Nephrogenic Diabetes Insipidus with partial response to ddAVP caused by a novel AVPR2 splice site mutation

Marie Helene Schernthaner-Reiter, David Adams, Ola Nilsson, Giampaolo Trivellin, Mary Scott Ramnitz, Margarita Raygada, Gretchen Golas, Fabio R Faucz, Kavitha Dileepan, Maya Lodish, Paul R. Lee, Thomas C. Markello, Cynthia J. Tifft, William A Gahl, Constantine A Stratakis

NICHD, NHGRI, National Institutes of Health, Bethesda, MD, USA; Karolinska Institutet, Stockholm, Sweden; Children's Mercy Hospital, Kansas City, MO, USA

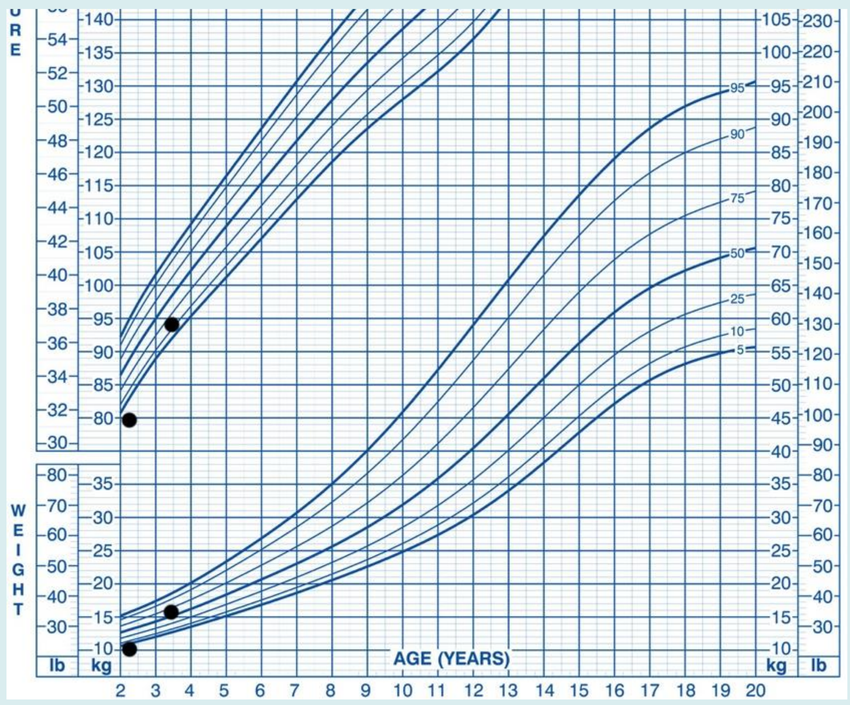


Fig 1. Growth chart demonstrating catch-up growth that occured after chronic hypernatremia was corrected using high-dose ddAVP

Conclusions:

- A novel AVPR2 splice site mutation causing of X-linked nephrogenic Diabetes Insipidus (NDI) was identified.
- Patients with DI of unknown etiology can harbor splice site mutations whose pathogenicity may be underestimated on routine sequence analysis.
- In NDI with partial response to ddAVP, high dose ddAVP treatment may be considered.

Introduction

Congenital diabetes insipidus (DI) can be due to mutations in the arginine vasopressin (*AVP*) gene (familial neurohypophyseal DI), the arginine vasopressin receptor type 2 (*AVPR2*) or aquaporin 2 (*AQP2*) genes (congenital nephrogenic DI, NDI). The clinical manifestation of congenital NDI, especially the response to arginine vasopressin (AVP), can vary greatly depending on the functional effect of the *AVPR2* mutation. Here we present two male siblings with DI and partial response to ddAVP.

Objective:

To identify the genetic cause of this condition.

Methods:

Whole exome sequencing was performed in selected family members. A minigene splicing assay was used to evaluate the effect of 2 identified splice site variants in AVPR2.

