mutation in *KIF1A* in hereditary spastic paraparesis. Genome Res. 2011;21:658–64. https://doi.org/10.1101/gr.117143.110.
24. Yuan J, Matsuura E, Higuchi Y, Hashiguchi A, Nakamura T, Nozuma S, et al. Hereditary sensory and autonomic neuropathy type IID caused by an *SCN9A* mutation. Neurology. 2013;80:1641–9. https://doi.org/10.1212/WNL.0b013e3182904fdd.
25. Riley CM, Day RL, et al. Central autonomic dysfunction with defective lacrimation; report of five cases. Pediatrics. 1949;3:468–78.
26. Slaugenhaupt SA, Blumenfeld A, Gill SP, Leyne M, Mull J, Cuajungco MP, et al. Tissue-specific expression of a splicing mutation in the *IKBKAP* gene causes familial dysautonomia. Am J Hum Genet. 2001;68:598–605.
27. Carmi S, Hui KY, Kochav E, Liu X, Xue J, Grady F, et al. Sequencing an Ashkenazi reference panel supports population-targeted personal genomics and illuminates Jewish and European origins. Nat Commun. 2014;5:4835. https://doi.org/10.1038/ncomms5835.
28. Maayan C, Kaplan E, Shachar S, Peleg O, Godfrey S. Incidence of familial dysautonomia in Israel 1977–1981. Clin Genet. 1987;32:106–8.
29. Close P, Hawkes N, Cornez I, Creppe C, Lambert CA, Rogister B, et al. Transcription impairment and cell migration defects in elongator-depleted cells: implication for familial dysautonomia. Mol Cell. 2006;22:521–31. https://doi.org/10.1016/j.molcel.2006.04.017.
30. Creppe C, Malinouskaya L, Volvert ML, Gillard M, Close P, Malaise O, et al. Elongator controls the migration and differentiation of cortical neurons through acetylation of alpha-tubulin. Cell. 2009;136:551–64. https://doi.org/10.1016/j.cell.2008.11.043.
31. Anderson SL, Coli R, Daly IW, Kichula EA, Rork MJ, Volpi SA, et al. Familial dysautonomia is caused by mutations of the *IKAP* gene. Am J Hum Genet. 2001;68:753–8. https://doi.org/10.1086/318808.
32. Norcliffe-Kaufmann L, Slaugenhaupt SA, Kaufmann H. Familial dysautonomia: history, genotype, phenotype and translational research. Prog Neurobiol. 2017;152:131–48. https://doi.org/10.1016/j.pneurobio.2016.06.003.
33. Dong J, Edelmann L, Bajwa AM, Kornreich R, Desnick RJ. Familial dysautonomia: detection of the *IKBKAP* IVS20(+6T → C) and R696P mutations and frequencies among Ashkenazi Jews. Am J Med Genet. 2002;110:253–7. https://doi.org/10.1002/ajmg.10450.
34. Lehavi O, Aizenstein O, Bercovich D, Pavzner D, Shomrat R, Orr-Urtreger A, et al. Screening for familial dysautonomia in Israel: evidence for higher carrier rate among Polish Ashkenazi Jews. Genet Test. 2003;7:139–42. https://doi.org/10.1089/109065703322146830.
35. Dyck PJ, Kawamura Y, Low PA, Shimono M, Solovy JS. The number and sizes of reconstructed peripheral autonomic, sensory and motor neurons in a case or dysautonomia. J Neuropathol Exp Neurol. 1978;37:741–55.
36. Axelrod FB, Iyer K, Fish I, Pearson J, Sein ME, Spielholz N. Progressive sensory loss in familial dysautonomia. Pediatrics. 1981;67:517–22.
37. Pearson J, Pytel BA. Quantitative studies of sympathetic ganglia and spinal cord intermedio-lateral gray columns in familial dysautonomia. J Neurol Sci. 1978;39:47–59.
38. Pearson J, Brandeis L, Goldstein M. Tyrosine hydroxylase immunoreactivity in familial dysautonomia. Science. 1979;206:71–2.
39. Bickel A, Axelrod FB, Schmelz M, Marthol H, Hilz MJ. Dermal microdialysis provides evidence for hypersensitivity to noradrenaline in patients with familial dysautonomia. J Neurol Neurosurg Psychiatry. 2002;73:299–302.
