Vitamin D Deficiency and Rickets

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Rickets – what is it?

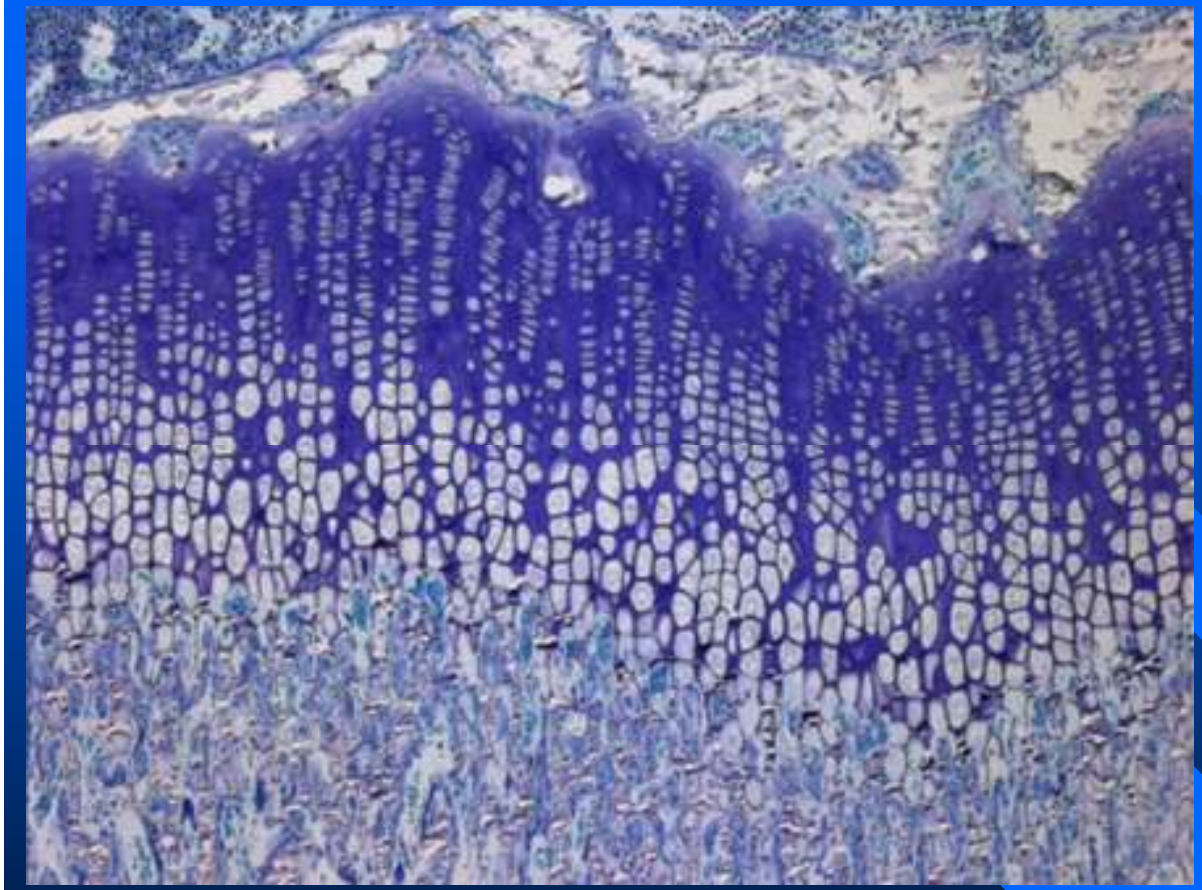
- Condition principally affecting the growth plate
- Disruption of the growth plate with:
  - distortion of the normal chondrocyte development
  - failure of normal apoptosis of chondrocytes
  - widening of growth plate
  - failure of vascularisation of cartilage
- Can't occur in adults
- Doesn't affect intramembranous bone (e.g. skull vault)

Osteomalacia – what is it?

- Failure of normal mineralisation of the osteoid surfaces during remodelling of bone
- Matrix unaffected
- Dependent upon supply of calcium and phosphate as mineral substrate
- Not clear the effect on bone strength

Osteoporosis – what is it?

