



NTRK1 Congenital Insensitivity to Pain with Anhidrosis

Synonym: Hereditary Sensory and Autonomic Neuropathy Type IV (HSAN IV)

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Summary

Clinical characteristics

NTRK1 congenital insensitivity to pain with anhidrosis (*NTRK1*-CIPA) 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 *NTRK1*-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 *NTRK1*-CIPA is established in a proband with suggestive clinical findings and biallelic pathogenic variants in *NTRK1* identified by molecular genetic testing.

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 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 eyes, prevention of corneal

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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.

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 to help prevent serious injuries and initiate early treatment. Annual follow up at a center that provides 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 *NTRK1* 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.

Genetic counseling

NTRK1-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 isodisomy).

- **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 isodisomy.** The risk to sibs of an affected individual is not increased over that of the general population.

For AR inheritance, once the *NTRK1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

For uniparental isodisomy, once the *NTRK1* pathogenic variant has been identified in an affected family member, carrier testing for at-risk family members is possible.

Diagnosis

Suggestive Findings

NTRK1 congenital insensitivity to pain with anhidrosis (*NTRK1*-CIPA) **should be suspected** in individuals with the following clinical findings and family history.

Clinical findings

- Impaired perception of pain:
 - In infants. Biting of the tongue, lips, or fingers after the first teeth erupt
 - In older individuals. Repeated traumatic injuries including bruising, bone fractures, and painless joint dislocations often associated with neurogenic arthropathy (Charcot joint) of the knees and ankles.
 - A history of failure to recognize burns and other injuries
 - Failure of painful stimuli fail to evoke either withdrawal or emotional change. For example, no tenderness or pain sensation is elicited even when apparently injured joints or broken bones are moved passively or actively.
 - Impaired visceral pain perception

- Impaired temperature perception, 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.
- Anhidrosis (absence of sweating), manifesting as recurrent febrile episodes beginning in early infancy
- Impairment of the autonomic nervous system, which may be evident by the presence of Horner syndrome and the cold pressor test
- Intellectual disability

Family history consistent with autosomal recessive inheritance, including affected sibs in a single generation, simplex cases (i.e., a single affected family member), and/or parental consanguinity

Establishing the Diagnosis

The diagnosis of *NTRK1* congenital insensitivity to pain with anhidrosis (*NTRK1*-CIPA) **is established** in a proband with biallelic pathogenic variants in *NTRK1* identified by molecular genetic testing (see Table 1).

Note: Identification of biallelic *NTRK1* variants of uncertain significance (or identification of one known *NTRK1* pathogenic variant and one *NTRK1* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *NTRK1*-CIPA has not been considered – perhaps because they are too young to manifest the full spectrum of clinical findings – are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *NTRK1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: Targeted analysis for pathogenic variants can be performed first in individuals of the following ancestry (see Table 5):

- **Israeli Bedouins.** Variant p.Pro621SerfsTer12 accounts for 89% of pathogenic variants [Shatzky et al 2000].
- **Japanese.** Variant p.Arg554GlyfsTer104 accounts for more than 50% of pathogenic variants, c.851-33T>A for 13%, and p.Asp674Tyr for 10% [Indo 2001].

Note: Homozygosity for an *NTRK1* pathogenic variant in an individual with *NTRK1*-CIPA may be the result of uniparental isodisomy for chromosome 1 (i.e., two copies of the chromosome 1 with the *NTRK1* pathogenic variant are inherited from one parent and no copy of chromosome 1 is inherited from the other parent). Therefore, accurate recurrence risk counseling relies on testing both parents to determine if each is heterozygous for that *NTRK1* variant (see Genetic Counseling).

A multigene panel that includes *NTRK1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of

uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 1. Molecular Genetic Testing Used in *NTRK1* Congenital Insensitivity to Pain with Anhidrosis

Gene ¹	Method	Proportion of Pathogenic Variants ² Detectable by Method
<i>NTRK1</i>	Sequence analysis ³	>97% ^{4, 5}
	Gene-targeted deletion/duplication analysis ⁶	<3% ^{7, 8}

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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. Miura et al [2000b], Indo [2001], Geng et al [2018], Li et al [2019], and data derived from the subscription-based professional view of Human Gene Mutation Databases [Stenson et al 2017]

5. While two variants common in Asian populations, c.851-33T>A and c.[851_798C>T;851_794C>G], are detectable by sequence analysis, they are outside the range normally analyzed [Indo 2001, Geng et al 2018, Li et al 2019].

