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Congenital Insensitivity to Pain Overview

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Summary

The goals of this overview on congenital insensitivity to pain (CIP) are the following.

Goal 1

To describe the clinical characteristics of congenital insensitivity to pain

Goal 2

To review the causes of congenital insensitivity to pain

Goal 3

To provide an evaluation strategy to identify the genetic cause of congenital insensitivity to pain in a proband

Goal 4

To inform genetic risk assessment of family members of a proband with congenital insensitivity to pain

Goal 5

To provide a brief summary of management of congenital insensitivity to pain

1. Clinical Characteristics of Congenital Insensitivity to Pain

Congenital insensitivity to pain (CIP) is an extremely rare phenotype characterized by the inability to perceive pain (absence of nociception) from birth. Individuals with CIP do not feel pain from any noxious stimuli, including inflammation and heat [Goldberg et al 2007]. This review does not cover conditions that cause a generalized sensory neuropathy.

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Inability to feel pain leads to repeated injuries and prevents normal healing.

Characteristic Findings

Age-Related

Infants and young children

- Self-mutilating injuries of the fingers (biting off fingertips) and oral cavity such as loss of the tongue tip, injuries to the inside of the teeth/gums, and avulsion of teeth are common (Figure 1A&B).
- Cuts and bruises may be present.
- Burns due to impaired temperature sensation [Cox et al 2006] can occur.
- Recurrent otitis media may be due to selectively reduced immunity to *Staphylococcus aureus* (see **Infections**) [Shatzky et al 2000].

Note: (1) Affected individuals may be able to differentiate large temperature changes, but are unable to sense if something is too hot or too cold. (2) A significant number of parents of affected children are suspected of physically abusing their child due to the nature of these injuries [Author, personal observation].

Older individuals

- Painless fractures and joint damage frequently occur and can lead to permanent damage.
- Bony deformities due to past fractures can occur.
  - Charcot joints (neuropathic arthropathy), most commonly of the ankles, hips, and lumbar spine, are almost universal (Figure 1C).
  - Charcot spine may present with progressive deformity or new motor and/or sensory deficits [Wheeler et al 2014, Staudt et al 2018].

Eyes

All affected individuals are at risk for corneal injuries due to absent corneal reflexes.

- Permanent corneal scarring can develop and is best assessed through a slit-lamp examination. It has been observed clinically that corneal transplants have an increased risk of failure, presumably due to the lack of nociceptive innervation of the new cornea and the continuing lack of nociceptive innervation of the conjunctiva.
- Emotional tearing, as opposed to pain induced tearing, is likely to be present [Shatzky et al 2000].

Infections

Apparent selectively reduced immunity to *Staphylococcus aureus* has been observed in some affected individuals, leading to recurrent soft tissue infections, abscesses, and osteomyelitis.

Temperature Regulation, Anhidrosis, and Hyperhidrosis

Some individuals have anhidrosis (lack of sweating), which disturbs thermoregulation and can lead to recurrent episodes of unexplained fever [Indo et al 1996, Indo 2001] (see Table 1).

Marked hyperhidrosis may be seen in those affected individuals who have a heterozygous pathogenic c.2432T>C (p.Leu811Pro) variant in *SCN11A* [Woods et al 2015].

Hyperpyrexia can be fatal if untreated [Shatzky et al 2000].

Hypothermia can occur in cold conditions.