- Primary defect in matrix formation resulting in secondary reduction in mineral deposition
- Leads to weakened bones and increased fracture tendency
- May be
  - primary e.g. OI or
  - secondary e.g. chronic steroid use



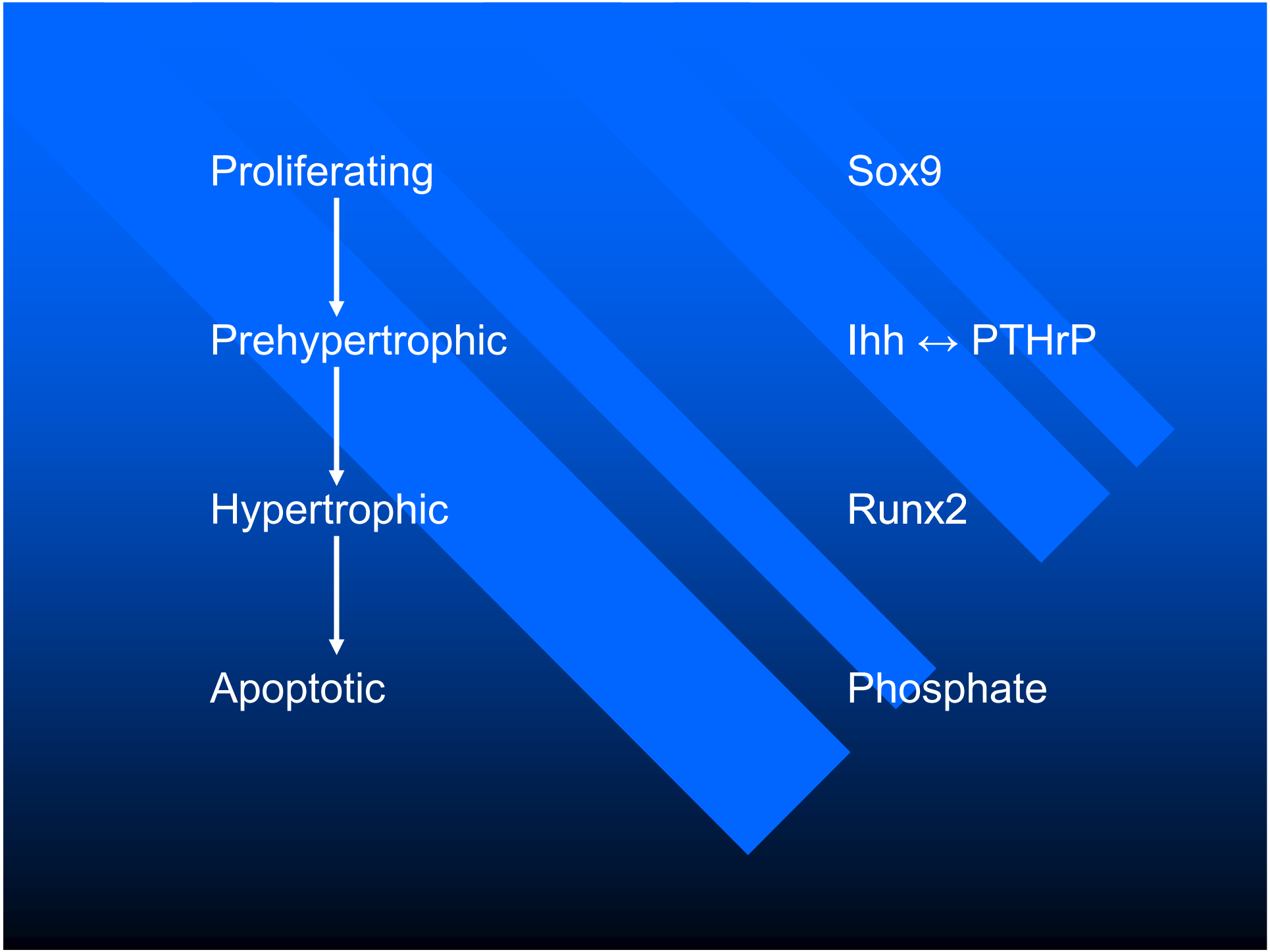
Proliferative

Prehypertrophic

Hypertrophic

Apoptotic

Calcified


Proliferating
Prehypertrophic
Hypertrophic
Apoptotic
Sox9
Ihh ↔ PTHrP
Runx2
Phosphate

