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Hereditary Sensory and Autonomic Neuropathy IV

[*Congenital Insensitivity to Pain with Anhidrosis; HSAN IV, HSAN Type IV*]

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Summary

Disease characteristics. Hereditary sensory and autonomic neuropathy type IV (HSAN IV) is characterized by congenital profound sensory loss affecting perception of pain and temperature, and absence of sweating. Secondary consequences of reduced pain perception include: oral self-mutilation (biting of tongue, lips, and buccal mucosa); fingertip biting; repeated bone fractures and joint trauma. Anhidrosis results in poor thermoregulation in hot environmental conditions and can cause recurrent febrile episodes. Although developmental milestones are usually normal to only mildly delayed, learning problems can be severe. Hyperactivity and emotional lability are common.

Diagnosis/testing. Axon flare after intradermal histamine phosphate injection is absent, a finding in all HSAN types that is not specific to HSAN IV. Mutations in *NTRK1* (*TRKA*), the only gene known to be associated with HSAN IV, are identified by sequence analysis in all individuals meeting HSAN IV diagnostic criteria.

Management. *Treatment of manifestations:* prevention of self-mutilation by smoothing or extracting teeth; prevention of secondary severe or debilitating orthopedic problems by daily evaluation for early signs of unrecognized injury; control of hyperthermia with acetaminophen and/or ibuprofen or direct cooling in a bath or cooling blanket; prevention of neurotrophic keratitis with tarsorrhaphy, corneal patch graft, keratoplasty, and/or scleral bandage lens. Antipsychotic and/or ADHD medications in conjunction with behavior modification as needed. Interventions for behavioral, developmental, and motor delays; educational and social support for school-age children and adolescents. *Prevention of secondary complications:* attention to temperature management during the perioperative period. *Surveillance:* annual evaluations with ophthalmology, dentistry, and orthopedics. *Agents/circumstances to avoid:* hot, dry climates; high-impact activities and sports; inadequate sedation in the postoperative period. *Testing of relatives at risk:* clarify the genetic status of at-risk infants by molecular genetic testing for the family-specific mutations in order to prevent hyperpyrexia in those who are affected.

Genetic counseling. HSAN IV is inherited in an autosomal recessive manner. Uniparental disomy (UPD) has been reported. Each child of known carriers has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible once the disease-causing mutations have been identified in a family.

Diagnosis

Clinical Diagnosis

The diagnosis of hereditary sensory and autonomic neuropathy type IV (HSAN IV; also known as congenital insensitivity to pain with anhidrosis; CIPA) is made clinically based on recognition of the following:

- **Profound sensory loss affecting pain and temperature perception**
  - Lack of response to painful stimuli (including pin prick; vigorous pressure on the Achilles tendons, testes, stylomastoid processes, and superior orbital rim)
  - Decreased perception of hot and cold, assessed quantitatively using standardized tests of thermal perception or through a history of unrecognized responses to burns
- **Absence of the axon flare response after intradermal histamine phosphate injection**. After intradermal injection of 0.1 ml histamine phosphate (1:10,000 dilution or 0.275 mg histamine phosphate/mL) usually an initial local area of erythema appears, followed within three to five minutes by a central wheal surrounded by a diffuse flare with irregular borders. In HSAN, the wheal is surrounded by a sharply circumscribed border.

  Note: (1) The histamine test is rapid, relatively inexpensive, and sensitive. (2) When used by itself the histamine test cannot distinguish the various HSAN types; however, when other clinical findings are considered, the histamine test is helpful in patient classification.
- **Absence of sweating**. Abnormalities in the postganglionic sympathetic cholinergic pathways that regulate sweating can be identified by the following tests:
  - Quantitative sudomotor axon reflex test (QSART). In this test acetylcholine (ACh) iontophoresed through the skin using a constant 2 mA anodal current induces sweating by eccrine sweat glands and activates postganglionic sympathetic sudomotor axons. The axon reflex-mediated sweat response is quantified by a hygrometer and a multicompartmental sweat cell.
  - Sympathetic skin response (SSR). The SSR, resulting from transient electrical activity of sweat glands and adjacent epidermal tissue, can be induced by a stimulus that elicits arousal of and consecutive discharges of sympathetic sudomotor fibers, i.e., preganglionic B-fibers and postganglionic unmyelinated C-fibers. Stimuli include electrical, acoustic, and inspiratory gasp. Usually the SSR is recorded simultaneously from the dorsum of the hands and feet.

