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REVIEW ARTICLE

Molecular Genetics of Hereditary Sensory Neuropathies

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Abstract

Hereditary sensory neuropathies (HSN), also known as hereditary sensory and autonomic neuropathies (HSAN), are a clinically and genetically heterogeneous group of disorders. They are caused by neuronal atrophy and degeneration, predominantly affecting peripheral sensory and autonomic neurons. Both congenital and juvenile to adulthood onset is possible. Currently, the classification of the HSN depends on the mode of inheritance, age at onset, and clinical presentation. Hallmark features are progressive sensory loss, chronic skin ulcers, and other skin abnormalities. Spontaneous fractures and neuropathic arthropathy are frequent complications and often necessitate amputations. Autonomic features vary between different subgroups. Distal muscle weakness and wasting may be present and is sometimes so prominent that it becomes difficult to distinguish HSN from Charcot-Marie-Tooth syndrome. Recent major advances in molecular genetics have led to the identification of seven gene loci and six-disease causing genes for autosomal-dominant and autosomal-recessive HSN. These genes have been shown to play roles in lipid metabolism and the regulation of intracellular vesicular transport, but also a presumptive transcriptional regulator, a nerve growth factor receptor, and a nerve growth factor have been described among the causative genes in HSN. Nevertheless, it remains unclear how mutations in the known genes lead to the phenotype of HSN. In this review, we summarize the recent progress of the molecular genetics of the HSN and the implicated genes.

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Index Entries: Hereditary sensory and autonomic neuropathy; HSN; HSAN; CMT2B, familial dysautonomia; CIPA; NGF.

Introduction

Hereditary sensory neuropathies (HSN), also known as hereditary sensory and autonomic neuropathies (HSAN), constitute a clinically and genetically heterogeneous group of disorders of low prevalence. They are part of the inherited neuropathies and are characterized by neuronal atrophy

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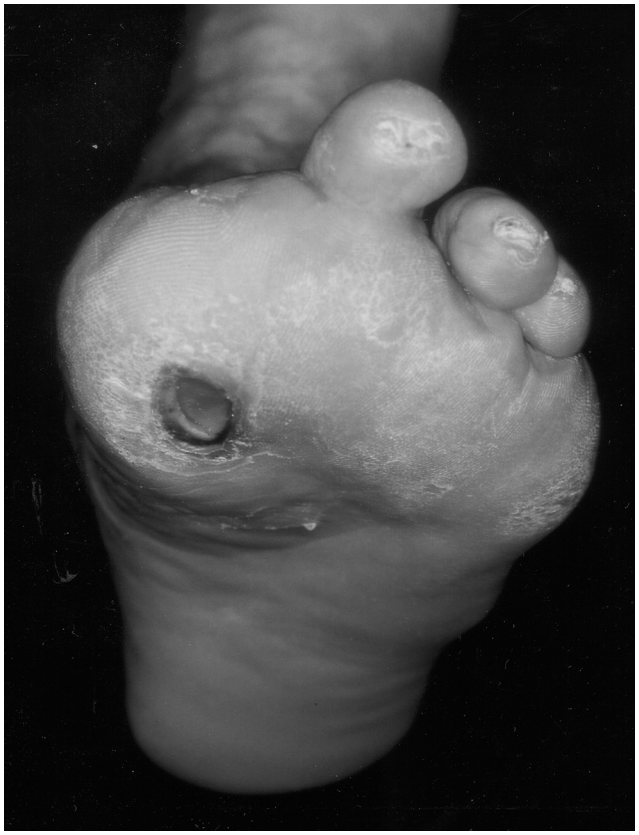

Fig. 1. Typical plantar foot ulceration and amputation of the first and fifth toe in a patient with adulthood-onset hereditary sensory neuropathy (HSN) excluded for mutations in the *SPTLC1*, *RAB7*, and *HSN2* genes.

and degeneration predominantly affecting peripheral sensory and autonomic neurons (Dyck, 1993). Congenital and juvenile to adulthood disease onset is possible. Hallmark features are progressive sensory loss, skin changes such as hyperkeratosis followed by chronic skin ulcers and dystrophic nail changes. Distal muscle weakness and wasting is variable, and spontaneous fractures and neuropathic arthropathy sometimes necessitating amputations are common (Dyck, 1993) (Fig. 1). Autonomic features vary between different subgroups. Occasionally, deafness may be observed. These impressive clinical findings are not only seen by neurologists but also by general practitioners, orthopedists, and dermatologists. Historically, various terms have been used to describe the HSN such as *familial trophoneurosis, familial syringomyelia*, and *mal perforant du pied*, among others (Dyck, 1993). The classification of the HSN proposed by Dyck et al. was suggested before the detection of responsible genes and was thus based on the age at onset, the mode of inheritance, and the predominant phenotype. It comprises five main subtypes (HSN, HSAN types 1–5) and is still useful in clinical practice. In the dermatological literature, the eponym *Thevenard's syndrome* (*L'acropathie ulcéromutilante familiale*) (Thevenard, 1942) is used to address hereditary forms, named after the author of the first report in 1942. A sporadic and clinically indistinguishable form is caused by neurotoxic agents, mainly alcohol and diabetes. This acquired form was first described in 1955 and is called Bureau–Barriere syndrome (*nonfamilial ulceromutilating neuropathy*) (Bureau, 1955).

