Genetics of Nephrolithiasis and Nephrocalcinosis - known genes and mechanisms

(putting genes in their place and the dark matter)

**Bodo B Beck, Institute of Human Genetics,
University Medical Center Cologne**

XII Ogolnopolska Konferencja Polskiego Towarzystwa Nefrologii Dzieciecej
Lublin Maja 23- 25.2013

In the great majority of cases, urolithiasis is a painful, but otherwise benign,condition …

Jungers et al. AJKD 2004

Nephrolithiasis is a common condition …
…lifetime risk of 6,3% in men and 4,1% in women
prevalence is increasing …
… imposes a high health and economic burden …

Sakhaee et al. KI 2011

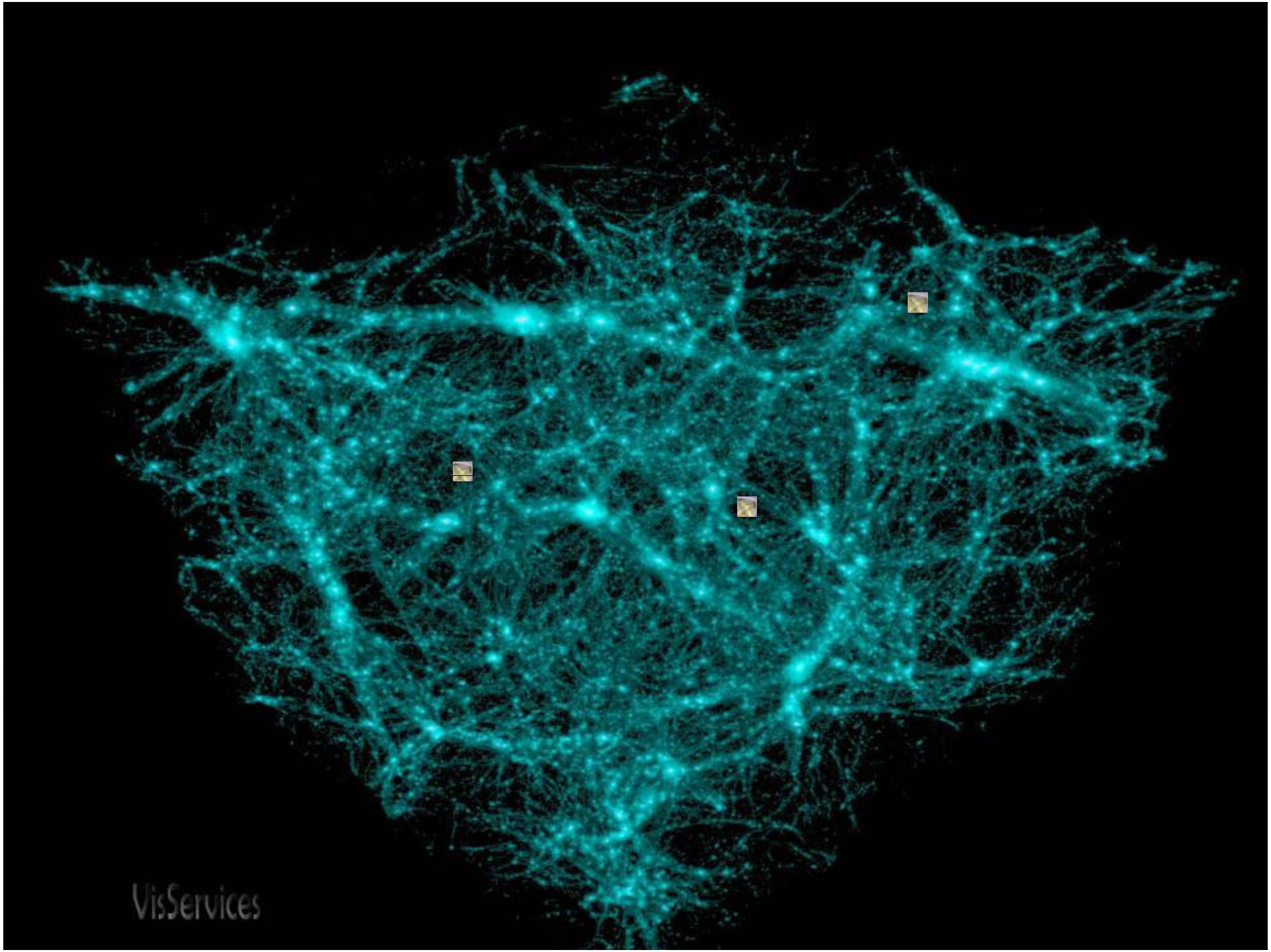

VisServices

Table 1. Demographic Characteristics of 45 Patients With Nephrolithiasis-Related ESRD With Respect to Stone Disease Type

	Struvite	Uric Acid	Calcium	Hereditary
No. of patients	19	8	12	6
Sex (M/F)	6/13	5/3	3/9	5/1
Unilateral nephrectomy	3	3	4	0
Acquired atrophy	3	2	1	0
Congenital atrophy	1	1	0	0
Single functioning kidney (%)	36.8*	75.0	41.7	0
Age at start of dialysis (y)	58.7 ± 12.8	71.1 ± 10.1†	61.2 ± 12.1	25.4 ± 5.5‡

NOTE. Values expressed as number of patients or mean ±1 SD unless otherwise noted.
*Overall chi-square, $P < 0.01$.
†Fisher's exact test, $P = 0.015$ for uric acid versus struvite.
‡Fisher's exact test, $P < 0.001$ for hereditary versus all other groups.

Jungers et al. AJKD 2004

…female patient (dob 1973) …, at the age of 3 years bilateral kidney stones were noted

1991 ESRD

1994 1st kidney transplant- delayed graft function

1995 graftectomy.

2002 2nd kidney transplant, complicated by acute graft deterioration

interpreted as acute rejection and treated with OKT3

renal function improved

do you agree?

Table 2. Evolution of the Prevalence of Nephrolithiasis-Related ESRD With Time

	1989-1994 (period I)	1995-2000 (period II)	*P*
Nephrolithiasis-related ESRD	28/680	17/711	0.07
Infection stones	11 (39.3)	8 (47.1)	0.42
Calcium stones	10 (35.7)	2 (11.8)	0.08
Hypercalciuria	3	1	
Medullary sponge kidney with hypercalciuria	5	0	
Primary hyperparathyroidism	1	1	
Sjögren's syndrome	1	0	
Uric acid stones	4 (14.3)	4 (23.5)	0.18
Hereditary diseases	3 (10.7)	3 (17.6)	0.13
Cystinuria	1	1	
Primary hyperoxaluria type 1	2	2*	

NOTE. Figures in parentheses are percentages relative to the number of nephrolithiasis-related cases of ESRD in the same period.

*One patient underwent preemptive liver-kidney transplantation.

Jungers et al. AJKD 2004

…female patient (dob 1973) …, at the age of 3 years bilateral kidney stones were noted (continued)

2003 oxalate deposition noted on graft biopsy, elevated urinary oxalate excretion

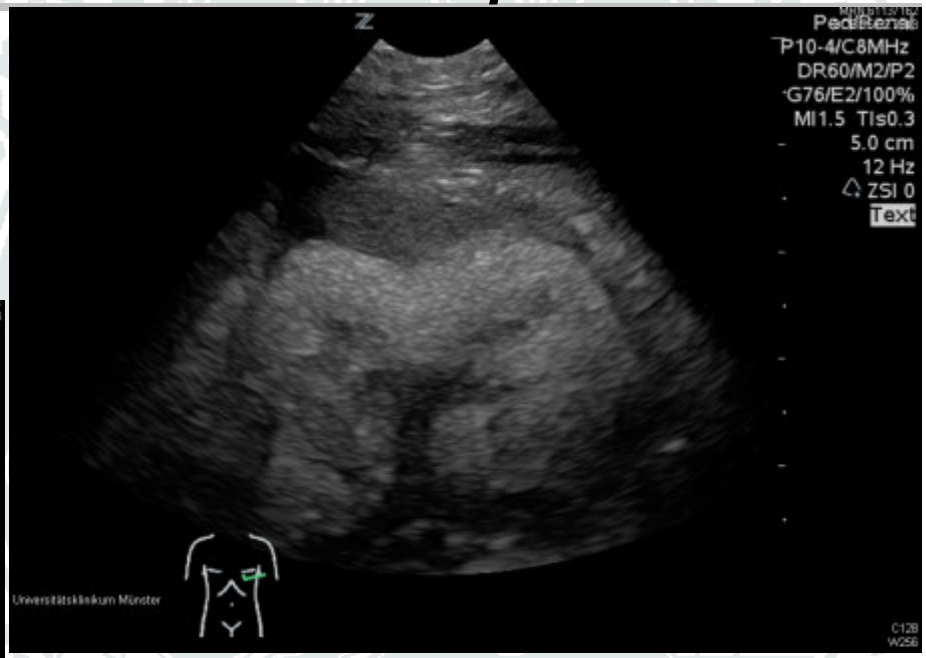
2004 back on dialysis

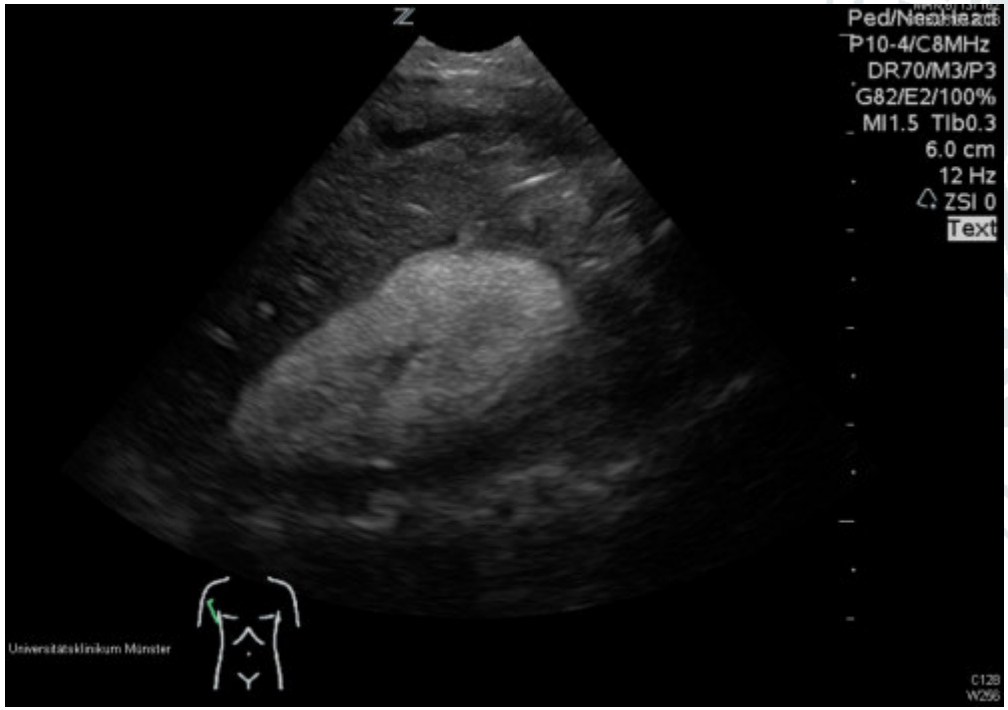
2013 treatment resistant hyperparathyroidism, multiple bone fractures

discussion about living related kidney donation!

