GATA3 mutation in a family with hypoparathyroidism, deafness and renal dysplasia syndrome

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Case report

Background: **The hypoparathyroidism, deafness and renal dysplasia (HDR) syndrome is an autosomal dominant disorder primarily caused by *GATA3* gene mutation. We report here a case that both of a Chinese boy and his father had HDR syndrome which caused by a novel mutation of *GATA3*.**

Methods: **Polymerase chain reaction and DNA sequencing was performed to detect the exons of the *GATA3* gene for mutation analysis.**

Results: **Sequence analysis of GATA3 revealed a heterozygous nonsense mutation in this family: a mutation of *GATA3* at exon 2 (c.515C >A) that resulted in a premature stop at codon 172 (p.S172X) with a loss of two zinc finger domains.**

Conclusion: **We identified a novel nonsense mutation which will expand the spectrum of HDR-associated *GATA3* mutations.**

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Key words: **HDR syndrome; mutation**

Introduction

Hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome is characterized by hypoparathyroidism, sensorineural deafness and renal dysplasia.[1] This syndrome is a rare autosomal dominant disorder primarily caused by mutations of the *GATA3* gene, in which protein is selectively expressed in the human embryonic parathyroids, inner ear, and kidneys. Deletion-mapping studies and subsequent mutation analysis revealed that haploinsufficiency for *GATA3* is the underlying mechanism of the HDR syndrome. We report herein a Chinese family, in which two of the members had a new mutation of *GATA3* at exon 2 (c.515C >A) causing HDR syndrome, which expand the spectrum of HDR-associated *GATA3* mutations.

Case report

Clinical information

A 12-year-old Chinese boy was admitted to our hospital because of recurrent tetany for several years. He was the first-born child to non-consanguineous parents, without phanerous dysmorphic features at birth, but failed in newborn hearing screening. He started unaided walking at about 15 months old, and with a mild developmental delay in language without cognitive impairment and autistic behaviors.

Laboratory examination revealed that serum calcium was 1.55 mmol/L (reference range, 2.2-2.7 mmol/L); serum phosphate, 2.93 mmol/L (reference range, 1.45-2.1 mmol/L); and serum parathyroid hormone, 32 pg/mL (reference range, 12-65 pg/mL). Abdomen ultrasonography found bilateral multiple renal cysts and right renal calculi. Pure tone audiometry test demonstrated bilateral severe sensory deafness. Echocardiography was normal. Computed tomography (CT) of the brain displayed the calcifications in the right subcortical white matter. His full-scale intellectual disability score was 71 in Wechsler Intelligence Scales for Children Revised (WISC-R). His father with mild mental retardation had right renal calculi and bilateral severe sensory deafness. Serum calcium level of his father was 2.2 mmol/L. His mother had no renal or auditory problems, and with a normal level of serum calcium.

Mutation analysis

Blood samples of the patient and his parents were collected after informed consent was obtained. Genomic DNA was extracted from peripheral blood leukocytes by TIANamp Bood DNA Kit (Tiangen

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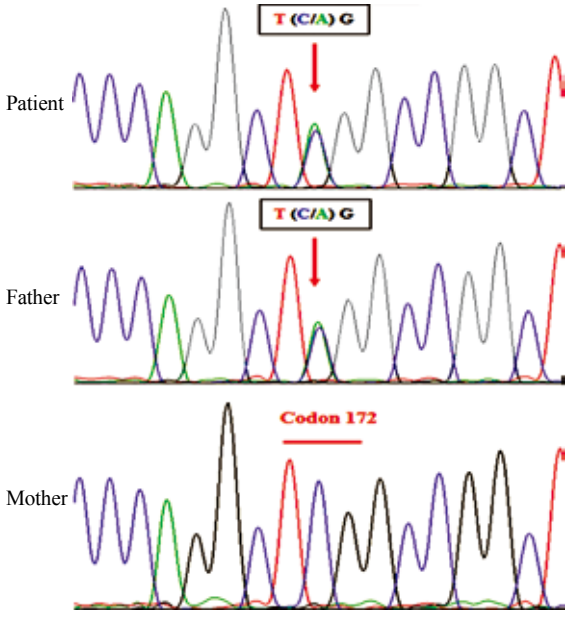

Fig. Sequence analysis of genomic DNA from the patient and his parents shows the nucleotide sequences around the codon 172 in exon 2 of *GATA3*. Arrow indicates the mutation site. The patient and his father are both heterozygous for a nonsense mutation in exon 2 (c.515C >A), which is not detected in his mother. The mutation results in a premature stop at codon 172 (p.S172X) with a loss of two zinc finger domains.