In the last 10 yr, the introduction of genome-wide linkage studies enabled genetic testing of several HSN families and helped elucidate the molecular genetic background. These studies confirmed the previously delineated phenotypes but they also showed considerable clinical and genetic heterogeneity. Many families described fit well into the existing classification by Dyck et al. Of special interest are kindreds in which there is pronounced and most prominent muscle involvement in addition to sensory disturbances and acro-mutilations (Auer-Grumbach et al., 2003; Houlden et al., 2004a). On clinical examination, it may be difficult to distinguish these forms of HSN from Charcot-Marie-Tooth (CMT) syndrome (De Jonghe et al., 1997; Elliott et al., 1997; Auer-Grumbach et al., 2000). Sometimes the same phenotype is caused by different genetic defects and sometimes, different phenotypes may be caused by the same mutation. Also, there may be a wide variation of the phenotype even within HSN families in cases with the same mutation (Auer-Grumbach et al., 2003). Table 1 shows the classification proposed by Dyck et al. and summarizes the known genes and gene loci and the phenotypic characteristics, which have been described in autosomal-dominant and autosomal-recessive forms of HSN. Here we review the disease-causing genes that are currently known for autosomal-dominant and autosomal-recessive HSN.

Serine Palmitoyltransferase Long-Chain Base Subunit-1 Gene

Serine palmitoyltransferase (SPT) is a pyridoxal-5′-phosphate dependent enzyme, which is suggested

Table 1
Classification of HSN and Associated Genes and Gene Loci

Type	Inheritance, phenotype, and characteristics	Locus	Gene	OMIM no.
HSN (HSAN) 1	AD, predominant loss of pain and temperature sensation, preservation of vibration sense, lancinating pain, variable distal motor involvement	9q22.1-q22.3	*SPTLC1*	162400
CMT2B (HMSN2B)	AD, prominent distal motor involvement, sensory loss of all qualities, acro-mutilating complications	3q21	*RAB7*	600882
HSN (HSAN) 1B	AD, predominant sensory neuropathy with cough and gastroesophageal reflux, rarely foot ulcerations	3p24-p22	?	608088
HSN (HSAN) 2	AR, onset in the first two decades, prominent sensory loss and mutilations in hands and feet, acropathy	12p13.33	*HSN2*	201300
HSN (HSAN) 3	AR, familial dysautonomia, Riley–Day syndrome, congenital onset, prominent autonomic disturbances and complications, absence of fungiform papillae of the tongue, alacrimia, excessive sweating	9q31	*IKBKAP*	223900
HSN (HSAN) 4	AR, CIPA, episodic fever, anhidrosis, mild mental retardation, no or reduced response to painful stimuli	1q21-q22	*NTRK1*	256800
HSN (HSAN) 5	AR, congenital insensitivity to pain, rare form, severe loss of deep pain perception, bone and joints fractures resulting in destroyed joints in childhood, normal intelligence	1p13.1	*NGFB*	608654

AD, autosomal-dominant; AR, autosomal-recessive; CIPA, congenital insensitivity to pain and anhidrosis.

to be a key enzyme for the regulation of sphingolipid levels in cells. Regulation of sphingolipid synthesis at the SPT step prevents a harmful accumulation of metabolic sphingolipid intermediates including sphingoid bases and ceramide, whereas repression of other anabolic steps in the spingolipid synthetic pathway may cause intermediates to accumulate. SPT in humans consists of two hetero subunits, serine palmitoyltransferase long-chain base subunit-1 (SPTLC1) and SPTLC2 (or LCB1 and LCB2 in mammals), which are both bound to the endoplasmic reticulum (Hanada, 2003). In the human genome, the ubiquitously expressed *SPTLC1* gene consists of 15 exons spanning approx 85 kb in the chromosome 9q22 region to which the HSN1 locus was previously mapped (Nicholson et al., 1996). In 2001, Dawkins et al. showed that specific missense mutations in the human gene *SPTLC1* cause autosomal-dominant HSN type 1. In this study, 11 out of 24 HSN families screened revealed mutations in the *SPTLC1* gene. The most common mutation was a single base substitution c.399T > G in exon 5 of the *SPTLC1* coding region resulting in a single amino acid substitution of cysteine to tryptophan (Cys133Trp). This mutation was found in eight HSN1 families of Australian, English, and Canadian origin. Two less common missense mutations in exons 5 and 6 (c.398G > A and c.431T > A, i.e., Cys133Tyr and Val144Asp) were identified in an Austrian family and an Australian/English (Dawkins et al., 2001) family. Furthermore, Dawkins' findings were independently confirmed at the same time by Bejaoui et al. (2001), who reported the Cys133Tyr and the Cys133Trp mutations in two unrelated families with HSN1.