„I think this is a sad case and it is too late …“

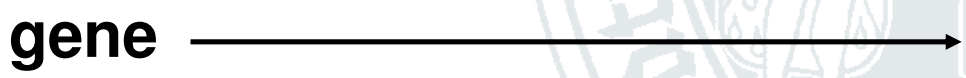
Nephrolithiasis and Nephrocalcinosis





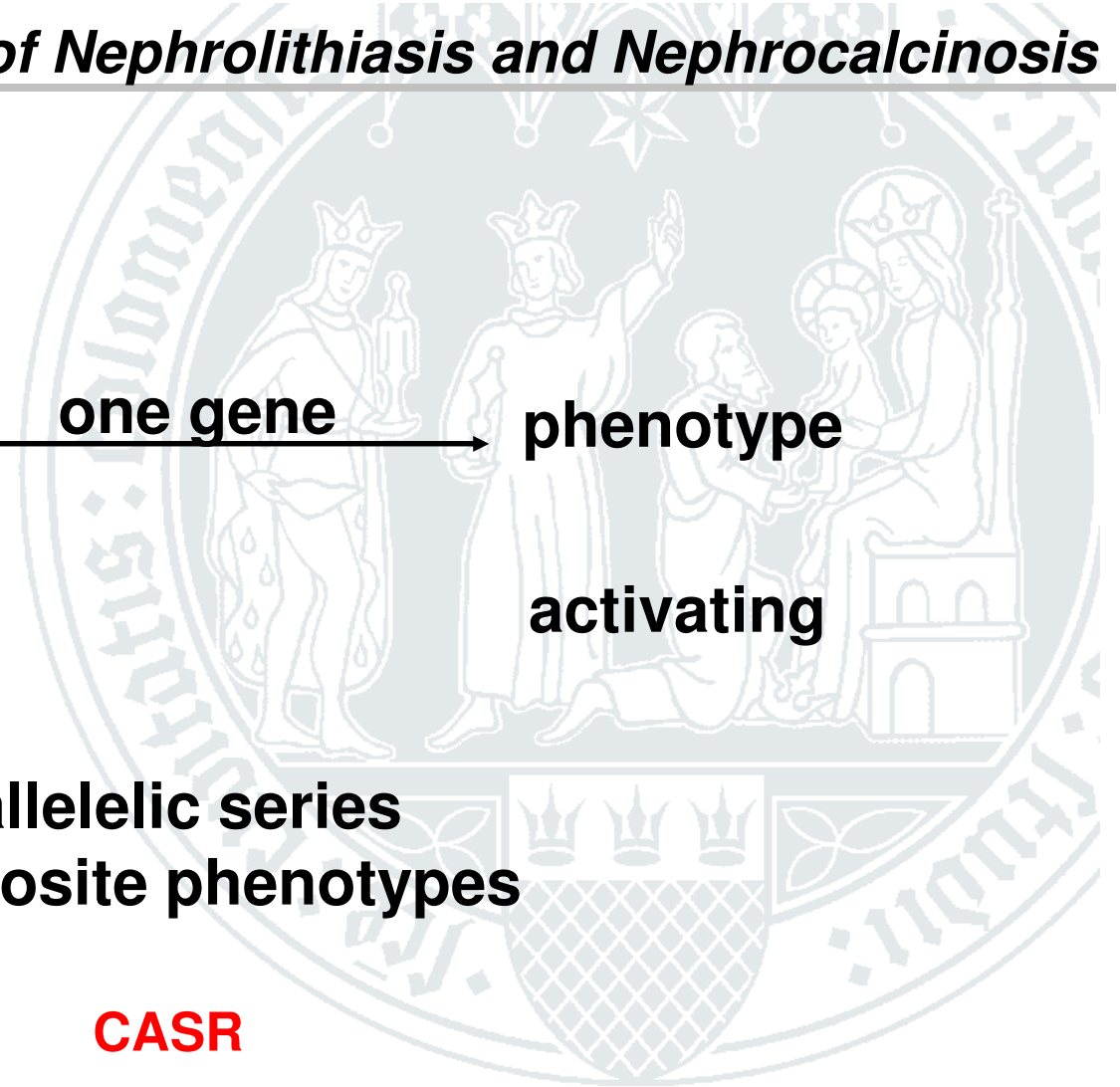
„ baby girl born February 25,2013 with diffuse NC and ARF“

- **familial disposition/disease**
- **early onset disease**
- **highly active stone disease (bilat, rec, and multiple concrements)**
- **associated (progressive) nephrocalcinosis**
- **renal failure**
- **extrarenal manifestations**
- **syndromal UL/NC (e.g. WBS)**
- **particular laboratory findings (Mg, Pi loss etc.)**
- **particular stone composition / crystalluria**
- **rec UTI?**
- **medications, dietary habits**


gene
phenotype

genetic heterogeneity

allelic series/spectrum



phenotype ← **one gene** → **phenotype**

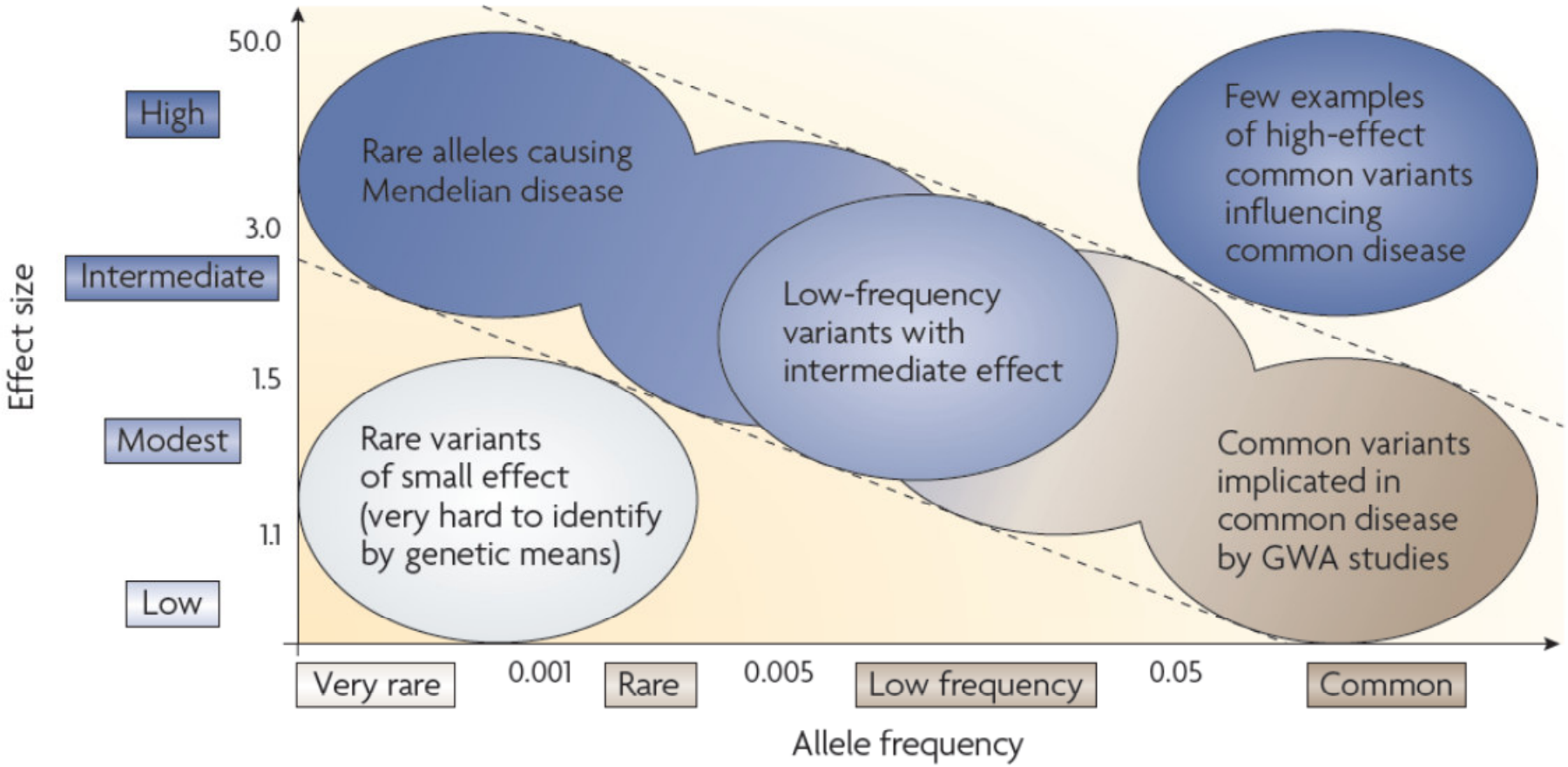
inactivating **activating**

allelelic series
opposite phenotypes

CASR

ad hypocalciuric hypercalcaemia and hyperparathryoidism

ad hypocalcaemic hypercalciuria and hypoparathyroidism



orphan diseases are not rare (on a cumulative basis) and affect 1/17

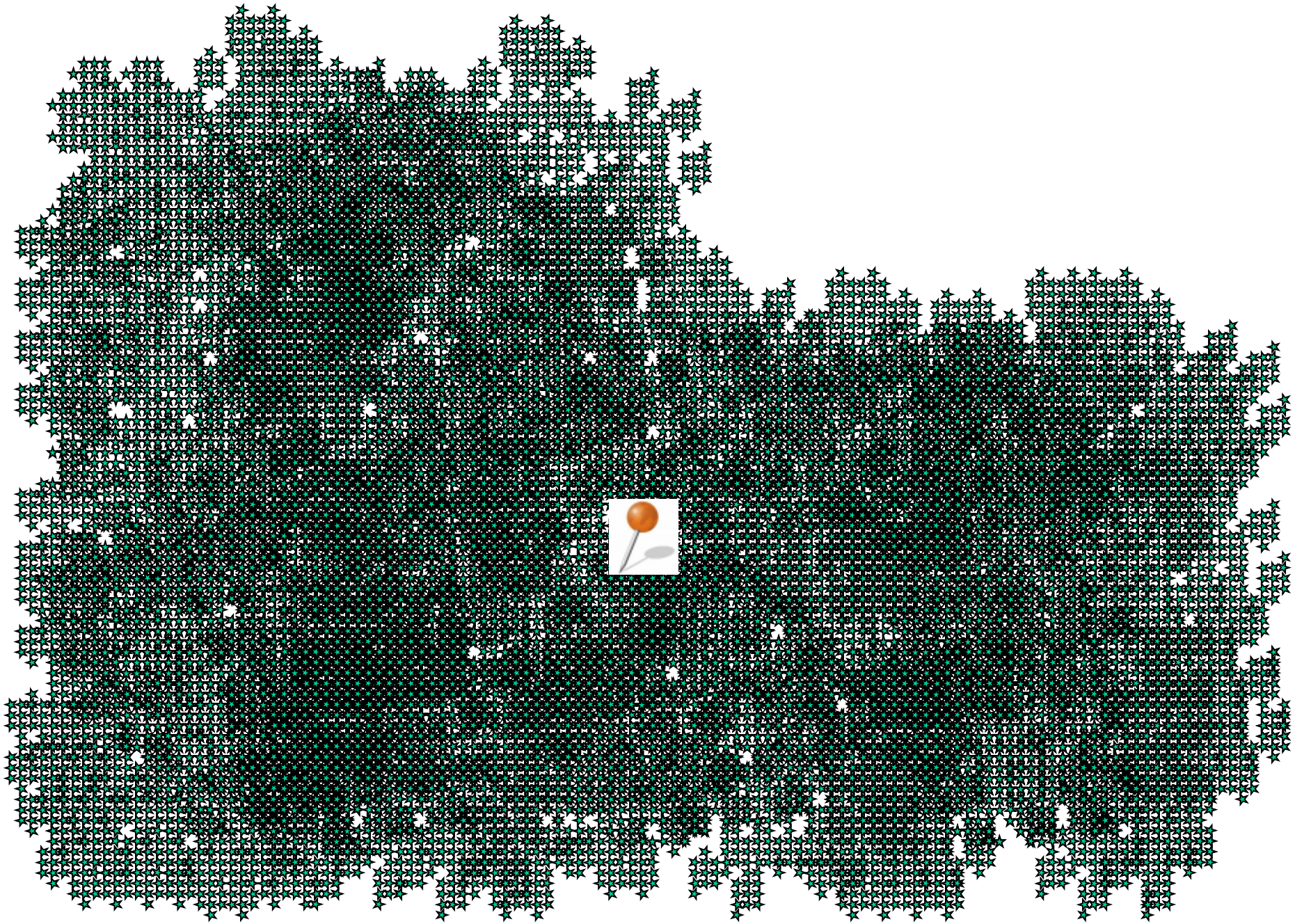
Antonarakis et al. nature reviews genetics, 2010

