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Genetic Pain Loss Disorders

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Abstract

Genetic pain loss includes congenital insensitivity to pain (CIP), hereditary sensory neuropathies (HSN) and, if autonomic nerves are involved, hereditary sensory and autonomic neuropathy (HSAN). This heterogeneous group of disorders highlights the essential role of nociception in protecting against tissue damage. Patients with genetic pain loss have recurrent injuries, burns and poorly healing wounds as disease hallmarks. CIP and HSAN are caused by pathogenic genetic variants in >20 genes that lead to developmental defects, neurodegeneration or altered neuronal excitability of peripheral damage-sensing neurons. These genetic variants lead to hyperactivity of sodium channels, disturbed heme metabolism, altered clathrin-mediated transport, and impaired gene regulatory mechanisms affecting epigenetic marks, long non-coding RNAs, and repetitive elements. Therapies for pain loss disorders are mainly symptomatic but the first targeted therapies are being tested. Conversely, chronic pain remains one of the greatest unresolved medical challenges, and the genes and mechanisms associated with pain loss offer new targets for analgesics. Given the progress that has been made, the coming years are promising both in terms of targeted treatments for pain loss disorders and the development of innovative pain medicines based on knowledge of these genetic diseases.

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[H1] Introduction

Pain is mediated by subtypes of sensory neurons that project to the spinal cord and, subsequently, the brainstem and brain (Fig 1). In humans, generalized pain loss is very rare and is mostly genetic in origin (Box 1), although some disorders, for example tertiary syphilis and leprosy can also cause regional painlessness[1]. Mendelian pain loss disorders are classified as congenital insensitivity to pain (CIP) or hereditary sensory neuropathy (HSN; Table 1). The term hereditary sensory and autonomic neuropathy (HSAN) is used to refer to individuals with autonomic symptoms. For clarity, HSNs are subsumed under the term HSAN in this Primer. In addition to alterations in pain sensing, CIP and HSN are associated with a wide range of other symptoms that affect different organ systems.

CIP is usually defined by its congenital onset whereas later onset is often referred to as HSAN; however, a uniform terminology is still lacking and the differences between CIP and HSAN are sometimes not clearly specified. Dominant forms of HSAN sometimes show incomplete penetrance and usually manifest later in life than recessive forms, which are often congenital (Table 1)[2,3]; however, some subgroups do not follow this rule. In all cases of CIP and HSAN, reduced pain perception is the hallmark of the disease and resulting injuries determine the clinical picture. The clinical symptoms of the recessive forms are usually more diverse than dominant forms. Children with recessive CIP often exhibit self-injurious behaviour, partly because the avoidance behaviour triggered by pain is absent. These patients may subsequently develop chronic pressure ulcers and osteomyelitis with bone destruction. In some forms of CIP and HSAN, autonomic nervous system involvement causes impaired heart rate variability with blood pressure fluctuations, altered sweating and digestive problems. CIP/HSAN develops through neurodegeneration, a developmental defect of sensory neurons or functional deficits of nociceptors.

This Primer aims to provide an overview of the CIP/HSAN disorders known to date, to highlight their mechanisms and clinical treatment, and to provide an outlook on future developments in the field.

[H1] Epidemiology

The worldwide prevalence of CIP and HSAN is unknown. Only a few reports estimating the prevalence of some types of HSAN have been reported, and all studies are using regional cohorts. In the cohort on inherited neuropathies at University College London, 7% of 1,458 patients were classified as HSAN (unpublished data, Mary M Reilly). Calculations from other cohorts suggest that HSAN affects ~4% of neuropathy patients (prevalence of peripheral neuropathy: 30 in 100,000 individuals) [4]. In the UK, CIP caused by pathogenetic *SCN9A* variants and HSAN caused by *NTRK1* variants have the same approximate prevalence of 1 in 500,000 to 1 in 1,000,000 individuals[5]. In Japan, the prevalence of HSAN4 is estimated as 1 in 600,000 to 1 in 950,000, and 1 in 2,200,000 to 1 in 4,200,000 for *NGF*-associated HSAN5 [6]. CIP and HSAN disorders that are inherited in an autosomal-recessive manner occur more frequently in geographical regions and ethnicities with high rates of consanguineous marriages[7]. The frequency of penta-nucleotide expanded *RFC1* alleles (pathogenic AAGGG expansion) in the general population is relatively high, resulting in an estimated prevalence of biallelic carriers at risk of cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS)-spectrum disorders of 1 in 200 to 1 in 20,000 **[Au: should this be 200,000 or is 200 correct? 200 is correct] [Au: edited based on your response to my query]** individuals [8]. This disorder has a complex phenotype. A substantial proportion of patients with idiopathic sensory axonal polyneuropathy carry biallelic *RFC1* expansions; however, the proportion of these patients that will progress to a more complex phenotype is unknown. This finding is likely to mean that a larger proportion of cases previously classified as chronic idiopathic axonal polyneuropathy (CIAP) have a genetic origin, particularly in the elderly population where acquired disorders rather than genetic causes are often considered by physicians.

Founder effects (the spread of a genetic variant within a population) bias estimations of the global prevalence. For example, most reported cases of *WNK1*-related HSAN (HSAN2) are due to two founder variants that occur in a French-Canadian population in Quebec, Canada[9]. Moreover, HSAN3 (also known as Riley-Day Syndrome or Familial dysautonomia) is mainly related to one founder variant in *ELP1* (c.2204+6T>C) that has a high prevalence in the Ashkenazi Jewish population and almost no carriers in other populations[10] (see gnomAD). Another founder mutation is the p.(Cys133Trp) variant in *SPTLC1* that causes a large proportion of HSAN1 cases [11-13], and which may originate from a common founder who lived in southern England before 1800 (Ref[14]).

Common misdiagnosis and underdiagnosis due to the low awareness of CIP and HSAN even among healthcare professionals and overlap with more common diseases like Charcot-Marie-Tooth (CMT) disorders likely under-estimate the prevalence of CIP and HSAN. For example, adults with *SCN9A*-related CIP who were not diagnosed as children will only present again when they develop Charcot arthropathy with the ensuing physical disability. Moreover, a lack of access to genetic testing in many areas of the world also leads to underdiagnosis of CIP and HSAN and, therefore, an under-estimation of prevalence.

[H1] Mechanisms/pathophysiology

CIP and HSAN are caused by developmental defects of sensory neurons, neurodegeneration or altered excitability. In many cases, overlapping mechanisms are present. The causative genes are grouped according to their functional properties in the following overview; however, many gene products have a role in different signalling pathways, so that this classification can only serve as an orientation. A summary is provided in **Table 1.**

[H2] Transport, endocytosis and cytoskeleton

Sensory neurons have a complex cytoskeletal architecture and sophisticated vesicle transport mechanisms. Mutations in genes involved in these processes compromise neuronal homeostasis.
Homozygous or compound heterozygous missense and truncating mutations in *DST* (encoding dystonin (DST)) cause HSAN6 and other neuropathies [15-18]. Neuronal DST is a cytoskeletal linker protein that interacts with actin, microtubule networks and organelles. Moreover, DST has a role in endoplasmic reticulum (ER) structure and function and in autophagy in different cellular models; however, a direct link to ER-phagy has not been established[19-25]. DST has multiple tissue-specific isoforms , therefore, *DST* mutations are associated with various clinical manifestations, including dysautonomia with contractures, psychomotor retardation and motor neuropathy, but also autosomal-recessive epidermolysis bullosa simplex[26,27]. Loss of Dst expression in mice results in a profound sensory ataxia [28]. Induced pluripotent stem cell (iPSC)-derived neurons from patients with HSAN6 have short and dystrophic neurites or no projections at all, compared with neurons from healthy individuals [16].

Clathrin is a sensor of membrane-curvature[29] and a molecular scaffold comprising self-assembling triskelions. Clathrin is recruited to membranes to sort proteins for intracellular trafficking and endocytosis. Clathrin heavy chain like 1 (CHC22) is one of the two clathrin heavy chain proteins in humans, and homozygous mutations in *CLTCL1*, which encodes CHC22, resulted in CIP, inability to feel touch and intellectual disability in three siblings from one consanguineous family[30]. Studies in cellular models revealed a role for CHC22 in neural crest development and in the development of damage and touch sensing neurons[30,31], supporting the finding that *CLTCL1* **[Au: edited to gene name here, ok? ok]** variants are causal for CIP. Reduction of CHC22 expression seems to alter an early stage of neural precursor differentiation and leads to a failure of development into differentiated cells [30,31].

Axonal transport of synaptic vesicles is mediated by kinesins, which include the motor protein KIF1A. Recessive mutations in *KIF1A* can lead to HSAN2 (Ref [32]). Pathogenic variants in *KIF1A* have also been found in patients with hereditary spastic paraplegia (autosomal recessive or autosomal dominant) or dominantly inherited complex neurological syndromes with cognitive involvement, axonal neuropathy, cerebellar atrophy and spastic paraparesis[33,34]. The underlying mechanisms that lead to the difference between symptoms could be explained by compensatory mechanisms by other kinesins or unknown genetic and epigenetic factors[35]. KIF1A is also associated with synaptic vesicles that contain proteins such as synaptotagmin, synaptophysin and Rab3A (which is an important regulator of vesicular transport) [36-38].
Mutations in another RAB-family member, ***RAB7A***, cause an autosomal-dominant HSAN with mild to severe ulcero-mutilations. Motor involvement is often the first prominent sign and the disorder has substantial clinical overlap with axonal Charcot-Marie-Tooth (CMT) neuropathies[39,40]. Defective *RAB7A*

diminishes the retrograde transport of the TrkA/NGF complex, which is internalised after NGF binding[41]. This retrograde signalling and neurotrophin signal transduction normally contributes to the survival of sensory neurons even after the completion of nervous system development. A transgenic zebrafish expressing mutant Rab7 demonstrated reduced vesicle speed using high-resolution *in vivo* imaging of endosomes as well as deficits in neurite outgrowth and branching, both *in vivo* and *in vitro*[42].