Severe learning disabilities and cognitive impairment are common [Indo 2002] but not universal [Ohto et al 2004; Oddoux et al, in preparation].

Testing

Histopathology

- **Skin biopsy.** Absence of eccrine sweat gland innervation and small nerve fibers in the epidermis
- **Sural nerve biopsy.** Reduced numbers of myelinated small-diameter fibers and unmyelinated small-diameter fibers associated with normal numbers of large-diameter fibers

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *NTRK1* (*TRKA*) is the only gene known to be associated with HSAN IV [Indo et al 1996] and accounts for all cases of properly classified HSAN IV.

Clinical testing

- **Sequence analysis.** Sequencing of the coding region and flanking intronic regions of *NTRK1* detects more than 90% of causative mutations [Oddoux et al, in preparation]. This estimate is based on results of sequence analysis in approximately 75 individuals who either fit the clinical diagnostic criteria for HSAN IV or had overlapping phenotypic characteristics but were not classified as having HSAN IV.
- **Linkage analysis** of the *NTRK1* locus has been performed successfully [Shatzky et al 2000]; however, it should be used with caution. Data from The International HapMap Consortium [2003] reveal that the gene is positioned in a recombination hot spot, making the likelihood of inconclusive or inaccurate results much higher than expected.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Hereditary Sensory and Autonomic Neuropathy IV

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method[1]	Test Availability
NTRK1	Sequence analysis	Sequence variants [2,3]	>99%	Clinical Testing

1. In individuals with impaired pain and temperature perception and anhidrosis

2. In affected Israeli-Bedouins, p.Pro621SerfsX12 accounts for 89% of mutations [Shatzky et al 2000]

3. In affected Japanese, p.Arg554GlyfsX104 accounts for more than 50% of mutations, p.Phe284TrpfsX36 for 13%, and p.Asp674Tyr for 10% [Indo 2001].

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Diagnosis of a proband is made primarily from the clinical findings of impaired pain and temperature perception and anhidrosis. The diagnosis may be confirmed by molecular genetic testing [Indo 2001, Indo 2002].

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.
Note: Given the rarity of the disorder and the likelihood of detecting variants of unknown clinical significance, full gene sequencing of reproductive partners of carriers who do not themselves have a family history of HSAN IV is not recommended.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family [Oddoux et al, in preparation].

Genetically Related (Allelic) Disorders

Controversy about the clinical criteria used to classify the individual hereditary sensory and autonomic neuropathies (HSANs) has led to the suggestion that *NTRK1* mutations may also be associated with HSAN V [Houlden et al 2001].

The finding that a boy diagnosed with HSAN V was homozygous for a mutation in *NTRK1* suggested that HSAN IV and HSAN V may be allelic [Houlden et al 2001]; however, no other examples have been reported. The report of a child with HSAN V with no mutations in *NTRK1* has further suggested that another gene or genes are causative in some individuals [Toscano et al 2002].

Somatic gain-of-function mutations that lead to constitutive tyrosine kinase activity that occurs as a result of genetic rearrangements between *NTRK1* and either *TPM3*, *TPR,* or *TFG* have been described in papillary thyroid carcinomas [Greco et al 2004, DeLellis 2006]. Constitutive activation of *NTRK1* has also been detected as a result of altered expression patterns of splice variants in neuroblastoma [Tacconelli et al 2004] and by induction of autocrine stimulation by nerve growth factor in breast and prostate cancers [Djakiew et al 1991, Dolle et al 2004].

