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ERKNet/ESPN Educational Webinars on
Pediatric Nephrology & Rare Kidney Diseases

WEBINAR
13/09/22

Diabetes Insipidus renalis

Speaker: Daniel Bichet (Montreal, Canada)

Moderator: Tom Nijenhuis (Nijmegen, the Netherlands)

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european society for paediatric nephrology

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04/10/22	Non-cystinotic renal fanconi syndrome Francesco Emma (Rome, Italy)
18/10/22	Rare disease aspects of pediatric dialysis Franz Schaefer (Heidelberg, Germany)

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IPNA

Diabetes Insipidus Renalis; Congenital Nephrogenic Diabetes Insipidus

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- Professor of Medecine, Pharmacology and Physiology,University of Montreal
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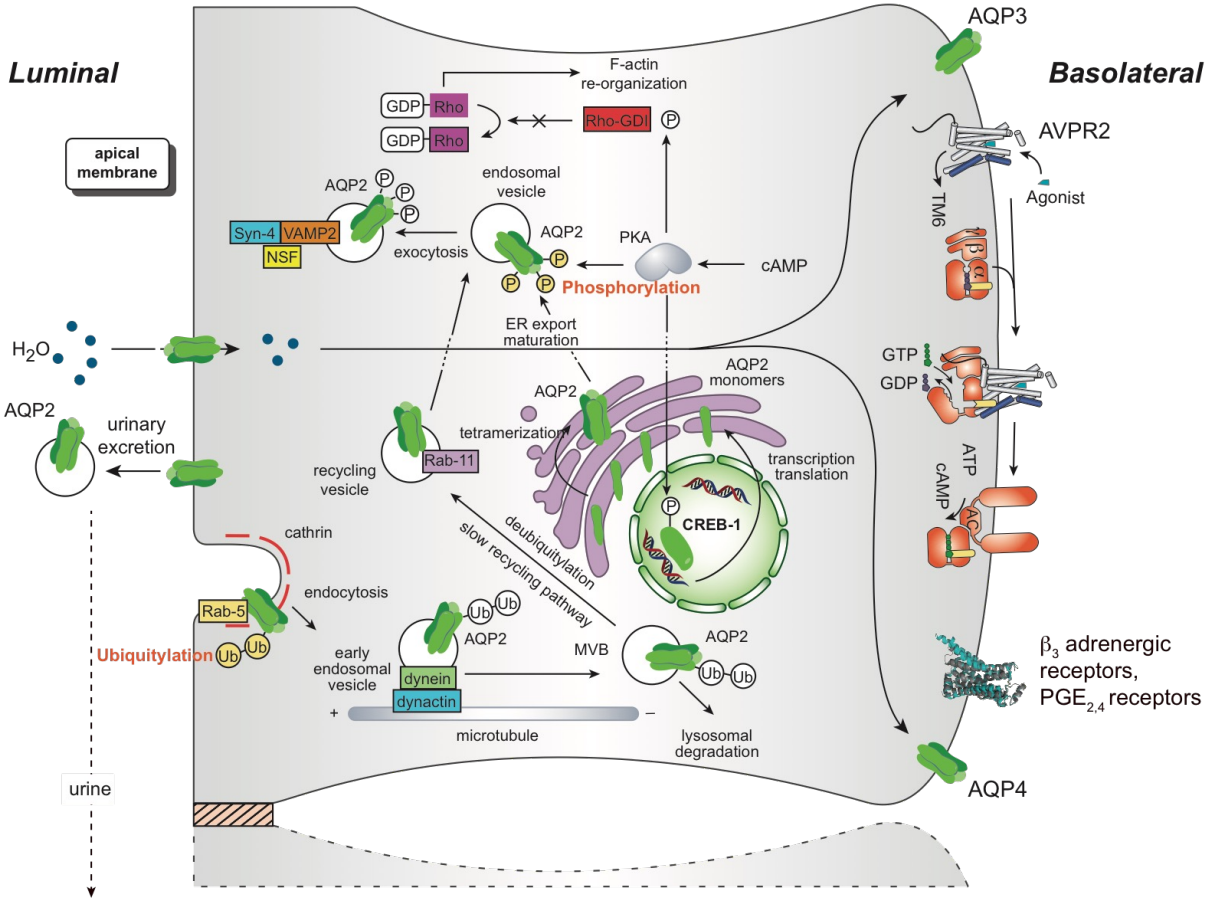
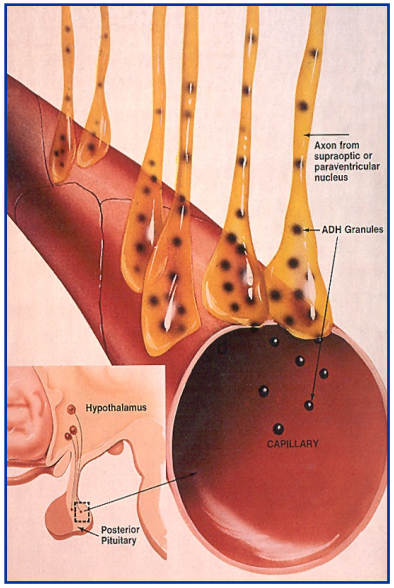




Nine V.A.M. Knoers, Elena N. Levtchenko. Daniel G. Bichet. Pediatric Nephrology, Inherited disorders of water handling, https://doi.org/10.1007/978-3-642-27843-3_112-1., ***Springer Nature 2021.***

Disclosures and References

- I am a consultant, I give conferences and receive grants from **Ferring, Otsuka Pharmaceuticals**, **Sanofi-Genzyme, Shire, and Amicus Pharmaceuticals**.
- These are declared and reviewed every year by my hospital and University.
- I am also writing chapters on Diabetes Insipidus and polyuria for **UpToDate**

- **Bichet D.G.** The Posterior Pituitary. In : The Pituitary, 4th ed, Melmed S. (ed), Elsevier, Academic Press, London, UK, Chapter 8; pp 251-288, 2017; in press, 5th ed, 2022.
- **Bichet, D.G. Clinical manifestations and causes of central diabetes insipidus.** In: UpToDate, Emmett, M. (ed). Waltham, MA, 2007-2022.
- **Bichet, D.G. Clinical manifestations and causes of nephrogenic diabetes insipidus.** In: UpToDate, Emmett, M. (ed). Waltham, MA, 2007-2022

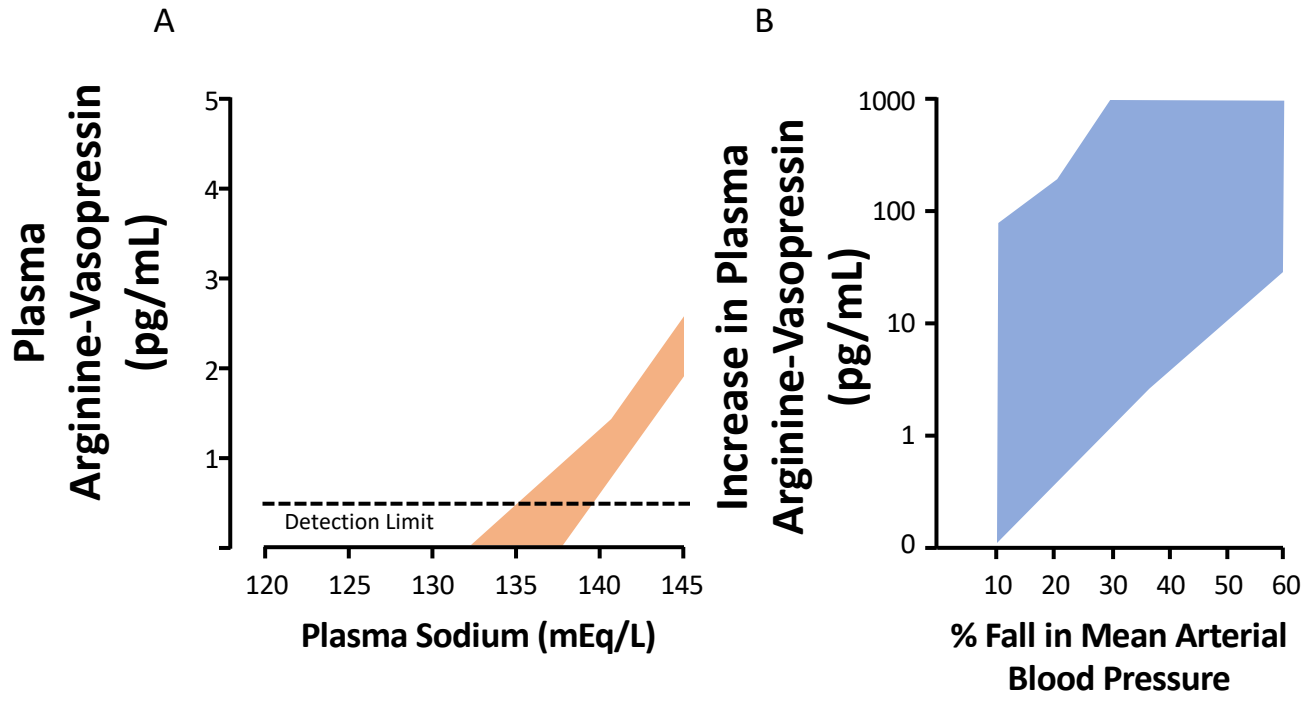
Learning objectives

1. **Discovery of *AVPR2* as the cause of Congenital Nephrogenic Diabetes Insipidus (NDI).**
2. **Hereditary Nephrogenic Diabetes Insipidus: *AVPR2* and *AQP2* are key genes responsible for vasopressin secretion and action**
3. **Gain of function of the vasopressin V2 receptor: hereditary hyponatremia**

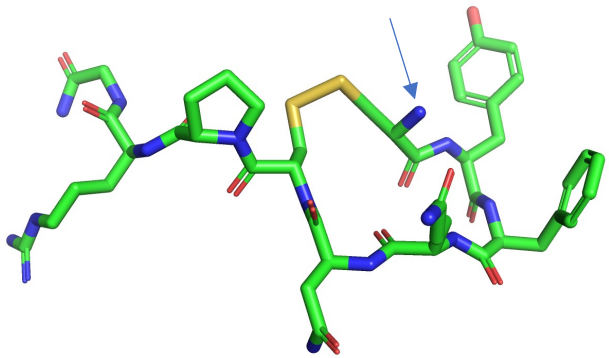
Vasopressin, 122 years

- **1901 :** Magnus and Schafer demonstrate oxytocic, vasoconstrictor and antidiuretic effects of pituitary extracts.
- **1913** : Farini and van den Velden are treating successfully diabetes insipidus with pituitary extracts
- The pressure effects, V_1 of vasopressin are first identified followed by its V_2, antidiuretic effects.
- **1955 :** Vincent du Vigneaud, is awarded the Nobel price in chemistry for the first synthesis of a peptide hormone, arginine-vasopressin, AVP.

