Idiopathic Infantile Hypercalcemia
Long term follow up

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בית החולים לילדים ספרא, תל השומר

שיבא
תל השומר

CASE DESCRIPTION

- ET was born at term by normal vaginal delivery, BW 3 kg
- Routine follow up of the pregnancy - normal except for findings of asymmetrical cerebral ventricles which were not enlarged
- Head ultrasound post partum was normal except asymmetry of ventricles
- Exclusive breast feeding for the first 6 months after which slow introduction of solid foods was initiated
- Vitamin D 2 drops (400 IU) administered once daily

- Growth was appropriate - at 5 months he weighed 6.2 kg
- Growth has since then faltered and at 7 months weighs 6.3 kg
- At 5 months:
  - makes eye contact and recognizes family members
  - lifts his head but does not roll
  - grasps objects and draws them to his mouth
- A deterioration was noted: hypotonia, head lag, weakness, sleepiness
- One week prior to admission his mother noted **erratic eye movements** and later an **upward gaze**
- A repeated head ultrasound was without change.

AT ADMISSION

- AT 7 months, he presented to the ER owing to worsening hypotonia and general weakness
- On examination he was noted to be apathic, pale and with marked developmental delay
- Initial laboratory workup showed hypercalcemia of 20 mg/dl with ionic calcium level of 2.9 mmol/l, a phosphate level of 3.4 mg/dl
- ECG showed sinus rhythm, PR interval 0.3 seconds

FAMILY HISTORY

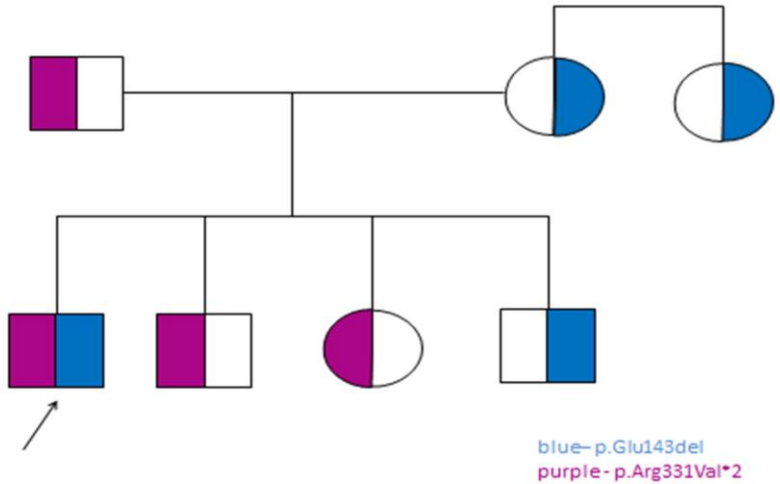
- Mother: 43 years old of Iraqui-Ashkenazi Origin
- Father: 47 years old of Libyan-Polish origin.
- 3 brothers, otherwise healthy.
- There is no family history of renal stones or hypercalcemia

TREATMENT

- IV fluid
- IV furosemide
- PO and prednisone
- SC calcitonin (3u/kg/dose q12)
- IV pamidronate (1 mg/kg)
  - A decreased in hypercalcemia from 20 mg/dl to 12.6 mg/dl over 36 hours

WORK UP

- Urine Ca/Crea 3350 mg/gr
- PTH: <3 pg/ml
- 25-OH VIT D: normal 52.9 ng/ml,
- 1,25 OH vitamin D: 92 pg/ml (20-100)



- Genetics for 24OH vitamin D CYP24A1 mutation:
  - Axon 2: delE143 - father
  - Axon 8: c.995_1001delCAAACAG (stop codon – truncation of the protein) – mother
  - His 3 brothers – heterozygote of one of the above mutations.

WORK UP

1) EEG in the PICU- normal

2) Head US prior to hospitalization - normal except asymmetry of the ventricles

3) head CT: ventricles mildly dilated including the third ventricle. 4th ventricle is in place.
No pathological enhancement, no evidence of space occupying lesion. normal venous sinuses. No evidence of a fresh bleeding or infarction.

