



# The First Case of Congenital Nephrogenic Diabetes Insipidus Caused by *AVPR2* Disruption Because of 4q25 Insertional Translocation

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Dear Editor,

Congenital nephrogenic diabetes insipidus (NDI) is characterized by an impaired renal response to arginine vasopressin (AVP) [1]. Approximately 90% of patients with NDI have mutations in the AVP receptor 2 gene (*AVPR2*) [2]. Mutations in *AVPR2* located in chromosome X result in X-linked NDI, which presents characteristic symptoms, including polyuria, polydipsia, and fever in male infants.

A two-month-old boy (Pt #1) presented to Seoul National University Hospital with irritability, polyuria, and mild fever in March 2023. Informed consent was obtained from the patient's guardian. During a water deprivation test, he exhibited an elevated serum sodium level and a continuous decrease in urine osmolality, which were not alleviated by subcutaneous vasopressin injection. The family history indicated X-linked recessive inheritance (Fig. 1A). The patient's second uncle (Pt #2) with similar symp-

tom as his nephew had also been diagnosed as having NDI as an infant.

We performed whole-exome sequencing of a blood sample of Pt #2. A soft-clipped region was observed in intron 2 of *AVPR2*, using Integrative Genomics Viewer (Fig. 1B). Analysis of chimeric reads revealed a putative chromosomal translocation between the long arms of chromosome 4 and chromosome X. Primers for the suspected breakpoints were designed, and PCR was performed. Subsequent Sanger sequencing revealed breakpoints at chrX:153,170,697 and chr4:109,062,641 (Fig. 1C). Karyotyping was performed to confirm the translocation. Surprisingly, chromosomal analysis revealed normal findings (data not shown). Subsequently, a chromosomal microarray assay was performed on peripheral blood from Pt #1, using the CytoScan Dx Assay (Affymetrix, Santa Clara, CA, USA) per the manufacturer's instructions. The fusion in Pt #1 was validated using break-

