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Advanced Webinars on Rare Kidney Disorders

Date: 30 March 2021

Topic: Genetics of stones

Speaker: Shabbir Moochhala

Moderator: Tom Nijenhuis

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Genetics of Kidney Stone Disease

ERKNet/ERA-EDTA Webinar
30 March 2021

Dr Shabbir Moochhala
UCL Department of Renal Medicine
Royal Free Hospital, London

UCL

Royal Free London NHS
NHS Foundation Trust

Disclosures

Consultant fees: Allena, Alnylam, Dicerna

Speaker fees: Sanofi

Disclosure: I am not a geneticist!

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Kidney stones – there's a lot of it about

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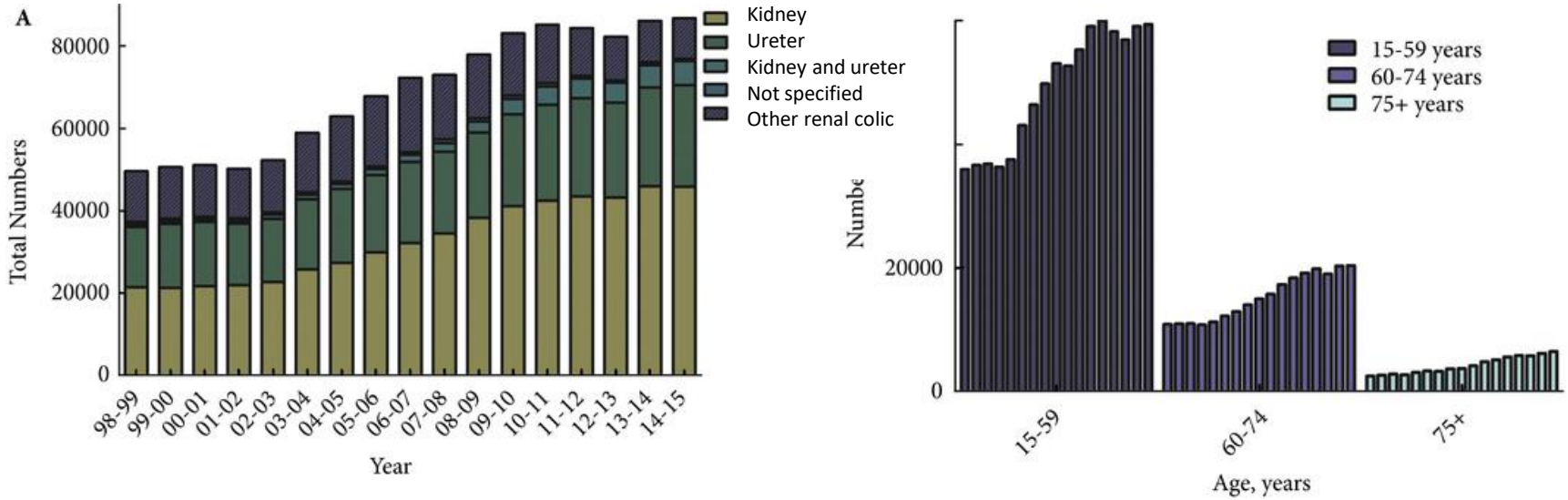
Kidney stones – a growing problem

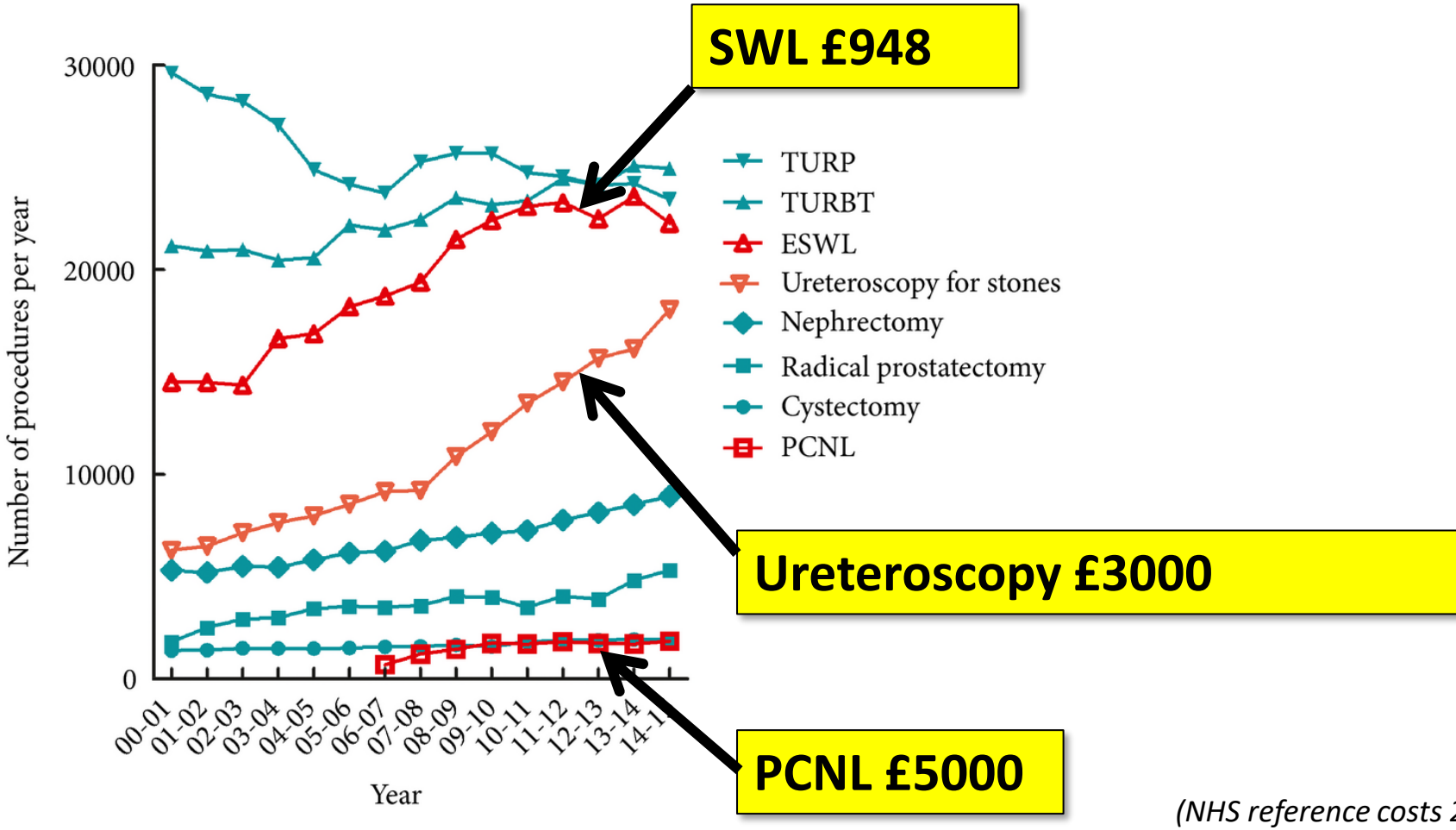


BJU International 118 (5) 785-789, May 2016

- Hospital episodes increased by 70% over a 15-year period between 2000 and 2015, from 51,035 episodes to 86,742 episodes (HES data)
- The lifetime prevalence of renal stone disease is 13%
- 49% increase from 12,062 in-patient treatments in 2009-2010, to 18,066 in 2014-2015 (HES data)
- Day-case treatments increased by 10% to 31,000 cases a year between 2010 and 2015

Data from: NICE Renal and ureteric stones: final scope, May 2017

Urologists: Expensive and Scary



(NHS reference costs 2015/16 from nice.org.uk/advice/mib138)

BJU International 118 (5) 785-789, May 2016

Q J Med
doi:10.1093/qjmed/hcu251 Advance Access Publication 18 December 2014

A London experience 1995–2012: demographic, dietary and biochemical characteristics of a large adult cohort of patients with renal stone disease

P.M. FERRARO[1,2], W.G. ROBERTSON[1,3], N. JOHRI[1], A. NAIR[1], G. GAMBARO[2], L. SHAVIT[1,4], S.H. MOOCHHALA[1] and R.J. UNWIN[1]

From the [1]UCL Centre for Nephrology, Royal Free Hospital, London, UK, [2]Division of Nephrology, Catholic University of the Sacred Heart, Rome, Italy and [3]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK

Nephrol Dial Transplant (2014) 0: 1–7
doi: 10.1093/ndt/gfu350

ndt Nephrology Dialysis Transplantation

Original Article

Effect of being overweight on urinary metabolic risk factors for kidney stone formation

Linda Shavit[1,2], Pietro Manuel Ferraro[3], Nikhil Johri[1], William Robertson[1,4], Steven B. Walsh[1], Shabbir Moochhala[1] and Robert Unwin[1]

[1]UCL Centre for Nephrology, University College London Medical School, Royal Free Campus and Hospital, London, UK, [2]Adult Nephrology Unit, Shaare Zedek Medical Center, Jerusalem, Israel, [3]Division of Nephrology, Catholic University of the Sacred Heart, Rome, Italy and [4]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK

Correspondence and offprint requests to: Linda Shavit; E-mail: lshavit@szmc.org.il

ABSTRACT

Background. The prevalence and incidence of kidney stone disease have increased markedly during the past several decades, and studies have demonstrated that inappropriate dietary habits are leading to more obesity and overweight (OW) in children and adults, which may be important in stone formation. Obese and OW patients share most of the same risk factors for cardiovascular morbidity, while the impact of being OW, rather than obese, on urinary metabolic parameters of kidney stone formers (KSF) is less well known. The aims of this study were to investigate urinary metabolic parameters, stone composition and probability of stone formation (Psf) in OW KSF when compared with normal weight

...demonstrated ... higher prevalence of diabetes, hypertension and gout. There were no statistically significant differences in U.Vol and U.Mg among the groups. However, significantly higher levels of U.Ca, U.Ox, U.Cit, by crude analysis, and U.UA (3.3 ± 1.1 versus 3.8 ± 1.2 versus 4.0 ± 1.2 mmol/L; P < 0.001 for trend), U.Na (151 ± 57 versus 165 ± 60 versus 184 ± 63 mmol/L; P < 0.001 for trend), and lower U.pH (6.3 ± 0.5 versus 6.1 ± 0.5 versus 6.0 ± 0.6; P < 0.001 for trend) by both crude and multivariate adjusted analysis models were demonstrated in OW and obese KSF. Stone composition data (*N* = 640) showed a significantly higher incidence of uric acid stones in OW and obese groups (P for trend < 0.001). In addition, higher Psf for CaOx, UA and CaOx/UA stone types were detected in OW and obese compared with NW KSF.

