Whole exome sequencing in congenital pain insensitivity identifies a novel causative intronic NTRK1-mutation due to uniparental disomy.

Abstract:
Congenital insensitivity to pain and anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV (HSAN IV), is characterized by recurrent episodes of unexplained high fever, loss of pain perception and temperature sensation, absent sweating, repeated traumatic and thermal injuries, and mild mental retardation. After exclusion of obviously pathogenic mutations in NTRK1, the most common cause of CIPA, whole exome sequencing (WES) was carried out in a CIPA patient with unrelated parents. No mutations in known HSAN genes were identified. However, filtering for genes carrying two rare sequence variations detected 13 homozygous single nucleotide variants (SNV), all being located on chromosome 1. Further analysis strongly suggested that this finding might be best explained by uniparental disomy of chromosome 1. Because NTRK1 is also located on chromosome 1, we re-evaluated WES data and detected a novel intronic sequence variation at position c.2188-12 C>A, homozygously because of uniparental disomy. Subsequent analysis of NTRK1 transcripts in peripheral blood cells of the patient revealed an influence of the variant on mRNA splicing. The C>A transversion generated a novel splice-site, which led to the
incorporation of 10 intronic bases into the NTRK1 mRNA and consequently to a non-functional gene product. © 2016 Wiley Periodicals, Inc.