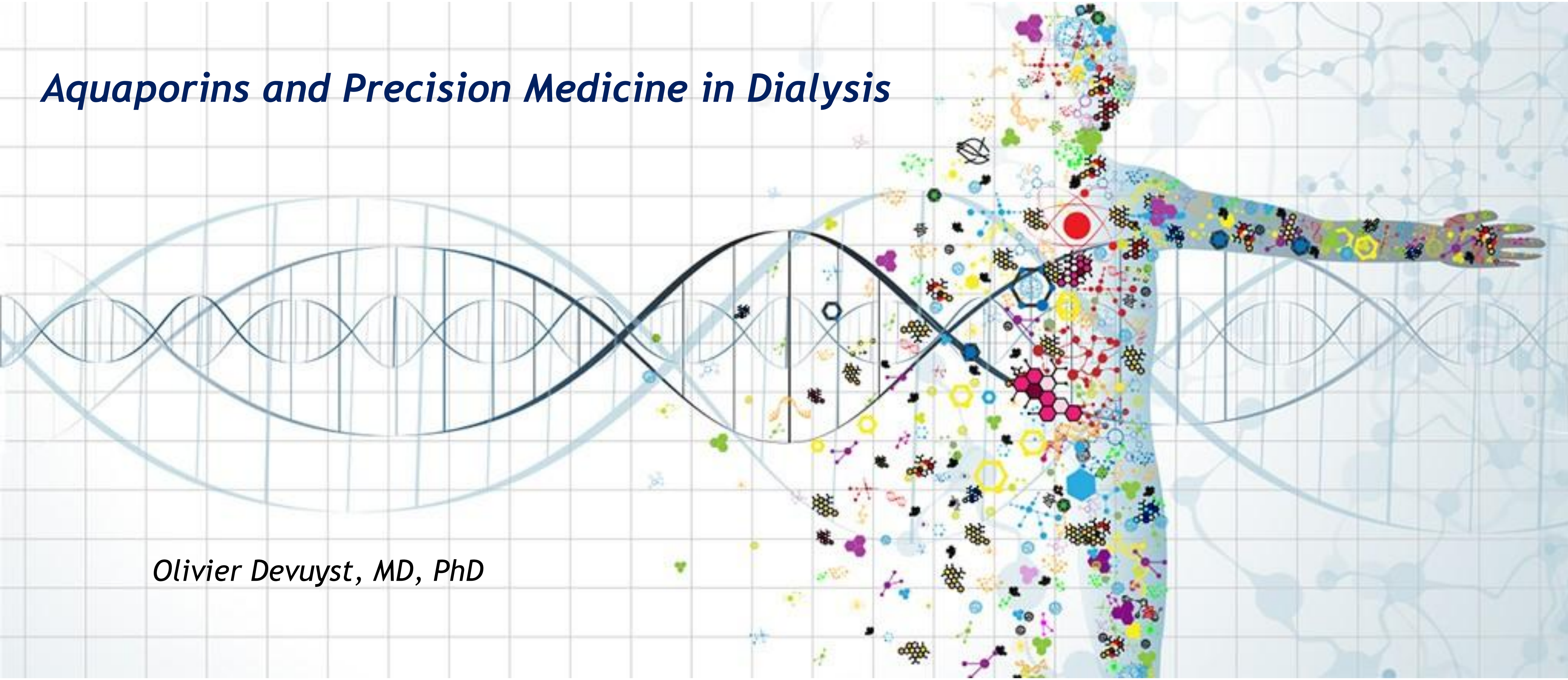
Aquaporins and Precision Medicine in Dialysis



Olivier Devuyst, MD, PhD

Actualités Néphrologiques, May 10, 2022

radiz University of Zurich[UZH] FNSNF EURenOmics UCL


Zurich, Switzerland, around 1850

Karl Wilhelm von Nägeli (1817 – 1891)

- 1840 doctorate from the University of Zurich
- 1855 professor of botany at UZH

Naegeli, Carl Wilhelm von. 1856.
Die Individualität in der Natur mit vorzüglicher Berücksichtigung des Pflanzenreiches.

Hypotonic Turgid (normal) — Isotonic Flaccid — Hypertonic Plasmolyzed)

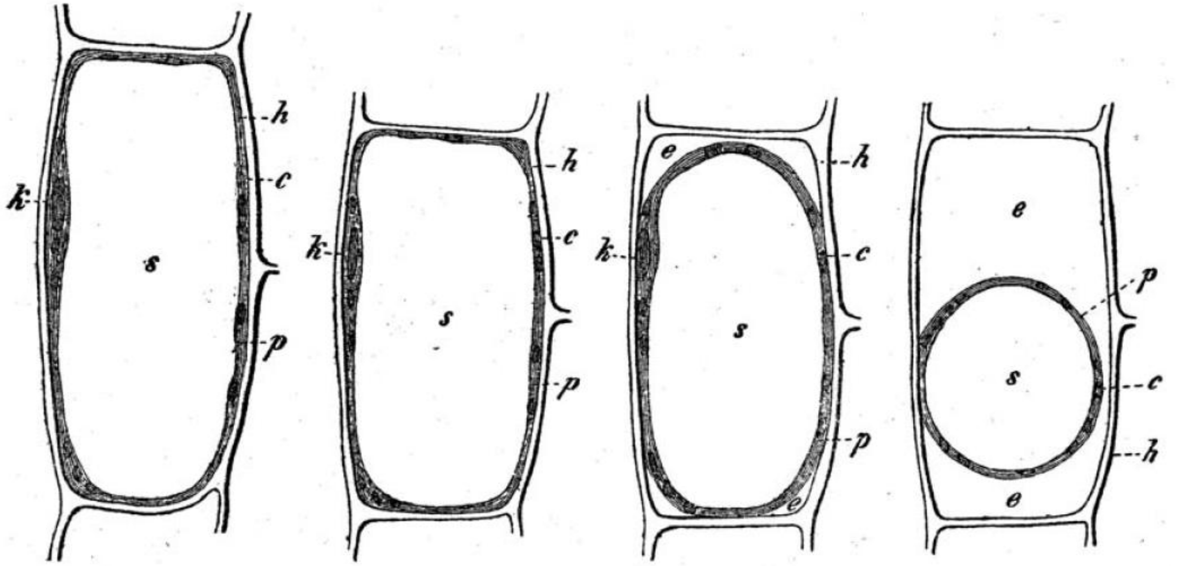
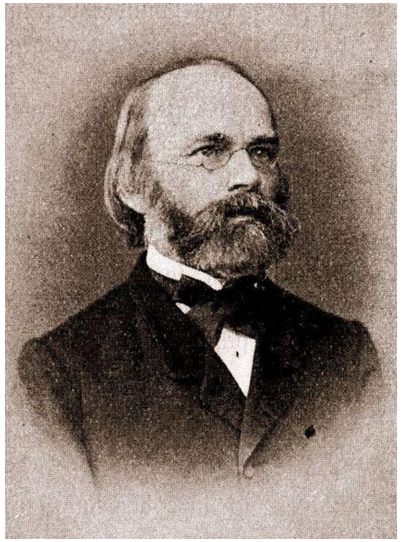
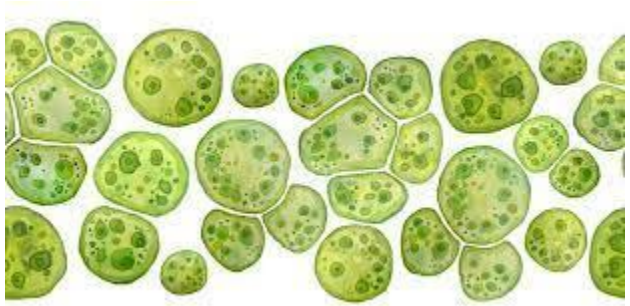


Fig. 1. Fig. 2. Fig. 3. Fig. 4.



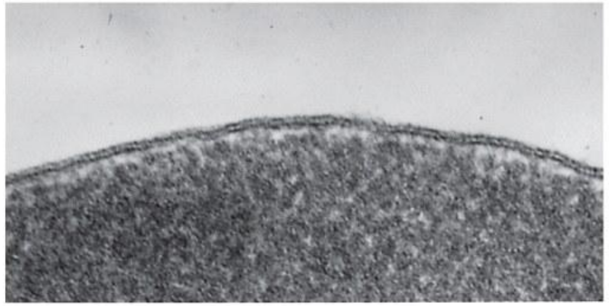
Investigated the process of osmosis in unicellular algae & plants

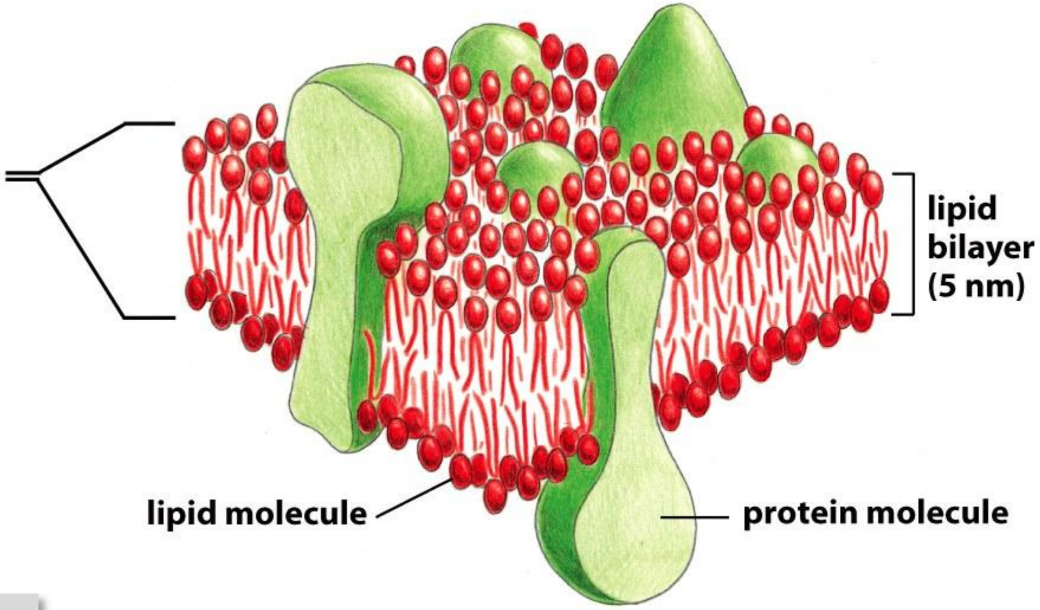


The Overton Rule (1899)

Ernest Overton
(1865-1933)
PD UZH – 1890 (Biologie)
Contributions on
membrane permeability

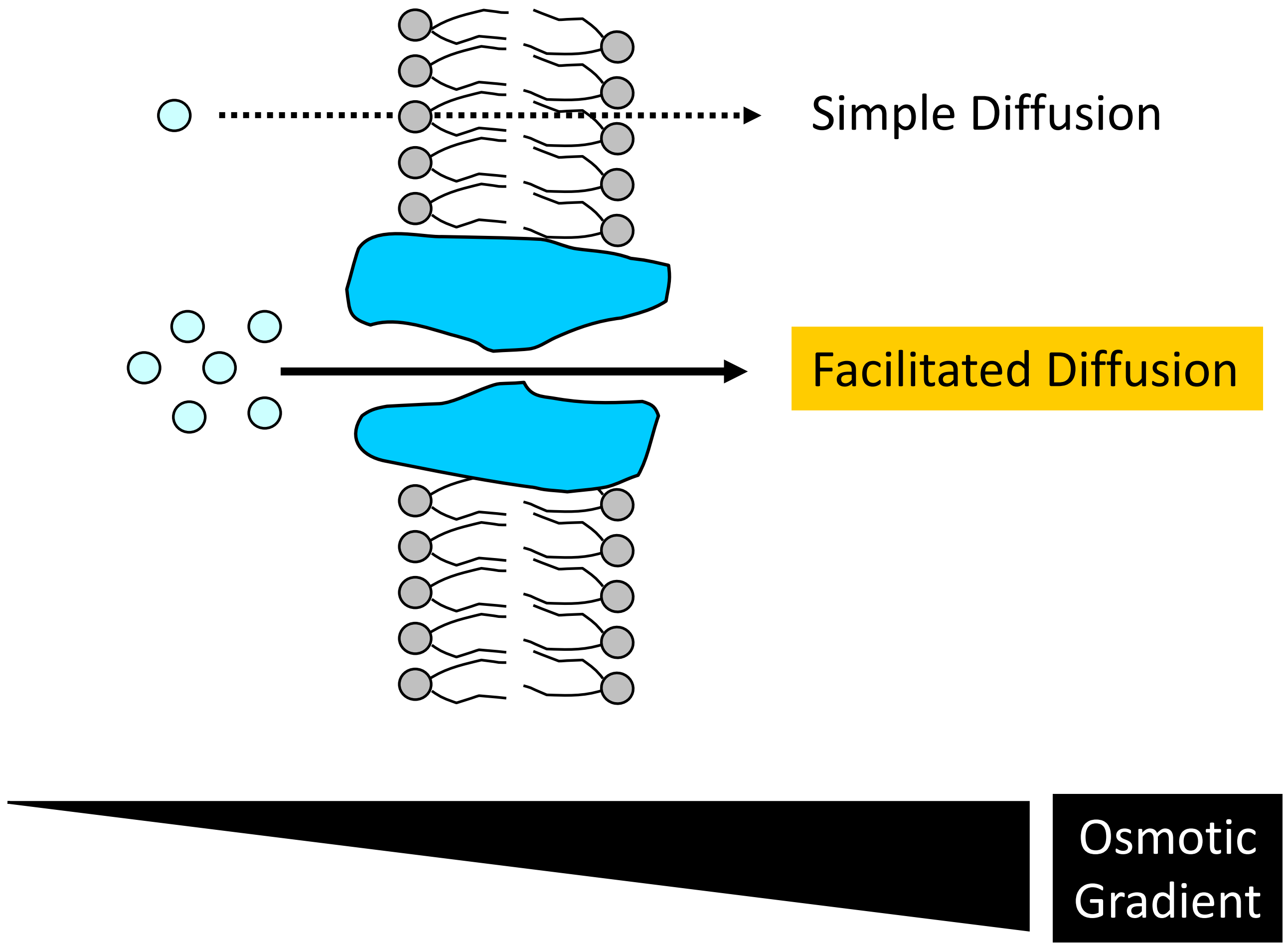
Non-lipophilic substances (incl. water) must use specific pathways to cross lipidic membranes





→ *Mosaic model for plasma membranes*

Mosaic Model for Water Transport



Macey et al. *Am J Physiol* 1984

THE JOURNAL OF BIOLOGICAL CHEMISTRY

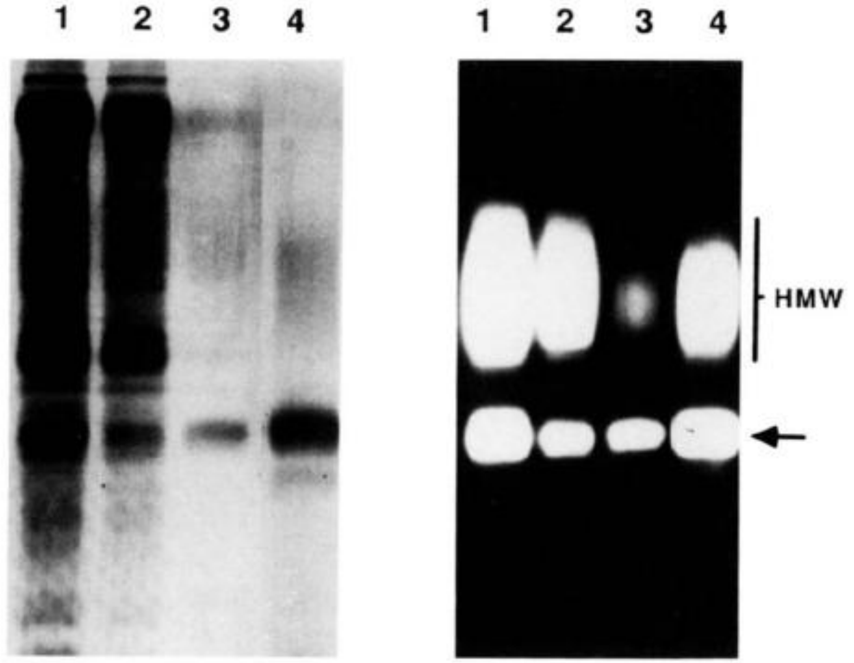
Vol. 263, No. 30, Issue of October 25, pp. 15634-15642, 1988
Printed in U.S.A.

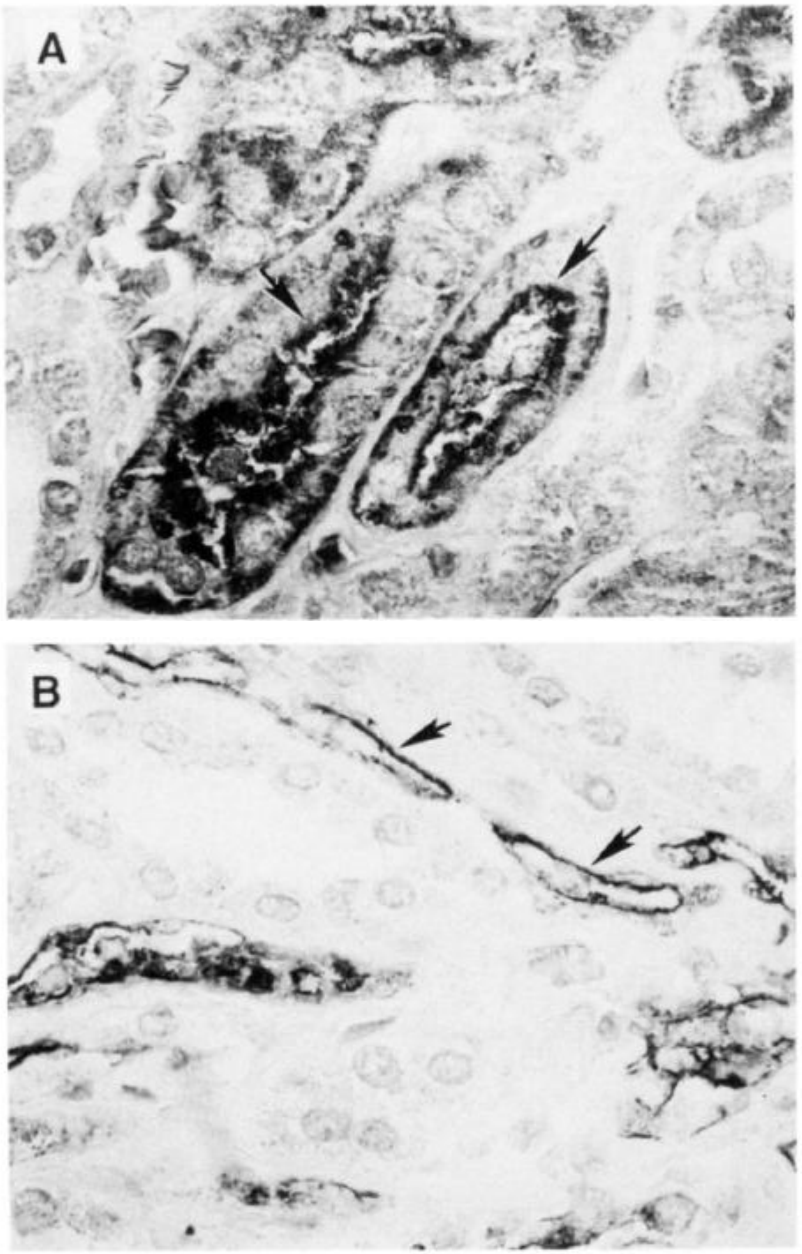
Identification, Purification, and Partial Characterization of a Novel M_r 28,000 Integral Membrane Protein from Erythrocytes and Renal Tubules*

(Received for publication, April 19, 1988)

Bradley M. Denker, Barbara L. Smith, Francis P. Kuhajda, and Peter Agre‡
From the Departments of Medicine and Cell Biology/Anatomy, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