Osmotic and baro-regulation control of vasopressin release, antidiuretic (V_2) and vascular, pressor (V_1) vasopressin receptors

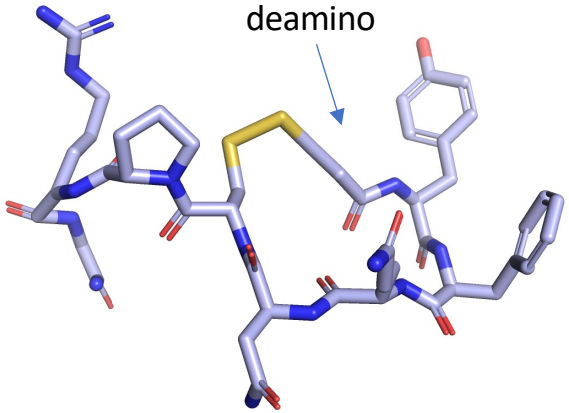


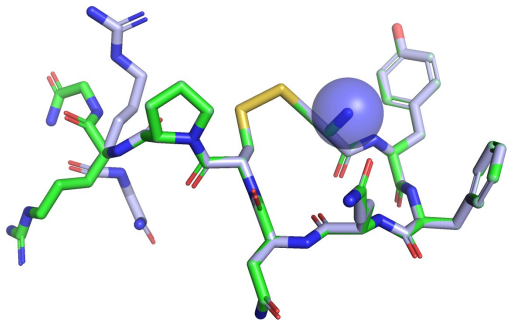
AVP



dDAVP

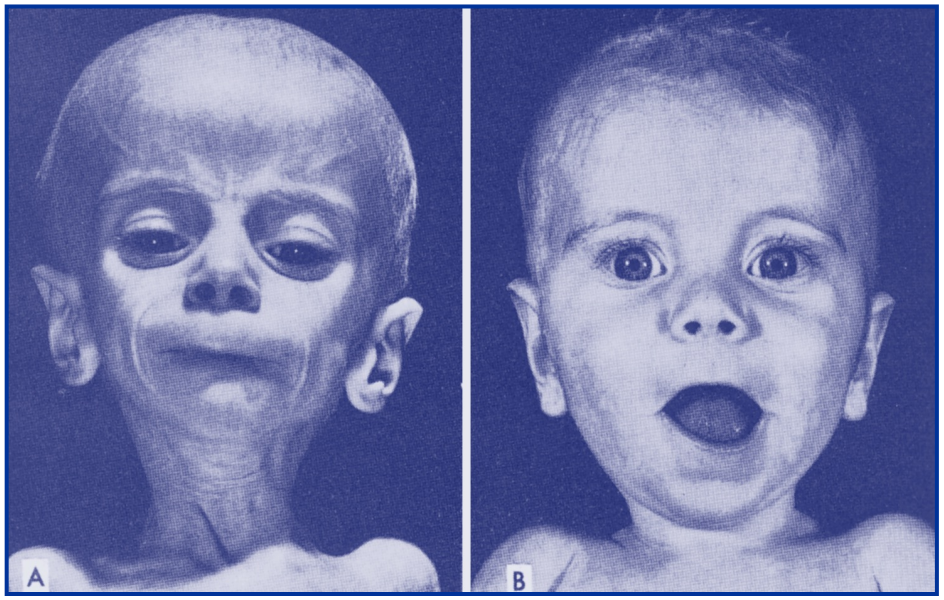
deamino



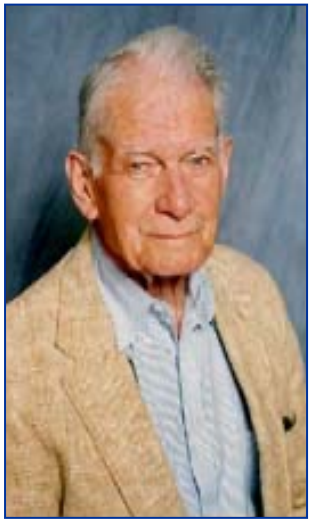


Superposition

Dehydration and Poor Nutrition in Hereditary Nephrogenic Diabetes Insipidus: the Canadian Hopewell Family extensively followed by Bode and Crawford in 1969