Condition	Biochemistry	Gene
'Nutritional' Vitamin D deficiency	↓Ca, ↓PO_4, ↑PTH, N 25OHD, ↓1,25$(OH)_2$D	
Nutritional Calcium deficiency	↓Ca, ↓PO_4, ↑PTH, N 25OHD, ↑ 1,25$(OH)_2$D	
Vitamin D dependent rickets	↓Ca, ↓PO_4, ↑PTH, N25OHD, ↓ 1,25$(OH)_2$D	1α-hydroxylase deficiency
Vitamin D receptor defect (VDRRII)	↓Ca, ↓PO_4, ↑PTH, ↑25OHD, ↑1,25$(OH)_2$D	VDR defect +/- alopecia
Hypophosphataemic rickets	NCa, ↓PO_4, NPTH, N25OHD, ↓1,25$(OH)_2$D	PHEX, FGF23, DMP1, ENPP1, Gsα, TOI
HHRH	NCa, ↓PO_4, NPTH, N25OHD, ↑1,25$(OH)_2$D	Na/Pi co-transporter

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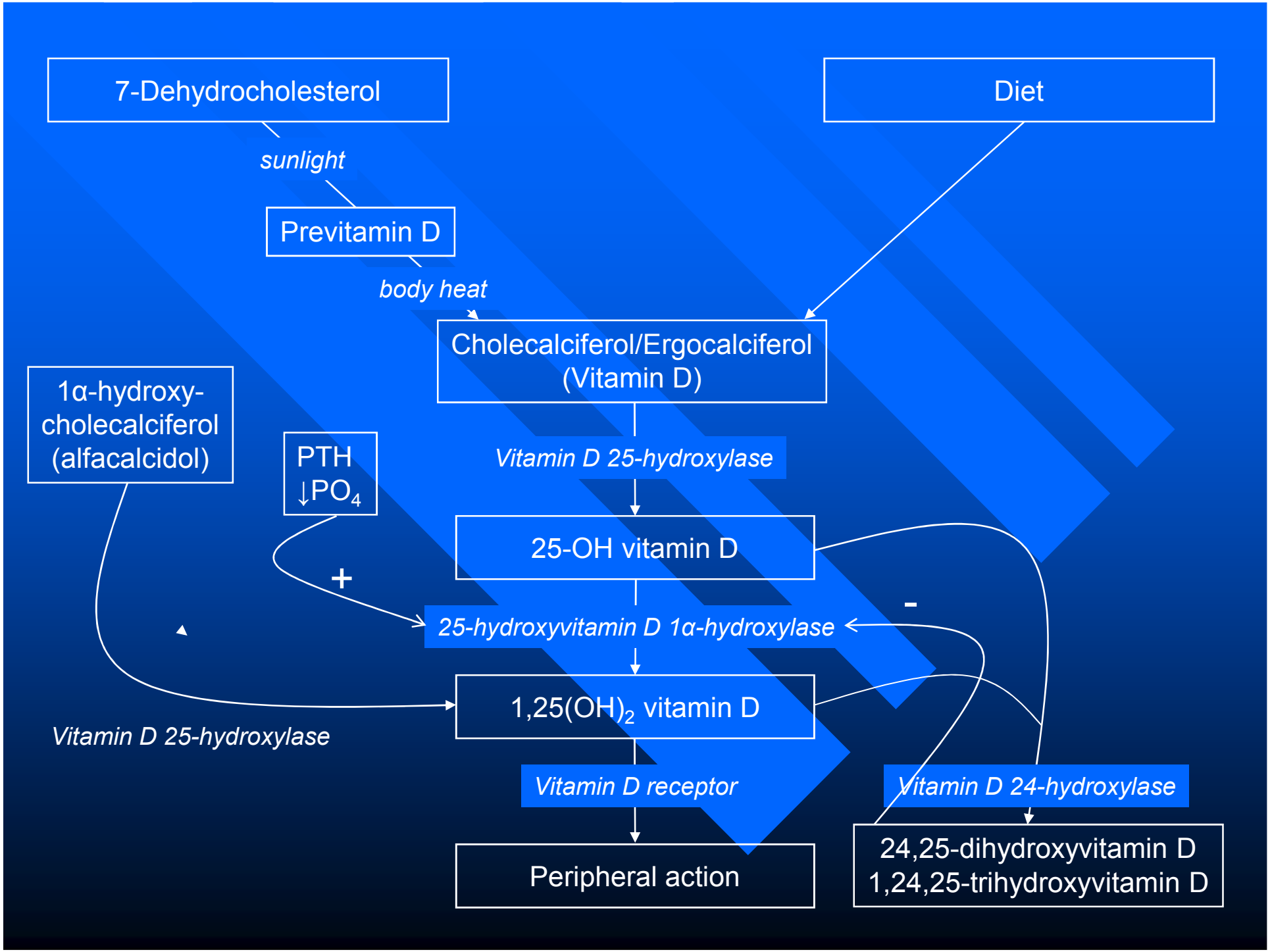
Classification of Rickets