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. Huehne et al [2008], Geng et al [2018], Xue et al [2018], Li et al [2019]

8. Detection rate varies by population. An intragenic deletion was observed in multiple Chinese families [Geng et al 2018].

Clinical Characteristics

Clinical Description

NTRK1 congenital insensitivity to pain with anhidrosis (*NTRK1*-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, Indo 2018].

Recurrent episodic fevers, usually the first clinical sign of *NTRK1*-CIPA, can begin in infancy or early childhood depending on environmental temperature. Recurrent febrile convulsions are also observed in some affected infants.

Occasionally, hypothermia is observed in cold environments.

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 insensible water loss.

Insensitivity to pain. While impaired pain perception may not be apparent in early infancy, parents may recall that their infant with *NTRK1*-CIPA did not cry during venipuncture or immunizations [Indo 2002, Indo 2018].

Tongue ulcers and fingertip biting, the characteristic self-mutilation signs observed in infants with *NTRK1*-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 *NTRK1*-CIPA [Bar-On et al 2002, Kim et al 2013].

Frequent orthopedic complications:

- 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, affecting even 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 *NTRK1*-CIPA have varying degrees of intellectual disability and show characteristic behaviors [Indo 2002, Indo 2018]. Affected individuals show defects in conceptual thinking, abstract reasoning, and social behavior, as well as moderate to severe emotional disturbance. Some may exhibit rage. Assessments of cognitive and adaptive behavior suggest that many children with *NTRK1*-CIPA have intellectual disability (or learning disabilities) and severe attention-deficit/hyperactivity disorder [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 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.

Normal findings

- 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

Neurophysiology of *NTRK1*-CIPA

See Indo [2018] ([full text](#)) for information on the neurophysiology of *NTRK1*-CIPA.

Genotype-Phenotype Correlations

Clinical phenotype varies widely even among individuals with the same two *NTRK1* pathogenic variants [Shatzky et al 2000].

Nomenclature

Terms previously used to describe *NTRK1*-CIPA include:

- Familial dysautonomia type II
- Congenital sensory neuropathy with anhidrosis

Prevalence

While *NTRK1*-CIPA (or HSAN IV) has been reported worldwide, it is extremely rare in most populations except the Japanese and Israeli Bedouins. Of note, the number of Japanese with *NTRK1*-CIPA was estimated between 130 and 210 [Haga et al 2015].

Relatively common founder pathogenic variants have been reported in the Japanese and Israeli Bedouin populations [Miura et al 2000b, Shatzky et al 2000, Indo 2001] (see Table 5):

- Three variants – c.851-33T>A, p.Arg554GlyfsTer104, and p.Asp674Tyr – account for roughly 70% of pathogenic *NTRK1* variants among Japanese.
- One variant – p.Pro621SerfsTer21 – accounts for 89% of pathogenic *NTRK1* variants among Israeli Bedouins [Shatzky et al 2000, Indo 2001].

Half of reported affected individuals are offspring of consanguineous parents [Axelrod 2002].

Specific carrier frequencies are not available.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *NTRK1*.

Differential Diagnosis

The differential diagnosis of *NTRK1* congenital insensitivity to pain with anhidrosis (*NTRK1*-CIPA) includes other genes associated with congenital insensitivity to pain (see [Congenital Insensitivity to Pain Overview](#)) as well as other hereditary disorders (see Table 2) and acquired conditions (see Table 3) with clinical manifestations similar to those of *NTRK1*-CIPA.