4) MRI: increased signal in the tegmental tract bilaterally

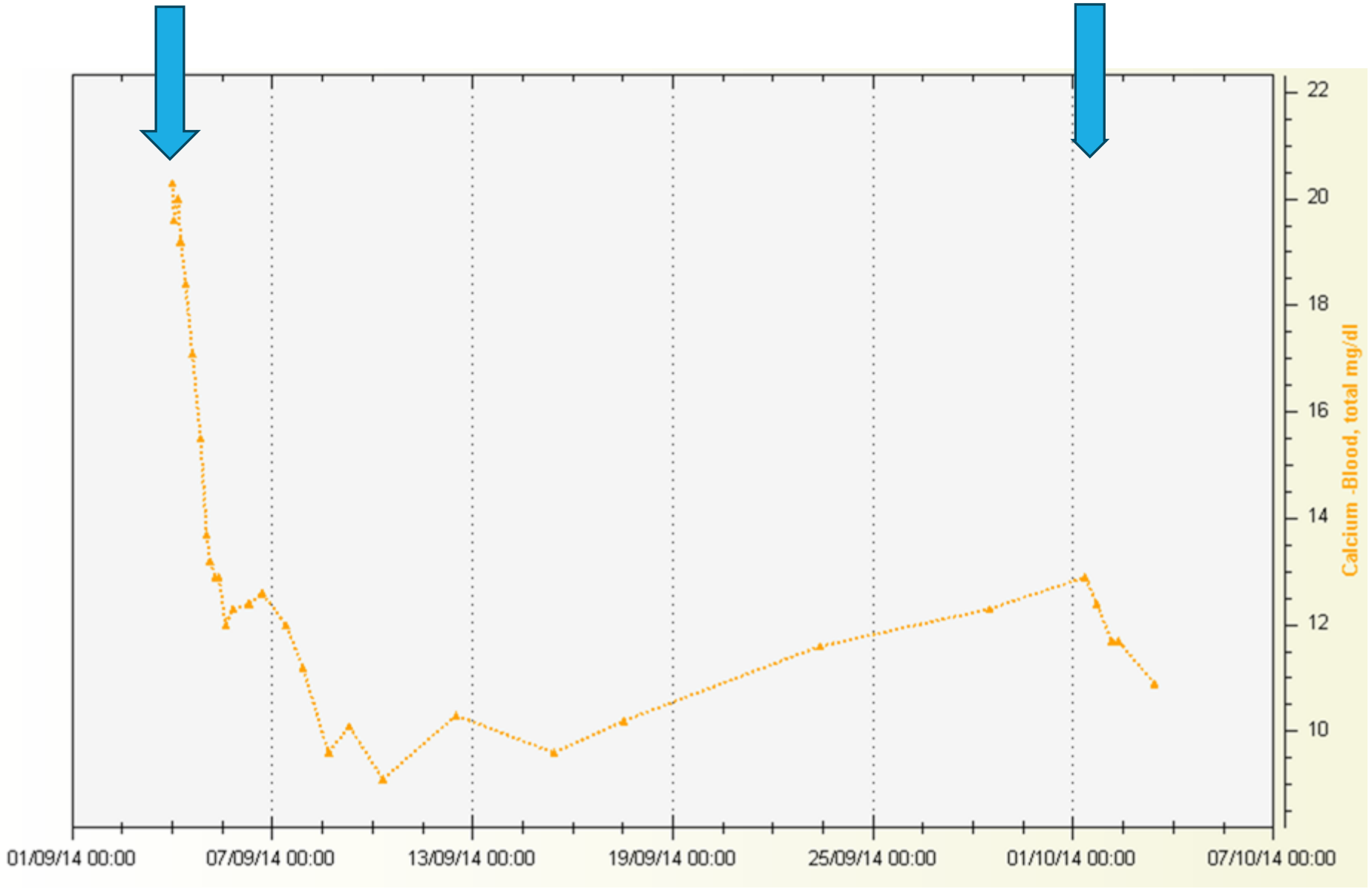
5) normal eye examination

6) BERRA normal

7) LP: normal

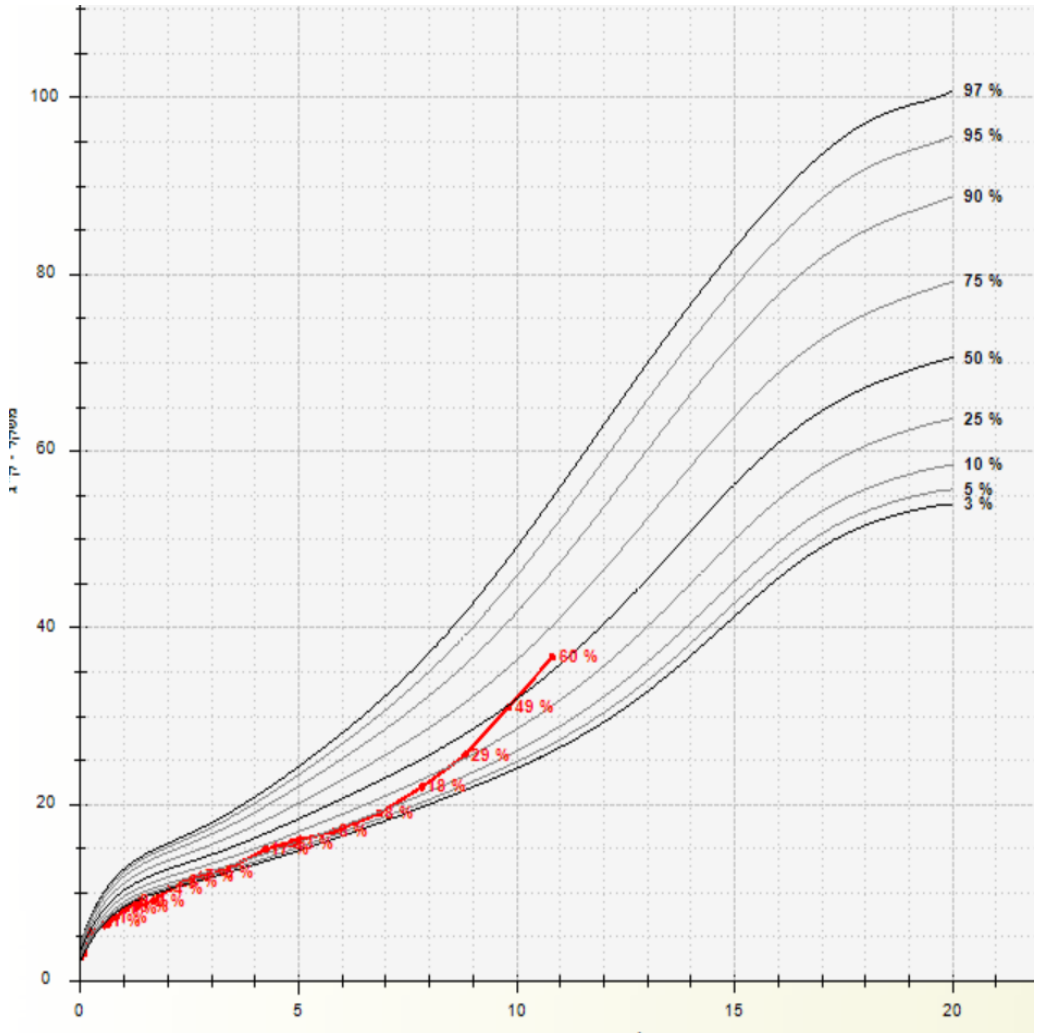
8) Renal US: without calcinosis or structural abnormalities

9) WES – no other pathogenic variant besides the known mutation


22
20
18
16
14
12
10
Calcium -Blood, total mg/dl
01/09/14 00:00
07/09/14 00:00
13/09/14 00:00
19/09/14 00:00
25/09/14 00:00
01/10/14 00:00
07/10/14 00:00