Haplotype analysis was then performed in the families reported by Dawkins and demonstrated that three Australian families of English extraction and three English families had the same haplotype on chromosome 9, suggesting a common founder (Nicholson et al., 2001). They also indicated that the sensorimotor neuropathy phenotype caused by the c.399T > G point mutation was the same as that reported by Campell and Hoffmann and, possibly, the same as that originally described by Hicks (Nicholson et al., 2001). Subsequently, screening of further HSN1 families from Czechia and Portugal confirmed the hitherto known mutations (Geraldes et al., 2004; Seman et al., 2005). A novel missense mutation c.1160G > C (Gly387Ala) in exon 13 was identified in twin sisters from Belgium (Verhoeven et al., 2004). Subsequently, it was therefore suggested that *SPTLC1* might be the causative gene in the majority of HSN1 patients. This assumption, however, was questioned in a recent study in which the authors found an *SPTLC1* mutation in only 1 of 25 families tested (Klein et al., 2005). (http://www.molgen.ua.ac.be/CMTMutations/summarizes all mutations that have been identified as a cause of HSN1.)

Phenotype–genotype correlation studies were carried out in several patients and families with mutations in the *SPTLC1* gene and demonstrated a variable spectrum of clinical and electrophysiological features. Disease onset varies between the second and fifth decade of life. Initial signs frequently consist of loss of pain and temperature sensation in the distal parts of the lower limbs, which spreads to more proximal parts, but also to the hands with progression of the disease. Later on, patients also have loss of pinprick and surface sense, while there is a relative preservation of vibration sense in some families (Auer-Grumbach et al., 2003; Houlden et al., 2004a). Many patients suffer from painless injuries and foot ulcers associated with osteomyelitis and necrosis, which may necessitate amputation of toes, feet, or even more proximal parts of the limbs. Later on, wound-healing disturbances and mutilations may also occur in the fingers and are then associated with finger amputations. Many patients experience severe shooting and lancinating pain in the limbs, but sometimes also in the trunk, which appeared to be a typical symptom of the disease. Prominent distal muscle weakness and wasting is common. Autonomic features are rarely observed. The disorder is slowly progressive, but is often severely disabling after a long duration of the disease (Auer-Grumbach et al., 2003; Houlden et al., 2004a).

There is only limited information of nerve conduction studies and biopsy findings in HSN1 patients, but a primarily axonal nerve damage of both the motor and sensory nerves has been suggested (Dyck, 1993). The study of Whitaker et al. in the family later shown to carry a *SPTLC1* mutation and the study by Dubourg et al. show motor conduction slowing, possibly implying a demyelinating process (Whitaker et al., 1974; Dubourg et al., 2000).

The Cys133Trp and Val144Asp *SPTLC1* mutations were originally suggested to increase the SPT function with higher levels of glycosyl ceramide compared with controls behaving as gain-of-function mutations (Dawkins et al., 2001). However, more recent studies showed that both mutations reduce the normal SPT activity in various mammalian cell types, including cultured lymphoblasts from HSN1 patients indicating that *SPTLC1* mutations are dominant inactivating (Bejaoui et al., 2002; Gable et al., 2002). The reason for the discrepancy of the two studies is unknown (Hanada, 2003). Recently, Dedov et al. carried out functional studies in order to detect mechanisms leading to the HSN1 phenotype. Their tests using cells from HSN1 patients with the mutation C.399T>G-(Cys133Trp) in the *SPTLC1* gene revealed a reduction of SPT activity in transformed lymphocytes of 44%. Interestingly, this had no effect on various spingolipid-associated functions as *de novo* biosynthesis, cellular sphingolipid content, cell proliferation, or death (apoptosis and necrosis). Other tests showed similar results with no effects on viability of cells after removal of extracellular shingolipids, on permeability to triton X-100 of primary lymphocytes, on viability or in whole blood counts. Thus, the authors concluded a sufficient activity of the nonmutant allele for adequate sphingolipid biosynthesis and cell viability. The authors speculated that neurodegeneration in HSN1 is owing to rather subtle and long-term effects like abnormal protein(s) similar to other neuredegenerations. A mouse model that exhibits some features of HSANI was recently generated by overexpressing the SPTLCI (Cys133Trp) mutation (McCampbell et al., 2005). The latter mice develop age-dependent mild sensory and motor loss, and loss of large myelinated axons in the spinal cord ventral root, as well as myelin thinning. These abnormalities were associated with increased

