

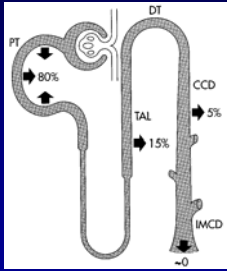


Clinical Case Studies of Genetically Altered Acid-Base Transport



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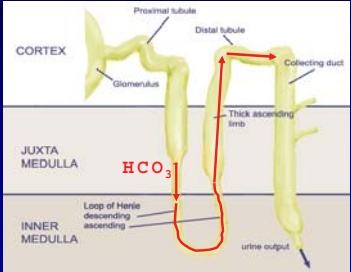
What happens when renal acid-base transport is abnormal?



PT 80%
TAL 15%
CCD 5%
IMCD -0%DT





Proximal Renal Tubular Acidosis (RTA) – Type II

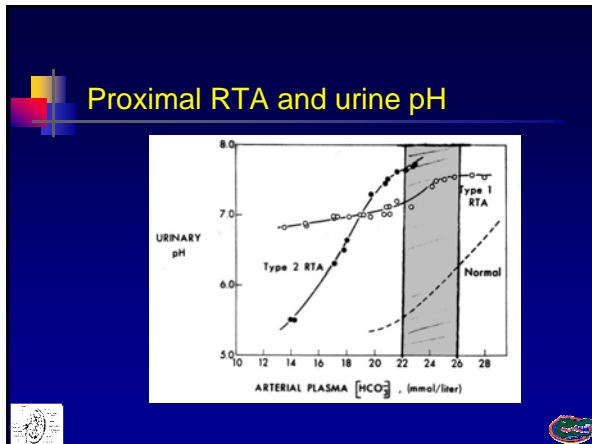


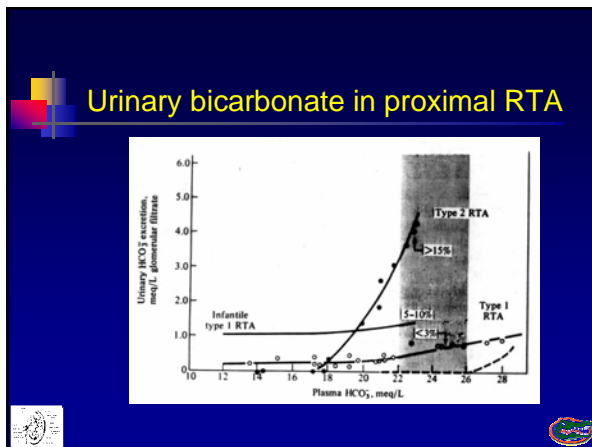
CORTEX
JUXTA MEDULLA
INNER MEDULLA

Proximal tubule
Distal tubule
Collecting duct
Thick ascending limb
Loop of Henle
descending
ascending
urine output

HCO_3^-



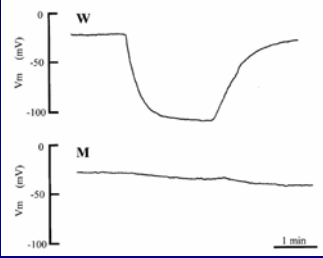




- ### Clinical characteristics of genetic proximal RTA
- Moderate metabolic acidosis
 - [HCO₃⁻] ~15 mmol/L
 - Hypokalemia
 - Short stature, variable
 - Phosphaturia, amino aciduria and glycosuria
 - Ocular abnormalities
 - Band keratopathy, glaucoma and cataracts

More on NBC-1 defects ...

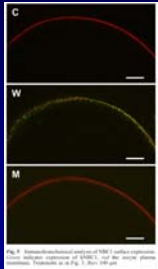
- Failure of expression



Inatomi J, et al, *Pflügers Arch* 448:438-44, 2004

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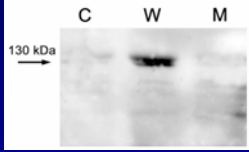
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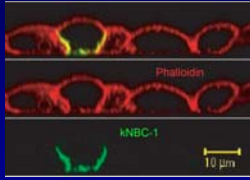
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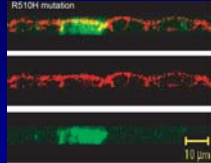
- Abnormal trafficking
- Must go to basolateral plasma membrane to contribute to bicarbonate reabsorption



Li HC, et al, *Am J Physiol Renal* 289: F61-71, 2005.