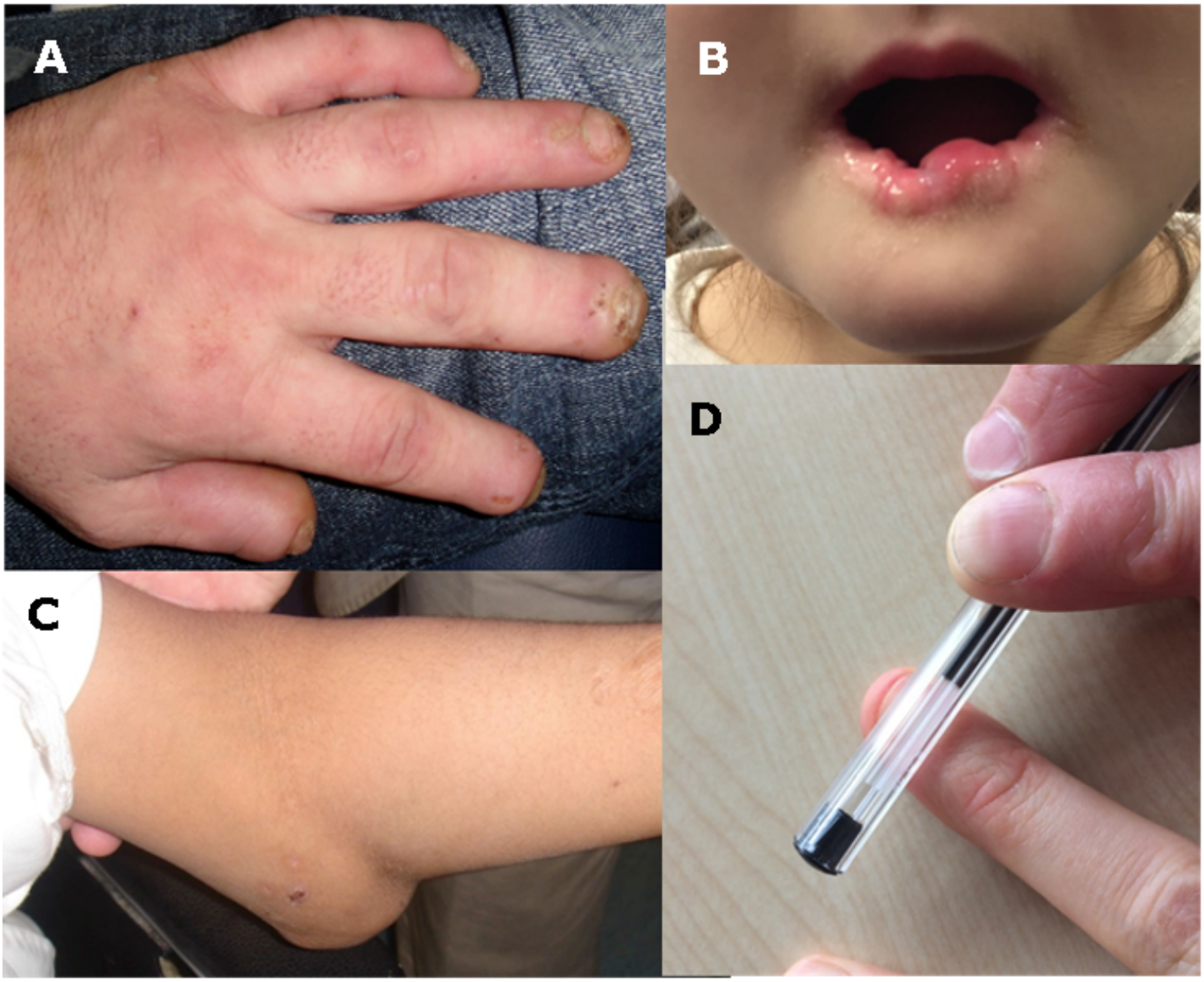

Figure 1. Examples of clinical findings in individuals with congenital insensitivity to pain (CIP)

A. Typical loss of fingertips secondary to trauma, poor wound healing, and chronic *Staphylococcal aureus* infections in a child age nine years with *NTRK1*-CIP

B. Child age seven years with *PRDM12*-CIP demonstrating loss of portions of the lower lip secondary to self-biting as a toddler

C. Example of a Charcot joint, or neuropathic joint, in an individual with *NGF*-CIP. The affected individual had chronic elbow dislocation, which is now permanent and results in significantly reduced arm movement.