amounts of long-chain ceramides in the affected tissues, suggesting a role for these lipids in damage to myelinating cells and axons. In summary, it is unclear why mutations in a protein widely expressed in all tissues, trigger pathology that is highly restricted to specific subsets of cells within a tissue (Dedov et al., 2004).

SPTLC2, the second gene for the SPT protein, is located on the chromosome 14q24.3-q31 region and consists of 12 exons (Hanada, 2003). Dawkins et al. screened 12 index patients from families with presumed sensory neuropathies without mutations in the *SPTLC1* gene. As they could not find any mutations in the *SPTLC2* gene they concluded that *SPTLC2* mutations are not a common cause for HSN (Dawkins et al., 2002).

Small GTPase Late Endosomal Protein *RAB7* Gene

RAB7 belongs to the Rab family of Ras-related GTPases. These Rab proteins are essential for the regulation of intracellular membrane trafficking. The *RAB7* gene consists of five exons and the protein has been localized to late endosomes and shown to be important in the late endocytic pathway. Rab proteins may have a role in linking vesicles and target membranes to the cytoskeleton (Echard et al., 1998; Nielsen et al., 1999). Genetic linkage studies in a large American family with autosomal-dominant CMT2, but also prominent ulcero-mutilation complications, revealed linkage to chromosome 3q13-q22 (Kwon et al., 1995). The disorder was genetically classified among the hereditary motor and sensory neuropathies (HMSN) and subcategorized as HMSN2B (CMT2B). The authors explained the classification among the HMSNs by the presence of prominent muscle involvement in addition to sensory disturbances and marked acromutilations (Kwon et al., 1995). However, this classification was questioned from the beginning and some authors argued that the disease should have been called HSN1 (Vance et al., 1996). Subsequently, this locus was confirmed in a small Scottish family and later on in an Austrian kindred considerably refining the critical interval (De Jonghe et al., 1997; Auer-Grumbach et al., 2000). Finally in 2003, two missense mutations in the gene coding for the small GTPase late endosomal protein RAB7 were identified as the causative mutations for CMT2B (Verhoeven et al., 2003). The Val162Met was found in exon 4 in the previously reported American and Scottish families but also in a small Austrian family. In the large Austrian family described in 2000, the Leu129Phe in exon 3 was found to be responsible for the disorder. This mutation was later also confirmed in further small Austrian families suggesting a common founder, and in patients from Belgium and Czechia (Verhoeven et al., 2003; Seeman et al., 2005). A third missense mutation in exon 4 of the *RAB7* gene (Asn161Thr) was reported in 2004 in an English family (Houlden et al., 2004b). The mutation is located in a highly conserved region adjacent to the reported Val162Met mutation, suggesting a functionally important hotspot for *RAB7* mutations (Houlden et al., 2004b). Interestingly, Klein et al. could not identify any mutations in the *RAB7* gene in their large series of HSN patients and sporadic HSN families, although several patients also had marked peroneal muscle wasting. They therefore concluded that further genetic linkage studies in large families are needed to identify new causative genes of HSN1 (Klein et al., 2005). Known mutations in the *RAB7* gene associated with CMT2B syndrome are shown at http://www.molgen.ua.ac.be/CMTMutations/.

The clinical and electrophysiological phenotype reported in the CMT2B families with *RAB7* mutations was similar, but broad variation of the disease severity even within families could be encountered. In the second or third decade CMT2B patients often develop foot deformity, distal motor weakness, and sensory loss as the initial sign of the disease and are therefore classified as hereditary motor and sensory neuropathy (HMSN, i.e., CMT) (Fig. 2). However, in addition, there is also often early onset of painless foot injuries, and hyperkeratosis at pressure points followed by foot ulceration with delayed healing. The latter is often complicated by bone infections, amputations, and Charcot arthropathy. The degree of muscle wasting and weakness varies and rarely muscle involvement can also be absent. Sensory loss is often located very distally, especially at the beginning of the disease and can therefore only be detected by careful clinical examination. The sensory loss affects all qualities to an equal degree including vibration sense. Pain is not a feature (Auer-Grumbach et al., 2000; Auer-Grumbach et al., 2003). In two female Austrian patients aged 51 and 58 yr