Table 2. Hereditary Disorders in the Differential Diagnosis of *NTRK1*-CIPA

Gene(s)	Disorder	MOI	Clinical Features of Differential Disorder	
			Overlapping w/ <i>NTRK1</i> -CIPA	Distinguishing from <i>NTRK1</i> -CIPA
<i>COL1A1</i> <i>COL1A2</i>	<i>COL1A1/2</i> -related osteogenesis imperfecta	AD	Multiple fractures	<ul style="list-style-type: none"> Fractures cause pain & occur w/ minimal or no trauma. Assoc w/other features incl blue sclera, short stature, joint hypermobility, deafness
<i>EDA</i> <i>EDAR</i> <i>EDARADD</i>	Hypohidrotic ectodermal dysplasia	XL AR AD	<ul style="list-style-type: none"> Hypohidrosis Risk of hyperthermia 	Insensitivity to pain not a feature
<i>ELP1</i> (<i>IKBKAP</i>)	Familial dysautonomia (HSAN III)	AR	↓ pain from birth	GI dysfunction, vomiting crises, recurrent pneumonia, cardiovascular & temperature instability
<i>HPRT1</i>	Lesch-Nyhan syndrome	XL	Progressive self-injurious behavior (biting fingers, hands, lips, cheeks; banging the head or limbs)	<ul style="list-style-type: none"> Hyperuricemia Progressive, severe DD/ID Abnormal involuntary movements
<i>MPV17</i>	<i>MPV17</i> -related hepatocerebral mitochondrial DNA depletion syndrome	AR	<ul style="list-style-type: none"> Absent pain responses from birth DD 	<ul style="list-style-type: none"> Infantile-onset liver dysfunction typically → liver failure; failure to thrive, lactic acidosis, & hypoglycemia More severe neurologic involvement; may incl white matter abnormalities on MRI & seizures
<i>NGF</i>	<i>NGF</i> -CIPA ¹ (HSAN V)	AR	Insensitivity to pain, anhidrosis, & ID ^{1, 2}	<i>NGF</i> -CIPA & <i>NTRK1</i> -CIPA cannot reliably be differentiated on a clinical basis. ²

AD = autosomal dominant; AR = autosomal recessive; CIPA = congenital insensitivity to pain with anhidrosis; DD = developmental delay; GI = gastrointestinal; HSAN = hereditary sensory and autonomic neuropathy; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Carvalho et al [2011]

2. Indo [2012]

Table 3. Acquired Conditions in the Differential Diagnosis of *NTRK1*-CIPA

Disorder	Overlapping Clinical Features	Clinical Features of the Disorder Distinguishing from <i>NTRK1</i> -CIPA
Leprosy ¹	<ul style="list-style-type: none"> Insensitivity to pain Painless injuries 	<ul style="list-style-type: none"> Skin lesions (hypopigmented macules, nodules, plaques, or diffuse skin infiltration) Enlargement of peripheral nerves Localized (not universal) insensitivity to pain Absence of anhidrosis

Table 3. continued from previous page.

Non-accidental /abusive injury	Multiple unexplained injuries	<ul style="list-style-type: none"> • Normal response to pain (although caregivers may deny this) • Different pattern of injuries (proportionate to size & development) • Absence of anhidrosis
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1. Daneshjou et al [2012], Iftikhar & Javed [2013]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *NTRK1* congenital insensitivity to pain with anhidrosis (*NTRK1*-CIPA), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *NTRK1* Congenital Insensitivity to Pain Disorders