BRIEF COMMUNICATION www.jasn.org

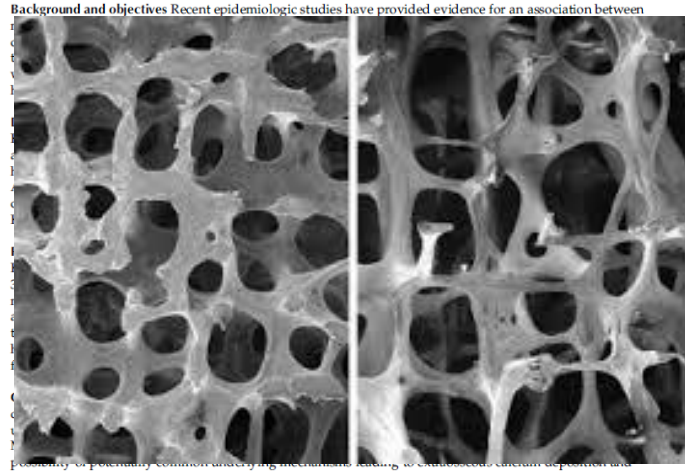
Dietetics and risk factors

Vascular Calcification and Bone Mineral Density in Recurrent Kidney Stone Formers

Linda Shavit,†* Daniela Girfoglio,* Vivek Vijay,* David Goldsmith,‡ Pietro Manuel Ferraro,§ Shabbir H. Moochhala,* and Robert Unwin**

Abstract

Background and objectives Recent epidemiologic studies have provided evidence for an association between

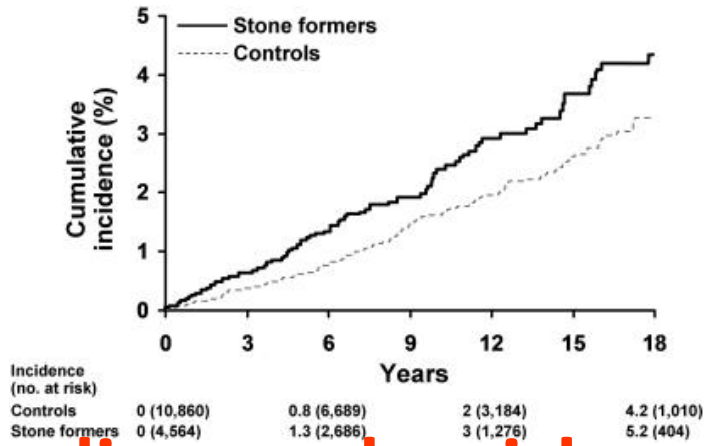


...osteoporosis in KSFs.

Clin J Am Soc Nephrol 10: 278–285, 2015. doi: 10.2215/CJN.06030614

...has traditionally been recognized as no more than an isolated and painful condition with few long-term ... kidney stone formers (KSFs) have a higher prevalence of subclinical atherosclerosis based on increased carotid

Treating bone disease



Cardiovascular risk

38% increased MI risk in stone formers

Rule et al. Clin J Am Soc Nephrol. 2010 Oct; 21(10): 1641-1644

Fourteen Monogenic Genes Account for 15% of Nephrolithiasis/Nephrocalcinosis

Jan Halbritter,* Michelle Baum,* Ann Marie Hynes,† Sarah J. Rice,†‡ David T. Thwaites,‡ ...e Spaneas,* Jonathan D. Porath,* Daniela A. Braun,* ...or Tasic,§ John A. Sayer,† and Friedhelm ...

...Division of Endocrinology, Department of Medicine, and ...ital, Harvard Medical School, Boston, Massachusetts; †Institute of ...‡Epithelial Research Group, Institute for Cell and Molecular ...Newcastle upon Tyne, United Kingdom; ...Medical Society ...acedonia; and **Howard Hughes Medical Institute, Chevy Chase,

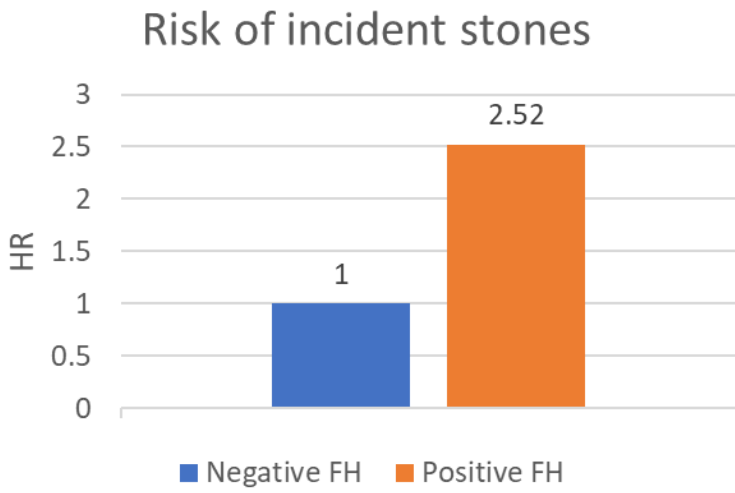
Genomics england

61,554 participants
(50,370 rare disease)
380+ data fields

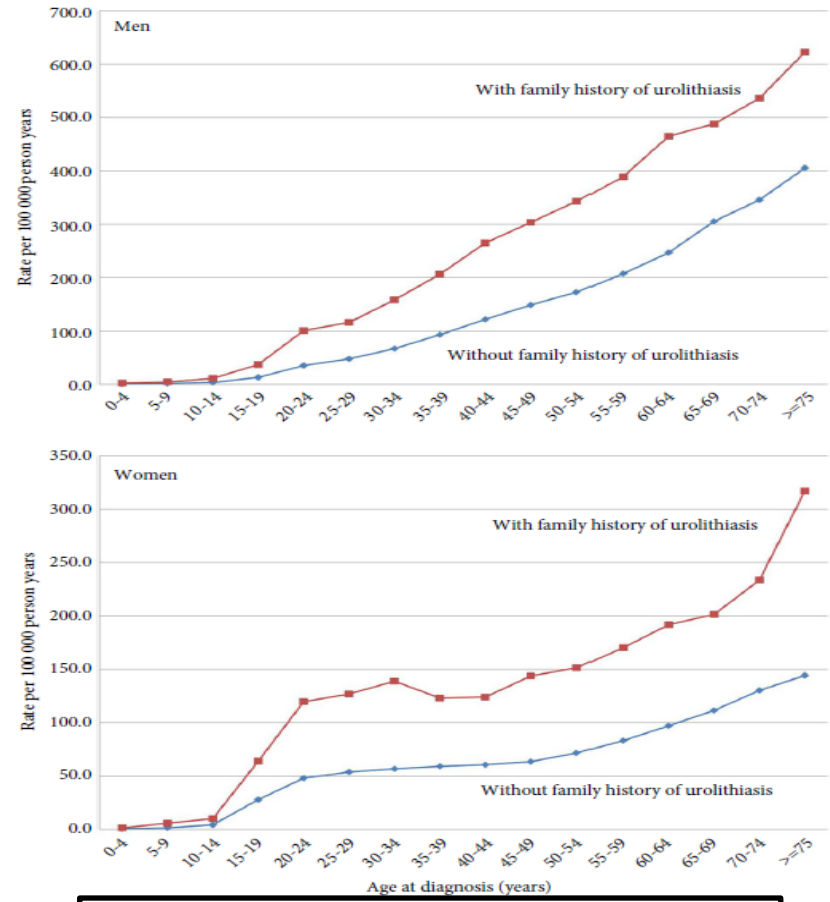
Genetics and rare diseases

Family history is a risk factor for recurrent kidney stones

About 30-50% of recurrent stone formers have a positive family history of stones



38,000 participants
8 years follow-up – 795 events



13,200,000 participants (Sweden pop)