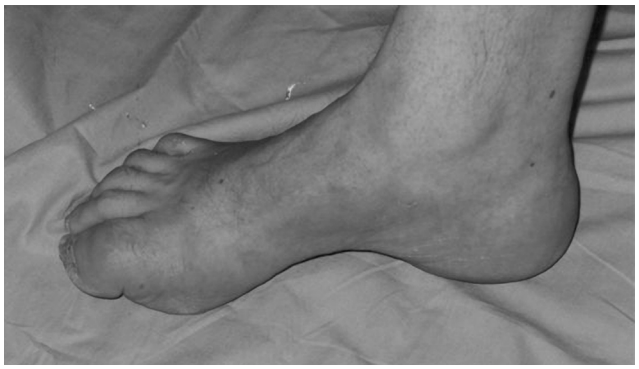

Fig. 2. Typical pes cavus foot deformity, dystrophic skin and nail changes in a patient with genetically proven CMT2B.

carrying the Val162Met and the Leu129Phe *RAB7* mutation the disorder was clinically not penetrant. However, both patients had highly pathological motor and sensory NCVs indicating subclinical involvement. Neurophysiological and histopathological studies in CMT2B patients showed a mixed motor and sensory neuropathy with axonal and sometimes also demyelinating nerve damage features (Auer-Grumbach et al., 2000; Auer-Grumbach et al., 2003). Although the function of RAB7 has already been studied in detail, it remains still unknown how mutations in the ubiquitously expressed *RAB7* gene cause a CMT2B neuropathy (Verhoeven et al., 2003).

HSN2 Gene

The *HSN2* gene is involved in an autosomal-recessively inherited form of HSN, corresponding to HSN (HSAN) type 2 in Dyck's classification (Dyck, 1993). HSN2 is characterized by early-onset sensory neuropathy in the first two decades. At the beginning of the disease, affected individuals complain of distal numbness in the upper and lower limbs in a glove-and-stocking distribution, aggravated by cold. Later on, they develop impairment of pain, temperature, and touch sensation then also involving the trunk. Other characteristics are loss of tendon reflexes, presence of plantar and finger ulcers, and spontaneous amputations, while muscle weakness is usually absent or mild. Autonomic dysfunction is not a regular feature. Mental development is normal. Sensory nerve action potentials are absent but motor nerves may be in the normal range.

The gene locus for HSN2 was assigned to chromosome 12p13.33 in Canadian isolated populations and three different mutations in a novel gene named *HSN2* were described (Lafreniere et al., 2004). The *HSN2* gene is a single-exon gene located within intron 8 of the *PRKWNK1* (WNK lysine-deficient protein kinase 1) gene, and is transcribed from the same strand as *WNK1*. Since the original description of the *HSN2* gene, further families of different ethnic origin (Lebanese, French, Austrian, Italian, and Belgian) were described exhibiting a distinct phenotype and rather uniform clinical features (Coen et al., 2006; Riviere et al., 2004; Roddier et al., 2005). All reported mutations are causing a truncation of the HSN2 protein. The hitherto known mutations in the *HSN2* gene, which are associated with HSN2 are summarised at http://www.molgen.ua.ac.be/CMTMutations/. The function of the protein, predicted to have 434 amino acids is unknown, but it is suggested that the protein may play a role in the development or maintenance of peripheral sensory neurons or their supporting cells (Coen et al., 2005, in press).

Inhibitor of κ-Light Polypeptide Gene Enhancer in B Cells, Kinase Complex-Associated Protein Gene

The kinase complex-associated protein *(IKBKAP)* gene is involved in familial dysautonomia (FD), originally termed the Riley–Day syndrome (Riley, 1949; Anderson et al., 2001; Slaugenhaupt et al., 2001). The *IKBKAP* gene encodes a protein termed IkB kinase complex-associated protein (IKAP), which is likely a component of the elongator complex and/or is a c-Jun N-terminal kinase-associated protein (Otero et al., 1999; Hawkes et al., 2002; Holmberg et al., 2002;). FD represents HSN (HSAN) type 3 in the classification proposed by Dyck (1993). FD is an autosomal-recessive disorder with prominent central and peripheral autonomic perturbances, as well as small-fiber sensory dysfunction. It has been suggested that FD is the most prevalent of the HSN (HSAN) types and also the most intensively studied (Axelrod and Hilz, 2003). FD has a remarkably high carrier frequency in individuals of Ashkenazi, or