40. Goldstein DS, Eldadah B, Sharabi Y, Axelrod FB. Cardiac sympathetic hypo-innervation in familial dysautonomia. Clin Auton Res. 2008;18:115–9. https://doi.org/10.1007/s10286-008-0464-1.
41. Pearson J, Pytel B. Quantitative studies of ciliary and sphenopalatine ganglia in familial dysautonomia. J Neurol Sci. 1978;39:123–30.

42. Goadsby PJ. Sphenopalatine ganglion stimulation increases regional cerebral blood flow independent of glucose utilization in the cat. Brain Res. 1990;506:145–8.
43. Axelrod FB, Hilz MJ, Berlin D, Yau PL, Javier D, Sweat V, et al. Neuroimaging supports central pathology in familial dysautonomia. J Neurol. 2010;257:198–206. https://doi.org/10.1007/s00415-009-5293-1.
44. Axelrod FB. Familial dysautonomia. Muscle Nerve. 2004;29:352–63. https://doi.org/10.1002/mus.10499.
45. Bernardi L, Hilz M, Stemper B, Passino C, Welsch G, Axelrod FB. Respiratory and cerebrovascular responses to hypoxia and hypercapnia in familial dysautonomia. Am J Respir Crit Care Med. 2003;167:141–9. https://doi.org/10.1164/rccm.200207-677OC.
46. Axelrod FB, Nachtigal R, Dancis J. Familial dysautonomia: diagnosis, pathogenesis and management. Adv Pediatr Infect Dis. 1974;21:75–96.
47. Hilz MJ, Stemper B, Axelrod FB. Sympathetic skin response differentiates hereditary sensory autonomic neuropathies III and IV. Neurology. 1999;52:1652–7.
48. Macefield VG, Norcliffe-Kaufmann L, Axelrod FB, Kaufmann H. Cardiac-locked bursts of muscle sympathetic nerve activity are absent in familial dysautonomia. J Physiol. 2013;591:689–700. https://doi.org/10.1113/jphysiol.2012.246264.
49. Norcliffe-Kaufmann L, Axelrod F, Kaufmann H. Afferent baroreflex failure in familial dysautonomia. Neurology. 2010;75:1904–11. https://doi.org/10.1212/WNL.0b013e3181feb283.
50. Norcliffe-Kaufmann L, Kaufmann H. Familial dysautonomia (Riley-Day syndrome): when baroreceptor feedback fails. Auton Neurosci. 2012;172:26–30. https://doi.org/10.1016/j.autneu.2012.10.012.
51. Norcliffe-Kaufmann L, Martinez J, Axelrod F, Kaufmann H. Hyperdopaminergic crises in familial dysautonomia: a randomized trial of carbidopa. Neurology. 2013;80:1611–7. https://doi.org/10.1212/WNL.0b013e31828f18f0.
52. Axelrod FB, Zupanc M, Hilz MJ, Kramer EL. Ictal SPECT during autonomic crisis in familial dysautonomia. Neurology. 2000;55:122–5.
53. Clayson D, Welton W, Axelrod FB. Personality development and familial dysautonomia. Pediatrics. 1980;65(2):269–74.
54. Indo Y, Tsuruta M, Hayashida Y, Karim MA, Ohta K, Kawano T, et al. Mutations in the *TRKA/NGF* receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet. 1996;13:485–8. https://doi.org/10.1038/ng0896-485.
55. Rekhtman Y, Bomback AS, Nash MA, Cohen SD, Matalon A, Jan DM, et al. Renal transplantation in familial dysautonomia: report of two cases and review of the literature. Clin J Am Soc Nephrol. 2010;5:1676–80. https://doi.org/10.2215/CJN.01750210.
56. Low PA, Burke WJ, McLeod JG. Congenital sensory neuropathy with selective loss of small myelinated fibers. Ann Neurol. 1978;3:179–82. https://doi.org/10.1002/ana.410030215.
57. Einarsdottir E, Carlsson A, Minde J, Toolanen G, Svensson O, Solders G, et al. A mutation in the nerve growth factor beta gene (*NGFβ*) causes loss of pain perception. Hum Mol Genet. 2004;13:799–805. https://doi.org/10.1093/hmg/ddh096.
58. Minde J, Toolanen G, Andersson T, Nennesmo I, Remahl IN, Svensson O, et al. Familial insensitivity to pain (HSAN V) and a mutation in the *NGFβ* gene. A neurophysiological and pathological study. Muscle Nerve. 2004;30:752–60. https://doi.org/10.1002/mus.20172.