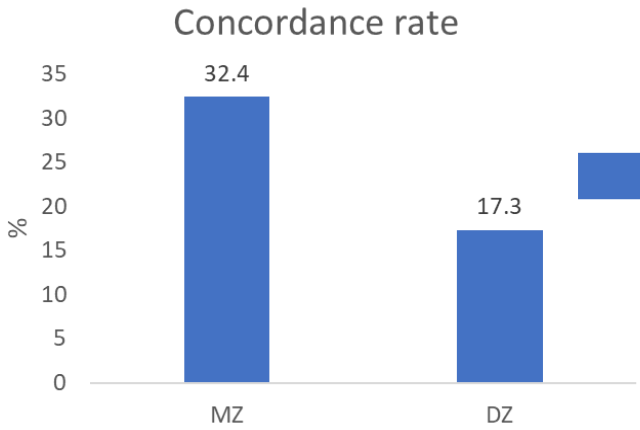
Curhan, J Am Soc Nephrol 1997; Hemminki, BJU Int 2018
Slide courtesy of Prof P M Ferraro

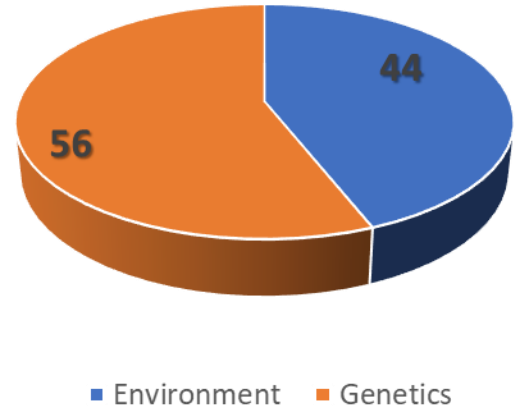
Environment - the other 50%

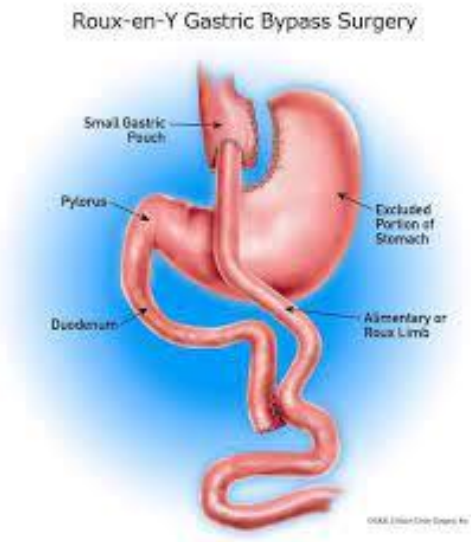
A twin study of genetic and dietary influences on nephrolithiasis: A report from the Vietnam Era Twin (VET) Registry

DAVID S. GOLDFARB, MARY E. FISCHER, YONA KEICH, and JACK GOLDBERG

Vietnam Era Twin Registry: 7,500 male twin pairs
Self-reported history KS + dietary habits





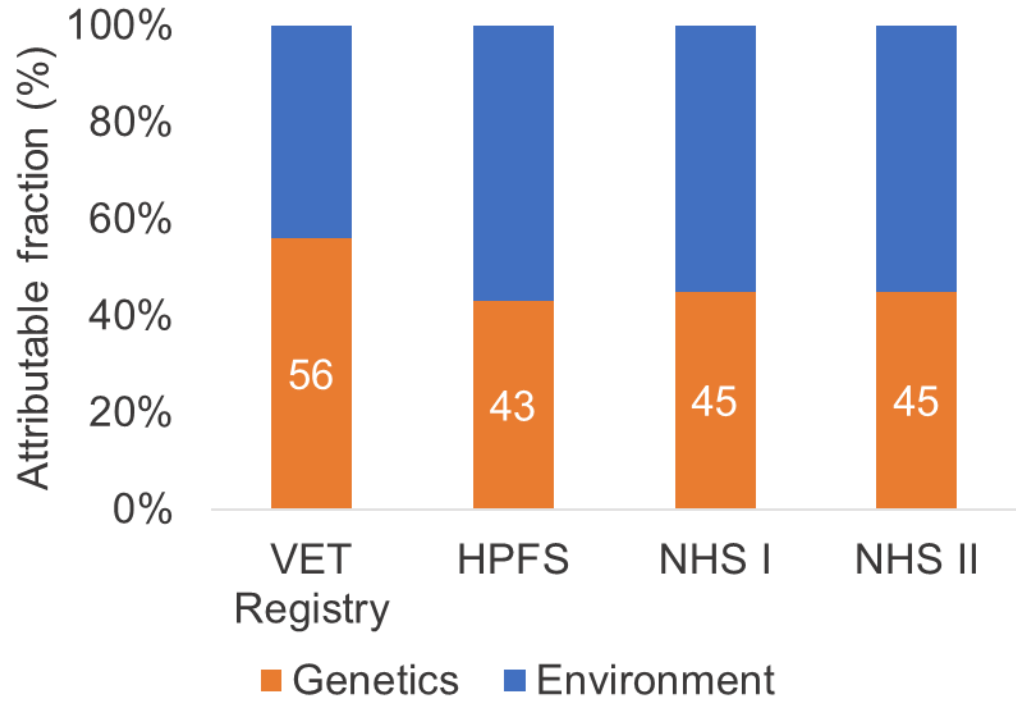


Goldfarb, Kidney Int 2005
Slide courtesy of Prof P M Ferraro

Some risk factors are modifiable

Dietary and Lifestyle Risk Factors Associated with Incident Kidney Stones in Men and Women

Pietro Manuel Ferraro,* Eric N. Taylor, Giovanni Gambaro and Gary C. Curhan†



Low fluid intake
Excess animal protein
Sugar-sweetened beverages
Inadequate calcium intake
High BMI
Inadequate fruit and vegetables

Goldfarb, Kidney Int 2005; Ferraro, J Urol 2017
Slide courtesy of Prof P M Ferraro

Which genes are responsible for stones?

GWAS

- If stone disease is actually a collection of rare genetic diseases, then it should pinpoint candidate genes
- Many involved in calcium regulation (not many are monogenic)
- Need to decide phenotype of interest and controls
  - Not always that easy

Box 2 | **Candidate genes from kidney stone GWAS**

- *ABCG2*: ATP-binding cassette subfamily G member 2
- *ALPL*: alkaline phosphatase, associated with biomineralization
- *AQP1*: aquaporin 1
- *BCAS3*: BCAS3 microtubule-associated cell migration factor
- *BCR*: BCR activator of RhoGEF and GTPase
- *CASR*: calcium-sensing receptor
- *CLDN14*: claudin 14
- *CYP24A1*: cytochrome P450 family 24 subfamily A member 1
- *DGKD*: diacylglycerol kinase-δ
- *DGKH*: diacylglycerol kinase-η
- *EPB41L2*: erythrocyte membrane protein band 4.1 like 2
- *FTO*: FTO α-ketoglutarate-dependent dioxygenase
- *GIPC1*: GIPC PDZ domain-containing family member 1
- *GCKR*: glucokinase regulator
- *HIBADH*: 3-hydroxyisobutyrate dehydrogenase
- *KCNK5*: potassium two-pore domain channel subfamily 5 member 5
- *POU2AF1*: POU class 2 homeobox-associating factor 1
- *SLC22A2*: solute carrier family 22 member 2
- *SLC34A1*: solute carrier family 34 member 1
- *SCNN1B*: sodium channel epithelial 1 β-subunit
- *SOX9*: SRY-box transcription factor 9
- *TFAP2B*: transcription factor AP-2β
- *TRPV5*: transient receptor potential cation channel subfamily V member 5
- *WDR72*: WD repeat domain 72
- *UMOD*: uromodulin

Howles SA, Thakker RV. Genetics of kidney stone disease. Nat Rev Urol. 2020 Jul;17(7):407-421

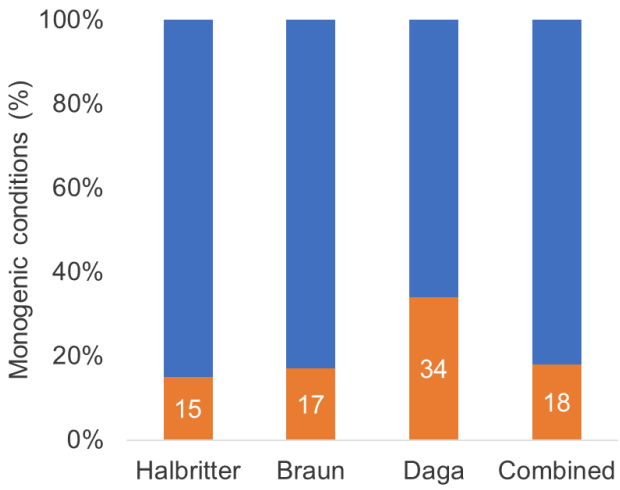
Other phenotypes are possible…

- 62F, screen positive for cystinuria, cystine excretion 288 umol/l, bilateral nephrocalcinosis, normal urinary acidification, hypercalciuric
- Parathyroid adenoma

- 73F, CaOx 80% ammonium urate 20%; CaOx 73% Uric acid 27%; hypocitraturia, abnormal acidification, osteoporosis
- Distal RTA

Monogenic causes of stone disease

In a stone clinic: 15-34% of stone formers have a monogenic cause



Condition	Freq (%)
Cystinuria	26 (5.4)
Hypophoshatemic rickets	17 (3.5)
FHHNC	8 (1.7)
Primary hyperoxaluria	8 (1.7)
Idiopathic hypercalciuria	7 (1.5)
Renal tubular acidosis	6 (1.3)
Renal hypouricemia	4 (0.8)
Dent disease	4 (0.8)
Bartter syndrome	4 (0.8)
Infantile hypercalcemia	3 (0.1)

