Mutation-in-Brief

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

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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.

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 m²). Abdominal ultrasound and CT scans revealed a hypoplastic right kidney (long diameter: 60 mm), while ⁹⁹mTc-mercaptoacetyltriglycine-3 renography showed low effective renal plasma flow in the right kidney (66.8 ml/min/1.73 m²). Moderate bilateral sensorineural hearing loss (45
dB in both ears) was confirmed by audiometry, and normal cardiac function was confirmed by the attending cardiologist.

**Table 1** Laboratory findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dl)</td>
<td>7.5</td>
<td>8.7–11.0</td>
</tr>
<tr>
<td>Inorganic phosphate (mg/dl)</td>
<td>6.9</td>
<td>2.7–4.7</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l)</td>
<td>321</td>
<td>270–1200</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.9</td>
<td>3.9–4.9</td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>15</td>
<td>10–65</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (pg/ml)</td>
<td>97.4</td>
<td>20–60</td>
</tr>
<tr>
<td>Urine calcium/creatinine ratio</td>
<td>0.009</td>
<td>0.05–0.15</td>
</tr>
<tr>
<td>Fractional excretion of calcium</td>
<td>0.007</td>
<td>0.02–0.04</td>
</tr>
</tbody>
</table>

**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.

**References**

4. Chiu WY, Chen HW, Chao HW, Yann LT, Tsai KS. Identification of three novel mutations in the GATA3 gene responsible for familial hypoparathyroidism and deafness in the Chinese population. J Clin Endocrinol Metab 2006;91: 4587–92. [Medline] [CrossRef]