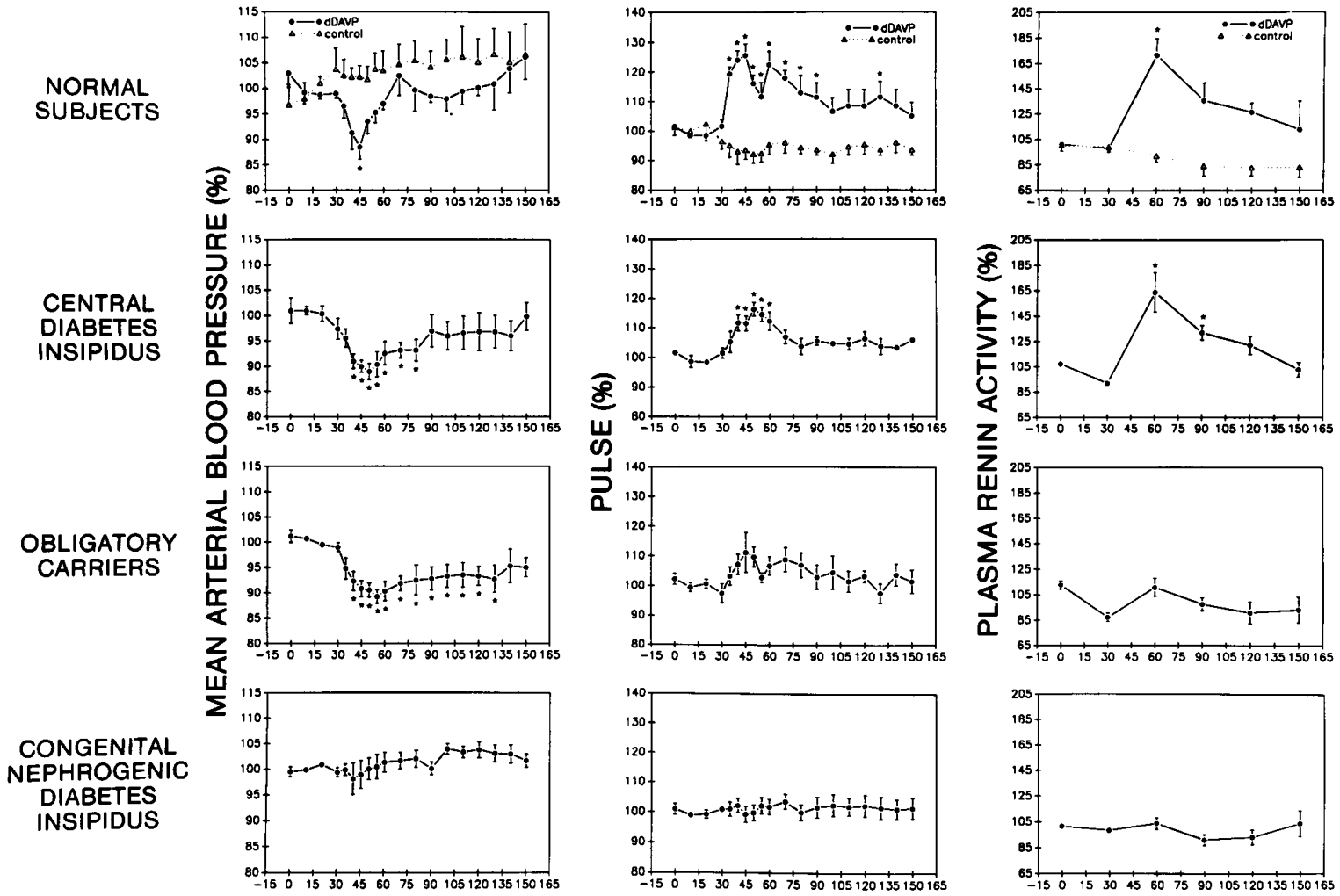


Perry et al. N. Engl J Med 276:721-725, 1967



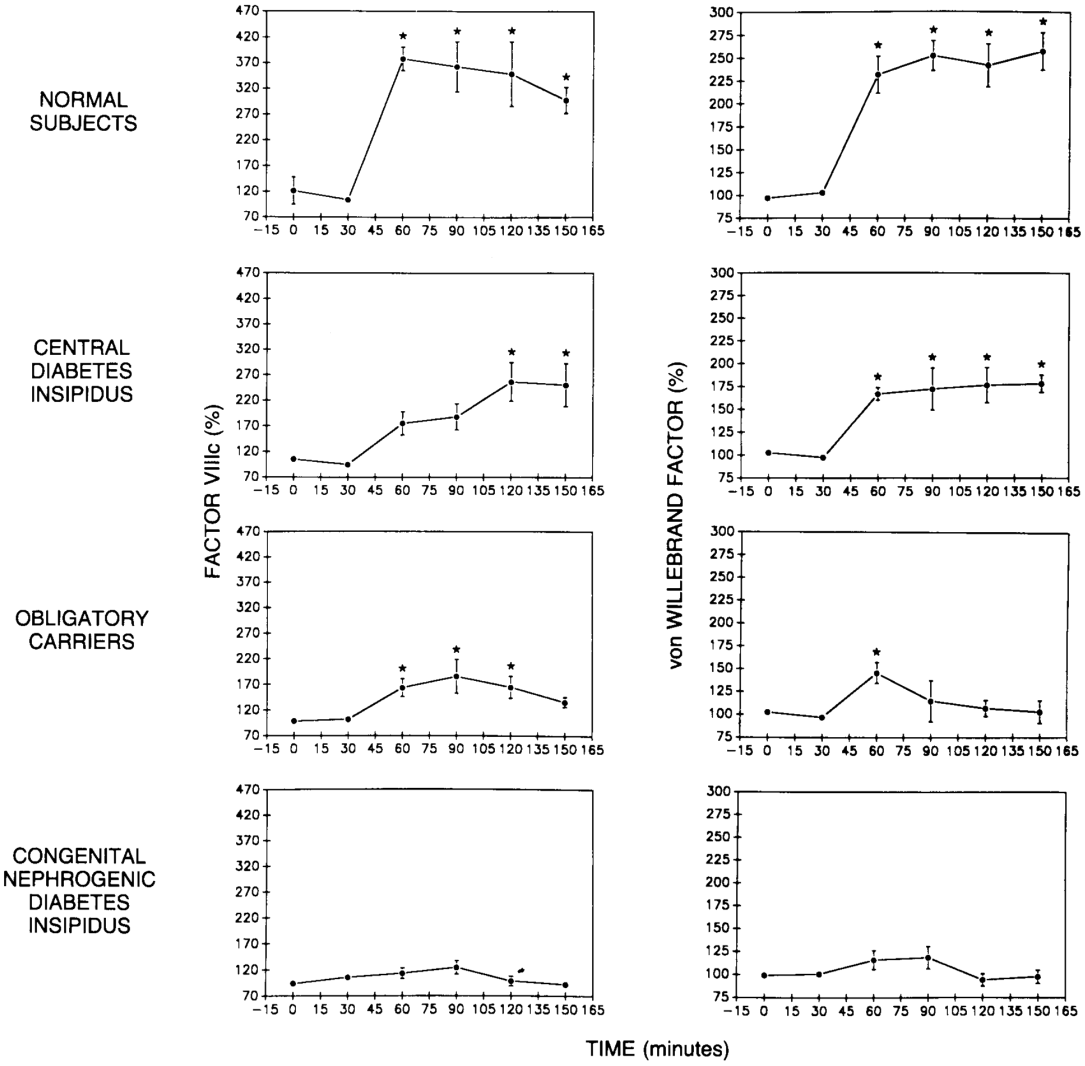
John D. Crawford

Hemodynamic responses to dDAVP infusion in the four study groups



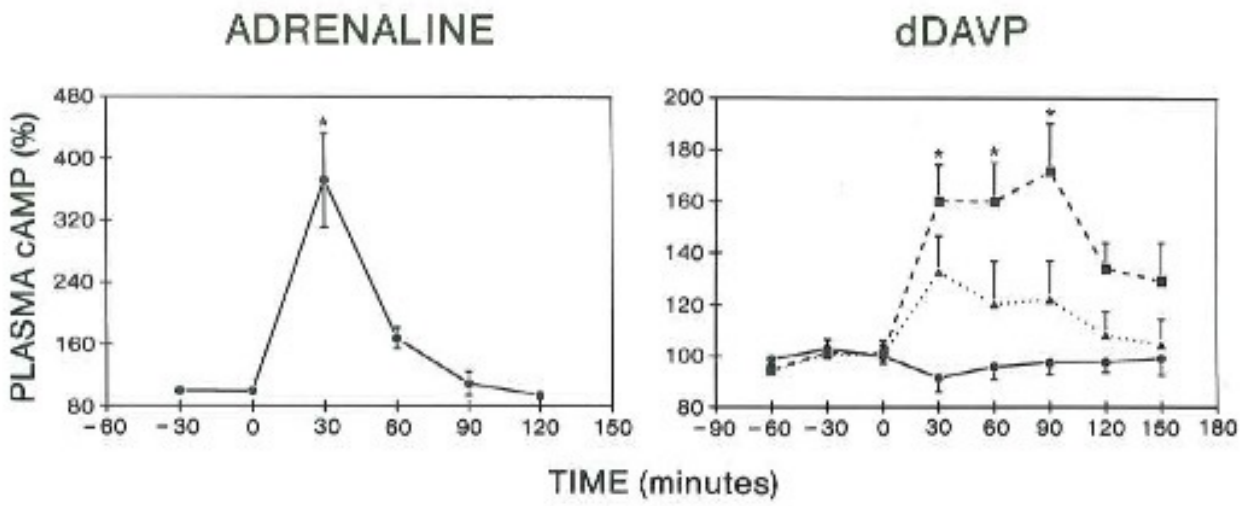
Bichet, D.G.,.. Hemodynamic and coagulation responses to 1-desamino[8-D-arginine]vasopressin (dDAVP) infusion in patients with congenital nephrogenic diabetes insipidus. N. Engl. J. Med., 318:881-887, 1988.

Coagulation Factor responses to dDAVP infusion in the four study groups



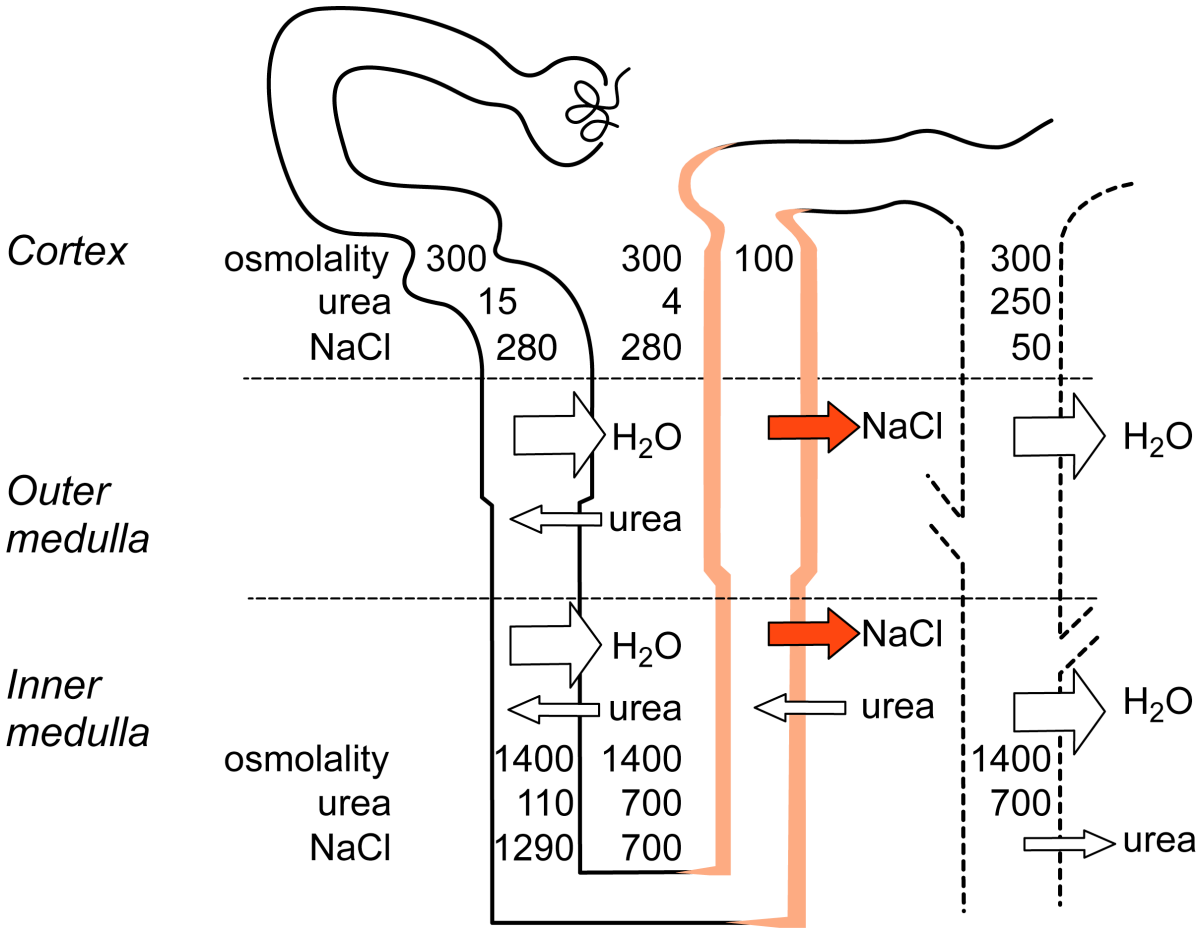
Bichet, D.G.,.. Hemodynamic and coagulation responses to 1-desamino[8-D-arginine]vasopressin (dDAVP) infusion in patients with congenital nephrogenic diabetes insipidus. N. Engl. J. Med., 318:881-887, 1988.

Plasma cyclic AMP responses to epinephrine and to dDAVP.



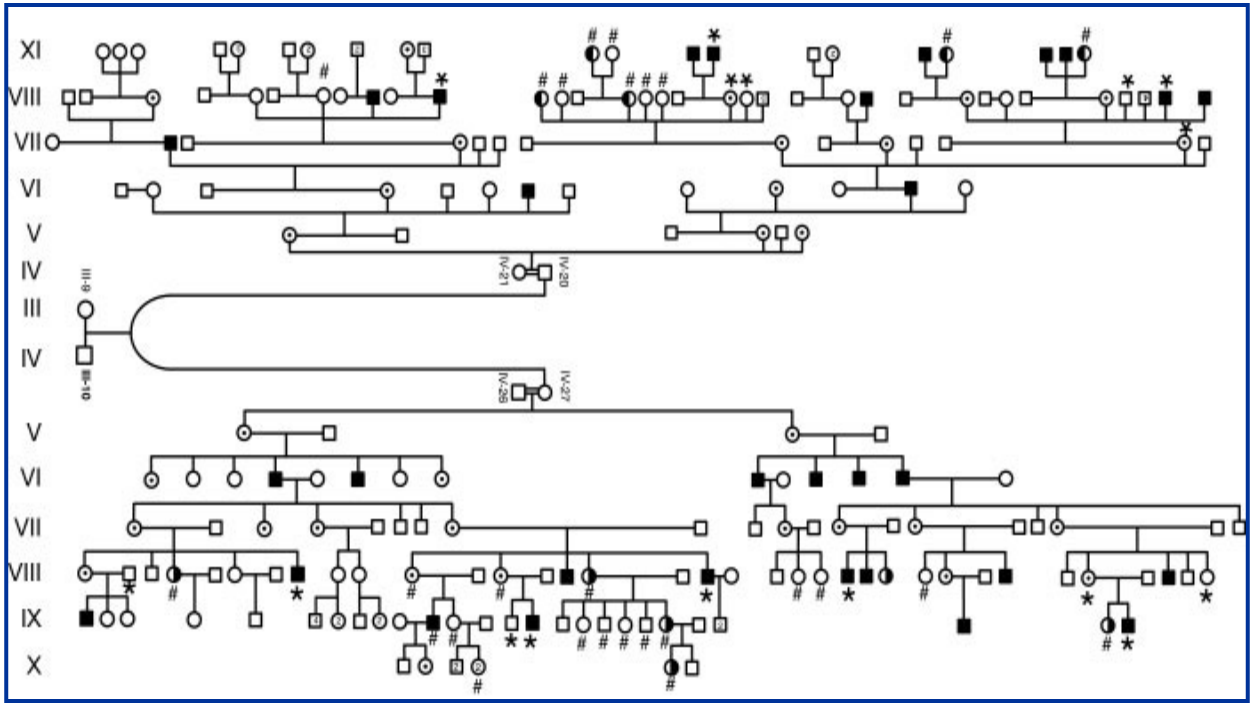
Bichet, D.G... Epinephrine and dDAVP administration in patients with congenital nephrogenic diabetes insipidus. Evidence for a pre-cyclic AMP V2 receptor defective mechanism. Kidney Int., 36:859-866, 1989.

The renal concentrating mechanism



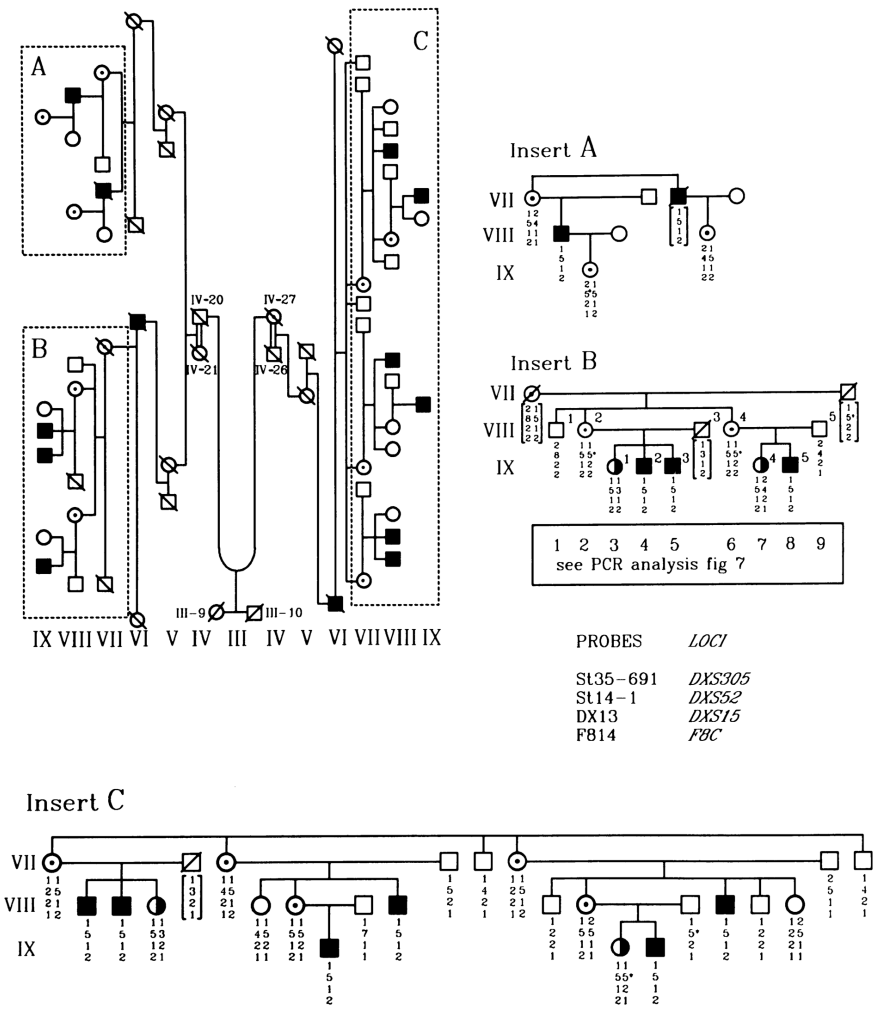
Heavy boundaries indicate very low permeability to water. Arrows indicate relative magnitude of solute and water fluxes in the various segments