it's not easy to make a correct diagnosis

- **general problems:**
- **there are many monogenic disease and syndromes (>7000)**
- **monogenic does not mean monotonous**
- **there might be no typical phenotype /clinical course**
- **textbook/literature might describe the atypical case/course**
- **we have good and bad days**
- **we are not as good as we like to think in clinical diagnosis**

it‘s not easy to make a correct diagnosis

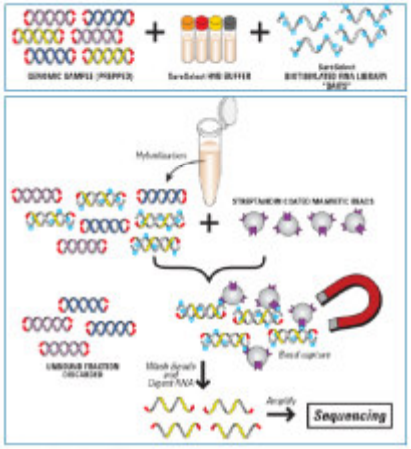
- **specific problems:**
- **procedure orientated medicine (stone surgery)**
- **tests (biochemical, genetic etc.) are not available**
- **no specific clinic / symptoms**
- **multisystemic disease obscures clinical hallmarks**
- **inter and intrafamilial phenotype variability**
- **genetic heterogeneity**



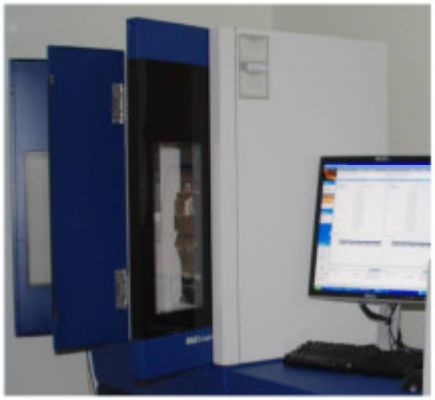
hypothesis free testing
massive parallel sequencing

Exome sequencing – genome-wide mutation detection

In liquid exome enrichment:
Agilent's SureSelect

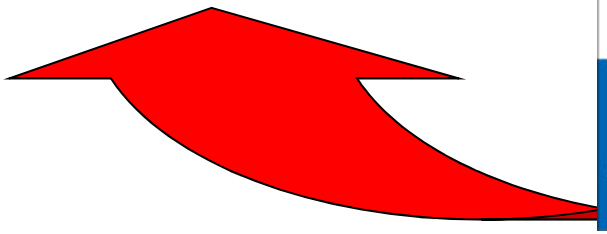


Next generation sequencing:
SOLiD™ 4 System



8 exomes per run

Human Genetics Nijmegen



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in Molecular Medicine
Sept. 30 - Oct. 02, 2012

The Genomic Future of Medicine

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Ernst Klenk Lecture - Han G. Brunner - Nijmegen, NL

Venue
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Building 44b, Joseph-Stelzmann-Str. 52

Scientific Organizers
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Brunhilde Wirth - Cologne, DE

CMMC Organizers
Thomas Benzing - Cologne, DE
Debora Grosskopf-Kreiher - Cologne, DE

18 CME credits

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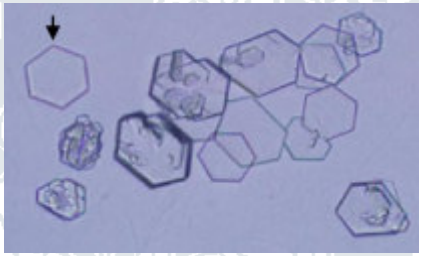
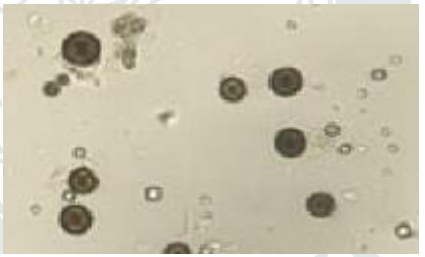
ar monogenic Urolithiasis a/o NC

Cystinuria (*SLC3A1*/*SLC7A9*): 1:7000 (?)



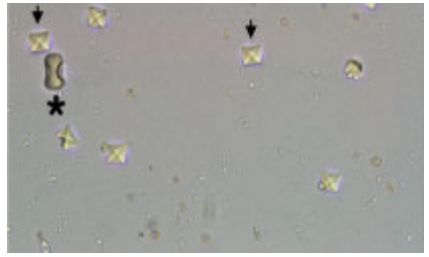
2,8 Dihydroxyadeninuria (APRT): 1:10^5



 # Prim. hyperoxaluria type I (*AGXT*): 1-3(9):10^6

 # Prim. hyperoxaluria type II (*GRHPR*): 50 patients (?)

 # Prim hyperoxaluria type III (*HOGA 1*): > 50 patients (?)



ar monogenic Urolithiasis a/o NC

Xanthinuria (*XDH* aka *XO*): >150 patients (?)

FHHNC (*CLDN16*)

FHHNC plus ocular involvement (*CLDN19*)

Bartter syndrome type 1 (*SLC12A1*)

Bartter syndrome type 2 (*KCNJ1*)

distal RTA (*ATP6N1B*/ATP6B1)

ar monogenic Urolithiasis a/o NC

hypophosphatemic ricketts c hypercalciuria (*SLC34A3*,NPT2c)

idiopathic infantile hypercalcemia (IHH) (*CYP24A1*)

ad monogenic Urolithiasis a/o NC

distal RTA (*SLC4A1/*AE1)

hypocalcaemic hypercalciuria hypoparathyroidism (*CASR*)

(# urolithiasis c bone demineralization *(NHERF1/SLC9A3*))

 # Williams-Beuren Syndrome (WBS; 7q11.23): 1:8000

 # Down Syndrome (47,+21)

XL monogenic Urolithiasis a/o NC

Dent‘s disease I (*CLCN5*)

Dent‘s (Lowe) disease II (*OCRL1*)

Lesch Nyhan Syndrome (*HPRT*): 1-9:10^6

good candidate genes for monogenic Urolithiasis a/o NC

genes involved in calcium phosphate metabolism

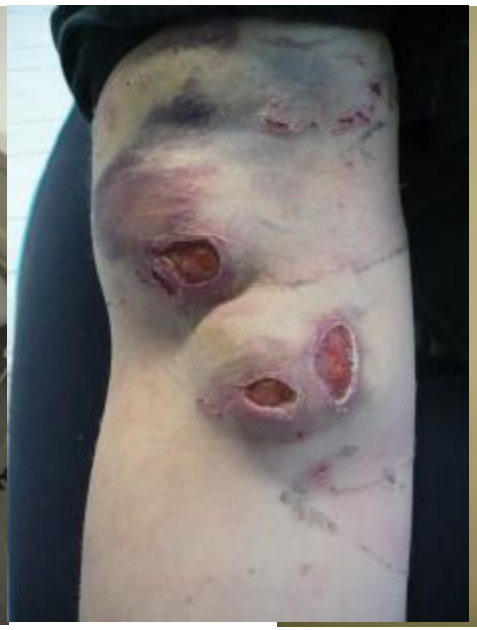
NHERF1 for UL with bone fractures and reduced bm

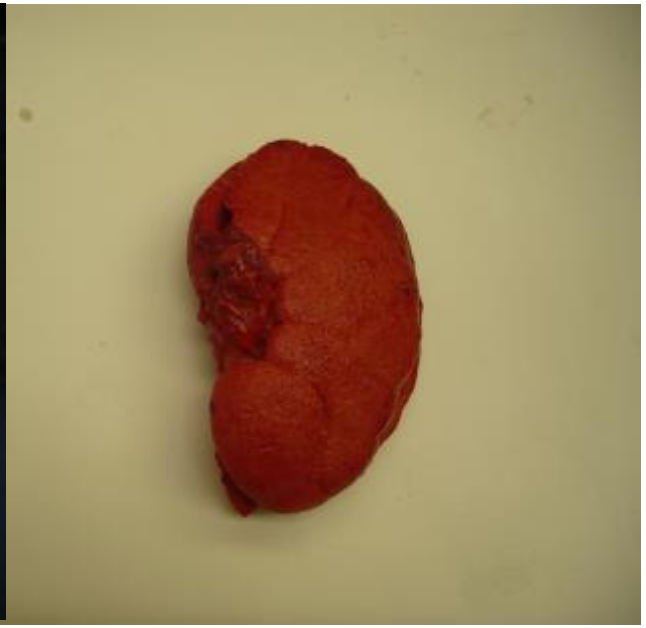
UMOD (MCKD II)

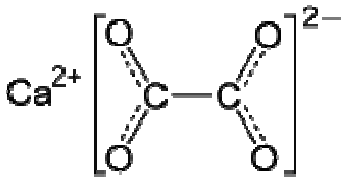
VDR

HOGA1 (PH III)

