EAR/RENAL SYNDROMES

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Objects

- Normal hearing
- Introduction
- Renal syndromes associated with hearing loss
- Is there a relationship between kidney function & hearing loss?

Normal hearing

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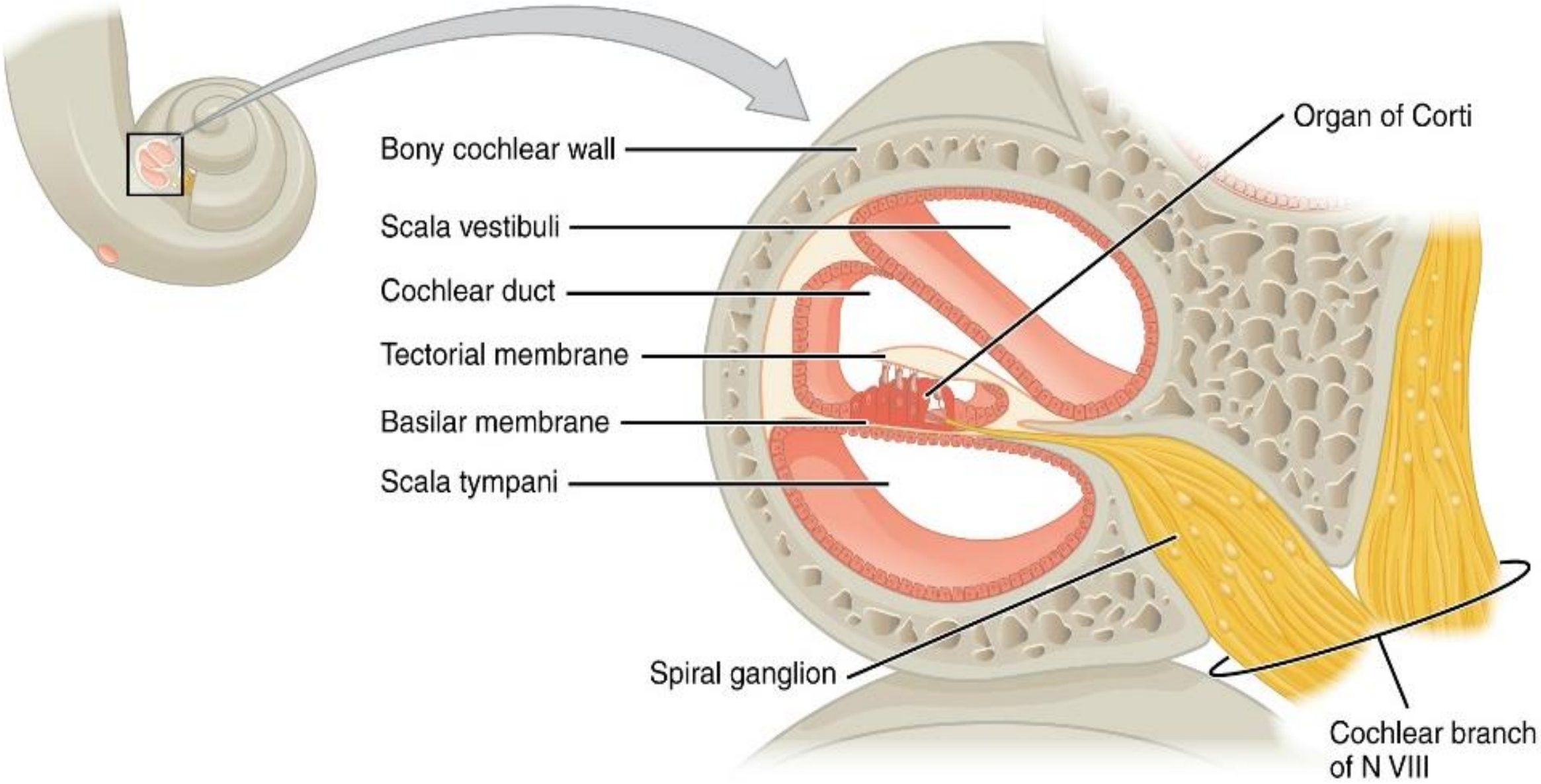
Bony cochlear wall
Scala vestibuli
Cochlear duct
Tectorial membrane
Basilar membrane
Scala tympani
Organ of Corti
Spiral ganglion
Cochlear branch of N VIII

Normal hearing

- Endolymph fluid:
  - Potassium 157 mM & sodium 1.3 mM
- Perilymph fluid:
  - Potassium 4.2 mM & sodium 148 mM

