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Congenital Insensitivity to Pain with Anhidrosis

Synonyms: Hereditary Sensory and Autonomic Neuropathy Type IV, HSAN IV

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Summary

Clinical characteristics

Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV (HSAN IV), is characterized by insensitivity to pain, anhidrosis (the inability to sweat), and intellectual disability. The ability to sense all pain (including visceral pain) is absent, resulting in repeated injuries including: oral self-mutilation (biting of tongue, lips, and buccal mucosa); biting of fingertips; bruising, scarring, and infection of the skin; multiple bone fractures (many of which fail to heal properly); and recurrent joint dislocations resulting in joint deformity. Sense of touch, vibration, and position are normal. Anhidrosis predisposes to recurrent febrile episodes that are often the initial manifestation of CIPA. Hypothermia in cold environments also occurs. Intellectual disability of varying degree is observed in most affected individuals; hyperactivity and emotional lability are common.

Diagnosis/testing

The diagnosis of CIPA is suspected in infants and children with recurrent fever and biting of the tongue, lips, or fingers after eruption of the first teeth, and in older individuals with repeat traumatic injuries. Evaluation of sensory and autonomic functions (including pharmacologic tests) and skin and nerve biopsies were used in the past for clinical diagnosis, however, the diagnosis can now be confirmed by identification of biallelic pathogenic variants in NTRK1.

Management

Treatment of manifestations: Treatment is supportive and is best provided by specialists in pediatrics, orthopedics, dentistry, ophthalmology, and dermatology. For anhidrosis: Monitoring body temperature helps to institute timely measures to prevent/manage hyperthermia or hypothermia. For insensitivity to pain: Modify as much as reasonable a child's activities to prevent injuries. Inability to provide proper immobilization as a treatment for orthopedic injuries often delays healing; additionally, bracing and invasive orthopedic procedures increase the risk for infection. Methods used to prevent injuries to the lips, buccal mucosa, tongue, and teeth

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include tooth extraction, and/or filing (smoothing) of the sharp incisal edges of teeth, and/or use of a mouth guard. Skin care with moisturizers can help prevent palmar and plantar hyperkeratosis and cracking and secondary risk of infection; neurotrophic keratitis is best treated with routine care for dry eyes, prevention of corneal infection, and daily observation of the ocular surface. Interventions for behavioral, developmental, and motor delays as well as educational and social support for school-age children and adolescents are recommended.

Prevention of secondary complications: Regular dental examinations and restriction of sweets to prevent dental caries; early treatment of dental caries and periodontal disease to prevent osteomyelitis of the mandible. During and following surgical procedures, potential complications to identify and manage promptly include hyper- or hypothermia and inadequate sedation, which may trigger unexpected movement and result in secondary injuries.

Surveillance: Daily evaluation by parents and caregivers for early signs of otherwise unrecognized injury. Regular examinations by specialists in pediatrics, orthopedics, dentistry, ophthalmology, and dermatology are recommended to help prevent serious injuries and initiate early treatment. Annual follow up at a center that fosters comprehensive care and communication between the various subspecialties that are needed for optimal care.

Agents/circumstances to avoid: Hot or cold environments; hot or cold foods; hot showers or baths; jumping or high-impact activities and sports.

Evaluation of relatives at risk: If the pathogenic variants in a family are known, molecular genetic testing can clarify the genetic status of at-risk infants, so that those who are affected can be monitored to avoid hyperpyrexia and its potential complications and oral injuries when the primary teeth erupt. If the pathogenic variants in the family are not known, monitoring of the body temperature of at-risk infants during the neonatal period (i.e., first 28 days of life) can help avoid hyperpyrexia.

Genetic counseling

Congenital insensitivity to pain with anhidrosis (CIPA) results from the presence of two NTRK1 pathogenic variants. Typically one pathogenic variant is inherited from each parent (autosomal recessive inheritance); however, in some instances both pathogenic variants are from one parent (uniparental disomy).

- Autosomal recessive (AR) 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.
- Uniparental disomy (UPD). The risk to sibs of an affected individual is not increased over that of the general population.

For both AR inheritance and UPD, carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible once the pathogenic variants have been identified in an affected family member.