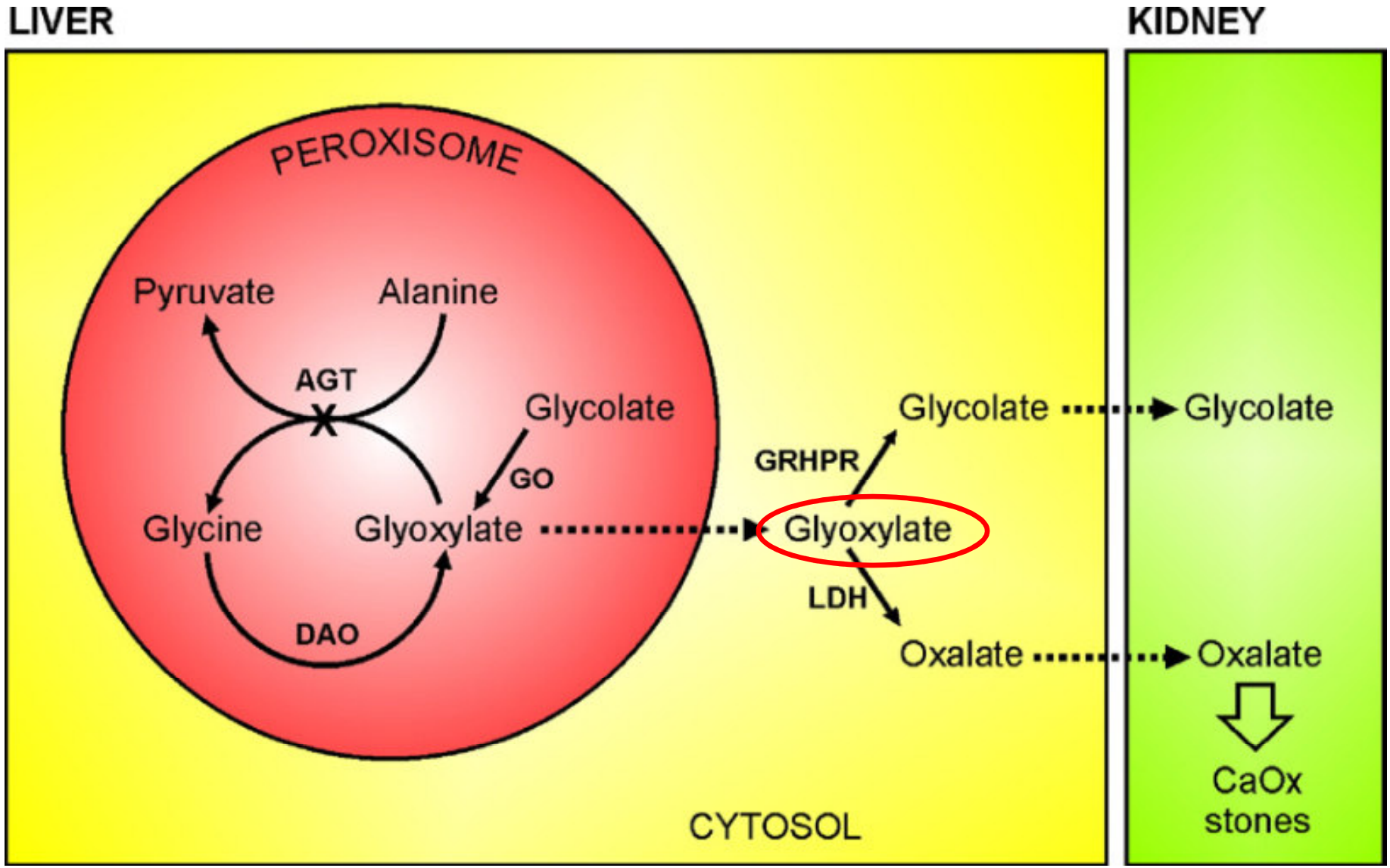
PH – and glyoxylate metabolism







PH and glyoxylate metabolism



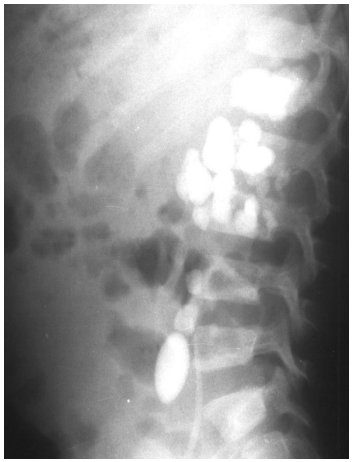
Danpure JC Biochimica et Biophysica Acta, 2006

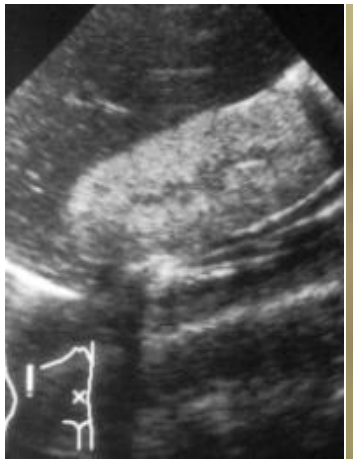
PH in a nutshell

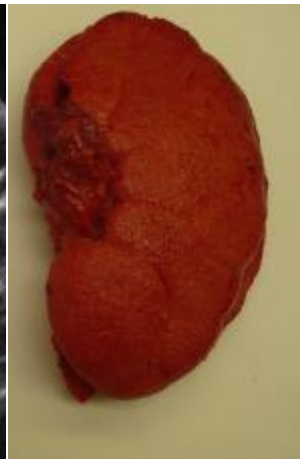
1925

Lepoutre

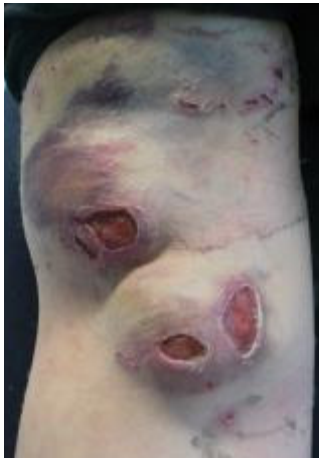
„Calculus multiples chez un enfant: infiltration du parenchyme renal par des depots de cristallino“







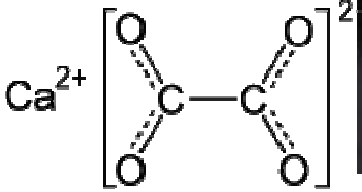
1958



Archer, Dormer, Scowen and Watts

„The aetiology of primary hyperoxaluria“

Hypothesis of endogenous oxalate generation in PH I



1967

Gibbs and Watts

„Biochemical studies on the treatment of primary hyperoxaluria“

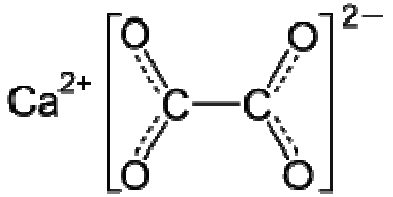
1st drug study in PH including Pyridoxine in 2 patients – no effect noted

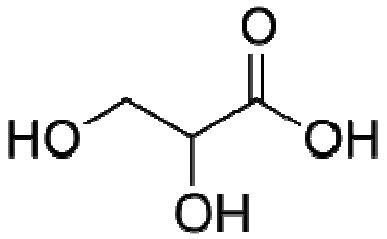
1968

Williams and Smith,

„L-glyceric aciduria: new genetic variant of primary hyperoxaluria“

PH Type II





PH in a nutshell

1986-1987

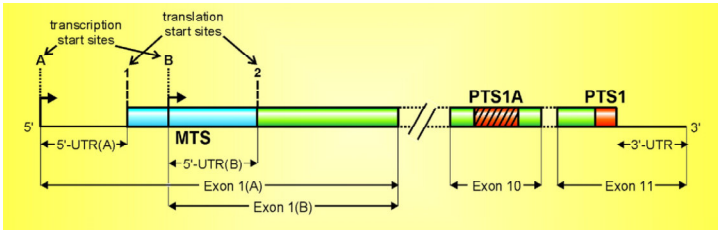
Hepatic AGT deficiency as the cause of PH I

>

new transplantation strategy

1989-1996

mistargeting mechanism of Gly170Arg

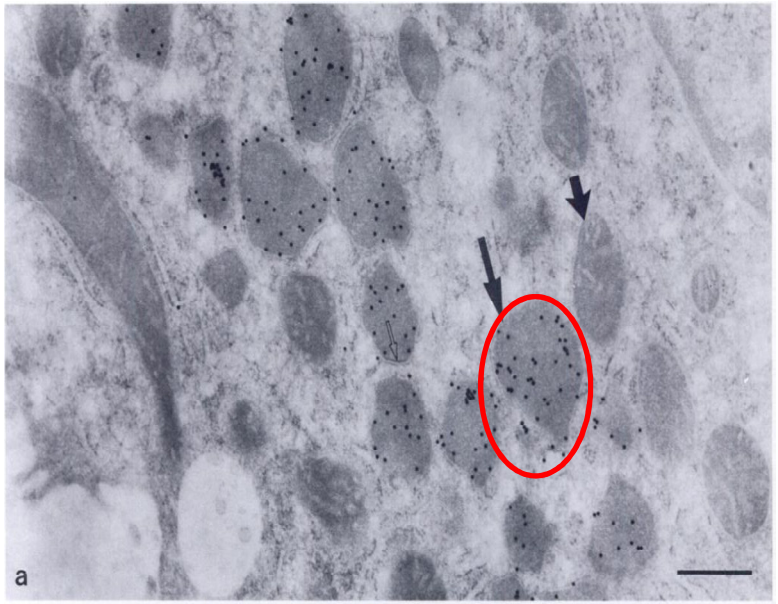


1990

***AGXT* mutations identified in PH I**

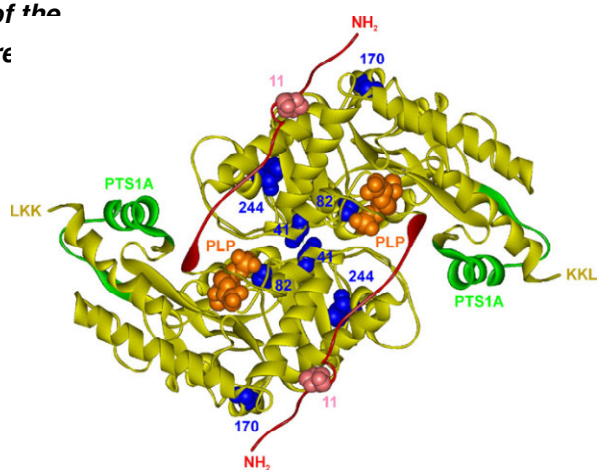
1999

***GRHPR* mutations identified in PH II**



2003

***Determination of the crystall structure human* AGT**

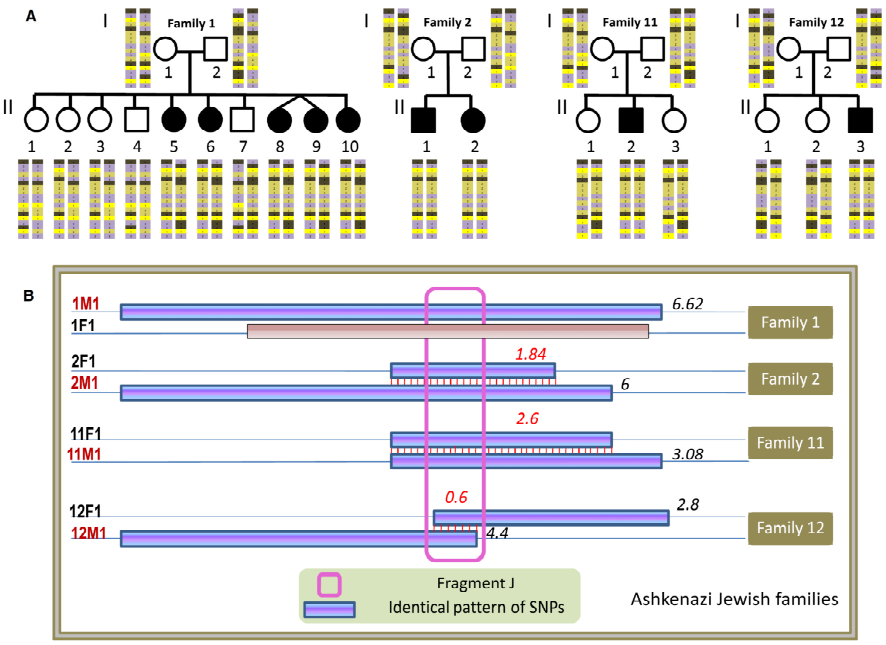


Cooper 1988, Zhang 2003, Danpure 2006

Genetik der PH III

HOGA1 (DHDPSL) ***mutations*** **identified as the cause of PH III**

2010



REPORT

Mutations in *DHDPSL* Are Responsible For Primary Hyperoxaluria Type III

Ruth Belostotsky,[1] Eric Seboun,[2,8] Gregory H. Idelson,[1,9] Dawn S. Milliner,[3] Rachel Becker-Cohen,[1,4] Choni Rinat,[1,4] Carla G. Monico,[3] Sofia Feinstein,[1,4] Efrat Ben-Shalom,[1,4] Daniella Magen,[5] Irith Weissman,[6] Celine Charon,[7] and Yaacov Frishberg[1,4,*]

