

# Congenital Insensitivity to Pain with Anhidrosis in an Iranian Patient

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## ABSTRACT

Congenital insensitivity to pain with anhidrosis is a rare disease of the nervous system which causes one to lose his/her feeling of pain. The disease is subtype four of hereditary sensory and autonomic neuropathy (HSAN IV) that results from NTRK1 gene defect. Direct sequencing was performed to screen NTRK1 for mutations. The result revealed a homozygous deletion of adenine on intron 14 that may cause the disease.

**A** 7 years old boy from city of Bam in Kerman province was admitted to genetic clinic of Afzalipour hospital for counseling. He was the only child of a first cousin couple. He presented with insensitivity to pain, palmoplantar hyperkeratosis, deep heel fissures (Fig. 1), amputation of left big toe, hypodontia (Fig. 2), dystrophic nails, non-healing ulcers, intellectual disability, anhidrosis, polyuria, polydypsia, hyperactivity, and stuttering.

He had history of several admissions with chief complain of cutaneous ulcers and recurrent episodes of unexplained fever. None of his family members had a history of genetic disorders. On physical examination, skin sympathetic reflex (SSR) was not detected. Nerve conduction velocity (NCV) and electromyography (EMG) did not show involvement of peripheral nerves. His fasting blood sugar (FBS), liver function tests (LFT), electrolytes, blood urea, creatinine, and urinary lab tests were within normal range.

The main diagnosis of the patient was hereditary sensory and autonomic neuropathy (HSAN). Five different HSAN subdivisions have been described. HSAN

IV is the second most common one that presents with extensive involvement of ectodermal structures including skin, bone and nervous system, especially absent or markedly decreased sweating (Axelrod, & Gold-von Simson, 2007). Toscano and colleagues announced anhidrosis, decreased pain perception and mental retardation as the main clinical features of HSAN IV (Toscano, Simonati, Indo, & Andria, 2002). With the primary clinical diagnosis of HSAN IV the patient was referred to our genetic lab for molecular analysis.

HSAN IV or congenital insensitivity to pain with anhidrosis (CIPA) is an autosomal recessive inherited condition caused by TRKA/NGF receptor gene on chromosome 1q (Indo et al., 1996; Greco, Villa, Fusetti, Orlandi, & Pierotti, 2000). This gene encodes a receptor tyrosine kinase for nerve growth factor (NFG) which is responsible for the differentiation and survival of sympathetic ganglion and nociceptive sensory neurons (Beigelman et al., 2009). Human TRKA (also named NTRK1) gene codes for a protein of 790 amino acid residues. A single transmembrane domain divides the TRKA protein into an extracellular and an intracellular domain (Schneider, & Schweiger, 1991; Barbacid, 1995). The extracellular

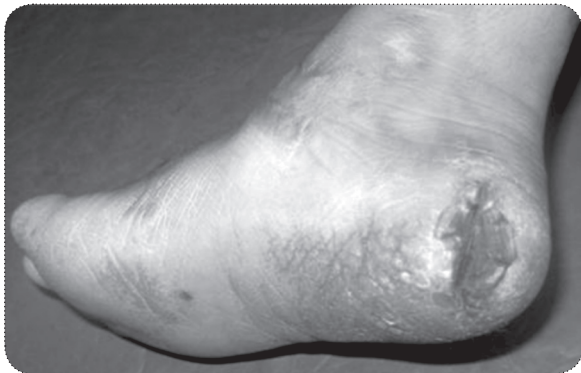
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NEURSCIENCE

**Figure 1.** Deep heel fissure and plantar hyperkeratosis



NEURSCIENCE

**Figure 2.** Fall of teeth

domain is important for specific NFG binding, whereas the intracellular domain includes a tyrosine kinase domain that is phosphorylated in response to NGF and is critical for intracellular signaling (Mardy et al., 1999).

There have been several reports on different types of NTRK1 gene mutation in CIPA patients. Initially, deletion of a single base C at nucleotide 1726 in exon C was reported by Indo and colleagues (Indo et al., 1996). The deletion causes a frame-shift mutation and premature termination codon downstream. Other mutations such as G-to-C transversion at nucleotide 2405 in exon 17 (Greco et al., 1999), G-to-C transversion in the first position of exon 4 (IVS4-1G-C) (Mardy et al., 1999), and 2-bp deletion (207delTG) in exon 1 (Suriu et al., 2009) were later found as the reasons of CIPA disorder.

A written consent for molecular study was obtained from all family members. Genomic DNA was isolated from peripheral blood using salt-saturation method as previously described (Miller, Dykes, & Polesky, 1988). Polymerase chain reaction (PCR) was performed to amplify DNA fragments covering all 17 exons of the gene using 12 pairs of previously published primers (Mardy et al., 1999). PCR product was checked on 1% agarose gel. Sequencing was carried out using an automated DNA sequencer. The sequencing data were aligned to the NCBI human reference sequence of NTRK1 (NG\_007493.1).

The results revealed that the proband was homozygote for a deletion of A (TGCA\_GCCC) in the intron 14 (IVS14+413) at position 65320 of NTRK1 gene. His mother was heterozygote for this deletion.