Clinical Description

Natural History

The profound sensory loss affecting pain and temperature perception and absence of sweating characteristic of hereditary sensory and autonomic neuropathy type IV (HSAN IV) are evident in infancy when the child fails to respond appropriately to painful stimuli such as the injections associated with routine pediatric immunizations. Because sweating plays an important role in maintaining normal body temperature, anhidrosis disturbs thermoregulation in hot environmental conditions and increases susceptibility to recurrent febrile episodes [Loewenthal et al 2005]. Hyperthermia in neonates can be the first sign of the disorder.

Decreased pain perception does not spare any area and even affects cranial nerves and visceral sensation [Yagev et al 1999, Shorer et al 2001]. Self-mutilation is common. Oral self-mutilation, such as biting injuries and scarring of soft tissues (tongue, lip and buccal mucosa), is very common. In infants oral self-mutilation is typically characterized by tongue ulcers. Most affected infants also exhibit fingertip biting that begins when the primary incisors erupt.

Radiographs demonstrate evidence of repeated fractures, joint deformities, joint dislocations, osteomyelitis, avascular necrosis, and acro-osteolysis [Schulman et al 2001]. Fractures are slow to heal and large weight-bearing joints appear particularly susceptible to repeated trauma and frequently become Charcot joints (i.e., neuropathic arthropathy). Osteomyelitis occurs frequently.

Anhidrosis, present on the trunk and upper extremities in 100% of cases, is more variable in other areas of the body [Ismail et al 1998, Axelrod 2002].

Often the skin is dry with lichenification of the palms; the nails are dystrophic; and the scalp has areas of hypotrichosis.

Speech is usually clear. Hypotonia is seen frequently in the early years, but strength and tone normalize as the individual gets older; tendon reflexes are normal [Axelrod 2002]. Defects are evident in conceptual thinking and abstract reasoning. Because a large proportion of individuals have severe learning disabilities, some have stated that HSAN type IV is characterized by cognitive impairment [Indo 2002].

Hyperactivity and emotional lability are common; approximately 50% of affected individuals exhibit rages.

In most individuals baseline tear flow is diminished resulting in superficial punctate keratopathy which predisposes to corneal ulcerations and infection [Yagev et al 1999, Amano et al 2006].

Other autonomic perturbations are mild to absent:

- Overflow or emotional tearing is normal.
- Postural hypotension with compensatory tachycardia may be present but episodic hypertension is not observed, suggesting that blood pressure problems in HSAN IV are secondary to disuse atrophy or deconditioning rather than sympathetic dysfunction [Axelrod 2002].
- Gastrointestinal dysmotility is mild or absent.
- Vomiting is not a feature.
- Cyclical crises do not occur.
- Insensitivity to hypoxia and hypercapnia has not been noted.

In some individuals, subnormal adrenal function and abnormalities in the first-phase insulin response to glucose challenge are observed [Toscano et al 2000, Schreiber et al 2005].

The prognosis for independent function depends on the degree of expression and the ability to control secondary clinical problems.

Neurophysiology

- Traditional electrophysiologic studies such as motor and sensory conduction velocities by electrical and mechanical stimuli are usually normal as are somatosensory, visual, and brain stem evoked potentials [Shatzky et al 2000, Shorer et al 2001].
- Microneurography shows neural activity from A-beta sensory fibers connected to low-threshold mechanoreceptors; however, pain and skin sympathetic C fiber nerve activity are absent [Indo 2002].
- Intraneural electrical stimulation that produces unbearable pain in normal controls does not evoke any painful sensation.

Neuropathologic studies demonstrate decreased numbers of unmyelinated and small myelinated fibers in sensory nerves, including the sural nerve and the cutaneous branch of the radial nerve [Swanson et al 1965, Goebel et al 1980, Itoh et al 1986].

Studies of the skin

- Histology demonstrates normal sweat glands, sebaceous glands, and hair follicles.

- Silver stain light microscopy shows normal number and appearance of dermal nerves.
- Electron microscopy reveals lack of innervation of the eccrine sweat glands with loss of unmyelinated sudomotor fibers, possibly accounting for the anhidrosis [Langer et al 1981].
- Immunohistochemistry demonstrates absent innervation of skin and sweat glands. The lack of C- and A-delta fibers in the skin is consistent with the loss of unmyelinated and small myelinated fibers in sural nerve biopsies [Nolano et al 2000] and provides a morphologic basis for insensitivity to pain as well as anhidrosis. Nolano et al [2000] also reported an almost complete absence of dermal fibers to blood vessels and erector pilomotor muscles.