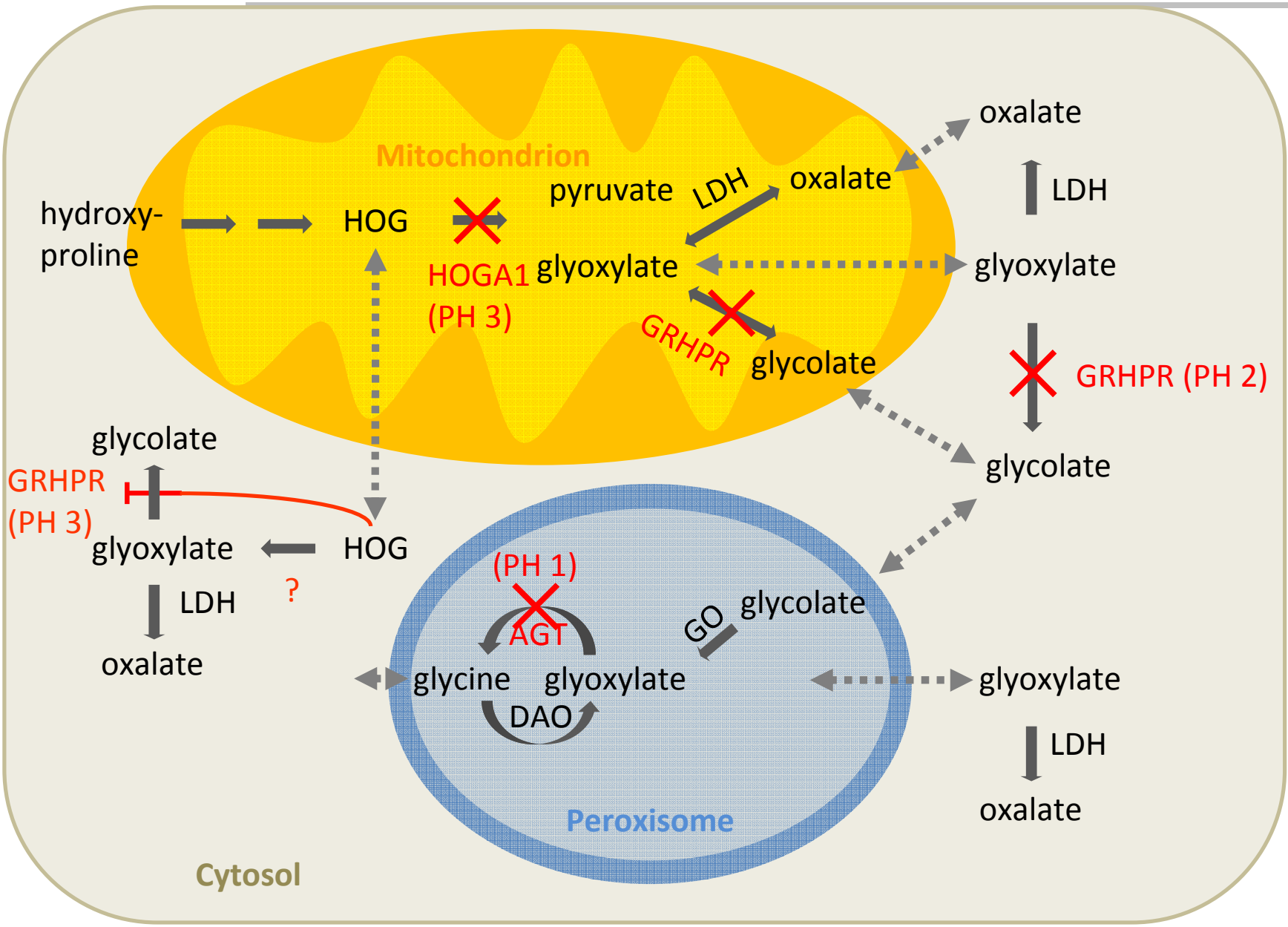
AJHG 2010

PH III – study Cologne

P/F sex age (yrs) EO	*HOGA1*	onset (yrs)	initial complaints	first imaging	UOx range	UCa range	procedures (number)	follow up (yrs)	clinical outcome	imaging outcome	biochemical outcome	cRF Screat (eGFR)
1; 1 f 12.5 Ger	c.700+5G>T (splice site) c.700+5G>T (splice site)	0.1	UTI, rec. UL	bilat UL	0.68- 1.95	1.70- 4.87	UC (1) dLB (1)	12.4	CR (5)	normal	HO 1.57	0.52 (120)
2; 2 m 14.5 Ger	c.700+5G>T (splice site) c.700+5G>T (splice site)	0.8	UTI, rec. UL	bilat UL	0.51- 2.49	2.03- 6.62	UC (1) PNCL (1) ESWL (16)	13.7	CR (12)	normal (13.9)	HO 2.49 HC 5.79	0.59 (117)
3; 3 f 6.0 Ger	c.700+5G>T (splice site) c.700+5G>T (splice site)	3.8	rec. UL	unilat UL	0.98- 2.01	1.33- 3.19	ESWL (3)	2.2	CR (5.5)	normal (6.0)	HO 2.01	0.46 (103)
4; 4 f 9.9 Ger	c.700+5G>T (splice site) c.700+5G>T (splice site)	1.5	UTI, rec. UL	bilat UL	0.90- 2.39	2.30- 4.00	ESWL (13)	8.4	CR (4.5)	normal	HO 0.90	0.39 (134)
5; 5 m 6.3 Pol	c.700+5G>T (splice site) c.700+5G>T (splice site)	0.1	UTI, rec. UL	bilat UL	0.68- 1.33	2.71- 7.15	dLB (1) ESWL (2)	6.1	CR (2)	HEK	HO 0.68 HC 5.26	0.46 (103)
6; 6* f 12.5 Ger	c.700+5G>T (splice site) c.700+5G>T (splice site)	0.75	UTI, rec. UL	unilat UL	0.11- 2.54	0.90- 4.30	dLB (1) PN (1) ESWL (1)	11.75	ongoing UL	unilat UL	nd	0.47 (120)
7;7 f 1 Ger	c.700+5G>T (splice site) c.700+5G>T (splice site)	0.1	rec. UL	unilat UL	270- 376†	0.4- 0.69†	none	0.9	CR (0.4)	normal	HO 376†	0.21 (100)
8; 8 m 2.9 Ger	**c.221T>G** (p.V74G) c.700+5G>T (splice site)	0.3	UTI, rec. UL	bilat UL	763- 639†	0.23- 0.62†	PNCL (2) ESWL (2)	2.6	ongoing UL	unilat UL	HO 639†	0.20 (144)

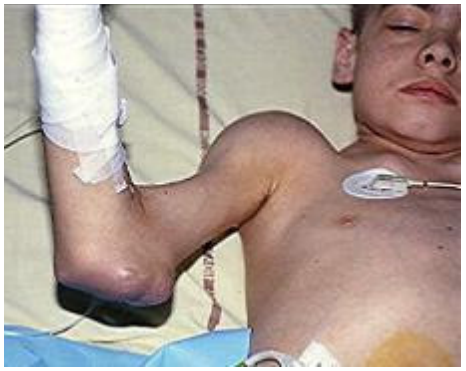
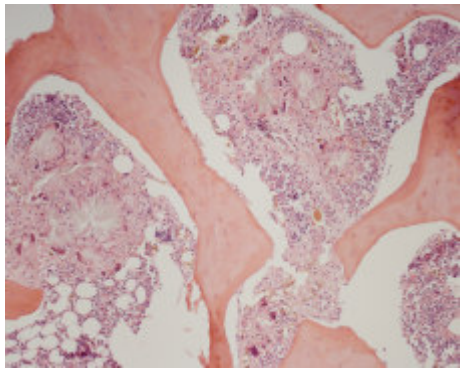
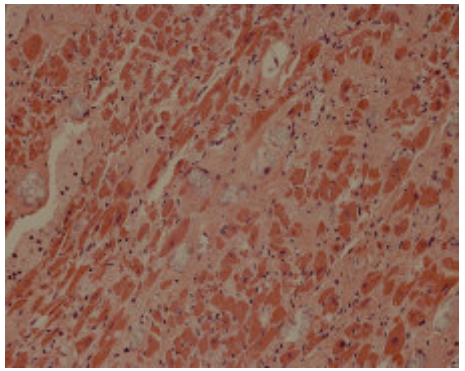
Beck et al. EJHG 2012

PH after 2010



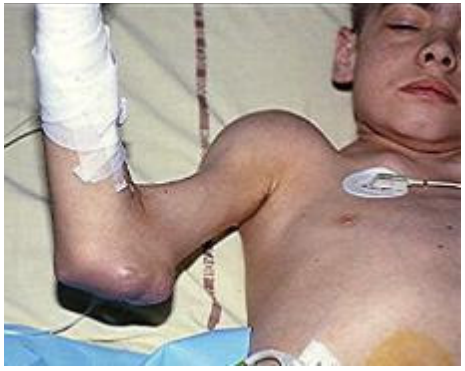
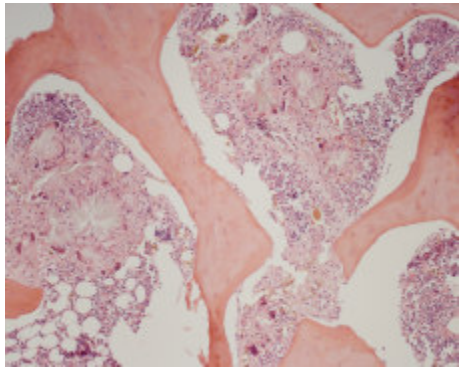
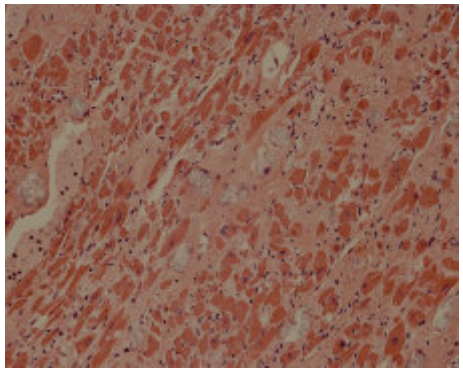
Hepatocyte

summary PH I - III

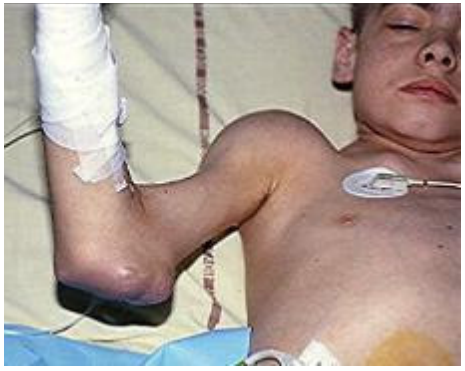
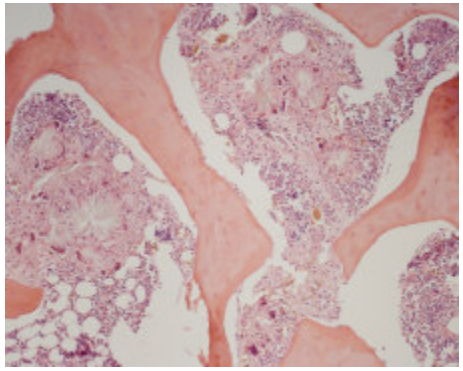
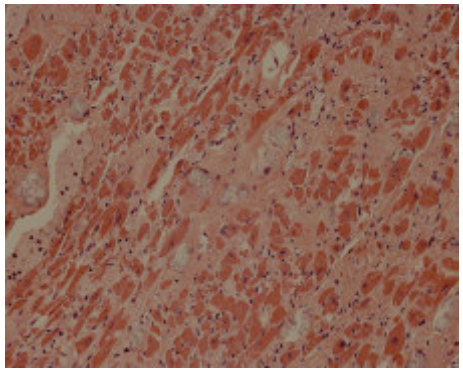
PH type	clinic	renal failure	infantile oxalosis	syst. oxalosis	CCR
I	UL, NC, UTI, RF	fast 100%	ca. 10-20%	bei NI	---
II	UL, (NC), UTI	ca. 20%	---	---	---
III	UL, UTI	---	---	---	66%

summary PH I- III

PH type	hyperoxaluria	hypercalciuria	L-glycerate	persistence
I	+++	++	---	+++ (unti ESRD)
II	++	---	+++	+++ (until ESRD)
III	++	++	---	++ (80% HO, 50% HC)