[H2] Endocannabinoid signalling

The endogenous cannabinoid (endocannabinoid) system affects a range of key physiological functions including anxiety and stress responses, pain modulation, learning and memory, wound healing and development[43]. This system comprises the CB1 and CB2 G protein-coupled cannabinoid receptors, endocannabinoid lipid ligands (such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG)), their synthesising enzymes (such as NAPE-PLD) and metabolising enzymes (fatty-acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)). Fatty-acid amide hydrolase normally degrades the pain-relieving endocannabinoid AEA and other fatty acid amides. Mice lacking FAAH cannot metabolize AEA correctly and show reduced pain sensation[44]. Altered endocannabinoid signalling was found in one 66-year old individual with CIP and a happy, non-anxious disposition[45]. A skin biopsy showed normal intraepidermal nerve fibre density for age and sex, indicating a lack of neurodegeneration. Genetic investigations of this patient revealed heterozygosity for an ~8kb microdeletion located downstream of *FAAH* (encoding fatty-acid amide hydrolase) and a heterozygous hypomorphic (partial loss of gene function) single nucleotide variant (SNV) in *FAAH* which conferred reduced activity of the enzyme [46]. The microdeletion removes the first two exons of a novel long non-coding RNA, known as ***FAAH-OUT***, which contains an intronic enhancer element called FAAH-AMP[47]. CRISPR interference experiments using a dead SaCas9 and guides targeting FAAH-AMP significantly reduced *FAAH* expression in HEK293 cells[47]. The genetic findings and elevated circulating fatty-acid amides in the patient's peripheral blood are consistent with a phenotype resulting from enhanced endocannabinoid signalling via *FAAH-OUT* impairment. Modulating the FAAH pathway could thus be a suitable means of pain therapy [44,47-51].

[H2] Epigenetics and transcription

The development and maintenance of pain pathways are influenced by various epigenetic factors. One such factor, DNA methyltransferase 1 (encoded by ***DNMT1***) is crucial for maintenance of DNA methylation patterns and regulates gene expression and chromatin stability. Heterozygous missense-mutations in *DNMT1* can cause adult-onset HSAN1 with dementia and hearing loss (HSAN 1E)[52]. In addition, other mutations have been found in patients with cerebellar ataxia, deafness and narcolepsy (ADCA-DN) [53]; however, these patients do not have HSAN or marked deficits in pain perception but may have mild sensory loss later in the disease. Mutations in *DNMT1* have also been identified in individuals with a broader spectrum of neurological disorders including myoclonic seizures, and auditory or visual hallucinations[54]; almost all of these patients have nerve conduction abnormalities, indicating peripheral neuropathy, that is often accompanied by ulcerations and/or amputations. Abnormal global methylation was observed in blood cells of affected individuals with HSAN[52] and DNMT1 dysfunction resulted in imbalanced protein homeostasis through aggresome-induced autophagy in heterologous expression systems[54], which may explain the neuronal degeneration. Remarkably, *DNMT1* mutations affect only the nervous system **[Au:OK?ok]**, although the protein is of global importance and is expressed in various cell types and tissues.

Other epigenetic regulators include PRDM family of proteins, which control neural specification and neurogenesis. ***PRDM12*** mutations lead to autosomal-recessive CIP or HSAN8 and a phenotype very

similar to HSAN4 and HSAN5 except for usually normal intellect[55]. Various types of mutations in *PRDM12* including a coding alanine repeat in the 3' region of the gene are disease-causative [56]. Studies in *Prdm12*-deficient mice demonstrated that Prdm12 is indispensable for nociceptor development and acts as a key factor in the orchestration of sensory neurogenesis. Moreover, impairment of *Prdm12* during embryogenesis causes defects in nociception, but depletion at an adult stage is dispensable for pain sensation and injury-induced hypersensitivity [57-60].

Lack of sensitivity to painful thermal and capsaicin stimulation, as well as painless injury, has been found in autosomal dominant Marsili syndrome caused by a mutation in ***ZFHX2***. *ZFHX2* encodes a zinc finger transcriptional regulator expressed in damage-sensing neurons[61]. This *ZFHX2* variant has only been reported in 6 affected members of a family. Intraepidermal nerve fibre density is normal in these patients [61]. *Zfhx2*-KO mice and mice with the corresponding patient variant showed altered expression of genes involved in peripheral pain and have impaired pain sensitivity[61].

[H2] Membrane-shaping and ER

Endoplasmic reticulum (ER) dysfunction via a class of membrane-shaping proteins (ATL1, ATL3, RETREG1 and ARL6IP1) is a central mechanism in HSAN. Mutations in ***ATL1*** were first discovered in patients with autosomal-dominant hereditary spastic paraplegia (HSP) characterized by spasticity, diminished vibration sense and urinary bladder disturbances[62]. Subsequent studies identified patients with HSAN1 and heterozygous mutations in *ATL1*[63]. Mild signs of upper motor neuron involvement have been reported in these families, suggesting an *ATL1*-associated disease spectrum [64,65]. Missense-mutations in the homologous ***ATL3*** can cause autosomal-dominant HSAN1 as well [66-69], characterized by delayed wound healing, adult onset painless chronic ulcerations and fractures of the metatarsals, which may result in severe bone destruction. Homozygous loss-of-function mutations in ***ARL6IP1*** can cause a complicated form of HSP with the typical signs of HSAN in terms of pain loss and acromutilations[70-75]. Moreover, homozygous loss-of-function mutations in ***RETREG1*** (formerly known as ***FAM134B***) result in HSAN2 [76]. *RETREG1*-associated HSAN2 is associated with variable autonomic disturbances, including hyperhidrosis, tonic pupils and urinary incontinence in those with more advanced disease [11,76-81].

ATL1, ATL3, RETREG1 and ARL6IP1 share a reticulon-(like) homology domain (RHD) [82,83] which inserts into lipid bilayers causing highly curved intracellular subdomains [84] and thereby modulating the architecture of the ER [85,86]. ATL proteins also have a cytoplasmic GTPase domain, via which ATL proteins dimerize and promote the fusion of ER-tubules [87-89]. Accordingly, disease associated *ATL3* variants disrupt the structure of the tubular ER in cellular models (including patient-derived cells) and impair the function of other organelles, leading to neurodegeneration [90-92]. Less is known for ARL6IP1 which comprises two RHDs [93]. ARL6IP1 knockdown in *Drosophila* results in fragmentation of the smooth ER and disrupts mitochondrial network organization within the distal ends of long motor neurons [94]. ARL6IP1 targets the inositol 5-phosphatase INPP5K to the ER, which participates in the control of ER organization. Knockdown either of INPP5K or ARL6IP1 increased the abundance of ER sheets, which may contribute to neurodegeneration [95].

ATL proteins and RETREG1 also support ER remodelling. ER remodelling involves the adaptation of the ER to changing cellular requirements, and seems to be critical for cellular homeostasis and prevention of disease[96-98]. Both ATL3 and RETREG1 mediate the degradation of ER subdomains via selective autophagy (ER-phagy) [99-103] (**Fig. 4**). ATL3 promotes the degradation of ER tubules[104] and RETREG1 promotes remodelling and degradation of ER sheets [99]. RETREG1 is also involved in the degradation of ER subdomains which contain ER-associated protein degradation (ERAD)-resistant misfolded proteins[105,106]. Notably, the HSAN2-related *RETREG1* variant p.(Gly216Arg) exhibited gain-of-function

defects, leading to hyperactive self-association and membrane scission and excessive ER-phagy[107]. Thus, both compromised and excessive ER-phagy via mutated RETREG1 can lead to progressive neurodegeneration.

One study demonstrated that WNK1 (a serine/threonine kinase known for the regulation of blood pressure via renal ion reabsorption) functions as an assembly factor for the ER membrane protein complex[108]. This multi-subunit complex ensures protein homeostasis at the ER, but also has roles in mitochondrial tethering and autophagosome formation [108]. Mutations of an alternatively spliced exon of a neuronal isoform of ***WNK1*** (formerly known as the HSN2 exon) causes early-onset autosomal recessive HSAN2 [9]. Compound heterozygosity for this mutation and a truncating mutation or copy number variant (CNV) affecting all isoforms of WNK1 can also cause this type of HSAN [109,110]. Interestingly, clinically healthy heterozygous carriers of a pathogenic *WNK1* mutation have increased sensitivity to heat and cold stimuli [111]. Notably, an additional role for WNK1 in axon morphogenesis and maintenance was demonstrated, however, the exact mechanism resulting in neurodegeneration is not yet known [112].

[H2] Neurotrophin signalling

The neurotrophin signalling pathway has a central and non-redundant role in the development of sensory neurons, regulating survival and target innervation[113,114]. In this pathway, NGF binds to the membrane-bound tyrosine kinase high-affinity receptor TrkA (encoded by *NTRK1*), which subsequently undergoes autophosphorylation and activates multiple pathways including Ras-MAPK signalling [115]. Silencing of both *Ngf* and *Ntrk1* in mice leads to small sympathetic and sensory ganglia with significantly impaired nociception and early lethality, owing to death of small diameter DRG neurons early in development[116,117] **[Au: edits for brevity ok?ok]**. ***NTRK1*** and ***NGF*** mutations in humans can lead to autosomal recessive HSAN4 and HSAN5, respectively [118,119]. *NTRK1*-associated HSAN (also known as CIP with Anhidrosis (CIPA)) is probably **[Au: are there any data in support of this? If so, please reference this statement. Done]** the most frequent cause of severe HSAN with congenital analgesia and varying degrees of intellectual disability [5]. A typical feature of the disease is the absence of sweating (anhidrosis) due to a lack of innervation of eccrine sweat glands, which can lead to life-threatening hyperthermia in childhood. Only few reports of NGF mutations exist, but the phenotype in large part resembles the *NTRK1*-related condition [120-122]. Failure of small diameter sensory neurons to develop explains the congenital onset of disease symptoms in these conditions.