FOLLOW UP

- Low calcium diet, avoid sun exposure, avoid vitamin D supplementation
- Due to hypotonia and developmental delay, he was treated with physiotherapy and occupational therapy
- Splints have been fitted for walking
- Now he is 11 years old
- Calcium level during years of F/W 9.5-10.7 mg/dl, phosphor 4.8-5.2, ca/crea urine 0.09-0.28, US kidneys normal
- Neurological – falling, cognitive impairment, social problems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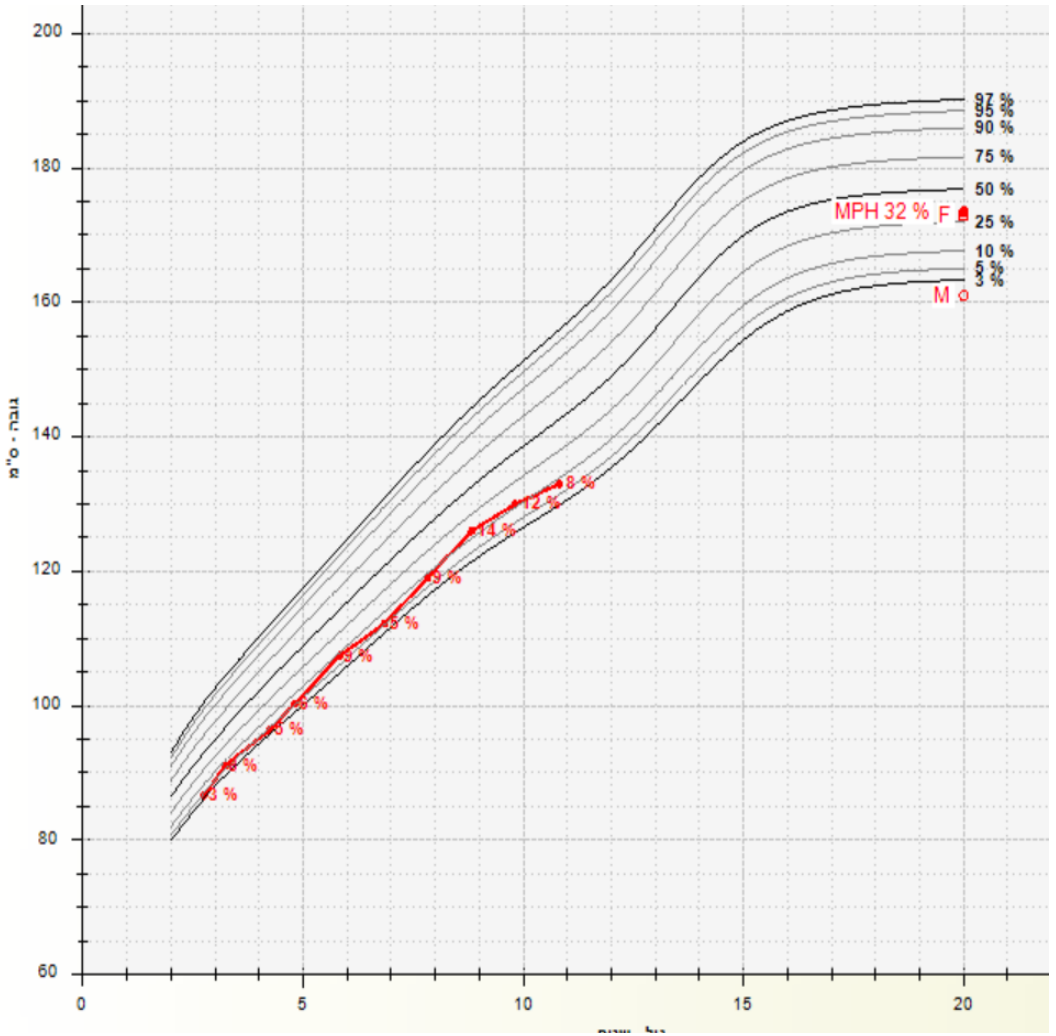
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97 %
95 %
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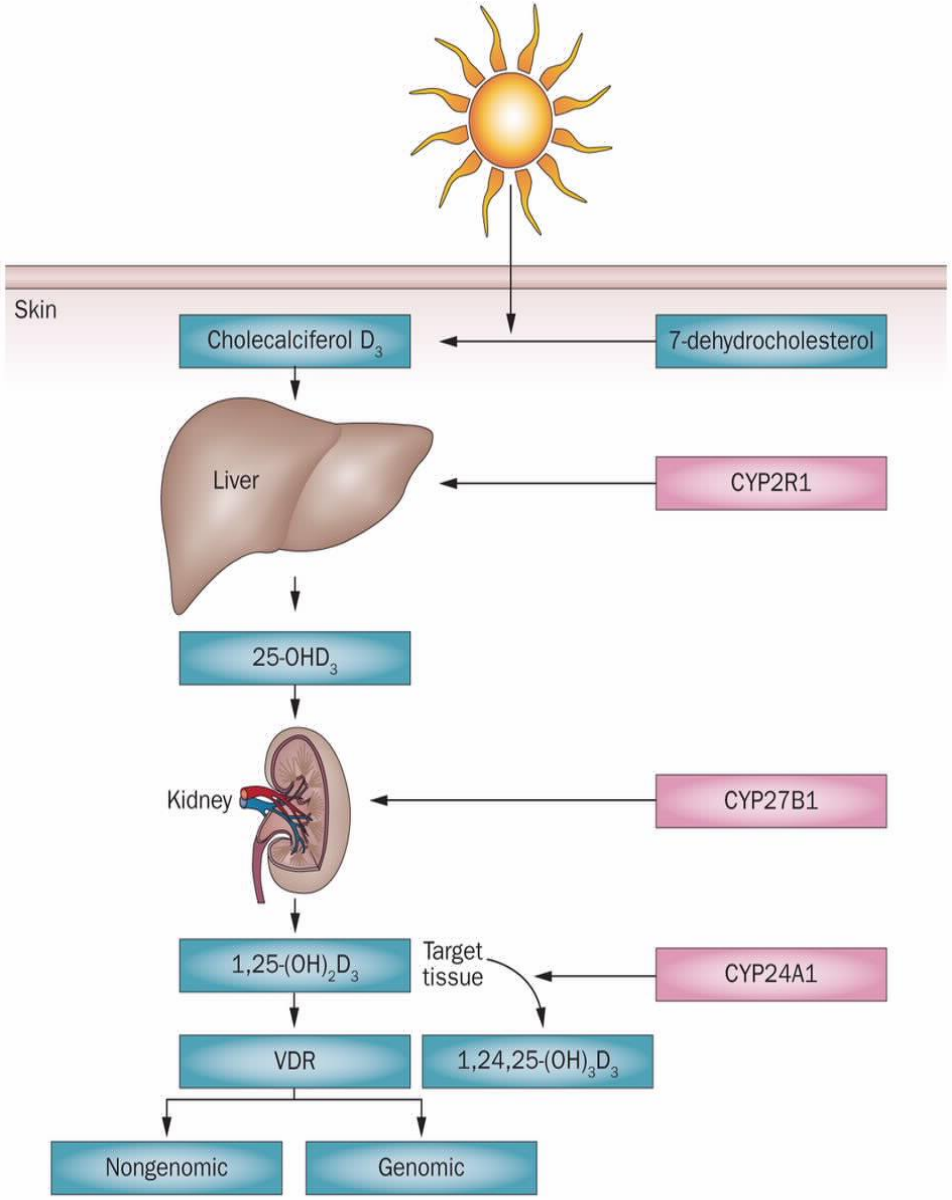
75 %
50 %
25 %
10 %
5 %
3 %
MPH 32 %
8 %
12 %
14 %

IIH

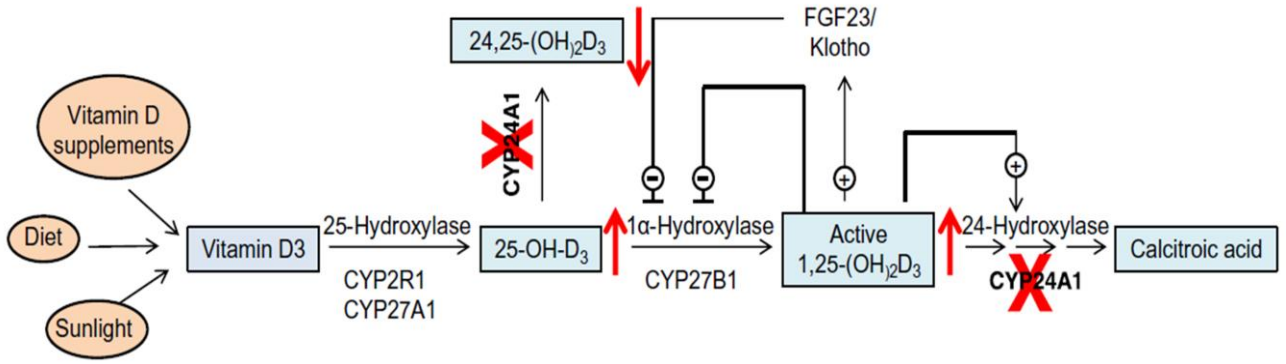
- IIH (OMIM#143880) was first described in the 1950s after an epidemic occurrence of unexplained hypercalcemia in infants receiving increased amounts of vitamin D for the prevention of rickets.