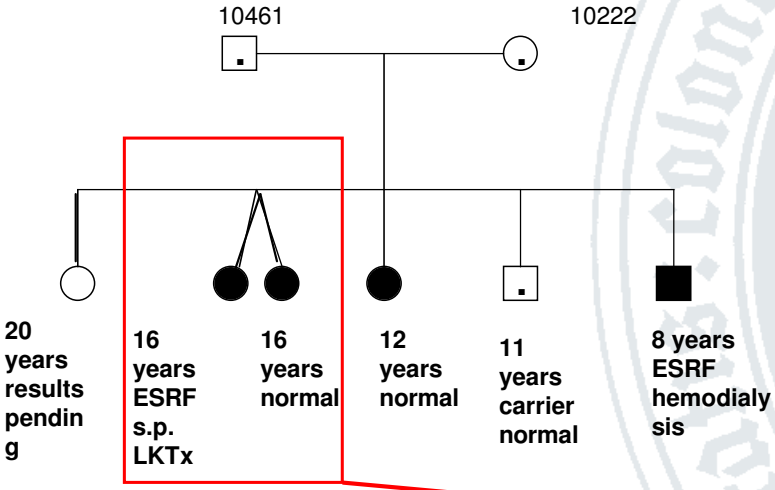
summary PH I - III

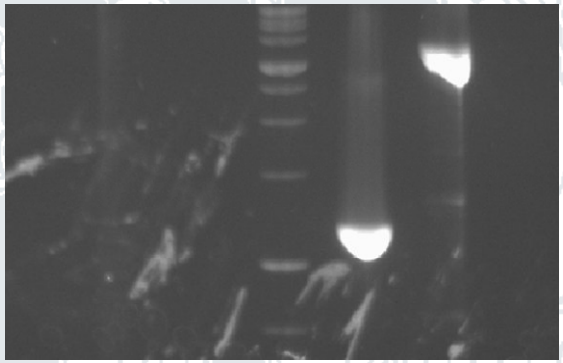





PH type	numbers	gene	mutational hot spot	(allelic frequency)
I	150 (> 500 Europe)	*AGXT*	c.508G>A	(40%)
II	15 (50 Europe)	*GRHPR*	c.103delG	(62%)
III	20 (50 worldwide)	*HOGA1*	c.700+5G>T	(47%)

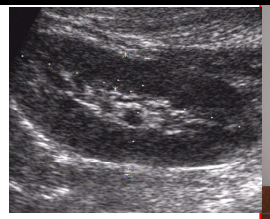
potential multiallelic disease

Discordance- Intrafamiliar phenotypic variability in PH I

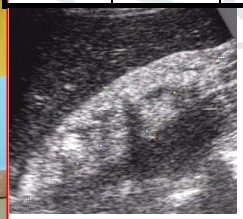




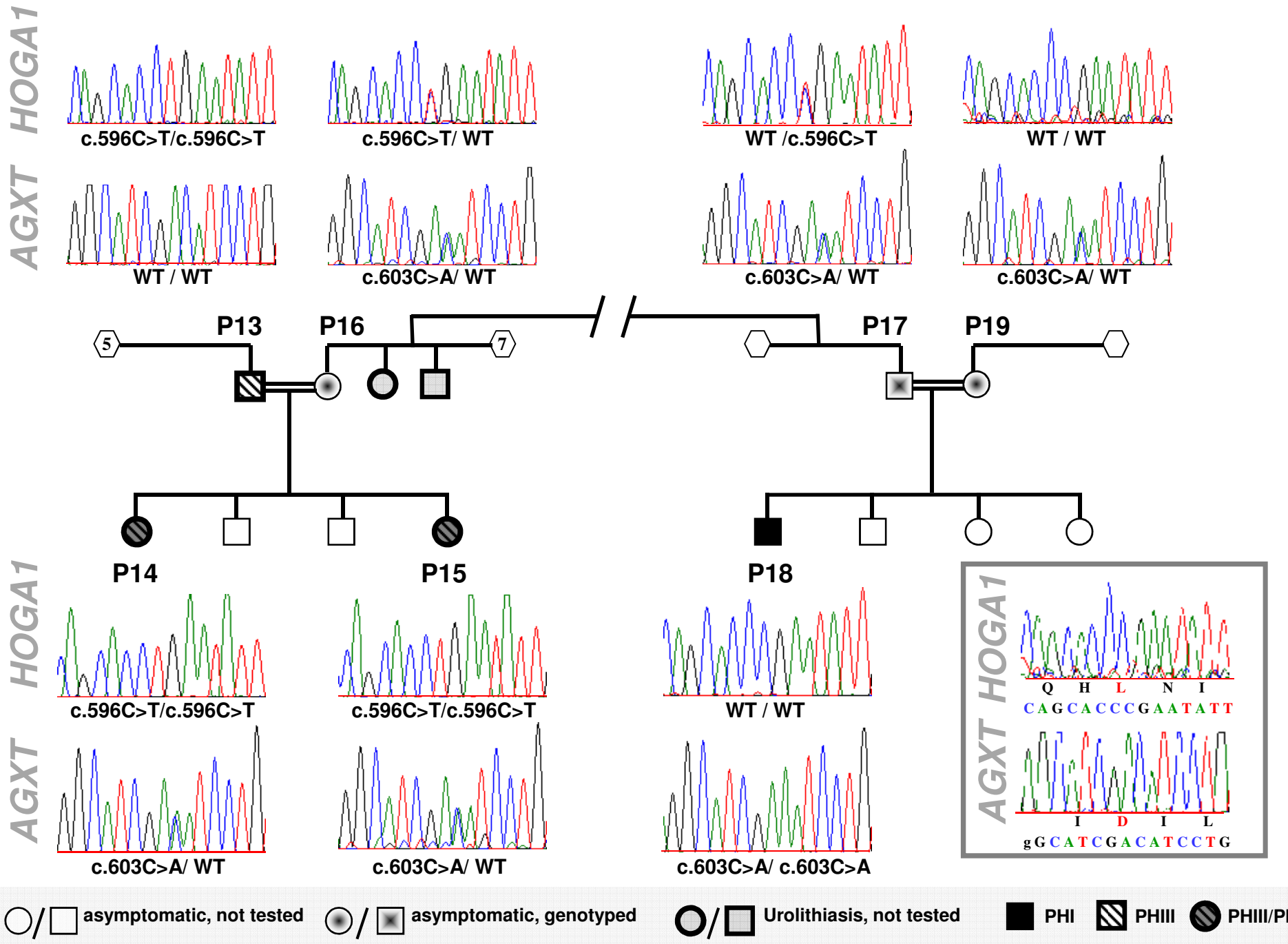
KK age (yrs)	11.9	12.9	13.1	14.4
creat (mg/dl)	0.7	0.76	0.75	0.7
Uox (mmol/d)	n.d.	1.84	1.91	1.0



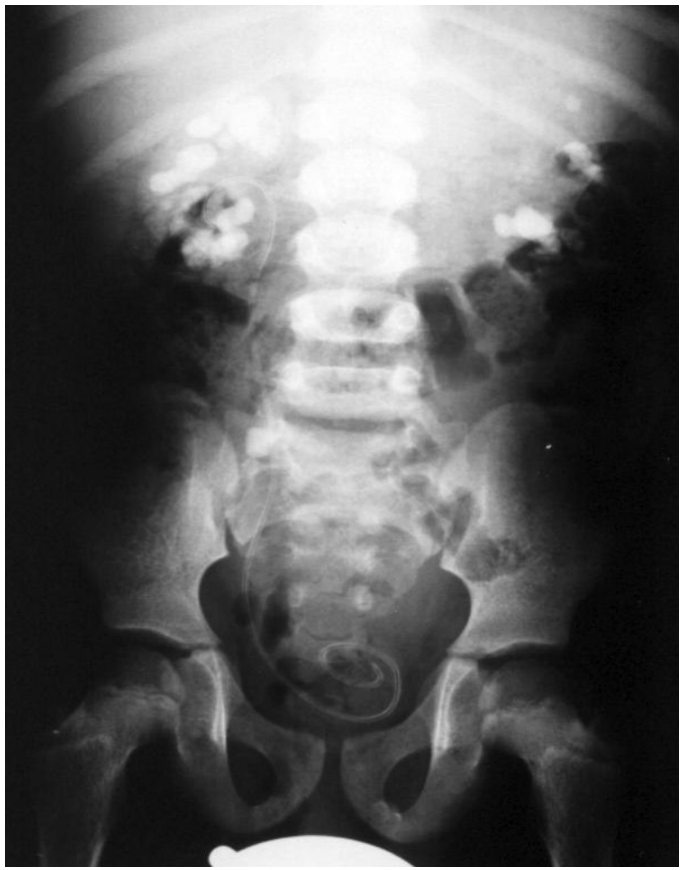
KJ age (yrs)	11.9	12.9	13.1	14.4
creat (mg/dl)	1.38	2.36	2.78	4.6
Uox (mmol/d)	3.65	3.1	2.2	2.1