Partial pedigree of the Hopewell kindred



Bichet DG, et al. J Clin Invest 92: 1262-1268, 1993

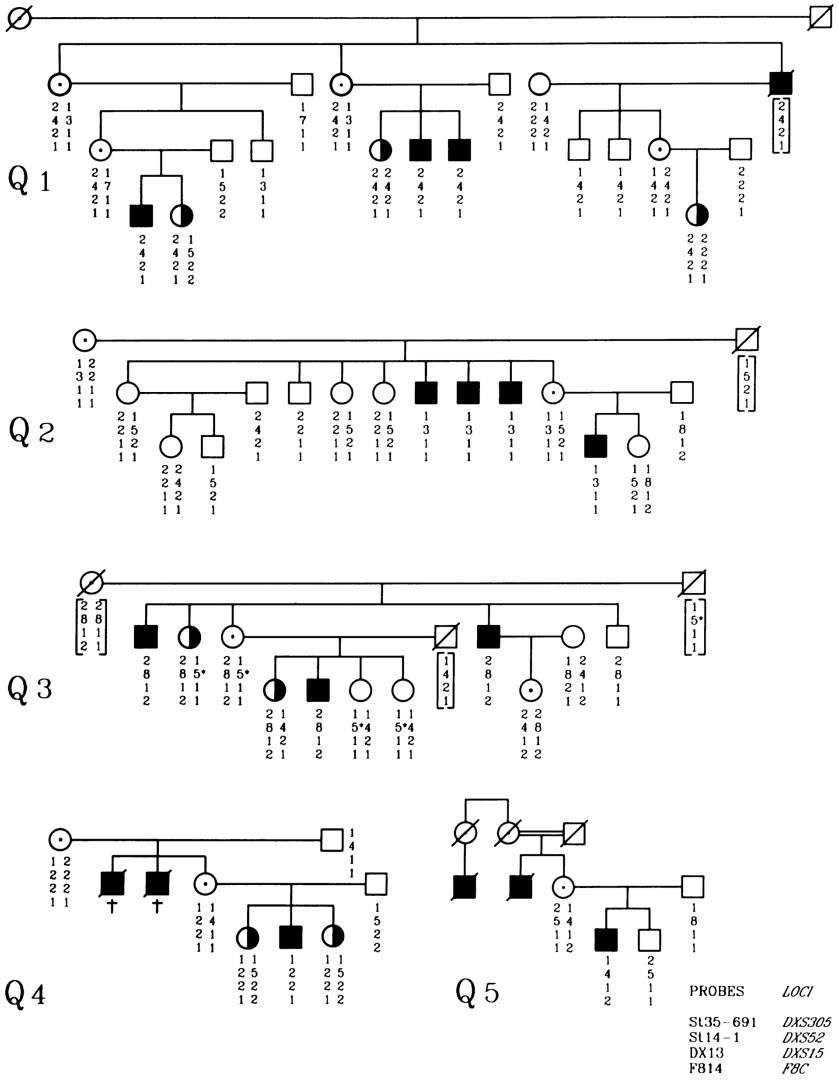
The nephrogenic Diabetes Insipidus (NDI) gene has been assigned to the Xq 28 region (1988) .
Bode and Crawford proposed that NDI patients in eastern North America shared a common ancestor who was an Ulster Scot and who had arrived in Halifax in 1761 on the ship Hopewell. A link between this family and a large Mormon pedigree (Cannon 1955) was also suggested.



The haplotype segregating with the disease in the Hopewell pedigree was not shared by other North American families (1).

The Hopewell hypothesis cannot explain the origin of NDI in many of the North American families, since they have no apparent relationship with the Hopewell early settlers, either by haplotype or by genealogical analysis.

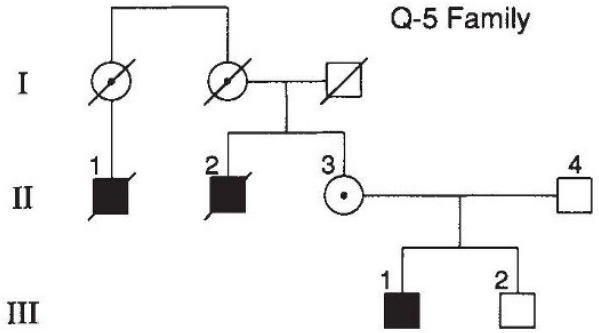
Bichet, D.G….Scriver, C.R. X-linked nephrogenic diabetes insipidus: From the ship Hopewell to restriction fragment length polymorphism studies. Am. J. Hum. Genet., 51:1089-1102, 1992.



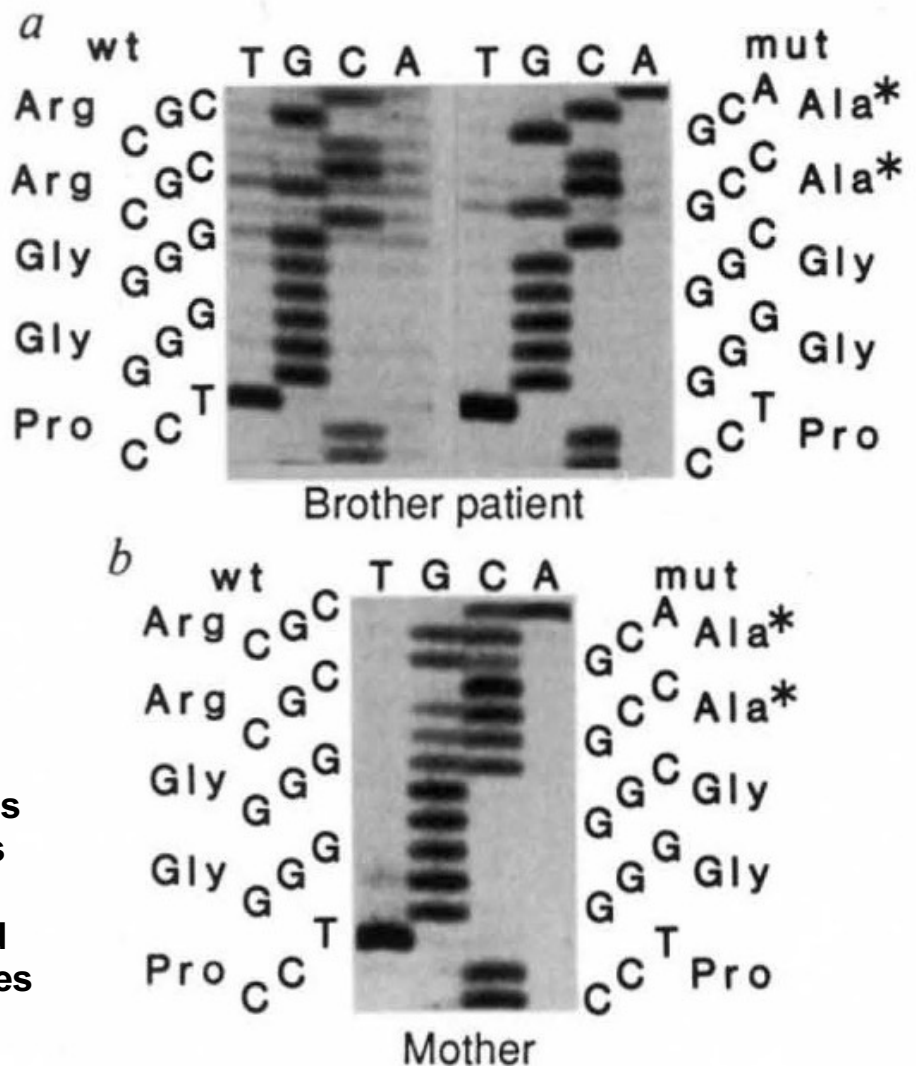
The haplotype segregating with the disease in the Hopewell pedigree was not shared by other North American families (2).

Bichet, D.G.…Scriver, C.R. X-linked nephrogenic diabetes insipidus: From the ship Hopewell to restriction fragment length polymorphism studies. Am. J. Hum. Genet., 51:1089-1102, 1992.

Rosenthal, W., Seibold, A., Antaramian, A., Lonergan, M., Arthus, M.D., Hendy, G., Birnbaumer, M., Bichet, D.G. Molecular identification of the gene responsible for congenital nephrogenic diabetes insipidus. Nature, 359:233-235, 1992.



a deletion of one out of six consecutive guanosines (nucleotides 733-738) in the cDNA sequences .This deletion changes codon 246 from GGG to GGC, shifts the reading frame with an altered amino-acid sequence beginning with codon 247, and introduces a premature stop codon (TGA) at position 270



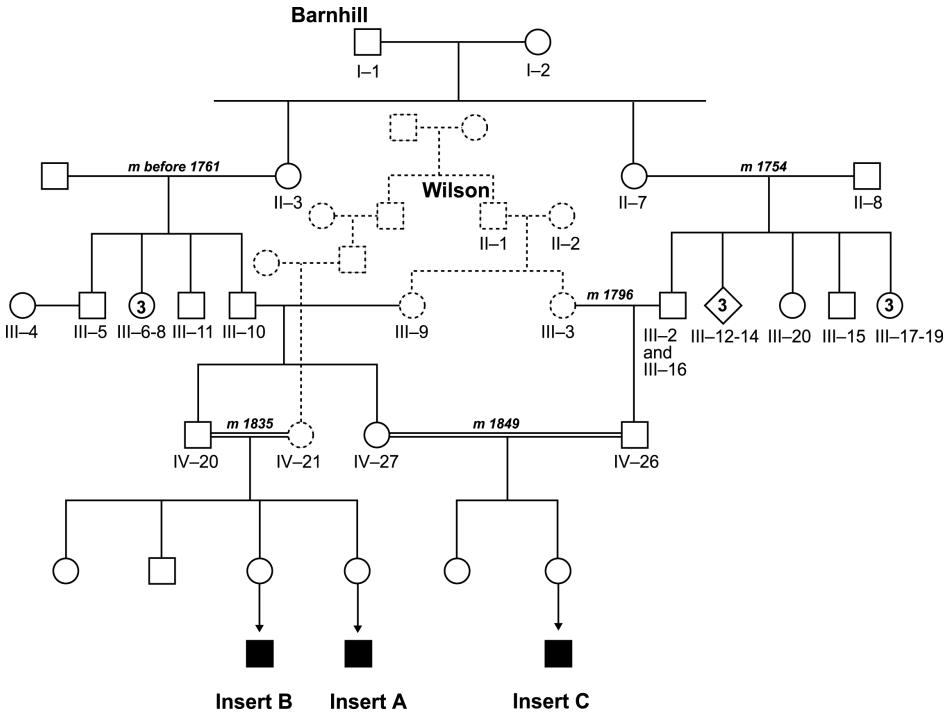
The water drinker curse

A Gypsy woman and her son were traveling the road and became thirsty. Pausing at the well in front of the next house, the Gypsy requested water for her son : the housewife refused, whereupon the Gypsy woman cast upon her a curse. Henceforth, the story goes, all the women's sons would be afflicted with a craving for water. The curse would be passed on by her daughters and visited upon their sons for generations to come.