The anhidrosis is probably secondary to decreased neuronal supply from thoracolumbar sympathetic outflow.

Autopsy has demonstrated absence of small neurons in the dorsal ganglia, lack of small fibers in the dorsal roots, absence of Lissauer's tract, and reduction in size of the spinal tract of the trigeminal nerve with paucity of small fibers [Swanson 1963, Swanson et al 1965]. These findings represent almost complete absence of the first-order afferent system generally considered responsible for pain and temperature sensation.

Genotype-Phenotype Correlations

Expression varies widely even among individuals with the same two deleterious mutations [Shatzky et al 2000], suggesting that interaction with other genetic and environmental factors may contribute to the phenotype.

Mutations occur in portions of the gene that encode the intracellular or extracellular domains of the protein, which may further affect the variability in presentation. Individuals who are compound heterozygotes (i.e., have two different abnormal *NTRK1* alleles, one on each chromosome of a pair) may in some cases have unusually mild presentations [Ohto et al 2004; Oddoux et al, in preparation]. A mild phenotype has been observed when one of the alleles is a missense mutation in the portion of the gene encoding in the carboxy terminus of the protein, suggesting that aspects of the signal transduction pathway interacting with the carboxy terminus of the protein may be tissue-specific and that this allele may function normally in some, but not all, tissues, thereby leading to the milder presentation.

Prevalence

HSAN IV is the second most common HSAN and has been reported worldwide.

HSAN IV is extremely rare among most populations with the exception of the Japanese and Israeli-Bedouins, in whom relatively common founder mutations have been reported [Miura et al 2000, Shatzky et al 2000, Indo 2001]:

- The three mutations p.Arg554GlyfsX104, p.Phe284TrpfsX36, and p.Asp674Tyr account for roughly 70% of Japanese HSAN IV alleles.
- Among Israeli-Bedouins, p.Pro621SerfsX12 accounts for 89% of HSAN IV alleles [Shatzky et al 2000, Indo 2001].

Half of reported cases have occurred in offspring who were born to consanguineous parents [Axelrod 2002, Indo 2002].

Specific carrier frequencies are not available.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Hereditary sensory and autonomic neuropathies (HSANs). HSAN IV belongs to the family of HSANs [Hilz 2002]. Five HSANs are recognized. HSAN type IV is the only HSAN that is associated with widespread anhidrosis.

Hereditary sensory neuropathy type I (HSAN I) is an axonal form of hereditary motor and sensory neuropathy distinguished by prominent early sensory loss and later positive sensory phenomena including dysesthesia and characteristic "lightning" or "shooting" pains. Loss of sensation can lead to painless injuries, which, if unrecognized, result in slow wound healing and subsequent osteomyelitis requiring distal amputations. HSAN1 is often associated with progressive sensorineural deafness. Motor involvement is present in all advanced cases and can be severe. After age 20 years, the distal wasting and weakness may involve proximal muscles so that in later life a wheelchair may be required for mobility. Drenching sweating of the hands and feet is sometimes reported and rare individuals have pupillary abnormalities; visceral signs of autonomic involvement are not present. Inheritance is autosomal dominant. Mutations in *SPTLC1* are identified in approximately 90% of individuals with a positive family history and approximately 10% of simplex cases (i.e., a single occurrence in a family).

Hereditary sensory neuropathy type II (HSAN II) (Morvan's disease; acrodystrophic neuropathy). Symptoms occur in infancy or early childhood. Affected individuals have acral anhidrosis; ulcers, paronychia, whitlows, or other trophic changes of the fingers and toes; and other autonomic dysfunction including tonic pupils, oromotor incoordination, constipation from gastrointestinal dysmotility, bladder dysfunction, intermittent fevers, impaired sensory perception, hypotonia, and apnea. Unrecognized injuries and neuropathic arthropathy (Charcot joint) occur. Except for decreased or absent tendon reflexes, general neurologic examination is normal. Inheritance is autosomal recessive.

