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, hypoosmolar 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 neurohypophyseal 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.

Objectives

FNDI, usually an autosomal dominant disorder, results from insufficient production of antidiuretic hormone arginine vasopressin, which is caused by mutations in arginine vasopressin-neurophysin II gene (*AVP-NPII*).

In this study, we present the clinical and molecular features of a male Turkish patient with autosomal dominant FNDI caused by a novel mutation (p.E108D).

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), fatique, and deep thirstiness from his infancy. His physical examination findings were generally normal (height: 180 cm, weight: 75 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.)**.

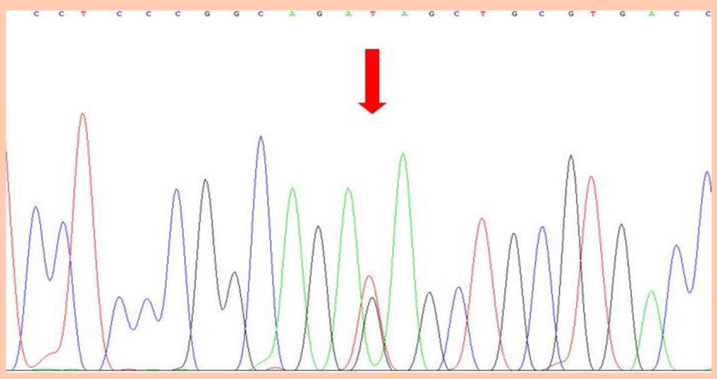

Figure 1.Sequence chromatograms demonstrating the heterezygous mutations (p. E108D). Arrow designate the mutation.

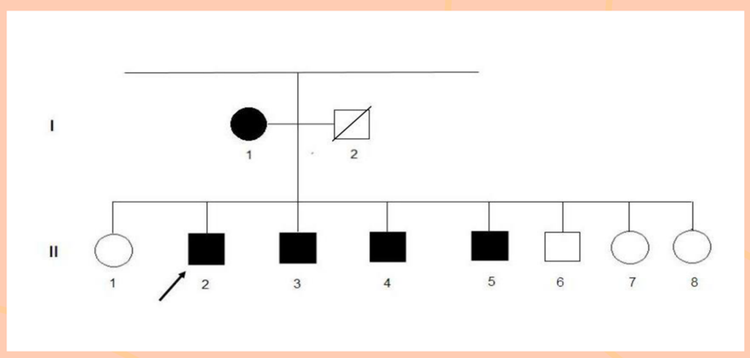

Figure 2. Pedigrees of familiy. The individuals marked with numbers are those who were available for mutation screening of the *AVP-NPII* gene. Black and white symbols represent clinically affected and unaffected individuals, respectively. Arrow designate the proband.

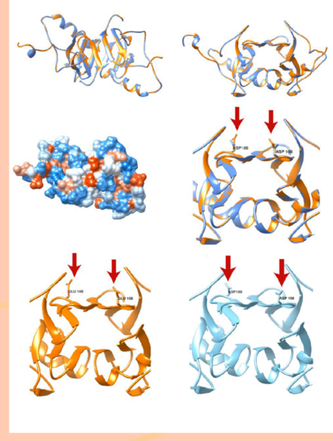

Figure 3. 3-D protein structures for wild type and mutant AVP were obtained with computational tools such as Swiss-Model and UCSF Chimera .

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,II.3,II.4 and II.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 the substitution of Glu (GAG) by a 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 characterization of the E108D mutation. We think that functional characterization 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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