Lightwood R et al Lancet 265: 255–256, 1953

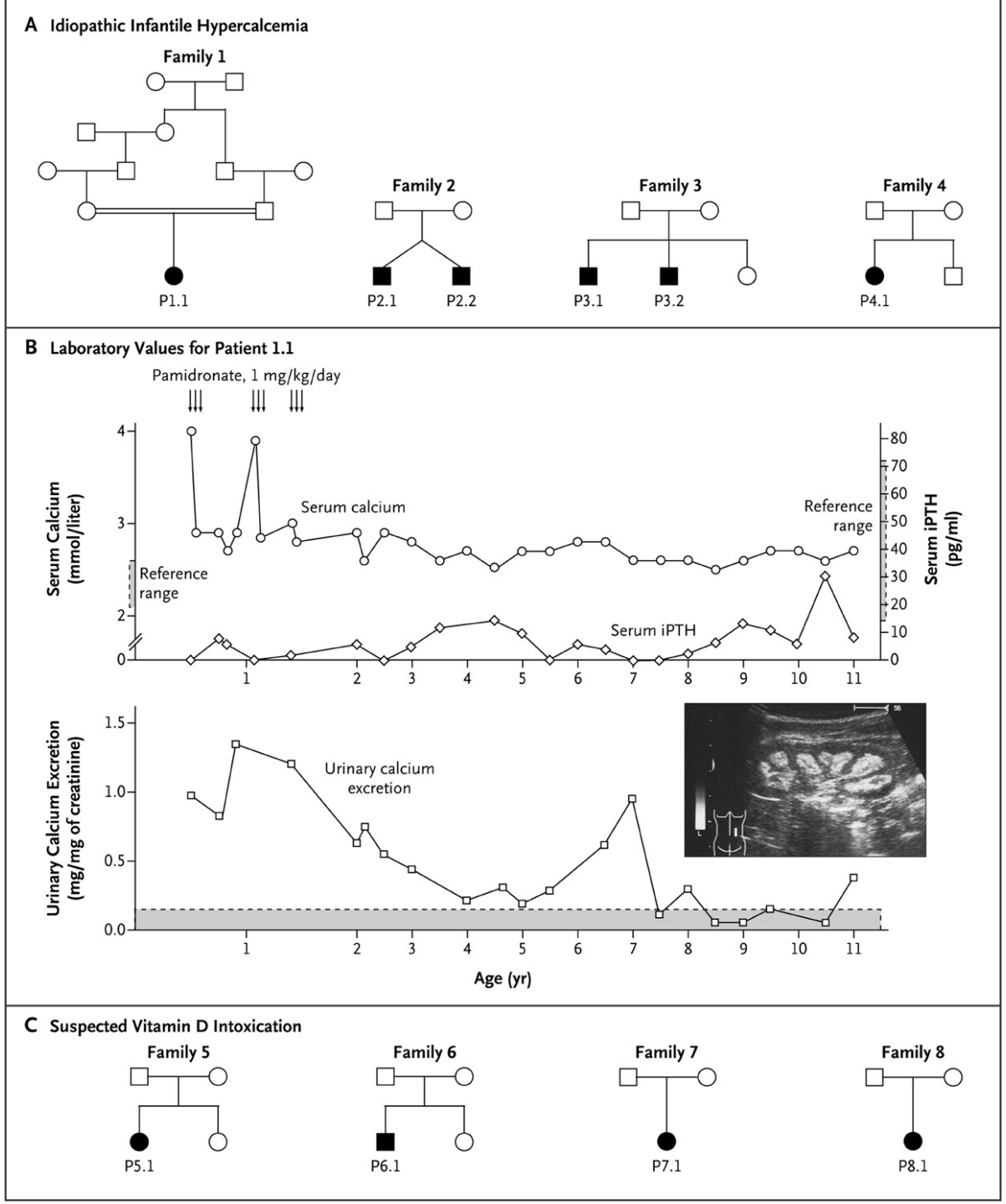


IHH

- The pathophysiology remained unknown until 2011 identification of inactivating mutations in CYP24A1.



Schlingmann KP et al. N Engl J Med 365: 410–421, 2011.



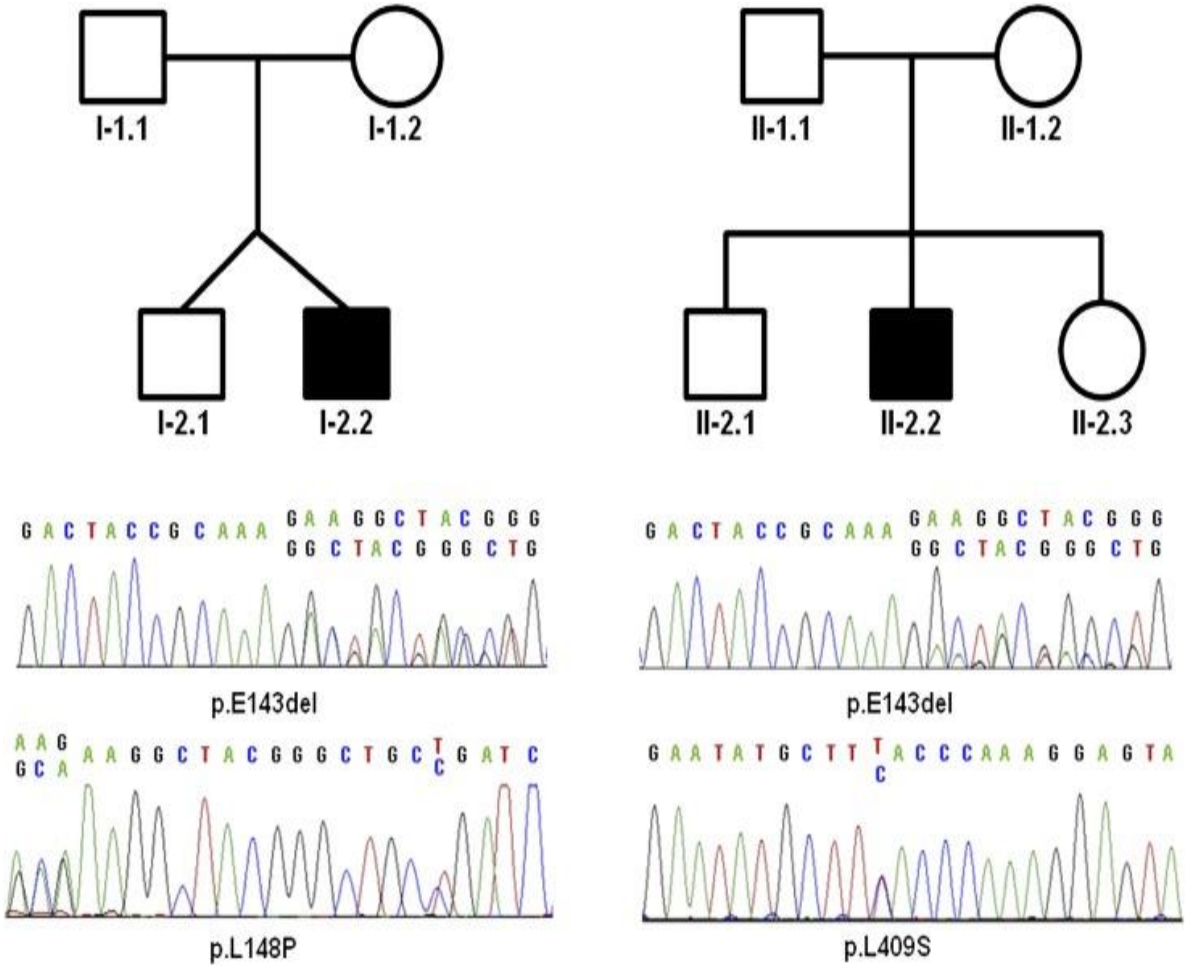
Mutations in *CYP24A1* and Idiopathic Infantile Hypercalcemia

KarlP. Schlingmann et al.