HSAN III (familial dysautonomia; FD) is a developmental disorder affecting small myelinated and unmyelinated neurons resulting in sensory and autonomic dysfunction. Symptoms are present from birth with the earliest signs being poor suck and hypotonia. The sensory dysfunction affects pain and temperature perception, but is not as profound as that in HSAN type IV, sparing the hands and feet. Autonomic dysfunction results in absent emotional tears, oromotor incoordination, and cardiovascular lability with postural hypotension and episodic hypertension. Patients are also prone to periodic vomiting crises comprising nausea, retching, hypersalivation, bronchorrhea, hypertension, tachycardia, and erythematous blotching of the skin. Clinical diagnostic criteria include absent lacrimation, absent deep-tendon reflexes, and absent lingual fungiform papillae. Inheritance is autosomal recessive. FD is caused by mutations in *IKBKAP* (RefSeq NM_003640.3), with the most common being a tissue-specific missplicing mutation in intron 20 (c.2204+6T>C) [Anderson et al 2001, Slaugenhaupt et al 2001]. More than 99% of affected patients are of Ashkenazi Jewish extraction and homozygous for the c.2204+6T>C mutation. Inheritance is autosomal recessive.

HSAN IV is hereditary sensory and autonomic neuropathy type IV or CIPA, the subject of this *GeneReview*.

HSAN V is characterized by selective loss of pain perception but normal response to tactile, vibratory, and thermal stimuli. Neurologic examination is otherwise normal. Three severely affected individuals with HSAN V born to consanguineous parents in a large Swedish family were homozygous for a mutation in *NGFB* [Einarsdottir et al 2004]. Inheritance is autosomal recessive.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with hereditary sensory and autonomic neuropathy type IV (HSAN IV), the following evaluations are recommended:

- Radiographs of extremities and weight-bearing joints
- Ophthalmologic examination to detect keratoconjunctivitis
- Dental examination

Treatment of Manifestations

The treatment of this disorder remains supportive and is oriented to (1) prevention of self-mutilation and orthopedic problems that potentially can cause severe and debilitating deformities and (2) control of hyperthermia. It is important to provide assistance and encourage therapies for behavioral, developmental, and motor delays that are appreciated during infancy and early childhood as well as to provide educational and social support for school-age children and adolescents.

Hyperthermia. Febrile spikes respond to use of acetaminophen and/or ibuprofen or direct cooling in a bath or cooling blanket [Axelrod 2002].

Orthopedic

- Careful daily evaluation for early signs of unrecognized injury is important.
- Braces may be required on the ankles to prevent injury to these weight-bearing joints.
- Sufficient sedation is necessary to avoid accidental fractures in a postoperative period.

Self-mutilation. Some children require smoothing of the teeth or extraction of the teeth to prevent self-mutilation of the tongue and lips caused by rubbing or chewing [Bodner et al 2002].

Dental. Absence of some teeth is common either as a result of self-extraction or prophylactic extraction in order to prevent injury. Early diagnosis and specific dental care for patients with HSAN IV can help prevent the fingertip biting and orofacial manifestations [Bodner et al 2002]. Management of the fingertip biting that begins as soon as the primary dentition erupts has required either smoothing of teeth edges or even dental extractions to prevent extreme consequences such as self-amputation of digits [Bodner et al 2002].

Eye. Neurotrophic keratitis is a frequent complication caused by the combination of decreased baseline moisture and corneal hypesthesia, resulting in deficient blink reflex and optimal wetting of the cornea. Treatments can include tarsorrhaphy, corneal patch graft, keratoplasty, and scleral bandage lens [Yagev et al 1999].

Behavior. Irritability, hyperactivity, impulsivity, and acting-out behaviors typically improve with age. Pharmacologic treatments with antipsychotic and/or attention-deficit/hyperactivity disorder (ADHD) medications in conjunction with behavior modification may be beneficial.