D. Method for applying pressure to the proximal nail bed to test pain appreciation

Development and Intellect

Development and intellect may be normal or delayed/disabled (see Table 1).

- Individuals with CIP caused by biallelic pathogenic variants in *SCN9A* and *PRDM12* typically have normal intellect.
- Individuals with CIP caused by biallelic pathogenic variants in *NTRK1* may have a variable degree of intellectual disability (see Table 1).

- Hyperactivity, impulsivity, and attention deficit are common in children with biallelic pathogenic variants in *NTRK1* [Levy Erez et al 2010].

Other

- Chronic anemia of unknown cause was observed in 22/28 Israeli affected individuals with congenital insensitivity to pain and anhidrosis [Shatzky et al 2000].
- A few individuals have neuropathic pain, although this does not limit activities [Wheeler et al 2014; Author, personal observation].

Establishing the Clinical Diagnosis of Congenital Insensitivity to Pain

There are no consensus clinical diagnostic criteria for CIP. However, a diagnosis requires visible proof of lack of nociception in a conscious individual of normal intellectual ability. In those with intellectual disability CIP may be more difficult to diagnose clinically.

Clinical Examination

Nociception is assessed by applying painful stimuli, which in people with normal nociception would be so difficult to bear that they would move the part of the body away from the stimulus and/or express discomfort. The authors have experience of children being incorrectly judged to have insensitivity to pain after an inadequately painful stimulus.

- The technique should not damage/scar prior to significant pain (e.g., sternal rub, which bruises before significant pain).
- Application of 5-10 kg pressure with a pen pressed onto the nail bed (the nail bed blanches for a few seconds afterward) is reliable (see Figure 1D).

Assessment of the remainder of the peripheral and central nervous system is typically normal (touch, vibration and position sense, motor functions, and deep tendon reflexes).

Supportive Laboratory Findings

Routine nerve conduction studies and electromyogram are typically normal [Shatzky et al 2000].

For more information about autonomic function testing for CIP with anhidrosis, click here (pdf).

Nerve biopsy is not routinely performed in clinical practice. Skin biopsy to determine intra-epidermal nerve fiber density and autonomic innervation is performed in adults in some centers.

2. Causes of Congenital Insensitivity to Pain

All causes of CIP affect nociceptors (specialized peripheral sensory neurons) and either cause nonfunctional nociceptors or failure of nociceptor neurodevelopment [Nahorski et al 2015b]. Congenital insensitivity to pain is an extremely rare phenotype and the exact proportion of individuals with pathogenic variants in each gene within the whole population is not known.

Table 1. Genes Associated with Congenital Insensitivity to Pain (CIP)

Gene	Proportion of Affected Individuals with Mutation of This Gene	MOI	Distinguishing Features
CLTCL1 [1]	Rare	AR	• Severe non-progressive learning disability • Delay in central nervous system myelination • One family reported
NGF [3]	Rare	AR	• Variable phenotype • Individuals w/biallelic null variants may have anhidrosis, mild/moderate ID, prematurely aged appearance, ↑ *Staphylococcus aureus* infections, & Charcot joints. • Individuals w/a homozygous missense variant had impairment of pain/temperature sensation & Charcot joints, normal intellect & normal sweating. [4]
NTRK1 [5]	Common	AR	• Anhidrosis • Tendency to develop corneal ulcers that heal poorly [6] • ID in a majority; always less intellectually able than unaffected family members • Predisposition to *Staphylococcus aureus* infections • Charcot joints • Dry skin w/lichenification • Also known as HSAN IV
PRDM12 [7]	Intermediate	AR	• Non-global pain insensitivity in some • Absent corneal reflex & impaired tear production • *Staphylococcus aureus* infections • No Charcot joints • Difficulties w/temperature regulation in some • Usually normal neurologic exam, development, intellect, & olfaction [8] • Known as HSAN VIII
SCN9A [9, 10]	Common	AR	• Anosmia [11] • Charcot joints • Normal corneal reflex & tear production
SCN11A [12]	Rare	AD	• Delayed motor development • Mild muscle weakness • Joint hypermobility • Gastrointestinal dysfunction (intestinal hypoperistalsis or diarrhea) • Pruritis • Hyperhidrosis in those w/c.2432T>C (p.Leu811Pro) variant

Table 1. continued from previous page.