N Engl J Med 2011;365:410-421

IIH

- Meanwhile, bi-allelic CYP24A1 mutations have also been described in 2 adults who primarily presented with nephrolithiasis while remaining asymptomatic during infancy.



Nesterova G et al Clin J Am Soc Nephrol 8: 649–657, 2013

Patients' blood laboratory values

	Ionized Ca^{2+} (mmol/L)	Parathyroid Hormone (pg/ml)	Plasma Creatinine (mg/dl)	25-OHD_3 (ng/ml)	1α,25$(OH)_2D_3$ (pg/ml)	24,25$(OH)_2D$ (ng/ml)
Patient 1	1.23–1.34	3	0.4	71	79–115	0.64
Patient 2	1.32–1.41	3–10	1.2–1.3	39–59	83–160	0.33
Normal reference range[a]	1.12–1.32	16–87	0.5–1.2	10–80	18–64	1.2–2.6[b]

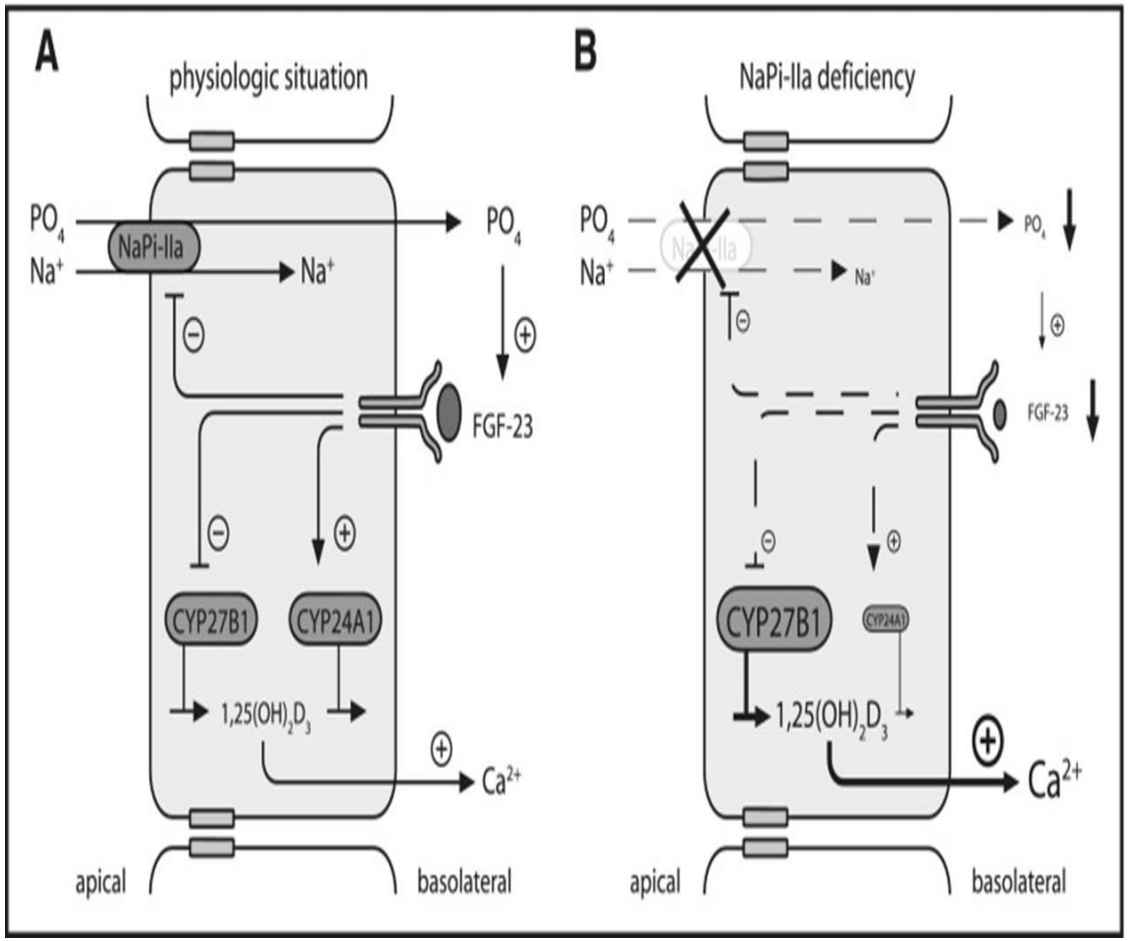
Patients' 24-hour urine values

	Urine pH	Calcium Excretion[a]	Calcium/ Creatinine Ratio[a]	Phosphate Excretion (g/24 h)	Fractional Excretion of PO_4 (%)
Patient 1	6.5	9.3 mg/kg per day	0.42	0.51	12
Patient 2	6.0	160–405 mg/d	0.33	0.97	34

Nesterova G et al Clin J Am Soc Nephrol 8: 649–657, 2013

IIH

- In 2015, Schlingmann et al identified four patients from three consanguineous families with typical IIH without mutations in CYP24A1.
- These patients also presented with renal phosphate wasting.
- The primary renal phosphate wasting caused by defective NaPi-IIa encoded by *SLC34A1.*
- Reduced expression or function of NPT2a leads to renal phosphate loss, hypophosphatemia, and reduced FGF23.