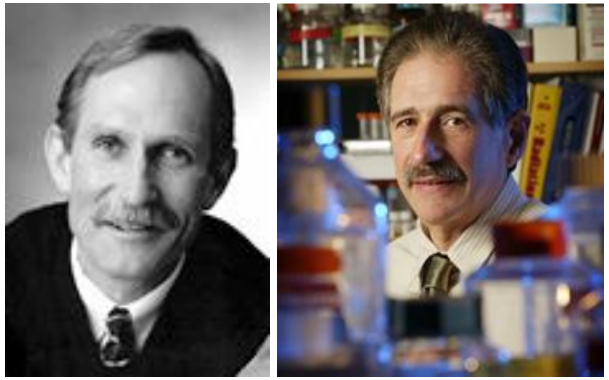
28 kD -

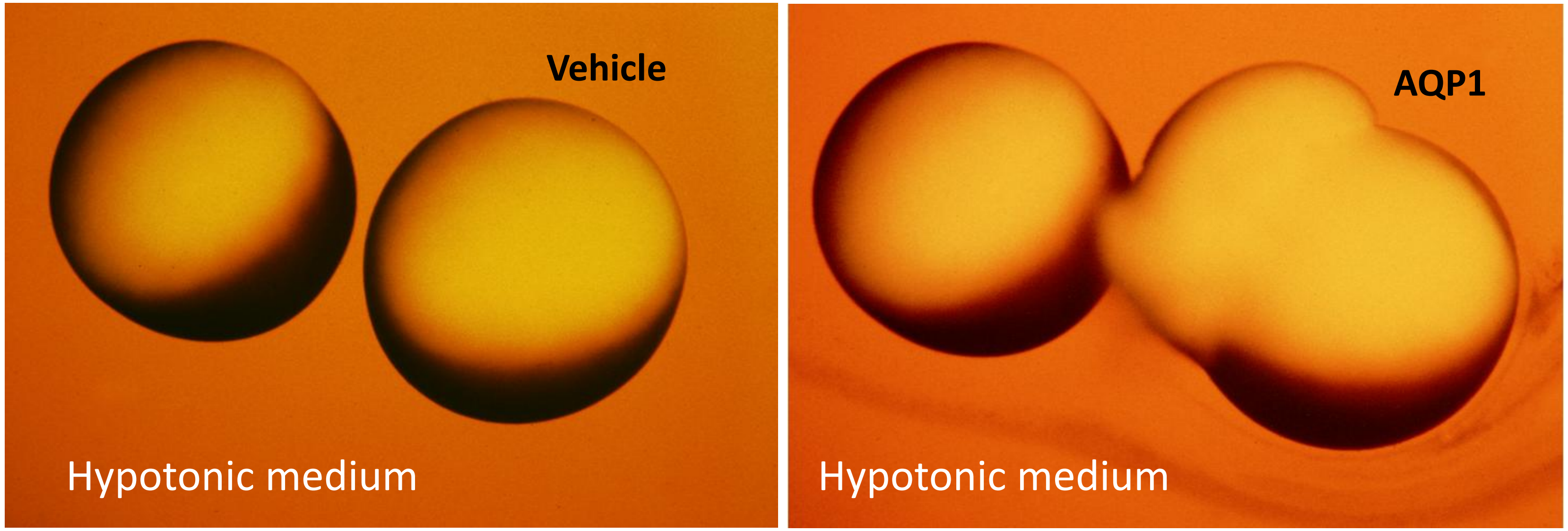




Appearance of Water Channels in *Xenopus* Oocytes Expressing Red Cell CHIP28 Protein

Gregory M. Preston, Tiziana Piazza Carroll,
William B. Guggino, Peter Agre*

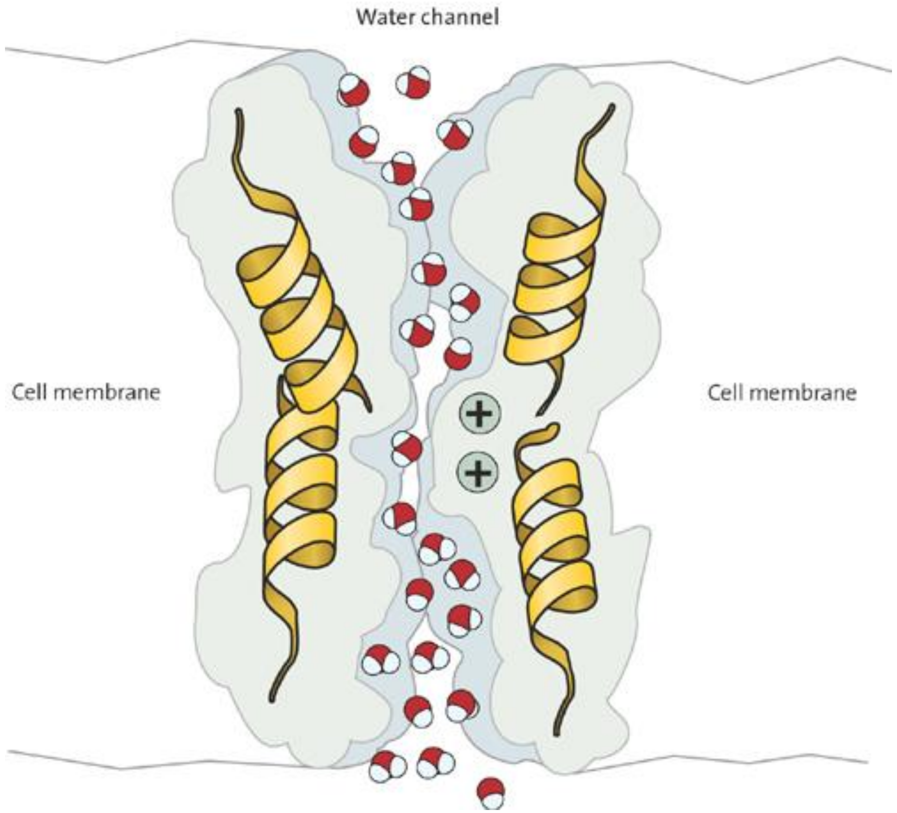


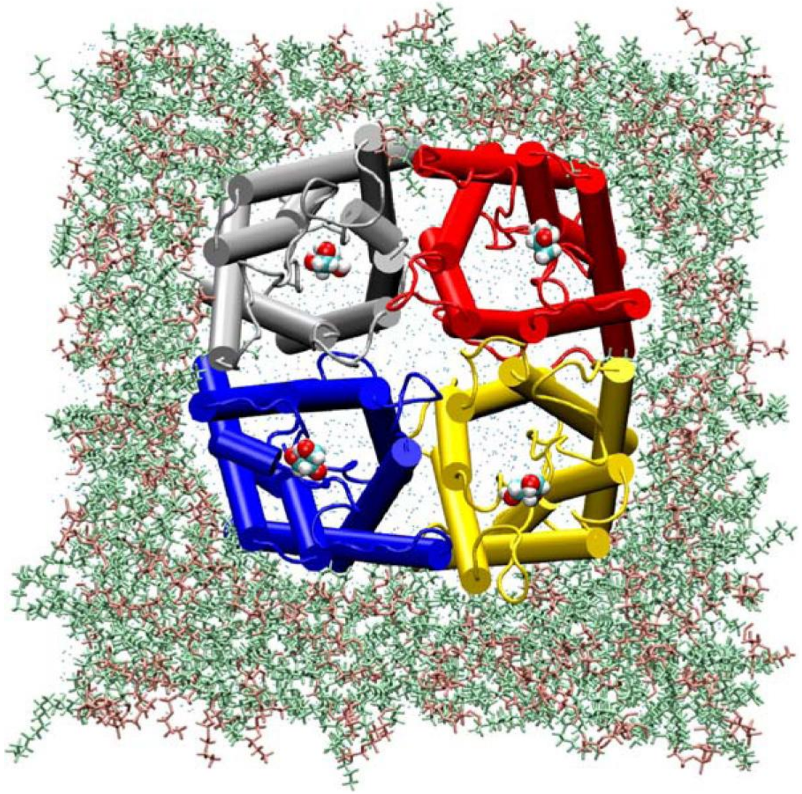


CHIP28/AQP1: Cell swelling → facilitated water transport

SCIENCE • VOL. 256 • 17 APRIL 1992

Structure of Aquaporins



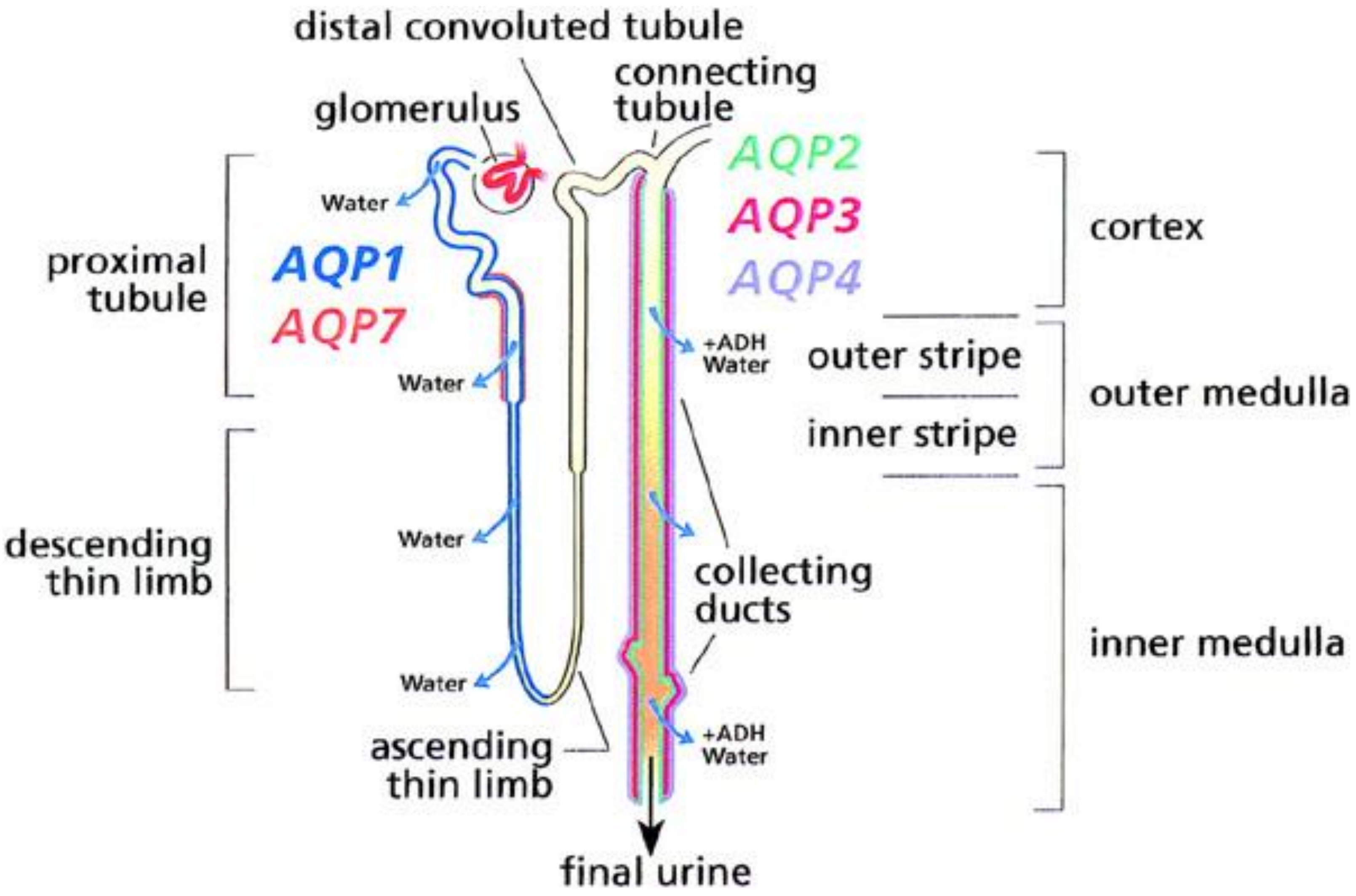


- Narrow pore : 2.8 Å
- Selectivity – charged R195

AQP1 tetramers: 3 billions of water molecules per second

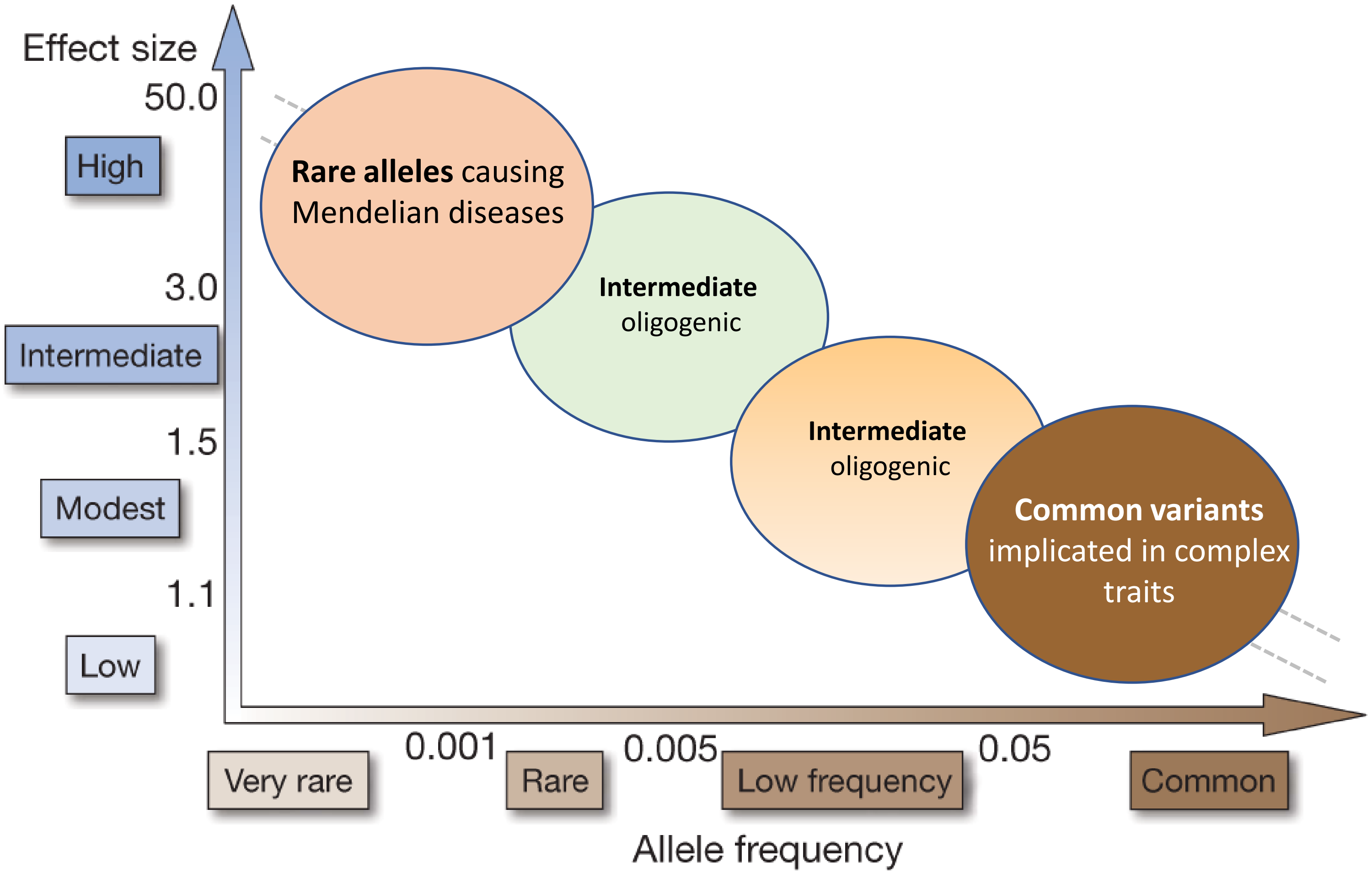
Walz T et al. *Nature* 387, 1997; Wang et al. *Structure* 13, 2005

Aquaporins along Nephron Segments



Nielsen S et al. *Physiol Rev* 82: 205-44, 2002

Effect of Genetic Variants in *AQP1* ?

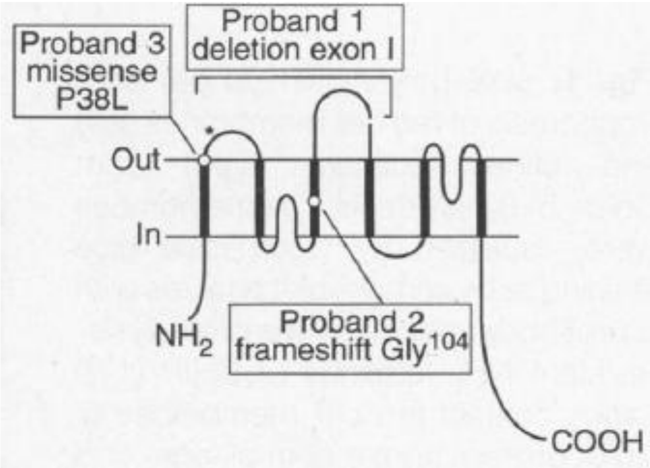


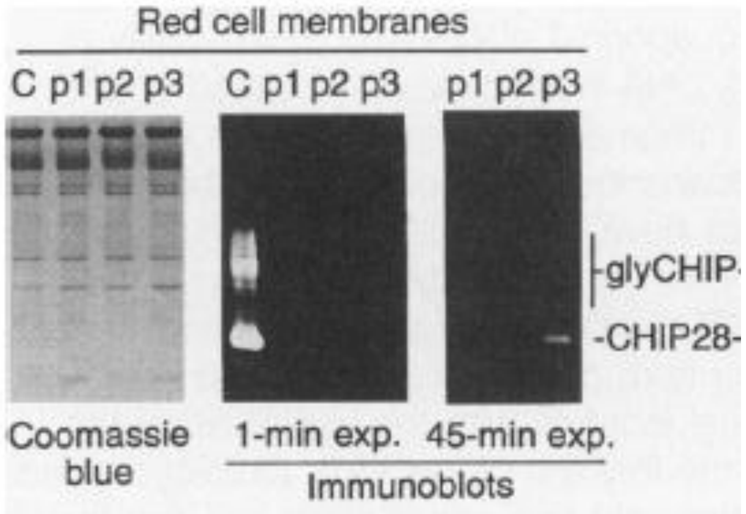
Manolio et al. Nature 461, 2009

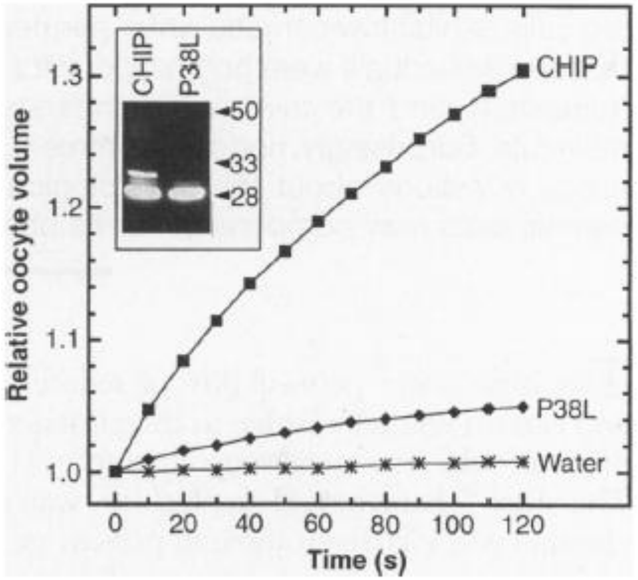
Mutations in *aquaporin-1* in Phenotypically Normal Humans Without Functional CHIP Water Channels

Gregory M. Preston, Barbara L. Smith, Mark L. Zeidel, John J. Moulds, Peter Agre*

Colton blood group: Ala45Val variant in AQP1
A few kindreds: Colton-null antigens







Absence of AQP1 – Phenotypically normal ?

