Congenital Insensitivity to Pain with Anhidrosis in an Iranian Patient

Nasrollah Saleh-gohari, Marzye Mohammadi-Anaie

1. Genetic Department, Medical School, Kerman University of Medical Sciences, Kerman, Iran.
2. Genetic Laboratory, Afzalipour Hospital, Kerman, Iran.

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.

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 (NGF) 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...
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 NRTK1 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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Declarations of Interest

I hereby declare that no part of this article has previously been submitted or published elsewhere. I also confirm that no impeding 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


