

Title: Congenital Insensitivity to Pain with Anhidrosis *GeneReview* - Special Studies
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Special Studies

The following studies have been used for clinical diagnosis prior to the availability of *NTRK1* molecular genetic testing.

1. Pain tests: (CAUTION: These tests should not be performed routinely for ethical reasons.) Painful stimuli that fail to evoke either withdrawal or emotional change in persons with CIPA include pin prick; vigorous pressure on the Achilles tendons, the testes, the stylomastoid processes, and the superior orbital rim; burning heat; immersion of the limbs in ice water; galvanic electrical stimulation of skin; and prolonged ischemia of the limbs [Swanson 1963].

2. Standardized tests of quantitative thermal perception. Decreased perceptions of hot and cold assessed quantitatively using standardized tests of thermal perception are also observed.

3. Histamine test: An intradermal injection of histamine, a chemical mediator that sensitizes and activates NGF-dependent primary afferents, can stimulate the axon reflex –the combination of extravasation of plasma (a wheal) and diffuse erythema (a flare) - in the following manner. (See also [NGF-dependent neurons and the role of TrkA](#).) A stimulus applied to one branch of a nerve induces an impulse that moves centrally to the point of division of the nerve and then down another branch to blood vessels [Indo 2002]. The activated neurons release neuropeptides (such as substance P and calcitonin gene-related peptide) that induce vasodilation and extravasation of plasma. An intradermal injection of histamine produces in controls both a local wheal and flare, but in individuals with CIPA only produces a local wheal and no flare [Swanson 1963]. Additionally, controls - but not individuals with CIPA - note burning pain or pruritus in the axon flare area.

4. Sweating tests: Individuals with CIPA lack sweating. Methods available in clinical practice to evaluate autonomic sweating (sudomotor) function [Illigens & Gibbons 2009] include:

- Thermoregulatory sweat testing (TST)
- Quantitative sudomotor axon reflex testing (QSART)
- Silicone impressions
- Sympathetic skin response (SSR)
- Acetylcholine sweat-spot test
- Quantitative direct and indirect axon reflex testing (QDIRT).

When used in combination these testing techniques can diagnose sudomotor dysfunction and localize pre- and postganglionic lesions, including abnormalities in the postganglionic sympathetic cholinergic pathways.

5. Clinical evaluations of autonomic nervous system:

Horner syndrome -which reflects absence of sympathetic innervation to the skin of the face and eyes - may be present [Brown & Podosin, 1966]. Horner syndrome comprises dry skin (anhidrosis), constricted pupils (miosis) due to paralysis of the pupillary dilator, and ptosis due to paralysis of the smooth tarsal muscle. Horner syndrome is bilateral.

Cold pressor test. Submersion of the forearm in ice-cold water usually causes an increase in blood pressure as an autonomic response; however, no increase in blood pressure is observed in individuals with CIPA [Pinsky & DiGeorge 1966].

6. Histopathologic studies

Skin biopsy. The skin appears normal, except for nonspecific changes secondary to traumatic injuries.

Histologic studies demonstrate normal sweat glands, sebaceous glands, hair follicles, and nerve receptors (such as Pacinian and Meissner's corpuscles) [see references in Indo 2002: Swanson 1963, Pinsky & DiGeorge 1966, Brown & Podosin 1966, Vassella et al 1968].

Electron microscopic studies reveal lack of innervation of the eccrine sweat glands with loss of unmyelinated sudomotor fibers [Rafel et al 1980, Langer et al 1981]. No nerve endings are demonstrated in the epidermis [Ismail et al 1998].

Immunohistochemistry demonstrates almost complete absence of innervation to sweat glands, blood vessels, and erector pilomotor muscles [Nolano et al 2000].

Nerve biopsy. Electron microscopic studies of cutaneous nerves reveal complete absence of small-diameter myelinated and unmyelinated nerve fibers without degenerative or regenerative changes [Rafel et al 1980]. Morphometric analysis confirms the reduced numbers of these small-diameter fibers compared with normal numbers of large-diameter myelinated fibers [Goebel et al 1980, Itoh et al 1986, Matsuo et al 1981].

Autopsy. Findings that represent almost complete absence of the first order afferent system generally considered responsible for pain and temperature sensation are (1) absence of the following: small neurons in the dorsal ganglia, small fibers in the dorsal roots, and Lissauer's tract, and (2) reduction in size of the spinal tract of the trigeminal nerve with a paucity of small fibers [Swanson 1965].

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