[H2] Repeat architecture

Biallelic pentanucleotide repeat (AAGGG) expansions in intron 2 of *RFC1* (encoding the replication factor complex subunit 1 RFC1) cause a spectrum of neurological disorders including cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS)[123,124]. Moreover, biallelic repeat expansions have been identified in a substantial number of patients (34% in one study [8]) in cohorts of sensory chronic idiopathic axonal polyneuropathy (CIAP) [8,125,126]. These patients are now classified as having a complex hereditary sensory neuropathy with pain loss. A surprisingly high percentage (42%) of sensory CIAP patients with *RFC1* repeat expansion **[Au:OK?ok]** presented with isolated sensory neuropathy, partly with chronic cough, whereas 58% also showed signs of vestibular or cerebellar involvement, though often subclinical. Another study revealed a high number of individuals with *RFC1* repeat expansion in a preselected cohort of patients with sensory CIAP (53%), but also some patients with minor and pronounced motor involvement [125]. *RFC1* repeat expansions have also been described in

patients with HSAN, cough and ataxia [127]. *RFC1* encodes the large subunit of replication factor C, which is required for eukaryotic DNA replication and repair. RFC1 may also have a role in telomere stability; however, the pathophysiology of RFC1 disorder is yet not fully understood.

[H2] Sodium channels

Voltage-gated sodium (Na_V) channels are essential for action potential generation; consequently, mutations in genes encoding nociceptor-expressed sodium channels affect pain sensation[128,129]. Nociceptors express high levels of $Na_V1.6$, $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$, which differ in their biophysical properties: for example, $Na_V1.9$ is active at resting membrane potential and amplifies sub-threshold stimuli, whereas $Na_V1.7$ sets the action potential threshold, and $Na_V1.6$ and $Na_V1.8$ are responsible for the fast upstroke of the action potential [130].

Individuals with loss-of-function mutations in both copies of ***SCN9A***, encoding $Na_V1.7$, have CIP [131] and, because $Na_V1.7$ is required for the function of C-low threshold mechanoreceptors, these patients also have impaired affective touch [132]. Injuries due to the complete lack of pain sensation are the main characteristic of this disorder, but patients with mutation-specific milder symptoms have also been described. Patients are usually anosmic (lack a sense of smell) but have no other symptoms [131,133,134]. Accordingly, $Na_V1.7$ is a key target for analgesic drug development [135]. Mouse models and other studies have confirmed an important role of *SCN9A* in pain, but have also revealed difficulties in developing pain therapies targeting $Na_V1.7$ [136-142] as many potent selective antagonists of $Na_V1.7$ have ultimately proven to be weak analgesics **[Au:OK?ok]**. Complete $Na_V1.7$ channel block and blood brain barrier permeability may be required to replicate the analgesic phenotype of null mutant humans and mice[135,143], which involves the activity of the endogenous opioid system to inhibit neurotransmitter release of glutamate and substance P at the first central synapse [144-146]. Of note, heterozygous gain-of-function variants of *SCN9A* **[Au:OK?ok]** lead to the devastating pain conditions, paroxysmal extreme pain disorder (PEPD), primary erythromelalgia (PE), or, small fiber neuropathy (SFN)[128,147-150].

Heterozygous gain-of-function mutations in ***SCN11A*** (encoding $Na_V1.9$) can cause CIP and HSAN7 [151-153]. The phenotype of $Na_V1.9$ pain-insensitivity is caused by distinct missense-mutations [151-153]. Paradoxically, unlike $Na_V1.7$, the gain of function of the ion channel leads to a lack of pain sensation [153,154]. Patients with *SCN11A*-related pain insensitivity have normal intelligence, but several additional symptoms, such as diarrhoea or sometimes severe constipation, muscle hypotonia, extreme itch and increased sweating [155]. Other heterozygous gain-of-function missense-mutations in *SCN11A* lead to episodic pain and SFN[156-158]. The explanation for these divergent clinical results is due to the degree of membrane depolarization: mutations leading to larger membrane depolarizations result in hypoexcitability and pain insensitivity as excessive depolarization leads to inactivation of action potential-relevant channels (such as $Na_V1.8$), whereas smaller depolarizations result in hyperexcitability and pain [151,159]. Heterozygous variants in *SCN10A* (encoding $Na_V1.8$, which is expressed in nociceptors), have been associated with episodic pain and SFN [160-162]; however, mutations in *SCN10A* that are associated with pain loss have not yet been found.

[H2] Sphingolipid metabolism

Sphingolipids are bioactive membrane lipids that are involved in cellular signal transduction, endocytosis and stress response, and are particularly important for neurons. The initial and rate limiting step of sphingolipid *de-novo* synthesis is the conjugation of L-serine and palmitoyl-CoA which is catalysed by serine palmitoyltransferase (SPT) [163]. Heterozygous missense mutations of two SPT-

coding genes, ***SPTLC1*** and ***SPTLC2***, lead to autosomal dominant HSAN1 [13,164,165]. The neuropathy is slowly progressive with usual onset between the second and fifth decade of life, which can have a later onset in females than in males **[Au:OK?ok]** [164,166]. The presenting feature is sensory loss, with often very painful (lancinating pain) neuropathy for which pain medications are rarely fully efficacious, followed by motor involvement that later leads to significant disability. Autonomic features are uncommon but have been described with some mutations. Among the verified HSAN1 mutations, three variants (*SPTLC1* p.(Ser331Tyr/Phe) and *SPTLC2* p.(Ile505Phe)) are associated with particularly severe HSAN1 [165,167,168]. In addition to the function described above, SPT also has activity towards other amino acid substrates, particularly alanine and glycine, forming an atypical and neurotoxic category of 1-deoxy-sphingolipids (1-deoxySL). A common feature of all HSAN-associated *SPTLC1* and *SPTLC2* mutations is that this alternative activity towards L-alanine and L-glycine is greatly enhanced [169]. In addition, low serine levels and an altered serine to alanine ratio leads to increased 1-deoxySL formation by wild-type SPT [170]. This condition is often seen in patients with type 2 diabetes mellitus and might contribute to the pathology of diabetic neuropathy, which is clinically very similar to HSAN1 [171,172,173,174]. The increased 1-deoxySL concentration causes mitochondrial swelling, mitochondrial dysfunction and alterations in the cytoskeleton of sensory neurons associated with neuronal cell death and axon loss mirroring the axon degeneration observed clinically in HSAN1 [175,176]. Induced human pluripotent stem cell (iPSC)-derived sensory neurons from *SPTLC1* mutation carriers similarly produced neurotoxic 1-deoxySLs [177]. Complex gangliosides, which are essential for membrane micro-domains and signalling, are reduced, and neurotrophin signalling is impaired in this cellular model, resulting in reduced neurite outgrowth [177]. Administration of L-serine attenuates the formation of toxic metabolites[178]. Interestingly, other missense variants in *SPTLC1* have been reported in a monogenic form of amyotrophic lateral sclerosis (ALS) [179,180]. In contrast to the substrate shift observed in patients with HSAN1, upregulated SPT activity and elevated levels of canonical SPT products underlies the ALS phenotype [179].

[H2] Other mechanisms leading to CIP and HSAN

Malfunction of various other molecules and pathways leads to syndromes associated with pain loss. ***ELP1*** (formerly known as *IKBKAP*) can cause HSAN3 (also known as Riley-Day syndrome or Familial dysautonomia) [181,182]. Notably, other mutations in *ELP1* have recently been described with medulloblastoma predisposition [183]. ELP1 is a key scaffolding subunit of the six-subunit elongator complex (ELP1-6), which has an important role in the chemical modification of transfer RNAs (tRNAs). These chemical modifications seem to influence translation efficiency, which in turn is dependent on the composition of synonymous codons of the degenerate genetic code. Therefore, ELP1 is a determinant of the cellular levels of specific proteins [184]. Cellular and mouse model systems have found that failed target innervation and/or impaired neurotrophic retrograde transport are the primary causes of neuronal cell death in the *ELP1* disease [184-186].

FLVCR1 encodes Feline leukemia virus subgroup C receptor-related protein 1, which is a ubiquitously expressed heme exporter [187]. Through its important role as cofactor for various enzymes and proteins, heme also contributes to neuronal growth and maintenance [188]. Mutations in *FLVCR1* were initially found to be associated with posterior column ataxia and retinitis pigmentosa (PCARP) [189]. Homozygous or compound heterozygous missense and nonsense mutations in *FLVCR1* can lead to HSAN [190-192]. Patient-derived fibroblasts showed impaired heme export, which triggers cytotoxic effects of accumulated intracellular heme [188].

Mutations in ***GMPPA*** have been found in patients with predominantly autonomic neuropathy and intellectual disability [193]. Alacrima and achalasia are lead clinical symptoms [194-196]. The GMPPA-disorder

belongs to the growing list of congenital disorders of glycosylation. GMPPA in a complex with GMPPB regulates the levels of GDP-mannose, a key metabolite essential for protein glycosylation and glycophosphatidylinositol anchor synthesis [193,197]. Cryo-EM data showed that, unexpectedly, the catalytically inactive subunit GMPPA displays a much higher affinity to GDP-Mannose than the active subunit GMPPB [198]. As a consequence, mutations in *GMPPA* result in increased GDP-mannose levels and thus increased incorporation of mannose into glycoproteins. This likely affects the functionality of different glycoproteins in the developing and mature brain. The mode of GMPPA/GMPPB action may be used for therapeutic intervention (see below).