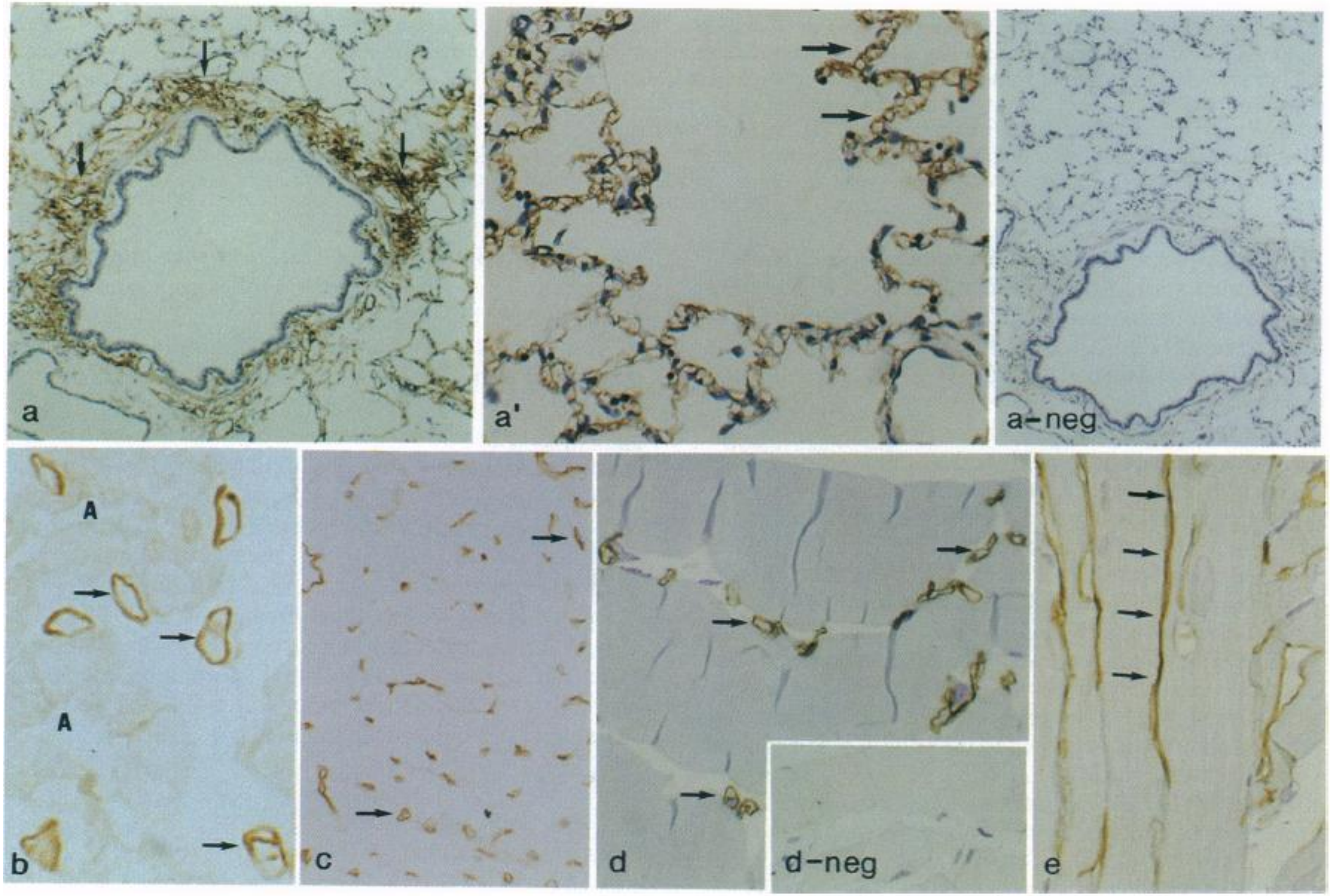
SCIENCE • VOL. 265 • 9 SEPTEMBER 1994

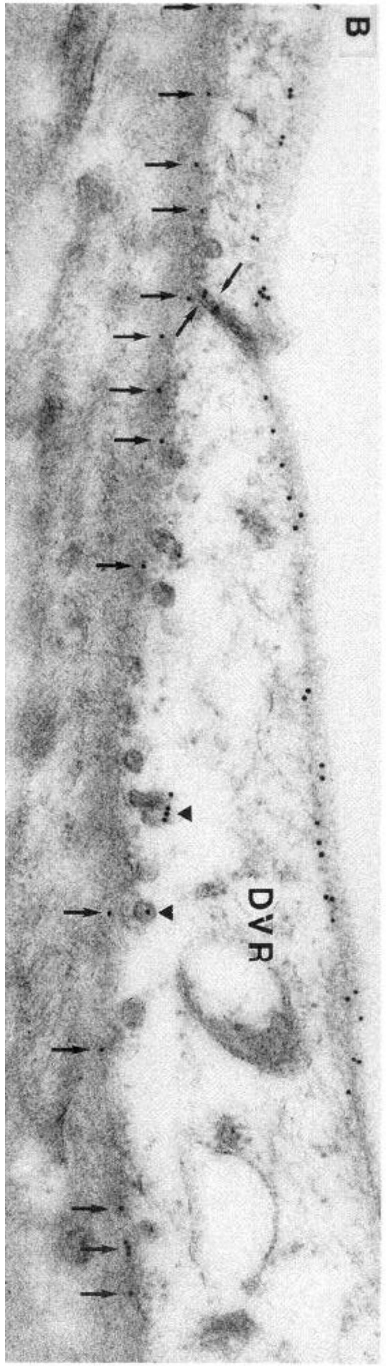
Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 7275–7279, August 1993
Cell Biology

Distribution of the aquaporin CHIP in secretory and resorptive epithelia and capillary endothelia

(water channel/choroid plexus/ciliary epithelium/bile ducts/intestinal lacteals)

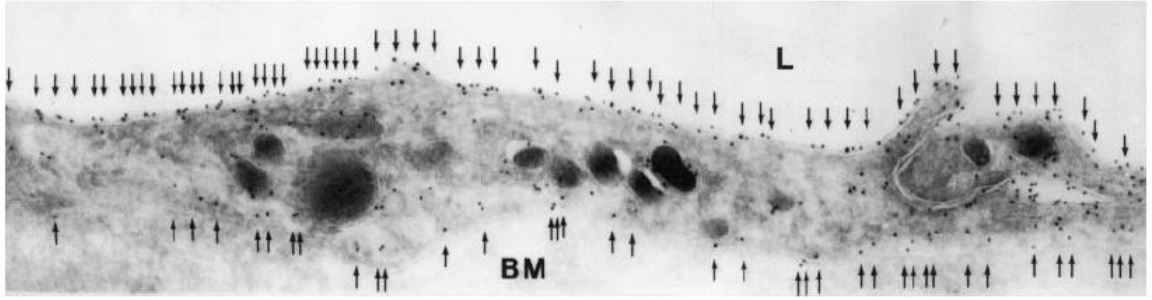
SØREN NIELSEN*, BARBARA L. SMITH†, ERIK ILSØ CHRISTENSEN*, AND PETER AGRE†‡

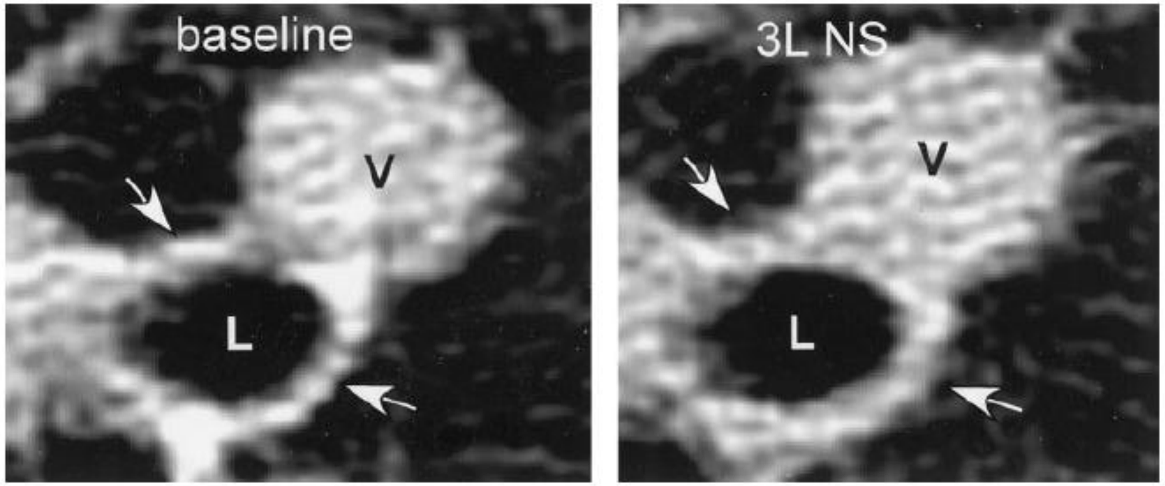




Decreased pulmonary vascular permeability in aquaporin-1-null humans

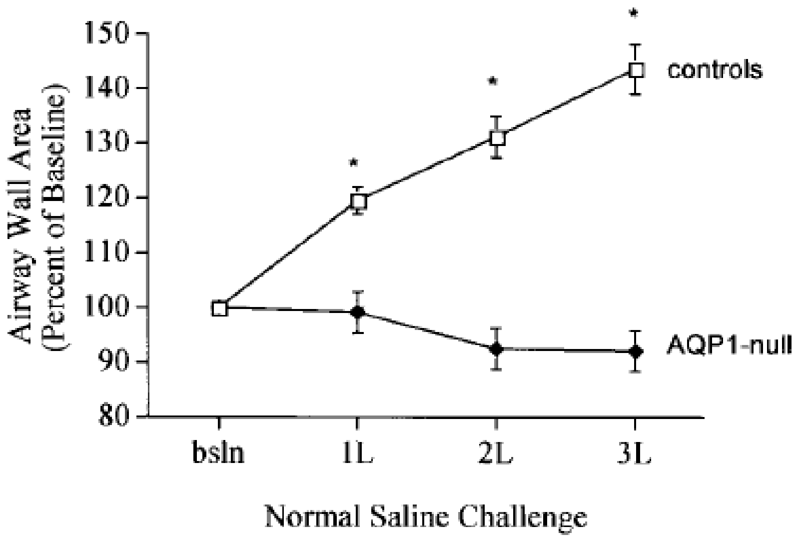
Landon S. King*†‡§¶, Søren Nielsen‖, Peter Agre†‡§, and Robert H. Brown*†§**††





Impaired thickening of airways after saline (arrows)

administration (arrows)



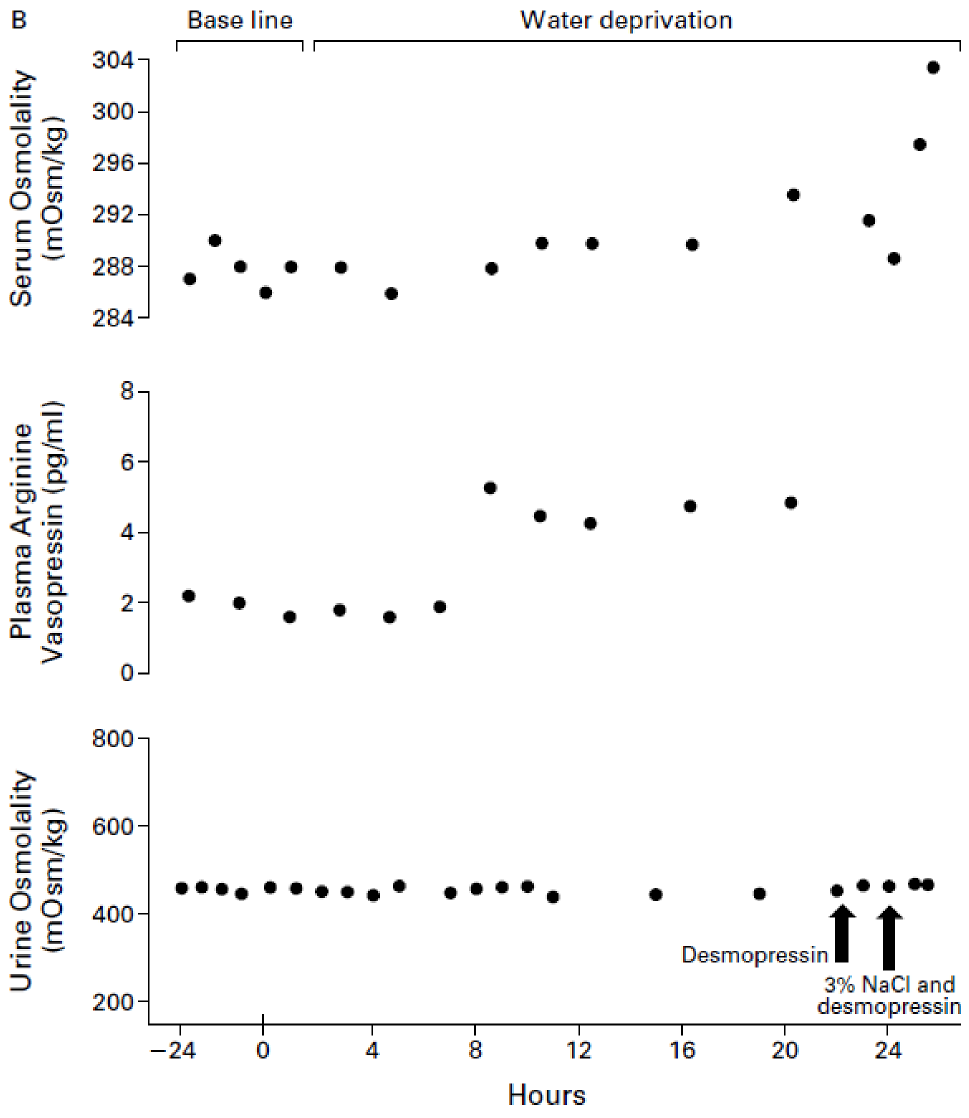
PNAS | January 22, 2002 | vol. 99 | no. 2 | 1059–1063

Brief Report

Defective Urinary Concentrating Ability Due to a Complete Deficiency of Aquaporin-1

Landon S. King, M.D., Michael Choi, M.D.,
Pedro C. Fernandez, M.D., Jean-Pierre Cartron, Ph.D.,
and Peter Agre, M.D.

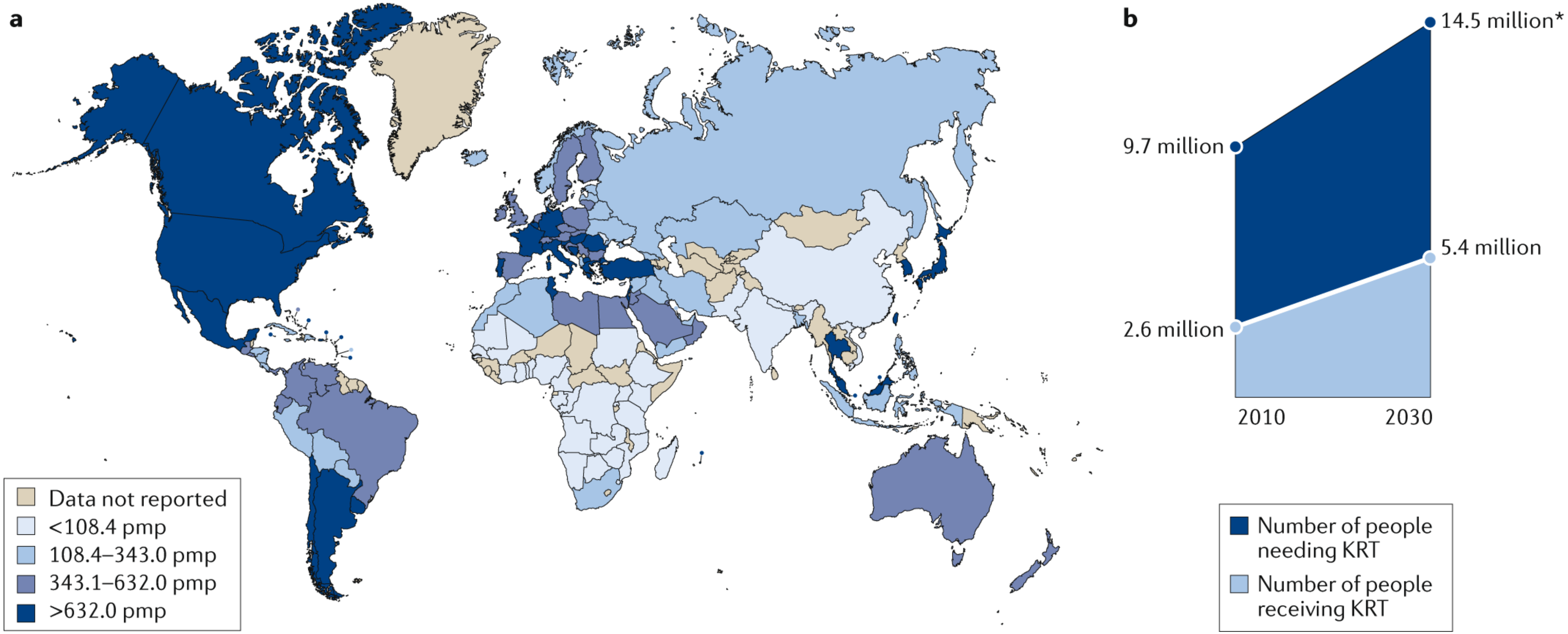
Impaired urinary concentrating ability
Mild phenotype – vas recta ?



N Engl J Med, Vol. 345, No. 3 · July 19, 2001

Peritoneal Dialysis: Osmosis and AQP1 in action

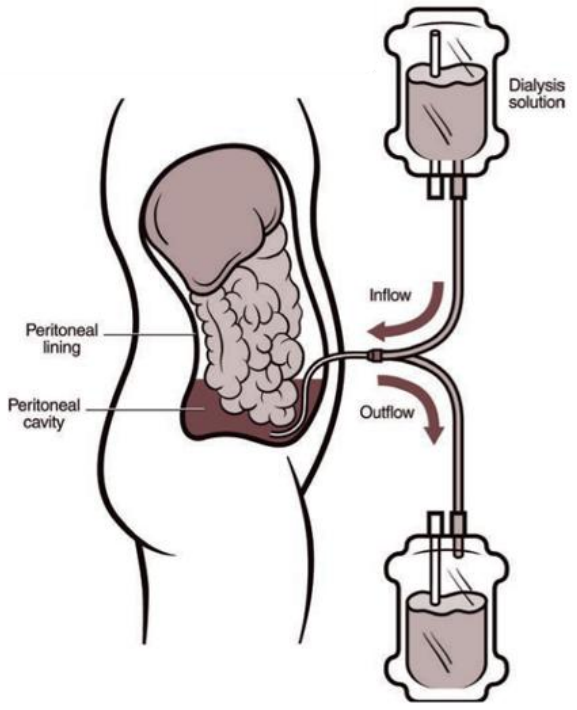
Global prevalence of kidney renal replacement therapy



a | Global prevalence of chronic dialysis. **b** | Estimated worldwide need and projected capacity for KRT by 2030.