Gene	Proportion of Affected Individuals with Mutation of This Gene	MOI	Distinguishing Features
ZFHX2 [13]	Rare	AD	• 1 family reported • Non-global pain insensitivity w/lower back pain, headaches, & pain during childbirth perceived • Normal intelligence • Scarce or absent sweating • Variably reduced sensitivity to heat and cold • Low sensitivity to capsaicin – able to eat large amount of hot pepper w/out discomfort • Some autonomic features such as fainting & vomiting

AD = autosomal dominant; AR = autosomal recessive; HSAN = hereditary sensory and autonomic neuropathy; ID = intellectual disability; MOI = mode of inheritance

1. Nahorski et al [2015a]

3. Einarsdottir et al [2004], Carvalho et al [2011], Shaikh et al [2018]

4. Three individuals from a large northern Swedish family who were homozygous for the NM_002506.2:c.661C>T, (p.Arg211Trp) pathogenic variant [Einarsdottir et al 2004]. A proportion of adults who were heterozygous for the NM_002506.2:c.661C>T, (p.Arg211Trp) pathogenic variant in this family had mild or moderate problems with joint deformities but were not believed to actually be affected by CIP.

5. See Congenital Insensitivity to Pain with Anhidrosis, Indo et al [1996], Indo [2001]

6. Yagev et al [1999]

7. Chen et al [2015], Zhang et al [2016]

8. Saini et al [2017] described a male age two years with a homozygous pathogenic splice site variant in *PRDM12* who had global developmental delay, dolicocephaly, frontal bossing, and deep-set eyes as well as congenital insensitivity to pain.

8. Cox et al [2006], Goldberg et al [2007]

10. Pathogenic variants are typically truncating, although one missense variant and one in-frame deletion have been described [Cox et al 2010].

11. Weiss et al [2011]

12. Recurrent *de novo* variants have been reported: NM_014139.2:c.2432T>C (p.Leu811Pro) and NM_014139.2:c.3904C>T, (p.Leu1302Phe). Another pathogenic *de novo* variant, NM_014139.2:c 1187T>C (p.Leu396Pro) has also been reported. Recurrent variants may be inherited. [Leipold et al 2013, Phatarakijnirund et al 2016, Huang et al 2017, King et al 2017].

13. Spinsanti et al [2008], Habib et al [2018]

Table 2. Other Disorders to Consider in the Differential Diagnosis of Congenital Insensitivity to Pain (CIP)

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of the Disorder	
			Overlapping w/CIP	Distinguishing from CIP
Hereditary				
Hypohidrotic ectodermal dysplasia	*EDA* *EDAR* *EDARADD*	XL AR AD	• Lack of sweating (overlap w/*NTRK1*- & *NGF*-CIP) • Risk of hyperthermia	Insensitivity to pain not a feature
Lesch-Nyhan syndrome	*HPRT1*	XL	Progressive self-injurious behavior (biting fingers, hands, lips, cheeks; banging the head or limbs)	• Hyperuricemia • Progressive, severe DD/ID • Abnormal involuntary movements

Table 2. continued from previous page.

