Novel NTRK1 mutation in Chinese patient with congenital insensitivity to pain with anhidrosis: A Case Report

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Case Report

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Abstract

Objective : Congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessively inherited disorder characterized by insensitivity to noxious stimuli and inability to sweat.

Methods : In this case report, an 18-year-old Chinese boy diagnosed with CIPA with the clinical features of loss of algesthesis, inability to sweat, self-mutilation, developmental delay and dislocation of the left hip joint. Blood samples from the patient was collected and subjected to genetic analysis.

Results : Sequencing analysis revealed a novel mutation, c.1769A>G, in the neurotrophic tyrosine kinase receptor type 1 gene (NTRK1). In silico studies suggested that the mutations described are detrimental to the function of the protein encoded by the NTRK1 gene.

Conclusions : The novel mutation widen the genetic mutation spectrum of NTRK1 in CIPA patients, and provide more evidence for precise diagnosis of the clinically suspected patients with CIPA.

Introduction

Congenital insensitivity to pain with anhidrosis (CIPA; MIM #256800), also known as hereditary sensory and autonomic neuropathy type 4 (HSAN4), is a rare autosomal recessively inherited disorder, which was first described in 1963 by Swanson [1]. CIPA is characterized by insensitivity to noxious stimuli, anhidrosis, and intellectual disability. Classic symptoms of CIPA include self-mutilating behavior, multiple injuries, repeated painless fractures, Charcot arthropathy, osteomyelitis, and repeated fever [2, 3].

The pathogenesis of CIPA is characterized by a genetic loss-of-function mutation of the NTKR1 gene, located in chromosome 1 which encodes one of the receptors for the nerve growth factor (NGF) [4, 5]. Upon binding to NGF, NTRK1 is autophosphorylated, and activates an intracellular signal transduction pathway, thus mediating the survival, growth, differentiation, and synaptic plasticity of neurons [6, 7]. In this study, we described a case report of Chinese CIPA patient with novel NTRK1 mutation.

Patient And Methods

Patient

This study was approved by the institutional ethics committee of Xuzhou Central Hospital. Written informed consent was obtained for publication from all individuals enrolled in this study. The patient was an 18-year-old boy diagnosed with CIPA. We investigated the patient and his parents. A comprehensive physical examination and genetic testing were performed to confirm the CIPA diagnosis. A nerve biopsy was not conducted because of the minimal benefit to the study.

Whole-Exome Sequencing (WES) and bioinformatics analysis

Genomic DNA was extracted from peripheral blood of patient and his parents using the TIANamp Blood DNA Kit (Tiangen Biotech Co. Ltd, Beijing, China). A minimum of 3 μg genomic DNA was sheared, end-repaired and ligated with special devices. Then adapters were ligated to both ends of the resulting fragments. Extracted DNA was then amplified by ligation-mediated PCR (LM-PCR), purified, and hybridized to the Nimblegen SeqCap EZ Library v3.0 (Roche/NimbleGen, Madison, WI) for enrichment. PCR was used to amplify the enriched library. Each captured library was then loaded on Hiseq2500 platform (Illumina, San Diego, CA). The mutation of the NTRK1 gene was further confirmed by Sanger Sequencing (ABI 3730 Genetic Analyzer, Applied Biosystems, Foster City, CA, USA) using primer pair 5'-GGACGGAGAAACAAGTTTGGGATCA-3' and 5'- AGGTCCATGGGATCGGAGGAAGCGG – 3'.

Result

Clinical Data

In this case report, an 18-year-old Chinese boy diagnosed with CIPA with the clinical features of loss of algesthesis, inability to sweat, self-mutilation, developmental delay and dislocation of the left hip joint. The patient experienced recurrent fevers of unknown causes (maximum body temperature 42℃). He bit his fingers and tongues after tooth eruption. He had an ulna fracture in right arm at age 6 years. A left hip joint dislocation occurred when he was 18 years old. He underwent a surgery of open reduction and internal fixation in 2018, but healed poor (Fig. 1). He developed osteomyelitis due to poor healing after a trauma or fracture surgery. Because of dislocation of the left hip joint, he required a wheelchair for ambulation.