Diagnosis

The diagnosis of congenital insensitivity to pain with anhidrosis (CIPA) is made clinically based on presence of the following:

- Impaired perception of pain and temperature, manifest in infants by biting of the tongue, lips, or fingers after the first teeth erupt; and in older individuals by repeated traumatic injuries including bruising, bone fractures and painless joint dislocations often associated with neurogenic arthropathy (Charcot joint) of the knees and ankles. There may be a history of failure to recognize burns and other injuries.

- Anhidrosis (absence of sweating), manifest as recurrent febrile episodes beginning in early infancy
- Intellectual disability

Neurologic examination supports the diagnosis:

- Insensitivity to superficial and deep painful stimuli is confirmed when painful stimuli fail to evoke either withdrawal or emotional change [Swanson 1963]. For example, no tenderness or pain sensation is elicited even when apparently injured joints or broken bones are moved passively or actively. See also **Special studies**.
- Impaired temperature perception is confirmed when:
  - Consistent errors are made in distinguishing between hot and cold moist substances.
  - Extreme cold or heat fails to elicit the usual withdrawal response. See also **Special studies**.
- Visceral pain perception is also impaired.
- Impairment of the autonomic nervous system may be evident by the presence of Horner syndrome and the cold pressor test. See **Special studies** (pdf) for more details.
- Normal findings are:
  - Touch, vibration and position senses
  - Motor functions (unless repeated trauma has caused secondary dysfunction of motor neurons or limbs).
  - Deep tendon reflexes and superficial abdominal and cremasteric reflexes. Note: No pathologic reflexes are observed.

Additional tests supporting the diagnosis of CIPA:

- Skin tests demonstrating abnormalities in sweating and the lack of the axon reflex. See **Special studies** for more details.

Note: Skin and nerve biopsies were used to confirm the diagnosis in the past; however, molecular genetic testing is now preferred.

Special studies. Click here (pdf) for details of pharmacologic tests, evaluations of sensory and autonomic function, and results of skin and nerve biopsy used for clinical diagnosis prior to the availability of *NTRK1* molecular genetic testing.

The diagnosis of CIPA is confirmed by identification of biallelic pathogenic variants in *NTRK1* (*TRKA*) [Indo et al 1996]. Mutation of *NTRK1* accounts for all cases of properly classified CIPA.

Table 1. Summary of Molecular Genetic Testing Used in Congenital Insensitivity to Pain with Anhidrosis

Gene [1]	Method	Proportion of Probands [2] with a Pathogenic Variant Detectable by Method
NTRK1	Sequence analysis [3]	>99% [4, 5, 6]
	Deletion/duplication analysis [7]	See footnote 8
	Uniparental disomy [9]	See footnote 10
	Linkage analysis	See footnote 11

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants.
2. Individuals with impaired pain and temperature perception and anhidrosis
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. This estimate is based on results of sequence analysis in approximately 75 individuals who either fit the clinical diagnostic criteria for CIPA or had overlapping phenotypic characteristics but were not classified as having CIPA.
5. In affected Israeli Bedouins, p.Pro621SerfsTer12 accounts for 89% of pathogenic variants [Shatzky et al 2000].
6. In affected Japanese, p.Arg554GlyfsTer104 accounts for more than 50% of pathogenic variants, p.Phe284TrpfsTer36 for 13%, and p.Asp674Tyr for 10% [Indo 2001].
7. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
8. One multiexon deletion is known [Huehne et al 2008]; see Molecular Genetics.
9. In this instance it would be uniparental isodisomy, where an identical chromosome, or segment, is present in duplicate. See Uniparental disomy and Molecular Genetics.
10. See Miura et al [2000a], Indo et al [2001].
11. Although linkage analysis of the *NTRK1* locus has been performed successfully [Shatzky et al 2000], 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.

Clinical Characteristics

Clinical Description

Congenital insensitivity to pain with anhidrosis (CIPA) is characterized by profound sensory loss affecting pain and temperature perception, absence of sweating (anhidrosis), and intellectual disability.