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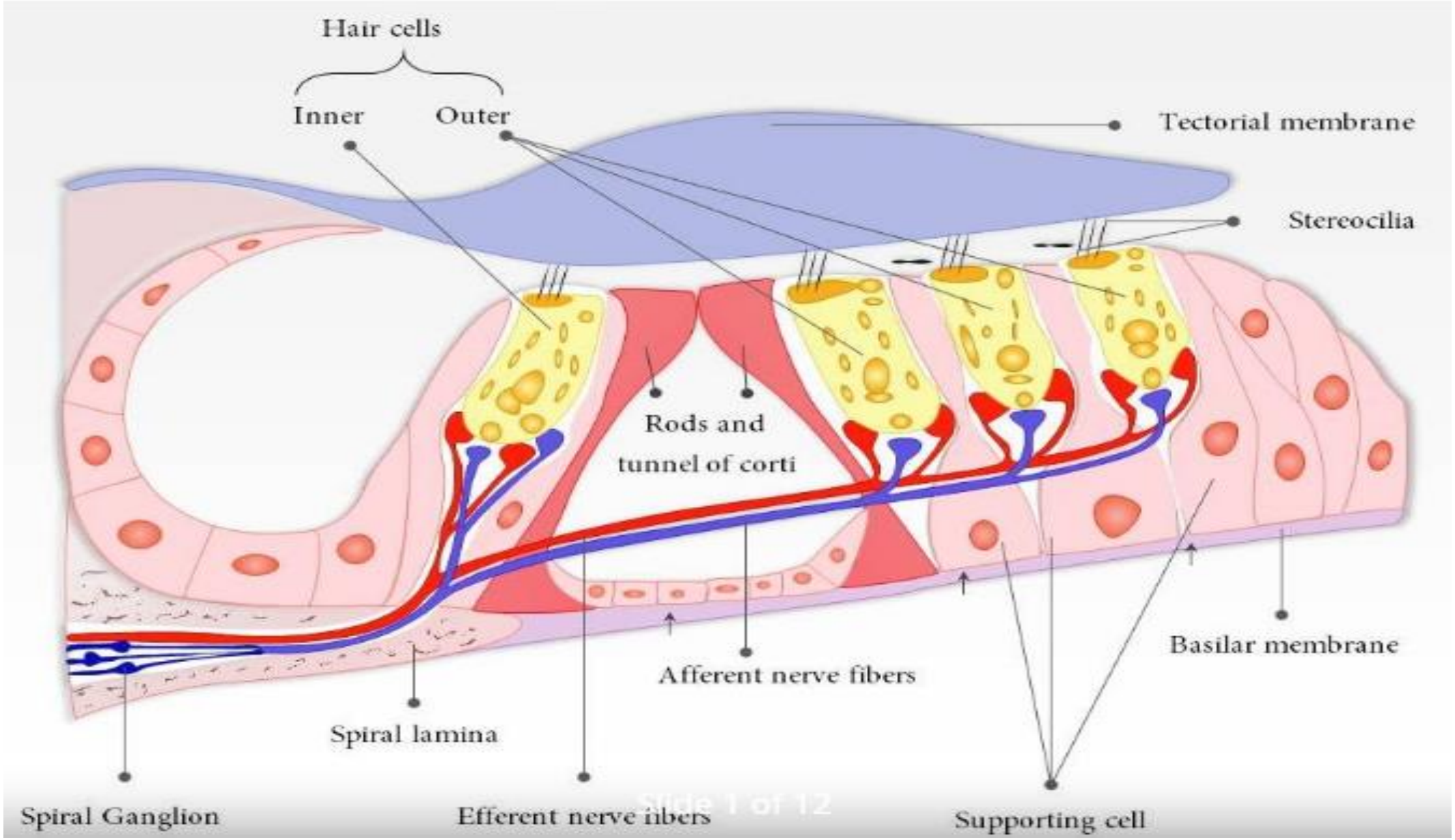
Cochlea and spiral organ



Normal hearing

- At birth we have about **12,000 hair cells.**
- Hair cells can be damaged & lost throughout our lifetime from **loud noises or other** conditions & once they are lost these cells do not regenerate.
- Given their essential role in hearing, the loss of hair cells results in permanent **SNHL.**

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EDUCATIONAL REVIEW

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Hearing loss and renal syndromes

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Abstract The association between ear and kidney abnormalities has long been recognized; however, the connection between these two disparate organs is not always straightforKidney diseases associated with ear abnormalities can include a wide variety of disorders, including glomerulopathies, congenital anomalies of the kidney and urinary tract (CAKUT),

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Introduction

- Although Alport syndrome is the most well-known, there are **over 20 disorders** that need to be considered in the DD of patients with both ear & kidney abnormalities.
- Commonalities are present between the kidney & ear in a number of:
  - Structural proteins
  - Developmentally important transcription factors
  - Ciliary proteins
  - Channel proteins

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Renal syndromes associated with hearing loss

1. **CAKUT**
2. **Ciliopathies**
3. **Glomerulopathies**
4. **Tubulopathies**

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Renal syndromes associated with hearing loss

Name	Gene	Inheritance	Renal/genitourinary findings	Extrarenal findings	Hearing loss frequency (%)
CAKUT					
Abruzzo–Erickson syndrome	*TBX22*	XL	Horseshoe kidney	Coloboma, cleft palate, hypospadias, short stature	Male: >80 Female: rare
Barakat syndrome	*GATA3*	AD?	Renal dysplasia, steroid-resistant nephrosis	Hypoparathyroidism	100
Baraitser–Winter syndrome	*ACTB*, *ACTG1*	AD	Hydronephrosis, horseshoe, ectopic kidney	Dysmorphic facial features, iris or retinal coloboma	30–43
Branchio-oto-renal syndrome	*EYA1*, *SIX1*, *SIX5*	AD	Renal hypoplasia/dysplasia, 5–10% ESKD	Variable penetrance; external ear anomalies, branchial fistulae or cysts	70
CHARGE syndrome	*SEMA3E*, *CHD7*	AD	Dysplasia, renal agenesis, ectopy	Coloboma, choanal atresia, genital anomalies, ear anomalies	70–90
Fronto-metaphyseal dysplasia	*FLNA*	XL	Hydronephrosis, hydroureter	Skeletal anomalies, cleft palate	Male: >95 Female: rare
Leopard/Noonan syndrome	*PTPN11*, *RAF-1*, *BRAF*, *MAP2K1*	AD	Unilateral renal agenesis	Multiple lentigines, conduction abnormalities, abnormal genitalia, pulmonic stenosis	20
Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart	*RERE*	AD	VUR, hypospadias, cryptorchidism	Developmental delay, eye abnormalities, congenital heart defects	28
Townes–Brocks syndrome	*SALL1*	AD	Renal hypoplasia/dysplasia	Imperforate anus, limb defects	65
Wolfram syndrome	*WFS1*	AR	Hydronephrosis, neurogenic bladder	Diabetes mellitus, optic atrophy, diabetes insipidus	66
Zellweger syndrome	*PEX1*	AR	Hydronephrosis, cortical cysts	Severe neurological dysfunction, craniofacial abnormalities, liver dysfunction	>75