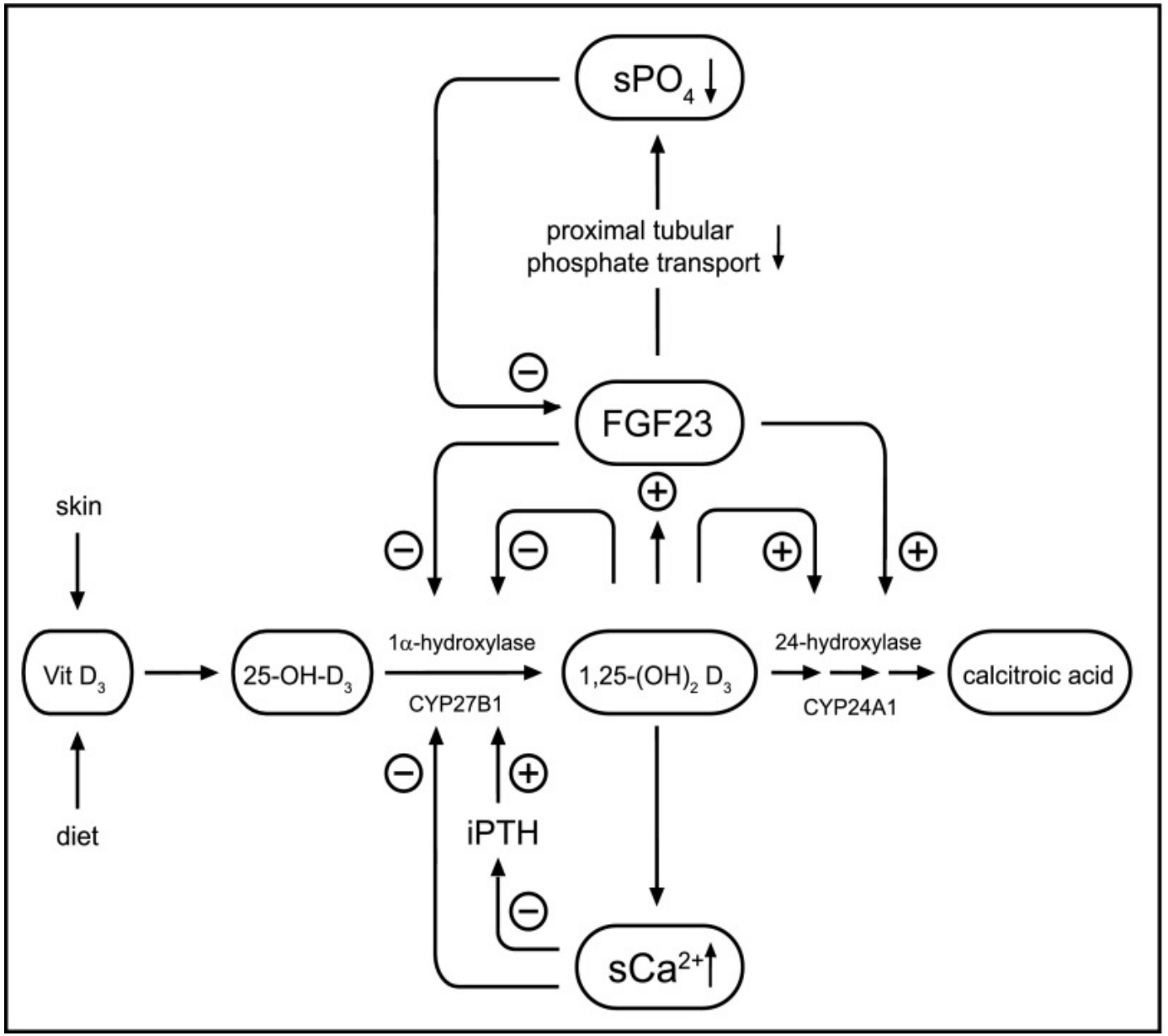


Schlingmann et al Journal of the American Society of Nephrology 2015

Meyer MB et al, J Steroid Biochem Mol Biol. 2020

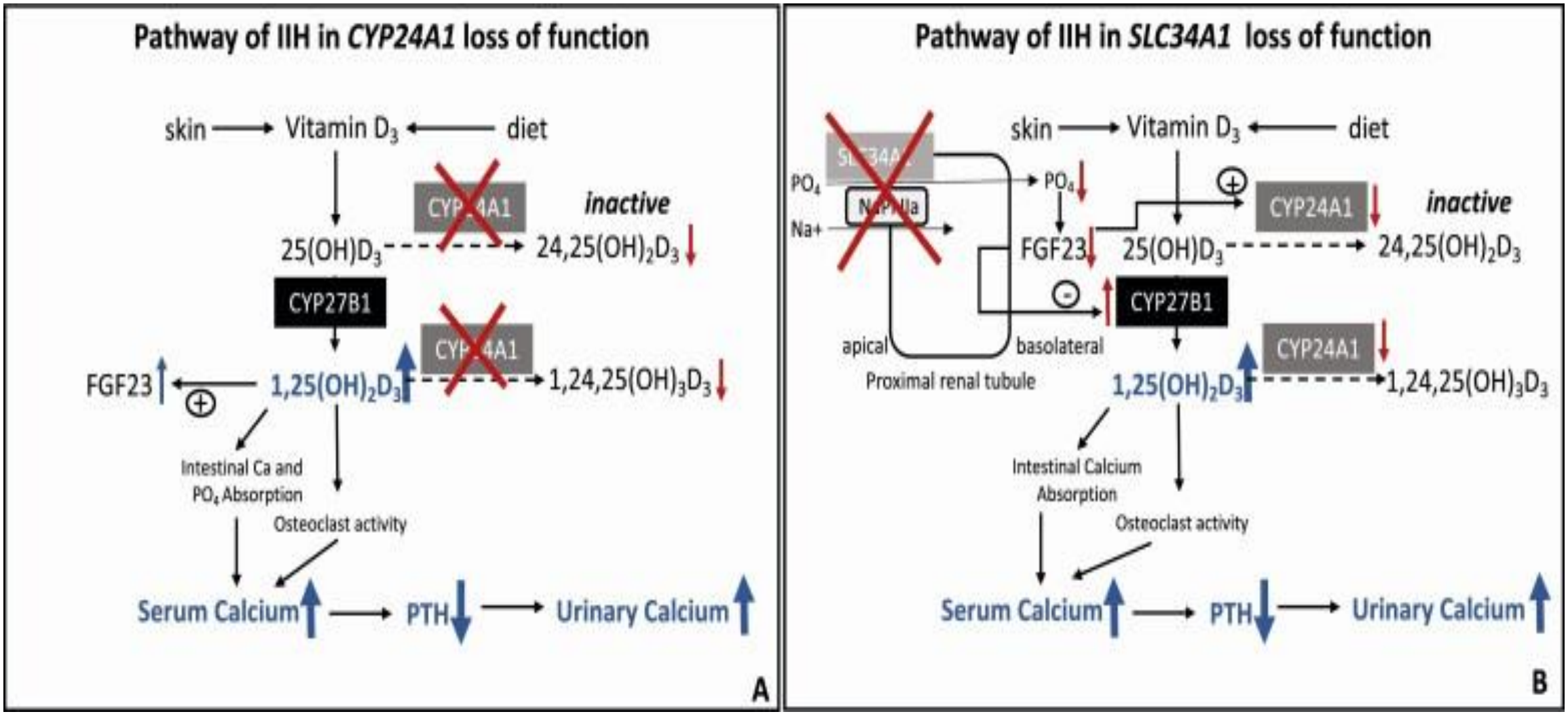
IHH

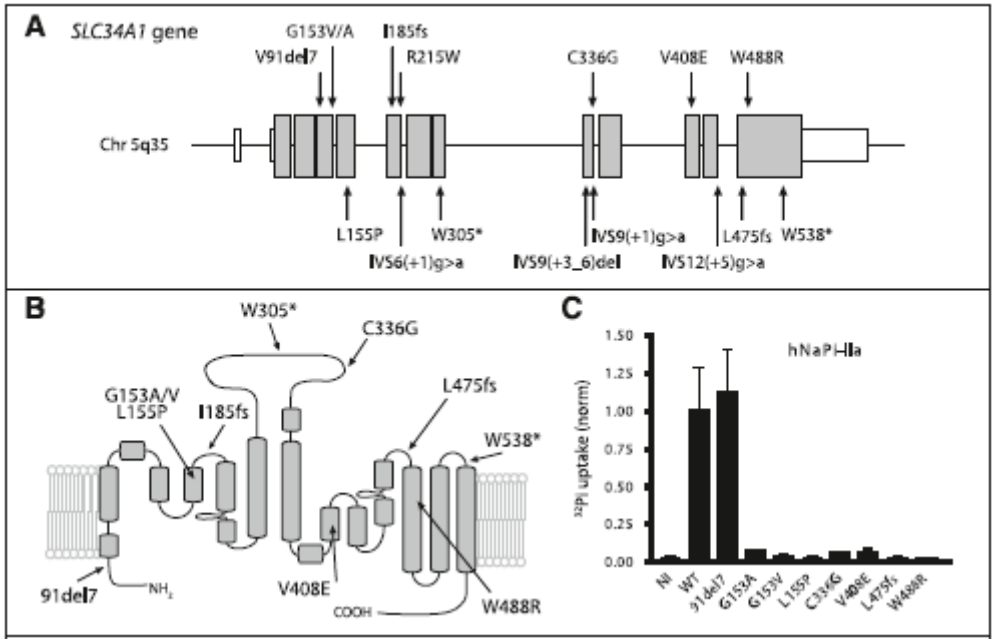
- In the presence of low FGF23, there is increased *CYP27B1* expression and decreased *CYP24A* expression, which together results in increased $1,25(OH)_2D$ production with hypercalcemia, hypercalciuria, as well as reduced PTH.