System/Concern	Evaluation	Comment	
Anhidrosis	Physical exam of the skin	Assess for dry skin & palmoplantar hyperkeratosis (often assoc w/cracking); determine if individual is using skin moisturizer daily.	
Regulation of body temperature	Inquire about history of hyperthermia or hypothermia.		
Insensitivity to pain	Multiple unintentional injuries	Physical exam of whole body	Assess for bruises, cuts, & burns, as well as fingertip biting.
	Orthopedic injuries	Exam of bones & joints by an orthopedist	Assess for fractures, avascular necrosis, septic arthritis/osteomyelitis, self-mutilation, joint subluxation, Charcot neuroarthropathy, leg length discrepancy, & scoliosis.
	Dental risks for injury	Exam for oral lesions	Assess for traumatic lingual injuries, burns, self-biting, auto-extraction of teeth, & overall dental health.
	Neuropathic keratitis	Ophthalmologic exam	Assess for superficial punctate keratopathy & corneal ulceration/perforation/infection.
Developmental delay	Neurologic exam & standardized tests for developmental milestones	Assess for DD & ID, incl defects in conceptual thinking & abstract reasoning.	
Behavioral problems	Formal eval of cognitive & adaptive functions	Assess for social behaviors & emotional disturbances; ADHD.	
Genetic counseling	By genetics professionals ¹	To inform affected persons & families re nature, MOI, & implications of <i>NTRK1</i> -CIPA in order to facilitate medical & personal decision making	
Family support/resources	Assess: <ul style="list-style-type: none"> • Use of community or online resources incl Parent to Parent; • Need for social work involvement for parental support. 		

ADHD = attention-deficit/hyperactivity disorder; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Treatment is supportive and is best provided by specialists in pediatrics, orthopedics, dentistry, ophthalmology, and dermatology at a center that provides comprehensive care and communication between the various subspecialties that are needed for optimal care.

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.

For details see [Table 3, Congenital Insensitivity to Pain Overview](#).

Prevention of Primary Manifestations

For details see [Table 4, Congenital Insensitivity to Pain Overview](#).

Prevention of Secondary Complications

For details see [Table 5, Congenital Insensitivity to Pain Overview](#).

Surveillance

In addition to daily evaluation by parents and caregivers for early signs of otherwise unrecognized injury, regular examinations by a pediatrician, orthopedist, dentist, dermatologist, and ophthalmologist are recommended to assess and advise on various physical, mental, and behavioral problems. For details, see [Table 6, Congenital Insensitivity to Pain Overview](#).

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 *NTRK1* 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.

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

Pregnancy Management

Women with CIP are able to become pregnant and bear children normally; however, reports regarding pregnancy in women with *NTRK1*-CIPA are rare.

Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

NTRK1 congenital insensitivity to pain with anhidrosis (*NTRK1*-CIPA) is an autosomal recessive disorder caused by biallelic *NTRK1* pathogenic variants. Typically, the proband has inherited one *NTRK1* pathogenic variant from each parent. Alternatively, in some families, the proband has *NTRK1*-CIPA as the result of uniparental isodisomy for chromosome 1 (i.e., 2 copies of chromosome 1 with the *NTRK1* pathogenic variant are inherited from one parent and no copy of chromosome 1 is inherited from the other parent).

Risk to Family Members

Parents of a proband

- In most families, both parents of an affected child are carriers (i.e., heterozygotes) for an *NTRK1* pathogenic variant.
- Less commonly, only one parent is heterozygous for an *NTRK1* pathogenic variant and the child has *NTRK1*-CIPA as the result of uniparental isodisomy for chromosome 1 and consequent homozygosity for the *NTRK1* pathogenic variant from the carrier parent [Miura et al 2000a, Indo et al 2001, Kurth et al 2016].
- Accurate recurrence risk counseling relies on carrier testing of both parents to determine if both are heterozygous for an *NTRK1* variant. If carrier testing detects the variant in only one parent:
 - And the child appears to have homozygous *NTRK1* pathogenic variants, possible explanations include a large deletion on one allele (if not previously tested for) and uniparental isodisomy for chromosome 1.
 - And the child has compound heterozygous *NTRK1* pathogenic variants, the child may theoretically have one inherited variant and one *de novo* pathogenic variant (*de novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017]).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If each parent is known to be heterozygous for an *NTRK1* pathogenic variant, each sib of an affected individual has at conception 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.
- If the proband has *NTRK1*-CIPA as the result of uniparental isodisomy for chromosome 1 and only one parent is heterozygous for an *NTRK1* pathogenic variant, each sib of an affected individual has at conception a 50% chance of being an asymptomatic carrier and a 50% chance of being unaffected and not a carrier (the risk to the sibs of being affected with *NTRK1*-CIPA is not increased over that of the general population).

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

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is heterozygous for an *NTRK1* pathogenic variant, his or her family members are at risk of being a carrier.