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Renal syndromes associated with hearing loss

Ciliopathies					
Alstrom syndrome	*ALMS1*	AR	Tubulointerstitial nephropathy	Retinitis pigmentosa, obesity, diabetes mellitus	88
Bardet–Biedl	*BBS1*, *BBS2*, *ARL6* (BBS3), *BBS4*, *BBS5*, *MKKS* (BBS6), *BBS7*, *TTC8* (BBS8), *BBS9*, *BBS10*, *TRIM32* (BBS11), *BBS12*, *MKS1* (BBS13), *CEP290* (BBS14), *WDPCP* (BBS15), *SDCCAG8* (BBS16), *LZTFL1* (BBS17), *BBIP1* (BBS18), and *IFT27* (BBS19)	AR	Polyuria/polydipsia, cysts, tubulointerstitial nephropathy	Obesity, retinopathy, polydactyly, developmental delay, diabetes mellitus, hypogonadism	11–50

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Renal syndromes associated with hearing loss

Name Glomerular dis:	Gene	Inheritance	Renal/GU findings	Extrarenal findings	Hearing loss (%)
Alport syndrome	COL4A3 COL4A4 COL4A5	AR, AD, XL	Hematuria, proteinuria, ESKD	Eye abnormalities (anterior lenticonus, maculopathy)	XL male: 80–90 XL female: 20
Charcot–Marie–Tooth	INF2	AD	Proteinuria, FSGS	Distal muscle weakness & atrophy, distal sensory loss	33
Cockayne syndrome	ERCC6 ERCC7	AR	Proteinuria, CKD	Growth retardation, neurological abnormalities, premature aging, cataracts, retinopathy	60–80
Fabry disease	GLA	XL	Hematuria, proteinuria, ESKD	Stroke, cardiac disease, acroparesthesias, angiokeratomas, hypohidrosis	18–55

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Question

- A 16-year-old boy with recently diagnosed X-linked Alport syndrome has proteinuria (1.5 g/day), normal BP, & eGFR of 85 ml/min/1.73 m^2 . What treatment should be initiated to slow the progression of CKD?

a) CNI

b) CCB

c) BB

d) Thiazide diuretic

e) ACE inhibitor

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Renal syndromes associated with hearing loss

Name Glomerular dis:	Gene	Inheritance	Renal/GU findings	Extrarenal findings	Hearing loss (%)
Coenzyme Q10	COQ6 COQ2	AR	NS (FSGS, DMS)	Encephalopathy, HCM, seizures	>90
MELAS syndrome	MTTL1	Mitochondrial	Proteinuria, FSGS	Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes	75
Muckle–Wells	NLRP3	AD	Amyloidosis	Recurrent fever, arthralgia, fatigue, urticarial rash	80–99
MYH-9 related disorders (Epstein, Fechtner syndromes)	MYH9	AD	Hematuria, proteinuria, ESKD	Macrothrombocytopenia, leukocyte inclusions, cataracts	58
Nephropathy with pretibial epidermolysis bullosa and deafness	CD151	?	Nephrotic proteinuria, ESKD Epidermolysis bullosa, beta	Epidermolysis bullosa, beta thalassemia major	66

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Question

- An 10-year-old girl has steroid-resistant nephrotic syndrome & FSGS on kidney biopsy. Treatment with coenzyme Q10 should be initiated if a mutation is identified in which of the following genes?

a) COQ2
b) MTTL1
c) INF2
d) CD151
e) COL4A5

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Question

- A 17-year-old boy has SN hearing loss, hematuria, & proteinuria with GBM thickening on EM, & thrombocytopenia. Mutation in which of the following genes is the most likely cause of his symptoms?

a) COL4A5
b) COL4A3
c) MYH9
d) COQ2
e) CD151

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Renal syndromes associated with hearing loss

Tubular disorders					
Bartter syndrome type IV	*BSND* (or double heterozygous *CLCNKA* and *CLCNKB*)	AR	Polyuria, hypokalemic salt-wasting tubulopathy, CKD		>90
Combined oxidative phosphorylation deficiency	*RMND1*	AR	Dysplasia, RTA	Hypotonia, liver dysfunction, lactic acidosis, encephalopathy	Unknown
Distal renal tubular acidosis with progressive nerve deafness	*ATP6B1*, *ATP6N1B*	AR	Distal RTA, nephrocalcinosis		66
EAST syndrome (SESAME syndrome)	*KCNJ10*	AR	Polyuria, sodium and potassium wasting	Seizures, ataxia, developmental delay	80–99
Pendred syndrome	*SLC26A4* (or double heterozygous *SLC26A4* and *FOXI1*)	AR	No renal phenotype at baseline, but may have hypovolemia and metabolic alkalosis when exposed to alkali load or thiazides	Goiter	100