eastern European, Jewish extraction with an estimated carrier frequency of the most common mutation in the Ashkenazi Jewish population between 1 in 27 and 1 in 32 (Dong et al., 2002; Sugarman, 2002). Disease onset is at birth and it is progressive, but individual expression varies widely. Early signs are prominent autonomic disturbances consisting of feeding difficulties owing to poor oral coordination and hypotonia. Recurrent misdirection, especially of liquids, and the high frequency of gastroesophageal reflux may lead to aspiration and may promote chronic lung disease. Other typical automomic manifestations are absence of tears (alacrima) with emotional crying; protracted episodes of nausea and vomiting, which may be triggered by emotional or physical stress; and excessive sweating. These characteristic episodes are also called "dysautonomic crisis." They are usually associated with a constellation of signs including agitation, tachycardia, and hypertension (Axelrod and Hilz, 2003). Patients can also exhibit extreme hypertension or postural hypotension and erythematous skin blotching. Taste in the tongue is decreased, especially affecting the recognition of sweet and corresponds to the absence of fungiform papillae on the tip of the tongue, which is a hallmark feature of FD. On examination, patients show decreased pain and temperature sensation, which is especially evident in the trunk and the lower limbs. With progression of the disease, vibration and joint position sense may also be abnormal. Although bone and skin pain are poorly received, sensitivity to visceral pain is intact. Deep tendon reflexes may be absent and infantile hypotonia is observed. Later on, motor involvement can promote juvenile scoliosis and gait abnormalities. Patients usually show a broad-based and ataxic gait. Somatic growth is poor and developmental milestones are commonly delayed, whereas intelligence remains normal. Half of the patients reach adulthood (Axelrod et al., 2002; Axelrod and Hilz, 2003; Axelrod, 2004).

The gene responsible for FD was mapped to the distal long arm of chromosome 9q31-q33 in 1993 (Blumenfeld et al., 1993). In 2001, Slaugenhaupt et al. and Anderson et al. reported a single base-change noncoding mutation in the donor splice site of intron 20 in the *IKBKAP* gene. This mutation was found in 99.5% of all FD cases and results in an apparent decrease in splicing efficiency that produces variable skipping of exon 20 in the *IKBKAP* message, producing truncated IKAP. A second mutation, a single G > C change in exon 19, was identified in four FD individuals of Ashkenazi Jewish extraction who were heterozygeous for the intron splice mutation (Anderson et al., 2001; Slaugenhaupt et al., 2001). Another disease-causing mutation, a proline to leucine missense mutation in exon 26 (Pro914Leu), has been seen only in one individual who was heterozygous for the common mutation but inherited the missense mutation from a non-Jewish parent (Leyne, 2003). Both the second and third mutations appear to disrupt phosphorylation. (http://www.molgen.ua.ac.be/CMT Mutations/ summarizes the disease-causing mutations in the *IKBKAP* gene reported so far.) Functional studies are ongoing, but it is still unclear how mutations in the *IKBKAP* gene predispose or cause FD (Axelrod, 2004).

Neurotrophic Tyrosine Kinase Receptor Type 1 Gene

Mutations in the neurotrophic tyrosine kinase receptor type 1 *(NTRK1)* gene (previously known as *TrkA*) have been found as a common cause of autosomal-recessive HSN (HSAN) type 4, also termed congenital insensitivity to pain and anhidrosis (CIPA) (Indo et al., 1996). TRKA protein is a receptor tyrosine kinase, which is phosphorylated in response to nerve growth factor (NGF). NGF supports the survival of sympathetic ganglion neurons and nociceptive sensory neurons in the dorsal root ganglia (Levi-Montalcini, 1987). Indo et al. also suggested that the NGF–NTRK system has a crucial role in the development and function of the nociceptive reception system, as well as establishment of thermal regulation via sweating in humans. The *NTRK1* gene maps to chromosome 1q21-q22. It contains 17 exons spanning 25 kb of DNA, of which exon 9 is alternatively spliced (Weier et al., 1995; Greco et al., 1996). Thirty-eight different missense, nonsense, and frameshift, as well as splice site mutations, have been described in families and patients with CIPA in most ethnic groups but with a relatively high prevalence in Israeli-Bedouin Arabs (Shatzky et al., 2000). The known mutations in the *NTRK1* gene leading to CIPA are listed in http://www.molgen.ua.ac.be/CMTMutations/.