More on NBC-1 defects ...

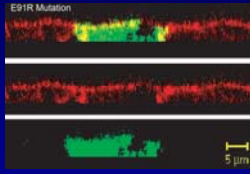
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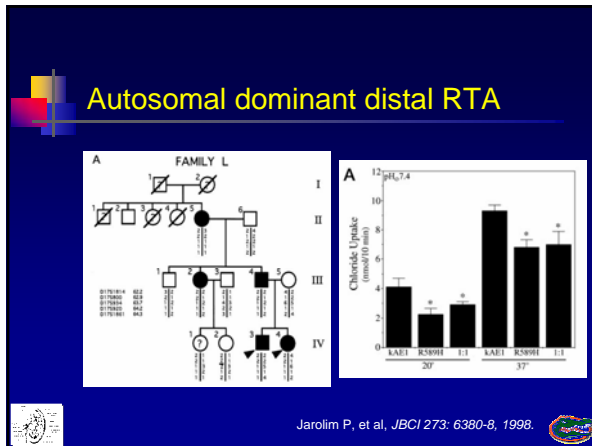
Clinical characteristics of distal RTA

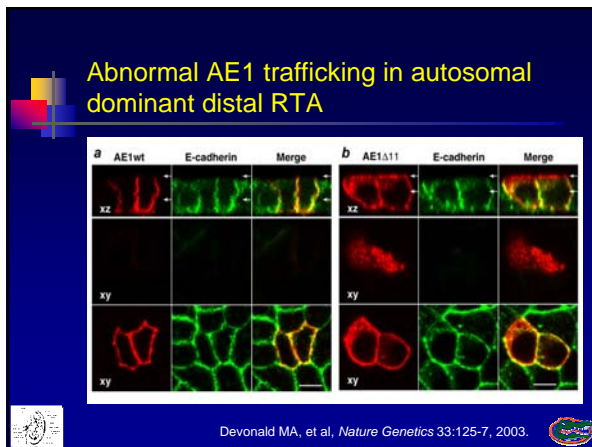
- Severe metabolic acidosis
- Hypokalemia
- Renal stone disease
 - Calcium-phosphate solubility in urine is pH dependent
 - Decreased at alkaline urine pH
- Growth retardation
 - Osteomalacia
 - Osteoporosis

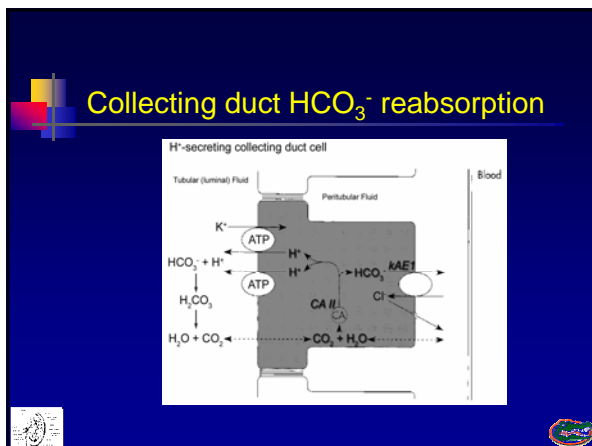
Lack of ability to acidify urine in distal (Type I) RTA

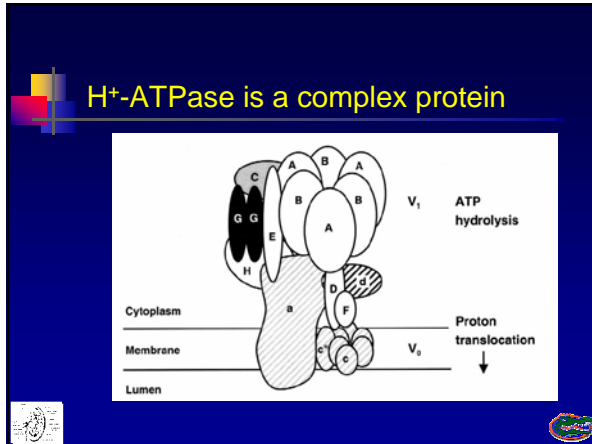
Arterial Plasma [HCO ₃ ⁻] (mmol/liter)	Normal Urinary pH	Type 2 RTA Urinary pH	Type 1 RTA Urinary pH
10	5.5	5.5	7.0
12	6.0	6.5	7.0
14	6.5	7.0	7.0
16	7.0	7.5	7.0
18	7.5	8.0	7.0
20	8.0	8.0	7.0
22	8.0	8.0	7.0
24	8.0	8.0	7.0
26	8.0	8.0	7.0
28	8.0	8.0	7.0

