

An Infant With Primary Tooth Loss and Palmar Hyperkeratosis: A Novel Mutation in the *NTRK1* Gene Causing Congenital Insensitivity to Pain With Anhidrosis

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ABSTRACT. Patients with congenital insensitivity to pain and anhidrosis (CIPA), caused by mutations in the *NTRK1* gene, can be difficult to diagnose because of their variable presentation, the lack of simple diagnostic tests, and the paucity of cases reported in North America. We describe a 1-year-old infant who had tooth loss and palmar hyperkeratosis as the primary manifestations of CIPA. He was initially evaluated by a pediatric dentist and epidermal dysplasia syndromes were considered, but insensitivity to pain was suspected after a skeletal survey revealed an unrecognized skull fracture. Nerve conduction studies were normal, as was his response to subdermal histamine injection. Sequence analysis of his *NTRK1* gene revealed 2 mutations: 1 mutation is novel, while the other has been described previously in a patient of northern European descent. An antibody directed against *NTRK1* revealed persistent expression in keratinocytes, consistent with the mutations in this patient. Skin biopsy specimens revealed a lack of epidermal and sweat gland innervation. Immunohistochemistry of skin biopsy specimens, together with routine nerve conduction studies, can provide quick and reliable confirmation if CIPA is clinically suspected. *Pediatrics* 2003;112:e237–e241. URL: <http://www.pediatrics.org/cgi/content/full/112/3/e237>; CIPA, *NTRK1*, tooth loss, hyperkeratosis, insensitivity to pain.

ABBREVIATIONS. CIPA, congenital insensitivity to pain with anhidrosis; *NTRK1*, neurotrophic tyrosine receptor kinase 1 gene; NGF, nerve growth factor; EMG, electromyography; PCR, polymerase chain reaction; bp, base pair.

Congenital insensitivity to pain with anhidrosis (CIPA) is an autosomal recessive disorder that was first described almost 40 years ago.¹ CIPA is characterized by recurrent episodic fevers or heat intolerance, anhidrosis (inability to sweat), absence of normal responses to painful stimuli, self-mutilatory behavior, and mental retardation. CIPA is caused by mutations in the neurotrophic tyrosine receptor kinase 1 gene (*NTRK1*, previously known as *TrkA*), which is the receptor for nerve growth factor (NGF).² In CIPA, there is a failure of differentiation

and migration of neural crest cells, leading to the complete absence of small myelinated and unmyelinated nerve fibers. As a consequence, patients have a loss of pain and temperature sensation. Furthermore, the sweat glands are not innervated, leading to anhidrosis.

The molecular diagnosis of CIPA has been confirmed in ~80 cases. Although patients with CIPA have been described in most ethnic groups, only 1 patient from the United States has been reported. Further, diagnosis has been hampered by the large gene size of *NTRK1* and the heterogeneity of mutations leading to CIPA. No simple screening test for CIPA has been described.

We present an infant of northern European descent, who lost several of his primary teeth and had excessive dryness, thickening, and cracking of his palms. Although initially suspected of having an ectodermal dysplasia syndrome, further history and work-up revealed mild heat intolerance and an apparently high pain threshold, including biting off a portion of his tongue, an unrecognized skull fracture, and failure to cry with immunizations or painful trauma to his hands. Skin biopsy immunohistochemistry demonstrated an absence of epidermal innervation, and routine nerve conduction studies (electromyography [EMG]) were preserved. His diagnosis of CIPA was confirmed using polymerase chain reaction (PCR)-based sequencing of the *NTRK1* gene. We demonstrate that the diagnosis of CIPA is straightforward when the characteristic clinical features of an abnormally high pain threshold and heat intolerance are documented together with an absence of epidermal and sweat gland innervation on skin biopsy and preserved nerve conduction studies.