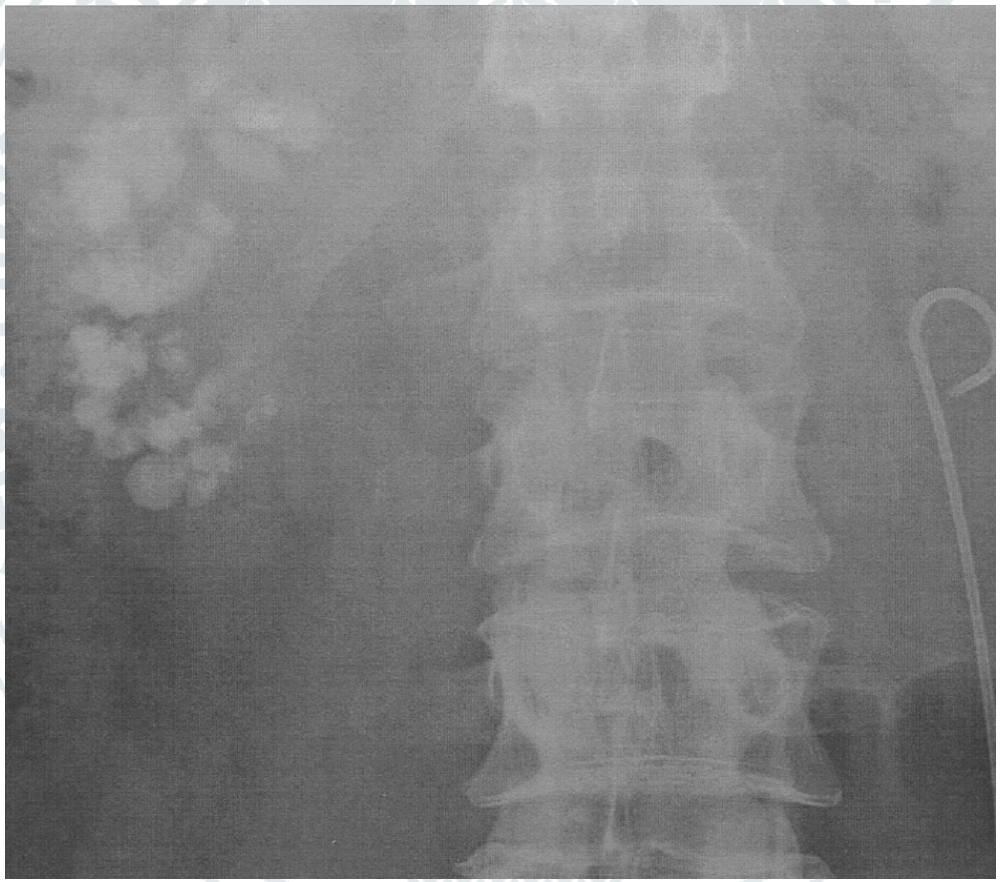
Picture courtesy of P. Sikora, MD


HOGA1
AGXT
c.596C>T/c.596C>T
c.596C>T/ WT
WT /c.596C>T
WT / WT
WT / WT
c.603C>A/ WT
c.603C>A/ WT
c.603C>A/ WT
5
7
P13
P16
P17
P19
P14
P15
P18
HOGA1
AGXT
c.596C>T/c.596C>T
c.596C>T/c.596C>T
WT / WT
c.603C>A/ WT
c.603C>A/ WT
c.603C>A/ c.603C>A
HOGA1
AGXT
Q H L N I
CAGCACCCGAATATT
I D I L
gGCATCGACATCCTG
asymptomatic, not tested
asymptomatic, genotyped
Urolithiasis, not tested
PHI
PHIII
PHIII/PHI

Primäre Hyperoxalurie (PH)



PH I

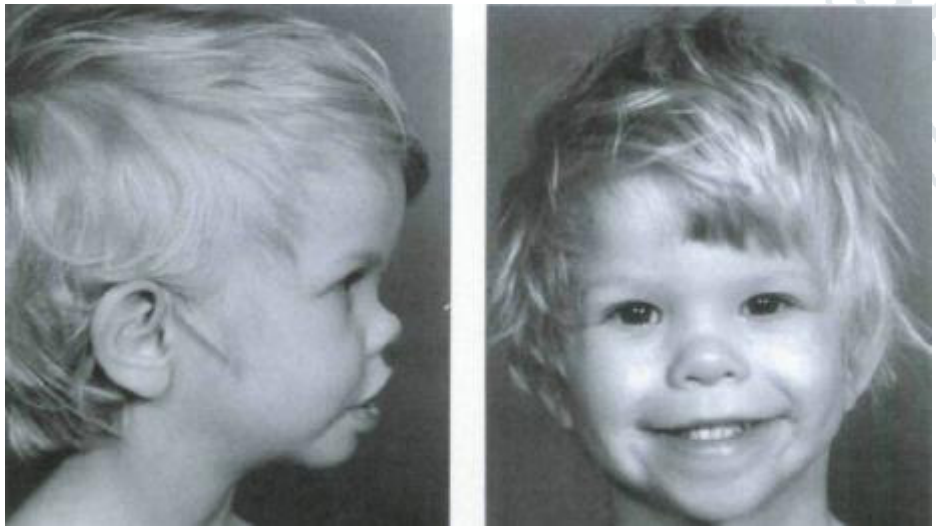


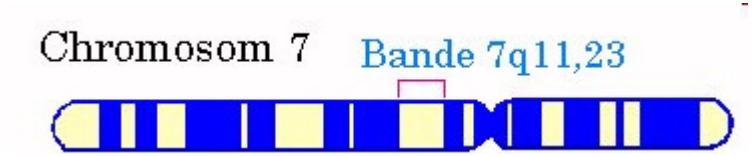
Non PH I-III

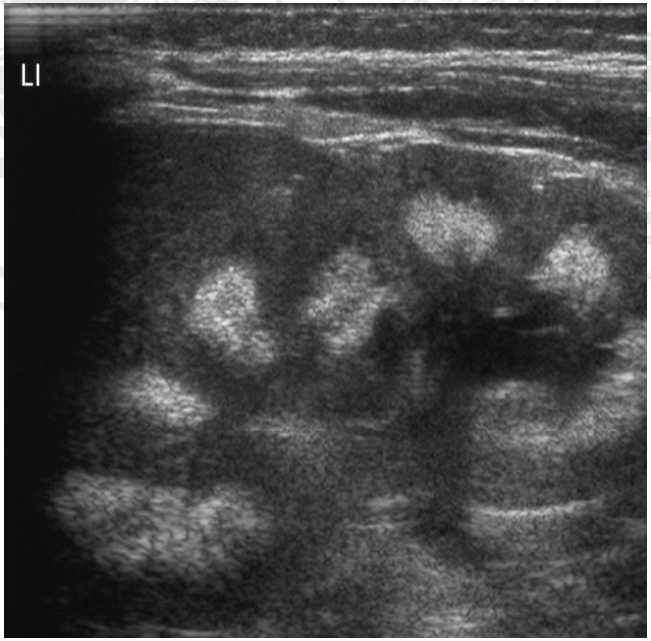
supplemental sources of vitamin D
UK in th 1950s up to 4,000 IU/d (200 cases of unexplained hypercalcemia in 2 years)
Bolus supplementation in the former GDR

1. Continous gene syndrome (1.5-1.8 Mb Deletion)

2. „milder“/nonsyndromal variant: „idiopathic infantile (IHH) hypercalcemia“-Lightwood Typ







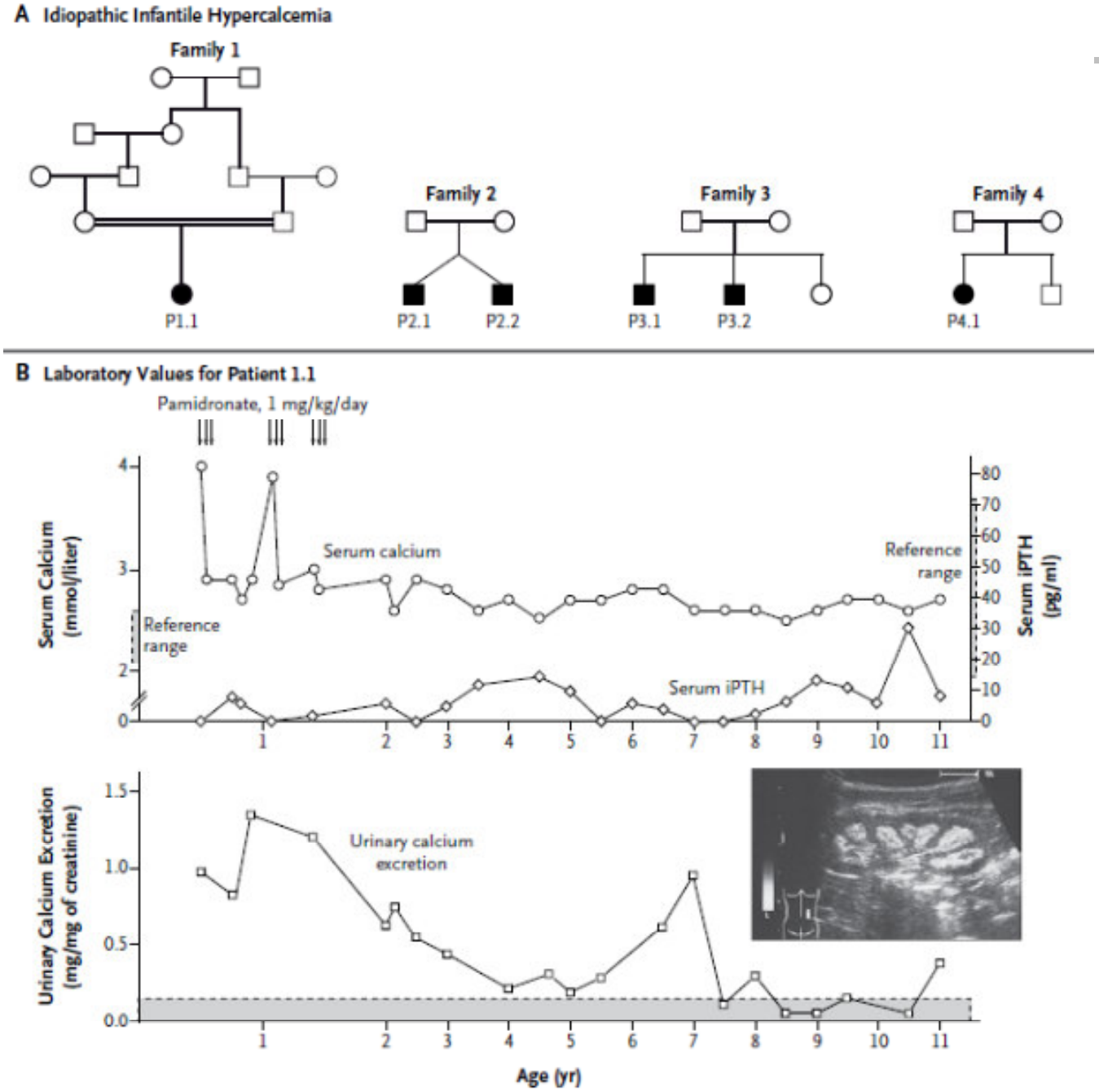
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

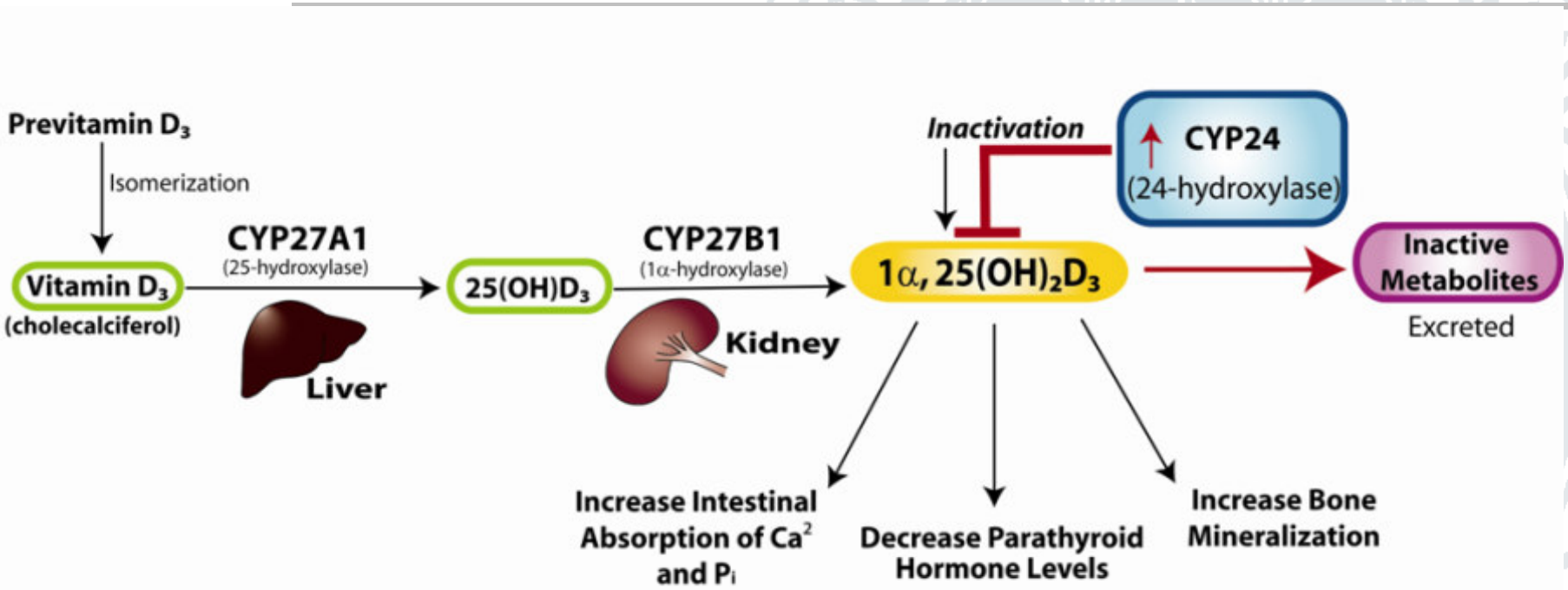
Mutations in *CYP24A1* and Idiopathic Infantile Hypercalcemia