59. Carvalho OP, Thornton GK, Hertecant J, Houlden H, Nicholas AK, Cox JJ, et al. A novel *NGF* mutation clarifies the molecular mechanism and extends the phenotypic spectrum of the HSAN5 neuropathy. J Med Genet. 2011;48:131–5. https://doi.org/10.1136/jmg.2010.081455.
60. Minde J, Svensson O, Holmberg M, Solders G, Toolanen G. Orthopedic aspects of familial insensitivity to pain due to a novel nerve growth factor beta mutation. Acta Orthop. 2006;77:198–202. https://doi.org/10.1080/17453670610045911.
61. Edvardson S, Cinnamon Y, Jalas C, Shaag A, Maayan C, Axelrod FB, et al. Hereditary sensory autonomic neuropathy caused by a mutation in *dystonin*. Ann Neurol. 2012;71:569–72. https://doi.org/10.1002/ana.23524.
62.• Manganelli F, Parisi S, Nolano M, Tao F, Paladino S, Pisciotta C, et al. Novel mutations in *dystonin* provide clues to the pathomechanisms of HSAN-VI. Neurology. 2017;88:2132–40. https://doi.org/10.1212/WNL.0000000000003992 **The authors described another HSAN-VI family harboring two novel heterozygous mutations of *DST* expanding the phenotype to include a nonlethal and non-syndromic form due to a different involved isoform of dystonin other than the one Evardson et al. described in 2012**.
63. Ichikawa H, Terayama R, Yamaai T, De Repentigny Y, Kothary R, Sugimoto T. Dystonin deficiency reduces taste buds and fungiform papillae in the anterior part of the tongue. Brain Res. 2007;1129:142–6. https://doi.org/10.1016/j.brainres.2006.04.044.
64. Leipold E, Liebmann L, Korenke GC, Heinrich T, Giesselmann S, Baets J, et al. A de novo gain-of-function mutation in *SCN11A* causes loss of pain perception. Nat Genet. 2013;45:1399–404. https://doi.org/10.1038/ng.2767.
65. Cummins TR, Dib-Hajj SD, Black JA, Akopian AN, Wood JN, Waxman SG. A novel persistent tetrodotoxin-resistant sodium current in SNS-null and wild-type small primary sensory neurons. J Neurosci. 1999;19:RC43.
66. Woods CG, Babiker MO, Horrocks I, Tolmie J, Kurth I. The phenotype of congenital insensitivity to pain due to the *NaV1.9* variant p.L811P. Eur J Hum Genet. 2015;23:1434. https://doi.org/10.1038/ejhg.2015.163.
67.•• Salvatierra J, Diaz-Bustamante M, Meixiong J, Tierney E, Dong X, Bosmans F. A disease mutation reveals a role for *NaV1.9* in acute itch. J Clin Invest. 2018;128:5434–47. https://doi.org/10.1172/JCI122481 **The authors studied the role of *$Na_V1.9$* in itching by using a $Na_V1.9^{-/-}$ and $Na_V1.9^{L799P/WT}$ mouse models. In the latter, pruritogens altered action potential parameters. $Na_V1.9^{-/-}$ mice exhibited reduction in scratching behavior in response to pruritogens, whereas $Na_V1.9^{L799P/WT}$ mice had increased spontaneous scratching**.
68. Chen YC, Auer-Grumbach M, Matsukawa S, Zitzelsberger M, Themistocleous AC, Strom TM, et al. Transcriptional regulator *PRDM12* is essential for human pain perception. Nat Genet. 2015;47:803–8. https://doi.org/10.1038/ng.3308.
69.• Zhang S, Malik Sharif S, Chen YC, Valente EM, Ahmed M, Sheridan E, et al. Clinical features for diagnosis and management of patients with *PRDM12* congenital insensitivity to pain. J Med Genet. 2016;53:533–5. https://doi.org/10.1136/jmedgenet-2015-103646 **The authors provide a thorough description of the phenotype and natural history of HSAN-VIII in five cases of *PRDM12* mutations following the initial description in 2015 by Chen et al.**
70. Auer-Grumbach M, De Jonghe P, Wagner K, Verhoeven K, Hartung HP, Timmerman V. Phenotype–genotype correlations in a CMT2B family with refined 3q13–q22 locus. Neurology. 2000;55:1552–7.