Bi-allelic ***MADD*** mutations cause a phenotypic spectrum ranging from developmental delay to a multisystem disorder with endocrine dysfunction, pancreatic insufficiency, pain insensitivity and autonomic dysfunction. MADD regulates vesicle trafficking, activity of small GTPases, and TNFα-induced signalling; however, the mechanism leading to pain loss yet remains unclear [199].

Pathogenic sequence variants in ***MPV17*** encoding a mitochondrial inner membrane protein lead to autosomal recessive axonal CMT [200], but also to mitochondrial DNA depletion syndrome 6 with many features of the CIP and HSAN disease spectrum [201-204].

TECPR2 mutations were reported to cause an autosomal-recessive complex form of spastic paraplegia or HSAN with dysautonomia, respiratory failure, and intellectual disability [205-209]. *Tecpr2* knockout-mice show a progressive neuroaxonal dystrophy associated with autophagosome accumulation [210-212]. TECPR2 functions as molecular scaffold linking early secretion pathway and autophagy [213].

In 2006, a single family with a homozygous missense variant in ***CCT5*** causing HSAN was reported [214]. Since then, no further HSAN families have been published and the role of CCT5 remains unclear. It should be noted that *RETREG1* is also located within the 25-cM linkage interval of that family, but was not known as disease-associated gene at this time [215]. Recently, another homozygous missense variant in CCT5 was described in a single case of early motor neuropathy [216].

[H1] Diagnosis, screening and prevention

[H2] Clinical features.

The clinical spectrum of CIP and HSAN is broad owing to their genetic heterogeneity, but impaired pain sensation is the predominant symptom. Although reduced perception of pain following evoked stimuli is common, it may be accompanied by unpleasant spontaneous pain that may be tonic or paroxysmal. Cuts, bruises and burns owing to impaired temperature sensation, together with painless fractures and neuropathic arthropathy (also known as Charcot joints) are also common in patients with CIP or HSAN. **[Au: green text moved to here from later on so the manifestations common to both early-onset and adult-onset CIP/HSAN are discussed together, ok? Please check very carefully.ok]** Muscle weakness and loss of muscle reflexes can also be observed in some patients with CIP or HSAN. In addition, a proportion of patients have autonomic dysfunction that may manifest as abnormalities of sweating (hypo- or hyperhidrosis), cardiac arrhythmias and heart rate variability, bladder dysfunction (atonic bladder), bowel dysfunction (incontinence, vomiting) and slow pupillary reaction to light. In some patients, such as those with HSAN3, dysautonomia is the cardinal feature.

In those with early-onset CIP or HSAN (which mostly have an autosomal-recessive inheritance pattern), the lack of awareness of potentially harmful stimuli often leads to self-mutilating behaviour (self-

inflicted destruction of body tissue), which manifests as cuts, amputations of digits or a bitten-off tip of the tongue (Fig 2). Of note, parents of these children can often be falsely suspected of child abuse [147,217,218]. Subtypes of CIP and HSAN with intellectual disability (ID) may be more difficult to diagnose clinically as these patients more often exhibit self-mutilating behaviour or may not self-report pain insensitivity. The lack of expression of pain may also be primarily due to ID as part of other syndromes, and distinguishing these patients from those with CIP or HSAN may be difficult. For example, dominant mutations in *PRKAR1B* cause a neurodevelopmental disorder with high pain tolerance and self-aggressive behaviour[219] and Lesch-Nyhan syndrome is caused by mutations in *HPRT1* and is accompanied by severe ID and self-inflicted wounds [220]. Comprehensive genetic tests (whole-exome or whole-genome sequencing) can distinguish between entities in many cases and sometimes require a different clinical management. Corneal injuries due to absent corneal reflexes are typical for early-onset CIP and HSAN forms.

Adult-onset forms of HSAN (mostly autosomal-dominant inheritance) are typically characterized by a gradual loss of pain with distal ulcerations, trophic disturbances and delayed wound-healing. Poorly healing wounds are also the result of the lack of pain-related protective behaviour after injury. Ulcerations (which can lead to osteomyelitis) and mutilations of hands and feet occur and may require amputations. Loss of nociceptive fibres results in an increased incidence of *Staphylococcus aureus* infections, particularly in those with *NTRK1*-associated, *NGF*-associated and *PRDM12*-associated CIP [221]. In most cases the infections are prolonged superficial skin infections, but osteomyelitis, septic arthritis and severe gingivitis are more severe complications that are not rare and should be actively screened for[5,120,222]. Autosomal dominant amyloidosis (ATTRv) caused by mutations in the *TTR* gene (encoding transthyretin) may have some phenotypic overlap with adult-onset forms of HSAN, as sensory neuropathy with ulcers as early sign and autonomic symptoms are part of the clinical spectrum. However, neuropathic pain is a major hallmark of ATTRv **[Au:OK?ok]** and, if left untreated, ATTRv leads to a complex multisystem disease. Recognising this differential diagnosis is of great importance as there are several treatment options for ATTRv (such as small interfering RNAs and antisense oligonucleotides) [223,224].

[H2] Clinical diagnosis

No international consensus guidelines for the clinical diagnosis of CIP and HSAN have been produced. These guidelines are likely very difficult to establish due to the variable age at onset, the varying severity of the clinical picture and the many additional symptoms of these disorders[3,225]. In part, recommendations for the clinical diagnostic work-up of CIP and HSAN are provided in national guidelines on hereditary neuropathies (for example German AWMF guidelines).

Clinical examination, detailed personal and family history (including a family tree survey) should be carried out initially in those with suspected CIP or HSAN. Medical history must include information on all symptoms, age at onset, previous illnesses and infections and contact with harmful substances and toxins. Differential diagnoses of spontaneous ulcers (caused by diabetes mellitus, atherosclerosis, venous ulcerations, vasculitis, neurotoxins) and other peripheral neuropathies (such as those caused by chemotherapy, leprosy or amyloidosis) should be excluded [226].

Diagnosis and treatment of CIP and HSAN is substantially different between high-income countries and low- and middle-income countries (LMICs). A comprehensive clinical assessment and molecular genetic diagnostics are often not available in LMICs. Accordingly, the patients' quality of life in LMICs is significantly more affected than those in high-income countries owing to a lack of prevention, therapy, hygiene measures and necessary aids.

[H3] Electrophysiology. **[Au: please ensure this section is referenced throughout. done]** Nerve conduction studies are a regular part of the diagnostics of CIP and HSAN. Sensory nerves are primarily affected and the legs are usually more severely affected than the arms in patients with these disorders. Electrophysiological findings include reduced or absent sensory nerve action potentials (SNAPs), and, in patients with HSAN1, nerve conduction velocity (NCV) slowing [167]. Moreover, compound muscle action potentials (CMAP) are variably reduced with preserved or reduced motor nerve conduction velocities (MNCV). Routine nerve conduction studies and electromyography can be normal in patients with CIP subtypes in which there is selective small fibre involvement (such as *SCN9A* [131,135]). Severely reduced or absent SNAPs with paucity of sensory symptoms and relative preservation of sensory modalities on examination is suggestive of a genetic rather than an acquired aetiology. However, electrophysiological findings are rarely pathognomonic of a particular gene and studies should be interpreted in the context of the clinical picture and other investigations. Significant motor nerve conduction velocity slowing, conduction blocks or temporal dispersion, non-length dependent reduction in SNAPs, or normal studies in the context of non-small fibre symptoms and signs (such as ataxia and motor involvement) should prompt further investigation for alternative diagnoses, including imaging of the neuroaxis and somatosensory evoked potentials, and other investigations for an acquired neuropathy.

[H3] Tissue biopsies. A skin punch biopsy is not regularly performed as part of the diagnostic work-up of suspected HSAN or CIP. However, this test can be used to assess the presence of reduction or absence of the terminals of small sensory neurons within the epidermis using PGP9.5 immunostaining. The biopsies, which are only a few millimetres in size, should be taken from standardised sites (lateral lower leg or upper thigh) and assessed in specialised centres according to international standards [227]. Morphologically normal sweat glands lacking innervation are a hallmark of the *NTRK1*-associated disorder. A decrease or absence of large and small, non-myelinated fibres may be observed in sensory nerve biopsies (such as sural nerve) in some HSAN subtypes[228]. Moreover, normal innervation is observed in some patients with CIP. However, nerve biopsies are rarely needed owing to the availability of genetic testing and skin biopsy[229]. Moreover, given the increased risk of delayed wound healing in patients with CIP or HSAN, tissue biopsies should be limited to a reasonable extent and in case of changes in the neurophysiological sensory conduction, a skin biopsy is not recommended. A relevant differential diagnosis that is being diagnosed by tissue biopsies as a gold standard, is vasculitis. Amyloid deposits as an important indication of ATTR amyloidosis can be detected by Congo red staining.

[H3] Quantitative sensory testing (QST). QST measures the stimulus-response function across a range of sensory modalities. QST protocols now exist for assessment of cold and warm detection thresholds, cold and heat pain thresholds, mechanical detection threshold, mechanical pain threshold and mechanical pain sensitivity, vibration detection threshold, or pressure pain threshold [230]. This enables a better classification of the disease and affected fibre systems in a standardised procedure. Respective measurements are not available at all medical centres.