METHODS

Case Report

The patient is a healthy white male born at term after an uncomplicated pregnancy and delivery (Fig 1A). There is no history of consanguinity; his family background is northern European (German/Danish/Swedish). His parents first became concerned at the age of 4 months when the patient developed a sore over his gum as his bottom teeth came in. At the age of 6 months he lost two teeth while riding in his stroller. Over the next 2 months he also developed bleeding of his gums and inner cheeks from chewing, dislodged more teeth while biting on his toys, and bit off the right anterolateral aspect of his tongue, requiring suture repair (Fig 1B). In addition, he developed hyperkeratosis of his palms (and to a lesser degree, his soles), had extensive interdigit

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Fig 1. Photographs of patient. A, face (age: 24 months old). B, Mouth showing toothless gums and sutures in tongue (age: 16 months old). C, Left hand showing hyperkeratosis and ulceration of his index finger from injury (age: 14 months old). D, Left foot showing hyperkeratosis and cracking of his skin (age: 28 months old).

skin fissuring, and had poor healing of minor skin wounds (Fig 1C and D). The patient was referred to a pediatric dentist, who obtained a skeletal survey to examine bone mineralization because of concerns for hypophosphatemia. This revealed an unsuspected parietal skull fracture. His teeth were structurally normal. Alkaline phosphatase, liver function tests, a complete blood cell count, and erythrocyte sedimentation rate were all normal. The patient has 2 older siblings; there are no other family members with similar symptoms.

The patient was seen in the genetics clinic at 14 months of age. Physical examination did not reveal any dysmorphic characteristics; he had normal tearing and eyelashes, hyperkeratosis of his palms and soles, and a severe bite injury of his right anterolateral tongue. Height, weight, and head circumference were all at the 5th percentile. His muscle tone and bulk were normal, as were strength, deep tendon reflexes, and gait. Gross and fine motor skills were appropriate for age; however, the patient was not yet speaking. Sensory examination was notable for failure to react normally to sharp sensation (including EMG needle insertion) or testicular squeeze; light touch and vibration sense appeared normal.

Further history revealed that he did not typically cry with falls or immunizations although he was noted to cry when bumping his head. His skin was reported to be extremely dry, particularly the palms and soles, with recurrent fissuring. During warm weather his cheeks would flush, and he would become lethargic.

PCR and Sequencing

Genomic DNA was prepared from peripheral blood lymphocytes from the patient and his parents using standard methods.³ Amplification of all 17 exons, including exon-intron boundaries, as well as 800 base pair (bp) of 5' promoter sequence, was performed using primers in standard PCR reactions (primer sequences available on request). PCR products were isolated in agarose gels, purified in cephareose columns (Qiagen, Valencia, CA), and sequenced using an automated DNA sequencer with fluorescently-labeled nucleotides (ABI 3700 capillary sequencer, Applied Biosystems, Foster City, CA). Mutations were detected by comparison of published cDNA and genomic sequence for the *NTRK1* gene and region with the PCR products, using sequence analysis software (Sequencher, Gene Codes Corporation, Ann Arbor, MI).

Electromyography and Histamine Testing

EMG testing included peroneal motor and sural sensory studies performed by application of a supramaximal stimulation. Needle EMG was performed using a 25-gauge 1-inch concentric recording electrode.

Histamine testing was performed by intradermal injection of 0.2 mL of 1:1000 histamine acid phosphate solution, with assay of Lewis triple responses.

Histopathology

Skin punch biopsies (3 mm) were obtained from the upper and lower leg, palm, and sole, and immediately placed in fresh paraformaldehyde/lysine/sodium m-periodate fixative. Using a free floating system, 50- μ m thick sections were prepared. Epidermal innervation was visualized using PGP 9.5, a pan-axonal marker (dilution 1:1000; Chemicon International, Temecula, CA).⁴ *NTRK1* expression was assessed using an antibody against the c-terminus of human *NTRK1* (dilution 1:500; Santa Cruz Biotechnology, Santa Cruz, CA).

RESULTS

EMG Testing

Left sural sensory response was normal (1.8 ms latency, conduction velocity 42.9 m/s, amplitude 17.6 mV), as was left peroneal motor response. The patient showed no apparent pain with EMG needle insertion, with recruitment of normal-appearing motor units. Insertional and spontaneous activity was normal. Intradermal histamine injection on 2 separate occasions generated a normal wheal-and-flare response.