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of the Disorder	
			Overlapping w/CIP	Distinguishing from CIP
COL1A1/2-related osteogenesis imperfecta	*COL1A1* *COL1A2*	AD	Multiple fractures	• Fractures cause pain • Fractures occur w/minimal or absent trauma • Assoc w/other features incl blue sclera, short stature, joint hypermobility, deafness
Familial dysautonomia (also known as HSAN III)	*ELP1* (*IKBKAP*)	AR	Reduced pain from birth	Gastrointestinal dysfunction, vomiting crises, recurrent pneumonia, cardiovascular & temperature instability
MPV17-related hepatocerebral mitochondrial DNA depletion syndrome	*MPV17*	AR	• Absent pain responses from birth • DD (can be seen in *NTRK1* & *NGF*-CIP)	• 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
Acquired				
Leprosy [1]	NA	NA	• Insensitivity to pain • Painless injuries	• Skin lesions (hypopigmented macules, nodules, plaques, or diffuse skin infiltration) • Enlargement of peripheral nerves • Localized (not universal) insensitivity to pain
Non-accidental / abusive injury	NA	NA	Multiple unexplained injuries	• Normal response to pain (although caregivers may deny this) • Different pattern of injuries (proportionate to size & development of child)

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; HSAN = hereditary sensory and autonomic neuropathy; ID = intellectual disability; MOI = mode of inheritance; NA = not applicable; XL = X-linked
1. Daneshjou et al [2012], Iftikhar & Javed [2013]

Prevalence

The prevalence of the CIP phenotype is unknown. Consideration of this diagnosis has increased considerably due to the identification of more causative genes and increased awareness from medical/scientific publications and media stories. Fewer than 30 cases are known in the UK [Authors, personal observation], giving an estimated prevalence of one in a million.

3. Evaluation Strategy to Identify the Genetic Cause of Congenital Insensitivity to Pain

The diagnosis of a specific Mendelian form of congenital insensitivity to pain **is established** in a proband with a suggestive history and/or presenting findings and a heterozygous pathogenic (or likely pathogenic) variant in *SCN11A* or biallelic pathogenic (or likely pathogenic) variants in one of the other genes listed in Table 1. The diagnosis can be difficult to establish on clinical grounds alone before age five years.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out a diagnosis.

Molecular genetic testing approaches can include a combination of **targeted gene testing** (multigene panel, single-gene testing) and **genomic testing** (comprehensive genomic sequencing).

Targeted gene testing requires the clinician to develop a hypothesis as to which specific gene(s) are likely to be involved, whereas genomic testing does not. Targeted testing is feasible based on phenotype in anyone older than approximately age five years (because of the difficulties of assessing subtle problems of intellectual developmental, sweating, temperature sensing, and autonomic features in infants and young children), with the exception of *SCN11A* (see **Serial single-gene testing** following).

Serial single-gene testing. The phenotype may guide the choice of which gene(s) to analyze first. Consider performing sequence analysis of:

- *SCN11A* first in a newborn with severe intestinal hypomotility.
- *SCN9A* first in an individual with normal intelligence who has anosmia.
- *PRDM12* first in an individual with normal intelligence, staphylococcal infections, and hypohidrosis.

  Because some individuals with *NTRK1*-CIP and *NGF*-CIP have minimal learning problems, sequence analysis of these two genes should be considered next if molecular genetic testing of *SCN9A* and *PRDM12* yield no pathogenic variants.
- *NTRK1* and *NGF* first in an individual with evidence of learning problems or late development, staphylococcal infections, and hypohidrosis. Unexplained fever due to anhidrosis (the inability to sweat) is a characteristic and often initial feature (more so in hot climates).

If no pathogenic variant is found in *SCN11A* or *ZFHX2* through sequence analysis OR if no or only one pathogenic variant is found through sequence analysis of the remainder of the genes listed in Table 1, gene-targeted deletion/duplication analysis should be considered.

Note: Whole-gene deletions have been reported in individuals with *NGF*-CIP [Fitzgibbon et al 2009] and *SCN9A*-CIP [Author, personal observation].

A multigene panel that includes genes for CIP and other genes of interest (see Table 2) may be considered. Note: 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing (when available) including exome and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Genetic Risk Assessment

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

Congenital insensitivity to pain (CIP) is inherited in an autosomal recessive manner, with the exceptions of *SCN11A*-CIP and *ZFHX2*-CIP, which are inherited in an autosomal dominant manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one CIP-related pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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.
- Heterozygotes (carriers) are asymptomatic and are not at risk for developing the disorder.