[H3] Autonomic tests. Testing autonomic function is carried out in patients with suspected CIP/HSAN and autonomic symptoms. Tests of autonomic dysfunction include the Schellong test or tilt table test, metronomic breathing, Valsalva manoeuvre, carotid sinus massage, ninhydrin test (sweating of palms

and soles), minor sweat test (whole body), quantitative sudomotor axon reflex test and Sudoscan (electrochemical skin conductance) [226].

[H3] Histamine axon flare test. The histamine axonal flare test examines the innervation of the skin by unmyelinated C-fibres. Diluted histamine is injected intradermally and triggers a local reaction, resulting in vasodilation and plasma exudation (neurogenic inflammation) through the release of vasoactive substances. Healthy individuals exhibit a sharply demarcated local reaction surrounded by a less well demarcated area of hyperaemia called an axon flare. However, a lack of C-fibre innervation, as in some forms of HSAN, does not trigger the axon flare reaction and is not pruritic. This test is not regularly done in clinical routine.

[H3] Laboratory findings and radiological diagnostics. Additional tests might be useful for excluding differential diagnoses and to evaluate tissue damage, bone damage and infection. Elevated plasma levels of 1-deoxySL are indicative of SPTLC1/2-related disorders. Uric acid levels in blood or urine should be tested to diagnose hyperuricemia in X-linked Lesch-Nyhan syndrome (also known as Hypoxanthine-Guanine Phosphoribosyltransferase (HPRT) Deficiency). The diagnosis is confirmed by detection of HPRT enzyme deficiency in peripheral blood or intact cells and by molecular genetic testing of *HPRT1*. The differential diagnosis of Lesch-Nyhan syndrome is also important because drug therapy is available with allopurinol and febuxostat.

[H2] Molecular genetic testing

Confirmation of the clinical diagnosis of CIP and HSAN is carried out via molecular genetic testing of DNA that is normally obtained from blood. A reliable diagnosis is needed to offer patients the best available treatment, to provide genetic counselling, to evaluate recurrence risks, and to avoid a diagnostic odyssey. Knowing the genetic basis of the disease is also a prerequisite for the development of targeted treatments.

[H3] Targeted approaches. In few cases with certain clinical manifestations, targeted gene sequencing (such as Sanger sequencing) can be useful (Table 1). Moreover, patients of certain ethnicities may prompt analysis of founder mutations first if known founder mutations have been identified in that population. Elevated plasma 1-deoxySLs are indicative of SPTLC1/2-related disorders and, therefore, Sanger sequencing of the causative genes (*SPTLC1* and *SPTLC2*) may be the first choice. The recently identified high number of patients with adult-onset sensory neuropathy carrying biallelic repeat expansions in intron 2 of *RFC1* argues for initial screening for expanded alleles in suspected cases (this can be done e.g. by specific repeat-primed PCR) [231]. In *RFC1*-positive cases the expansion size ranges from 249 to 2386 repeat units [8].

[H3] Next-generation sequencing. High-throughput next-generation sequencing (NGS), including disease specific panels (such as inherited neuropathy panels), whole exome-sequencing or whole genome sequencing, are the most appropriate approach for genetic diagnosis of CIP or HSAN as it is fast and allows a broad screening of many genes. Multiple gene testing is particularly important as the yield per gene remains quite low in most cases. A ‘genome-first’ approach will quickly become established as sequencing costs fall.

[H3] General considerations in molecular genetic testing. A consanguineous background often facilitates the detection of the pathogenic variant in a patient. However, homozygosity of a sequence

variant should be verified by segregation analyses in the family to exclude pseudo-homozygosity due to a deletion on one allele or uniparental disomy (both alleles being derived from the same parent). Parallel testing of the patient and their parents for variant(s) (known as trio testing) can improve the diagnostic yield and identify *de novo* variants. Once the molecular diagnosis has been confirmed in the patient, further affected and/or healthy family members can be offered targeted carrier testing. Country-specific regulations are available for the consent and diagnosis of individuals without symptoms of CIP and HSAN, particularly for minors. In case the diagnosis is molecularly confirmed, prenatal or preimplantation diagnostics may be offered to couples after genetic counselling. Once a molecular diagnosis is established, the CMT neuropathy score and the CMT paediatric score are widely used clinical scores to define disease severity.

[H3] Challenges in variant interpretation. The number of genetic variants to be evaluated as part of the diagnostic work up of CIP and HSAN is increasing owing to expansion of genetic testing. Options for variant assessment include population and clinical databases to estimate the frequency of a variant (such as gnomAD [232], ExAC [233], goNL [234], ClinVar [235]). Essential to increase the diagnostic yield are (automated) literature searches (such as DisGeNET [236], PubTator [237]), large biological data resources (STRING [238], GTEx [239]) and bioinformatics pathogenicity prediction tools (such as MutationTaster [240], PolyPhen-2 [241], SIFT [242] and M-CAP [243]). Standard bioinformatics tools have relatively poor performance in relation to predicting pathogenicity of missense variants in genes encoding voltage-gated sodium channels although recent machine learning algorithms have improved performance [244]. Family segregation analyses are essential for proper evaluation of genetic variants. Functional analyses of newly identified disease-causing genes are valuable especially for novel causal relationships. VarSome [245] or VarFish [246] are increasingly used for reporting of genetic variants. Interpretation of variants should be performed according to the recommendations by ACMG [247] or ESHG [248]. Standardizing NGS practices is important to improve patient care [249]. This also applies to the large number of variants of unknown significance (VUS). Future progress will help to elucidate more cases and will also uncover non-Mendelian inheritance such as multigenic inheritance patterns or genetic modifiers in axonopathies [250].

[H3] Special features in the molecular diagnostics of CIP/HSAN. HSAN-causing variants affecting non-canonical alternative transcripts and isoform-specific mutations (for example *WNK1* and *DST* gene [19,109]) can be easily missed by routine NGS diagnostics. Similarly, structural variations including copy number variations (CNV), chromosomal rearrangements and translocations, are commonly missed by panel or exome-wide NGS approaches. Gross deletions in *NTRK1* and (deep) intronic pathogenic variants including U12-type introns in, for example, *NTRK1* or *SCN9A* have been described [251-254]. However, although algorithms are improved, proper CNV detection is still challenging [255] and intronic variants are difficult to interpret and are often missed. For these variants, RNA-sequencing and/or a functional validation of their splicing effect may be required.
Of note, the 3´-located GC-rich coding repeat in *PRDM12* is poorly covered in most exome-sequencing analyses and pathogenic expansions might easily be missed [55]. Accordingly, a separate targeted sequencing approach is recommended for this locus if the molecular cause remains unclear in NGS analyses and the clinical suspicion points to a *PRDM12*-associated disease. However, heterozygous expansions for this repeat are even more challenging because of a preferential amplification of the shorter (“normal”) allele. Genome sequencing approaches, third-generation sequencing methods based on long reads and improved bioinformatics algorithms may solve many of these obstacles [256].

[H3] Diagnostic yield. The diagnostic yield depends on the type of disease, but exact percentages are not meaningful to state due to the small cohort sizes. For very early onset disease, pathogenic variants in *SCN9A*, *NTRK1* or *PRDM12* are most frequently detected overall [7]. The diagnosis rate in children is usually higher than in adult-onset cases, this may change with the identification of a high number of individuals with *RFC1* repeat expansions.

[H1] Management

[H2] Symptomatic therapies

Owing to the rare nature of pain loss disorders, guidance on their symptomatic management is generally based on expert opinion and experience, and case reports or case series within the literature. No comprehensive treatment guidelines are available.

[H3] General advice Optimal symptomatic management involves a multidisciplinary approach including paediatricians, neurologists, orthopaedic surgeons, dentists, ophthalmologists, dermatologists and therapists as needed. Education about complications and simple supportive measures in countries with poor medical infrastructure can also help to improve patient care [5]. Accordingly, the patient, together with their family and caregivers (including schoolteachers) should be educated on the complications of CIP and HSAN, emphasising that prevention of complications is key to minimise morbidity and mortality. Limbs, especially feet, should be inspected daily for signs of trauma. Moreover, risky activities such as jumping, contact sports and those involving potential for blunt injury or trauma should be avoided. Optimising foot wear is critical and protective gloves may also be needed when handling hot objects[5]. For more active children, non-contact sports such as swimming can often be useful to maintain fitness.

[H3] Ophthalmic. Annual ophthalmic review is recommended in at risk patients as diminished corneal sensation and reduced tearing leaves the cornea susceptible to abrasions and scarring. This is especially relevant for early-onset forms caused by *NTRK1* and *PRDM12* mutations, in which eye involvement is prominent. Regular use of lubricating eye drops can prevent painless corneal lesions, exposure to chemicals should be avoided and eye protection may be needed in windy or dusty conditions [60]. Tarsorrhaphy (a surgical procedure in which the eyelids are partially sewn together to narrow the eyelid opening) can be considered if conservative measures fail to stop abrasions and scarring [257]. However, the cornea has great potential for healing without scarring, and most patients maintain good vision.

[H3] Orthopaedic. Foot care is central to prevention of orthopaedic complications in CIP and HSAN. Many subtypes resemble a 'pseudodiabetic foot syndrome' and advice and management can be based on guidelines for diabetes mellitus [166]. Custom made, pressure relieving shoes may be required to prevent foot ulcers. Many cases of delayed fractures, such as stress fractures, are best managed non-surgically, [258-260] but early surgical intervention in cases of more severe trauma, soft tissue breakdown and joint infection is critical for optimal outcome, as seen in individuals with diabetes mellitus. Early involvement of plastic surgeons, microbiologists and wound care teams is essential to avoid long term complications after fractures and osteomyelitis [261]. Spinal surgery in cases of kyphoscoliosis should be

considered once curve progression is documented, although there is a relatively high, multifactorial failure rate[262]. Charcot arthropathy should be assessed by an experienced orthopaedic surgeon and the merits of surgery weighed-up [258-260]. Infections are most commonly osteomyelitis, septic arthritis and within the soft tissue[5]. *Staphylococcus aureus*, is the most frequently isolated organism, and is often multi-drug resistant, which should be considered when selecting antimicrobial therapy [263].