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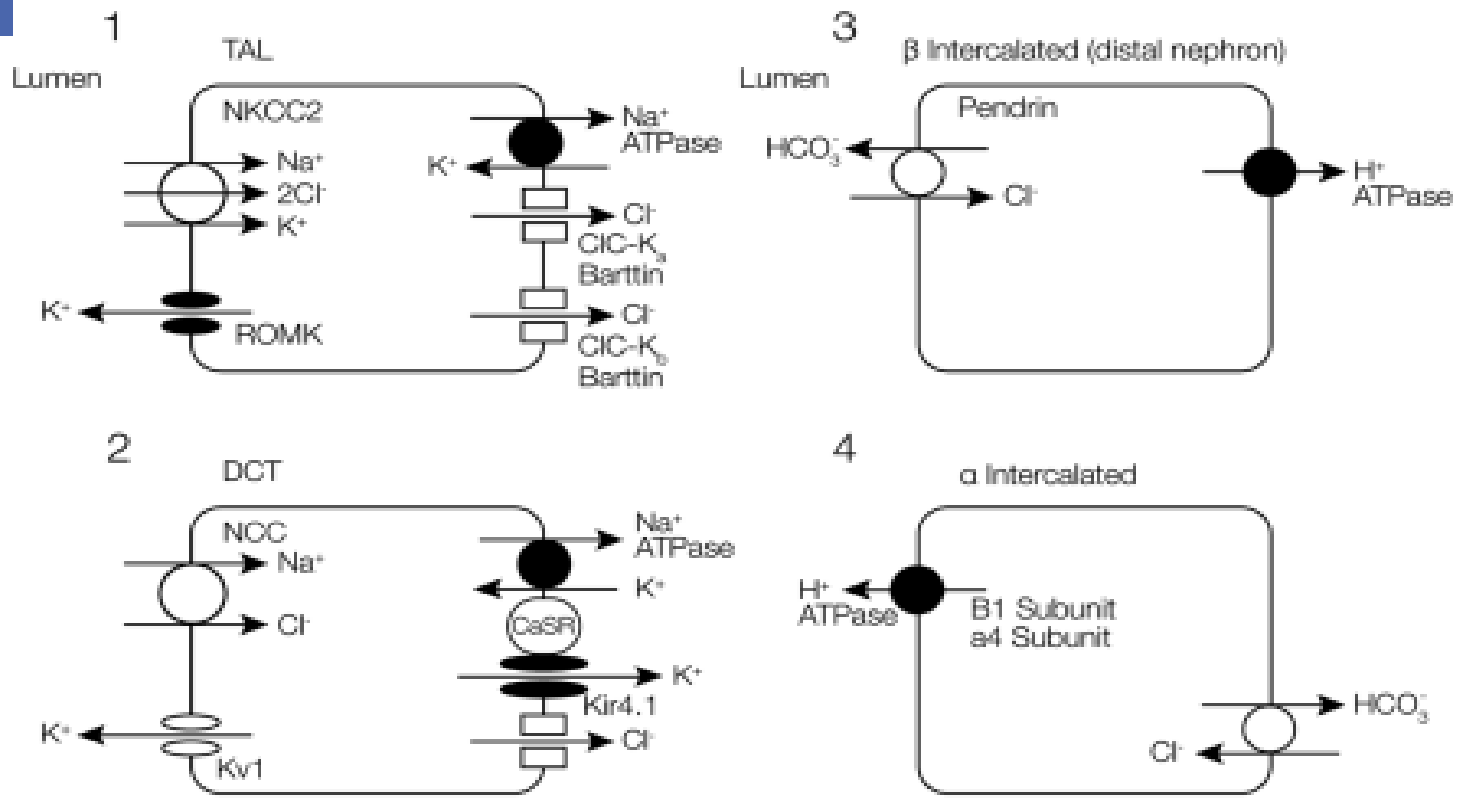