PCR and Sequencing

We amplified and sequenced all 17 exons of *NTRK1* (including exon-intron boundaries), as well as 800 bp of 5' promoter sequence, in the patient and his parents. The patient is a compound heterozygote for 2 different mutations inherited from each of his parents.

In exon 6 the patient has a missense T-to-C mutation at nucleotide 722 of the mRNA sequence (c.722T>C), resulting in an amino-acid change from leucine to proline at position 213 (L213P). This mis-

sense mutation is present in the patient's father. The L213P mutation has also been described in a child of Czech-English-German ancestry.⁵

In exon 13 the patient has a deletion of guanine at nucleotide 1556 (c.1556delG), leading to a frame shift at glycine 519 (G519fs), in the tyrosine kinase domain. This frame-shift mutation also is present in the patient's mother, and causes a premature termination codon 28 amino acids downstream. This is a novel mutation in *NTRK1*, and is predicted to cause truncation of apparently half of the protein product, including the tyrosine kinase domain.

Histopathology

The skin biopsies revealed an absence of small nerve fibers in the epidermis of the patient (Fig 2B), as well as a lack of innervation of the eccrine sweat glands (Fig 2D). Large-fiber innervation appears to be maintained, as Meissner corpuscles are still visualized in the patient (Fig 2B, arrows), a result consistent with studies of the *NTRK1*-knockout mouse.⁶ *NTRK1* expression, however, was present (Fig 2F), and appears to be at levels comparable to normal (Fig 2E).

DISCUSSION

The human *NTRK1* gene encodes 1 of the receptors for NGF, and consists of 17 exons distributed over a 25-kb region on chromosome 1q21–22. On binding of NGF to *NTRK1*, *NTRK1* dimerizes and autophosphorylates, and phosphorylated *NTRK1* activates several downstream signaling pathways that mediate the effects of NGF (reviewed in Kaplan and Miller⁷).