Anhidrosis. Because sweating plays an important role in maintaining normal body temperature, anhidrosis (the failure to sweat) disturbs thermoregulation in hot environmental conditions and increases susceptibility to recurrent febrile episodes [Indo 2002].

Recurrent episodic fevers, usually the first clinical sign of CIPA, can begin in infancy or early childhood depending on environmental temperature [Swanson 1963]. Recurrent febrile convulsions are also observed in some affected infants.

Occasionally, hypothermia is observed in cold environments [Swanson 1963].

Anhidrosis is present on the trunk and upper extremities in 100% of cases and more variable in other areas of the body [Ismail et al 1998, Axelrod 2002]. Although with warming the intertriginous areas of the neck, axillae, and groin can become slightly moist, no definite sweating is noted. This moisture is probably due to delayed evaporation of insensible water [Swanson 1963].

Insensitivity to pain. While impaired pain perception may not be apparent in early infancy, parents may recall that their infant with CIPA did not cry during venipuncture or immunizations [Indo 2002].

Tongue ulcers and fingertip biting, the characteristic self-mutilation observed in infants with CIPA, begin when the primary incisors erupt, and can result in a bifid or absent tongue. Although taste buds are normal, traumatic injuries of the tongue, such as a partial loss of papillae and scar formation, may cause secondary hypogeusia or decreased taste sensation [Amano et al 1998].

Biting of the fingers and ulcerated fingertips is common.

Bruises, cuts, and burns do not elicit normal reactions and are often unrecognized at the time that they occur. Accidental injuries such as falls or burns lead to multiple scars and can lead to cellulitis in the skin.

Orthopedic problems are one of the most characteristic and serious complications of CIPA [Szöke et al 1996, Bar-On et al 2002, Kim et al 2013].

Frequent orthopedic complications are:

- Multiple fractures often with hyperplastic new bone formation, avascular necrosis, and osteomyelitis
- Auto-amputation, self-mutilation (including self-inflicted soft tissue injuries)
- Leg length discrepancy
- Joint subluxation and dislocation resulting in Charcot neuroarthropathy of the feet, ankles, knees, and hips
- Septic arthritis
- Progressive scoliosis

Amputations of fingers or limbs are common as a result of these complications.

Decreased pain perception does not spare any area and even affects cranial nerves and visceral sensation [Yagev et al 1999, Shorer et al 2001].

Neurotrophic keratitis (degenerative disease of the corneal epithelium resulting from impaired corneal sensation) manifests initially as superficial punctate keratopathy which later can result in corneal ulceration and even perforation [Yagev et al 1999, Amano et al 2006, Mimura et al 2008]. Of note, tearing (both overflow or emotional) is normal.

Intellectual disability. Most individuals with CIPA have varying degrees of intellectual disability and show characteristic behaviors [Indo 2002]. Affected individuals show defects in conceptual thinking, abstract reasoning, and social behavior, as well as moderate to severe emotional disturbance [Swanson 1963, Pinsky & DiGeorge 1966]. Some may exhibit rage. Assessments of cognitive and adaptive behavior suggest that many children with CIPA have intellectual disability (or learning disabilities) and severe attention-deficit-hyperactivity disorder (ADHD) [Levy Erez et al 2010].

Irritability, hyperactivity, impulsivity, and acting-out behaviors typically improve with age.

The prognosis for independent functioning varies.

Other

- Often the skin is dry with lichenification; the nails are dystrophic. Palmoplantar hyperkeratosis (thickening of the soles and the palms) appears in late infancy, often with scars and abrasions [Bonkowsky et al 2003]. Significant fissuring of the plantar skin is common. Some affected individuals develop painless deep heel ulcers that are slow to heal [Mardy et al 1999].
- Hypotonia is seen frequently in the early years, but strength and tone normalize as the individual gets older; tendon reflexes are normal [Axelrod 2002].
- Gastrointestinal dysmotility is mild or absent.
- Vomiting is not a feature, but can be observed in some affected individuals.

- Speech is usually clear.
- Gao et al [2013] have reported oral and craniofacial manifestations, including nasal malformation, submucous cleft palate, and developmental abnormalities of the teeth.

Neurophysiology of CIPA

- Click here (pdf) for information on additional challenges and risks associated with CIPA.
- Click here (pdf) for information on the neurophysiology of CIPA.