Himmelfarb et al. *Nat Rev Nephrol* 16, 2020

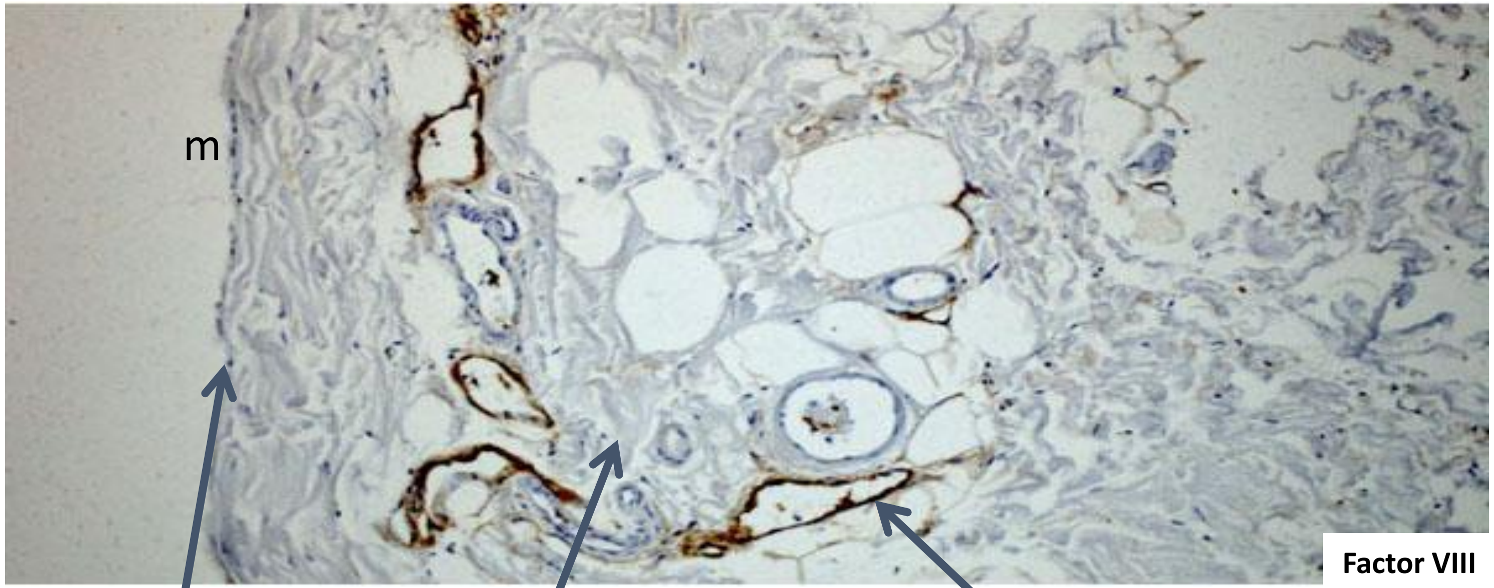
Peritoneal Dialysis



- Renal replacement therapy used in >300,000 patients worldwide (10-15%)
- Dialysis through a biological, natural membrane
- Home-based | Increased flexibility and autonomy | *Empowerment*
- Cost-effective, similar overall survival

- Progressive structural and functional alterations in the peritoneal membrane
- Loss of ultrafiltration capacity
- Higher cardiovascular morbidity
- Risk of acute peritonitis

Structure of the Peritoneal Membrane



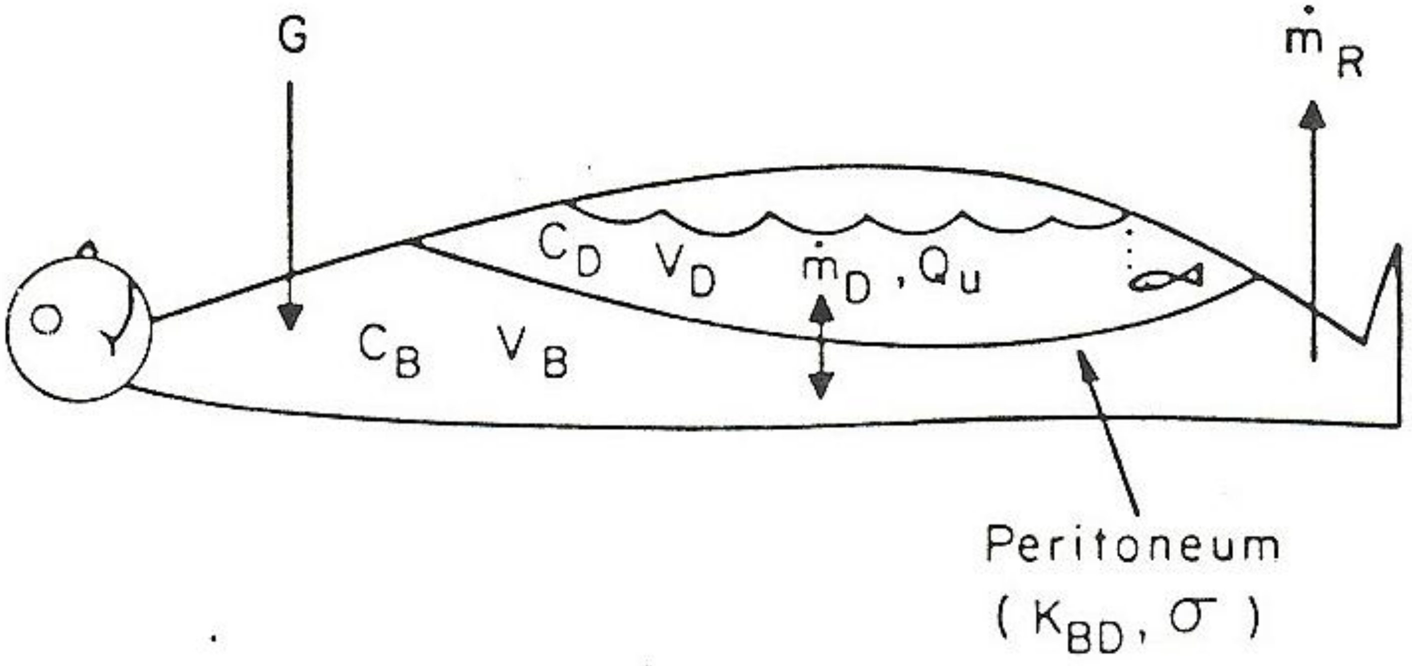
Mesothelium

Interstitium

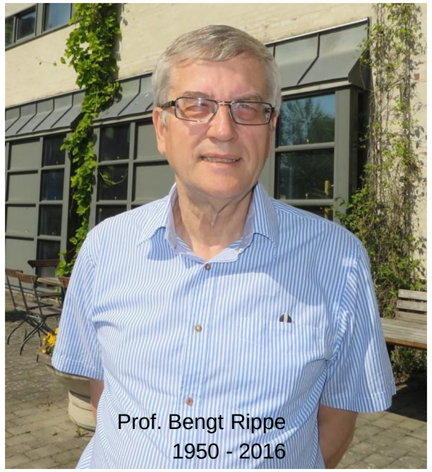
Capillary endothelium
Main functional barrier to solute & fluid transport

- Osmosis driven by PD fluid inserted in cavity
- Water transport – Ultrafiltration
- Uremic solute removal

Peritoneal Transport: the « Black-box » Model in the 1980s…



Transport Kinetics, In: Peritoneal Dialysis, 3rd Edition, Kluwer Academic Publ, Eds. Popovich, Moncrief and Pyle, Chap. 6, pp. 96-116, 1989



A phenomenological interpretation of the variation in dialysate volume with dwell time in CAPD

Gunnar Stelin and Bengt Rippe

Kidney International, Vol. 38 (1990), pp. 465–472

Lund University

Computer simulations of peritoneal fluid transport in CAPD

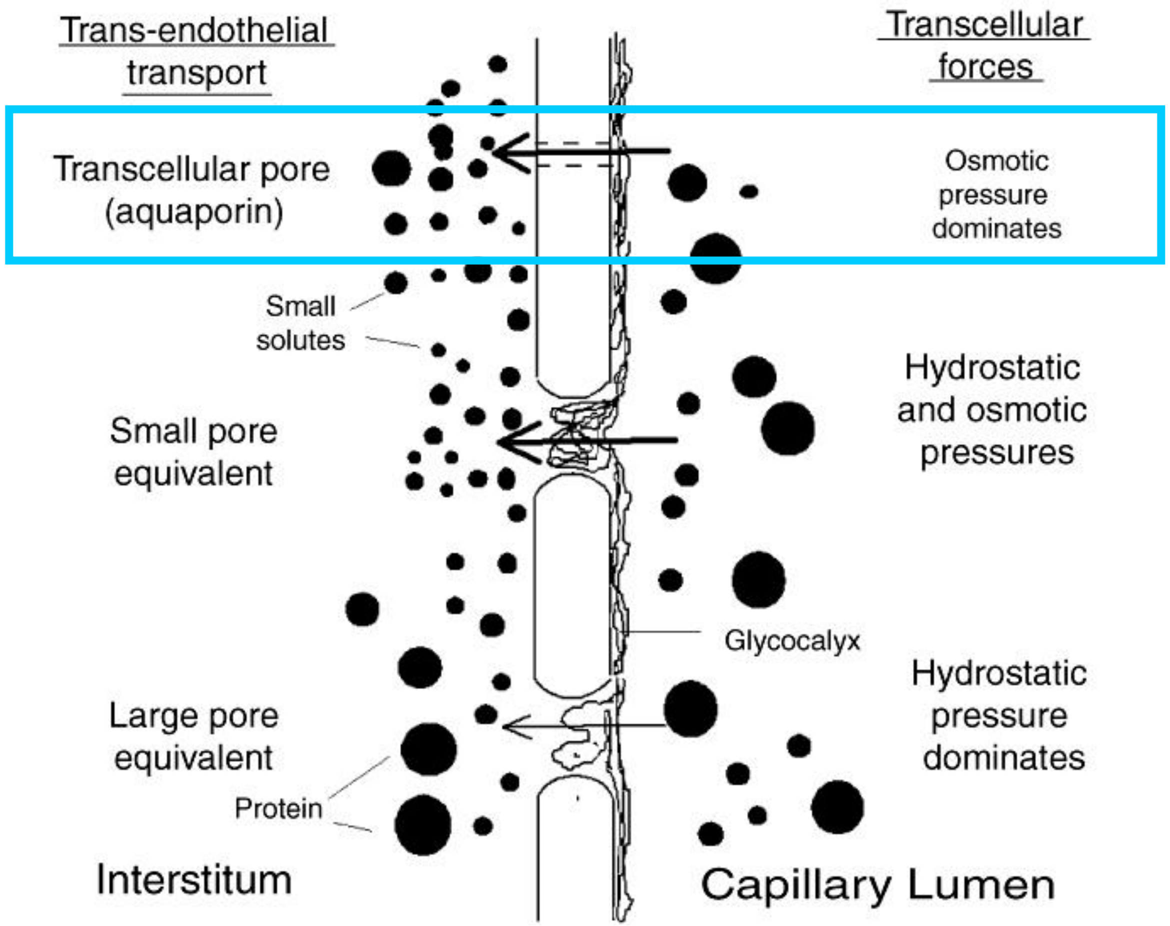
Bengt Rippe, Gunnar Stelin, and Börje Haraldsson

Kidney International, Vol. 40 (1991), pp. 315–325

According to the model, the peritoneum behaves as a membrane having a large number of "small pores" (radius 40 - 60 Å) and a very low number of "large pores" (radius 200 - 300 Å).

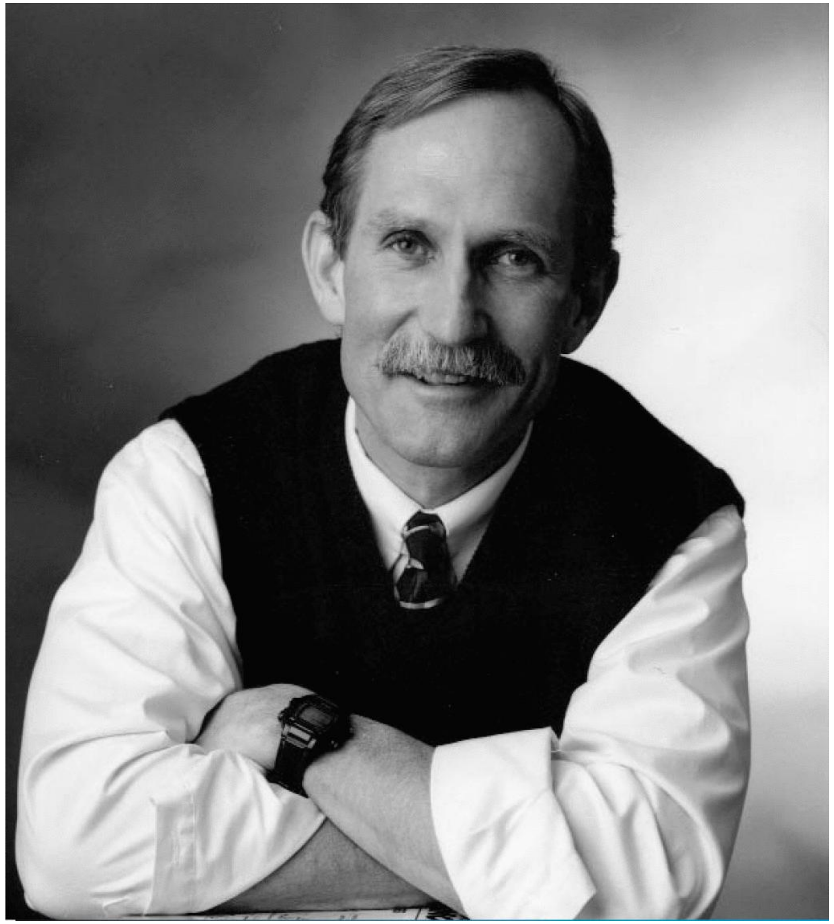
A third transperitoneal exchange route is predicted to exist, namely a transcellular ("ultra-small" pore) pathway, having an approximate pore radius of 4 to 5 Å.

Ultrasmall Pores across the Endothelium



Ultrasmall pores : predict to facilate water transport during crystalloid osmosis

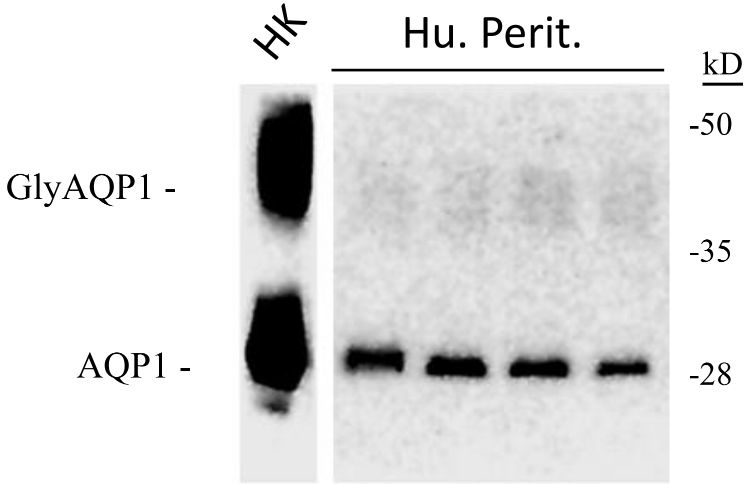
A conversation with Peter Agre

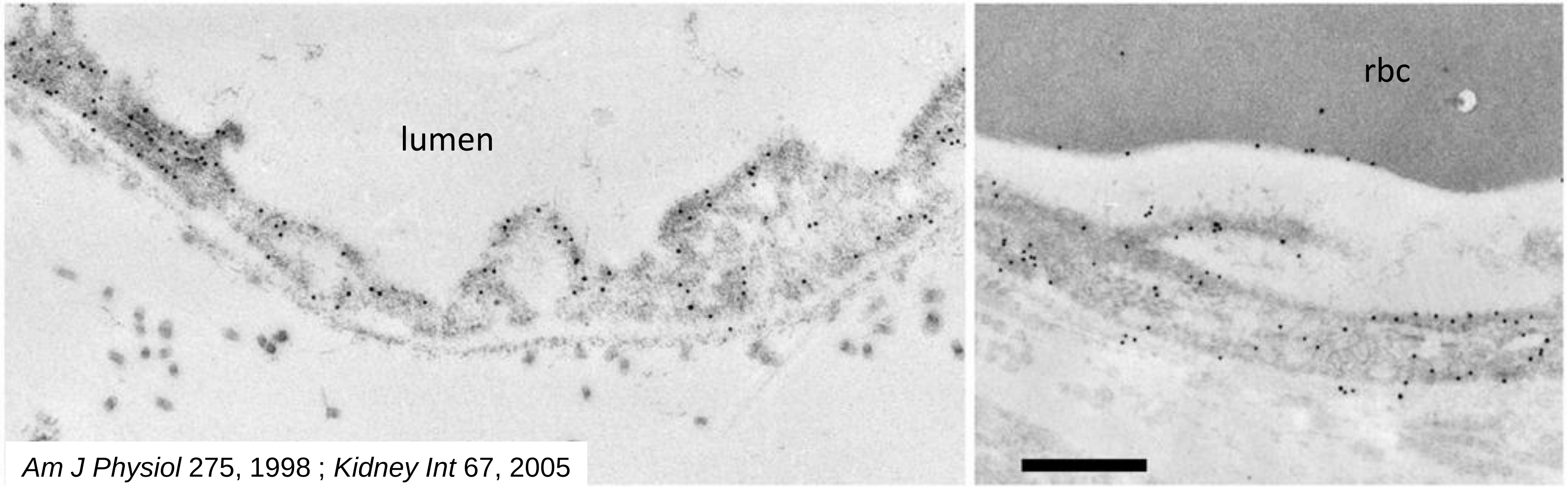


Johns Hopkins Medical School, Baltimore, MD - 1995

J Clin Invest 124, 2014

Distribution of AQP1 in the Endothelium Lining Peritoneal Capillaries





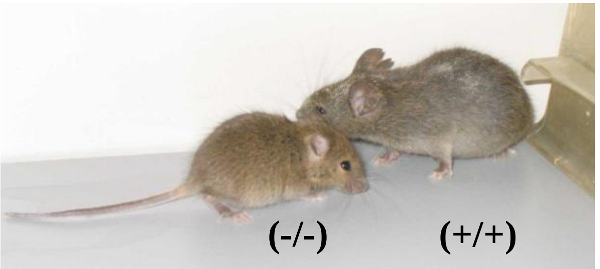
Am J Physiol 275, 1998 ; *Kidney Int* 67, 2005

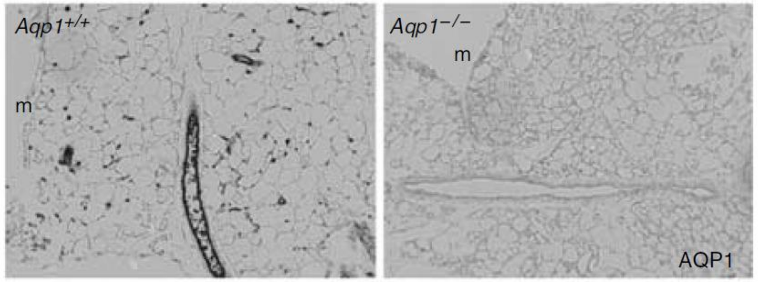
http://www.kidney-international.org

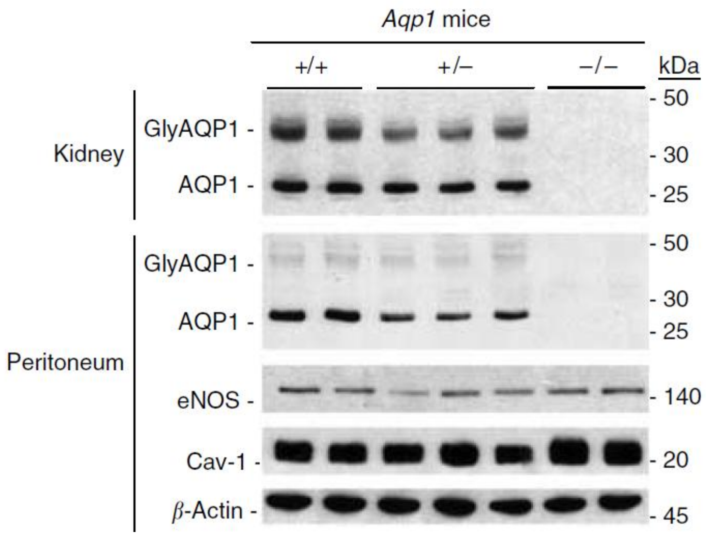
see commentary on page 1494

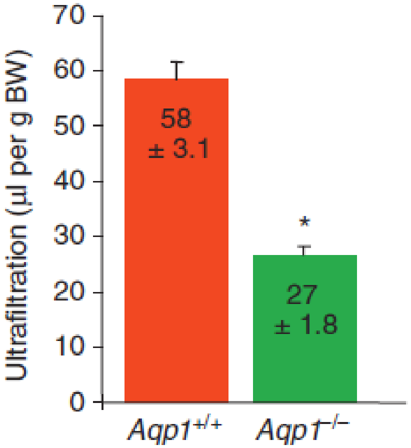
Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis

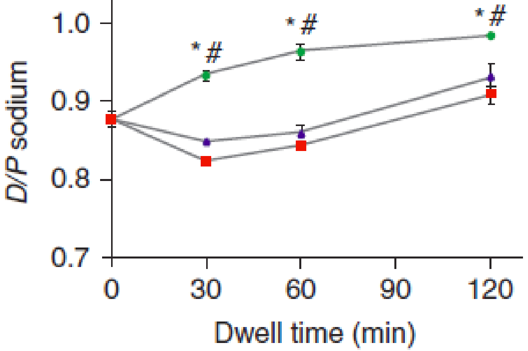
J Ni[1], J-M Verbavatz[2], A Rippe[3], I Boisdé[2], P Moulin[1], B Rippe[3], AS Verkman[4] and O Devuyst[1]