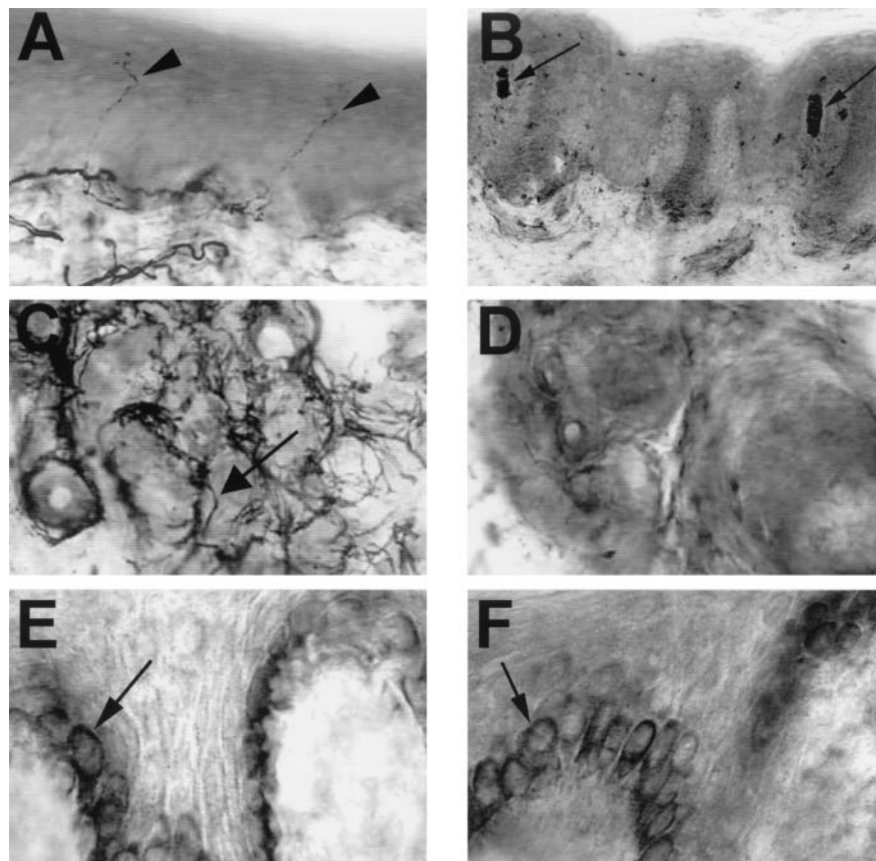


Fig 2. Immunohistochemical sections of skin of patient at 26 months of age (magnification 40 \times). A and B: Epidermis labeled with PGP 9.5 (visualizes axons). A, normal epidermis with axons (arrowheads); B, epidermis of patient; no axon staining is seen, although Meissner corpuscles are visible (arrows). C and D: Sweat glands labeled with PGP 9.5. C, normal sweat gland with bundles of axons visible (arrow); D, sweat gland of patient, no axons seen. E and F: Epidermis labeled with antibody against *NTRK1*, keratinocytes are labeled in the control as well as the patient (arrows). E, normal; F, patient.

In the nervous system, *NTRK1* is expressed in the sympathetic, trigeminal, and dorsal root ganglia as well as in cholinergic neurons of the basal forebrain and striatum. The dorsal root ganglia contain the cell bodies of afferent somatosensory neurons of the entire body (with the exception of the head and neck). *NTRK1* is necessary for innervation of the skin by peripheral sensory axons,⁸ as well as for the development and mature phenotype of neurons in the dorsal root ganglia (which carry pain sensation). In the skin, *NTRK1* is expressed in specialized sensory cells (Meissner corpuscles, Pacinian corpuscles, and Merkel-neurite mechanoreceptors).⁹ Innervation and development of Merkel cells has been shown to be dependent on *NTRK1*.¹⁰ Thus, *NTRK1* is apparently responsible for normal development of several aspects of peripheral pain sensation.

Interest in *NTRK1* as a potential cause of CIPA originated after studies in transgenic mice revealed an analogous phenotype (insensitivity to pain, corneal opacities, self-mutilations) in mice lacking *NTRK1*.¹¹ *NTRK1*-deficient mice lack neurons in the dorsal root ganglia, exhibit neuronal cell loss in the sympathetic ganglia, and have a decrease in cholinergic neurons in the basal forebrain.

Patients with CIPA have the clinical triad of indifference to pain, anhidrosis, and heat intolerance, often manifested as unexplained fevers. Other reported features include an abnormal intradermal histamine test (wheal but no flare), failure to sweat after stimulation with pilocarpine, and the complete electrophysiological absence of sympathetic skin responses.¹² CIPA is autosomal recessive, and has been demonstrated to result from mutations in the *NTRK1* gene.²

We have found 2 apparently pathogenic mutations in *NTRK1* in our patient, confirming his diagnosis of CIPA (despite his atypical presentation). In exon 6, the missense nucleotide change c.722T>C causes an amino-acid change from leucine to praline (L213P). Biochemical and functional studies have shown that the L213P mutation leads to a decrease in autophosphorylation, an inability to transform fibroblasts, and altered intracellular trafficking such that the mutant receptor does not reach the cell surface.^{13,14} Thus, the L213P mutation has a clear loss-of-function effect. The L213P mutation has been described in one other patient, who was also of northern European descent.⁵

We have also found a novel mutation, a frameshift in exon 13, leading to premature translation termination (G519fs). This is expected to result in a substantially shortened *NTRK1* protein product, with loss of almost half of the *NTRK1* protein, including the tyrosine kinase domain, which is necessary for signaling.

The correlation between the specific mutation in the *NTRK1* gene and the phenotypes exhibited is not known. For example, whether certain mutations are more likely to result in more severe mental retardation is not known. Also, detailed functional analysis is necessary to distinguish pathogenic CIPA mutations (such as the L213P mutation) from rare poly-

morphisms in nucleotide or amino-acid sequence that do not have functional consequences.

Currently, our patient is 28 months old; he has had no hospitalizations, no incidences of cellulitis or osteomyelitis, and no corneal involvement. Shortly after his severe tongue injury, a number of teeth were removed prophylactically to prevent further oral injury. He has had 2 burn injuries, both to the hands; once when touching a hot grill, and once via inadvertent placement of his palm over a dishwasher vent. A distal finger-tip injury occurred when his hand was caught in a car door. Developmental screening using the Denver II reveals only a mild speech delay; he is currently receiving speech therapy.