Hildebrandt studies
Halbritter, J Am Soc Nephrol 2015
Braun, Clin J Am Soc Nephrol 2016
Daga, Kidney Int 2017
Courtesy of Prof P M Ferraro

In real life: 2% of stone formers have a monogenic cause

Disorder	Genes	Inheritance
Hypercalciuria		
Familial hypercalciuria	*ADCY10, VDR*	AD
Autosomal dominant hypocalcaemia	*CASR, GNA11*	AD
Bartter syndrome	*NKCC2 (SLC12A1), ROMK (KCNJ1), CLCNKB, BSND, CASR, CLCN5*	AD, AR or XLR
Dent disease	*CLCN5, OCRL*	XLR
Hypophosphataemic rickets	*SLC34A1, SLC34A3, SLC9A3R1*	AR
Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis	*CLDN16, CLDN19*	AR
Infantile hypercalcaemia	*CYP24A1, SLC34A1*	AR
Cystinuria		
–	*SLC3A1, SLC7A9*	AR or AD with incomplete penetrance
Hyperuricosuria		
Defective purine metabolism	*HRPT1, PRPS1*	XLR
Renal uric acid wasting	*SLC22A12, SLC2A9*	AD or AR
Xanthinuria		
–	*XDH, MOCOS, MOCS1, MOCS2, GPHN*	AR
Failed urinary acidification		
–	*SLC4A1, ATP6VB1, ATP6VA4, CA2*	AD or AR
Hyperoxaluria		
–	*AGXT, GRHPR, HOGA1, SLC26A1*	AR
Dihydroxyadenine crystals		
–	*APRT*	AR

Howles SA, Thakker RV. Genetics of kidney stone disease. Nat Rev Urol. 2020 Jul;17(7):407-421

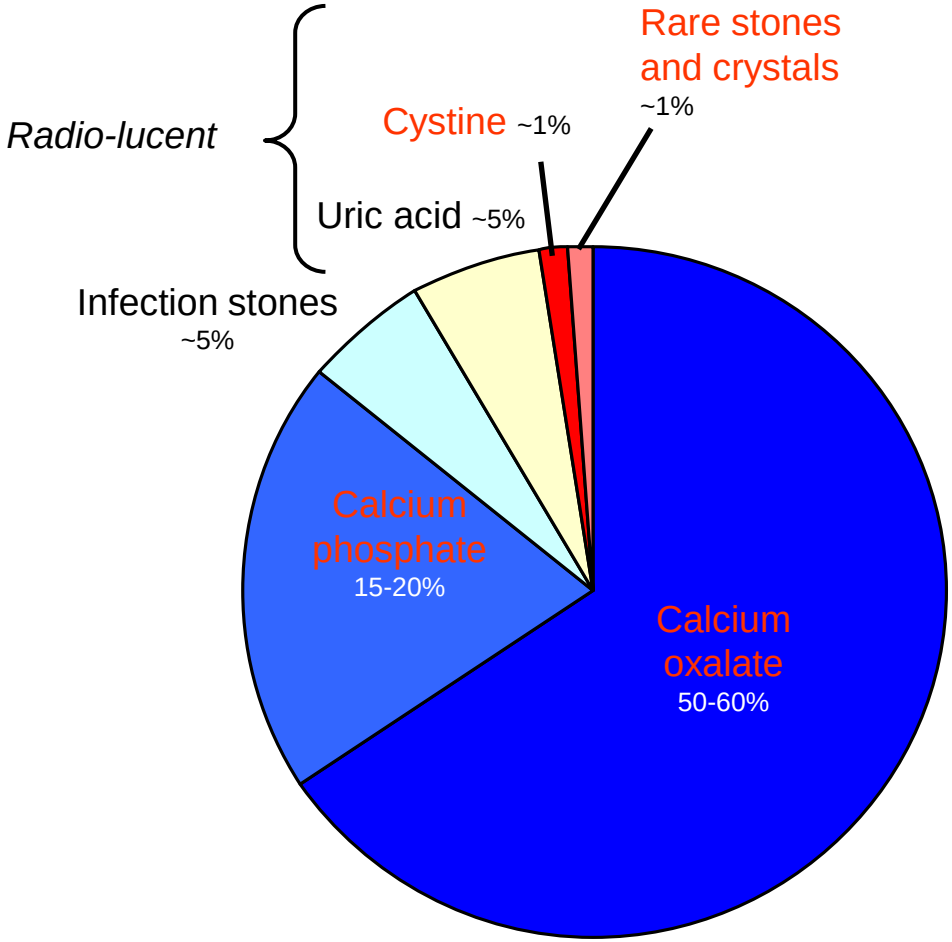
Table 3. Pointers to inherited disease in renal stone patients
Early onset
Family cases
Consanguineous parents
Highly-active stone disease (bilateral, multiple stones, frequently recurrent)
Associated nephrocalcinosis
Renal hyperechogenicity
Tubular dysfunction and related manifestations (*statural growth deficit, polyuria, bone disorders*)
Renal failure
Extrarenal manifestations (*sensorineural hearing defects, ocular abnormalities, neurological disorders*)
Particular stone composition and crystalluria
Monohydrate calcium oxalate (*whewellite*)
Cystine
Dihydroxyadenine
Xanthine

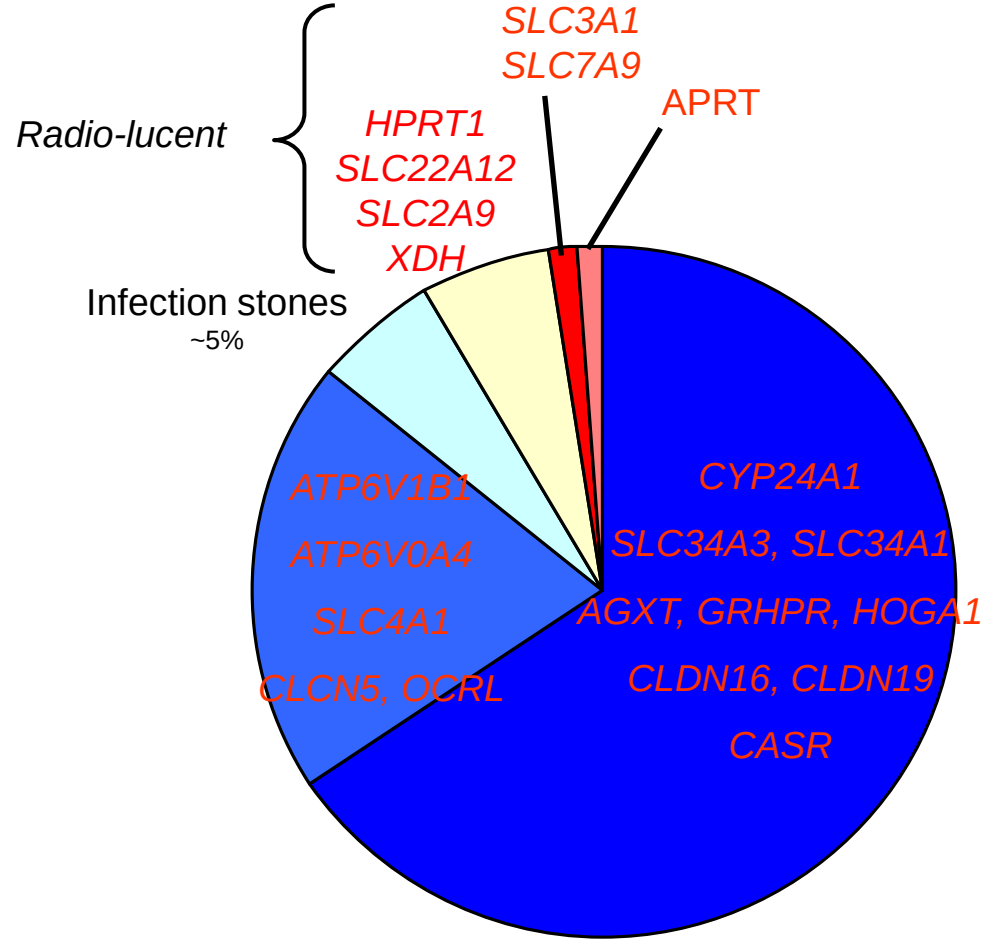
Clues for monogenic stone disease

1. Young patients (esp. with family history)
2. Very frequent stones
3. Looks like a tubulopathy
4. Unusual stone type

- low phosphate
- low mol weight proteinuria
- nephrocalcinosis
- progressive CKD
- deafness
- worsening DEXA

Ferraro PM, D'Addessi A, Gambaro G. Nephrol Dial Transplant. 2013 Apr;28(4):811-20.


