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Longitudinal Evaluation of Bone Density in Children & Young Adults with Neurofibromatosis Type 1

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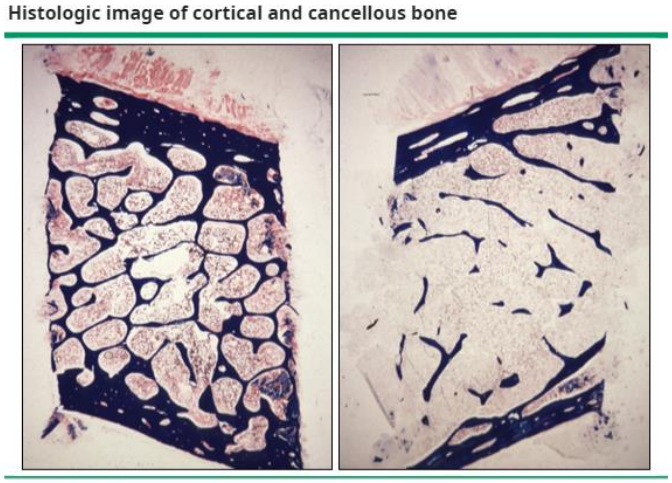
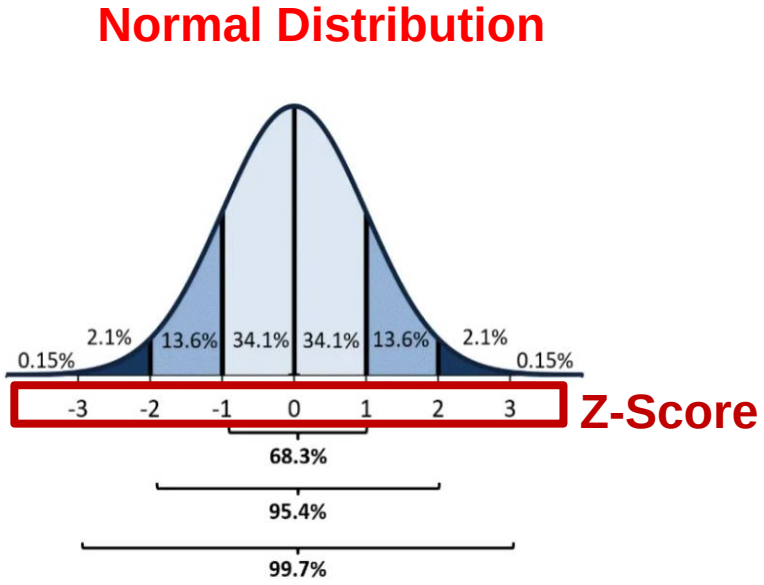
Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Bone Mineral Density (BMD) & NF1

- Measured with dual-energy x-ray absorptiometry (DEXA)
- NF1 associated with osteopenia and osteoporosis in adults
  - Up to 20% of adults with NF1 have osteoporosis
- Challenges to normalizing pediatric BMD
  - Bone size, height, pubertal status, ethnicity
  - Diagnosis of osteoporosis requires history of fracture
- Need to use Height, Age and Sex-Adjusted Z-scores



https://www.uptodate.com/contents/normal-skeletal-development-and-regulation-of-bone-formation-and-resorption



Bone Mineral Density & Pediatric NF1

- Decreased BMD in many children with NF1
  - **Stevenson et al 2007**: Decreased BMD in multiple body regions compared to normal controls (n=84 with NF1)
  - **Lodish et al 2012:** 47% of patients had impaired BMD in at least one bone site (n=69)
  - Other studies have shown similar results
- Limited prior longitudinal evaluations of BMD in children and young adults:
  - **Brunetti-Pierri et al 2008**:
    - Two-year follow up on 8 patients with abnormal BMD and elevated parathyroid hormone
      - Started on Vitamin D & Calcium therapy
      - No improvement in BMD after 2 years

Objectives

- Using the NCI NF1 Natural History Cohort*, evaluate changes in BMD Height-Adjusted Z-Score (HAZ) over time
  - Differences by number/type of bony abnormalities or fracture history
  - Any detectable effect of PN-directed treatment initiated between scans
- Gauge any correlation between bone-related labs and BMD HAZ and changes over time

*Includes patients that were published by Lodish et al 2012

Methods

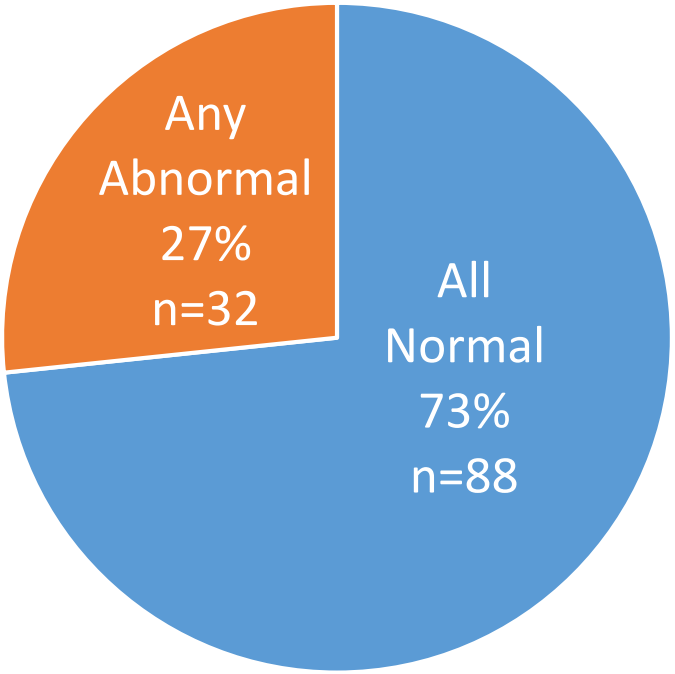
- Baseline subject characteristics, bony abnormalities, fracture history
- Serial DEXA scans (baseline vs most recent)
- Calculated HAZ for subtotal body, Lumbar Spine, and femoral neck
  - Excluded scans including hardware
- Labs to evaluate bone health:
  - Calcium, alkaline phosphatase, intact parathyroid hormone, 25-OH Vitamin D
- Statistical analyses:
  - Paired and unpaired t-tests for BMD comparisons
  - Spearman correlations to comparer bone labs and BMD Z scores