Bode HH, Crawford JD. N Engl J Med 280: 750-754, 1969

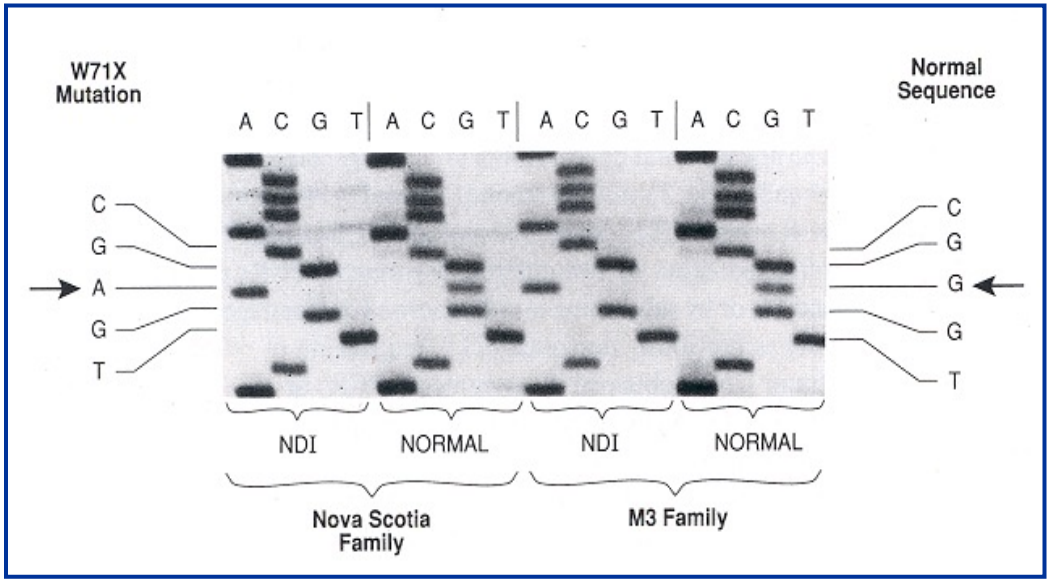
The Hopewell Pedigree 2009

Additional Maritime families confirm that carriers of the Hopewell mutation were prevalent in the Maritime area at the time the Hopewell ship landed



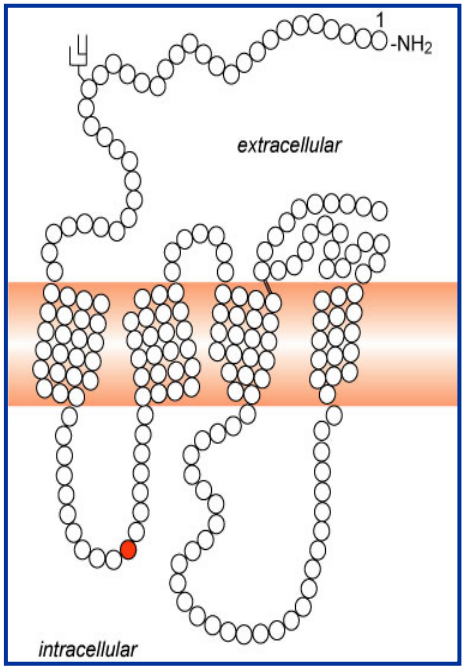
Bichet DG. Sem Nephrol 26: 224-233, 2006