Radio-lucent
Rare stones and crystals ~1%
Cystine ~1%
Uric acid ~5%
Infection stones ~5%
Calcium phosphate 15-20%
Calcium oxalate 50-60%


Radio-lucent
SLC3A1
SLC7A9
APRT
HPRT1
SLC22A12
SLC2A9
XDH
Infection stones ~5%
ATP6V1B1
ATP6V0A4
SLC4A1
CLCN5, OCRL
CYP24A1
SLC34A3, SLC34A1
AGXT, GRHPR, HOGA1
CLDN16, CLDN19
CASR

Metabolic screen £100

•	pB	Collection Period[Hours]		24	Hours			
•	pB	Urine Volume [mL]		3816	mL			
•	pB	Ur. Phosphate conc.		3.7	mmol/L	[	]	
•	pB	Urine Phosphate		14.1	mmol/24 hr	[12.9 - 42.0	]	
•	pB	Ur. Calcium conc.		2.8	mmol/L	[	]	
•	pB	Urine Calcium	*	10.7	mmol/24 hr	[2.5 - 8.0	]	* high
•	pB	Ur. Magnesium conc.		1.5	mmol/L	[	]	
•	pB	Urine Magnesium		5.7	mmol/24 hr	[2.5 - 8.5	]	
•	pP	Urine Citrate Concentration		0.66	mmol/L			
•	pP	Urine Citrate Excretion		2.52	mmol/24 hr	[1.3 - 6.0	]	
•	pP	Urine Oxalate conc.		375	umol/L	[	]	
•	pP	Urine Oxalate excretion	*	1431	umol/24 hr	[< 460	]	* high
•	pB	Creatinine for CCL		Serum creatinine required for creatinine clearance				
•	pB	Collection Period[Hours]		24	Hours			
•	pB	Urine Volume [mL]		3816	mL			
•	pB	Ur. Urea conc.		55	mmol/L	[	]	
•	pB	Urine Urea		210	mmol/24 hr	[170 - 580	]	
•	pB	Ur. Potassium conc.		14	mmol/L			
•	pB	Urine Potassium		53	mmol/24 hr	[25 - 125	]	
•	pB	Ur. Sodium conc.		36	mmol/L	[	]	
•	pB	Urine Sodium		137	mmol/24 hr	[40 - 220	]	
•	pB	Ur. Creatinine conc.		3.17	mmol/L	[	]	
•	pB	Urine Creatinine		12.1	mmol/24 hr	[7 - 14	]	
•	pB	Creatinine Clearance		Unable to calculate				
•	pB	Ur. Urate conc.		0.72	mmol/L	[	]	
•	pB	Urine Urate		2.7	mmol/24 hr	[1.2 - 5.9	]	
•	pB	Ur. Protein conc.		0.05	g/L	[	]	
•	pB	Urine Protein	*	0.19	g/24 hr	[< 0.15	]	* high
•	pB	Urine Protein/Creatinine Ratio		16	mg/mmol	[< 30	]	
•	pB	Urine cystine spot screen		Negative				

Genetic screen £1000

PanelApp Panels Genes and Entities Activity Log in

Panels / Nephrocalcinosis or nephrolithiasis

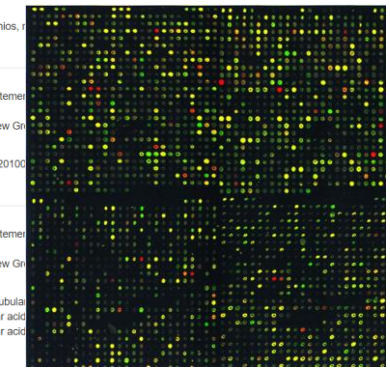
Version 2.2 of this panel was signed-off for the GMS. The current version, shown here, may differ from the signed-off version.

Nephrocalcinosis or nephrolithiasis (Version 2.16)

Level 3: Disorders of function
Level 2: Renal and urinary tract disorders

Relevant disorders: Renal tract calcification (or Nephrolithiasis or nephrocalcinosis), Renal tract calcification (or Nephrolithiasis/nephrocalcinosis), R256
Panel types: Rare Disease 100K, GMS Rare Disease Virtual, GMS Rare Disease, GMS signed-off

Green	XDH	3 reviews	BIALLELIC, autosomal or pseudoautosomal	Sources: Expert, Expert Review Green Phenotypes: Xanthinuria, type I, 278300 Tags
Green	STRADA	3 reviews 1 green 1 red	BIALLELIC, autosomal or pseudoautosomal	Sources: Expert Review Green, Other Phenotypes: Polyhydramnios, Tags
Green	SLC7A9	2 reviews 1 green	BOTH monoallelic and biallelic (but BIALLELIC mutations cause a more SEVERE disease form), autosomal or pseudoautosomal	Sources: Eligibility statemer, Expert, Expert Review Gr Phenotypes: Cystinuria 220100 Tags
Green	SLC4A1	2 reviews	BOTH monoallelic and biallelic, autosomal or pseudoautosomal	Sources: Eligibility statemer, Expert, Expert Review Gr Phenotypes: distal renal tubular, Renal tubular acid, Renal tubular acid Tags
Green	SLC3A1	2 reviews 1 green	BOTH monoallelic and biallelic (but BIALLELIC mutations cause a more SEVERE disease form), autosomal or pseudoautosomal	Sources: Eligibility statement prior genetic testing, Expert, Expert Review Green Phenotypes: Cystinuria 220100 Tags
Green	SLC34A3	2 reviews	BIALLELIC, autosomal or pseudoautosomal	Sources: Expert



https://panelapp.genomicsengland.co.uk/panels/149/

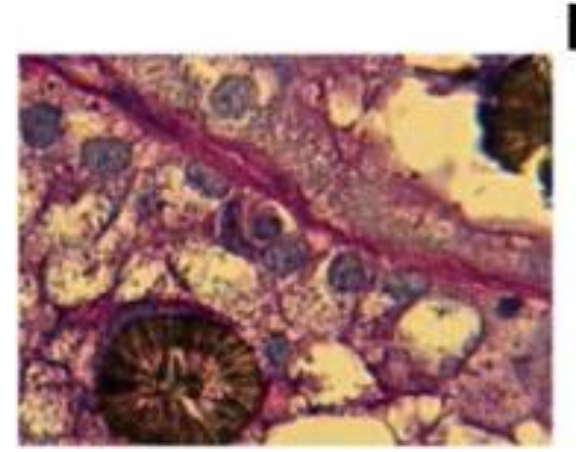
Some stone diseases don’t always present with stones!

Case 1

67 year old man

1. Hypertension since 2002 (controlled)
2. Stage 4 chronic kidney disease
    - Creatinine 129umols/l 2011
    - Creatinine 136umols/l September 2011
    - Creatinine 156umols/l April 2014
    - Creatinine 178umols/l April 2015
    - Creatinine 187umols/l August 2015 (eGFR 37mls/min corrected for ethnicity)
    - Creatinine 290 umols/l Dec 2016
    - Normal renal ultrasound 10 cm echogenic kidneys; no obstruction
    - Haematuria –ve
    - Trace proteinuria
3. Chronic low back pain since 2005
    - Attends Pain clinic
4. Prolactinoma

The patient had a renal biopsy. Diagnosis?



Adenine phosphoribosyltransferase (APRT) deficiency

Confirmed on enzyme analysis

High dose allopurinol. Creat 170 umol/l Feb 2021.

Defect: Enzyme
Inheritance: Autosomal recessive
Renal transplant: CAUTION!

APRT deficiency

Adenine phosphoribosyltransferase deficiency

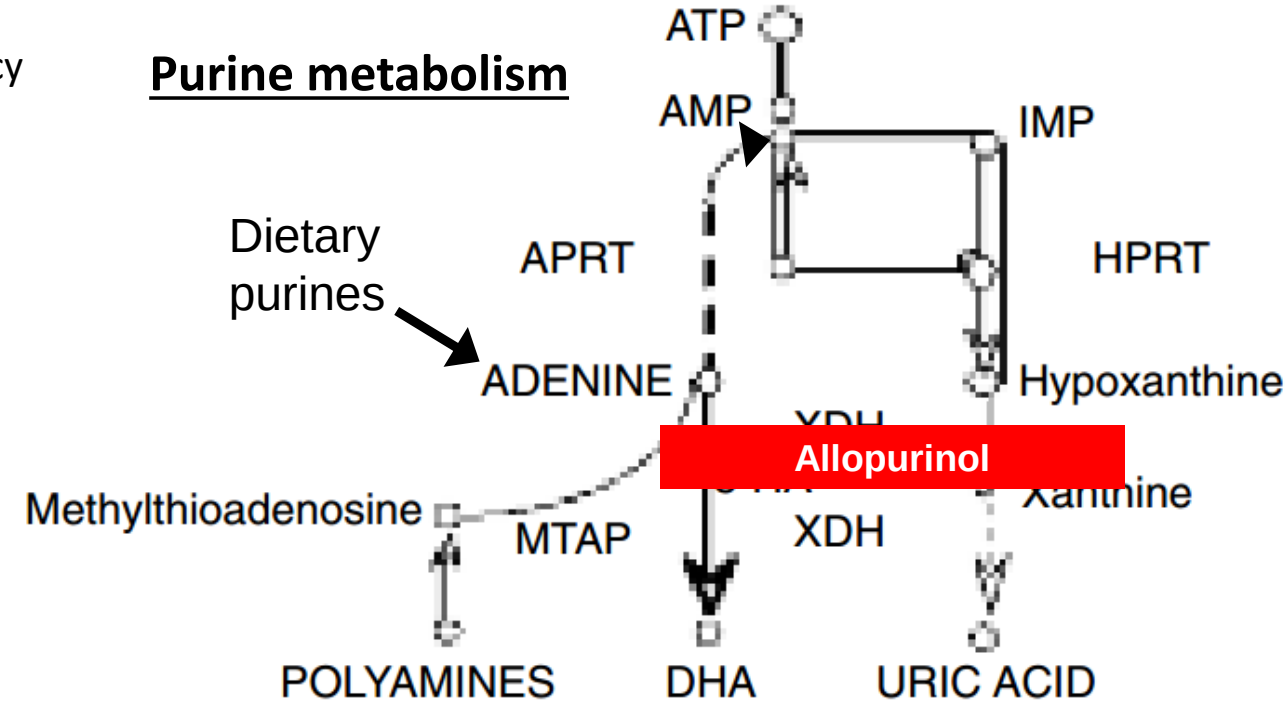
- Stones, sediment, or asymptomatic/CKD
- Only affects the kidney
- May “recur” after transplantation
- Presents at any age

