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Mutation-in-Brief

Novel splice site mutation in *GATA3* in a patient with HDR syndrome

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Key words: HDR syndrome, *GATA3*, novel splice site mutation

Introduction

HDR syndrome (OMIM: 146255) is an autosomal dominant disorder characterized by the triad of hypoparathyroidism, sensorineural deafness, and renal dysplasia. It is caused by haploinsufficiency of the dual zinc finger transcription factor GATA3 on chromosome 10p15 (1, 2). To date, more than 70 mutations in *GATA3* have been registered in the Human Genome Mutation Database (HGMD, www.hgmd.cf.ac.uk). However, intronic mutations in *GATA3* have not yet been reported, except for those affecting the first or second donor or acceptor splice sites. Herein, we report the first case of HDR syndrome caused by a novel intronic mutation in *GATA3*.

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Case Report

A 15-yr-old Japanese boy developed syncope while traveling; hypocalcemia was detected in a local hospital, for which he was referred to our hospital for evaluation. At the age of 9 yr, the patient had been diagnosed with moderate bilateral sensorineural hearing loss; a nonverbal learning disability was suspected. Furthermore, he had experienced leg cramps since childhood. Based on his clinical features, HDR syndrome was suspected. There was no history of HDR syndrome in the patient's family, nor did he present with other hypocalcemic symptoms such as the Trousseau sign. Laboratory findings are summarized in Table 1. The serum calcium level was low (7.5 mg/dl) and the inorganic phosphate level was high (6.9 mg/dl), while both the urine calcium/creatinine ratio and fractional excretion of calcium were low (0.009 and 0.007, respectively). Despite hypocalcemia, the intact PTH level was also low (15 pg/ml). Proteinuria and hematuria were not detected, and creatinine clearance was normal (116.4 ml/min/1.73 m^2). Abdominal ultrasound and CT scans revealed a hypoplastic right kidney (long diameter: 60 mm), while ^{99m}Tc-mercaptoacetyltriglycine-3 renography showed low effective renal plasma flow in the right kidney (66.8 ml/min/1.73 m^2). Moderate bilateral sensorineural hearing loss (45

Table 1 Laboratory findings

		normal range
Calcium (mg/dl)	7.5	8.7–11.0
Inorganic phosphate (mg/dl)	6.9	2.7–4.7
Alkaline phosphatase (IU/l)	321	270–1200
Albumin (g/dl)	4.9	3.9–4.9
Intact PTH (pg/ml)	15	10–65
1,25-dihydroxyvitamin D (pg/ml)	97.4	20–60
Urine calcium/creatinine ratio	0.009	0.05–0.15
Fractional excretion of calcium	0.007	0.02–0.04