Genetic analysis

Using WES, a compound heterozygous NTRK1 mutations (c.1750G > A; c.1769A > G) in the coding region of exon 13 of the NTRK1 gene (NM_001012331.1) was identified in the patient, which were inherited from his parents (Fig. 2). Both parents are carriers of one heterozygous mutation. The paternal mutation c.1750G > A has previously been shown to be a pathogenic mutation [5]. The maternal mutation c.1769A > G has not been previously reported (HGMD). c.1769A > G is a missense mutation, which can lead to the aspartic acid changing into Glycine, which has a great impact on the structure and function of the protein theoretically.

Discussion

CIPA was first described in 1932 [8, 9]. Since the pathogenic gene NTRK1 was first discovered and identified in 1996[4], 120 NTRK1 gene mutations have been recorded by HGMDpro [10]. NTRK1 gene contains 17 exons, code 796 amino acids [11]. The NTRK1 gene encodes tropomyosin receptor kinase A (TrkA), which is a high affinity receptor for nerve growth factor (NGF) [12]. The NGF-TRKA system regulates the growth and development of peripheral and central neurons, maintains the survival of neurons, and plays a key role in pain, itching, and inflammatory infections [13, 14]. Recent studies have

found that NGF-TrkA is involved in vascularization and ossification of bone during embryonic development [15, 16].

The clinical manifestation of CIPA is recurrent fever in infant or early childhood due to anhidrosis, which is not sensitive to analgesic-antipyretic, but can be relieved by physical cooling, sometimes with epilepsy [17]. The other classic symptoms of CIPA are loss of algesthesis and inability to sweat [18]. Because of their insensitivity to pain, patients often show self-harm behaviors occurring in the soft tissues of the hands, lips and tongue [19]. In addition, patients are prone to repeated painless fractures and joint dislocations [20, 21]. Patients may still have psychomotor retardation, with an IQ of about 60 [22]. In this study, patient had recurrent fevers since birth which is not sensitive to analgesic-antipyretic. He bit his fingers and tongues after tooth eruption. His medical history revealed loss of algesthesis, inability to sweat, ulna fracture in right arm and dislocation of the left hip joint.

In this study, a compound heterozygous NTRK1 mutations (c.1750G > A; c.1769A > G) in the coding region of exon 13 of the NTRK1 gene (NM_001012331.1) was identified in the patient, which were inherited from his parents. The mutation c.1750G > A has previously been reported to be a pathogenic mutation. The maternal mutation c.1769A > G is a missense mutation which has not been previously reported (HGMD) and can lead to the aspartic acid changing into Glycine and has a great impact on the structure and function of the protein theoretically. According to the guide of ACMG gene mutation interpretation, this site was interpreted as a pathogenic mutation: no population carrying rate; the complex heterozygosis pathogenic mutation site has great influence on protein structure and function theoretically.

In conclusion, the novel mutation broaden the genetic mutation spectrum of NTRK1 in CIPA patients, and provide more evidence for precise diagnosis of the clinically suspected patients with CIPA. But the in-depth study of this mutation pathogenic mechanism is needed to further clarify.

Abbreviations

CIPA: Congenital insensitivity to pain with anhidrosis; NTRK1: Neurotrophic tyrosine kinase receptor type 1 gene; HSAN4: hereditary sensory and autonomic neuropathy type 4; NGF: nerve growth factor; WES: Whole-Exome Sequencing; TrkA: tropomyosin receptor kinase A.

Declarations

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Authors' contributions

JS and YX conceived of this study and prepared the manuscript. ZCX and HXX collected data and performed data analysis. BZ and JFZ carried out the statistical analysis. YLZ and XW carried out the data

search, selection, and study quality assessment. All authors have read and approved the final version of the manuscript and agreed with the order of presentation of the authors.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by Xuzhou Central Hospital Ethics Committee. The approval number is XZXY-LJ-20180320-012.

Consent for publication

All authors consent for publication.

Competing interests

There are no competing interests.