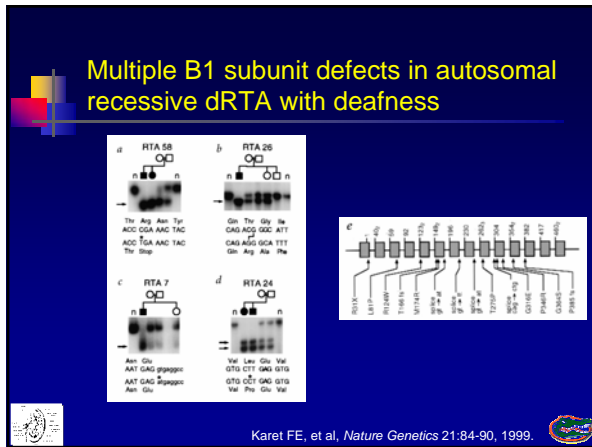
Collecting duct HCO₃⁻ reabsorption

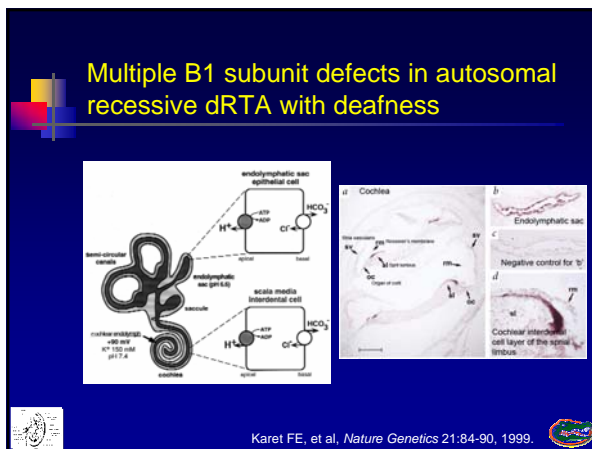












Autosomal recessive distal RTA with preserved hearing

- Gene localized to 7q33-34
- Encodes *ATP6N1B*
 - 840 aa novel kidney-specific isoform of ATP6N1A
 - 116 kDa non-catalytic accessor subunit

Smith AN, et al, *Nature Genetics* 26:71-5, 2000.

Summary

- Genetic experiments of nature have confirmed our models of renal acid-base transport
- Close observation of nature's "knock-out" experiments has led to new understandings

Autosomal recessive distal RTA with preserved hearing

Patient	Origin	Age at diagnosis	Age at audiology	Serum		Urine	Hypen-riolista	History of	ATP6N1B mutation				
				pH (lab)	HCO ₃ ⁻ (mEq/L)								
4-1	f	Turkey	6.5 y	3 wk	4.5 y	7.10	5.5	2.4	8.0	y	n	Q 753 X	
5-1	f	Turkey	10 y	1 y	9 y	7.12	11.0	3.1	7.0	y	n	G 803 R	
15-1*	f	Pakistan	22 y	1 wk	4y	7.25	12.0	2.7	7.6	y	y	intronic 17 donor splice GT →AT	
20-1	f	Turkey	16 y	3 mo	12 y	7.50	12.0	2.8	7.5	y	n	V55 F	
34-1	m	Turkey	4 y	8 mo	2.5 y	7.23	16.0	2.1	6.8	y	y	M 580 T	
37-1	f	Turkey	13 y	2 mo	9 y	7.50	5.5	2.2	7.0	n	n	intronic 6 acceptor splice AG →AA	
49-1	m	Saudi Arabia	13 y	5 mo	n/a	7.21	14.0	2.8	7.5	y	n	Q276 F	
62-1*	f	Turkey	8 y	3 y	7 y	7.20	7.6	3.0	7.0	y	n	-	
63-1	m	Turkey	3 y	6 mo	1 y	7.50	6.1	2.1	7.0	n	y	F 524 L	
				mean		7.16±0.06	10.0±3.9	2.6±0.4	7.3±0.4				
				ATP6N1B mutations	mean		7.20±0.09	10.0±2.5	3.1±0.7	7.3±0.6			

Smith AN, et al, *Nature Genetics* 26:71-5, 2000.