Genotype-Phenotype Correlations

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

Nomenclature

Terms previously used to describe CIPA include:

- Familial dysautonomia type II;
- Congenital sensory neuropathy with anhidrosis.

Prevalence

Although CIPA (or HSAN IV) has been reported worldwide, CIPA is extremely rare in most populations except the Japanese and Israeli Bedouins. Of note, in 2009 the number of Japanese with CIPA was estimated at between 130 and 210 [Haga et al 2013].

In the Japanese and Israeli Bedouin populations relatively common founder pathogenic variants have been reported [Miura et al 2000b, Shatzky et al 2000, Indo 2001]:

- Three variants – p.Phe284TrpfsTer36, p.Arg554GlyfsTer104, and p.Asp674Tyr – account for roughly 70% of pathogenic *NTRK1* alleles in the Japanese.
- One variant – p.Pro621SerfsTer12 – accounts for 89% of pathogenic *NTRK1* alleles among Israeli Bedouins [Shatzky et al 2000, Indo 2001].

Half of reported cases have occurred in offspring of consanguineous parents [Axelrod 2002].

Specific carrier frequencies are not available.

Genetically Related (Allelic) Disorders

Controversy about the clinical criteria used to classify the individual hereditary sensory and autonomic neuropathies (HSANs) led Houlden et al [2001] to suggest that mutation of *NTRK1* may also be associated with HSAN V following the identification of homozygous *NTRK1* pathogenic variants in a boy with HSAN V. No other examples have been reported.

Subsequently a child with HSAN V, reported with no pathogenic variants in *NTRK1* [Toscano et al 2002], was found to have pathogenic loss-of-function variants in *SCN9A* [Goldberg et al 2007].

Sporadic tumors (including papillary thyroid carcinoma and neuroblastoma) occurring as single tumors in the absence of any other findings of this syndrome frequently harbor somatic pathogenic variants in *NTRK1* that are **not** present in the germline; thus, predisposition to these tumors is not heritable. For more details see Molecular Genetics, Cancer and Benign Tumors.

Differential Diagnosis

Congenital insensitivity to pain (CIP) includes several genetic disorders associated with the inability to detect noxious stimuli [Indo 2012]. Individuals with CIP lack pain sensation. CIP is divided into two types: with anhidrosis (the inability to sweat) and without anhidrosis. (See also Congenital Insensitivity to Pain Overview.)

Hereditary Sensory and Autonomic Neuropathies (HSANs)

Congenital insensitivity to pain with anhidrosis (CIPA; also known as hereditary sensory and autonomic neuropathy type IV (HSAN IV) belongs to the family of hereditary sensory and autonomic neuropathies (HSANs). Seven HSANs are recognized.

CIPA (HSAN 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. HSAN I 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. Six different forms have been identified:

- **HSAN1A.** Mutation of *SPTLC1* is 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).
- **HSAN1B** (OMIM 608088). Cough and gastroesophageal reflux disease are seen, but not foot ulcers. Maps to chromosome 3p24-p22. No gene has been identified.
- **HSAN1C** (OMIM 613640). Neuropathy is phenotypically similar to HSN1A but without autonomic signs. Mutation of *SPTLC2* is causative.
- **HSN1D** (OMIM 613708). Mutation of *ATL1* is causative.
- **HSN1E.** A late-onset mild sensory neuropathy associated with ataxia and deafness. Mutation of *DNMT1* is causative.
- **HSN1F** (OMIM 615632). Mutation of *ATL3* is causative.

Hereditary sensory and autonomic neuropathy type II (HSAN II, Morvan's disease). 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 IIA is caused by mutation of *WNK1*; HSAN IIB by mutation of *RETREG1;* and HSAN IIC by mutation of *KIF1A*.

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 CIPA, 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. Mutation of *ELP1* (*IKBKAP*) (RefSeq NM_003640.3) is causative. The most common pathogenic allele is a tissue-specific missplicing variant in intron 20 (c.2204+6T>C). More than 99% of affected individuals are of Ashkenazi Jewish extraction and homozygous for the common pathogenic variant.