71. Schuster R, Stewart D, Schuster L, Greaney G, Waxman K. Preoperative oral rofecoxib and postoperative pain in patients after laparoscopic cholecystectomy: a prospective, randomized, double-blinded, placebo-controlled trial. Am Surg. 2005;71:827–9.
72. Auer-Grumbach M, De Jonghe P, Verhoeven K, Timmerman V, Wagner K, Hartung HP, et al. Autosomal dominant inherited neuropathies with prominent sensory loss and mutilations: a review. Arch Neurol. 2003;60:329–34.

73. Mauermann MLaK, C. J. Hereditary sensory and autonomic neuropathies and miscellaneous inherited neuropathies with autonomic involvement. In: Low PA and Benarroch EE, editors. Clinical autonomic disorders. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2008: 468–481.
74. Axelrod FB KH. Hereditary Sensory and Autonomic Neuropathies. In: Basil Darras H. Royden Jones JMRDDV, editor. Neuromuscular disorders of infancy, childhood, and adolescence. 2nd ed.: Elsevier; 2015.:340–353.
75. Nolano M, Crisci C, Santoro L, Barbieri F, Casale R, Kennedy WR, et al. Absent innervation of skin and sweat glands in congenital insensitivity to pain with anhidrosis. Clin Neurophysiol. 2000;111:1596–601.
76. Dyck PJ. Histologic measurements and fine structure of biopsied sural nerve: normal, and in peroneal muscular atrophy, hypertrophic neuropathy, and congenital sensory neuropathy. Mayo Clin Proc. 1966;41:742–74.
77. Minde J, Andersson T, Fulford M, Aguirre M, Nennesmo I, Remahl IN, et al. A novel *NGFβ* point mutation: a phenotype study of heterozygous patients. J Neurol Neurosurg Psychiatry. 2009;80:188–95. https://doi.org/10.1136/jnnp.2007.136051.
78. Norcliffe-Kaufmann L, Axelrod FB, Kaufmann H. Developmental abnormalities, blood pressure variability and renal disease in Riley Day syndrome. J Hum Hypertens. 2013;27:51–5. https://doi.org/10.1038/jhh.2011.107.
79. Axelrod FB, Liebes L, Gold-Von Simson G, Mendoza S, Mull J, Leyne M, et al. Kinetin improves *IKBKAP* mRNA splicing in patients with familial dysautonomia. Pediatr Res. 2011;70:480–3. https://doi.org/10.1203/PDR.0b013e31822e1825.
80. Slaugenhaupt SA, Mull J, Leyne M, Cuajungco MP, Gill SP, Hims MM, et al. Rescue of a human mRNA splicing defect by the plant cytokinin kinetin. Hum Mol Genet. 2004;13:429–36. https://doi.org/10.1093/hmg/ddh046.
81. Axelrod FB, Berlin D. Pregabalin: a new approach to treatment of the dysautonomic crisis. Pediatrics. 2009;124:743–6. https://doi.org/10.1542/peds.2008-3318.
82. Axelrod FB. Familial dysautonomia: a review of the current pharmacological treatments. Expert Opin Pharmacother. 2005;6:561–7. https://doi.org/10.1517/14656566.6.4.561.
83. Axelrod FB M. Familial dysautonomia. 17th ed. Gellis and Kagen's current pediatric therapy. 2002.
84.• Spalink CL, Barnes E, Palma JA, Norcliffe-Kaufmann L, Kaufmann H. Intranasal dexmedetomidine for adrenergic crisis in familial dysautonomia. Clin Auton Res. 2017;27:279–82. https://doi.org/10.1007/s10286-017-0442-6 **The authors reported in this pilot study that Intranasal dexmedetomidine is safe and feasible in acute treatment of adrenergic crisis in patients with HSAN-III**.
85. Axelrod FB, Goldberg JD, Rolnitzky L, Mull J, Mann SP, Gold von Simson G, et al. Fludrocortisone in patients with familial dysautonomia—assessing effect on clinical parameters and gene expression. Clin Auton Res. 2005;15:284–91. https://doi.org/10.1007/s10286-005-0288-1.
86. Auer-Grumbach M. Hereditary sensory neuropathy type I. Orphanet J Rare Dis. 2008;3:7. https://doi.org/10.1186/1750-1172-3-7.