Prevention of Secondary Complications

Temperature needs to be monitored carefully during the perioperative period; the patient should not be put on a heating blanket.

Of note, the use of muscle relaxants is not a problem and malignant hyperthermia is not associated with HSAN [Tomioka et al 2002].

Surveillance

Individuals with HSAN type IV should be followed annually at a center that fosters comprehensive care and communication between the various subspecialties that are needed for optimal care. Clinical specialties that are essential are ophthalmology, dentistry, and orthopedics.

Agents/Circumstances to Avoid

- Hot, dry climates
- Jumping or high-impact activities and sports
- Inadequate sedation in the postoperative period. The decreased number of peripheral pain fibers may not be adequate to result in conscious awareness of pain yet may be sufficient to trigger an unconscious physiologic response to pain. Therefore, if tachycardia and hypertension occur in the postoperative period, the possibility of inadequate analgesia should be considered.

Testing of Relatives at Risk

Once the disease-causing mutations for a given family are known, molecular genetic testing may be used to evaluate at-risk infants, so that those who are affected can be monitored to avoid hyperpyrexia and its potential complications, including febrile seizures.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Hereditary sensory and autonomic neuropathy IV (HSAN IV) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry a single copy of an *NTRK1* disease-causing mutation.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- In families demonstrating autosomal recessive inheritance, at conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Two instances of uniparental disomy (UPD) have been reported [Miura et al 2000, Indo et al 2001]. When a proband has HSAN IV as the result of UPD, the risk to the sibs is not increased over that of the general population.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- The offspring of an individual with HSAN IV are obligate heterozygotes (carriers) for an *NTRK1* disease-causing mutation.
- The risk that a reproductive partner of an individual with HSAN IV is a carrier of an *NTRK1* disease-causing mutation is extremely low.

Other family members of a proband. Each sib of the proband's parents is at 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is possible once the disease-causing mutations have been identified in the family. Carrier testing of reproductive partners of known carriers should be considered for those individuals of Japanese or Israeli-Bedouin descent. However, given the rarity of the disorder in other populations and the likelihood of detecting variants of unknown clinical significance, full gene sequencing of reproductive partners of carriers who do not themselves have a family history of HSAN IV is not recommended.

With the exception of individuals of Japanese or Israeli-Bedouin descent, population screening is not appropriate for this rare genetic disorder.

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hereditary Sensory and Autonomic Neuropathy IV

Gene Symbol	Chromosomal Locus	Protein Name
NTRK1	1q21-q22	High affinity nerve growth factor receptor

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hereditary Sensory and Autonomic Neuropathy IV

191315	NEUROTROPHIC TYROSINE KINASE, RECEPTOR, TYPE 1; NTRK1
256800	INSENSITIVITY TO PAIN, CONGENITAL, WITH ANHIDROSIS; CIPA

Table C. Genomic Databases for Hereditary Sensory and Autonomic Neuropathy IV

Gene Symbol	Entrez Gene	HGMD
NTRK1	4914 (MIM No. 191315)	NTRK1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Individuals with HSAN type IV have loss-of-function mutations in *NTRK1,* which encodes the nerve growth factor (NGF) receptor. NGF supports the survival of nociceptive neurons and embryonic sensory and sympathetic neurons from the neural crest and ascending cholinergic neurons of the basal forebrain. Persons with HSAN IV have decreased development, survival, and maintenance of various NGF-dependent neurons [Mardy et al 1999, Indo 2002].

Subnormal adrenal function and abnormalities in the first-phase insulin response to glucose challenge emphasize the importance of the NGF-TrkA pathway in the physiology of the neuroendocrine system and its response to stress [Toscano et al 2000, Schreiber et al 2005]. Presence of a *TrkA* mutation in B cells can result in a lymphocyte signaling defect [Melamed et al 2004], which may explain some of the delayed healing observed in this disorder.