Offspring of a proband. The offspring of an individual with CIP are obligate heterozygotes (carriers) for a pathogenic variant in a CIP-related gene.

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

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the CIP-related pathogenic variants in the family.

Autosomal Dominant Inheritance (*SCN11A*-CIP and *ZFHX2*-CIP) – Risk to Family Members

See *SCN11A* and *ZFHX2* in Table 1 for information on these very rare conditions.

Parents of a proband

- Some individuals diagnosed with *SCN11A*-CIP have an affected parent.
- Some individuals diagnosed with *SCN11A*-CIP have the disorder as the result of a *de novo* pathogenic variant. Information on the frequency of *de novo* pathogenic variants is currently very limited.
- Inheritance in the one family reported to date with *ZFHX2*-CIP was autosomal dominant, with six affected individuals in three generations [Habib et al 2018].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.

- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%. Based on currently available, but limited, information, *SCN11A*- and *ZFHX2*-CIP appear to be completely penetrant. Phenotypic variability within families has not been reported.
- If the parents have been tested for the pathogenic variant identified in the proband and:
  - A parent of the proband has the pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Based on currently available (limited) information, *SCN11A*- and *ZFHX2*-CIP appear to be completely penetrant without familial phenotypic variability.
  - If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. The sibs of a proband with clinically unaffected parents are still at increased risk for CIP because of the theoretic possibilities of reduced penetrance in a parent or parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with *SCN11A*- or *ZFHX2*-CIP has a 50% chance of inheriting the pathogenic variant. Based on currently available (limited) information, *SCN11A*- and *ZFHX2*-CIP appear to be completely penetrant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SCN11A* or *ZFHX2* pathogenic variant or is clinically affected, the parent's family members may be at risk.

Related Genetic Counseling Issues

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. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the CIP-related pathogenic variant(s) have been identified in an affected family member, prenatal 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

5. Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with congenital insensitivity to pain (CIPA), the evaluations summarized Table 3 (if not performed as part of the evaluation that led to the diagnosis) should be considered. Based on the underlying genetic cause and/or specific pathogenic variant, not all evaluations need to be done in every individual with CIPA but should be guided by the specific phenotypic features seen in association with the genes discussed in Table 1.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Congenital Insensitivity to Pain Disorders

System/Concern	Evaluation	Comment
Skin [1]	Physical exam of the skin	Assess for dry skin & palmoplantar hyperkeratosis (often assoc w/cracking); determine if person is using a skin moisturizer daily.
Regulation of body temperature	Inquire about history of hyperthermia or hypothermia.	

Table 3. continued from previous page.

System/Concern		Evaluation	Comment
Insensitivity to pain	**Multiple unintentional injuries**	Physical exam of the whole body	Assess for bruises, cuts, burns, biting & *Staphylococcus aureus* infections.
	Orthopedic injuries	Exam of the bones & joints by an orthopedist	• Assess for fractures; avascular necrosis; septic arthritis / osteomyelitis; self-mutilation; joint subluxation; Charcot neuroarthropathy; leg length discrepancy; scoliosis. • Consider baseline radiography of lower spine, hips, knees, & ankles, if ambulatory.
	Dental risks for injury	Exam for oral lesions	Assess for traumatic lingual injuries, burns, self-biting, & auto-extraction of teeth, as well as overall dental health.
	Neuropathic keratitis	Ophthalmologic exam	Assess for superficial punctate keratopathy, as well as corneal ulceration / perforation / infection.
Developmental delay [2]		Neurologic exam & standardized tests for developmental milestones	Assess for development delay, as well as intellectual disability, incl defects in conceptual thinking & abstract reasoning.
Behavior problems [3]		Formal eval of cognitive & adaptive functions	Assess for social behaviors & emotional disturbances; ADHD.
Anosmia [4]		Inquire about sense of smell.	Affected persons may be unaware of body odor & rancid food.
Genetic counseling		By genetics professionals [5]	To inform affected persons & families re nature, MOI, & implications of CIPA in order to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.	