Clinical cases:

Two male siblings presented with failure to thrive, polyuria, and polydipsia. Laboratory evaluation showed hypernatremia, elevated serum osmolality, and low urine osmolality. During water deprivation urine osmolality remained low. ddAVP administration (1 mcg) increased urine osmolality modestly to 150-350 mOsm/kg, consistent with partial NDI. The two parents, a sister and a brother were unaffected. Initial Sanger Sequencing reported no pathogenic variants in AVPR2 or AQP2, with mention of a possible splice site variant, AVPR2 c.276 A>G, of unknown significance.

Fig 2. Minigene assay. cDNA from untransfected HEK293, empty vector-transfected HEK293 (EV), the AVPR2 wt and three mutants in pSPL3, and negative controls. The arrow points to the mutation-specific band.

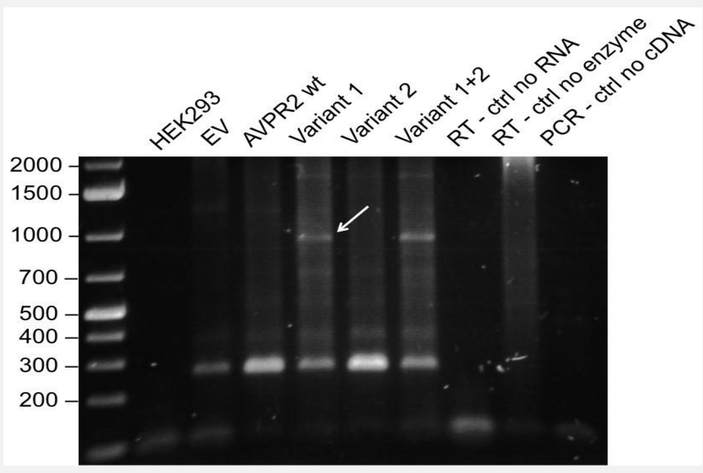
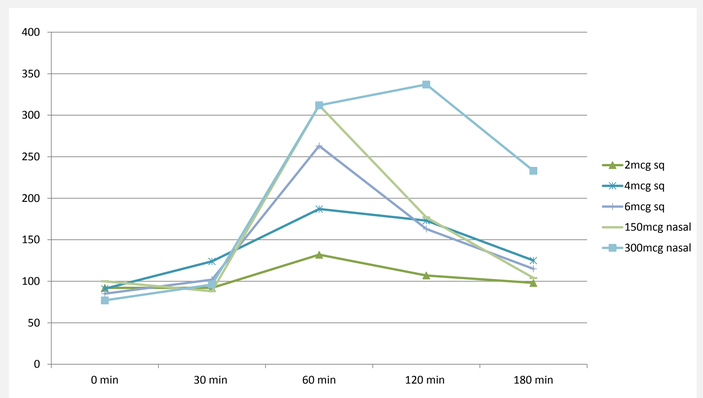


Fig 3. Increasing doses of ddAVP resulted in increasing ability to concentrate urine, indicating a subnormal and dose-dependent response to ddAVP.



Results:

Exome sequencing identified the same splice variant. In fact, both the patient and brother were found to be hemizygous for two AVPR2 variants with in silico predicted effects on mRNA splicing. A minigene assay revealed that only one, the novel AVPR2 c.276 A>G mutation created a cryptic splice acceptor site that led to 5' truncation of AVPR2 exon 2 when tested in HEK293 cells (Fig 2). This truncation leads to a frameshift and premature stop codon, which is likely to be the cause for these familial cases of NDI with partial responsiveness to AVP (Fig 3). Both patients were treated with high dose ddAVP and showed improvement of DI symptoms as well as improved growth and weight gain (Fig 1).

Karolinska Institutet & University Hospital
Ola Nilsson, MD, PhD, Associate professor
Division of Pediatric Endocrinology, Q2:08
SE-171 76, Stockholm
Sweden

E-mail: ola.nilsson@ki.se
Telephone: +46(0)8-5248 2425
Website: ki.se/en/kbh/growth-and-cartilage-biology

ESPE 2015 530-P2
Puberty and Neuroendocrinology
Ola Nilsson
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
PosterSessionOnline.com