This is the first report to describe CIPA in the Bam city of Kerman province. There have been several reports on different types of HSAN from different parts of Iran (Gharagozlou, Zandieh, Tabatabaei, & Zamani, 2006; Safari, Khaledi, & Vojdani, 2011; Mobini, Javadzadeh, & Forghanizadeh, 2009), but none of them were genetically investigated.

In the present work we found a homozygous deletion of Adenine in the intron 14 of NTRK1 gene in a patient that his mother was heterozygote for this deletion. It was impossible to check this gene defect on his father, since he was dead.

Most of the mutations in CIPA patients were found in NTRK1 gene exons. The homozygous deletion of Adenine, located close to exon 15 (exon15 -10), may interfere with splicing and causes the disease. Miura and colleagues previously reported an intronic mutation, IVS7AS-33 T-A, in a CIPA patient from Japan (Miura et al., 2000).

Although DNA analysis of NTRK1 gene covers majority of the common mutations, it is not sufficient to detect mutations that hamper the splicing process. A better diagnostic approach such as whole exome sequencing or microarray expression analysis will help identifying all relevant mutations of CIPA disease.

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### Declaration of Interest

I hereby declare that no part of this article has previously been submitted or published elsewhere. I also confirm that no impending conflict do exist for it. Kerman University of Medical Sciences supported this work financially and I, as a faculty member of the University, take complete responsibility for the integrity of the data and writing of the paper.

### References

- Axelrod, F. B., & Gold-von Simson, G. (2007). Hereditary sensory and autonomic neuropathies: types II, III, and IV. *Orphanet Journal of Rare Diseases*, 39(2), 1-12.
- Barbacid, M. Structural and functional properties of the TRK family of neurotrophin receptors. *Annals of the New York Academy of Sciences*, 766(7), 442-58.
- Beigelman, A., Levy, J., Hadad, N., Pinsk, V., Haim, A., & Fruchtman, Y., et al. (2009). Abnormal neutrophil chemotactic activity in children with congenital insensitivity to pain with anhidrosis (CIPA): the role of nerve growth factor. *Clinical Immunology*, 130(3), 365-372.
- Gharagozlou, M., Zandieh, F., Tabatabaei, P., & Zamani, G. (2006). Congenital sensory neuropathy as a differential diagnosis for phagocytic immunodeficiency. *Iranian Journal of Allergy, Asthma, and Immunology*, 5(1), 35-7.
- Greco, A., Villa, R., Fusetti, L., Orlandi, R., & Pierotti, M. A. (2000). The Gly571Arg mutation, associated with the autonomic and sensory disorder congenital insensitivity to pain with anhidrosis, causes the inactivation of the NTRK1/nerve growth factor receptor. *Journal of Cellular Physiology*, 182(1), 127-33.
- Greco, A., Villa, R., Tubino, B., Romano, L., Penso, D., & Pierotti, M. A. (1999). A novel NTRK1 mutation associated with congenital insensitivity to pain with anhidrosis. (Letter) *Am. J. Hum. Genet.*, 64, 1207-1210.
- Indo, Y., Tsuruta, M., Hayashida, Y., Karim, M. A., Ohta, K., & Kawano, T., et al. (1996). Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. *Nature Genetics*, 13(4), 485-8.
- Mardy, S., Miura, Y., Endo, F., Matsuda, I., Sztrih, L., & Frosard, P. et al. (1999). Congenital insensitivity to pain with anhidrosis: novel mutations in the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor. *American Journal of Human Genetics*, 64(6), 1570-9.
- Miller, S. A., Dykes, D.D., & Polesky, H. F. (1988). A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Research*, 16(3), 1215-1216.
- Miura, Y., Mardy, S., Awaya, Y., Nihei, K., Endo, F., & Matsuda, I. et al. (2000). Mutation and polymorphism analysis of the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor in congenital insensitivity to pain with anhidrosis (CIPA) families. *Hum. Genet.*, 106, 116-124.
- Mobini, M., Javadzadeh, A., & Forghanizadeh, J. (2009). Neuropathic osteoarthropathy in a patient with congenital insensitivity to pain. *Archives of Iranian Medicine*, 12 (6), 599-602.
- Safari, A., Khaledi, A. A., & Vojdani, M. (2011). Congenital Insensitivity to Pain with Anhidrosis (CIPA): A case report. *Iranian Red Crescent Medical Journal*, 13(2), 134-138.
- Schneider, R., & Schweiger, M. (1991). A novel modular mosaic of cell adhesion motifs in the extracellular domains of the neurogenic trk and trkB tyrosine kinase receptors. *Oncogene*, 6(10), 1807-11.
- Suriu, C., Khayat, M., Weiler, M., Kfir, N., Cohen, C., & Zinger, A. et al. (2009). Skoura—a genetic island for congenital insensitivity to pain and anhidrosis among Moroccan Jews, as determined by a novel mutation in the NTRK1 gene. *Clin. Genet.*, 75, 230-236.
- Toscano, E., Simonati, A., Indo, Y., & Andria, G. (2002). No mutation in the TRKA (NTRK1) gene encoding a receptor tyrosine kinase for nerve growth factor in a patient with hereditary sensory and autonomic neuropathy type V. *Ann Neurol*, 52(2), 224-7.