DNA sequence analysis of the Hopewell mutation, W71X

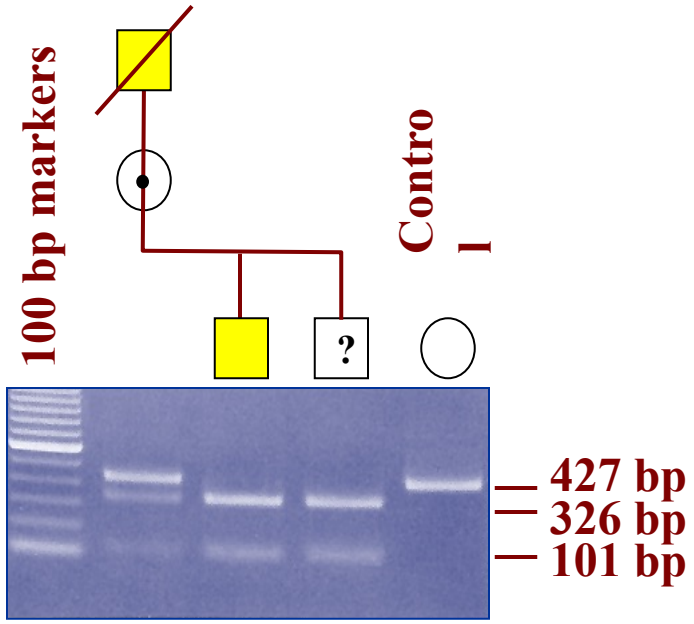


Bichet DG,..Birnbaumer M. J Clin Invest 92: 1262-1268, 1993

Perinatal diagnosis

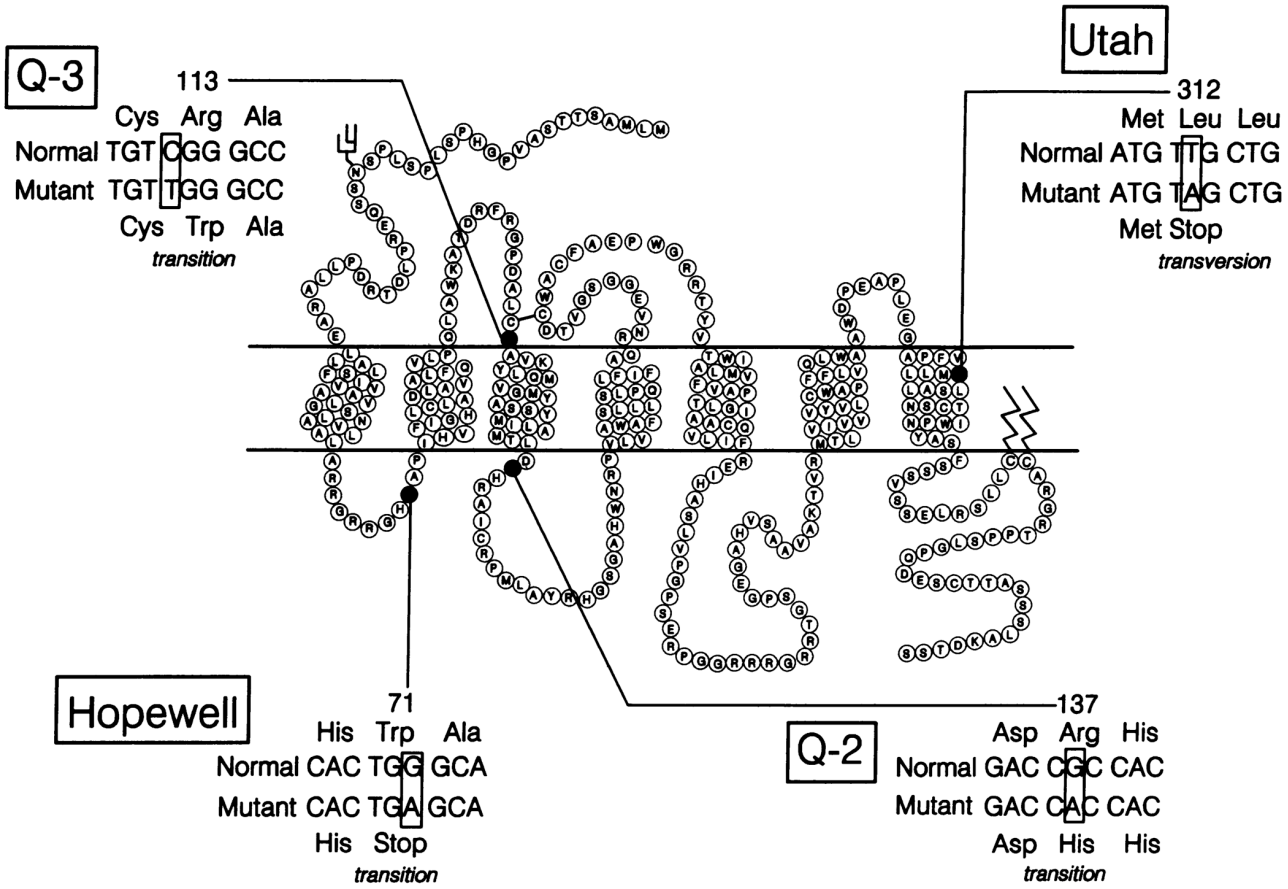


Bichet DG. Seminars in Nephrology 14:349-356, 1994



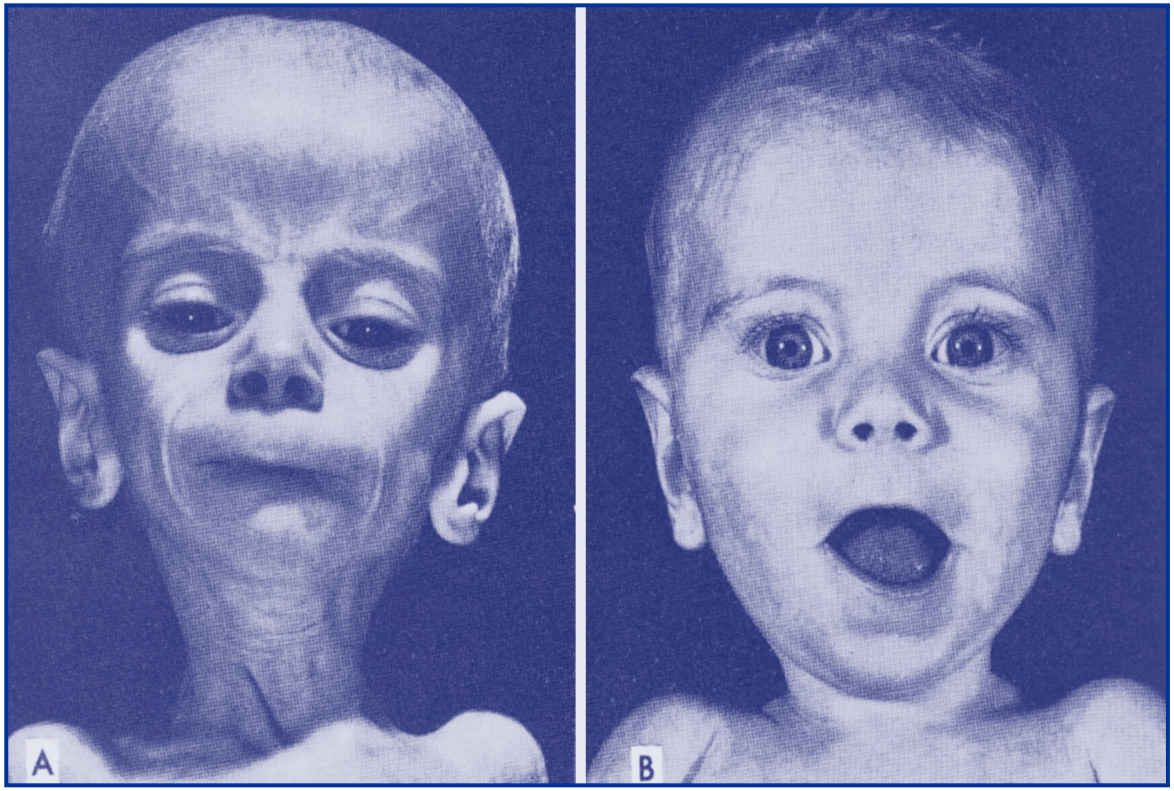
***Bsi*HKA 1 digestion**

Independent origins of the Hopewell, Utah and other North-American families



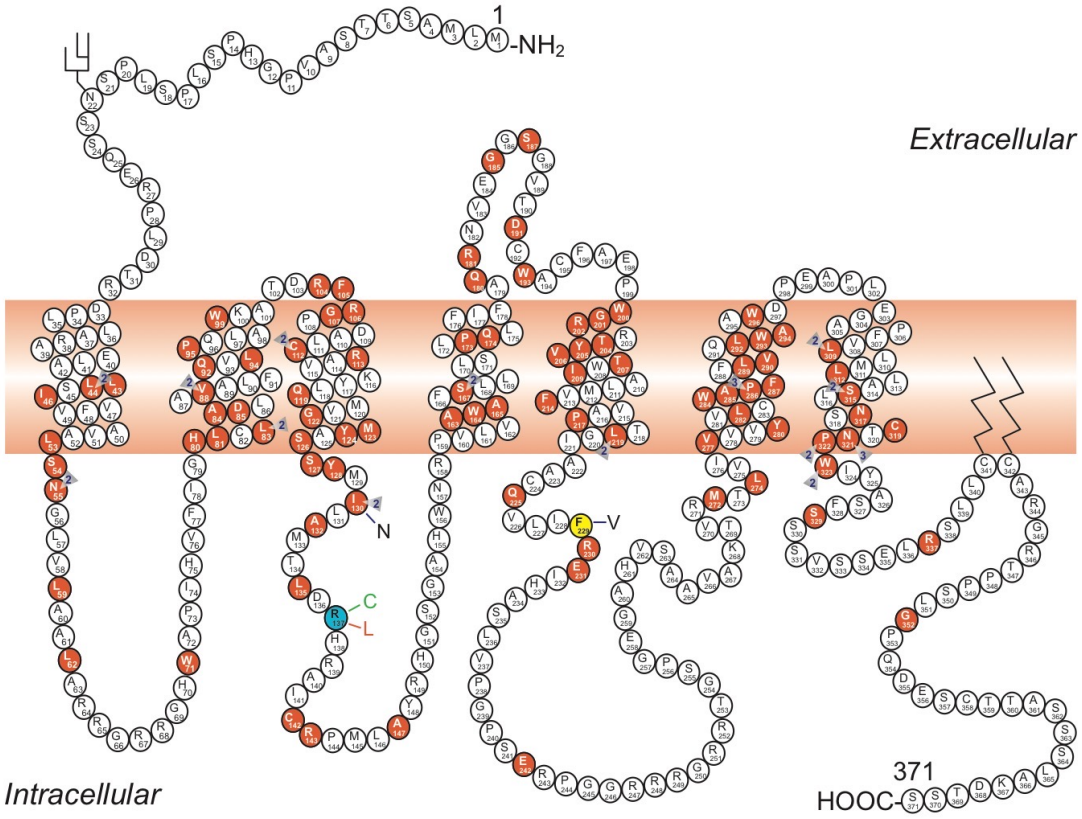
Bichet, D.G...Birnbaumer, M. X-linked nephrogenic diabetes insipidus mutations in North America and the Hopewell hypothesis. J. Clin. Invest. 92:1262-1268, 1993.

A dehydrated boy bearing the W71X *AVPR2* loss-of-function mutation



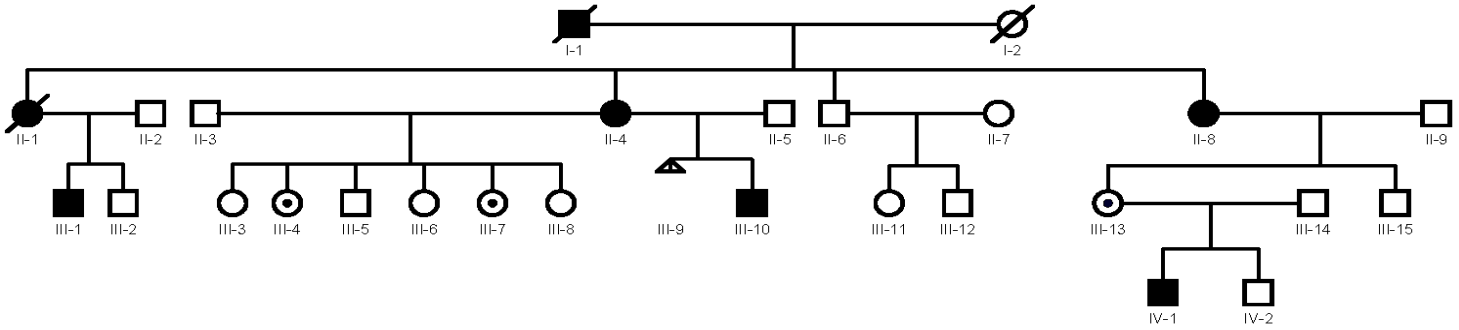
Perry TL, Robinson GC, Teasdale JM, Hansen S: Concurrence of cystathioninuria, nephrogenic diabetes insipidus and severe anemia. N Engl J Med 1967, 276:721-725.

A large number of ancestrally independent *AVPR2* mutations responsible for X-linked Nephrogenic Diabetes Insipidus



Nine V.A.M. Knoers, Elena N. Levtchenko. Daniel G. Bichet. Pediatric Nephrology, Inherited disorders of water handling, https://doi.org/10.1007/978-3-642-27843-3_112-1. *Springer Nature 2021.*

Most *AVPR2* mutations are associated with a full polyuric phenotype but V88M is associated with both partial and complete nephrogenic diabetes insipidus



The affected individuals have polyuria and hyposthenuria at baseline, but 4 patients showed a substantial increase in urinary concentration after DDAVP of up to 570 mosm/kg. One male and one female patient, however, did not respond to vasopressin analogues.

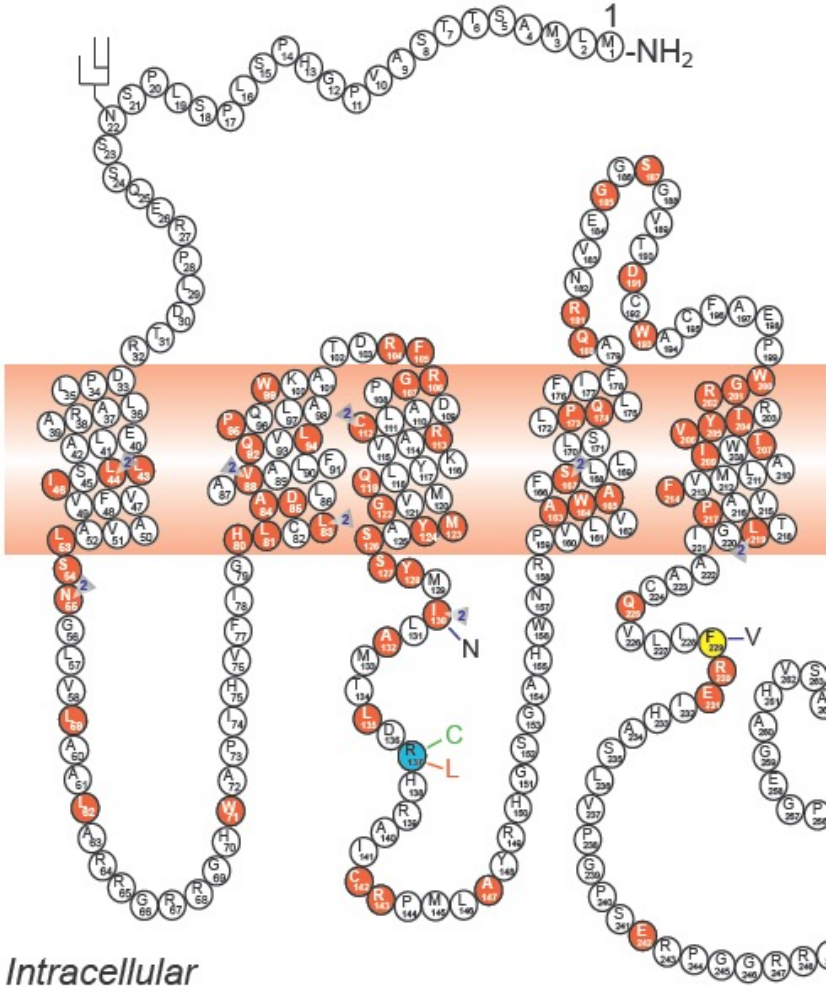
Bockenhauer, D.,., Bouvier, M., Bichet, D.G. Vasopressin type 2 receptor V88M mutation: molecular basis of partial and complete nephrogenic diabetes insipidus. Nephron Physiol. 2009 Oct 8;114(1): p1-p10.

Incidence of X-linked Nephrogenic Diabetes insipidus

- We estimated the incidence of X-linked NDI in the general population from patients born in the province of Quebec, Canada, during the 10-yr period 1988–1997 to be 4 in 454,629,or approximately 8.8 per million male live births. Thus, X-linked NDI is generally a rare disorder.
- By contrast, NDI was known to be a common disorder in Nova Scotia .
- These males are descendants of members of the Hopewell pedigree studied by Bode and Crawford and carry the nonsense mutation W71X.
- We estimated the incidence in these two maritime provinces (Nova-Scotia and New Brunswick) to be 6 in 104,063, or approximately 58 per million male live births for the 10-yr period 1988–1997.

- ***Arthus, M-F…Bichet, D.G., Fujiwara, T.M. Report of 33 novel AVPR2 mutations and analysis of 117 families with X-linked nephrogenic diabetes insipidus. J. Am. Soc. Nephrol. 11:1044-1054, 2000.***

Loss-of-function: X-linked Nephrogenic Diabetes Insipidus.
Gain of fonction: Nephrogenic Syndrome of Inappropriate Antidiuresis



Carpentier, E.et al. **Identification and characterization of an activating F229V substitution in the V2 vasopressin receptor in an infant with NSIAD.**

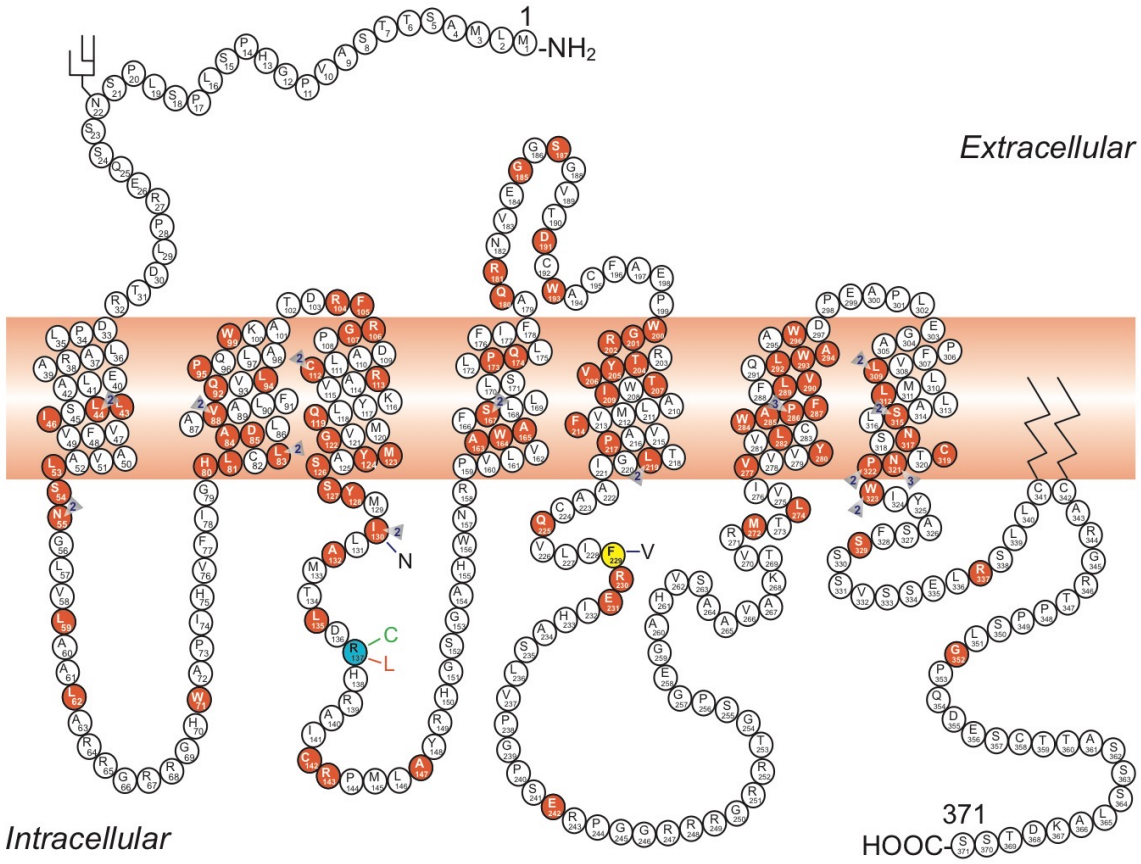
Journal of the American Society of Nephrology. 23:1635-40, 2012.