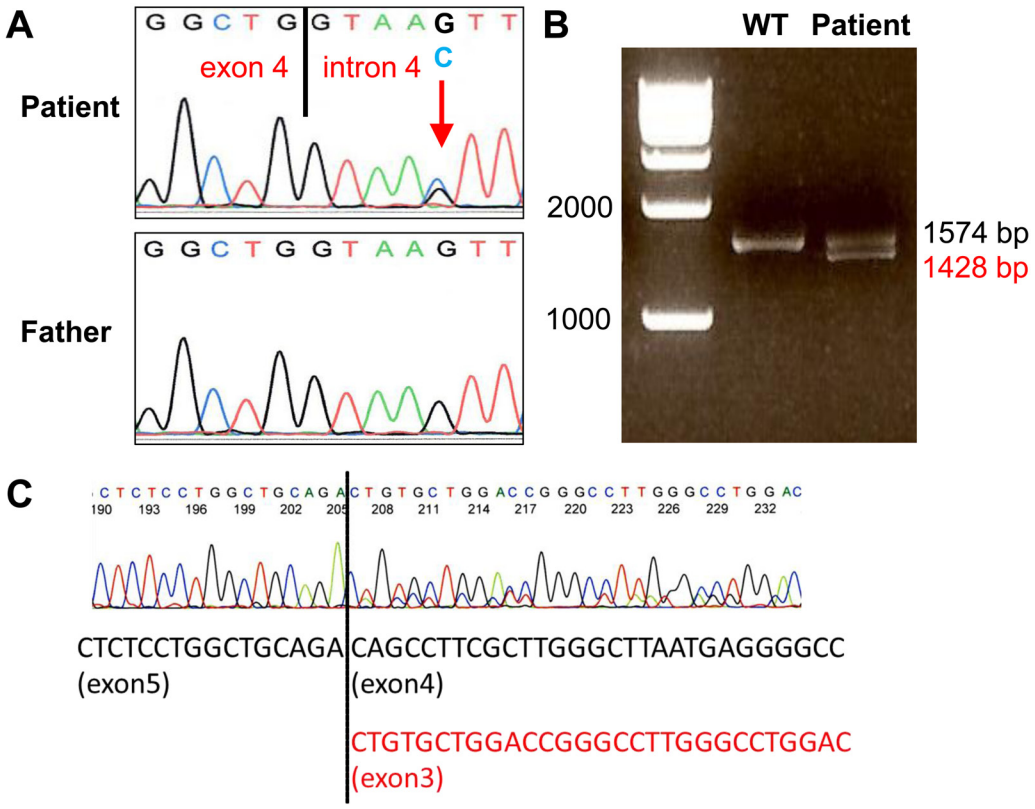

Fig. 1. Analysis of the *GATA3* mutation. (A) The patient was heterozygous for a novel intronic mutation (IVS4 +5G>C) which was not detected in his father. (B) Electrophoresis of the RT-PCR product revealed that the patient's cDNA produced two distinct bands: a 1574-bp band produced by the wild-type sequence and a 1428-bp band produced by the mutant sequence. (C) Skipping of exon 4 in *GATA3* mRNA was detected by RT-PCR-based direct sequencing of both the forward and reverse sequences.

dB in both ears) was confirmed by audiometry, and normal cardiac function was confirmed by the attending cardiologist.

Genetic Analysis

To confirm the diagnosis of HDR syndrome, we investigated mutations present in *GATA3*

in the patient and his father, after obtaining written informed consent; however, the patient's mother refused to undergo genetic analysis. Genomic DNA was extracted from peripheral blood samples. PCR-based direct sequencing of all coding exons and flanking introns of *GATA3* revealed that the patient was heterozygous for a novel missense intronic mutation (IVS4 + 5G>C) (Fig. 1). This mutation was not detected in his father and was not included in the Ensembl database (www.ensembl.org). To assess the effect of the mutation on splicing, *GATA3* mRNA expression was investigated. Total RNA was extracted from a peripheral blood sample and *GATA3* mRNA was analyzed by RT-PCR-based direct sequencing; it was determined that exon 4 was skipped (Fig. 1).

Discussion

This is the first report of HDR syndrome caused by an intronic mutation in *GATA3*, other than mutations in the donor and acceptor splice sites. Analysis of mRNA expression revealed the skipping of *GATA3* exon 4, which includes the first zinc-finger domain. This frameshift mutation (p.Glu260ValfsX43) was predicted to produce an aberrant GATA3 protein that also lacked the second zinc-finger domain. Therefore, this mutation was likely pathogenic because it resulted in the production of an aberrant protein that lacked both zinc-finger domains involved in DNA binding.

HDR syndrome has a wide phenotypic spectrum (3). Our patient presented with the triad typical of HDR syndrome. A familial *GATA3* splice site donor mutation (IVS4+2T>GCTTACTTCCC) predicted to cause skipping of exon 4 has previously been reported (4), where both patients had hypoparathyroidism and sensorineural hearing loss, while bilateral renal hypoplasia was detected only in the daughter but not in the proband. Our patient had unilateral renal hypoplasia, suggesting that the renal anomalies associated with HDR syndrome tend to vary. In conclusion, a novel splice site mutation in *GATA3* was detected in a patient with HDR syndrome.

Conflict of Interest: The authors have no conflicts of interest to declare.

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