Carrier Detection

Carrier testing for parents, sibs, and other at-risk relatives requires prior identification of the *NTRK1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk infants 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/preimplantation genetic 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 are 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 Testing

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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. NTRK1 Congenital Insensitivity to Pain with Anhidrosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>NTRK1</i>	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 NTRK1 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

NTRK1 encodes TrkA, a receptor tyrosine kinase for nerve growth factor (NGF) [Indo et al 1996, Mardy et al 1999, Indo 2001, Mardy et al 2001]. 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.

NGF-dependent neurons in the peripheral nervous system (PNS) include sympathetic postganglionic neurons and NGF-dependent primary afferents that depend on the NGF-TrkA system during development [Indo 2012]. NGF-dependent primary afferents are defined as primary afferent (sensory) neurons with small-diameter, thinly myelinated A δ (delta) fibers, or unmyelinated C-fibers. NGF-dependent neurons also exist in the central nervous system (CNS) [Indo 2014].

NGF-dependent neurons in the PNS also contribute to inflammatory processes; therefore, control of various neuronal or inflammatory processes via these neurons in pain, itch, and inflammation response is likely abnormal in the absence of TrkA [Indo 2010].

These NGF-dependent neurons play pivotal roles in interoception to represent the physiologic status of all tissues of the body, as well as in stress response [Indo 2018]. It is also likely that these neurons are required for neurobiologic processes of "emotions and feelings" in our species. (For more information about the neuroscience of NGF-dependent neurons, click [here](#).)

Mechanism of disease causation. *NTRK1*-CIPA is caused by loss-of-function variants in *NTRK1* resulting in loss of TrkA function.

Lack of all NGF-dependent neurons in the PNS causes:

- Absence of pain due to absence of primary afferents (sensory neurons) in the dorsal root ganglion, which carry nerve impulses from painful and temperature stimuli;
- Anhidrosis due to absence of sympathetic postganglionic neurons, which innervate sweat glands.

Intellectual disability and characteristic behaviors are probably neuron-deficient within the CNS (brain).

***NTRK1*-specific laboratory technical considerations.** Several individuals with *NTRK1*-CIPA have been reported with homozygosity for an *NTRK1* pathogenic variant resulting from uniparental isodisomy for

chromosome 1 [Miura et al 2000a, Indo et al 2001, Kurth et al 2016]. In these instances, two copies of chromosome 1 with the *NTRK1* pathogenic variant were inherited from one parent and no copy of chromosome 1 was inherited from the other parent. If parental testing for an apparently homozygous *NTRK1* pathogenic variant detects the variant in only one parent, possible explanations include a large deletion on one allele (if not previously tested for) and uniparental isodisomy for chromosome 1.

Table 5. Notable *NTRK1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_002529.3 NP_002520.2	c.287+2dupT	Aberrant splicing (skipping of exon 2)	Observed in multiple Korean [Lee et al 2009] & Chinese families [Geng et al 2018]
	c.851-33T>A (IVS7-33T>A ¹)	p.Phe284TrpfsTer36	Common pathogenic variant in Japanese, Korean, & Chinese populations [Indo 2001, Lee et al 2009, Geng et al 2018, Li et al 2019]
	c.1660delC (c.1642delC ² , 1726delC ¹)	p.Arg554fsTer104 (p.Arg548GlyfsTer104 ²)	Pathogenic variants common in Japanese population [Indo 2001]
	c.2020G>T (c.2002G>T ² , c.2086G>T ¹)	p.Asp674Tyr (p.Asp668Tyr ²)	
	c.1860_1861insT (c.1842_1843insT ² , 1926_1927insT ¹)	p.Pro621SerfsTer12 (p.Pro615SerfsTer12 ²)	Founder variant in Israeli Bedouins [Shatzky et al 2000]
	c.1633-1G>T (c.1615-1G>T ²)	Aberrant splicing (skipping of exon 14)	Founder variant in Turkish population [Tüysüz et al 2008]

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
2. Named according to [NM_001012331.1 \(NP_001012331.1\)](#)

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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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