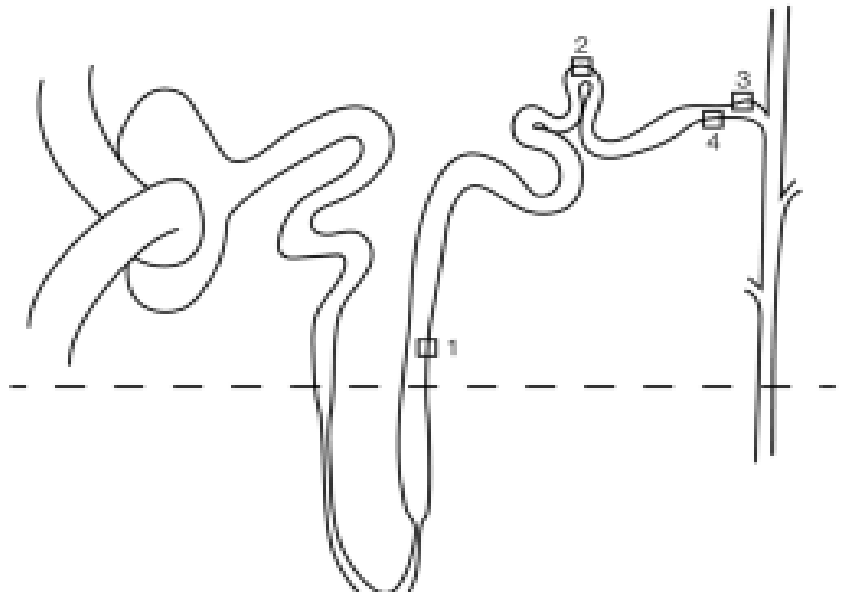

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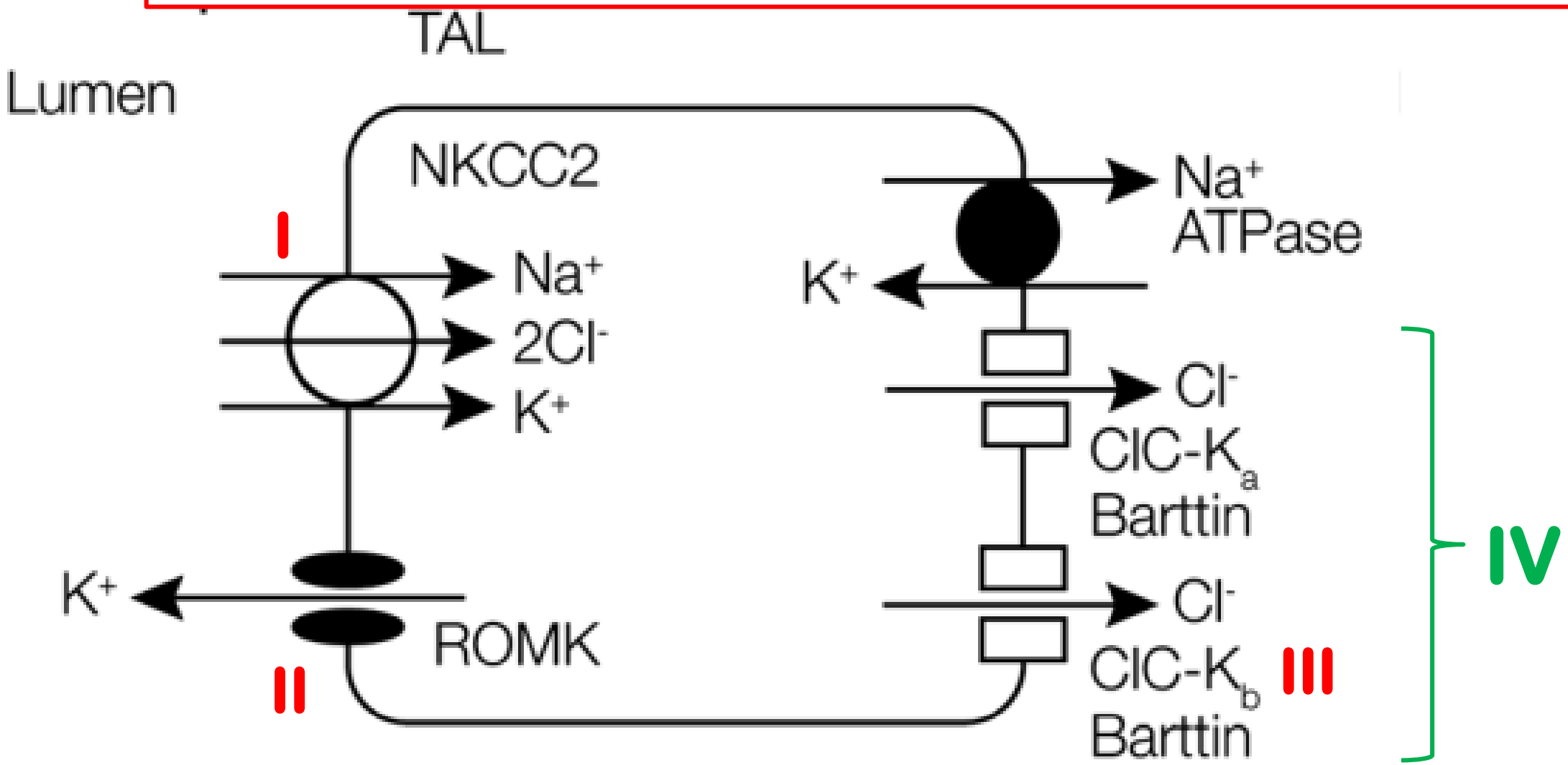
Bartter Syndrome



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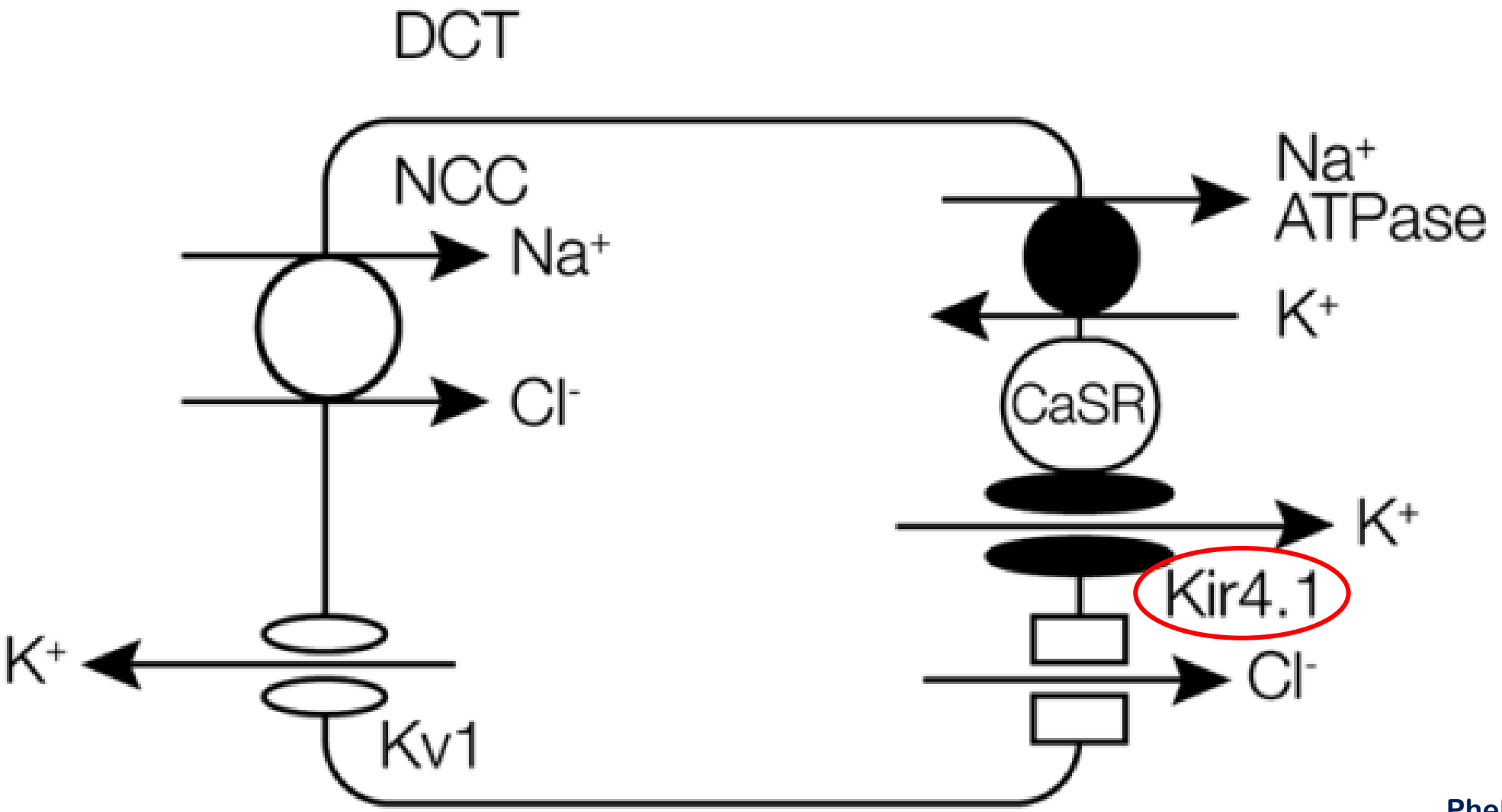
EAST synd: Epilepsy Ataxia Sensorineural-deafness Tubulopathy



