A Novel E108D Mutation of AVP-NPII Gene in a Turkish Patient with Central Diabetes Insipidus

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Introduction

Water homeostasis of the body is rigidly controlled by the antidiuretic hormone arginine vasopressin (AVP). In the kidney, AVP binds to the arginine vasopressin type 2 receptors (AVPR2) and water transport occurs by the aquaporin 2 (AQP2), which are special water channels of the collecting duct. These mechanisms are extremely important for the regulation of the water intake of the body. Diabetes insipidus (DI), which is characterized by polyuria, polydipsia, hypocsmolar urine and hypernatremia, is the end result of the defects in these mechanisms. The disease has different types and three different genes were identified for these types. Familial central or neurohypophysial diabetes insipidus (FNDI) results from inadequate arginine vasopressin hormone production. FNDI is caused by mutations in arginine vasopressin-neurophysin II gene (AVP-NPII). Since then, more than 60 mutations in the AVP-NPII gene have been associated with FNDI.

Methods

The prospective clinical data were collected for the proband patient and his family members. The patient had severe polyuria (10.9 L/day), polydipsia (12 L/day), fatigue, and deep thirstiness from his infancy. His physical examination findings were generally normal (height: 180 cm, weight: 76 kg, arterial blood pressure: 130/80 mm-Hg, pulse: 80 per min.). While being performed water deprivation test, diagnosis of central diabetes insipidus was confirmed according to increase in urine osmolality from 139 mOsm/kg to 431 mOsm/kg after desmopressin acetate injection. Some of family members of this patient had severe polyuria, nocturia, polydipsia, fatigue as well. The genomic DNA of the proband and the other family members were isolated and the amplification of the AVP-NPII gene was carried out with polymerase chain reaction. We sequenced all exons and intron-exon boundaries of the gene (Figure 1). Comparison of three dimensional protein structures for wild type and mutant AVP-NPII were obtained with Swiss-Model. These structures were superimposed using UCSF Chimera 1.9. Ribbon display was obtained, mutant aminoacid was labeled and atomic structure was shown (Figure 3).

Results

A total of five affected and one unaffected individuals were studied. We found a novel mutation (p. E108D) in exon 3 of AVP-NPII gene in proband (case II.2) and four affected members (cases I.1, I.1.1, I.1.4 and I.5) from two generations of family. Unaffected sister (case II.1) had no mutation (Figure 2.) Sequence analyses of the AVP-NPII coding region revealed the presence of heterozygous missense mutation at codon 108, which causes the substitution of Glu (GAG) by an Asp (GAT) in exon 3 (Figure 1). According to bioinformatics analyses based on DNA sequence, there was no difference between a three-dimensional protein structure prediction of mutant AVP-NPII protein and wild type protein (Figure 3.).

Conclusions

In this study, we describe a novel mutation (p. E108D) of AVP-NPII gene in Turkish family with FNDI. FNDI is a progressive disease, age of onset and severity of symptoms can differ depending on the mutation in same family. FNDI-associated mutations supports patogenic cascade such as mutant prohormone synthesis, misfolding of protein, ER retention and accumulation and degeneration of AVP-producing neurons. In our study, we present a novel mutation in NPII region of the AVP-NPII gene and this mutation can obviously cause inappropriate folding of the protein. Therefore, the pathway of water homeostasis via AVPR2 and AQP2 can be improper and it can be the reason of DI. We suggest that future functional investigations of the E108D mutation may provide a basis for understanding the pathophysiology of the FNDI. For that reason, in our future studies we are planning to do functional characterizaiton of the E108D mutation. We think that functional characterizaiton of this mutant protein will improve the clinical and theoretical knowledge of this area.

In conclusion, genetic testing and appropriate parent counseling should be enforced autosomal dominant FNDI families to ensure adequate treatment and avoid chronic water deprivation.

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References:

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