Nephrogenic Syndrome of Inappropriate Antidiuresis

Characteristics of the Two Patients		
	Patient 1	Patient 2
Age at presentation (months)	3.0	2.5
Clinically significant findings	Irritability	Generalized seizures
Sodium (mmol/liter)	123	118
AVP (pg/ml)	< 1	< 1

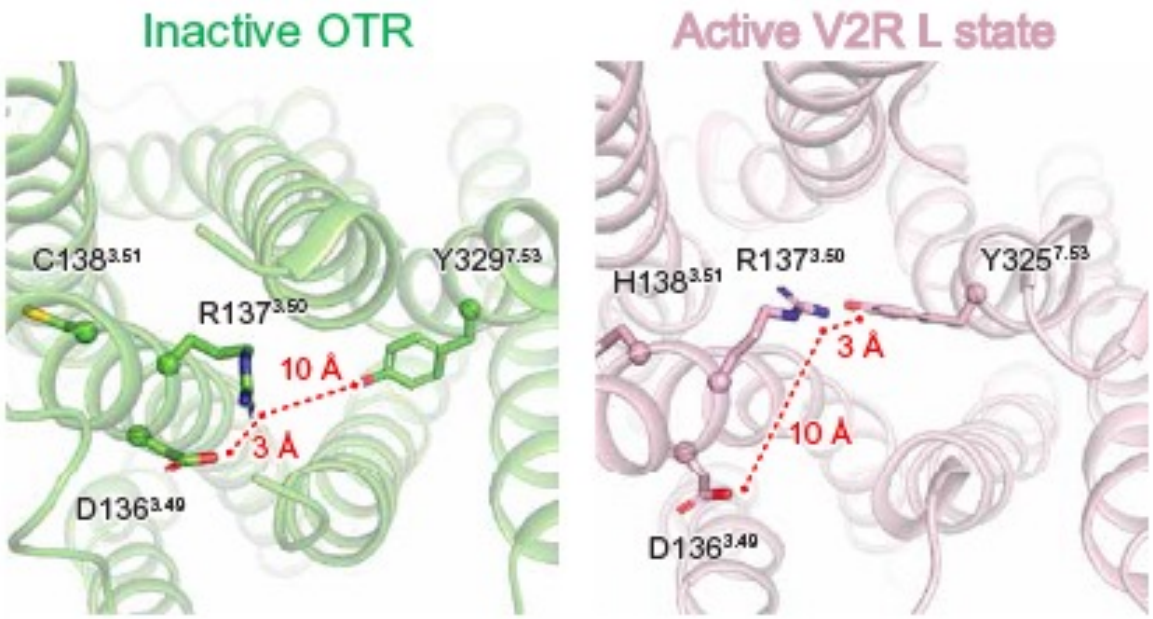
Feldman BJ et al. N Engl J Med. 2005 May 5;352(18):1884-90.

The limitations of the « flat »representation of a 7-transmembrane receptor like V2R: impossible to convey structure-fonction



Nine V.A.M. Knoers, Elena N. Levtchenko. Daniel G. Bichet. Pediatric Nephrology, Inherited disorders of water handling, https://doi.org/10.1007/978-3-642-27843-3_112-1. *, Springer Nature 2021.*

Ionic lock motif between positively charged R137$^{3.50}$ and negatively charged D136$^{3.49}$ in the inactive structure of OTR (left) and in the active V2R L state structure (right).

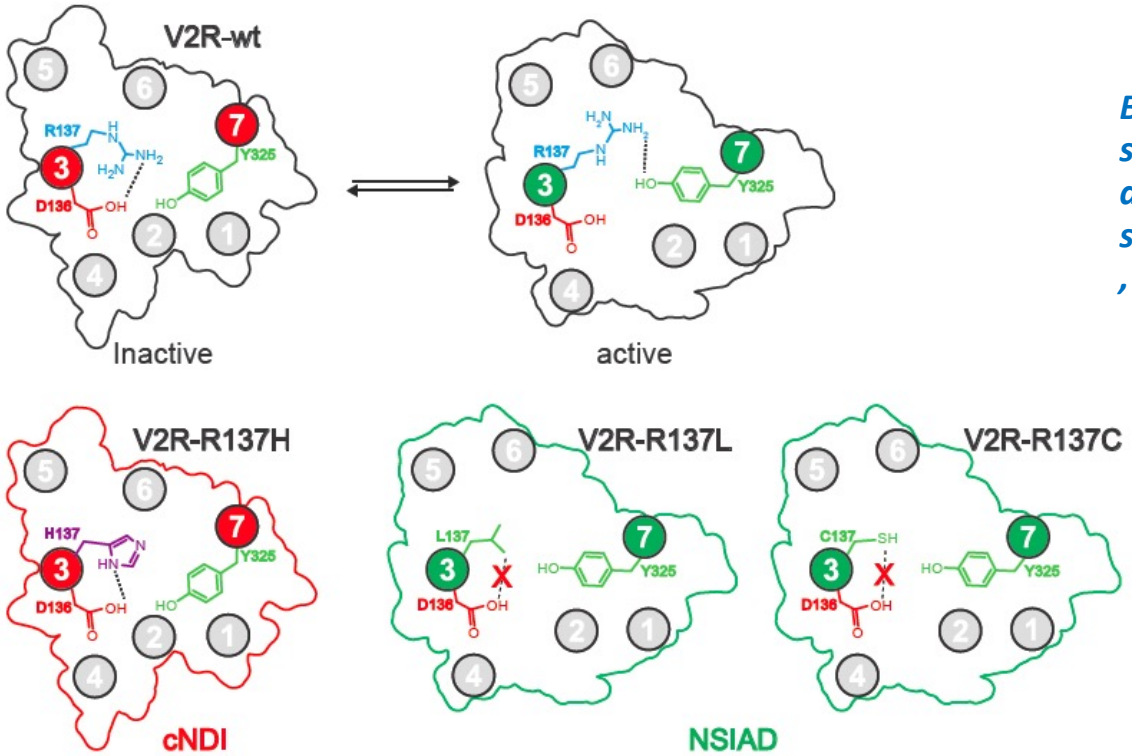


In the inactive OTR, the distance between positively charged R137$^{3.50}$ and negatively charged D136$^{3.49}$ is 3 Å (locked conformation), whereas it is 10 Å in the active V2R (open conformation).

Bous et al. Cryo-electron microscopy structure of the antidiuretic hormone arginine-vasopressin V2 receptor signaling complex , Science Advances, *2021 May 21;7(21)*

The ionic lock is a common feature of many GPCRs and is part of the conserved (D/E)RY motif at the intracellular (IC) end of TM3. This motif forms an intrahelical salt bridge between the D130 and R131 (in B2AR), as well as an interhelical salt bridge between TM3 and TM6 (R131 and E268 in B2AR) that stabilizes the inactivated form of B2AR

Schematic representation of R137 $^{3.50}$ mutations responsible for either congenital Nephrogenic Diabetes Insipidus or Nephrogenic Syndrome Inappropriate Anti Diuresis. Breakage of the R137$^{3.50}$-D136$^{3.49}$ ionic lock is shown in the R137C and R137L mutants.



Bous et al. Cryo-electron microscopy structure of the antidiuretic hormone arginine-vasopressin V2 receptor signaling complex , Science Advances, 2021 May 21;7(21)

A 20-month-old boy with polyuria and a plasma sodium of 159 mmol/L.

- A 20-month-old boy presents to his GP with polyuria/polydipsia (approximately 3 litres per day).
- A diagnosis of diabetes insipidus was suspected and confirmed with a water deprivation test, during which his plasma Na and osmolality rose to 159 mmol/l and 319 mosm/kg, respectively, with a urine osmolality (Uosm) of 100 mosm/kg .
- A DDAVP test the following day showed no response (Uosm pre: 63, post: 65 mosm/kg) and a diagnosis of NDI was made.
- With respect to his food aversion and potential motor development delay (walking independently achieved at age 20 months) an MRI was scheduled, which required general anesthesia.

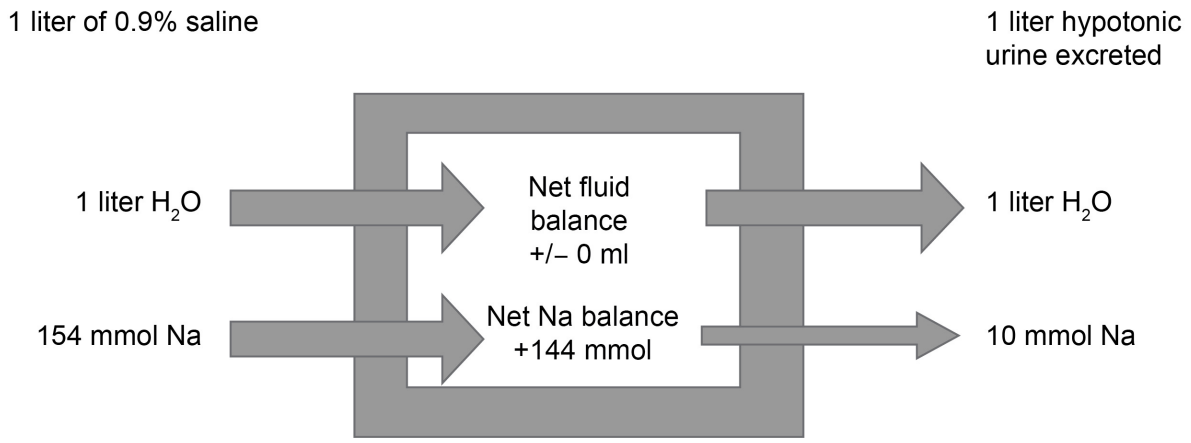
Bockenhauer D, Bichet DG. Nephrogenic diabetes insipidus Curr Opin Pediatr. 2017 Apr;29(2):199-205.

Hypernatremia and osmotic demyelination in a male child with Nephrogenic Diabetes Insipidus

- Despite the recent diagnosis of NDI, he was starved prior to the procedure without intravenous fluids. The scan was delayed and after ~8 h of no fluid intake, he became unwell and bloods at the time revealed a plasma Na of 174 mmol/l. The emergency response team was called who administered 2 boluses of 20 ml/kg of 0.9% saline and he became unresponsive. He was therefore admitted to intensive care for intubation and placement of a central line and he received another 20 ml/kg bolus of 0.9% saline. A subsequent blood test now revealed a plasma Na concentration of 198 mmol/l. A subsequent MRI showed diffuse white matter abnormalities consistent with demyelination.
- Subsequent genetic testing showed a nonsense mutation c.599G>A; p.Trp200* in *AVPR2*, coding for the vasopressin V2 receptor.