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

HSAN V is an autosomal recessive or dominant disorder characterized by selective loss of pain perception and thermal sensation, painless fractures, and joint deformities. Response to tactile and vibratory stimuli is normal. Some individuals with HSAN V show intellectual disability and anhidrosis [Carvalho et al 2011], but others do not [Minde et al 2004]. Mutation of *NGF* is causative. The clinical heterogeneity seen in HSAN V is probably attributable to differences in *NGF* pathogenic variants [Einarsdottir et al 2004, Minde 2006, Carvalho et al 2011, Capsoni 2014].

HSAN VI (OMIM 614653). Inheritance is autosomal recessive. Mutation of *DST* is causative.

HSAN VII (OMIM 615548). Inheritance is autosomal dominant. Mutation of *SCN11A* is causative.

Unclassified. Studies have identified the genetic bases of other forms of CIP, including a channelopathy due to pathogenic loss-of-function variants in *SCN9A* [Cox et al 2006, Ahmad et al 2007, Goldberg et al 2007]. See Congenital Insensitivity to Pain Overview.

See Hereditary Sensory and Autonomic Neuropathy: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Other Conditions

The clinical manifestations of CIPA can be similar to those seen in the following:

- Leprosy [Daneshjou et al 2012, Iftikhar & Javed 2013]
- Hypohidrotic ectodermal dysplasia
- Lesch-Nyhan syndrome (self-mutilation)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with congenital insensitivity to pain with anhidrosis (CIPA) (also known as hereditary sensory and autonomic neuropathy type IV [HSAN IV]), the following evaluations are recommended:

- General physical examination for evidence of self-mutilation of tongue, lips, buccal mucosa; skin injury including infection and/or palmoplantar hyperkeratosis, bone injury including old poorly healing fractures and/or joint injury including dislocations, as well as behavioral and developmental problems
- Orthopedic consultation regarding assessment of injuries of the extremities and weight-bearing joints, including radiographs as necessary
- Dental examination to assess for auto-extraction of teeth, evidence of dental caries and/or abscess, as well as overall dental health
- Ophthalmologic examination to assess for evidence of neuropathic keratitis and its sequelae (corneal infection, ulceration, and/or perforation)

- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Treatment is supportive and is best provided by specialists in pediatrics, orthopedics, dentistry, ophthalmology, and dermatology.

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 or hypothermia. Monitoring of the body temperature helps to institute timely measures to prevent hyperthermia or hypothermia. Hyperthermia responds to direct cooling in a bath or cooling blanket; hypothermia responds to warming by a blanket as necessary.

Control of environmental temperatures is essential to prevent hyperthermia or hypothermia.

Orthopedic. Bone fractures of weight-bearing bones and joints can lead to failure of bone union and hypertrophic osseous callous formation, as well as neurogenic arthropathy (Charcot joint) [Szöke et al 1996, Schulman et al 2001, Bar-On et al 2002, Kim et al 2013, Feldman et al 2009]. Because such injuries and their sequelae are difficult to treat, the goal of orthopedic management is to prevent severe articular destruction and the need for surgical amputation.

Although the parents and caregivers of an affected child are advised to modify the child's activities to prevent injuries, it is often very difficult due to the child's inability to perceive pain. While protective appliances, such as braces to prevent injury to the lower limbs can be tried, they are associated with a high risk of secondary skin injury and, thus, infection.

Careful daily evaluation by parents and caregivers for early signs of otherwise unrecognized injury is important for early detection and treatment of injuries.

Appropriate footwear and periods of non-weight-bearing are important in the prevention and early treatment of ulcerating foot lesions [Bar-On et al 2002].

In the treatment of various injuries the absence of pain perception makes immobilization difficult, often resulting in delayed healing. Additionally, infection is a serious potential complication of any invasive procedure, such as treatment of bone fractures with an external fixator [Kim et al 2013].

Of note, longstanding infections require wide surgical debridement.

Bone and joint deformities can be managed by corrective osteotomy; leg length discrepancy can be managed by shoe lifts and/ or epiphysiodesis [Bar-On et al 2002]; however, the value of surgical intervention needs to be weighed against non-surgical approaches including close monitoring [Kim et al 2013]. Joint dislocations are best treated conservatively.

