Mutation of Glu78 of the AVP-NPII Gene Impairs Neurophysin as a Carrier Protein for Arginine Vasopressin in a Family with Neurohypophyseal Diabetes Insipidus

Yong-Wha Lee,*1 Kyung Wook Lee,*2 Ji Won Ryu,2 Ji Oh Mok,2 Chang-Seok Ki,3 Hyeong Kyu Park,2 Yeo Joo Kim,2 Sang Jin Kim,2 Dong Won Byun,2 Kyo Ill Suh,2 Myung Hi Yoo,2 Hee Bong Shin,1 You Kyoung Lee,1 and Chul-Hee Kim2

1Department of Laboratory Medicine, Bucheon Hospital and Soonchunhyang University College of Medicine, Bucheon; 2Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon; and 3Department of Laboratory Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Abstract. Familial neurohypophyseal diabetes insipidus (FNDI; OMIM 192340) is a rare inherited disorder with an autosomal dominant inheritance pattern. It is characterized by persistent polydipsia and polyuria induced by deficient or absent secretion of arginine vasopressin (AVP). We report a Korean kindred in whom FNDI is associated with a novel deletion mutation in exon 2 of the AVP-NPII gene encoding the neurophysin II moiety. An 18-yr-old man with polyuria and polydipsia was shown to have central diabetes insipidus by using the water deprivation test. Four family members were suspected to have symptomatic vasopressin-deficient diabetes insipidus. Direct sequencing of the AVP-NPII gene showed a heterozygous GAG deletion mutation in exon 2, which results in in-frame deletion of glutamic acid (c.232_234delGAG; p.Glu78del). The mutation was predicted to yield an abnormal AVP precursor lacking Glu78 (E78) in its neurophysin II moiety. Because Glu78 is essential for neurophysin II molecules to form a salt bridge with AVP, the function of neurophysin as a carrier protein for AVP would be impaired. The proband’s mother and sister have the same mutation. Presence of this mutation suggests that the portion of the neurophysin peptide encoded by this sequence is important for the appropriate expression of vasopressin.

Keywords: diabetes insipidus, AVP-NPII gene, neurophysin, arginine vasopressin

Introduction

Familial neurohypophyseal diabetes insipidus (FNDI; OMIM 192340) is a rare inherited disorder with an autosomal dominant inheritance pattern. It is characterized by persistent polydipsia and polyuria induced by deficient or absent secretion of arginine vasopressin (AVP). The 2.5 kb AVP-NPII gene is located on chromosome 20p13 and consists of 3 exons [1]. Since the first report of a mutation in this gene [2], 53 different mutations have been identified (Human Gene Mutation Database, Institute of Medical Genetics, Cardiff, Wales, UK). Among the AVP-NPII mutations related to FNDI, deletion mutations have been reported in only 4 cases [3-6]. We report a Korean family with FNDI in whom we identified a novel in-frame deletion mutation (c.232_234delGAG; p.Glu78del) in the AVP-NPII gene.

Materials and Methods

The proband was an 18-yr-old man admitted to our hospital because of a long-lasting history of polyuria and polydipsia. His mother, sister, uncle, and cousin reported having the same symptoms for a long period of time (Fig. 1). The patient underwent a water deprivation test. The patient’s mother, sister, uncle, and cousin refused to undergo this test.
After we had obtained informed consent, blood samples were collected from the proband and his family members for genetic analysis. Genomic DNA was isolated from peripheral blood leukocytes using a Wizard genomic DNA purification kit (Promega, Madison, WI, USA), following the manufacturer’s instructions. All 3 coding exons of the AVP-NPII gene were PCR-amplified using primers designed by the authors (primer sets available upon request). After treatment of the amplicon (5 μl) with 10 U shrimp alkaline phosphatase and 2 U exonuclease I (USB Corp., Cleveland, OH, USA), sequencing was done with the BigDye terminator cycle sequencing ready reaction kit (Applied Biosystems, Foster City, CA, USA) and ABI Prism 3100 genetic analyzer (Applied Biosystems). All novel mutations were confirmed by sequencing 100 control chromosomes.