Normal allelic variants: *NTRK1* comprises 17 exons and 16 introns and spans at least 23 kb. Two main isoforms have been characterized coding for a protein of 790 or 796 amino acid residues, respectively. The longer isoform is neuronal specific and includes six amino acid residues encoded by exon 9 that form part of the extracellular domain of the neuronal-specific receptor. Additional isoforms have been detected but have yet to be fully characterized. An isoform lacking exons 6, 7, and 9 appears to be stimulated by hypoxic conditions in neuronal tissue and has been implicated in progression of neuroblastoma [Tacconelli et al 2004].

Mardy et al [1999] originally discovered the putative mutations p.His604Tyr and p.Gly613Val in *cis* with p.Gln9X. Subsequent analyses demonstrated that p.His604Tyr and p.Gly613Val are normal allelic variants; in vitro expression analysis showed normal activity of the expressed proteins carrying the variants p.His604Tyr or p.Gly613Val [Mardy et al 2001], and healthy individuals homozygous for p.Gly613Val have also been described [Shatzky et al 2000].

Pathologic allelic variants: A variety of intragenic mutations have been described including frameshift, nonsense, missense, and splicing defects, but no large insertions, deletions, or rearrangements. The mutations are not localized to any particular domain and span both the extracellular and intracellular domains. The mutation p.Pro621SerfsX12 is a common founder mutation among Israeli-Bedouins, in whom it accounts for approximately 89% of HSAN IV alleles [Shatzky et al 2000].

Among Japanese individuals affected with HSAN IV, common founder mutations are responsible for roughly 70% of cases [Indo 2001]. The most common of these founder mutations, found on more than 50% of HSAN IV-causing Japanese alleles, is the frameshift mutation p.Arg554GlyfsX104. The missense mutation p.Asp674Tyr and the splice site mutation c.851-33T>A each account for an additional 10% of cases. Multiple additional private mutations have been described in individuals from Japan.

Among other populations, a wide variety of private mutations have been described.

Table 2. *NTRK1* Allelic Variants Discussed in This *GeneReview*

Class of Variant Allele	DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change (Alias [1])	Reference Sequence
Normal	c.1810C>T (c.1876C>T)	p.His604Tyr (p.His598TyrY)	NM_002529.3 NP_002520.2
	c.1838G>T (c.1904G>T)	p.Gly613Val (p.Gly607Val)	
Pathologic	c.25C>T	p.Gln9X	
	c.851-33T>A (IVS7-33T>A)	p.Phe284TrpfsX36 (r934_935ins137)	
	c. 1660delC (c.1726delC)	p.Arg554GlyfsX104 (RArg548fs)	
	c.1860_1861insT (c.1926_1927insT)	p.Pro621SerfsX12 (Pro615fs)	
	c.2020G>T (c.2086G>T)	p.Asp674Tyr (p.Arg668Tyr)	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

1. Variant designation that does not conform to current naming conventions. For *NTRK1*, variant designations are based on the shorter isoform that is not neuronal specific.

Normal gene product: The longer neuronal-specific isoform (RefSeq NM_002529.3, NP_002520.2) encodes a 796-amino-acid membrane protein, whereas the shorter isoform expressed in non-neuronal tissues is 790 amino acids long. The gene encodes the receptor tyrosine kinase for NGF. The extracellular domain is responsible for specific binding to NGF. Binding of NGF results in dimerization of the receptor followed by autophosphorylation of the intracellular tyrosine kinase domain and C-terminal tail, which in turn is responsible for intracellular signaling. Mutations in many domains of the protein ultimately interfere with the signal transduction by the receptor.

Abnormal gene product: Mutations occur across the entire protein sequence and give rise to altered full-length products, or truncated or deletion products of varying lengths, some of which may be too short to be expressed or properly targeted in the cell.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Tomorrow: The Japan Association of Patients with Congenital Insensitivity to Pain with Anhidrosis (CIPA)
Provides information about HSAN IV in English and Japanese
Email: info@tomorrow.or.jp
www.tomorrow.or.jp

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

Specific guidelines regarding genetic testing for this disorder are in preparation [Oddoux et al, in preparation].

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Chapter Notes

Author Notes

http://www.med.nyu.edu/genetics

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