Dental. Early and routine preventative oral/dental care and timely treatment of the dental and oral conditions associated with CIPA can help reduce the characteristic oral and dental manifestations [Amano et al 1998, Ikeda & Nihei 1999, Bodner et al 2002, Ikeda et al 2004].

In infants, the incisal edges of newly erupted mandibular primary incisors traumatize the ventral surface of the tongue with sucking and nursing. This ulceration of the tongue can lead to bleeding and infection of the tongue, and halitosis, as well as systemic problems such as poor weight gain and failure to thrive.

The oral self-mutilation (i.e., the severe biting injuries [and resultant scarring] of the fingertips and/or oral soft tissues [tongue, lip, and buccal mucosa]) is found in most affected individuals. Although self-mutilation appears

to decrease with age and with intellectual, social, and/or emotional development, such behaviors cannot be completely eliminated.

Methods used to prevent injuries to the lips, buccal mucosa, tongue, and teeth include tooth extraction, and/or filing (smoothing) of their sharp incisal edges [Bodner et al 2002], and/or use of a mouth guard, a protective plate of thermoplastic resin ~0.6-0.8 mm thick [Ikeda & Nihei 1999, Ikeda et al 2004]. Mouth guards must be refashioned as new teeth erupt and the jaw grows. Although use of a mouth guard is a reasonable approach, mouth guards can be difficult to prepare and/or retain.

The high rate of missing teeth and untreated carious teeth observed in individuals with CIPA suggests that dental examination and/or care is underutilized or that tooth decay may be overlooked because of the insensitivity to pain. Serious tooth decay can cause osteomyelitis that can lead to mandibular bone fracture.

Eye. Care for dry eyes, prevention of corneal infection, and daily observation of the ocular surface are crucial for maintaining good visual function [Amano et al 2006]. Of note, surgical treatment of neurotrophic keratitis has not been successful as poor outcomes of lateral tarsorrhaphy, corneal patch graft, and penetrating keratoplasty have been reported [Yagev et al 1999].

Skin. Daily care with a skin moisturizer is recommended to prevent or reduce skin cracking which can lead to bruising, and skin infections, which can progress to more significant infections such as cellulitis or osteomyelitis.

Parents or guardians should practice skin care to prevent serious infections, including daily observation of the whole skin surface and early treatment of even minor skin lesions.

Behavior. Interventions for behavioral, developmental and motor delays as well as educational and social support for school-age children and adolescents are important.

Although irritability, hyperactivity, impulsivity, and acting-out behaviors typically improve with age, medications for antipsychotic and/or attention-deficit/hyperactivity disorder (ADHD) in conjunction with behavior modification may be beneficial. The advantages and disadvantages should be weighed for each individual with CIPA.

Prevention of Secondary Complications

Dental care includes the following:

- Regular dental examinations and restriction of sweets to prevent dental caries
- Early treatment of dental caries and periodontal disease to prevent osteomyelitis of the mandible.

During surgical procedures, the following potential complications need to be considered and avoided:

- Inadequate sedation. The congenital absence of peripheral pain fibers may result in analgesia, but inadequate sedation in the postoperative period may trigger unexpected movement, causing secondary injuries. Therefore, tachycardia and hypertension in the postoperative period should raise consideration of the possibility of inadequate sedation.
- Hyper- or hypothermia. Temperature needs to be monitored carefully during the perioperative period; heating blankets should not be used.

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

Surveillance

Appropriate surveillance includes:

- Daily evaluation by parents and caregivers for early signs of otherwise unrecognized injury;
- Regular examinations by specialists in pediatrics, orthopedics, dentistry, ophthalmology, and dermatology to identify serious injuries and initiate early treatment;
- Annual follow up at a center that fosters comprehensive care and communication between the various subspecialties that are needed for optimal care.

Agents/Circumstances to Avoid

Avoid the following:

- Hot or cold environments; hot or cold foods; hot showers or baths
- Jumping or high-impact activities and sports

Evaluation of Relatives at Risk

If the pathogenic variants in a family are known, molecular genetic testing may be used to clarify the genetic status of at-risk infants so that those who are affected can be monitored to avoid:

- Hyperpyrexia and its potential complications, including febrile seizures;
- Injuries to the tongue, lips, and teeth when the primary teeth erupt.