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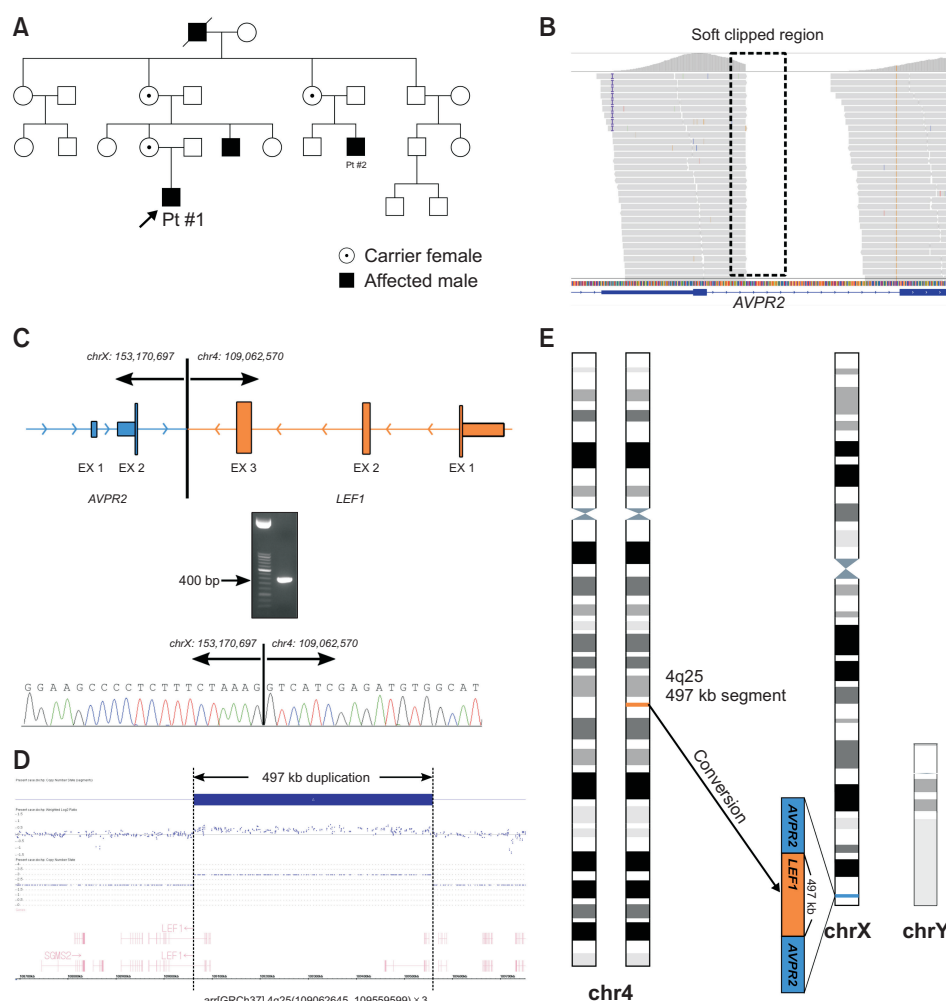
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**Fig. 1.** *AVPR2* next-generation sequencing and breakpoint analysis results. (A) Pedigree showing a typical X-linked recessive inheritance pattern. (B) Next-generation sequencing results revealed a soft clipped region in intron 2 of *AVPR2*. (C) Based on the results of analysis of the chimeric reads, PCR was performed targeting the suspected breakpoint. A fragment with the expected amplicon size of 400 bp was identified in gel electrophoresis. Sanger sequencing confirmed that the upstream from chrX:153,170,697 and the downstream from chr4:109,062,641 were joined. Specifically, exons 1–2 of *AVPR2* and exons 1–3 of *LEF1* were joined in opposite transcriptional orientations. (D) In chromosomal microarray analysis, a 497-kb heterozygous duplication in the 4q25 region was observed and described as “arr[GRCh37] 4q25(109062645\_109559599) × 3” according to the International System for Human Cytogenetic Nomenclature. (E) Based on the combined results, we concluded that a 497-kb insertional translocation occurred in the center of *AVPR2*.

point PCR (data not shown). Chromosomal analysis revealed a 497-kb duplication, encompassing exons 1–3 of the lymphoid enhancer-binding factor 1 gene (*LEF1*) (Fig. 1D). *AVPR2* copy number variation was not observed (data not shown). Considering the combined results, we hypothesized that a fusion between *AVPR2* and *LEF1* had occurred through the insertional translocation of the 497-kb segment within the 4q25 region, involving exons 1–3 of *LEF1* (Fig. 1E). The insertional translocation of the 497-kb segment generates a fusion with *AVPR2* and *LEF1* exons in opposite transcriptional orientations. Consequently, this fusion is expected to cause loss of function of

*AVPR2* as it cannot produce a normal transcript.

Studies have suggested an association between monoallelic/biallelic loss-of-function variants in *LEF1* and ectodermal dysplasia [3, 4]. Our patient did not show any symptoms associated with ectodermal dysplasia. This discrepancy may be attributed to the presence of two normal *LEF1* alleles, regardless of the insertional translocation. As the resolution of karyotyping typically is around 5 Mb, the 497-kb insertional translocation was not detected by this method. Given the challenges in detecting insertional translocation using next-generation sequencing, gap-PCR is recommended for undiagnosed cases of NDI with suspected

X-linked recessive inheritance.

In conclusion, we identified a novel disruption of *AVPR2* due to 4q25 insertional translocation in a family with NDI. To the best of our knowledge, this is the first documented case of NDI resulting from insertional translocation.

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None.

## AUTHOR CONTRIBUTIONS

Kim B and Kim MJ conceived the idea. Kim MJ and Ahn YH drafted the manuscript and designed the figure. Park JH wrote the methods part and provided the raw figure. Lim HS and Chae SW performed the experiments. Kim MJ and Seong M supervised the study. All authors reviewed the manuscript and approved the final manuscript.

## CONFLICTS OF INTEREST

None declared.

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