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Figures

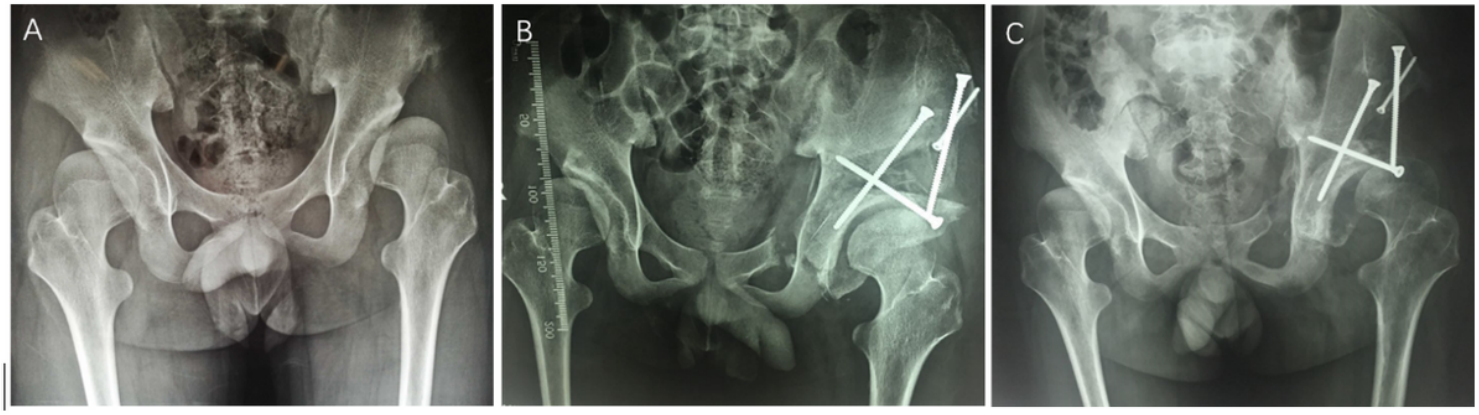

Figure 1

X-ray images of the patient. A: Before the operation, B: One month after the operation, C: Three month after the operation.

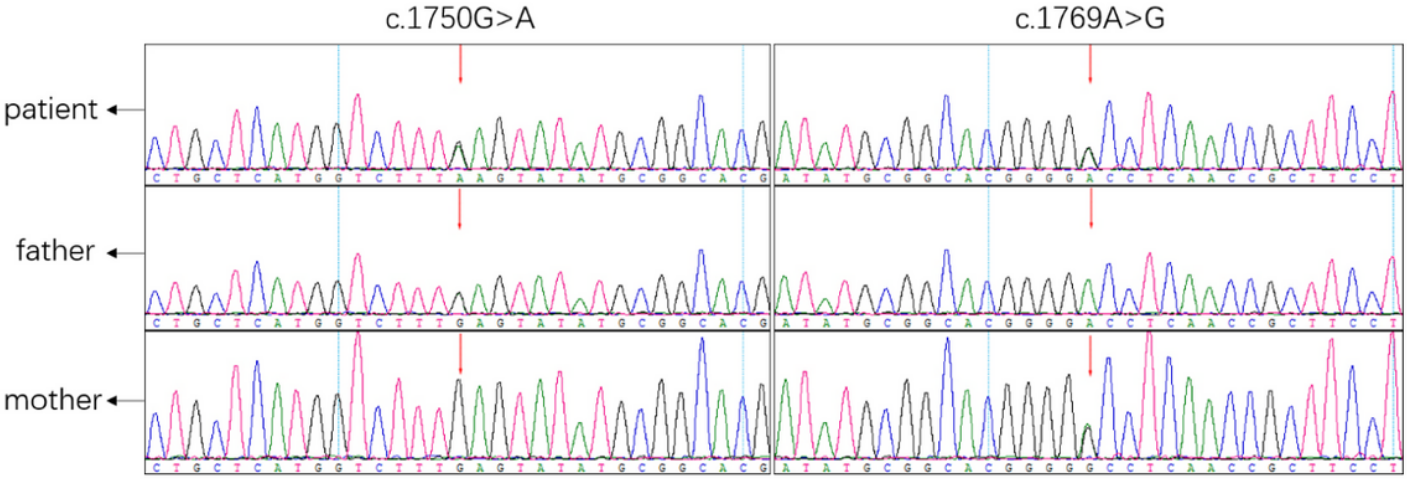

Figure 2

Sequencing chromatographs of NTRK1 revealing mutations in the patient and their parents. Mutations are indicated by red arrows.