If the pathogenic variants in the family are not known, monitor the body temperature of at-risk infants during the neonatal period (i.e., first 28 days of life).

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

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. —ED.

Mode of Inheritance

Congenital insensitivity to pain with anhidrosis (CIPA) results from the presence of two *NTRK1* pathogenic variants. Typically one pathogenic variant is inherited from each parent (autosomal recessive inheritance); however, rarely both pathogenic variants are from one parent (uniparental disomy) (see Molecular Genetics) [Miura et al 2000a, Indo et al 2001].

Risk to Family Members – Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry a single copy of an *NTRK1* pathogenic variant.

- When the child appears to be homozygous for an *NTRK1* pathogenic variant, carrier testing of both parents is warranted to evaluate for uniparental disomy, in particular uniparental isodisomy in which an identical chromosome (or chromosome segment) is present in duplicate [Miura et al 2000a, Indo et al 2001].
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- 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.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with CIPA are obligate heterozygotes (carriers) for an *NTRK1* pathogenic variant.

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

Risk to Family Members – Uniparental Disomy

Parents of a proband. One parent is heterozygous for the pathogenic variant present in the homozygous state in the proband.

Sibs of a proband

- When a proband has CIPA as the result of uniparental disomy, the risk to the sibs is not increased over that of the general population.
- The risk to each sib of a proband of being a carrier is 50%.

Offspring of a proband. The offspring of an individual with CIPA are obligate heterozygotes (carriers) for an *NTRK1* pathogenic variant.

Other family members of a proband. Each sib of the proband's pathogenic variant-carrying parent is at a 50% risk of being a carrier.

Carrier (Heterozygote) Detection

Carrier testing for at-risk family members is possible once the pathogenic variants have been identified in the family. However, given the rarity of the disorder and the likelihood of detecting allelic variants of unknown clinical significance, full gene sequencing of reproductive partners of carriers who do not themselves have a family history of CIPA is not recommended.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating 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 affected, 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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *NTRK1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for CIPA are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**

  Congenital insensitivity to pain with anhidrosis

- **Tomorrow: The Japan Association of Patients with Congenital Insensitivity to Pain with Anhidrosis (CIPA)**

  Provides information about CIPA (HSAN IV) in Japanese

  Kitami 8-15-35-307

  Tokyo 157-0067

  Japan

  Phone: 03-5761-2860

  Fax: 03-5761-2861

  Email: cipa@tomorrow.or.jp

  www.tomorrow.or.jp

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Congenital Insensitivity to Pain with Anhidrosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NTRK1	1q23.1	High affinity nerve growth factor receptor	NTRK1 homepage - Leiden Muscular Dystrophy pages	NTRK1	NTRK1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Congenital Insensitivity to Pain with Anhidrosis (View All in OMIM)

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

Molecular Pathogenesis

Congenital insensitivity to pain with anhidrosis (CIPA) results from pathogenic loss-of-function variants in *NTRK1*, which encodes the protein TrkA, a receptor tyrosine kinase for nerve growth factor (NGF) [Indo et al 1996, Mardy et al 1999, Indo 2001, Mardy et al 2001]. Pathogenic variants in *NTRK1* lead to an absence of functional TrkA protein.

Defects in NGF-TrkA signal transduction cause the loss of various NGF-dependent neurons during developmental apoptosis, resulting in the selective loss of NGF-dependent neurons in otherwise intact systems. Thus, individuals with CIPA lack all NGF-dependent neurons, including NGF-dependent primary afferents and sympathetic postganglionic neurons in the peripheral nervous system (PNS). The absence of pain and the presence of anhidrosis are caused by the absence of NGF-dependent primary afferents and sympathetic postganglionic neurons, respectively.

NGF-dependent neurons in the PNS also contribute to inflammatory processes. Due to the lack of NGF-dependent neurons, individuals with CIPA probably cannot mediate various neuronal or inflammatory processes via these neurons in pain, itch, and inflammation. (Read more about NGF-dependent neurons and the role of TrkA.)