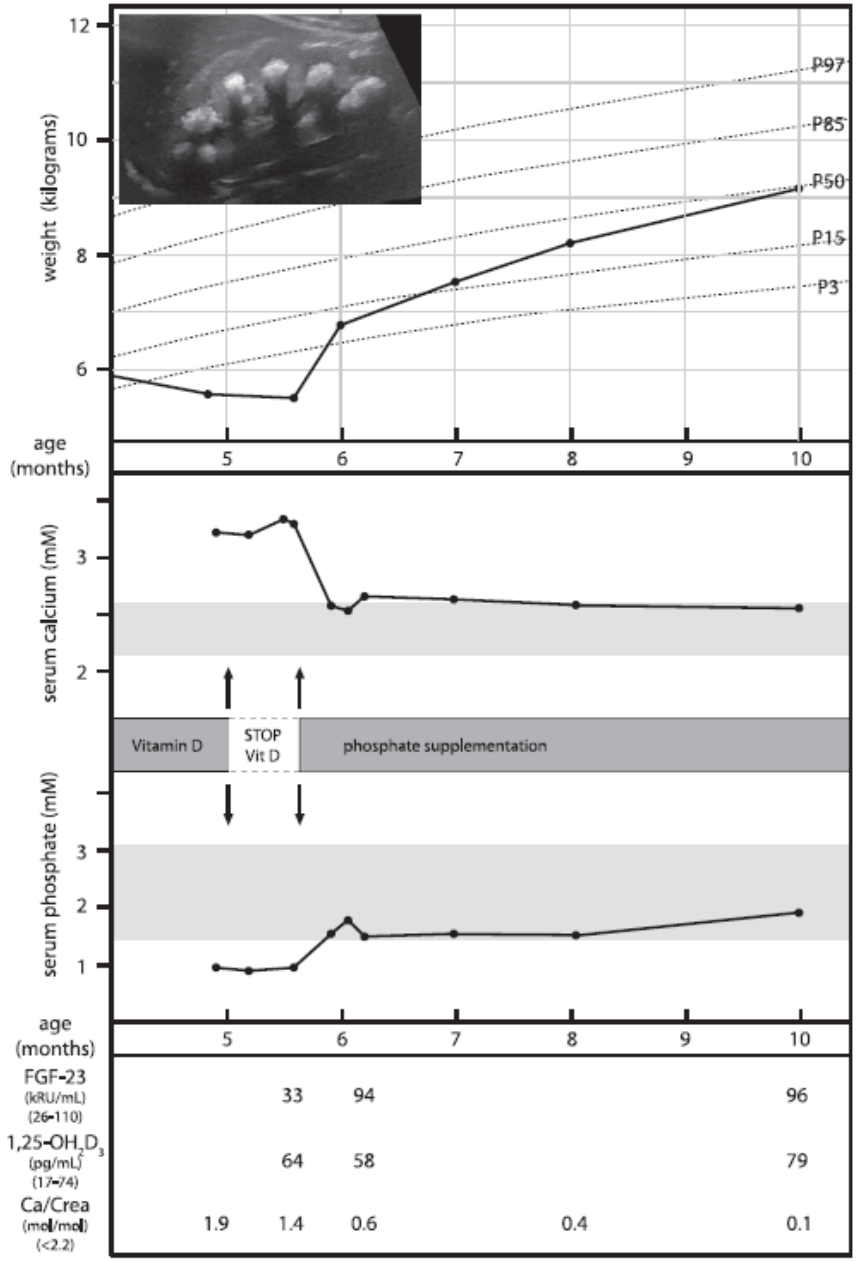
Schlingmann et al J Ame Soc Nephrol2015

Meyer MB et al, J Steroid Biochem Mol Biol. 2020


Pathway of IIH in CYP24A1 loss of function
skin
Vitamin D3
diet
CYP24A1
inactive
25(OH)D3
24,25(OH)2D3
CYP27B1
CYP24A1
FGF23
1,25(OH)2D3
1,24,25(OH)3D3
Intestinal Ca and PO4 Absorption
Osteoclast activity
Serum Calcium
PTH
Urinary Calcium
A
Pathway of IIH in SLC34A1 loss of function
skin
Vitamin D3
diet
PO4
Na+
NaPiIIa
PO4
FGF23
CYP24A1
inactive
25(OH)D3
24,25(OH)2D3
CYP27B1
apical
basolateral
Proximal renal tubule
CYP24A1
1,25(OH)2D3
1,24,25(OH)3D3
Intestinal Calcium Absorption
Osteoclast activity
Serum Calcium
PTH
Urinary Calcium
B



- Clinical and laboratory findings persist despite cessation of vitamin D prophylaxis but rapidly respond to phosphate supplementation.
- Therefore, early differentiation between SLC34A1(NaPi-IIa) and CYP24A1 (24-hydroxylase) defects appears critical for targeted therapy in patients with IIH.



Schlingmann et al J Amr Soci Neph 2015

Wang et al. Orphanet Journal of Rare Diseases (2024) 19:126
https://doi.org/10.1186/s13023-024-03135-8

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Biallelic and monoallelic pathogenic variants in CYP24A1 and SLC34A1 genes cause idiopathic infantile hypercalcemia

Qiao Wang[1], Jia-jia Chen[1], Li-ya Wei[1], Yuan Ding[1], Min Liu[1], Wen-jing Li[1], Chang Su[1] and Chun-xiu Gong[1*]