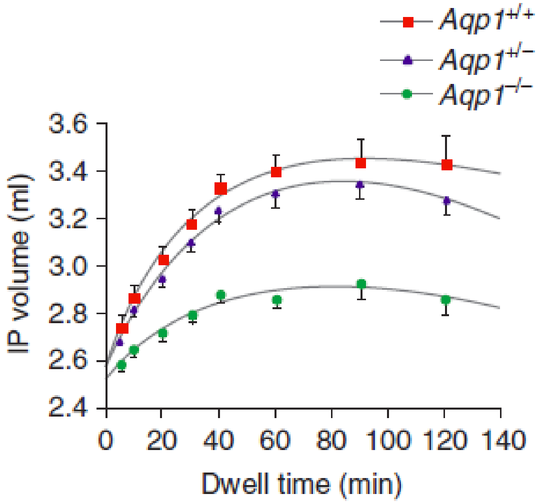






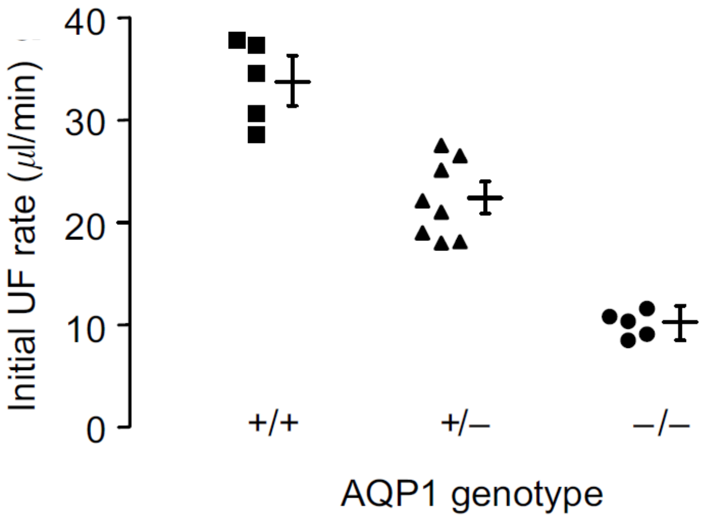






Ni J et al. *Kidney Int* 2006; 69: 1518-25

Peritoneal Dialysis in *Aqp1* Knockout Mice



AQP1 dose-effect: Heterozygous mice – intermediate phenotype

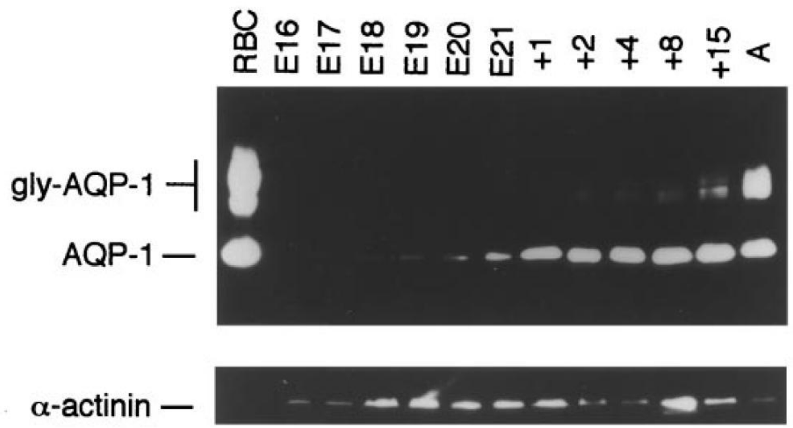
Ni J et al. *Kidney Int* 2006; 69: 1518-25

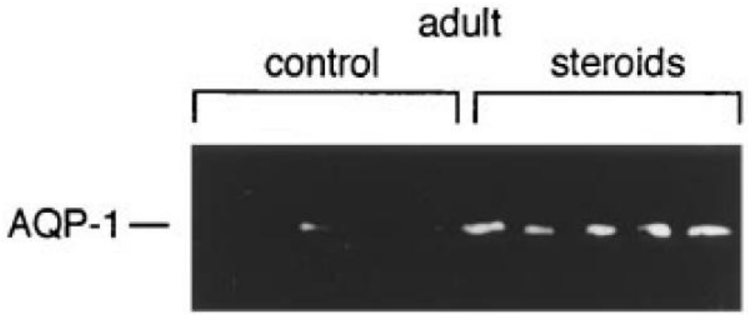
Aquaporin-1 Water Channel Protein in Lung

Ontogeny, Steroid-Induced Expression, and Distribution in Rat

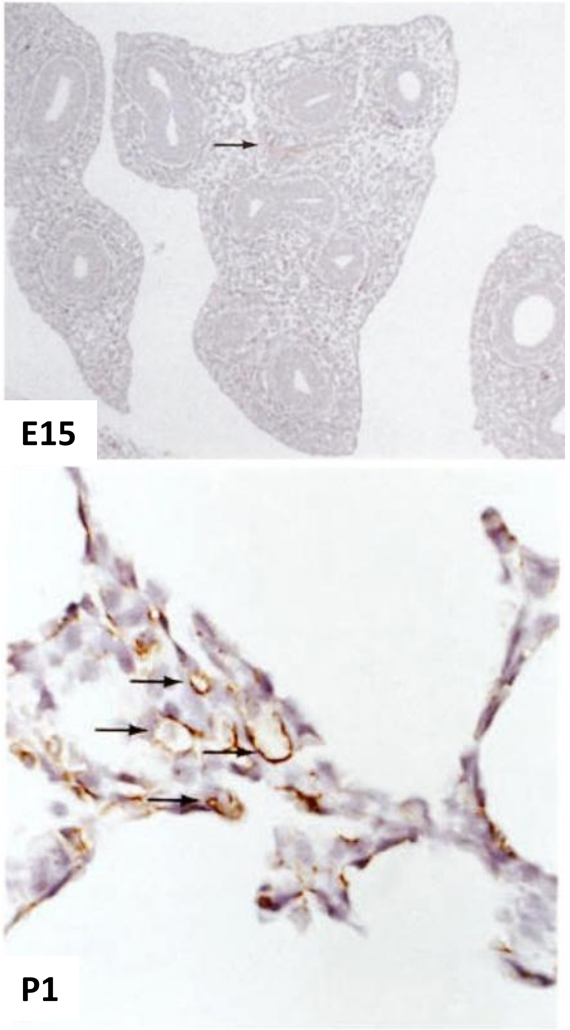
Landon S. King,*‡ Søren Nielsen,§ and Peter Agre*‖

J Clin Invest 97, 1996

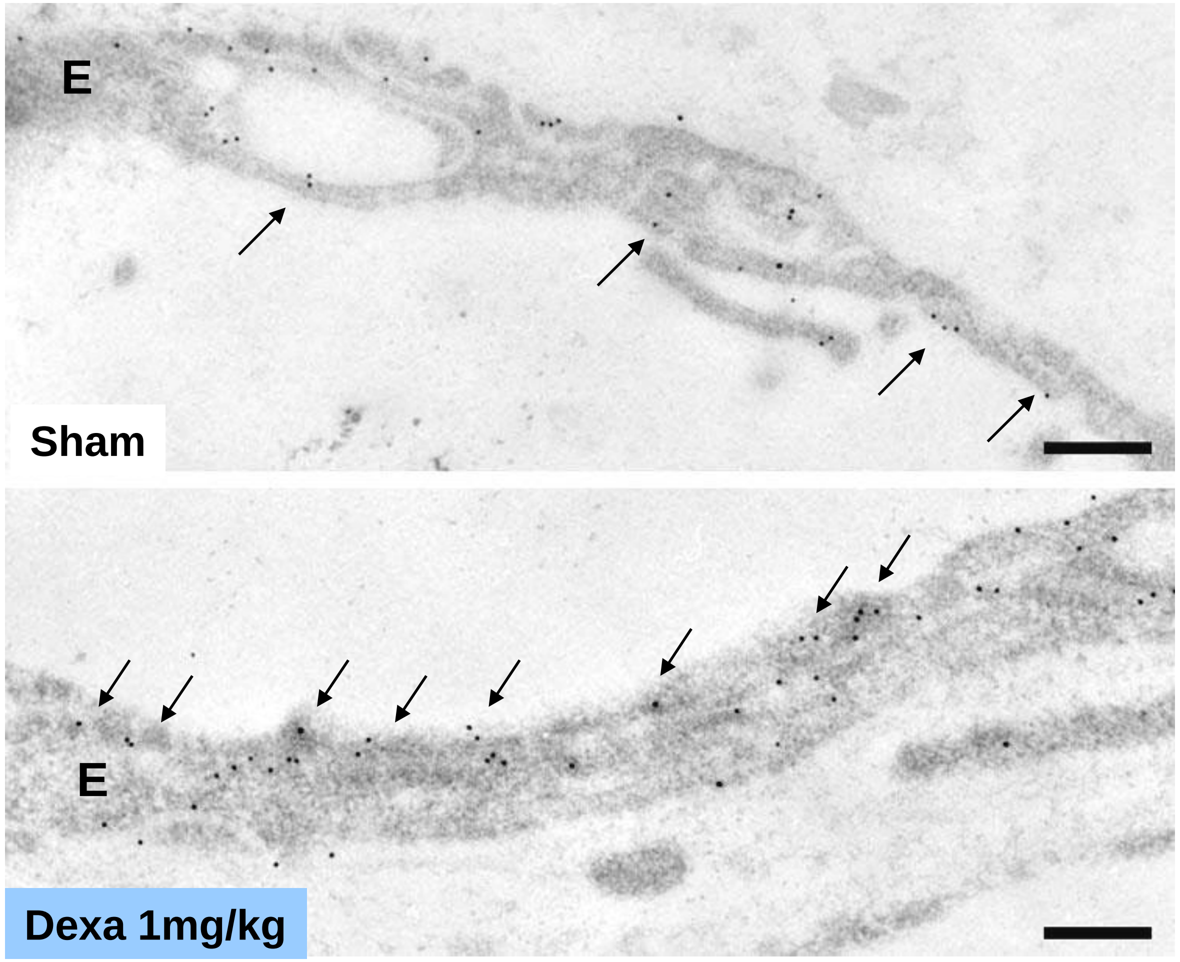


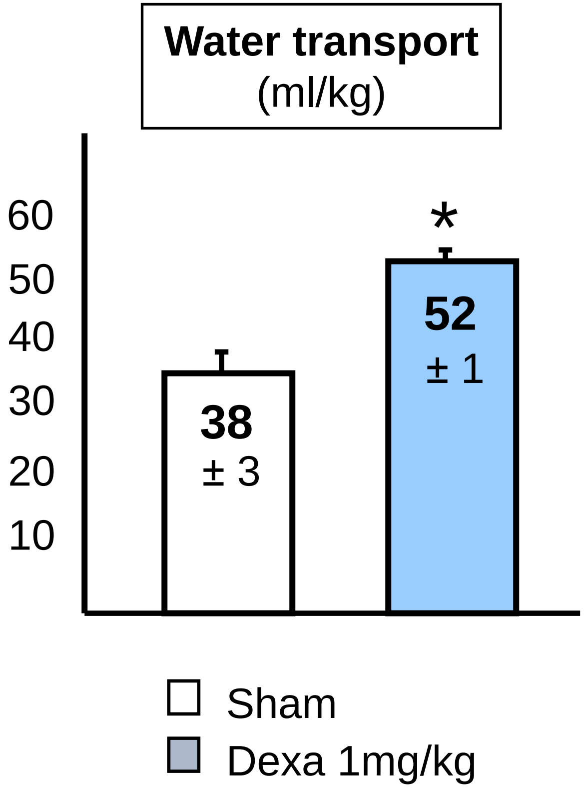


saline or betamethasone (0.35 mg/kg)



Glucocorticoids upregulate AQP1 in peritoneal capillaries





- Mediated by GRE: RU486
- No change in osmotic gradient

Stoenoiu et al. JASN 14: 555-65, 2003

Low Ultrafiltration→ Higher Mortality & Technique Failure

Higher Peritoneal Transport Status Is Associated with Higher Mortality and Technique Failure in the Australian and New Zealand Peritoneal Dialysis Patient Populations

Markus Rumpsfeld,*† Stephen P. McDonald,* and David W. Johnson*‡

**Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia; †Department of Renal Medicine, University of North Norway, Tromso, Norway; and ‡Department of Renal Medicine, University of Queensland at Princess Alexandra Hospital, Brisbane, Australia*

J Am Soc Nephrol 17: 271–278, 2006.

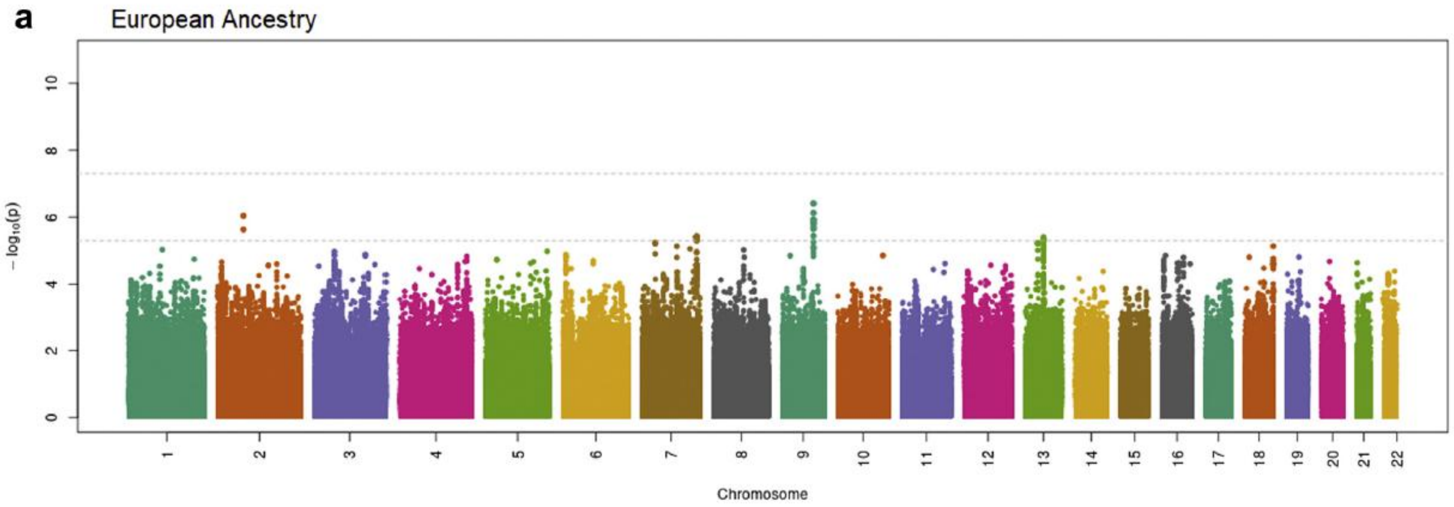
Meta-Analysis: Peritoneal Membrane Transport, Mortality, and Technique Failure in Peritoneal Dialysis

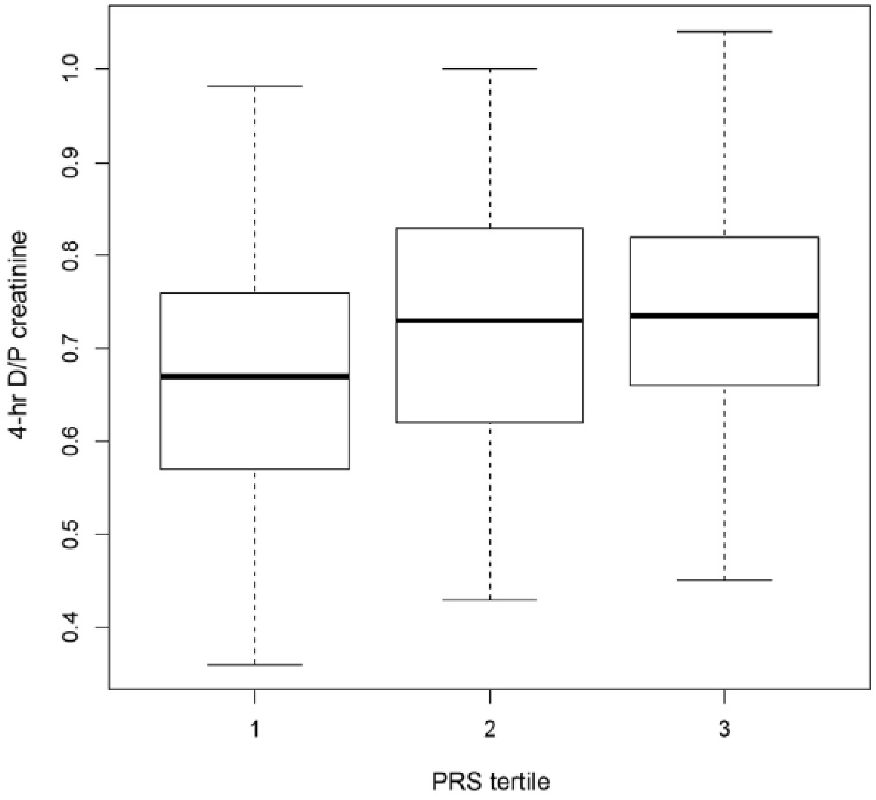
K. Scott Brimble,*† Michelle Walker,* Peter J. Margetts,*† Kiran K. Kundhal,‡ and Christian G. Rabbat*†

**Department of Medicine, McMaster University, and †Division of Nephrology, St. Josephs Healthcare, Hamilton, Ontario, and ‡Department of Nephrology, University of Toronto, Toronto, Ontario, Canada*

J Am Soc Nephrol 17: 2591–2598, 2006.

A genome-wide association study suggests correlations of common genetic variants with peritoneal solute transfer rates in patients with kidney failure receiving peritoneal dialysis





- In 2212 participants of European ancestry, no signal reached genome-wide significance but 23 single nucleotide variants at four loci demonstrated suggestive associations with PSTR. Meta-analysis in 2850 participants revealed *five single-nucleotide variants at four loci with suggestive correlations with PSTR*.
- The estimated heritability of PSTR was 19%, and a polygenic risk score was significantly associated with PSTR.

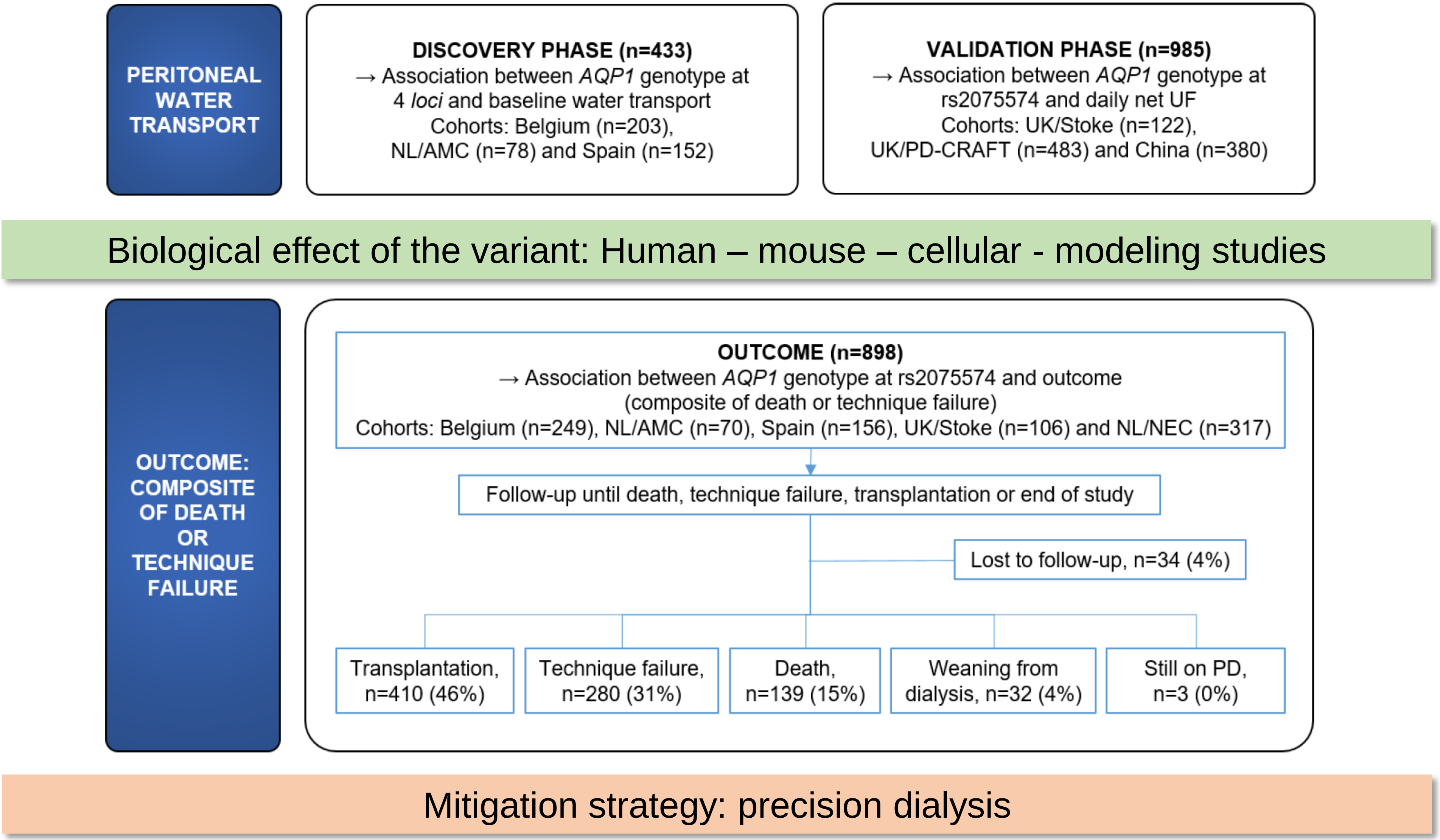
Kidney International (2021) **100,** 1101–1111