Investigations

- Urine microscopy
- Stone analysis
- Red cell APRT enzyme activity
- (APRT genetics)
- Renal biopsy

Treatment

- Fluids, low purine diet, allopurinol 300-600 mg/day



2,8-DHA is plasma bound in the circulation, but precipitates out in the kidney

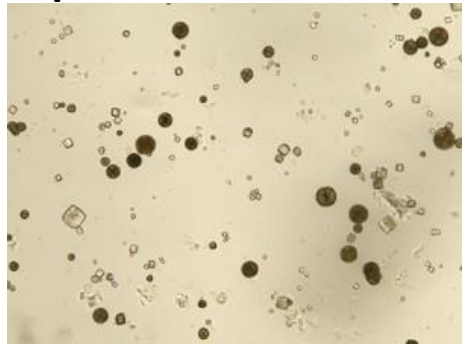


Image from rarerenal.org; flowchart from pumpa.org.uk

Nephrocalcinosis = calcification of the kidney that is NOT in the collecting system

Table 36.4 Causes of nephrocalcinosis

Cause	Disease	Location of nephrocalcinosis
Acute hyperphosphaturia	Acute phosphate nephropathy (due to sodium phosphate bowel prep), tumour lysis syndrome	Intracellular; cortical or medullary
Hypercalciuria + hypercalcaemia	Primary hyperparathyroidism (20 % have nephrocalcinosis), sarcoidosis, Vitamin D or milk-alkali syndrome	Medullary
Hypercalciuria + normocalcaemia	Tubulopathies (dRTA, MSK)	Medullary
	Rarer tubulopathies (all causes listed in 'genetic causes of calcium stones' table (Tables 36.1 and 36.2))	Medullary
Hyperoxaluria	Primary or secondary hyperoxaluria (see above)	Medullary
Structural or other disease	Severe disease of renal cortex (chronic glomerulonephritis, renal allograft rejection, renal cortical necrosis), renal tuberculosis	Cortical
Drugs	Analgesic nephropathy (chronic papillary necrosis)	Medullary

From: Moochhala SH, Unwin RJ, Renal Stone Disease, in: Practical Nephrology, Ed. M Harber, 2012

Case 2

- 39 year old male
- Left nephrectomy 2014
  - Non functioning left kidney with impacted stone in the left upper ureter
- This time, renal colic: AKI on the urology ward: peak creatinine 247 umol/l
- Multiple calcium oxalate stones in remaining kidney
  - Stone analysis from left PCNL in 2013: Calcium oxalate 96% (monohydrate 90%)
  - No family history of stones
- Chronic loose stool – normal gastro investigations 2019
- Follow up clinic – creatinine now 115 umol/l
- 24 h urine collection: normal calcium excretion, oxalate 789 umol/24h (<450)

Diagnosis?

The likeliest diagnosis is:

A. Primary hyperoxaluria

B. Secondary hyperoxaluria

C. Ethylene glycol poisoning

D. Primary hyperparathyroidism

Answer: Could be A or B

Defect: Enzyme
Inheritance: Autosomal recessive
Renal transplant: CAUTION!

Primary hyperoxaluria

Disorders of glyoxylate metabolism

Alanine:glyoxylate aminotransferase (AGT) **= PH1 (liver peroxisomes)**

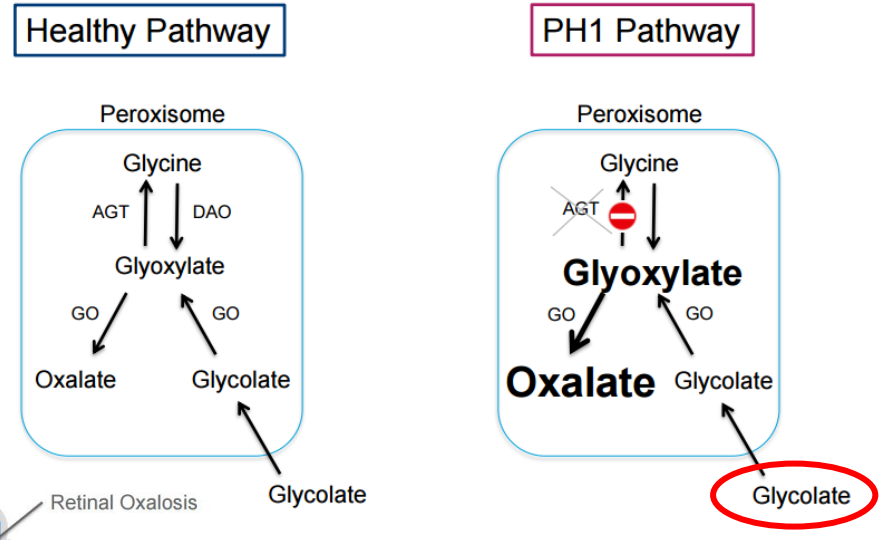
glyoxylate/hydroxypyruvate reductase (GRHPR) **= PH2 (cytosol)**

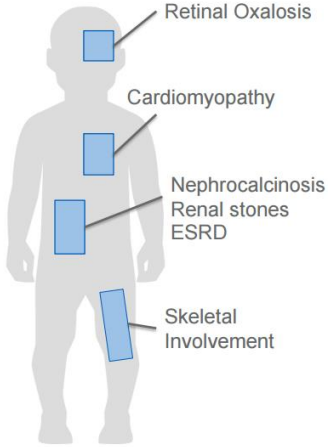
4-hydroxy-2-oxoglutarate aldolase (HOGA1) **= PH3 (mitochondrial)**

Gut malabsorption **= Secondary hyperoxaluria**

Investigations:
24h urine oxalate (abnormal >400 umol)
Urine glycolate, glycerate, hydroxyoxoglutarate
PH genetics
(PH1 enzyme testing) requires liver biopsy

Treatment for PH1:
Fluids, pyridoxine, dialysis, liver-kidney transplant +/- dialysis, RNAi therapy





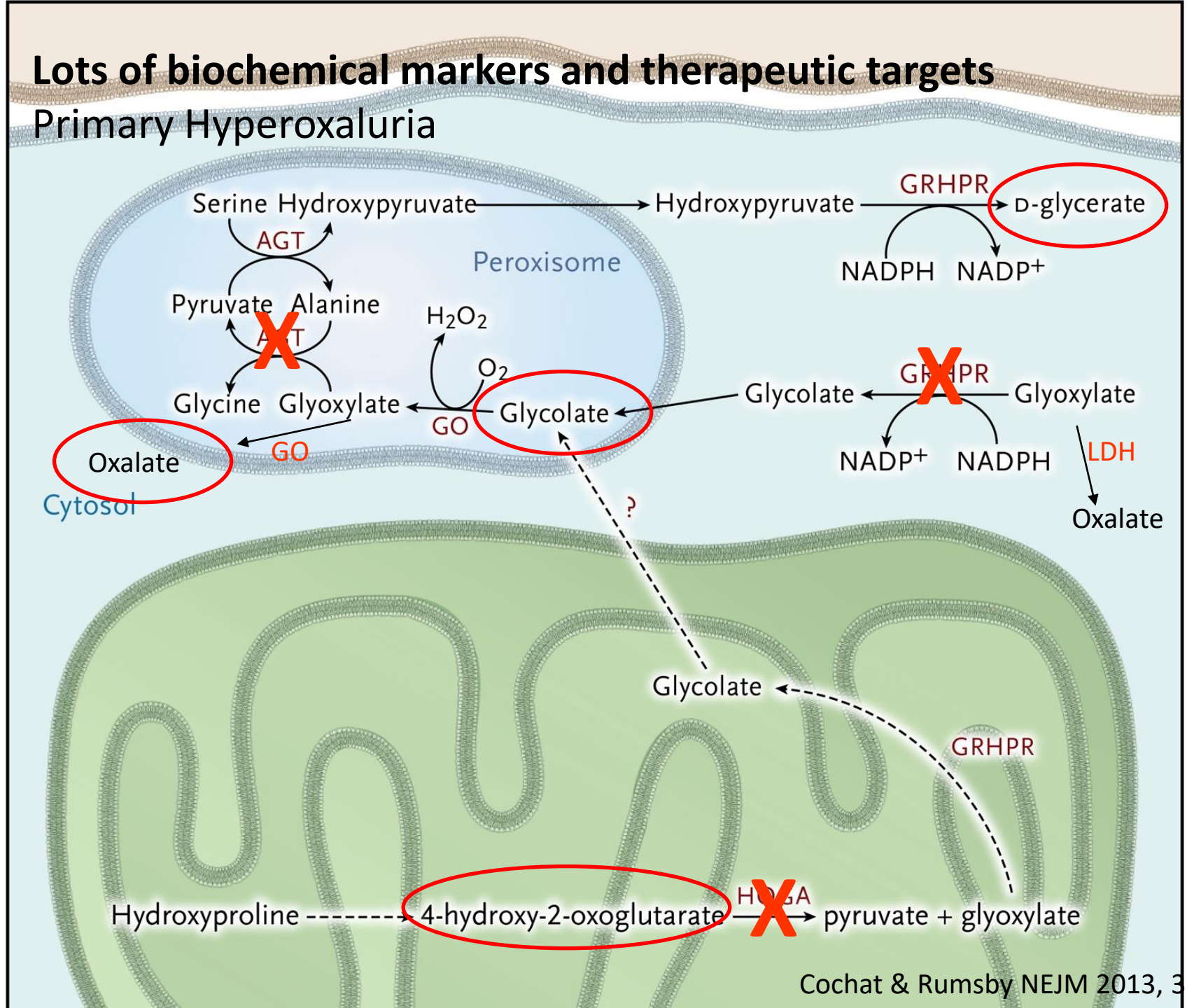
Symptoms:

Paediatric:
growth/ESRD
Stones (not always)
Systemic oxalosis

Images from alnylam.com

Lots of biochemical markers and therapeutic targets

Primary Hyperoxaluria

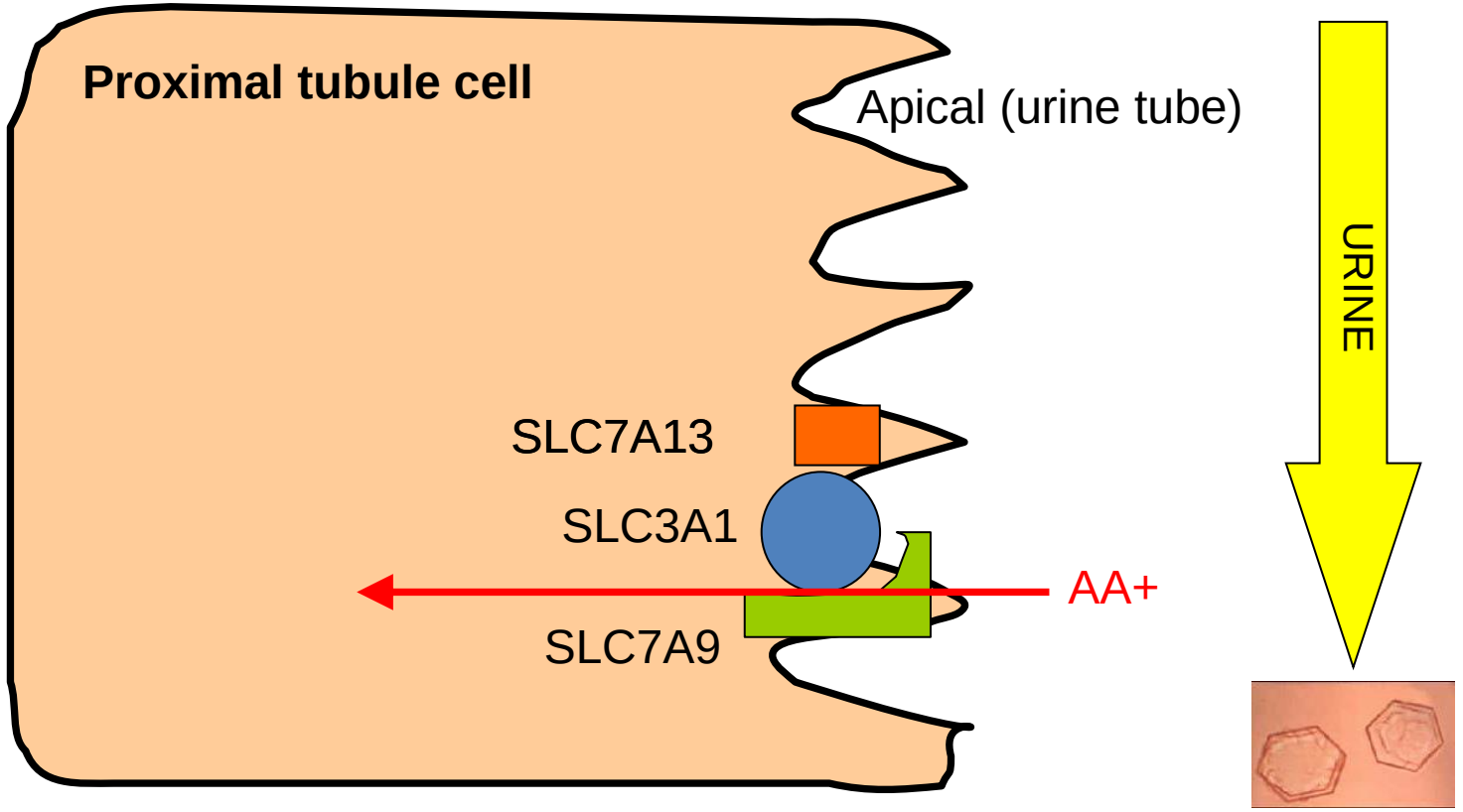


Cochat & Rumsby NEJM 2013, 369,658

Cystinuria

Defect: Transporter
Inheritance: Autosomal recessive
Renal transplant: safe

- The commonest inherited stone-forming tubulopathy
- A genetic disease
  But genetics not needed for diagnosis or treatment!



SLC3A1 (rBAT)+SLC7A13 (AGT) complex:

- is present in the late proximal tubule
- can transport cystine

Nagamori 2016 PNAS

Does the diagnosis make clinical sense?

Case 3

Bilateral tiny renal stones
- presented age 34
- Long distance lorry driver
- spontaneous passage x2 (2010, 2012) then lithotripsy 2012
- Stone analysis: predominantly calcium oxalate
- positive family history (mother)

Positive cystinuria screen/low level aminoaciduria
- not hypercalciuric

QUALITATIVE CYSTINE SCREEN Positive

Urine cystine/creatinine 22.0(3-12)
Urine Ornithine/Creatinine 8.5 (0.5-2.0)
Urine Lysine/Creatinine 214.7(6-41)
Urine Arginine/Creatinine 3.7(0-3.7)

All levels raised or borderline, but not grossly so. There is NO generalised aminoaciduria, which given the relatively moderate cystine excretion would suggest heterozygous rather than homozygous state.

Low level aminoaciduria with calcium stones and family history
- preliminary result Jul 2017: SLC7A9 c.562G>A, p.(Val188Met)

De novo or inherited from mother?

Borderline dibasic aminoaciduria but makes calcium stones

Does he have cystinuria?

Case 4

- 52 M, recurrent renal stones
  - Right PCNL 2002, bilateral URS x5 since
  - Bilateral stones but stable on latest scan
  - Spontaneous passage Aug 2016
- Proteinuric CKD stage 4
  - Slow decline, creat 335 umol/l Jan 2017, uPCR 255 mg/mmolCr
- Family history of stones and renal disease
  - Uncle had stones and renal transplant

Which test would be the most helpful diagnostically?

A. Infra-red stone type analysis
B. 24h urine oxalate excretion
C. Urinary retinol binding protein excretion
D. Renal biopsy
E. Cystinuria gene exon sequencing (SLC3A1, SLC7A9)

Dent disease

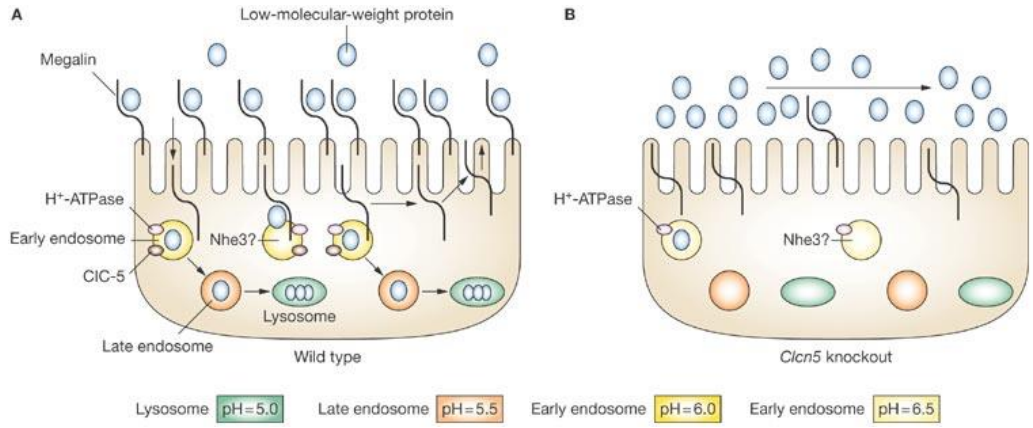
Defect: Transporter
Inheritance: X-linked recessive
Renal transplant: safe

Proximal tubular transporter defect
- Like cystinuria
- Defective chloride channel CLCN5 (sometimes OCRL)

X-linked recessive
- Unlike the other conditions; males only

Clinical features
- LWM proteinuria (sometimes nephrotic range)
- Hypercalciuria
- Stones/nephrocalcinosis/bone disease
- CKD/ESRD (independent of stones)

Differential diagnosis
- Other causes of proximal tubular dysfunction (tenofovir, cystinosis, myeloma, ifosfamide)



Guggino. *Nat Clin Pract Nephrol.* 2007;3:449–455.