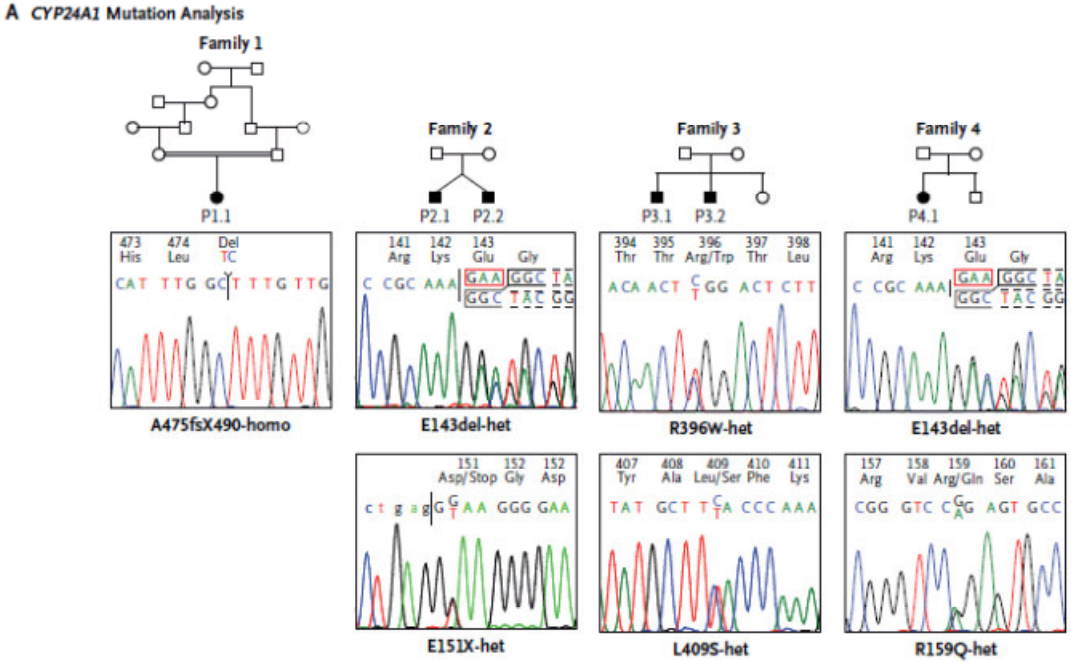
Karl P. Schlingmann, M.D., Martin Kaufmann, Ph.D., Stefanie Weber, M.D., Andrew Irwin, B.Sc., Caroline Goos, Ulrike John, M.D., Joachim Misselwitz, M.D., Günter Klaus, M.D., Eberhard Kuwertz-Bröking, M.D., Henry Fehrenbach, M.D., Anne M. Wingen, M.D., Tülay Güran, M.D., Joost G. Hoenderop, Ph.D., René J. Bindels, Ph.D., David E. Prosser, Ph.D., Glenville Jones, Ph.D., and Martin Konrad, M.D.

N Engl J Med 2011;365:410-21.


A Idiopathic Infantile Hypercalcemia
Family 1
P1.1
Family 2
P2.1
P2.2
Family 3
P3.1
P3.2
Family 4
P4.1
B Laboratory Values for Patient 1.1
Pamidronate, 1 mg/kg/day
Serum Calcium (mmol/liter)
Serum calcium
Reference range
Serum iPTH
Reference range
Serum iPTH (pg/ml)
Urinary Calcium Excretion (mg/mg of creatinine)
Urinary calcium excretion
Age (yr)

IIH-CYP24A1


Previtamin D_3
Isomerization
Vitamin D_3
(cholecalciferol)
CYP27A1
(25-hydroxylase)
Liver
25(OH)D_3
CYP27B1
(1α-hydroxylase)
Kidney
1α, 25(OH)$_2D_3$
Inactivation
CYP24
(24-hydroxylase)
Inactive Metabolites
Excreted
Increase Intestinal Absorption of Ca^2 and P_i
Decrease Parathyroid Hormone Levels
Increase Bone Mineralization


A CYP24A1 Mutation Analysis
Family 1
P1.1
Family 2
P2.1 P2.2
Family 3
P3.1 P3.2
Family 4
P4.1
A475fsX490-homo
E143del-het
R396W-het
E143del-het
E151X-het
L409S-het
R159Q-het

- **typical: severe hypercalciuria, hypercalcaemia, PTH ↓↓**
  1,25 OH Vit D3 ↑
- **nota bene: wider phenotypic spectrum**
- **identified in adults with NC (no infantile course)**
- **identified in patients with Ca Ox nephrolithiasis**
- **therapeutic implications**

avoid Vit D
Inhibitor 25 OH Vit D-1alpha-hydroxylase (Ketoconazol)

cystinuria

age (years)	AGXT/GRHPR/ HOGA1	Onset (years)	Initial complaints	First imaging	UOx range	UCa range	Procedures (number)	Follow-up (years)	Clinical outcome (years)	Imaging outcome (years)	Biochemical outcome	cRF Screat or CKD_stage
37/29 f 5.1	Neg.	3.7	IF	NC II	0.71–1.98	5.03–9.96	None	1.5	CR	NC II	HO 1.58 HC 9.96	0.32
38/29 m 5.1	Neg.	3.7	IF	NC II–III	0.54–2.47	7.9–15.40	None	1.5	CR	NC II	HO 1.53 HC 7.3	0.67
39/30 f 1.1	Neg.	ND	UTI, UL	Bilat UL	0.62–1.20	8.60–12.20	ND	ND	ND	ND	HO 2.47 HC 7.90	Wnl
40/31 f 3.4	Neg.	0.3	rec UL	Bilat UL	401–562[b]	0.48–1.23[b]	None	3.1	CR	Normal	HO 106[b]	0.31
41/31 f 17.7	Neg.	6	UL	Bilat UL	0.39	3.85	None	11.7	CR (7)	Normal	Normal	0.55
42/31 m 39	Neg.	3	rec UL	Bilat UL	0.60–1.10[a]	ND	ESWL (3) PNCL (2) unilat nephrectomy	17	ESRD (33)	ND	NA	ESRD
43/32 m 29	Neg.	21	Hematuria, rec UL	Bilat UL	0.79–1.09	ND	UC (1)	8.0	rec UL CKD2	Bilat UL	HO 0.79	CKD2
44/33 m 58	Neg.	27	rec UTI, rec UL NC III	Bilat UL NC III	0.65–0.96	2.72–7.04	ESWL (5) JJ stenting (4)	21	rec UL, rec UTI CKD3	Bilat UL NC III	HO 0.92	CKD3
45/34 m; 41	Neg.	10	rec UL	Bilat UL	ND	ND	ND	31	rec UL CKD2	Bilat UL	ND	CKD2
46/35 m 41	Neg.	15	rec UL	Bilat UL	ND	ND	UC (2)	26	CKD 4	Atrophic kidneys	NA	CKD4
47/36 m 37	Neg.	6	rec UL	ND	ND	ND	PNCL unilat nephrectomy	31	ESRD (25)	Atrophic kidney	NA	ESRD
48/37 m 49	Neg.	ND	rec UL	ND	ND	ND	ND	ND	ESRD (45)	Atrophic kidneys	NA	ESRD
49/38 m 49	Neg.	ND	rec UL	ND	ND	ND	ND	26	ESRD (23)	ND	NA	ESRD

cystinuria

24	3653740	chr19:40149171-40149171	snp	missense	benign	184	43	uc021uun.1,LGALS16,+,164G->A,1,non-syn,A
	2600626	chr19:40151145-40151145	snp	missense	benign	62	53	uc021uun.1,LGALS16,+,414C->A,2,non-syn,A
25	3664810	chr19:47585502-47585502	snp	missense,intronic	possibly damaging	15	13	uc002pga.4,ZC3H4,-,1269T->A,2,non-syn,Glu uc002pgb.1,ZC3H4,-,intronic:
	2615678	chr19:47589655-47589655	snp	missense,intronic	benign	610	49	uc002pga.4,ZC3H4,-,856C->G,0,non-syn,Glu uc002pgb.1,ZC3H4,-,intronic:
26	3886751	chr19:54848144-54848144	snp	missense	benign	89	44	uc002qfi.3,LILRA4,-,1025T->A,1,non-syn,His3 uc002qfj.3,LILRA4,-,1223T->A,1,non-syn,His4
	3886752	chr19:54848145-54848145	snp	missense	benign	92	42	uc002qfi.3,LILRA4,-,1024G->A,0,non-syn,His3 uc002qfj.3,LILRA4,-,1222G->A,0,non-syn,His4
27	1340872	chr2:44508562-44508562	snp	missense	probably damaging	44	98	uc002rty.3,SLC3A1,+,647C->T,1,non-syn,Thr uc002rtz.2,SLC3A1,+,647C->T,1,non-syn,Thr uc002rua.3,SLC3A1,+,647C->T,1,non-syn,Th uc002rub.2,SLC3A1,+,647C->T,1,non-syn,Th uc002ruc.4,SLC3A1,+,647C->T,1,non-syn,Thr
28	2576618	chr2:173451103-173451103	snp	missense,noncoding	benign	120	100	uc010zdz.1,PDK1,+,578G->A,1,non-syn,Arg1 uc002uhq.1,PDK1,+,1103G->A,1,non-syn,Arg uc002uhs.3,PDK1,+,1043G->A,1,non-syn,Arg uc010zeb.2,PDK1,+,1103G->A,1,non-syn,Arg uc010zea.1,PDK1,+,noncoding:

41 46/35 m	Neg.	15	rec UL	Bilat UL	ND	ND	UC (2)	26	CKD 4	Atrophic kidneys	NA	CKD4
41 47/36 m 37	Neg.	6	rec UL	ND	ND	ND	PNCL unilat nephrectomy	31	ESRD (25)	Atrophic kidney	NA	ESRD
48/37 m 49	Neg.	ND	rec UL	ND	ND	ND	ND	ND	ESRD (45)	Atrophic kidneys	NA	ESRD
49/38 m 49	Neg.	ND	rec UL	ND	ND	ND	ND	26	ESRD (23)	ND	NA	ESRD

thank you for your attention