[H3] Anaesthetic: In individuals with CIP or HSAN without autonomic involvement, data from case studies suggest that normal doses of general anaesthetics are used, except for perioperative opioid use in CIP patients which ranged from none to normal doses based solely on clinician preference **[Au: what is the reasoning for this?sentence changed]** [264]. During induction, there should be a focus on minimising the risk of regurgitation and aspiration, as gastrointestinal dysautonomia, if present, can lead to delayed gastric emptying, and rapid sequence induction has been proposed as the safest induction method [265]. Intraoperative autonomic instability, including hyperpyrexia (life-threatening rise in the body temperature), hypotension and bradycardia (a resting heart rate slower than 60 bpm), is a rare but life-threatening complication in some patients; close temperature monitoring should be used with active cooling or heating if required, and patients prehydrated [266,267]. However, in those with familial dysautonomia, peri-operative complications are common and careful planning and monitoring are required [268].

[H3] Dental. At risk patients (those with CIP or early-onset HSAN) should undergo six-monthly assessments with the aim of preventing dental disease, as it can lead to severe infection and self-inflicted orofacial trauma. Treatments include grinding sharp tooth surfaces or restoring them with resin composite. Mouthguards can be used, and tooth extraction should be a last resort [269].

[H3] Dysautonomia. In individuals with CIP or HSAN with dysautonomia, body temperature should be regularly monitored and conservative cooling and warming measures should be used as needed, including paracetamol and ibuprofen for pyrexia. Hypotension can be treated with increased salt and fluid intake, and failing these, fludrocortisone or midodrine [257]. Supine hypertension can be avoided by raising the head of the bed. Gastroesophageal reflux disease and impaired swallowing should be managed to avoid respiratory complications due to aspiration. Fundoplication (a surgical procedure to treat gastroesophageal reflux disease) and gastrostomy tubes can be considered [225]. During acute dysautonomic attacks, traditional agents such as diazepam, clonidine and clonazepam can be used for nausea and vomiting, [257] and intravenous hydration may be required. Small trials in familial dysautonomia found that pregabalin and carbidopa may benefit symptoms of nausea and vomiting [270,271]. Similarly, carbidopa can be beneficial in reducing blood pressure variability during attacks [272]. In addition to diazepam and clonidine, intranasal dexmedetomidine can be effective in treating hypertension in adrenergic crises in familial dysautonomia [273].

[H3] Cognitive. Early assessment by a multidisciplinary team is important in children showing signs of intellectual disability or developmental delay, with early intervention where possible. Concurrent psychiatric comorbidities should be evaluated and treated [274].

[H3] Pain. Although not commonly seen in loss-of-pain disorders, patients with HSAN1 due to *SPTLC1* and *SPTLC2* variants can experience severe neuropathic pain. Despite consistently demonstrating only modest efficacy in trials, first line treatments for neuropathic pain include anti-epileptic drugs (gabapentin and pregabalin) and antidepressants (amitriptyline, duloxetine and venlafaxine). Second

line treatments like strong opioids and topical lidocaine have a weaker evidence base. Sodium channel blockers such as lacosamide may have particular efficacy in relation to rare gain-of-function variants in $Na_V1.7$ associated with SFN [275]. Interventional therapies can be used in refractory cases. [276,277]

[H3] Physical therapies. Focused studies regarding the use of physical therapy in patients with CIP and HSAN are lacking. One centre proposed both auditory and visual feedback systems for correcting gait abnormalities in patients with HSAN4 and HSAN5 [278]. Patients with sensory ataxic neuropathy of various causes showed improvement of dynamic balance through multisensory balance training [279].

[H2] Preclinical specific therapies

[H3] L-serine therapy in SPTLC1/2 disorders. Oral L-serine supplementation reduces the production of neurotoxic 1-deoxy-sphingolipids (1-deoxySL) in mice and humans with *SPT*-associated HSAN1 [280]. A pilot study in patients with the C133Y *SPTLC1* mutation found that L-serine supplementation is associated with a marked reduction in 1-deoxySL levels [280] . Moreover, a randomized, double-blinded, placebo-controlled, 2-year trial with 18 participants showed that high-dose oral L-serine was well-tolerated and decreased 1-deoxySL levels[281]. The primary outcome of this trial was the proportion of patients with a 1-point increase in CMT neuropathy scores (CMTNS) after one year; although statistical significance was not achieved presumably due to the small sample size, patients taking L-serine showed a quantitative improvement in CMTNS compared to those taking placebo. The most prominent benefits of L-serine treatment were patient-reported improvement of sensory symptoms and upper and lower extremity strength on examination, compared with placebo. Of note, patients taking L-serine did not have fewer skin ulcers, and both skin infections and osteomyelitis occurred with higher frequency in the L-serine group compared with placebo. Other adverse events included localized abdominal pain and dyspepsia.
Supplementation of L-serine was only tested in a single patient with a *SPTLC2* mutation. Although maximum dose of L-serine (400/mg/kg/day) did not cause any adverse effects and 1-deoxySL levels were decreased after treatment for 52 weeks, CMTNS were increased by one point in the same timeframe [282]. Of note, results from these trials may not be applicable to all *SPTLC* mutations. For example, two *SPTLC1* mutants (p.(Ser331Phe/Tyr)) and one *SPTLC2* mutant (p.(Ile504Phe)) showed a significantly increased canonical enzyme activity, which may result in treatment resistance to L-serine [283]. In the ALS-associated *SPTLC1* variants, the already increased canonical enzyme activity could be further stimulated by the addition of L-serine.

[H3] Gene silencing in sphingolipid metabolism disorders. Gene silencing has been suggested as a useful treatment for *SPTLC1/2* mutations owing to their gain of function mechanism. Strategies for gene silencing include artificial miRNA (amiRNA)-mediated allele-specific knockdown of mutant *SPTLC1* mRNA. Silencing mutant *SPTLC1* and sparing the wildtype allele can potentially reduce 1-deoxySL production. Another strategy is to deliver a dual-function rAAV that expresses both amiRNA and a functional *SPTLC1* cDNA, in which the amiRNA-recognized endogenous miRNA machinery degrades endogenous *SPTLC1* mRNA and amiRNA-resistant *SPTLC1* transcript produces wildtype SPTLC1[179,284].Further results from preclinical studies are needed to plan a trial in humans.

[H3] Transcriptional upregulation. Increasing ELP1 levels with a small molecule, kinetin, rescued proprioceptive neurons and improved the phenotype in an HSAN3 mouse model (TgFD9;Ikbkap$^{\Delta 20/flox}$)

and highlighted the potential therapeutic value of a splice-modulating therapy for HSAN3 [285]. Phenotypic improvements correlated with increased amounts of full-length ELP1 mRNA and protein in multiple tissues, including the peripheral nervous system [286]. Other studies using small molecules, additive FDA-approved drugs, or antisense-oligonucleotides showed a reduced loss of proprioceptive neurons in preclinical models. [285,287,288]

[H3] Diet in the GMPPA-disorder. GMPPA disruption enhances mannose incorporation into glycoproteins including α-dystroglycan in mice and humans. In knockout mice, mannose restriction starting after weaning corrected hyperglycosylation and abundance of α-dystroglycan, normalised skeletal muscle morphology and prevented neurodegeneration and motor deficits [197]. However, changes in the cortical layers and the cognitive functions were not improved [197].

[H2] Clinical trials and databases:

Only a few studies on CIP or HSAN have been conducted or initiated (see also: https://www.clinicaltrials.gov/ct2/results?cond=HSAN). However, the development of new therapies for rare diseases has increased rapidly. More molecular diagnoses are giving an increasing number of patients access to targeted therapies, and not all patients or physicians can keep track of the multitude of new therapies for rare diseases. Increasing the visibility of these therapies is, for example, the aim of the Treatabolome project within Solve-RD[289,290]. For the superordinate group of hereditary peripheral neuropathies, including CIP and HSAN, the efficacy of pharmacological and gene-based treatments was collected and treatable forms are compiled from randomised controlled trials (RCT), observational studies and case reports in the Treatabolome database [291].

[H1] Quality of life

Quality of life can be almost unaltered for some forms of CIP and HSAN, but in many cases, the disease has a significant effect on quality of life (Box 2)[5]. In particular, externally visible mutilations and complicating additional medical problems represent a major restriction for quality of life [7]. Personal experience has shown that it can be improved by adequate symptomatic therapy, but a systematic data collection, for example by means of questionnaires, has not been carried out due to the rarity of the diseases.

[H2] CIP

The most important strategy to improve quality of life is education and awareness about which stimuli are potentially toxic, for example, situations that result in burns, colds and injuries occur, when protective postures are required in case of injuries and what is needed to reduce fever to avoid overheating. Awareness of such hazards increases patients' life expectancy and contributes to a healthy life. This is where parents, doctors and patient organizations play a crucial role. Learning avoidance mechanisms is more difficult in patients with ID. The burden on the parents of a child with CIP can be heavy and can be associated with self-mutilating behaviour with corresponding disfigurements and potentially even the accusation of child abuse. With *SCN9A*-associated CIP there appears to be a paucity of adult males, with excess risk taking leading to accidents and chronic disability been the hypothesized explanation.

[H2] Later onset HSAN

When symptoms appear later in life, one of the major problems that limit quality of life are chronic injuries (often unnoticed pressure marks on the feet). As wound healing is impaired in these patients, chronic wounds become infected and amputations with a restriction of mobility may result. Patient education is crucial to prevent these injuries. Moreover, giving up leisure activities that have been pursued for years may also be needed to prevent these injuries and disabilities. Some patients cannot continue in their profession because of the increased risk of injury and have to start a retraining or take early retirement. The restrictions in leisure and professional life compared to life before disease onset may therefore require psychological care.