ADHD = attention-deficit/hyperactivity disorder; MOI = mode of inheritance

1. Anhidrosis is more common in individuals with pathogenic variants in *NTRK1*, *ZFHX2*, and biallelic null variants in *NGF*; hyperhidrosis may be present in those with the c.2432T>C (p.Leu811Pro) pathogenic variant in *SCN11A*; pruritis is typically seen in those with pathogenic variants in *SCN11A*.

2. Most often associated with pathogenic variants in *CLTCL1*, *NGF*, *NTRK1*, and *SCN11A*.

3. Most often associated with pathogenic variants in *NTRK1*.

4. Most often associated with pathogenic variants in *SCN9A*.

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

Treatment of Manifestations

No consensus treatment or surveillance guidelines have been developed.

Treatment is supportive and is best provided by specialists in pediatrics, orthopedics, dentistry, ophthalmology, and dermatology (see Congenital Insensitivity to Pain with Anhidrosis).

Table 4. Treatment of Manifestations in Individuals with Congenital Insensitivity to Pain

Manifestation/Concern	Treatment	Considerations/Other
Dental & oral lesions	Tooth extraction &/or filing (smoothing) of sharp incisal edges [Bodner et al 2002]; use of a mouth guard [Hutton & McKaig 2010]	
Bone fractures	Standard treatment w/careful & regular review, assuming healing may not occur, & low threshold for repeat radiological imaging until normal	Treatment w/an external fixator may → potentially serious infectious complications.
Bone & joint deformity	Corrective osteotomy	Prolonged & intensive monitoring is necessary to avoid deformity or incomplete healing.
Leg length discrepancy	Shoe lift or epiphysiodesis [Bar-On et al 2002]	The value of surgical intervention needs to be weighed against nonsurgical approaches incl close monitoring [Kim et al 2013].
Corneal ulceration/ perforation/infection	Standard treatment w/careful & regular review, assuming healing may not occur	Corneal transplants will have increased risk of failure.
Dry eyes	Lubricating eye drops or ointments	Surgical treatment of neurotrophic keratitis has not been successful [Yagev et al 1999].
Long-standing infections	Wide surgical debridement	Prevention may be difficult but is important (See Prevention of Primary Manifestations and Prevention of Secondary Complications.)
Ulcerating foot lesions	Standard treatment w/careful & regular review, assuming healing may not occur	Appropriate footwear & ankle support & periods of non-weight-bearing may be appropriate.
Hyperthermia	Direct cooling in bath or w/cooling blanket	Control of environmental temperatures is essential.
Hypothermia	Warming by blanket	
Skin dryness & cracking	Topical moisturizer (lotion or cream)	Untreated dry skin can → skin infections, which ↑ risk for serious infections (cellulitis or osteomyelitis).
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Developmental delay / intellectual disability educational issues may be seen in those with *CTCL1*-CIP, *NGF*-CIP, *NTRK*-CIP, or *SCN11A*-CIP.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.

- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications when necessary.

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

Prevention of Primary Manifestations

Table 5. Prevention of Primary Manifestations in Individuals with Congenital Insensitivity to Pain