AQP1 Promoter Variant, Water Transport, and Outcomes in Peritoneal Dialysis

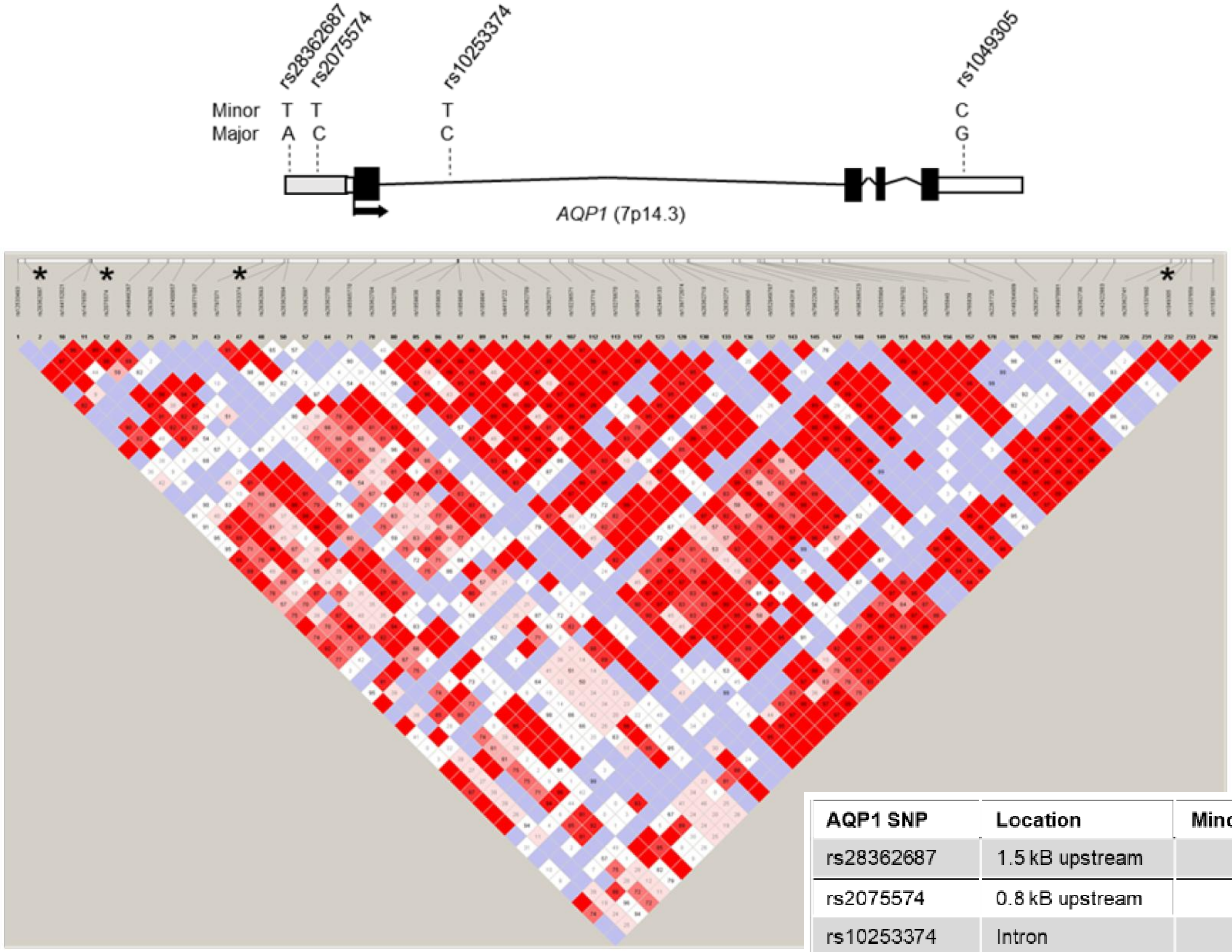
We gathered clinical and genetic information from 1851 patients in seven cohorts to determine whether variants in *AQP1* were associated with ultrafiltration and outcomes in peritoneal dialysis. Studies in cells, mouse models, and samples obtained from humans were performed to substantiate the functional relevance of the variants and to develop strategies that may ultimately mitigate the deleterious effects of *AQP1* variation in patients treated with peritoneal dialysis.

Morelle et al. N Engl J Med 385: 1570-80, 2021

AQP1 Genotype and Peritoneal Dialysis: Flowchart of the study



Single Nucleotide Polymorphisms and Linkage Disequilibrium Map in *AQP1*



AQP1 SNP	Location	Minor allele	MAF	Transcript change
rs28362687	1.5 kB upstream	T	0.13	c.-1576A>T
rs2075574	0.8 kB upstream	T	0.37	c.-781C>T
rs10253374	Intron	T	0.46	c.384+1141C>T
rs1049305	3 prime UTR	G	0.46	c.*578G>C

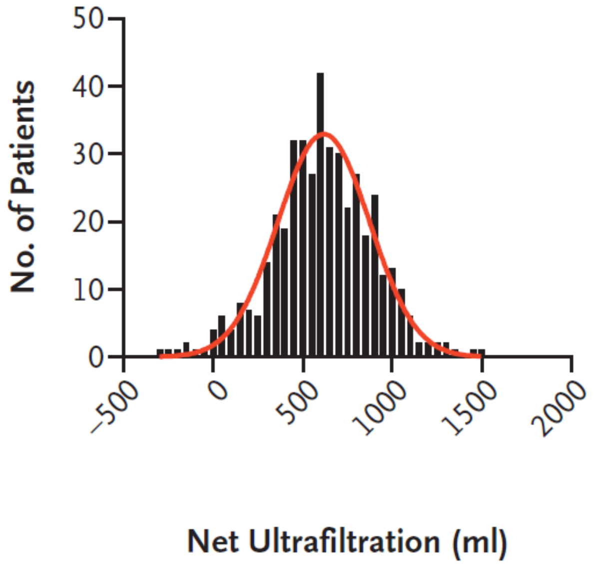
7 Cohorts: BEL – NL – SP – UK - China

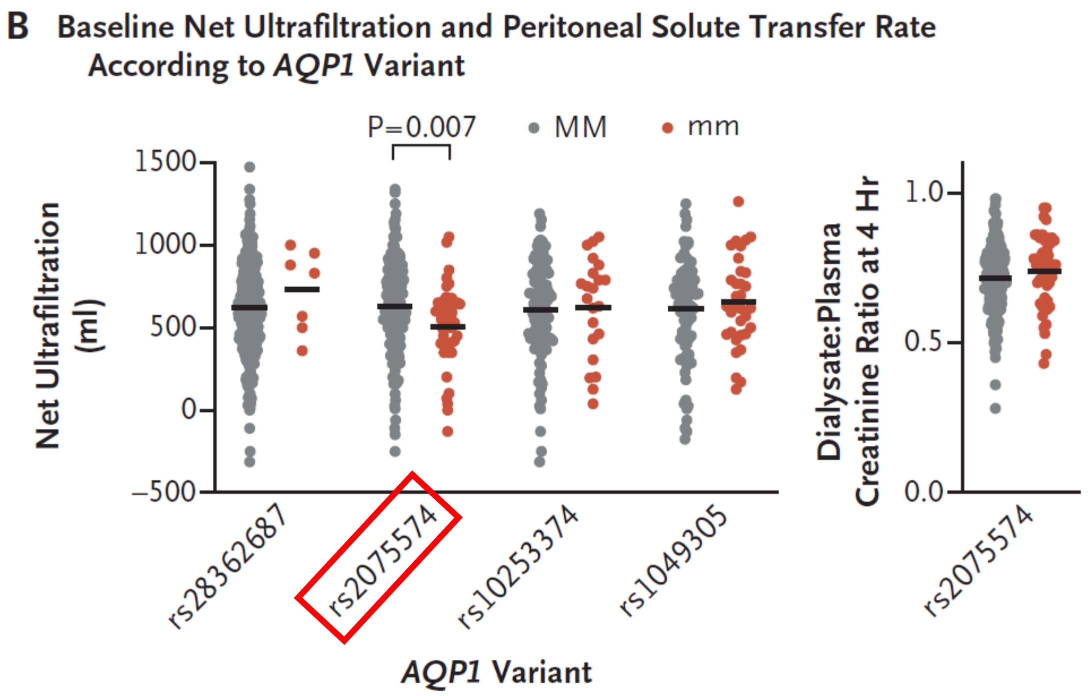
Table 1. Baseline Characteristics of the Patients According to Study Cohort.*

Characteristic	Overall (N=1851)	Belgium (N=277)	Netherlands, AMC (N=81)	Spain (N=156)	Netherlands, NECOSAD (N=344)	United Kingdom, Stoke-on-Trent (N=130)	United Kingdom, PD-CRAFT (N=483)	China (N=380)
Age at start of peritoneal dialysis — yr	54±16	54±19	55±15	53±14	53±14	47±16	58±16	52±14
Female sex — no./total no. (%)	695/1851 (38)	105/277 (38)	42/81 (52)	51/156 (33)	111/344 (32)	64/130 (49)	158/480 (33)	164/380 (43)
Body-mass index†	24.5±4.9	24.0±4.2	24.7±4.2	26.7±5.3	25.0±3.8	25.8±4.5	24.8±6.5	22.9±3.4
Race — no./total no. (%)‡								
European	1372/1833 (75)	258/277 (93)	80/81 (99)	148/153 (97)	344/344 (100)	120/129 (93)	422/469 (90)	0/380
African	22/1833 (1)	7/277 (3)	1/81 (1)	0/153	0/344	3/129 (2)	11/469 (2)	0/380
Asian	421/1833 (23)	12/277 (4)	0/81	2/153 (1)	0/344	4/129 (3)	23/469 (5)	380/380 (100)
Other	18/1833 (1)	0/277	0/81	3/153 (2)	0/344	2/129 (2)	13/469 (3)	0/380
Cardiovascular disease — no./total no. (%)	276/1310 (21)	76/260 (29)	26/81 (32)	28/155 (18)	85/316 (27)	20/119 (17)	—	41/380 (11)
Diabetes — no./total no. (%)	426/1780 (24)	72/276 (26)	22/81 (27)	32/156 (21)	64/317 (20)	23/119 (19)	127/452 (28)	86/380 (23)
Daily urine volume — ml	948±771	879±715	—	—	1150±816	1134±731	1182±763	585±631
Peritoneal membrane function								
Dialysate:plasma creatinine ratio at 4 hr	0.68±0.13	0.73±0.12	0.75±0.13	0.70±0.10	0.72±0.12	0.64±0.14	0.69±0.14	0.62±0.12
Net ultrafiltration during baseline 3.86% glucose–based PET — ml	611±280	623±309	563±292	621±228	—	—	—	—
Daily net ultrafiltration — ml	488±633	—	—	—	—	210±788	627±635	401±521
AQP1 genotype at rs2075574 — no. (%)								
CC	758 (41)	129 (47)	37 (46)	60 (38)	147 (43)	46 (35)	203 (42)	136 (36)
CT	842 (45)	119 (43)	36 (44)	76 (49)	148 (43)	64 (49)	216 (45)	183 (48)
TT	251 (14)	29 (10)	8 (10)	20 (13)	49 (14)	20 (15)	64 (13)	61 (16)

Morelle et al. N Engl J Med 385: 1570-80, 2021

Discovery Phase in 433 patients





	Univariate			Multivariate		
	Coeff.	95% CI	*P*	Coeff.	95% CI	P
Diabetes	-76.22	-137.54, -14.91	0.02	-70.14	-127.21, -13.06	0.02
D/P creatinine	-943.16	-1159.73, -726.59	<0.001	-910.74	-1124.74, -696.74	<0.001
AQP1 genotype at rs2075574						
CC	(ref.)	-	-	(ref.)	-	-
CT	-0.97	-56.83, 54.90	0.97	-1.64	-53.31-50.04	0.95
TT	-120.03	-207.15, -32.91	0.007	-108.41	-188.66, -28.17	0.008

Morelle et al. N Engl J Med 385: 1570-80, 2021

Validation in 985 patients (UK + China)

Effect of *AQP1* variant: Discovery & Validation

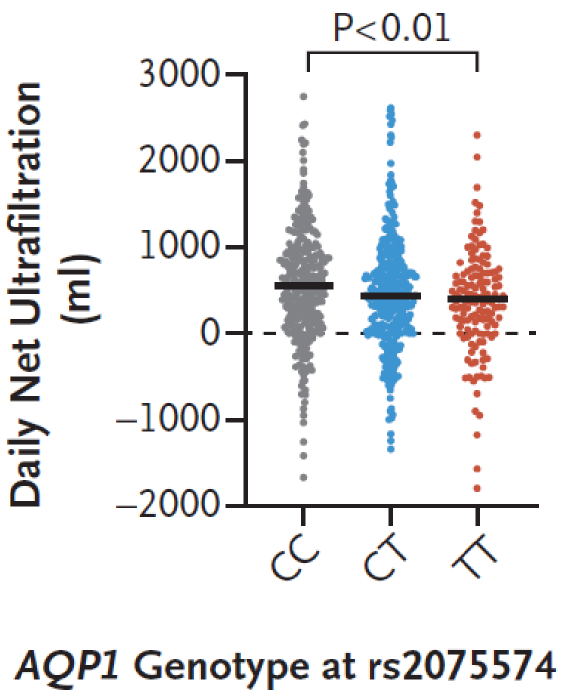


Table 2. Association of the *AQP1* Genotype at rs2075574 with Peritoneal Water Transport and Outcomes in Patients Treated with Peritoneal Dialysis.*

Variable	Overall	CC	CT	TT	P Value†
Peritoneal water transport					
Discovery phase					
No. of patients	433	184	199	50	—
Net ultrafiltration during baseline 3.86% glucose–based PET — ml	611±280	626±283	625±282	506±237	0.02
Validation phase					
No. of patients	985	383	459	143	—
Daily net ultrafiltration — ml	488±633	563±641	463±629	368±603	0.003

Δ 120 mL

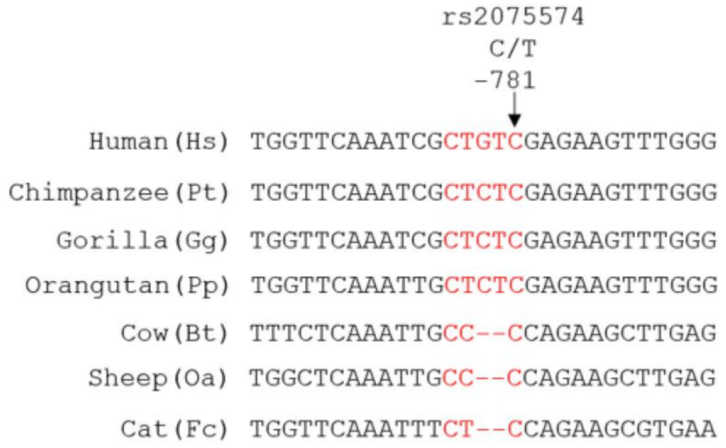
Δ 200 mL

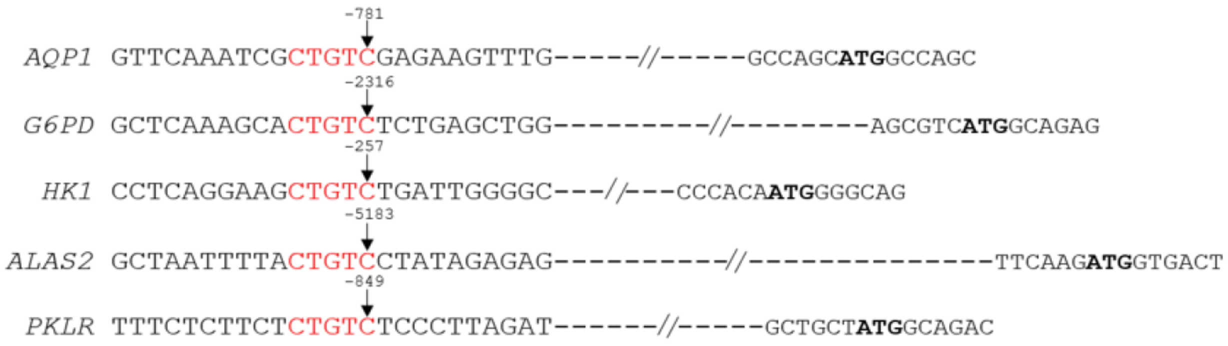
These data indicate an independent association between the *AQP1* genotype at rs2075574 and peritoneal ultrafiltration in a racially diverse cohort of patients treated with PD.

Morelle et al. N Engl J Med 385: 1570-80, 2021

Characterization of the Promoter Sequence of *AQP1*

Conserved CTGTC – Erythroid-specific genes

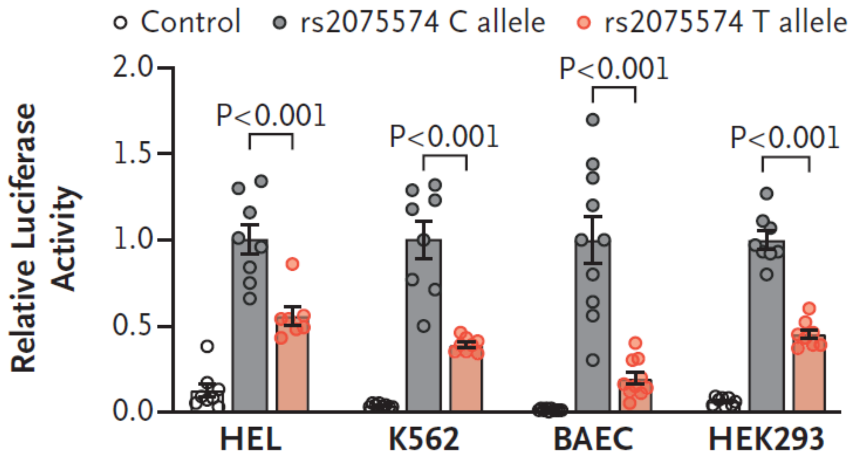




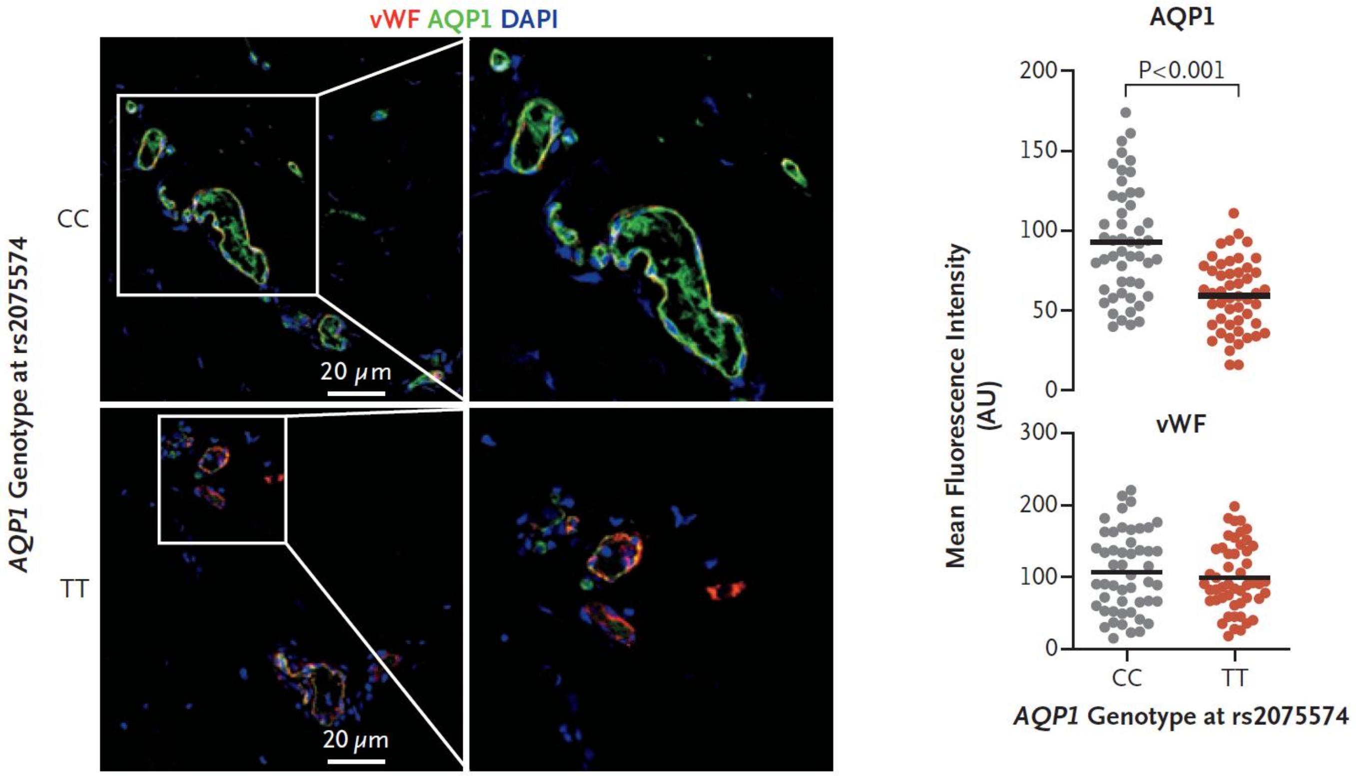
P value	SNP	SNP position	Assessed allele	Other allele	Z score	Gene	No. Cohorts	No. Samples	FDR	Bonferroni P
3.77E-19	rs2075574	30950744	T	C	8.9434	*AQP1*	20	14275	0	4.81E-11
5.32E-06	rs10253374	30953049	T	C	4.5519	*AQP1*	27	18746	0	1
0.00155	rs1049305	30963822	C	G	3.1653	*AQP1*	32	30233	0.9	1