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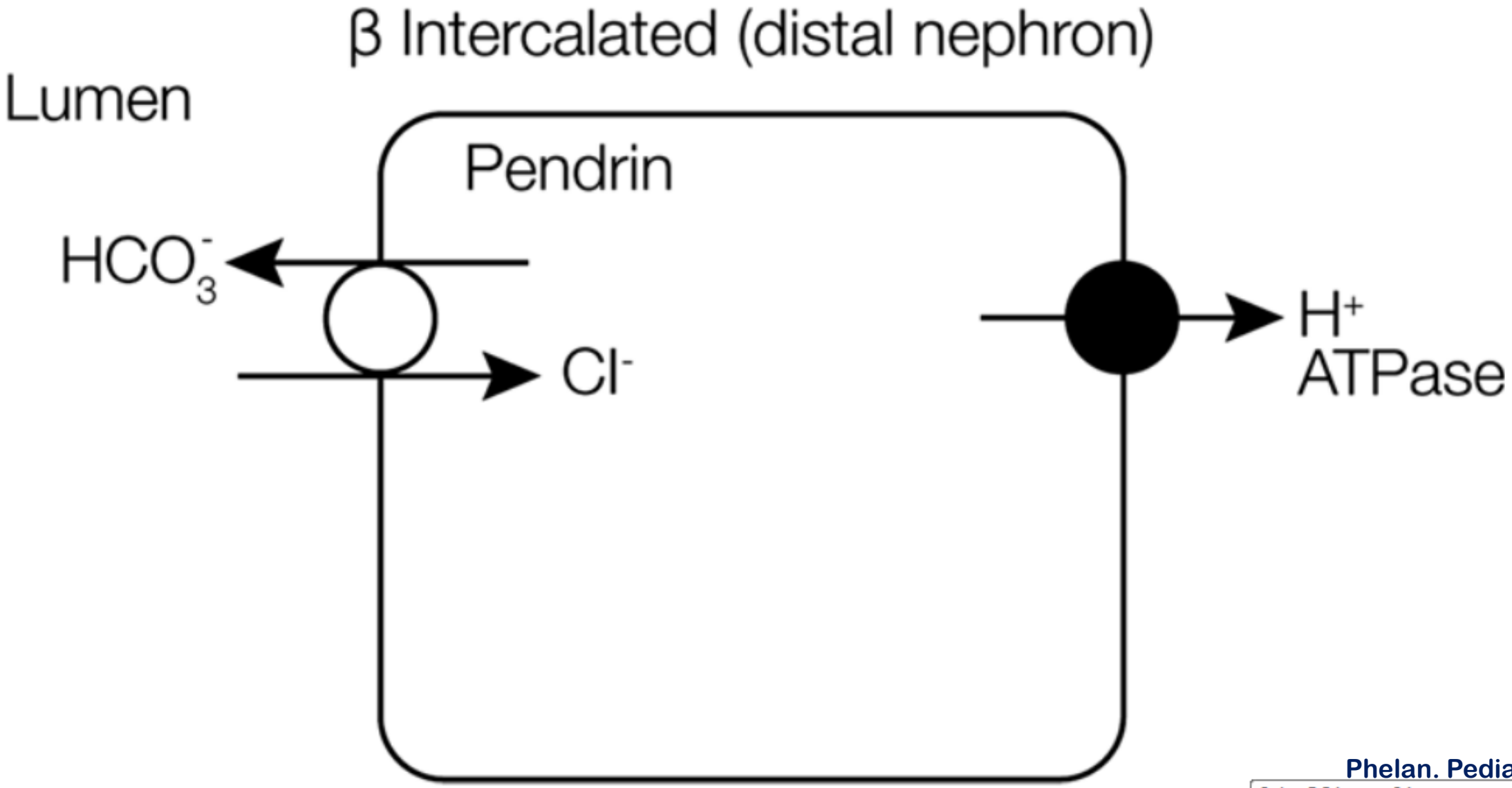
Pendred syndrome