Manifestation/Concern	Prevention	Considerations/Other
Injuries occurring around the home	Stair gates; soft-round edging on tables & protruding objects; guard all heating devices; close supervision of younger children in the kitchen	
Injuries occurring at school	Inform personnel at school of diagnosis; seek help when accident occurs but child does not seem hurt.	
Self-inflicted injuries	Education of affected individuals about their condition.	Communicating w/other families of individuals w/CIP (especially affected adults)
Corneal abrasion	At least annual ophthalmologic eval; artificial tears	• Artificial tears are particularly helpful to those w/*PRDM12*-CIP. • All persons w/congenital corneal anesthesia have had *SCN9A*-CIP [Author, personal observation].
***Staphylococcus aureus* infections**	• Good hand hygiene & care; use of antiseptic soaps; early use of topical antibiotics • Investigation of swollen joints, limping, & limb underuse for infection by x-ray & C-reactive protein	Affects those w/*NTRK1*-, *NGF*-, *CLTCL1*-, & *PRDM12*-CIP; infections are specific for *S aureus* only.

Prevention of Secondary Complications

Table 6. Prevention of Secondary Manifestations in Individuals with Congenital Insensitivity to Pain

Manifestation/Concern	Prevention	Considerations/Other
Inability to use pain as indicator in diagnosing or assessing injury severity	Laminated information letters/ MediAlert bracelets	Consider providing laminated letter confirming diagnosis, stating pathogenic variant(s), & giving advice on diagnosis & treatment.

Table 6. continued from previous page.

Manifestation/Concern	Prevention	Considerations/Other
Osteomyelitis of mandible	Early treatment of dental caries & periodontal disease	Regular dental exams & restriction of sweets
Bone & joint injury due to strenuous activity when individual has poor baseline conditioning	Activities that lead to increased strength, balance, & body awareness	Dancing (particularly ballet), swimming, cycling, & non-traumatic martial arts may be considered.
Inadequate sedation in postoperative period may trigger unexpected movement, causing secondary injury.	Adequate sedation during procedures	Tachycardia & hypertension in postoperative period should raise consideration of the possibility of inadequate sedation.
Hyper- or hypothermia	Careful monitoring of temperature during perioperative period	

Surveillance

In addition to regular evaluations by a pediatrician and dermatologist (to assess and advise on skin infections/injuries) the measures in Table 7 are recommended.

Table 7. Recommended Surveillance for Individuals Congenital Insensitivity to Pain

Manifestation/Concern	Evaluation	Frequency/Comment
Dental caries / Tooth damage	Dental care	Regular exams (at least every 6 mos)
Early injuries	Eval by parents & caregivers for signs of unrecognized injury	Daily
Bone health	Prompt investigation & treatment of orthopedic consequences of CIP by named orthopedic surgeon	At least annually; more frequently depending on bony injuries
Corneal damage	Ophthalmology eval	At least annually; more frequently as indicated
Hyper- or hypothermia	Monitoring of body temperature may allow timely treatment of hyper- or hypothermia.	As needed
Charcot joints	Expert orthopedist assessment incl radiography of lower spine, hips, knees, & ankles	Every 1-3 yrs

Agents/Circumstances to Avoid

Avoid the following:

- Jumping, high-impact/contact sports, pastimes and jobs that involve the potential for blunt injury or severe bone and joint trauma

  The paucity of males with CIP who are older than age 20 years correlates with behaviors fueled by inability to feel pain (e.g., greater risk taking, deliberately picking fights, participation in extreme sporting events).

- Hot or cold environments; hot or cold foods, hot showers or baths; heating blankets, particularly in the perioperative period

Pregnancy Management

Women with CIP are able to become pregnant and bear children normally.

Obstetric staff must be made aware of the diagnosis of CIP. Labor progresses normally, but will be painless, while other senses (stretch and touch) are intact. A delay in detecting pelvic fractures in an affected woman in the postnatal period has been reported [Wheeler et al 2014].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Other

Individuals with CIP typically learn that others have pain and tend to respond to others' pain normally. They often learn to simulate having pain in appropriate situations, e.g., being tackled during football.

The possibility that naloxone may temporarily relieve CIP analgesia has been suggested [Minett et al 2015]. While this medication could be of use in detecting the source of injury/illness in an affected individual, it may also expose the affected person to widespread pain from accumulated injuries.

Chapter Notes

Author Notes

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