Specific rs2075574: cis-eQTL in WBC

The rs2075574 variant is associated with decreased expression of AQP1

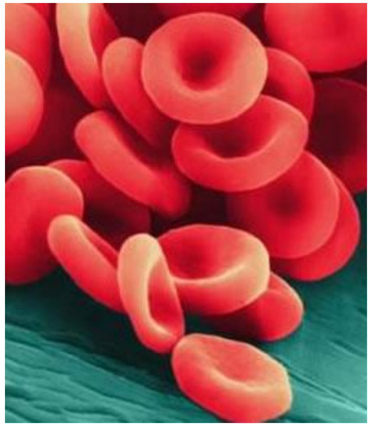


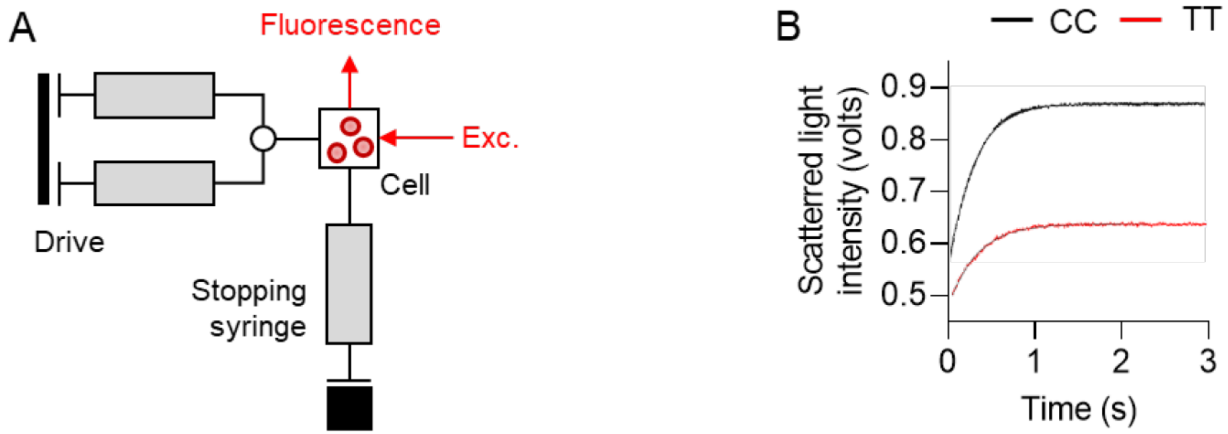
Promoter activity *in vitro*

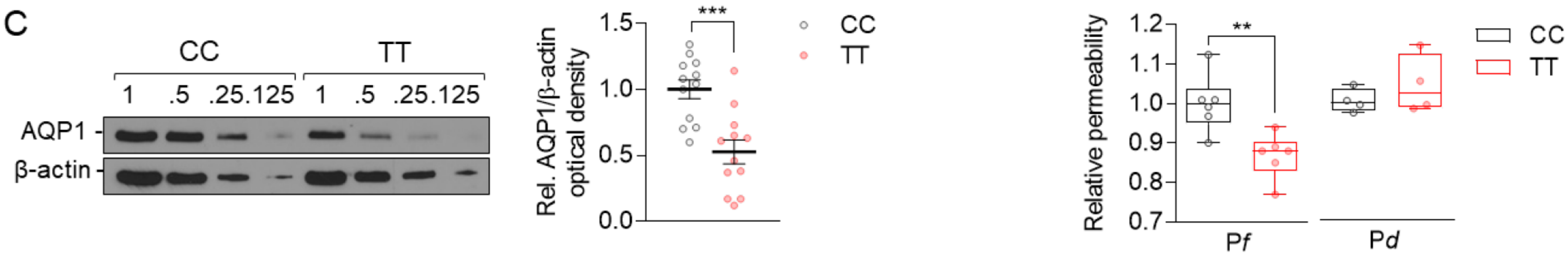


Analysis of human peritoneal biopsies

Stopped-Flow Light Scattering Experiments and Membrane Permeability in Human Red Blood Cells Stratified for the *AQP1* Risk Variant







INSTITUT NATIONAL DE LA TRANSFUSION SANGUINE

Morelle et al. N Engl J Med 385: 1570-80, 2021

AQP1 Promoter Risk Variant and Outcomes in Peritoneal Dialysis

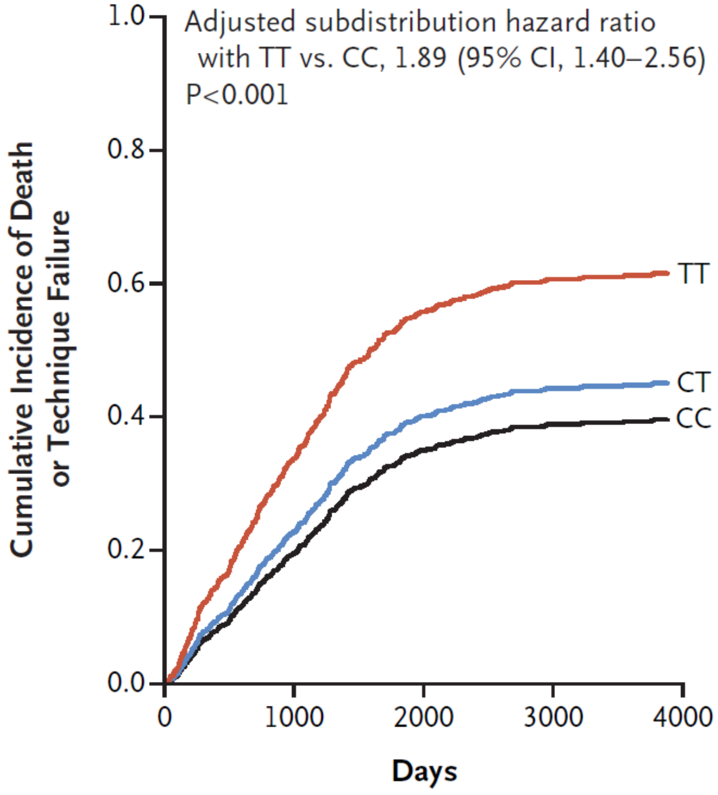
Table 3. **Hazard Ratios for Time to the Composite of Death or Technique Failure According to the *AQP1* Genotype at rs2075574.**

Analysis and Genotype	Cox Regression Model		Fine and Gray Regression Model for Competing Risks	
	Hazard Ratio vs. CC (95% CI)	P Value vs. CC	Subdistribution Hazard Ratio vs. CC (95% CI)	P Value vs. CC
Unadjusted analysis (N=898)				
CC	1.00	—	1.00	—
CT	1.14 (0.93–1.41)	0.21	1.18 (0.96–1.46)	0.11
TT	1.51 (1.13–2.02)	0.005	1.67 (1.24–2.25)	0.001
Adjusted analysis (N=767)*				
CC	1.00	—	1.00	—
CT	1.19 (0.95–1.50)	0.13	1.19 (0.95–1.49)	0.13
TT	1.70 (1.24–2.33)	0.001	1.89 (1.40–2.56)	<0.001

TT carriers (low AQP1) have a higher risk of composite death & technical failure

Analysis in 898 patients (91% data recovery)

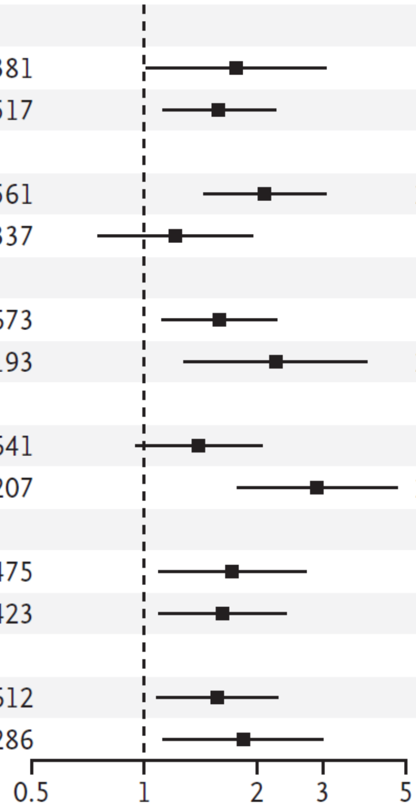
AQP1 Promoter Risk Variant and Outcomes in Peritoneal Dialysis



No. at Risk

TT	114	42	5	4	0
CT	400	168	32	3	0
CC	384	160	25	6	0

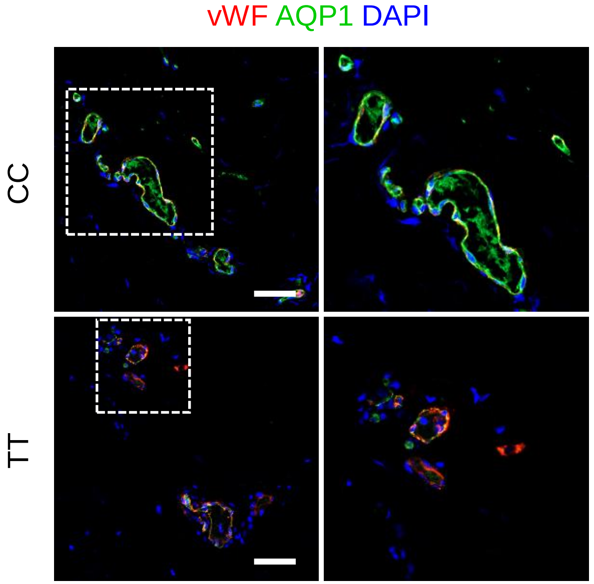
Subgroup	No. of Patients	Subdistribution Hazard Ratio for Death or Technique Failure with TT vs. CC (95% CI)
Age		
<50 yr	381	1.75 (1.01–3.06)
≥50 yr	517	1.58 (1.12–2.25)
Sex		
Male	561	2.10 (1.44–3.07)
Female	337	1.21 (0.75–1.95)
Diabetes		
Absent	673	1.59 (1.11–2.27)
Present	193	2.25 (1.28–3.95)
Cardiovascular disease		
Absent	641	1.40 (0.95–2.07)
Present	207	2.90 (1.77–4.75)
Body-mass index		
<25	475	1.72 (1.09–2.71)
≥25	423	1.62 (1.09–2.40)
Dialysate:plasma creatinine ratio at 4 hr		
<0.80	612	1.57 (1.08–2.28)
≥0.80	286	1.84 (1.12–3.01)

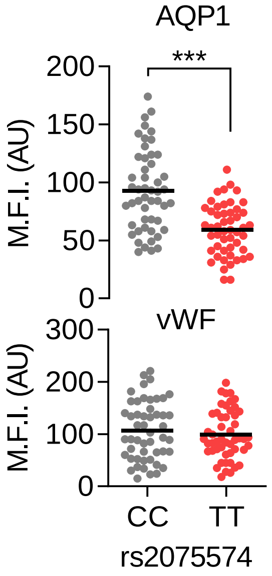


Morelle et al. N Engl J Med 385: 1570-80, 2021

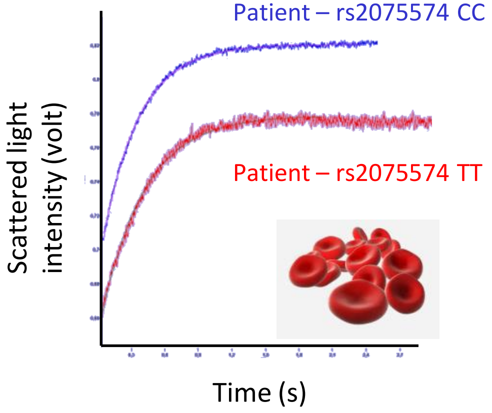
AQP1 Promoter Variant:
Influences Expression, Water Transport and Outcome during PD

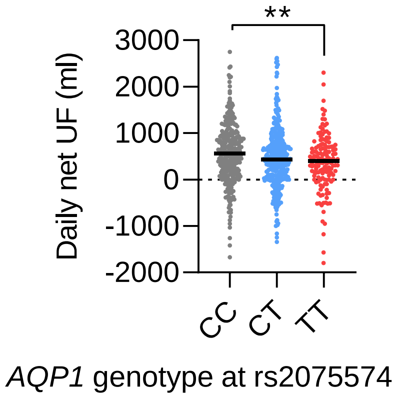
The TT variant of rs2075574 - decreased *AQP1* gene expression in peritoneal microvasculature





Water transport in human erythrocytes and across the peritoneal membrane



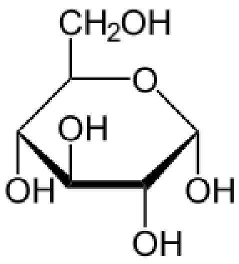


Outcome:
Patient & technique survival

Peritoneal Dialysis: can we mitigate the effect of the *AQP1* variant ?

Crystalloid *versus* Colloid Osmotic Agents

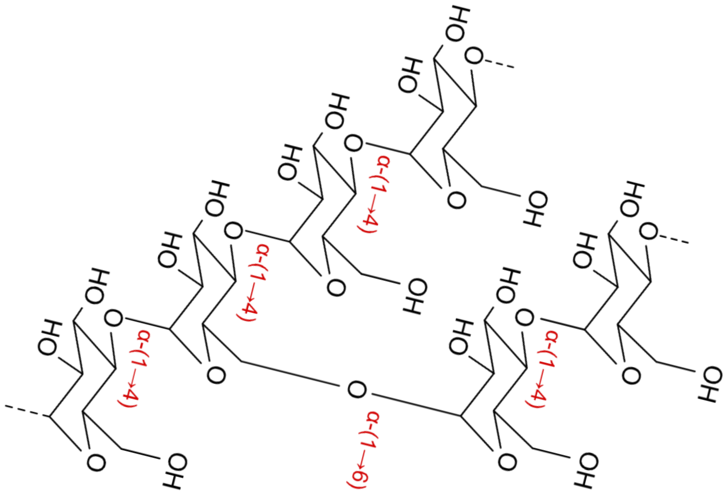
Crystalloid osmotic agents



- Prone to crystallization
- Small molecular size
- Diffuse readily through membranes
- Hypertonicity required for osmosis
- AQP1-dependent water transport

Glucose - aminoacids

Colloid osmotic agents (*Κoλλα*, glue)



- Do not crystallize
- Large molecular size - polymers
- Poor penetration across membranes
- Isotonic osmosis
- AQP1-independent water transport

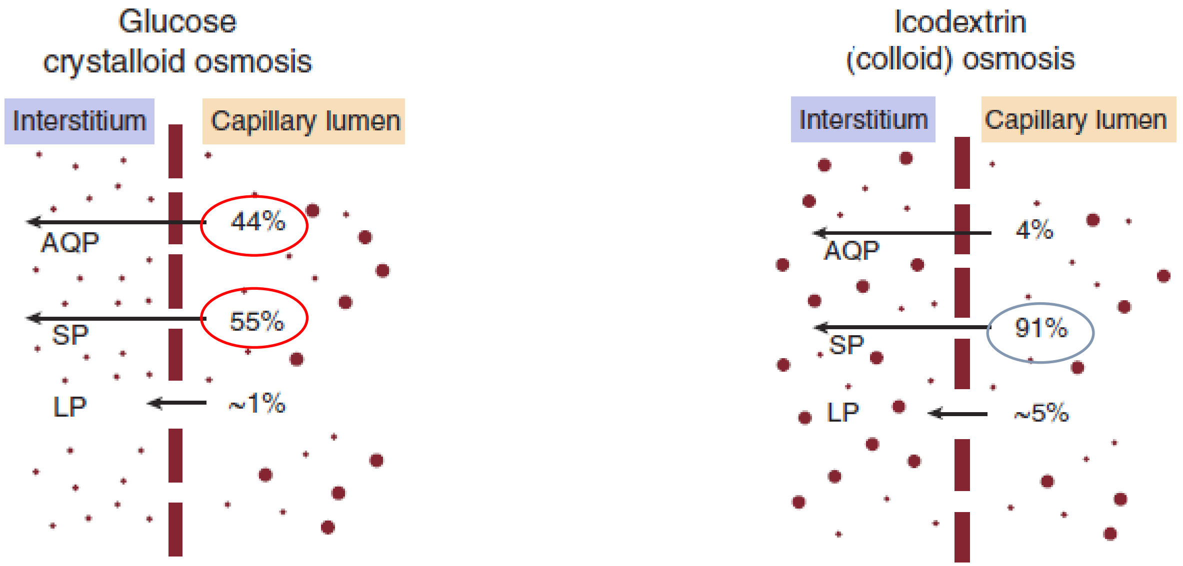
Large fractions of icodextrin

The *AQP1* Promoter Variant: Choice of Dialysate ?