Traditional	**Revised**
Calciopaenic (inc Vitamin D related)	↑PTH mediated
Phosphopaenic	↑FGF23 mediated
Renal	Renal phosphaturia

Tiosano D & Hochberg Z J Bone Miner Metab 2009; 27:392-401


7-Dehydrocholesterol
Diet
sunlight
Previtamin D
body heat
Cholecalciferol/Ergocalciferol
(Vitamin D)
1α-hydroxy-
cholecalciferol
(alfacalcidol)
PTH
↓PO4
Vitamin D 25-hydroxylase
25-OH vitamin D
+
-
25-hydroxyvitamin D 1α-hydroxylase
1,25(OH)2 vitamin D
Vitamin D 25-hydroxylase
Vitamin D receptor
Vitamin D 24-hydroxylase
Peripheral action
24,25-dihydroxyvitamin D
1,24,25-trihydroxyvitamin D

Classification of Calciopaenic, PTH dependent rickets

- Vitamin D deficiency
  - true deficiency (poor sunlight exposure)
  - malabsorption etc
- 25-hydroxylase deficiency
- 1α-hydroxylase deficiency (VDDR1)
- HVD receptor defect (VDDR2)
  - with alopecia (receptor defect)
  - without alopecia (nuclear defect)
  - unknown cause
- Calcium deficiency

Definition of Deficiency (25OHD)

Toxic	>200 nmol/L
Fully replete	75-200 nmol/L
Replete	51-75 nmol/L
Insufficient	26-50 nmol/L
Deficient	15-25 nmol/L
Seriously deficient	<15 nmol/L

Clinical Syndromes

- Congenital rickets
- Dilated cardiomyopathy
- Classical rickets (+/- convulsions)
- Hypocalcaemic convulsions
- Generalised aches and pains, muscle weakness etc

Conclusions

- Vitamin D receptor mutations result in:
  - severe rickets with poor development
  - Poor growth
- Treatment with intravenous calcium (and magnesium and phosphate) corrects the biochemical abnormalities and heals the rickets
- Oral treatment may be sufficient thereafter if adequate supplements are given

Allgrove's Adage 1

THE TREATMENT OF VITAMIN D DEFICIENCY IS VITAMIN D

Allgrove's Adage 2

YOU CAN'T MAKE A DIAGNOSIS RELATED TO RICKETS OR HYPOCALCAEMIA UNTIL VITAMIN D DEFICIENCY HAS BEEN EXCLUDED OR CORRECTED

Allgrove's Adage 3

VITAMIN D SUPPLEMENTATION IS THE MOST COST-EFFECTIVE MEASURE THAT WOULD IMPROVE THE HEALTH OF THE POPULATION OF THE EAST END OF LONDON

Thank you