Gene structure. The longest *NTRK1* transcript variant NM_002529.3 comprises 17 exons and 16 introns and spans at least 23 kb. Two main transcript variants have been characterized coding for a protein of 790 or 796 amino acid residues, respectively. The longer isoform NP_002520.2 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 (*see NTRK1*). 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]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Mardy et al [1999] originally discovered the variants p.His604Tyr and p.Gly613Val in *cis* configuration with p.Gln9Ter. Subsequent analyses demonstrated that p.His604Tyr and p.Gly613Val are benign variants; in vitro expression analysis showed normal activity of the expressed proteins carrying p.His604Tyr or p.Gly613Val [Mardy et al 2001]. Healthy individuals homozygous for the benign variant p.Gly613Val have also been described [Shatzky et al 2000].

Pathogenic variants. A variety of intragenic pathogenic variants have been described including frameshift, nonsense, missense, and splicing defects, but no large insertions, deletions, or rearrangements. The pathogenic variants are not localized to any particular domain and span both the extracellular and intracellular domains. A multiexon deletion of 1381 bp has been reported in an affected individual [Huehne et al 2008]. The frequency of such deletions is not known.

The pathogenic variant p.Pro621SerfsTer12 is a common founder variant among Israeli Bedouins, in whom it accounts for approximately 89% of CIPA alleles [Shatzky et al 2000].

Among Japanese with CIPA, common founder variants are responsible for about 70% of cases [Indo 2001]. The most common of these founder variants, found on more than 50% of CIPA-causing alleles in the Japanese, is the frameshift variant p.Arg554GlyfsTer104. The missense variant p.Asp674Tyr and the splice site variant c.851-33T>A each account for an additional 10% of cases. Multiple additional private variants have been described in individuals from Japan.

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

Uniparental disomy. Two cases of uniparental disomy have been reported [Miura et al 2000a, Indo et al 2001]. Uniparental disomy was defined as the presence of a chromosome pair (or chromosome segment) that derives

from only one parent in a diploid individual [Engel 1980]. If both chromosomes (or chromosome segments) in the affected individual are derived from the one parental chromosome with the *NTRK1* pathogenic variant, the affected individual will be homozygous for the pathogenic variant (a situation termed "isodisomy") and only one parent will be a carrier. See the *GeneReviews* Glossary, uniparental disomy.

Table 2. *NTRK1* Variants Discussed in this *GeneReview*

Variant Classification	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
Benign	c.1810C>T (1876C>T)	p.His604Tyr (His598Tyr)	NM_002529.3 NP_002520.2
	c.1838G>T (1904G>T)	p.Gly613Val (Gly607Val)	
Pathogenic	c.25C>T	p.Gln9Ter	
	c.851-33T>A (IVS7-33T>A)	p.Phe284TrpfsTer36 (r.934_935ins137) [2]	
	c.1660delC (1726delC)	p.Arg554GlyfsTer104 (Arg548fs)	
	c.1860_1861insT (1926_1927insT)	p.Pro621SerfsTer12 (Pro615fs)	
	c.2020G>T (2086G>T)	p.Asp674Tyr (Asp668Tyr)	
	1381-bp deletion [3]		

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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.

2. A splice variant in which the change is at the RNA level [Miura et al 2000b]

3. Multiexon deletion [Huehne et al 2008]

Normal gene product. The gene encodes the receptor tyrosine kinase for NGF. The longer neuronal-specific isoform NP_002520.2 encodes a 796-amino-acid membrane protein, whereas the shorter isoform NP_001007793.1, which is expressed in non-neuronal tissues, is 790 amino acids long. 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.

Abnormal gene product. Pathogenic variants 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. Pathogenic variants in regions encoding many domains of the protein ultimately interfere with the signal transduction by the receptor.

Cancer and Benign Tumors

Somatic gain-of-function variants 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, Dollé et al 2004].

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Chapter Notes

Author Notes

Dr Indo's work is in the fields of Pediatrics, Clinical and Molecular Genetics, and Clinical Neuroscience.

Kumamoto University Repository – An interview with the researcher (in Japanese)

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