The presence of immunohistochemical staining demonstrating *NTRK1* expression in keratinocytes is consistent with the molecular basis of our patient's CIPA. Because the antibody recognizes the C-terminus of *NTRK1*, the truncated (and presumably non-functional) *NTRK1* (G519fs) is unable to transduce NGF signaling but is still recognized by the antibody. The *NTRK1* containing the missense mutation (L213P) is recognized by the antibody but is also nonfunctional.^{13,14} However, the partial expression of *NTRK1* may allow heterodimerization and thus explain our patient's milder phenotype; only future evaluation and comparison with skin biopsies in other patients with CIPA will clarify this issue.

Although our patient's presentation with primary tooth loss in the first year of life is unusual, studies in mice indicate that *NTRK1*-knockout mice lack nerve fibers in the tooth pulp, including sympathetic fibers, and showed only sparse innervation of the periodontal ligament.⁶ In addition, there are several reports of children with CIPA who bit off a portion of their tongue or pulled out their own teeth.¹⁵⁻¹⁷

Health care maintenance issues are important for children with CIPA: Rosemberg et al¹⁸ reported that an estimated 20% die from hyperpyrexia in the first 3 years of life, while Shorer et al¹² report sepsis leading to death in 23% of their CIPA patients. However, other groups have not reported similar mortality rates. Hyperpyrexia, especially if severe and recurrent, could contribute to the cognitive deficits that a substantial portion of patients demonstrate. Mental retardation is a consistent feature of CIPA patients, although its severity is variable. Severe osteomyelitis has been reported to occur in CIPA patients,^{19,20} which may be attributable in part to an impaired immune response.²¹ In addition, 67% of children with CIPA develop corneal opacities and neuroparalytic keratitis, some requiring surgical intervention.²² Other medical problems reported in CIPA patients include Charcot joints, bone fractures with poor healing, and limb autoamputations.

Close observance of children with CIPA is necessary to prevent self-injury and fractures. To prevent hyperthermia during hot weather, parents should carry a self-misting bottle. Patients should also routinely see an ophthalmologist to check for corneal opacities, and wear protective eyewear under appropriate circumstances.

Our case highlights the variability in clinical pre-

sentation associated with this disorder, particularly early in infancy. An unexplored and poorly defined aspect of CIPA is determining the range of phenotypes exhibited (eg, hyperpyrexia, impaired immune response, tooth loss, etc), and whether any clinical features are 100% sensitive for diagnosis. Our patient did exhibit a wheal response to histamine injection, although Shorer et al¹² reports that a lack of response to histamine injection characterizes all of their CIPA patients.

The heterogeneity of CIPA mutations and the apparent rareness of the condition have contributed to the current unavailability of clinical diagnostic genetic testing. However, this study and that of Mardy et al⁵ suggest that it may be appropriate to screen for the L213P mutation in CIPA patients of northern European descent. CIPA patients from Japanese or Bedouin backgrounds should be screened for 2 specific mutations that occur at a high frequency in these populations.

Recognition of CIPA can be complicated by atypical presentations and lack of familiarity with this disease. The differential for pain insensitivity includes a diverse group of syndromes including Riley-Day syndrome, hereditary and sensory neuropathy types I and II, and a number of other sensory and autonomic neuropathy phenotypes. Other causes of childhood tooth loss include disorders such as Papillon-Lefevre syndrome, dentinogenesis imperfecta type II, ectodermal dysplasia syndromes, and hypophosphatemia. However, the combination of pain insensitivity and tooth loss, with anhidrosis, is highly suggestive of CIPA.

Molecular analysis of potential CIPA mutations is cumbersome because of the high number of exons (17), large genomic area spanned by *NTRK1* (>23 kb), and numerous polymorphisms. A combination of 1) routine EMG demonstrating normal nerve conduction studies (to exclude other peripheral neuropathies), together with 2) skin biopsy demonstrating absence of epidermal and sweat gland innervation; provide a sensitive, reliable and rapid means for confirming a suspected diagnosis of CIPA. Thus, molecular confirmation is not necessary to diagnose CIPA in the setting of a typical clinical presentation together with the EMG and skin biopsy results.

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