Biotech, Beijing, China).The exons in the *GATA3* gene were amplified by polymerase chain reaction (PCR), followed subsequently by direct sequencing. The primer sequences and the PCR condition were designed according to the method used by Van Esch et al.[2]

Sequence analysis identified a novel heterozygous nonsense mutation of the *GATA3* gene at exon 2 (c.515C >A) in the patient and his father, but not in his mother, which resulted in a premature stop at codon 172 (p.S172X) (Fig.).

Discussion

HDR syndrome was first reported by Bilous in 1992.[3] Clinically, HDR syndrome is characterized by symptomatic or asymptomatic hypocalcemia with an undetectable or low level of serum parathyroid hormone (PTH). Bilateral sensorineural deafness is usually present at birth and moderately serious. Renal anomalies such as cystic kidney, renal dysplasia, hypoplasia or aplasia, vesicoureteric reflux, glomerular nephropathy and nephrotic syndrome are common variables, but renal anomalies are not seen in HDR syndrome in some cases.[4,5] Moreover, many additional features have been found in patients with HDR syndrome.[5-9]

The typical triad of HDR syndrome, as well as heart defect, immune deficiency, facial dysmorphism and mental retardation also occurred in the DiGeorge syndrome 2, which was associated with deletion of 10 p, and within the same genomic region of HDR syndrome. Lindstrand et al[10] defined the critical regions involved in severe mental retardation, language impairment and autism. In our case, both the boy and his father had a typical triad of HDR syndrome and mild mental retardation, but without heart defect, facial dysmorphism and autism. The mental retardation might be caused by the absence of the treatment for sensory deafness at birth. Intracranial calcification in the patient may be due to the disorders of calcium phosphate metabolism. Although the proportion of calcification was limited, with the progress of the disease and duration of calcium metabolic abnormalities, the extending calcification could cause neuropsychological and behavioral changes.[11,12] This finding suggests that early diagnosis and treatment are essential.

HDR syndrome is primarily related to haploinsufficiency of the *GATA3* gene, which is located on chromosome 10p15, including six exons, and encodes a transcription factor. *GATA3* contains two transactivating domains (TA1 and TA2) at the N-terminus and two zinc finger DNA-binding domains (ZnF1 and ZnF2) at the C-terminus. Mutations of *GATA3* involving ZnF2 or adjacent basic amino acids result in a loss of DNA binding, and mutation at ZnF1 leads to a loss of interaction with the multi-type zinc finger Friends of GATA proteins or alters DNA-binding affinity.[13] By searching in the Human Mutation Database (HGMD, http://www.hgmd.org/), a total of 37 mutations of *GATA3* have been identified. To date, 6 nonsense mutations causing HDR syndrome have been reported.[3,14-17]

In the present study, we identified a novel nonsense mutation of *GATA3* at exon 2 (c.515C >A) that resulted in a premature stop at codon 172 (p.S172X). This mutation is considered to be pathogenic and will truncate *GATA3* protein to be lack of both zinc finger domains, thus finally leading to HDR syndrome through haploinsufficiency. The phenotypes of HDR syndrome vary, even in the affected members of a single family with the same *GATA3* mutation.[18] In our study, both patient and his father had the same *GATA3* mutation but didn't show identical clinical features, which were consistent with previous studies. The haploinsufficiency of *GATA3* is the major cause of HDR syndrome. The haploinsufficiency of genes in human development display is known to have a wide range of penetrance and expressivity based on other genes and environment factors[2] for the clinical heterogeneity.[19]

In summary, we found the new mutation of the *GATA3* gene in HDR syndrome patients which could expand the spectrum of HDR-associated *GATA3* mutations. *GATA3* mutation analysis might be useful for

accurate genetic diagnosis and early treatment of HDR syndrome.

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Ethical approval: This study was approved by the Ethics Committee of Nanjing Children's Hospital Affiliated to Nanjing Medical University. Written consent for publication was obtained from the parents of the patient.

Competing interest: No benefits in any form have been received or will be received from any commercial party related directly or indirectly to the subject of this article.

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