Genetic information
AQP1 variant – low expression

→

Prescription:
Choice of dialysate



Devuyst & Rippe, *Kidney Int* 85, 2014

AJKD

Original Investigation

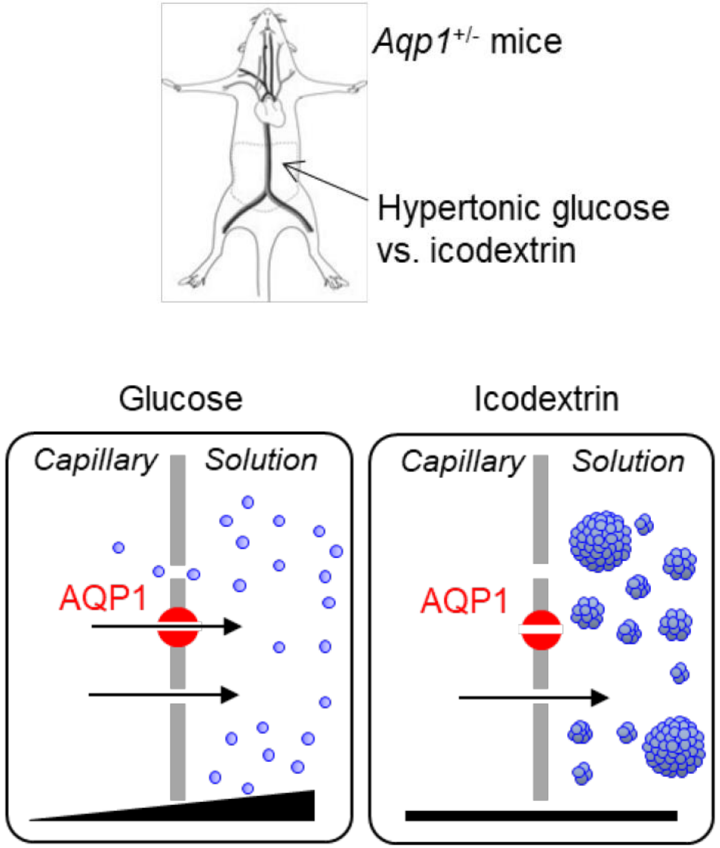
Icodextrin Versus Glucose Solutions for the Once-Daily Long Dwell in Peritoneal Dialysis: An Enriched Systematic Review and Meta-analysis of Randomized Controlled Trials

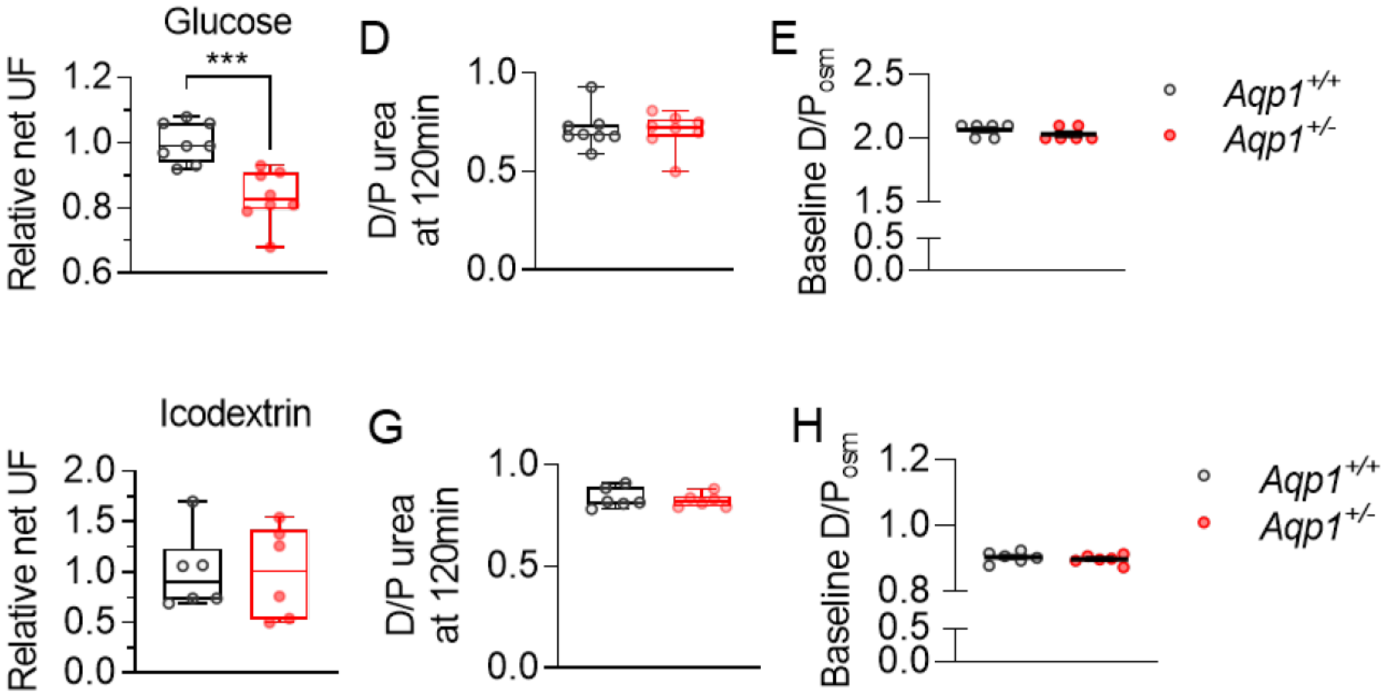
Käthe Goossen, Monika Becker, Mark R. Marshall, Stefanie Bühn, Jessica Breuing, Catherine A. Firanek, Simone Hess, Hisanori Nariai, James A. Sloand, Qiang Yao, Tae Ik Chang, JinBor Chen, Ramón Paniagua, Yuji Takatori, Jun Wada, and Dawid Pieper

AJKD Vol 75 | Iss 6 | June 2020

Conclusions: Icodextrin for once-daily long-dwell PD has clinical benefit for some patients, including those not meeting ultrafiltration targets and at risk for fluid overload.

Heterozygous Deletion of *Aqp1* Alters Peritoneal Glucose- but not Icodextrin-Driven Water Transport in a Mouse Model of Peritoneal Dialysis





Morelle et al. N Engl J Med 385: 1570-80, 2021

Regression Analyses of Net Ultrafiltration Achieved with 3.86% Glucose or 7.5% Icodextrin-Based Dialysis Solution

	Glucose		Icodextrin	
	Coeff.	**95% CI**	**Coeff.**	**95% CI**
Parametric analyses				
rs2075574				
CC	0.0 (ref.)	-	0.0 (ref.)	-
CT	36.5	-65.8, 138.8	-3.6	-70.9, 63.8
TT	-200.1	-361.7, -38.6	21.9	-69.2, 112.9

n=144 patients using glucose at baseline and later icodextrin.

Patients with the TT genotype have a significantly lower net UF when using glucose-based osmosis.

In contrast, no association between the rs2075574 variant and osmosis induced by icodextrin.

→ The use of a colloid osmotic agent mitigated the water-transport defect associated with the *AQP1* risk variant

Morelle et al. N Engl J Med 385: 1570-80, 2021

AQP1 Promoter Variant, Water Transport, and Outcomes in Peritoneal Dialysis

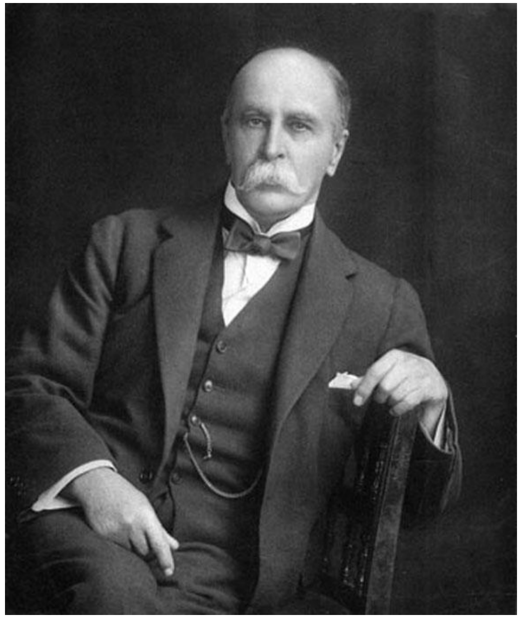
- The *AQP1* promoter variant rs2075574 influenced osmotic water transport and ultrafiltration and was independently associated with an increased risk of death or technique failure in patients treated with PD.

- The higher risk of the composite outcome in patients with the TT genotype was driven by a significantly higher risk of death from any cause with the TT genotype.

- The rs2075574 variant influenced *AQP1* promoter activity, the expression of aquaporin-1 in peritoneal microvessels, and osmotic water transport.

- The use of colloid osmotic agents may mitigate the risk associated with the rs2075574 variant.

→ These results substantiate the influence of genetic factors on the efficiency of peritoneal dialysis and provide a perspective for precision medicine in dialysis treatment.



“The good physician treats the disease; the great physician treats the patient who has the disease”.

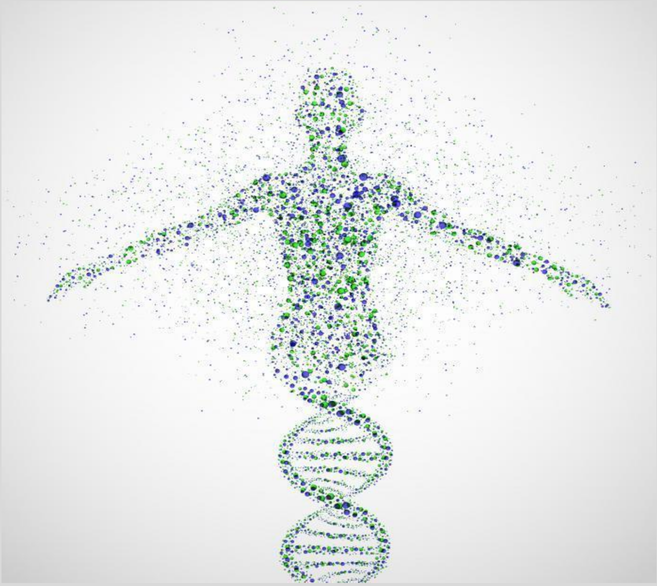
Sir William Osler, 1903

2021: Precision (stratified) medicine in dialysis

* Using genetics as predictive tools to evaluate health risks

* Identifying patients with particular responses to treatments

* Define treatments that are effective for subgroups of patients



Acknowledgements

UCL Brussels - Nephrology
J. Ni, J. Morelle
S. Combet, N. Hautem, C. Marechal
Y. Cnops, H. Debaix, S. Druart
E. Goffin

S. Davies, M. Lambie, R. Selgas, RT. Krediet
P. Evenepoel, B. Bammens, Ph. Bovy
R. Mehrotra

University of Lund, Sweden
B. Rippe, A. Rippe, C. Oberg

University of Adelaïde, Australia
A. Yool, E. Campbell
E. Beckett, G. Booker

Max Planck Institute of Molecular Cell Biology, Dresden, Germany
JM. Verbavatz

INSERM & INTS - Paris
P. Ripoche

University of Nagasaki
T. Nishino

P. Agre, A. Verkman, W.B. Guggino

Université catholique de Louvain

University of Zurich UZH

Lund University

The University of Adelaide Australia

Baxter *Extramural Grant Program*

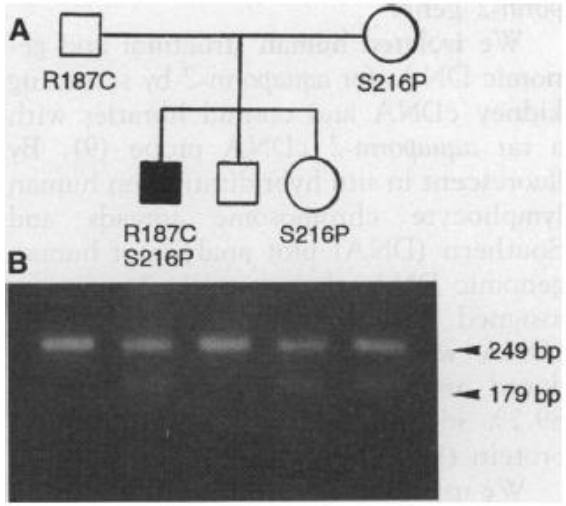
fnrs La liberté de chercher

European Commission | Horizon 2020 European Union funding for Research & Innovation

Kidney Control of Homeostasis
Swiss National Centre of Competence in Research

Requirement of Human Renal Water Channel Aquaporin-2 for Vasopressin-Dependent Concentration of Urine

Peter M. T. Deen, Marian A. J. Verdijk, Nine V. A. M. Knoers, Bé Wieringa, Leo A. H. Monnens, Carel H. van Os,* Bernard A. van Oost*

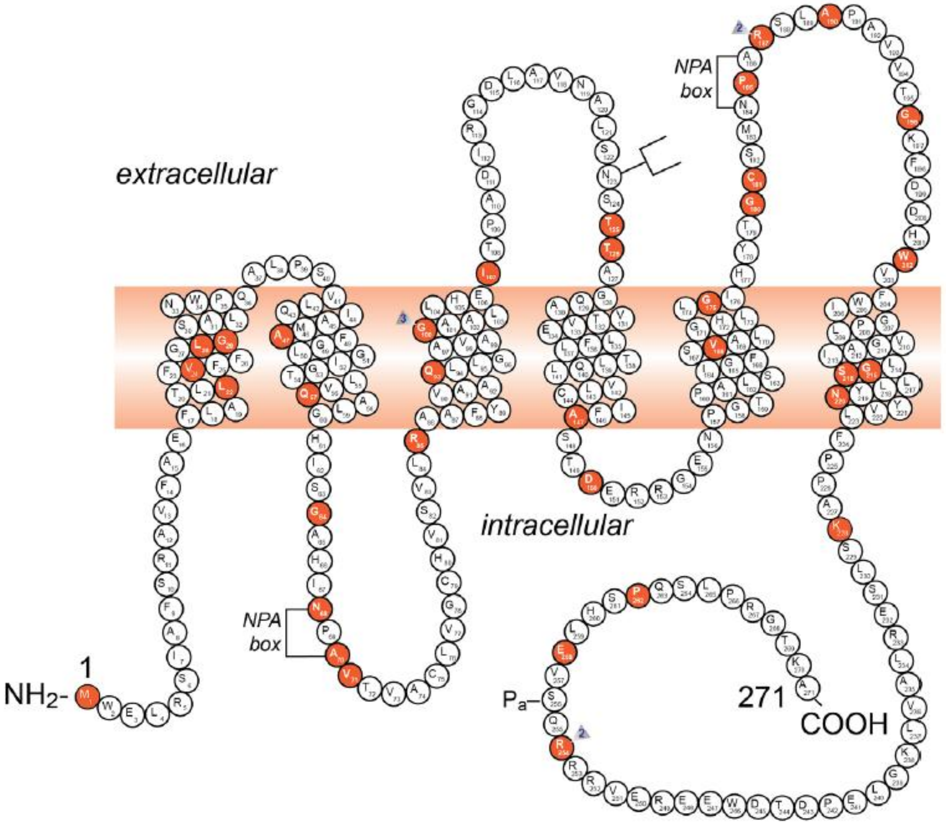


Injection	P_f(μm/s)*
5 ng of *aquaporin-2*	196 ± 26 (22)
Water control	20 ± 13 (16)
10 ng of R187C mutant	17 ± 11 (10)
10 ng of S216P mutant	18 ± 7 (11)
5 ng of *aquaporin-2* + 5 ng of R187C mutant	187 ± 38 (19)
5 ng of *aquaporin-2* + 5 ng of S216P mutant	192 ± 41 (18)

*Average ± SEM, with the number of assays in parentheses.

Compound heterozygote for two recessive mutations in AQP2

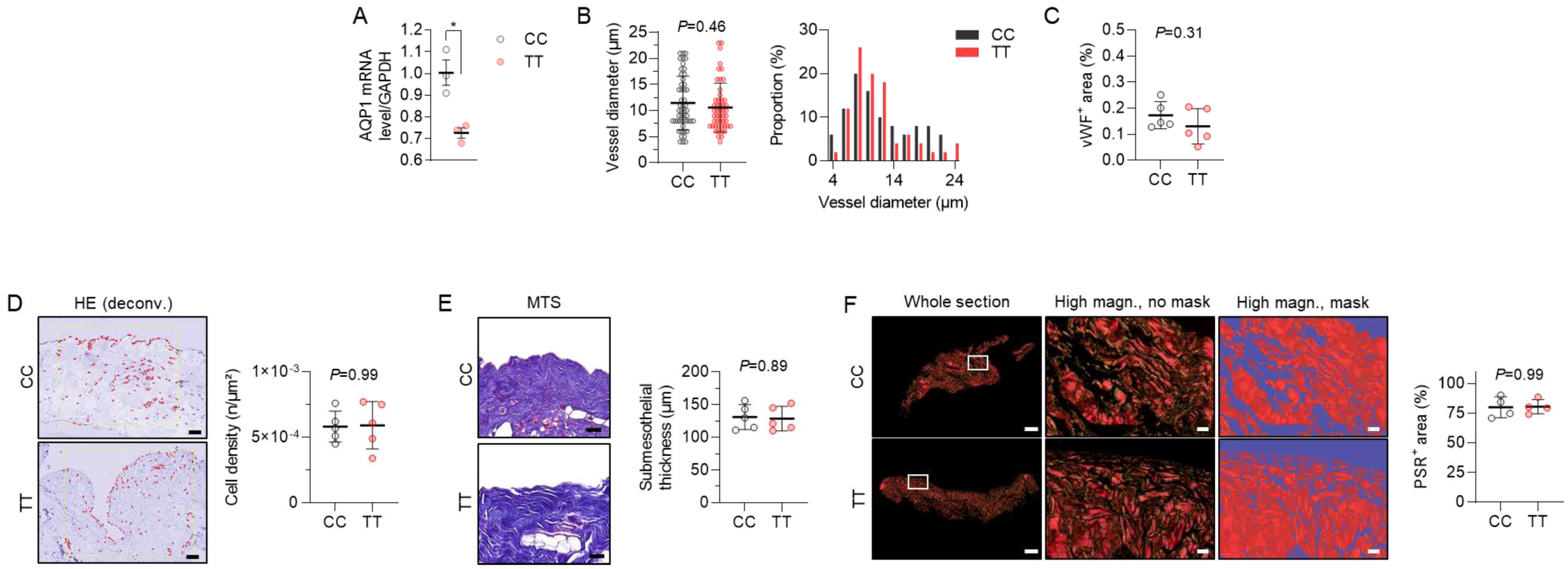
Mutations in AQP2 - NDI



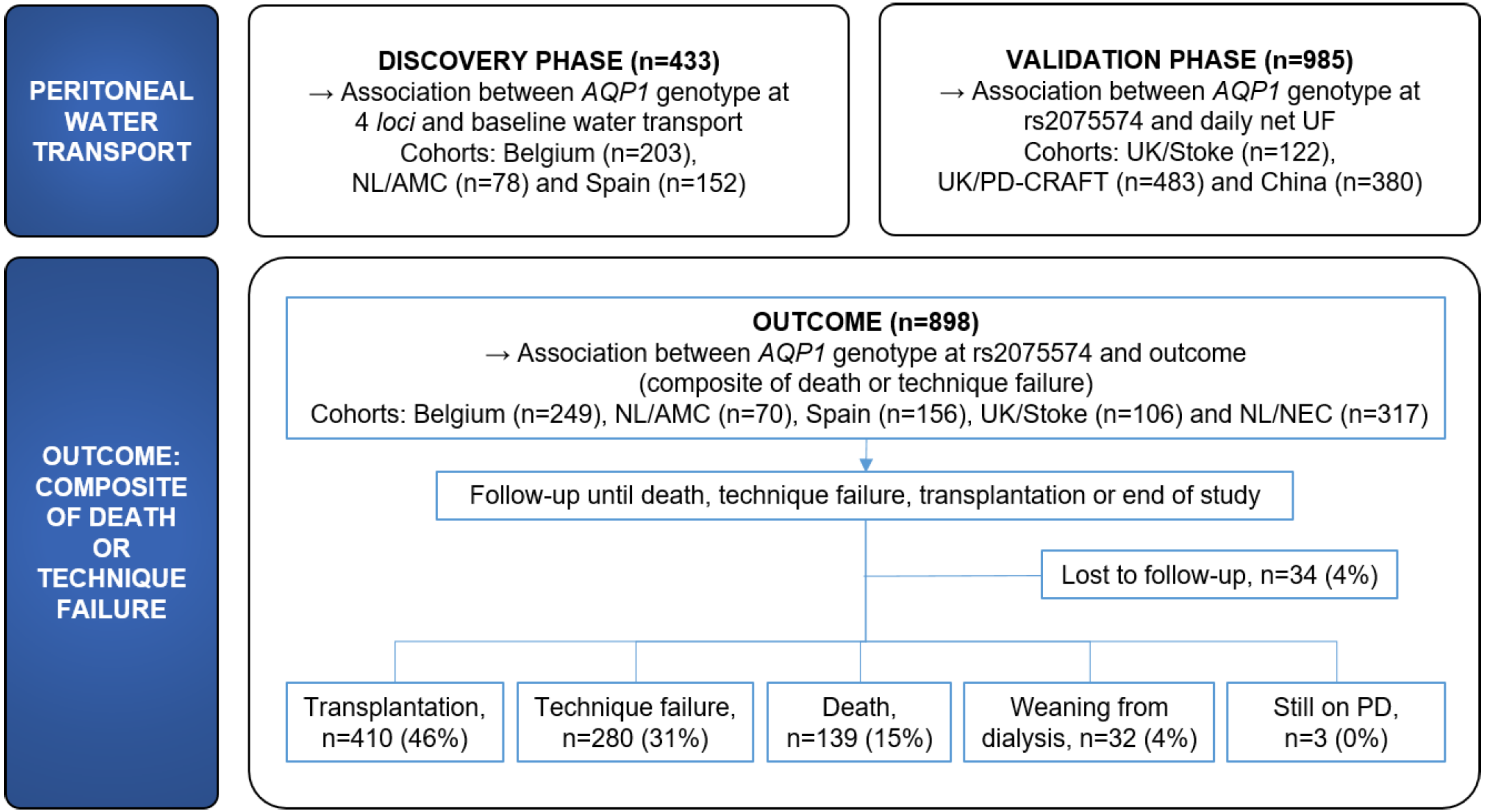
48 putative disease-causing AQP2 mutations

Bichet D. Eur J Endocrinol (2020) 183

Effects of *AQP1* Risk Variant on the Structure of the Human Peritoneal Membrane



4 phases to highlight: discovery – molecular counterpart – outcome – therapeutic strategy



Human – mouse – cellular - modeling studies