Apart from the physical and psychological effects directly caused by the disease, patients with CIP or HSAN and their families often have years of uncertainty about the cause of their afflictions due to lack of awareness of the disease, with numerous visits to doctors without a conclusive diagnosis. Fortunately, whole exome and genome analyses, which are being performed with increasing frequency in a timely manner for diseases of unclear genesis, promise significant improvement with a markedly faster diagnosis for the patients.

[H1] Outlook

[H2] Clinical developments

Consensus diagnostic and treatment guidelines are not available for CIP and HSAN, but are needed to improve diagnosis and management, raise awareness of these rare conditions and improve trial-readiness in the age of genetic therapies. The awareness of CIP and HSAN could also be improved through the active communication of physicians and scientists with patient advocacy groups and through joint public relations work. At the same time, centres for rare diseases can offer a contact point here for patients and clinicians. A major need is international longitudinal cohort studies in CIP and HSAN to define the natural history of the subtypes and develop responsive outcome measures to be trial ready for the emerging candidate therapies arising from pre-clinical studies [292].

[H2] Sequencing technology

NGS has accelerated and improved the molecular diagnosis of CIP and HSAN in some regions; however, this does not apply to low-income countries, in which NGS **[Au:OK?ok]** is often only possible within international research projects. Moreover, routine NGS normally does not detect unconventional mutations. Emerging genomic technologies such as long-read sequencing, and possibly single cell sequencing will lead to a better understanding of the genetic landscape of CIP or HSAN for patients harbouring unconventional mutations. These technologies will also likely identify novel disease-causing genes and mutation types, such as alterations in long-range enhancers and other non-coding elements, altered methylation, somatic mosaicism, repeat expansions, digenic inheritance and deep intronic mutations. Application of multi-OMICs technologies integrating metabolomics, genomics, transcriptomics, and proteomics will also improve understanding of the genetics of CIP and HSAN.

[H2] Human iPSCs and organoids

Models of human sensory neurons are important for research into the pathogenesis of CIP and HSAN and to test potential therapies. IPSCs can differentiate into sensory neurons – including mechano-sensing neurons [293] and nociceptors [294] – *in vitro* when treated with small molecule pathway inhibitors [295], or by transcriptional programming via controlled co-expression of NGN2 and BRN3A [296](**Fig. 5**). These cellular models can be used to test responses to potential therapies [135,297,298]. However, although iPSCs can be used to study the effect of mutations on neurons, it is not possible to generate the full array of distinct nociceptor sub-populations from iPSCs and the nociceptors generated do not have full adult maturity, such as in the pattern of voltage-gated sodium channel expressed [299,300].
More complex cellular models have been developed, such as co-cultures of human iPSC-derived sensory neurons and Schwann cells [301] and future developments may occur, such as new sophisticated organoid models to study complex intercellular interactions [302,303]. Single-cell sequencing studies of sensory neurons and their **[Au:OK?ok]** projection pathways using rodent and human tissue will increasingly inform pain research [304-309].

[H2] Gene therapy

The expanding field of targeted molecular therapies (including gene therapy) holds promise for treating CIP and HSAN[141,310]. Expense and some toxicity issues cloud the horizon for AAV-based and other therapies, and technical limitations and target cell accessibility also pose further hurdles in the application of gene therapies [311,312]. From a mechanistic point of view, disorders associated with neural dysfunction and neurodegeneration are likely to be more tractable than neurodevelopmental defects.

[H2] Analgesics for the general population

Rare pain disorders highlight molecules and pathways that are critical for pain perception, therefore, studying these disorders could be used to identify potential analgesics, such as antibodies that block NGF binding to NTRKA, which are effective for inflammatory and arthritic pain, and *SCN9A*/$Na_V1.7$ blockers, which are both analgesics and allow opiates to be used at smaller doses (**Box 3**). In addition to targeted drug development, entirely new avenues could be explored, such as silencing an essential pain gene using viral CRISPR-Cas based gene therapy and the use of adenovirus associated viruses (AAVs) to target nociceptors with genes that will switch off pain signalling from the periphery to the central nervous system. This latter approach may be of great significance as the majority of pain that has become chronic has a continuing peripheral input. Moreover, the further dissection of the complexity of human pain processing should lead to precision medicine for pain, with the specific analgesic being able to be chosen to target the correct overactive pain pathways in each individual patient experiencing pain.

Figures and Tables

Table 1. Clinical hallmarks besides gradual or congenital loss of pain perception.
[Au:OK?ok]

Gene (protein)	Protein function	Inheritance	Classification	Typical age at onset	Prominent and distinguishing features
ARL6IP1 (ARL6IP1)	Organization of endoplasmic reticulum and mitochondrial networks	AR	nd	Congenital	Spastic paraplegia and severe acromutilations

ATL1 (ALT1)	Membrane-shaping molecule	AD	HSAN1 *(Allelic with spastic paraplegia, SPG3A)*	Adulthood	Impaired sensation of touch, involvement of upper motor neurons (some cases), fractures and osteomyelitis
ATL3 (ALT3)	Membrane-shaping molecule	AD	HSAN1	Adulthood	Spasticity (some cases), fractures, osteomyelitis and severely delayed wound healing
CLTCL1 (CLH-22)	Clathrin coated vesicles	AR	nd	Congenital	Inability to feel touch and cognitive delay
DNMT1 (DNMT1)	Epigenetic regulation	AD	HSAN1	Adulthood	Sensorineural hearing loss, progressive dementia and sleep disorder
DST (DST)	Organization of the cytoskeleton	AR	HSAN6 *(Allelic with epidermolysis bullosa, isoform-dependent)*	Congenital	Severe psychomotor retardation, joint contractures, alacrimia, feeding difficulties, cardiovascular instability, hypomimia and muscle weakness
ELP1 (ELP1/IKAP)	Transcription elongation factor complex	AR	HSAN3 *(Allelic with medulloblastoma predisposition syndrome)*	Congenital	Loss of proprioception leading to spinal deformities, alacrimia, gastrointestinal dysfunction, cardiovascular instability and autonomic crises
FAAH-OUT (non-coding RNA)	Endocannabinoid signalling	AD/AR	CIP	Congenital	Impaired anxiety
FLVCR1 (FLVCR1)	Heme metabolism	AR	Nd *(Allelic with posterior column ataxia with retinitis pigmentosa, PCARP)*	Congenital	Psychomotor delay, delayed wound-healing, anemia and retinitis pigmentosa
GMPPA (GMPPA)	Protein glycosylation	AR	AAMR	Congenital	Psychomotor delay, achalasia (swallowing disorder) and alacrimia (lack of tears)
KIF1A (KIF1A)	Axonal transport	AR	HSAN2	Childhood	Muscle weakness and autonomic involvement

MADD (MADD)	TNF-α signalling	AR	DEEAH	Congenital	Psychomotor delay, exocrine and endocrine dysfunction and pancreatic insufficiency
MPV17	Maintenance of mitochondrial DNA (mtDNA)	AR	CMT2EE *(Allelic with MTDPS6)*	Juvenile - Adulthood	Distal sensory impairment, signs of CMT, restrictive lung disease, steatosis and muscle weakness
NGF (NGF)	Neurotrophin signalling	AR	HSAN5	Congenital	Variable degree of intellectual disability, fractures, osteomyelitis, corneal lesions and anhidrosis (lack of sweating leading to hyperthermia and fever episodes)
NTRK1 (TRKA)	Neurotrophin signalling	AR	HSAN4	Congenital	Variable degree of intellectual disability, painless fractures, osteomyelitis, corneal lesions and anhidrosis (lack of sweating leading to hyperthermia and fever episodes)
PRDM12 (PRDM12)	Epigenetic regulation	AR	HSAN8	Congenital	Normal intellect, but in a few cases intellectual disability, facial injuries, corneal lesions and hypohidrosis
RAB7A (RAB7)	Axonal transport	AD	HSAN *(Also classified as Charcot-Marie-Tooth, CMT2B)*	Adulthood	Strong motor involvement
RETREG1 (RETREG1 / FAM134B)	Selective autophagy of the ER (ER-Phagy), Golgi	AR	HSAN2	Childhood	Spasticity, muscle weakness may occur, osteomyelitis and hyperhidrosis
RFC1 (RFC1)	DNA synthesis during replication or after damage	AR	CIAP / HSAN *(Allelic with CANVAS syndrome)*	Adulthood	Large clinical spectrum: sensory neuropathy, numbness (sometimes with pain), chronic cough, cerebellar and vestibular dysfunction, afferent ataxia/proprioceptive loss
SCN9A (NaV1.7)	Voltage-gated sodium channel	AR	CIP / HSAN2	Congenital	Anosmia (absent sense of smell) and fractures

	(neuron excitability)				
SCN11A (NaV1.9)	Voltage-gated sodium channel (neuron excitability)	AD	CIP / HSAN7	Congenital	Pruritus, delayed motor development, joint hypermobility, skin ulcers (cervical region), intestinal dysmotility and sometimes abdominal pain
SPTLC1 (SPTLC1)	Sphingolipid-Metabolism	AD	HSAN1 *(Allelic with amyotrophic lateral sclerosis, ALS)*	Adulthood	Mild motor involvement (some cases more pronounced), osteomyelitis, amputations, autonomic involvement rare, shooting and lancinating pain
SPTLC2 (SPTLC2)	Sphingolipid-Metabolism	AD	HSAN1	Adulthood	Mild motor involvement (some cases more pronounced), osteomyelitis, amputations, autonomic involvement rare, shooting and lancinating pain
TECPR2	Autophagy	AR	HSAN9 *(Allelic with spastic paraplegia, SPG49)*	Congenital	Dysautonomia and respiratory failure
WNK1 (WNK1)	Kinase activity, ion transport and ER	AR	HSAN2	Childhood	Severe acral mutilations
ZFHX2 (ZFHX2)	Transcription	AD	CIP	Congenital	Normal intellect

CANVAS: Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome; CIAP: Chronic Idiopathic Axonal Polyneuropathy; MTDPS6: mitochondrial DNA depletion syndrome-6

Fig. 1: Pain processing pathway.