The CIPA phenotype consists of characteristic features: disease onset at birth, absence of normal responses to painful stimuli, mild mental retardation, repeated traumatic, and thermal injuries. Sweating

is markedly decreased or absent and causes episodic fever and recurrent hyperpyrexia. Anhidrosis is responsible for the thick and calloused appearance of the skin with lichenification of the palms, areas of hypotrichinosis on the scalp and for dystrophic nail changes (Pinsky and DiGeorge, 1966; Axelrod and Hilz, 2003). Affected children also often demonstrate severe mutilations of the hands and feet but also the tongue and lips, and corneal scarring. Emotional tearing is normal. Hyperactivity and emotional lability are common. On examination there is widespread anhidrosis, decreased temperature sensation, as well as other sensory abnormalities but muscle strength and deep tendon reflexes are usually preserved (Pinsky and DiGeorge, 1966; Axelrod and Hilz, 2003). Nerve conduction velocity studies are normal (Bonkowsky et al., 2003), but sympathetic skin responses are absent. Typically, the histamine test shows no axon flare response, and there is no tear formation and no sweating with pilocarpine (Houlden et al., 2004a). In a skin biopsy of a 1-yr-old male with genetically confirmed HSN4, the absence of epidermal and sweat gland innervation was demonstrated (Bonkowsky et al., 2003). Histopathological findings of a biopsy performed in a 9-yr-old girl demonstrated complete absence of small myelinated and unmyelinated fibers in the cutaneous branch of the radial nerve (Rafel et al., 1980). Another sural nerve biopsy in a 2-mo-old boy with CIPA showed that unmyelinated fibers were essentially lacking, and that the number of small myelinated fibers was decreased (Matsuo et al., 1981).

An animal model showed that mice lacking the gene for *TrkA* shared dramatic features of CIPA, including loss of responses to painful stimuli, although anhidrosis was not an apparent feature in the animals (Smeyne et al., 1994). In 1996, based on this, the mouse model (Indo et al., 1996) studied human *NTRK1* encoding for NTKR1, which is autophosphorylated in response to NGF. This candidate gene turned out to be the major gene involved in CIPA and a deletion, a splice site aberration, and a missense mutation in the tyrosine kinase domain of *NTRK1* were identified (Indo et al., 1996).

Nerve Growth Factor-β Gene

In 2004, a large multigenerational consanguineous family from northern Sweden was reported in which affected members exhibited severe loss of deep pain perception that prevented them to recognize pain from bone fractures and joints resulting in destroyed joints in childhood (Minde et al., 2004). Most neurological functions, including sweating and mental abilities remained intact. Nerve conduction velocity studies were normal but temperature thresholds were increased. Because severe reduction of unmyelinated nerve fibers and moderate loss of thin myelinated nerve fibers were also observed, the disease was classified as HSN type 5 (HSAN5), a rare variant of HSN. Using a model of recessive inheritance, the authors identified an 8.3-Mb region on chromosome 1p13.2-p11.2 shared by the affected individuals. Analysis of candidate disease genes showed that all three severely affected family members were homozygeous for a c.661C > T transition in the coding region of the *NGF*-β gene (http://www.molgen.ua.ac.be/CMTMutations/). This *NGF*-β mutation results in a substitution of tryptophan for arginine on position 211 in a highly conserved region of the protein. The mutation seems to separate the effects of NGF involved in development of central nervous system functions (such as mental abilities) from those involved in peripheral pain pathways (Einarsdottir et al., 2004). To date, no further HSN5 patients with a mutation in the *NGF*-β gene have been reported. The separation of HSN5 from HSN4 may be difficult. The main difference between these two variants was thought to be the pattern of nerve fiber loss, and the greater severity of anhidrosis in the former and the lack of mental retardation in patients with the latter. In 2001, an affected boy of a consanguineous Pakistani family with HSN5 was reported who showed a mutation in the *NTRK1* gene. The authors therefore concluded that HSN types 4 and 5 are therefore likely to be allelic (Houlden et al., 2001). Moreover, further genetic heterogeneity of HSN5 has been suggested (Houlden et al., 2004a).

HSN With Cough and Gastroesophageal Reflux Linked to Chromosome 3p22-*p*24

In 2002, a family with an autosomal-dominant hereditary HSN was described in which patients

had distal sensory loss usually without foot ulcers and adult onset of gastroesophageal reflux and cough. Cough could be triggered by noxious odors and could lead to syncope. Nerve conduction velocity studies, sural, and skin biopsies revealed a sensory axonal neuropathy. Audiometry showed sensorineural hearing loss in 4 of 10 affected individuals (Spring, 2002). The disease locus in this family was linked to a 3.42 cM interval on chromosome 3p22-p24 in 2003, and was also confirmed in a second family with a similar phenotype (Kok et al., 2003). Since then, no further families with this rare form of HSN have been described. The gene involved in this disease remains to be identified.