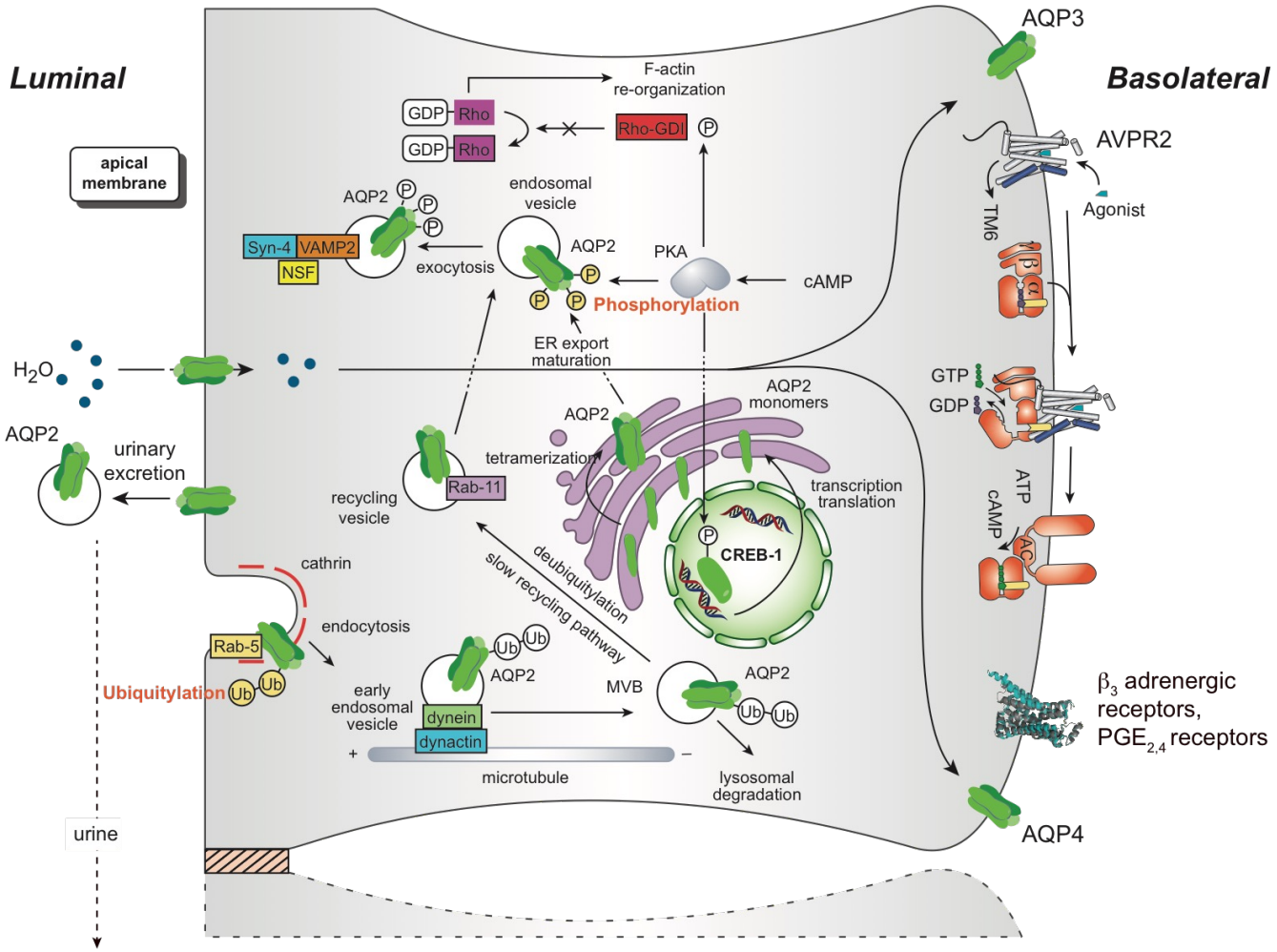
Bockenhauer D, Bichet DG. Nephrogenic diabetes insipidus Curr Opin Pediatr. 2017 Apr;29(2):199-205.

Emergency treatment of hypernatraemic dehydration in a patient with NDI: do not use 0.9% saline as this will result in excess sodium chloride administration and thus worsen the hypernatraemia.



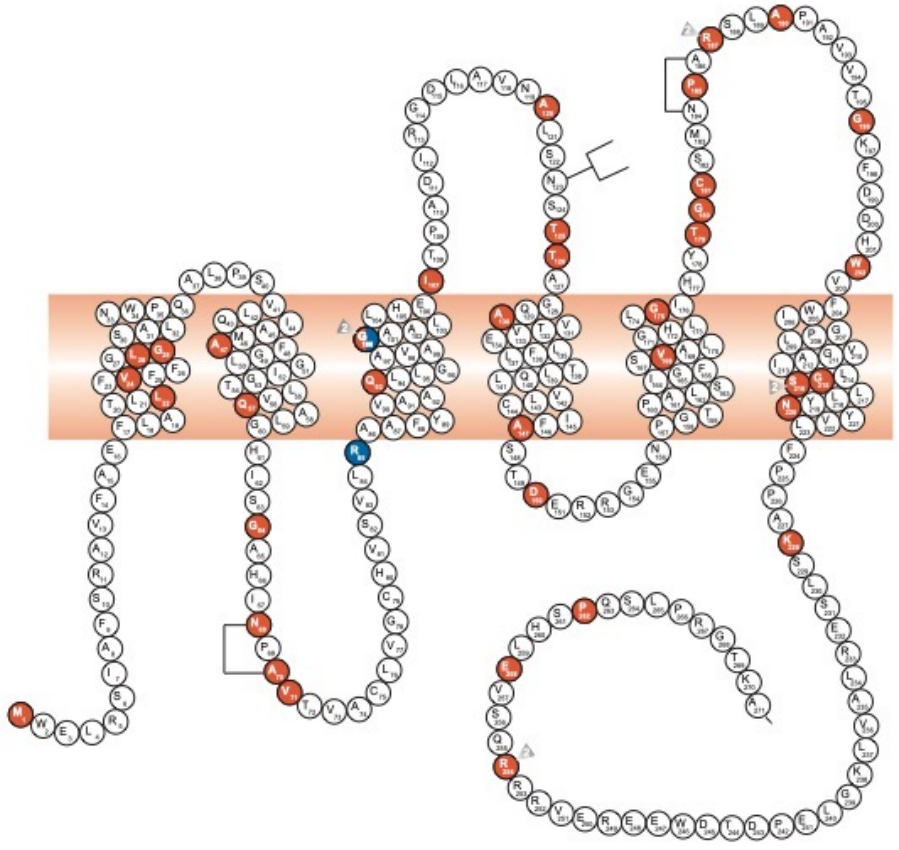
A patient with NDI excretes hypotonic urine, typically with a Na concentration less than 10 mmol/l. If 1 l of urine output is replaced with 1 l of 0.9% saline, this will not change the fluid balance, but lead to a net gain of 144 mmol of Na. In a patient of 10 kg with estimated 7 l of total body water, this would lead to an increase in the plasma Na concentration of approximately 144 mmol/l = 20 mmol

.Bockenhauer D, Bichet DG. Curr Opin Pediatr. 2017 Apr;29(2):199-205.



AVP, AVPR2, cAMP, insertion of AQP2 into luminal membranes, water reabsorption

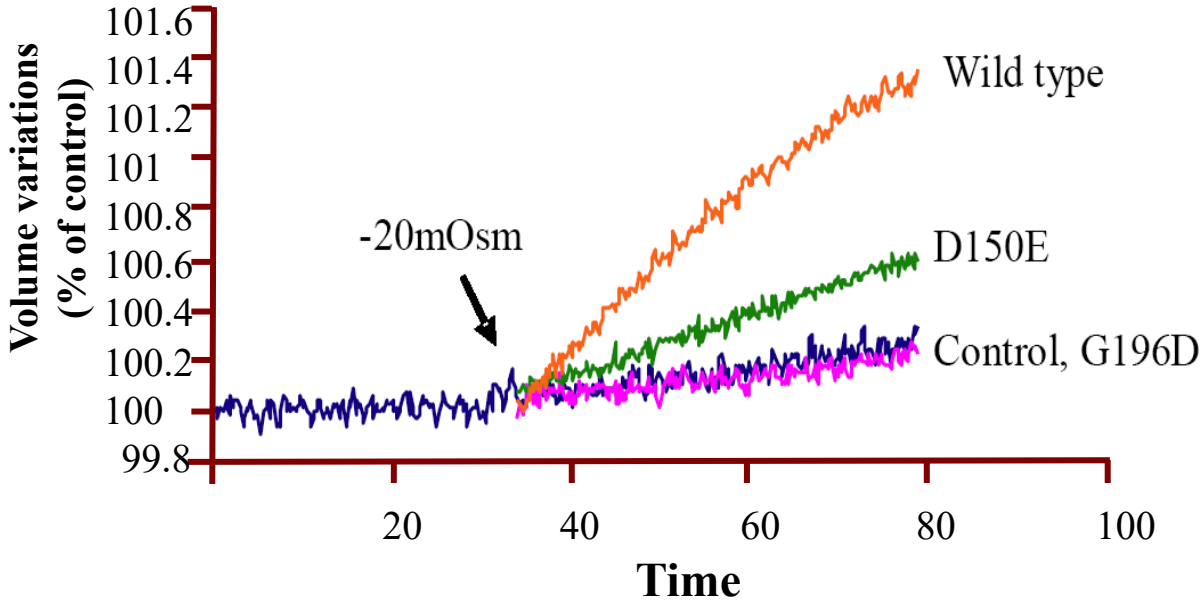
Nine V.A.M. Knoers, Elena N. Levtchenko. Daniel G. Bichet. Pediatric Nephrology, Inherited disorders of water handling, https://doi.org/10.1007/978-3-642-27843-3_112-1. *, Springer Nature 2021.*



A representation of the AQP2 protein and identification of 49 putative disease-causing AQP2 mutations

Bichet, D.G. The Posterior Pituitary. In: The Pituitary, 5th ed., Melmed, S. (ed.), Chapter 8, Elsevier, Academic Press, London, UK, 2022, pp 1-41 (proofs), in press.

Function of wt and AQP2 mutants



Conclusion

- The identification of *AVPR2*, the gene responsible for X-linked Nephrogenic Diabetes Insipidus was facilitated by the clinical observations of unchanged low urine osmolality after dDAVP, an end-organ resistance.
- A pre-cAMP defect was inferred from dDAVP and epinephrin infusion studies.
- Perfect segragation was observed with Xq28 markers and cloning by expression (generation of cAMP by AVP) was done by M. Birnbaumer.
- Ancestrally independent families with different Xq28 markers were found to bear different *AVPR2* loss-of-function mutations.
- *AVPR2* gain-of function mutations are responsible for hereditary hyponatremia and break the R1373.50-D1363.49 ionic lock as demonstrated by the cryo-electron microscopy data.
- Pre- and peri-natal testing should be done in all families with NDI to prevent dehydration episodes.
- New compounds are tested to concentrate urine in these NDI patients.

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- I thank all the members of my laboratory and of the clinical research unit who participated to this research.
- I thank all the patients and their families who participated to these studies, including dDAVP infusions, haplotype analysis, mutation identification and expression testing.
- We continue to receive blood from hereditary polyuric patients and we continue to provide free sequencing analysis for AVPR2 and AQP2.