Pt 1 – CYP24A1 het

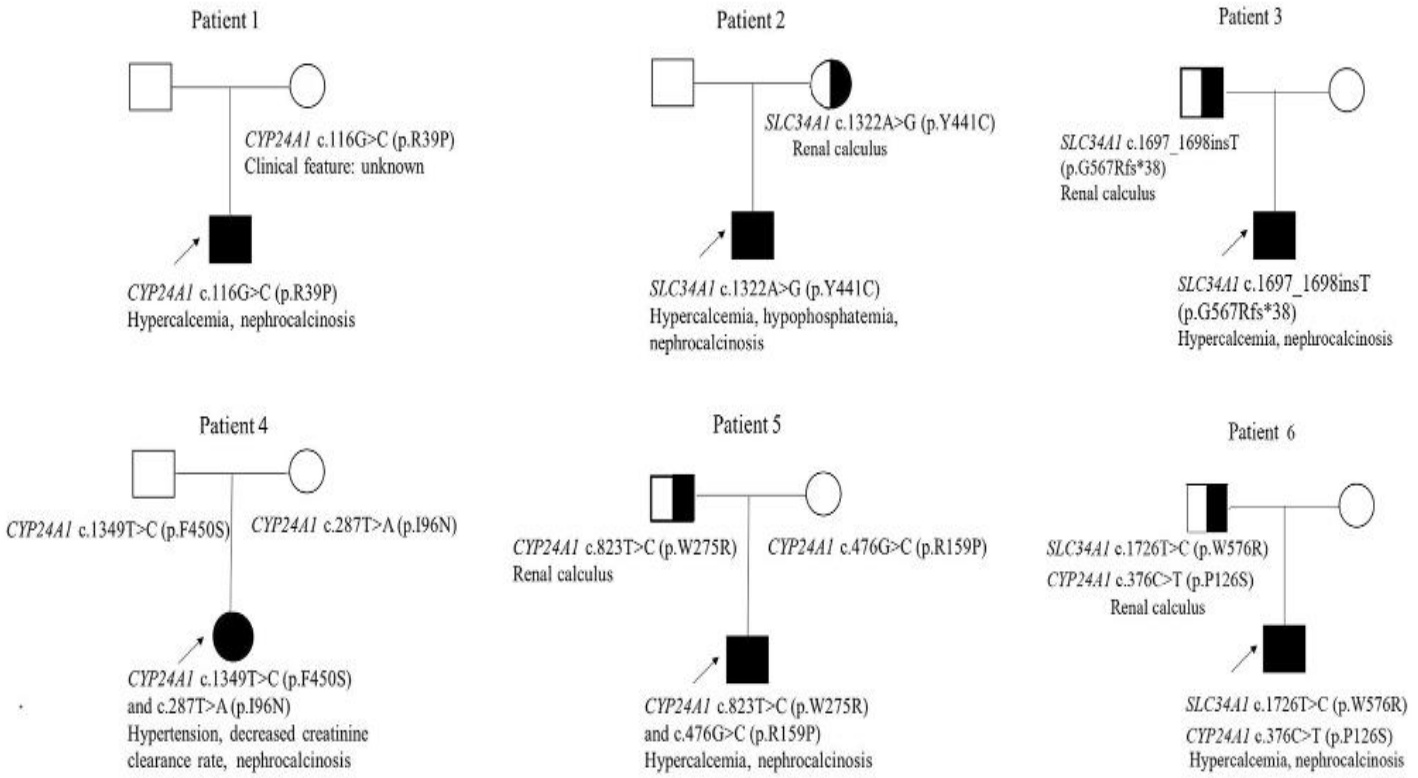
Pt 2 – SLC34A1 het

Pt 3 – SLC34A1 het

Pt 4 – CYP24A1 compound het

Pt 5 – CYP24A1 compound het

Pt 6 – CYP24A1 het+ SLC34A1 het



		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	
Sex		M	F	M	F	M	M	
Age of onset		3 mo	3 mo	5 days	2 mo	1 mo	1 mo	
Age at diagnosis		9 mo	6 mo	1 mo	11 yr	8 mo	1 yr	
Symptoms	Fever					+		
	Feeding difficulty	+	+	+	+	+	+	
	Vomiting	+	+	+	+	+		
	Poor weight	+	+	+	+	+	+	
At initial presentation								
								Normal range
Serum Ca (mmol/L)		3.79	4.19	4.31	2.35	3.36	2.88	2.1–2.8
Serum Pi (mmol/L)		1.52	1.05	1.57	1.72	1.19	1.15	1.37–1.99
Serum Mag (mmol/L)		0.74	0.85	0.86	0.91	0.58	0.81	0.8–1.2
ALP (U/L)		260	124	178	436	154	329	143–406
PTH (pg/ml)		1.00	1.00	0.01	31.58	2	ND	10–69
$25(OH)D_3$ (nmol/L)		30.8	25.3	24.4	ND	> 400	77.4	≥ 50
$1,25(OH)_2D_3$ (pg/ml)		ND	ND	ND	110	ND	ND	
Urine Ca/Cr (mmol/mmol)		1.67	ND	ND	3.19	1.35	0.24	0.00-0.20
24 h urine Ca (mmol/kg/24 h)		0.22	0.22–0.31	0.17–0.22	ND	0.21	ND	< 0.2
GFR (mL/min/1.73 m2)		84.2–127.0	42.5–94.7	45.9	89.7	66.9-136.3	104.2	< 90

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	
Sex	M	F	M	F	M	M	
Age of onset	3 mo	3 mo	5 days	2 mo	1 mo	1 mo	
Age at diagnosis	9 mo	6 mo	1 mo	11 yr	8 mo	1 yr	
At last observation							
Age	2 year 6 mo	6 year 8 mo	4 mo	13 year	1 year 5 mo	1 year 5 mo	
Serum Ca (mmol/L)	2.2	2.40	2.55	2.45	2.56	2.45	2.1–2.8
Serum Pi (mmol/L)	ND	1.57	1.9	ND	1.87	1.37	1.37–1.99
ALP (U/L)	ND	270	320	ND	ND	44.8	143–406
PTH (pg/ml)	ND	ND	1.2	ND	ND	ND	10–69
Urine Ca/Cr (mmol/mmol)	ND	0.09	0.44	0.16	ND	0.09	0.00-0.20
GFR (mL/min/1.73 m2)	ND	131.7	100.6	77.7	ND	137.1	< 90
Imaging examination							
Nephrocalcinosis	+	+	+	+	+	+	
Gene analysis	*CYP24A1* c.116G > C het	*SLC34A1* c.1322 A > G het	*SLC34A1* c.1697_1698insT het	*CYP24A1* c.1349T > C and c.287T > A	*CYP24A1* c.823T > C and c.476G > C	*SLC34A1* c.1726T > C het and *CYP24A1* c.376 C > T het	

HYPERCALCEMIA DUE TO CYP24A1 MUTATIONS: A SYSTEMATIC DESCRIPTIVE REVIEW

- Of the 221 patients identified, 136 (61.5%) harbored biallelic (either homozygous (*n* = 56, 41.2%)) or compound heterozygous (*n* = 77, 56.6%)) variants, and 85 (38.5%) monoallelic variants.
- The results of the current systematic review identified a milder biochemical and clinical phenotype in the monoallelic pathogenic variants carriers.
- Symptomatic hypercalcemia was reported in 20 pregnancies over the 25 identified in the literature (80%), often during the second or third trimester or even post-partum
- The risk of vitamin D supplementation, particularly during early infancy and pregnancy.

Cappellani et al 2022

QEUSTIONS

1. **Does the patient's neurological picture result solely from hypercalcemia?**
2. **Long-term follow-up of patients with biallelic variants:**
   - What is the risk of recurrence of significant hypercalcemia in patients with biallelic variants?
   - How does this affect the recommendation of long-term f/u?
3. **Follow-up for carriers of monoallelic variants**
4. **Recommendations for follow-up during pregnancy:**
   - What are the recommendations for managing women with monoallelic or biallelic during pregnancy?

ENDO NEPHRO GENETICS

תודה על ההקשבה

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