Proximal tubular transporter not working

Cystinuria

Problem with cystine transport

Autosomal recessive

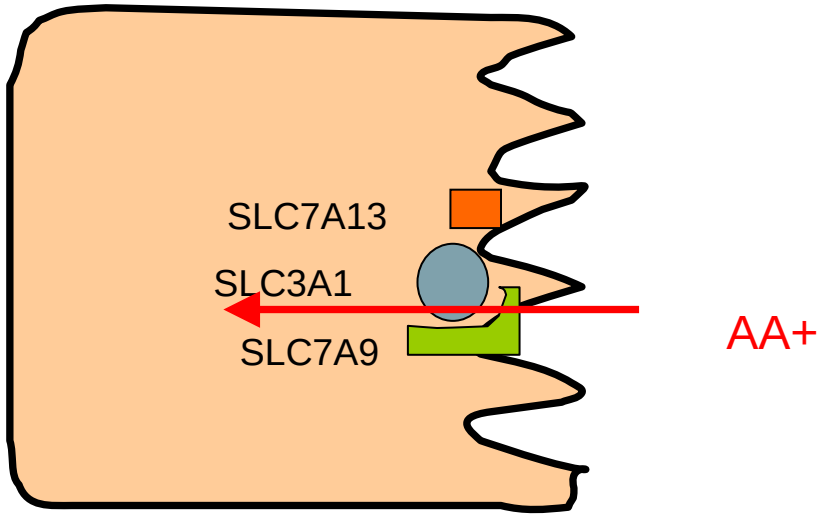
Sometimes dominant

Clinical features

Stones

No deficiency state

No kidney failure (by itself)



Dent disease

Problem with chloride channel CLCN5

X-linked recessive

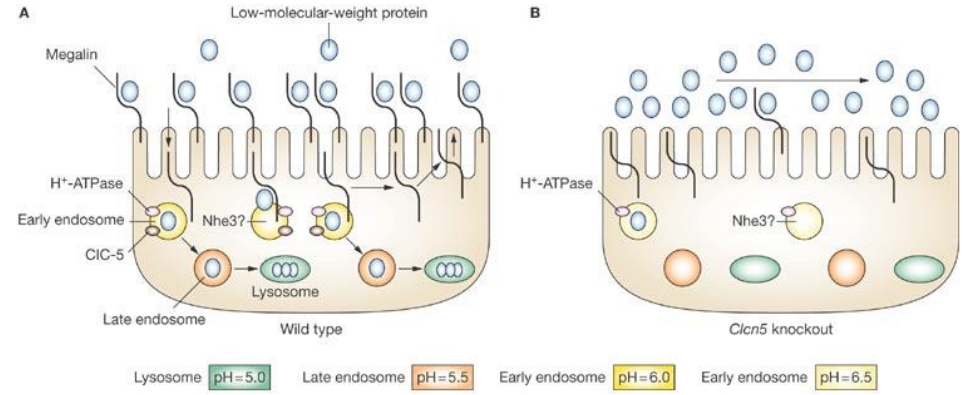
Only affects males

Clinical features

Protein leakage

Stones/hypercalciuria/bone disease

Kidney failure



Case 5

Clinical history is essential to interpreting the tests!

- 23 year old female, professional dancer
- Bilateral medullary nephrocalcinosis and stones since age 13
- URS x7, SWLx3
- Calcium oxalate 100% (monohydrate 40% dihydrate 60%)
- Urine oxalate 1431 umol/24h March 2016
- FH of stones (mother presented in her 50s)
- Vitamin D 130 nmol/l with low PTH (0.8 pmol/l) and hypercalciuria (10 mmol/24h) in 2016

Spent a year travelling around Spain and Jamaica

- Abnormal urine furosemide/fludrocortisone acidification (min pH 6.44) in 2017
- Abnormal urine ammonium chloride acidification (min pH 5.6 at 5 hours) in 2017
- Normal urine citrate. Serum potassium 4.3 mmol/l, bicarbonate 23 mmol/l (norma
- Bone density May 2018: lumbar T score -0.1, femoral T score +1.1 (normal)

Became vegan in 2016

DIAGNOSIS Feb 2019

Hereditary autosomal dominant distal Renal Tubular Acidosis

Genotype: SLC4A1 c.980C>G p.Pro327Arg

Distal renal tubular acidosis

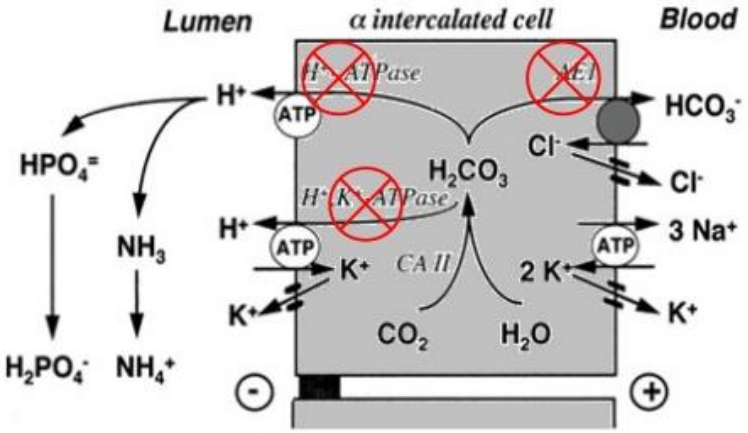
Defect: Transporter
Inheritance: Autosomal dominant or recessive; or acquired
Renal transplant: safe

- Not proximal, but distal
- Transporter defect
- Autosomal dominant (AE1) or autosomal recessive (H+/ATPase)
- More commonly acquired: Autoimmune (esp Sjogren's), ifosfamide, NSAIDs

Diagnosis
- Normal anion gap metabolic acidosis
- Hypercalciuria
- Hypokalaemia (due to secondary hyperaldosteronism)
- Bone and stone disease (calcium phosphate)
- Acidification defect

Treatment
- Alkalinisation (potassium citrate)

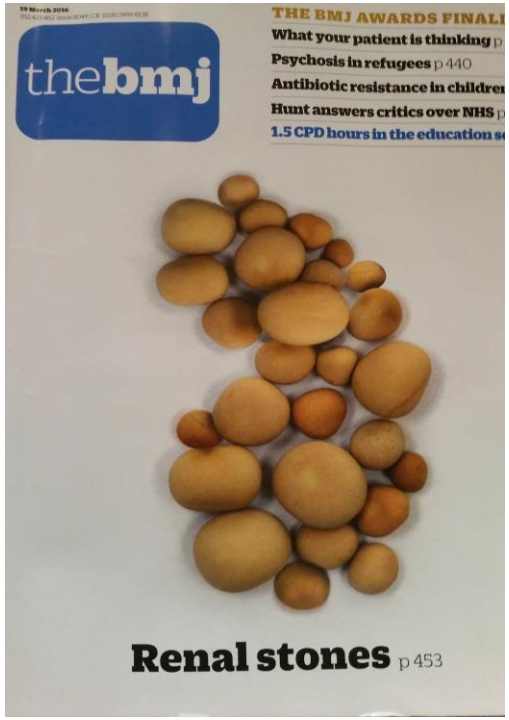
Autosomal recessive	***Autosomal dominant***
Deafness	*No deafness*
ATP6V0A4 *ATP6V1B1*	*SLC4A1*



Soriano. *J AM Soc Neph.* 2002;13:2160–2170.

Rare Disease Groups (RADAR)

- Autosomal Dominant Polycystic Kidneys Disease (ADPKD)
- Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)
- Alport Syndrome
- Adenine Phosphoribosyltransferase Deficiency (APRT-D)
- Autosomal Recessive Polycystic Kidney Disease (ARPKD)
- Atypical Haemolytic Uraemic Syndrome (aHUS)
- Calciphylaxis
- Cystinosis
- Cystinuria
- Dent Disease & Lowe Syndrome
- Fabry Disease
- Fibromuscular Dysplasia
- Haemolytic Uraemic Syndrome
- Hepatic Nuclear Factor 1B mutation (HNF1b)
- Hyperoxaluria (Primary Hyperoxaluria, Oxalosis)
- Hypokalaemic Alkaloses
- IgA Nephropathy
- Membranous Nephropathy
- MPGN, DDD & C3 Glomerulopathy
- Nephrotic Syndrome
- Pregnancy and Chronic Kidney Disease
- Pure Red Cell Aplasia (PRCA)
- Retroperitoneal Fibrosis
- Tuberous Sclerosis
- Vasculitis



Population prevalence:
-Renal vasculitis 0.001%
-End stage renal failure 0.06%
-Renal stone disease ~1%
- Rare renal stone disease 0.01%

Diagnosing rare stone disease is difficult!

- Often autosomal recessive, therefore often no family history of stones
- Often crystallopathies/nephrocalcinosis, therefore often no personal history of stones
- Common stone types can have a rare cause
- The standard “stone screen” doesn’t always pick up rare causes

Conclusions – practical points

- You need to decide on clinical grounds which stone forming patients you are going to (a) investigate (b) treat
- The (patho)physiology usually directs the genetics
- Certain monogenic stone disorders **must** be identified to avoid recurrence in renal transplant – remember the clues!
- Stones are increasing in prevalence, and associated with obesity and cardiovascular disease

Next Webinars

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

Date: **13 April 2021**

Speaker: **Rosanna Coppo**

Topic: **IgA nephropathy and Henoch-Schönlein nephritis**

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

Date: **20 April 2021**

Speaker: **Nicole van de Kar**

Topic: **STEC associated HUS**

ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders

Date: **04 May 2021**

Speaker: **Michael Somers**

Topic**: Acute post-streptoccocal GN**

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