87. Kazachkov M, Palma JA, Norcliffe-Kaufmann L, Bar-Aluma BE, Spalink CL, Barnes EP, et al. Respiratory care in familial dysautonomia: systematic review and expert consensus recommendations. Respir Med. 2018;141:37–46. https://doi.org/10.1016/j.rmed.2018.06.017.
88. Mass E. A review of the oro-dento-facial characteristics of hereditary sensory and autonomic neuropathy type III (familial dysautonomia). Spec Care Dentist. 2012;32:15–20. https://doi.org/10.1111/j.1754-4505.2011.00225.x.
89. Sands SA, Giarraffa P, Jacobson CM, Axelrod FB. Familial dysautonomia's impact on quality of life in childhood, adolescence, and adulthood. Acta Paediatr. 2006;95:457–62. https://doi.org/10.1080/08035250500440386.
90. Anderson SL, Qiu J, Rubin BY. Tocotrienols induce *IKBKAP* expression: a possible therapy for familial dysautonomia. Biochem Biophys Res Commun. 2003;306:303–9.
91. Lee G, Papapetrou EP, Kim H, Chambers SM, Tomishima MJ, Fasano CA, et al. Modelling pathogenesis and treatment of familial dysautonomia using patient-specific iPSCs. Nature. 2009;461:402–6. https://doi.org/10.1038/nature08320.
92. Hims MM, Ibrahim EC, Leyne M, Mull J, Liu L, Lazaro C, et al. Therapeutic potential and mechanism of kinetin as a treatment for the human splicing disease familial dysautonomia. J Mol Med (Berlin). 2007;85:149–61. https://doi.org/10.1007/s00109-006-0137-2.
93. Keren H, Donyo M, Zeevi D, Maayan C, Pupko T, Ast G. Phosphatidylserine increases *IKBKAP* levels in familial dysautonomia cells. PLoS One. 2010;5:e15884. https://doi.org/10.1371/journal.pone.0015884.
94. Cheishvili D, Maayan C, Holzer N, Tsenter J, Lax E, Petropoulos S, et al. Tocotrienol treatment in familial dysautonomia: open-label pilot study. J Mol Neurosci. 2016;59:382–91. https://doi.org/10.1007/s12031-016-0760-5.
95. Boone N, Loriod B, Bergon A, Sbai O, Formisano-Treziny C, Gabert J, et al. Olfactory stem cells, a new cellular model for studying molecular mechanisms underlying familial dysautonomia. PLoS One. 2010;5:e15590. https://doi.org/10.1371/journal.pone.0015590.
96. Gold-von Simson G, Goldberg JD, Rolnitzky LM, Mull J, Leyne M, Voustianiouk A, et al. Kinetin in familial dysautonomia carriers: implications for a new therapeutic strategy targeting mRNA splicing. Pediatr Res. 2009;65:341–6. https://doi.org/10.1203/PDR.0b013e318194fd52.
97. Gold-von Simson G, Leyne M, Mull J, Rolnitzky LM, Goldberg JD, Berlin D, et al. *IKBKAP* mRNA in peripheral blood leukocytes: a molecular marker of gene expression and splicing in familial dysautonomia. Pediatr Res. 2008;63:186–90. https://doi.org/10.1203/PDR.0b013e31815ef74b.
98. Jun BK, Chandra A, Kuljis D, Schmidt BP, Eichler FS. Substrate availability of mutant *SPT* alters neuronal branching and growth cone dynamics in dorsal root ganglia. J Neurosci. 2015;35:13713–9. https://doi.org/10.1523/JNEUROSCI.1403-15.2015.
99. Garofalo K, Penno A, Schmidt BP, Lee HJ, Frosch MP, von Eckardstein A, et al. Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1. J Clin Invest. 2011;121:4735–45. https://doi.org/10.1172/JCI57549.
100.•• Fridman V, Suriyanarayanan S, Novak P, David W, Macklin EA, McKenna-Yasek D, et al. Randomized trial of l-serine in patients with hereditary sensory and autonomic neuropathy type 1. Neurology. 2019;92:e359–e70. https://doi.org/10.1212/WNL.0000000000006811 **This randomized, placebo-controlled trial proved that high-dose oral L-serine is safe and potentially effective at slowing disease progression in patients with HSAN1 (Class I evidence)**.