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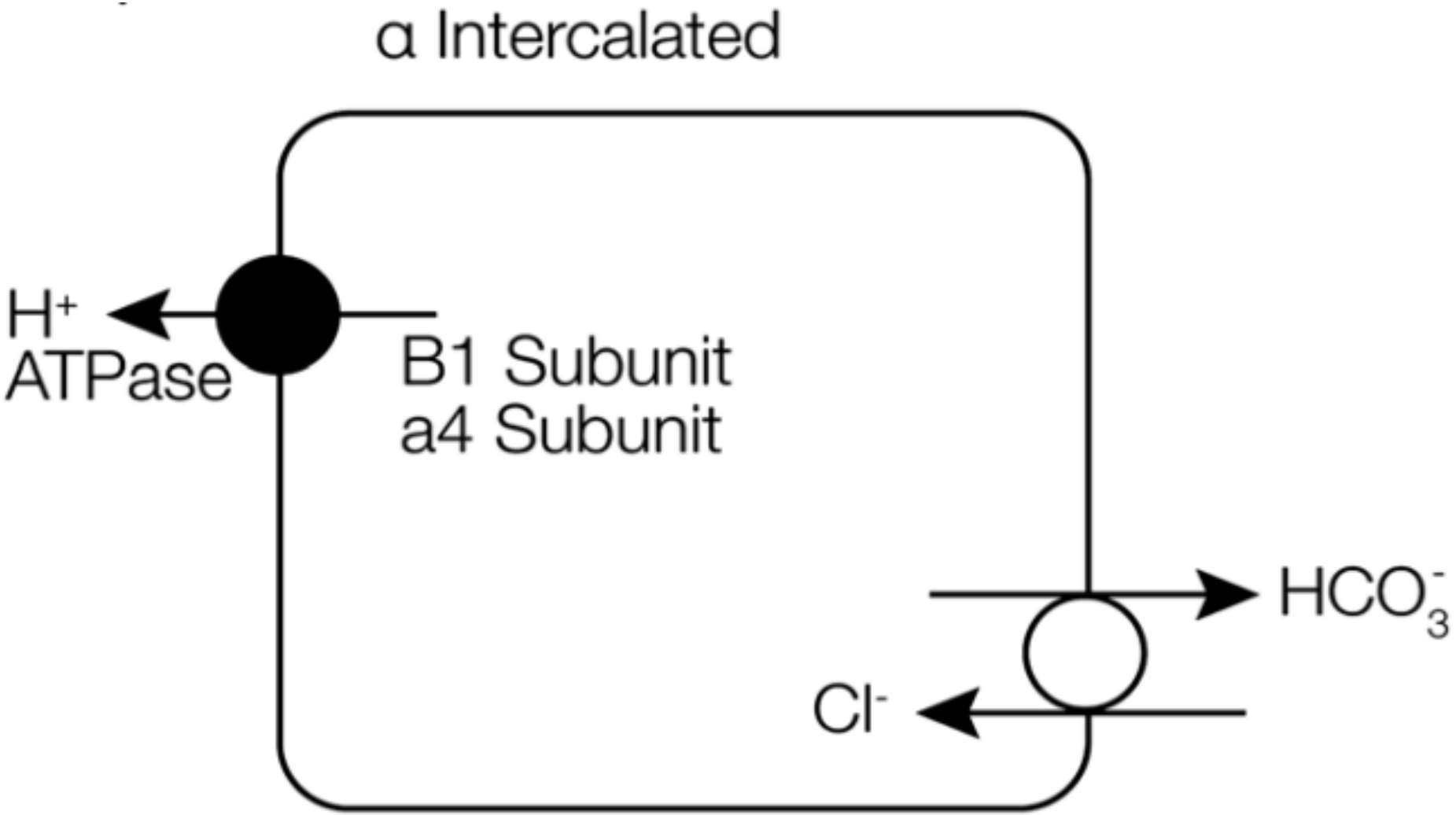
dRTA with deafness



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Question

- A 8-year-old has SN deafness, hypokalemia, metabolic alkalosis, & polyuria. Mutation in which of the following genes is likely to be the cause of his symptoms?

a) SLC12A1 (Na-K-2Cl co-transporter)

b) KCNJ1 (ROMK potassium channel)

c) KCNJ10 (Kir4.1 potassium channel)

d) BSND (Barttin)

e) ATP6B1 (B1 subunit of H+ -ATPase)

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IS THERE A RELATIONSHIP BETWEEN KIDNEY FUNCTION AND HEARING LOSS?

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Original Article

Pediatrics

Check for updates

Renal Syndromic Hearing Loss Is Common in Childhood-onset Chronic Kidney Disease

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OPEN ACCESS

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Methods

- Retrospective study of a tertiary referral center
- Childhood-onset CKD patients (stage 2–5, age at onset of renal symptom <18 ys).
- Cases with genetic or syndromic diseases, or extra-renal anomalies in addition to HL & CKD = "renal" syndromic HL

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Items	Patients
Sex, male:female	279 (66.3):142 (33.7)
Age at the last follow-up, yr	15.8 (10.9–19.2)
Median age at onset of renal symptom, yr	1.7 (0–7.3)
Median follow-up duration, yr	8.4 (4.1–14.0)
Stage of CKD at the last follow-up	
Stage 2	68 (16.2)
Stage 3	82 (19.5)
Stage 4	30 (7.1)
ESRD	241 (57.2)
Median age at ESRD, yr	9.0 (4.7–13.3)
Causes of CKD	
CAKUT	184 (43.7)
GP	105 (24.9)
CYST	39 (9.3)
PP	29 (6.9)
Others	64 (15.2)
Hearing loss	82 (19.5)
SNHL	51 (12.1)
CHL	30 (7.1)
Mixed	1 (0.2)

Baseline characteristics of the patients (n = 421)

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Hearing loss according to CKD stage