Subtypes of peripheral sensory neurons mediate the sensations of temperature, touch, pressure, vibration, itch and pain. Nociceptors are sensory neurons (predominantly thin myelinated Aδ and unmyelinated C-fibers) that detect tissue injury. Nociceptors innervate skin, bone and inner organs and project to the dorsal horn of the spinal cord. After processing within complex spinal circuits, projection neurons transmit this information to relays such as the parabrachial nucleus and thalamus and ultimately a distributed cortical network including those regions processing the discriminative aspects of pain (primary somatosensory cortex) and affective components (e.g. anterior cingulate and insular cortex). The descending pain modulatory system, which includes the peri-aqueductal gray and

rostral ventromedial medulla, can suppress or facilitate nociceptive signalling within the spinal cord[313,314].

Fig. 2. Clinical images of patients with CIP or HSAN. Owing to the insensitivity to pain, patients with CIP or HSAN may present with a variety of severe clinical symptoms including self-inflicted mutilations of tongue, lips and distal phalanges, corneal opacities, foot ulcers and deformities. Excessive scratching may occur leading to painless tissue damage, and recurring fractures can result in malposition of bones and joints, here represented by a knee joint in a patient with *SCN11A* mutation. The affected genes are indicated, respectively. Some images have been reproduced with permission [55,67,76,153].

Fig. 3. Overview on cellular mechanisms in CIP and HSAN. The dysregulation of various cellular compartments can lead to CIP and HSAN. Whilst dysfunction of voltage-gated ion channels (*SCN9A*/$Na_V1.7$, *SCN11A*/$Na_V1.9$) leads to dysregulated action potentials, mutations in *NGF* and the gene encoding its receptor TRKA (*NTRK1*) may cause disturbed nerve outgrowth. Further dysregulated mechanisms in CIP/HSAN include transcription and epigenetic regulation in the nucleus (such as with *DNMT1* and *PRDM12* mutations), axonal transport (such as with *KIF1A* and *RAB7A* mutations), sphingolipid metabolism (*SPTLC1* and *SPTLC2* mutations) as well as homeostasis of the endoplasmic reticulum (such as mutations in *ATL1, ATL3* and *RETREG1*).

Fig. 4. HSAN and ER-Phagy. ATL1, ATL3 and RETREG1 (also known as FAM134B) mediate the degradation of endoplasmic reticulum (ER) subdomains via selective autophagy (ER-phagy). RETREG1 bridges ER membranes with the autophagosomal membrane via a C-terminal LC3 interacting region, whereas ATL3 binds via two N-terminal GABARAP interacting motifs. ATLs promote the degradation of ER tubules and RETREG1 promotes the remodelling and degradation of ER sheets. In respective HSAN subtypes, dysfunction of this molecular pathway leads to neurodegeneration.

Fig. 5. Human iPSC models in CIP/HSAN research. A| Induced pluripotent stem cells (iPSCs) can undergo differentiation to nociceptors *in vitro*[295,315]. B| Differentiation of iPSCs to nociceptors using lentiviral mediated ectopic expression of neurogenin 1 (NGN1) in neural crest like cells (NCLCs). Cells are transduced with a lentiviral vector carrying the coding sequences of NGN1, GFP and a puromycin resistence (PuroR) under the control of a doxycycline inducible promoter (TetON)[316]. C| Immunostaining of human iPSC-derived sensory neurons with β-III-tubulin (green), BRN3A (red) and Hoechst 33342 (blue). D| iPSC-derived sensory neurons can be used to assess potential treatments for HSAN and CIP. In this example **[Au:OK?ok]** , neurite outgrowth (assessed using NF200 immunostaining) is reduced in iPSC-derived sensory neurons from patients with HSAN1 carrying the *SPTLC1* p.(Cys133Trp) mutation. Neurotrophin administration does not rescue neurite outgrowth; however, supplementation with L-serine (which reduces the production of toxic 1-deoxySLs) significantly enhances neurite outgrowth. Adapted and modified from Clark *et al*. [177].

Box 1. Researching rare diseases.

[Au: please ensure the data in this box are referenced accordingly] In the European Union, a rare disease is considered a disorder that affects no more than 5 in 10,000 people. Other regions have different definitions of a rare disease, such as a prevalence of no more than 1 in 1,500 people in the USA and 1 in 2,500 in Japan[317]. Over 6,000 phenotypes with a known molecular basis are listed in the Online Mendelian Inheritance in Man Database (OMIM) (https://www.omim.org/statistics/entry) and

a total of >9,000 phenotypes with a Mendelian basis are suspected. About 8,000 diseases are classified as rare according to the International Rare Disease Consortium (IRDiRC, https://irdirc.org/). Around 263-446 million people worldwide are estimated to have a rare disease. CIP and HSAN are exceptionally rare and only through appropriate national and international networking, it is possible to generate maximum synergies that can sustainably improve research, patient care and therapy for these diseases.

Box 2. Analgesic targets derived from monogenic pain disorders.

6 – 7 % of people have daily debilitating pain [318]. As populations age, the problem is becoming worse because pain occurs preferentially in old age, and the hundreds of thousands of deaths associated with opioid use underscore the urgent need to understand and treat the problem of pain [319]. Mendelian pain insensitivity disorders are ideally suited to uncover pharmacological targets for potent analgesics.

[bH1] SCN9A

Blocking the voltage-gated sodium channel $Na_V1.7$ is a possibility for pain management as patients with $Na_V1.7$ null-mutations have complete analgesia with few additional symptoms. Pharmaceutical companies have tried targeting $Na_V1.7$ [320] for analgesia; however, there are many pitfalls before such compounds may come into clinics such as subtype selectivity and degree of $Na_V1.7$ inhibition to be efficient [142]. Links between $Na_V1.7$ and opioid signalling may be used therapeutically as $Na_V1.7$ blockers combined with low-dose opioids or enkephalinase inhibitors may produce profound analgesia [144].

[bH1] NGF/NTRK1

Target molecules that lead to developmental defects of nociceptors in those with Mendelian pain loss disorders (HSAN4 and HSAN5), may nevertheless be interesting approaches for pain therapy **[Au:OK?yes]** . Examples include clinical trials with nerve growth factor (NGF) or tropomyosin receptor kinase A (TRKA) antibodies [321]. A neutralising monoclonal antibody to NGF has been rejected by the FDA for osteoarthritis pain due to potential adverse reactions leading to joint replacement [322].

[bH1] FAAH

Activation of the endogenous cannabinoid system by targeting the enzyme fatty acid amide hydrolase (FAAH) might be a promising strategy to treat pain and inflammation.

Target (gene/protein)	Drug candidate	Modality	Trials (completed, ongoing)
SCN9A/Nav1.7	Vixotrigine	Small molecule inhibitor	NCT03339336 and NCT03070132
SCN9A/Nav1.7	BIIB-095	Small molecule inhibitor	-
SCN9A/Nav1.7	AM-6120, AM-8145, and AM-0422	Peptide derived from tarantula venom	-
SCN9A/Nav1.7	VY-NAV-01	Gene therapy	-
NGF/NGF	Tanezumab	Monoclonal antibody	NCT02528253 and NCT02528188
NGF/NGF	Fasinumab	Monoclonal antibody	NCT03161093 and NCT02620020
NTRK1/TRKA	ASP7962	Small molecule inhibitor	NCT02611466
NTRK1/TRKA	GZ389988A	Small molecule inhibitor	NCT02845271
FAAH/FAAH	JNJ-42165279	Small molecule inhibitor	-

Box 3. Patient and family experience.

Our eldest of three sons has felt no pain since birth. But that's not quite true for him. Sometimes he has severe pain in his feet that lasts for 30-60 seconds, which is unbearable. He can also perceive showers and warm drops of water on his skin as extremely unpleasant. On the other hand, he breaks his thigh bone without it causing him any pain. He is very social and has an extremely good sense of humour. He is cheerful. He has hobbies like all 16-year-old boys. He likes computer games, mountain biking and meeting friends. But he has plenty of medical problems. When he is sick, it normally means he is really sick. Broken bones, operations, bone infections and his poor wound healing have led to a leg length discrepancy that makes walking difficult. He has an insatiable itch, so that he inflicts extensive wounds on himself by scratching and rubbing. He inflicted large mutilations on his nose when he was still a child. When people look and talk because of his mutilations, he says, let them look, I don't mind. It hurts us as parents, but he copes admirably and that is a real strength of him. Weight gain is extremely difficult due to his gastrointestinal motility disorder, he has a sweat regulation disorder, continence problems and he still often bites his fingernails completely. Specialists from various disciplines take care of each of his medical needs, but often one does not talk to the other. What we have always lacked enormously and what would be a great help for him and for us is a central contact person who simply keeps an eye on him, who knows him, who directs his medical care and keeps the specialists mutually informed. This aspect becomes even more relevant if the transition into adulthood is to succeed. This is where we are really concerned. We need the linking of the various doctors and constant care by a central contact point. Respective structures are obviously neglected in our health system.

From a discussion with a family with a boy with SCN11A-related CIP.

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