Cytosolic Chaperon-Containing t-Complex Peptide-1 Gene in Rodents

A spontaneous autosomal-recessive mutation in the cytosolic chaperon-containing t-complex peptide-1 *(Cct4)* gene was identified in the Sprague-Dawley rat strain with an early-onset sensory neuropathy. The HSN phenotype consists of ataxia, insensitivity to pain, and foot ulceration starting shortly after birth. Pathological features include a severe reduction in the number of sensory ganglia and fibers. This mutant was suggested to be an excellent model for human HSN. The disease locus was mapped to the distal end of rat chromosome 14, a region syntenic to human 2p13-p16 and proximal mouse 11. Sequence analysis revealed a 1349G > A mutation in the chaperonin (Δ) subunit 4 *(Cct4)* gene. This change resulted in the substitution of a highly conserved cysteine for tyrosine at amino acid 450. However, screening of the human *Cct4* in HSN patients did not reveal any mutations demonstrating that this gene may not be a cause of HSN in humans. However, this study was the first report suggesting that misfolding proteins may be a cause in HSN (Lee et al., 2003).

Conclusions and Management

With the discovery of several distinct HSN loci, and ultimately the deciphering of gene defects and the identification of the proteins involved, it is now also possible to define this group of inherited neuropathies based on molecular genetic grounds. The recent genetic studies have confirmed the accuracy of the previously suggested classification, but have also shown phenotypic variation. Whereas the congenital forms of HSN usually exhibit a distinct phenotype and are easy to address, it is sometimes difficult to separate HSN with juvenile and adulthood onset from CMT disease. Thus, clinicians and genetic counselors must keep in mind that ulcero-mutilating complications are the most prominent and leading diagnostic feature in these autosomal-dominant variants of HSN and should use this sign as the most important diagnostic criterion of juvenile and adulthood HSN. However, one must consider that intrafamilial variability and reduced penetrance may mask HSN. Therefore, it is often most helpful to study additional family members to define the correct phenotype before genetic testing.

The painless neuropathic foot ulcerations observed in HSN1, CMT2B, and HSN2 mimic diabetic ulcers and resemble a *pseudodiabetic foot syndrome.* Lafreniere et al., who identified the *HSN2* gene, pointed out that HSN2 in many respects resembles the pathology of diabetic neuropathies both clinically and morphologically. They also discussed the possibility that a therapeutic, targeted to upregulate HSN2, or a protein therapeutic derived from HSN2, could be used to prevent the nerve-degeneration features of diabetic neuropathy, which currently has no specific treatment modality. Moreover, they speculated that mutation carriers might be at increased risk of neuropathic complications secondary to other diseases, such as diabetes. The same could be true for HSN1 and CMT2B. However, no studies addressing the question whether distinct polymorphism in the *SPTLC1*, *RAB7,* or *HSN2* genes are associated with a higher risk developing diabetic foot complications have been published so far. In HSN5 (HSAN5), mutations in the *NGF* gene have been identified. Interestingly, in diabetic neuropathy NGF has been shown to be depleted in early human skin biopsies, in correlation with dysfunction of nociceptor fibers, but clinical trials using rhNGF have been disappointing (Anand, 2004).

Therapy strategies have recently been shown in FD (HSN/HSAN HSN3), based on the type of the most prevalent causative mutation, resulting in aberrant splicing and a truncated protein (Anderson et al., 2003b). Searching agents altering the level

of splice-regulating proteins, the authors reported the ability of tocotrienols, members of the vitamin E family, to increase transcription of IKAP mRNA in FD-derived cells, with corresponding increases in the correctly spliced transcript and normal protein. Their findings suggested that in vivo supplementation with tocotrienols might elevate *IKBKAP* gene expression and in turn increase the amount of functional IKAP protein produced in FD patients. In an additional paper they also suggested the possible use of epigallocatechin gallate (EGCG), a polyphenol, to downregulate the expression of hnRNP A2/B1 in FD-derived cells (Anderson et al., 2003a). The authors further report on possible therapeutic effects of a combination of tocotrienol and EGCG.

No gene-based therapies are available till date for any variant of HSN. Yet, accurate diagnosis is important and requested by patients and at risk family members and enables appropriate genetic counseling. Treatment of foot ulcers and infections match exactly the guidelines for diabetic foot care. Principles of therapy are removal of pressure to the ulcer, eradication of infection, and specific protective footwear afterward. In recent years, patient care for foot problems has reached a level, which allows treatment in shorter time, on an outpatient basis, and thus avoids often hospitalization and complications like amputations. The patients seek medical advice at general practitioners, surgeons or dermatologists, yet they and also their physicians are often not aware that they are dealing with a neurological disease, thus delaying an appropriate work-up.

In summary, the increasing understanding of the molecular basis of HSN combined with the initial glimpses into their pathophysiology raise hopes for adequate treatments of these patients in the future. Finally, this knowledge might also be an important contribution in the detection of causative mechanisms and appropriate treatment in similar acquired disorders such as diabetic neuropathies.

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