Items	Patients with SNHL	Patients with CHL	Patients with mixed HL	Total patients with HL
No. of patients (male:female)	51 (32:19)	30 (19:11)	1 (0:1)	82 (51:31)
CKD stage				
Stage 2	5/68 (7.4)	3/68 (4.4)	-	8/68 (11.8)
Stage 3	9/82 (11.0)	1/82 (1.2)	-	10/82 (12.2)
Stage 4	3/30 (10.0)	1/30 (3.3)	-	4/30 (13.3)
ESRD	34/241 (14.1)	25/241 (10.4)	1/241 (0.4)	60/241 (24.9)
GA[a]				
Very preterm	4/19 (21.1)	1/19 (5.3)	-	5/19 (26.3)
Moderately preterm	2/14 (14.3)	1/14 (7.1)	-	3/14 (21.4)
Late preterm	4/41 (9.8)	5/41 (12.2)	-	9/41 (22.0)
Term	41/347 (11.8)	23/347 (6.6)	1/347 (0.3)	65/347 (18.7)

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Risk factors of hearing loss

Factors	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
CKD stage[a]	1.43	1.13–1.81	0.003	NA		
Stage of CKD at the last follow-up						
CKD stage 2–4	Reference			Reference		
ESRD	2.38	1.40–4.06	0.001	2.06	1.18–3.63	0.012
Disease group						
Non-glomerulopathies	Reference			Reference		
Glomerulopathies	2.03	1.21–3.41	0.007	1.58	0.91–2.73	0.105
Age at the last follow-up	1.03	1.00–1.07	0.082	NA		
Age at ESRD	0.96	0.93–1.01	0.099	NA		
Onset age of renal symptoms	0.95	0.90–1.00	0.058	NA		
Sex				NA		
Female	Reference					
Male	0.80	0.48–1.32	0.385			
Prematurity	1.29	0.71–2.37	0.404	NA		

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Conclusion

- **One-fifth** of the childhood-onset CKD had HL.
- HL was more common as CKD stage progressed, especially CHL in **ESRD**.
- SNHL was more common in the **GP** groups than in other groups.
- Collectively, **renal syndromic HL** comprised half of the HL in this study.
- To improve the quality of life in patients with childhood-onset CKD, we suggest that HL should be considered, requiring **surveillance**, & if necessary, early intervention.

Ji Hyun Kim. JKMS, 2020

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BMC Nephrology

RESEARCH ARTICLE Open Access

The association between reduced kidney function and hearing loss: a cross-sectional study

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Abstract

Background: The relationship between kidney function and hearing loss has long been recognized, but evidence of this association mostly comes from small observational studies or other populations. The aim of this study is to explore the association between reduced kidney function and hearing loss in a large population-based study among the middle-aged and elderly Chinese.

Question

- What is the leading cause of adult-onset hearing loss?

A. Genetic mutations

B. Noise exposure

C. Use of ototoxic drugs in treatment

D. Chronic diseases such as HTN & DM

E. Aging

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Background

- The WHO reported that approximately 432 million adults suffered from disabling hearing loss in 2018 & estimated that over 900 million people will have disabling hearing loss by 2050

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Background

- The **kidney & cochlea** have common antigenicity & similar physiologic mechanisms involving the transport of fluid & electrolytes, which might explain the hearing loss in patients with kidney disease.
- Some possible **etiological factors** related to hearing loss in kidney failure patients have also been reported, including:
  - Electrolyte disturbances
  - HTN
  - The use of ototoxic drug
  - Hemodialysis treatment

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Methods

- Data collected from the Chinese Health & Retirement Longitudinal Study (CHARLS) in 2015
- A cross-sectional study was conducted among 12,508 participants aged ≥ 45 ys.
- Hearing loss, was defined according to interviewees' responses to 3 survey questions related to hearing in the CHARLS.
- eGFR was employed to assess kidney function, & participants were classified into 3 categories based on eGFR: ≥90, 60–89 & < 60 mL/min/1.73 m2 .
- Multivariable logistic regression was employed

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Hearing related questions in the CHARLS survey

(1) Do you have a hearing problem? 1. Yes 2. No

(2) Do you ever wear a hearing aid? 1. Yes 2. No

(3) Would you say your hearing is excellent, very good, good, fair, or poor? (How is your hearing with a hearing aid if you normally use it? How is your hearing without a hearing aid if you normally don't use it?) 1. Excellent 2. Very good 3. Good 4. Fair 5. Poor

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Prevalence of hearing loss in different age & eGFR groups

	Individuals	Hearing loss	Prevalence (%)
Total	12,508	2946	23.6
Age groups (years)			
45–54	3935	534	13.6
55–64	4498	902	20.1
≥ 65	4075	1510	37.1
eGFR groups (mL/min/1.73 m^2)			
≥ 90	7498	1456	19.4
60–89	4315	1241	28.8
< 60	695	249	35.8

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ORs & 95% CIs for hearing loss in relation to the eGFR categories

Variable	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
eGFR (mL/min/1.73 m^2)								
≥ 90	Reference		Reference		Reference		Reference	
60–89	1.68 (1.54–1.83)	< 0.001	1.08 (0.98–1.19)	0.122	1.11 (1.00–1.22)	0.043	1.11 (1.00–1.23)	0.043
< 60	2.32 (1.96–2.73)	< 0.001	1.30 (1.09–1.55)	0.004	1.29 (1.08–1.54)	0.006	1.25 (1.04–1.49)	0.017

Model 1: Unadjusted;
Model 2: Adjusted for age;
Model 3: Adjusted for age, gender, education, area of residence, smoking, and drinking;
Model 4: Adjusted for age, gender, education, area of residence, smoking, drinking, BMI, central obesity, hypertension, diabetes, stroke, HDL cholesterol, and LDL cholesterol

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Conclusion

- Reduced kidney function is independently associated with hearing loss.
- Testing for hearing should be included in the integrated management of patients with CKD.

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Take-home message

Attention to hearing in patients with kidney disease is important for both diagnosis & management purposes


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