**Results**

The water deprivation test of the index patient, shown in Table 1, confirmed the presence of complete AVP-responsive diabetes insipidus. The basal plasma AVP level was 2.4 pg/ml. Plasma levels of PRL, GH, IGF-1, FSH, LH, ACTH, cortisol, TSH, free T4, and T3 were within the normal ranges. MRI of the pituitary showed a normal neurohypophysis and pituitary stalk. The patient was started on desmopressin treatment, after which his polyuria and polydipsia were satisfactorily controlled.

Direct sequencing analysis of the AVP-NPII gene in the proband revealed a heterozygous GAG deletion mutation in exon 2, which results in an in-frame deletion of glutamic acid (c.232_234 delGAG; p.Glu78del). The AVP-NPII genes of the patient’s mother and sister were found to have the same mutation (Fig. 2).

**Table 1. Results of water deprivation test in the index case.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Body wt (Kg)</th>
<th>Serum osmolality (mOsm/kg)</th>
<th>Urine osmolality (mOsm/kg)</th>
<th>Urine flow (ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 AM</td>
<td>64.5</td>
<td>283</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>9 AM</td>
<td>64.0</td>
<td>274</td>
<td>135</td>
<td>350</td>
</tr>
<tr>
<td>10 AM</td>
<td>63.9</td>
<td>272</td>
<td>157</td>
<td>250</td>
</tr>
<tr>
<td>11 AM</td>
<td>63.7</td>
<td>274</td>
<td>150</td>
<td>120</td>
</tr>
<tr>
<td>noon</td>
<td>62.5</td>
<td>270</td>
<td>206</td>
<td>250</td>
</tr>
<tr>
<td>1 PM</td>
<td>62.5</td>
<td>273</td>
<td>212</td>
<td>200</td>
</tr>
<tr>
<td>2 PM*</td>
<td>62.6</td>
<td>272</td>
<td>230</td>
<td>120</td>
</tr>
<tr>
<td>3 PM</td>
<td>62.7</td>
<td>279</td>
<td>536</td>
<td>20</td>
</tr>
</tbody>
</table>

* Injection of 5 IU of arginine vasopressin.

**Discussion**

We report a novel mutation of the AVP-NPII gene that is associated with FNDI in a Korean family. In the first Korean kindred with FNDI, Tae et al [7] reported a family with a deletion mutation of a single nucleotide within the splice acceptor site of intron 2 (IVS2+1 delG). The mutation in the pedigree identified here consisted of a 3-bp deletion (GAG) affecting 2 consecutive sequences (nucleotides 232–234) in exon 2. The mutation was predicted to yield an abnormal AVP precursor lacking Glu78 (E78) in its neurophysin II moiety. Because Glu78 is essential for neurophysin as a carrier protein for AVP, the function of neurophysin as a carrier protein for AVP would be impaired [6]. As a result, AVP most likely undergoes accelerated proteolytic degradation [6]. Interestingly, at the same locus the transition
A233G, causing substitution of Glu78Gly, was previously reported in a family with FNDI [8]. The mutation in our patient's family is quite different and unusual, however, because the deletion of Glu78 is followed by a frameshift that affects only the following codon but not the remainder of the reading frame, which is entirely preserved.

Although the other family members were not evaluated for diabetes insipidus, autosomal dominant transmission of the disease is indicated by the fact that the proband's sister, mother, uncle, and cousin each has a long history of polyuria and polydipsia. Also, the proband's grandfather might have been the first person in the family to be affected, and thus would be expected to have milder signs, although he was not tested.

In summary, we detected a deletion mutation in the AVP-NPII gene of a Korean kindred with FNDI. While not directly clarifying the mechanism underlying development of FNDI, this novel mutation provides a basis for understanding the characteristics of neurophysin II that cause precursor misprocessing.

References