Subject Characteristics

	Baseline Characteristics	
	All Baseline (n = 120)	**Baseline with Follow-Up (n = 78)**
Median Age, years (range)	12.8 (5, 32.2)	11.4 (5.1, 28.3)
Sex – Male/Female	68/52	43/35
Presence of at least 1 Bony Abnormality (%)	99 (83)	67(86)
Scoliosis (%)	88 (73)	60 (77)
Sphenoid Wing Dysplasia (%)	17 (14)	11 (14)
Long Bone Dysplasia	6 (5)	3 (4)
History of Fracture (%)	35 (29)	26 (33)
Median Time Between Scans	N/A	3.9 years

Response Evaluation in REiNS Neurofibromatosis & Schwannomatosis

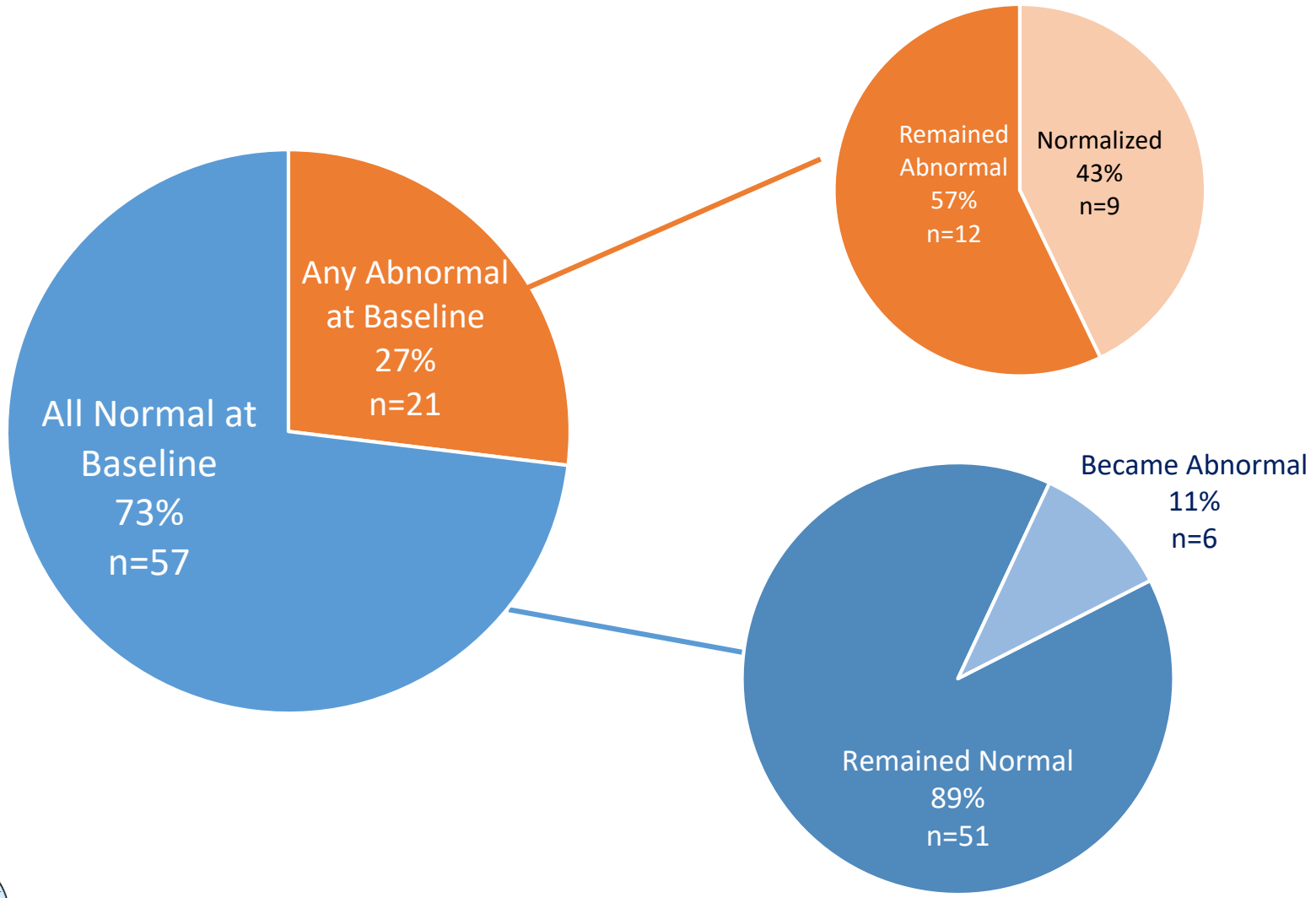
All Baseline Height-Adjusted Z-Scores (n = 120)



	n	Median Height Adjusted Z-Score	# Abnormal* (%)
Subtotal Body	87	-0.78	17 (19.5)
Lumbar Spine	109	-0.51	9 (8.2)
Femoral Neck	115	-0.98	20 (17.3)

*Abnormal Z-Score is ≤ -2

Height-Adjusted Z-Scores with Follow-Up (n = 78)



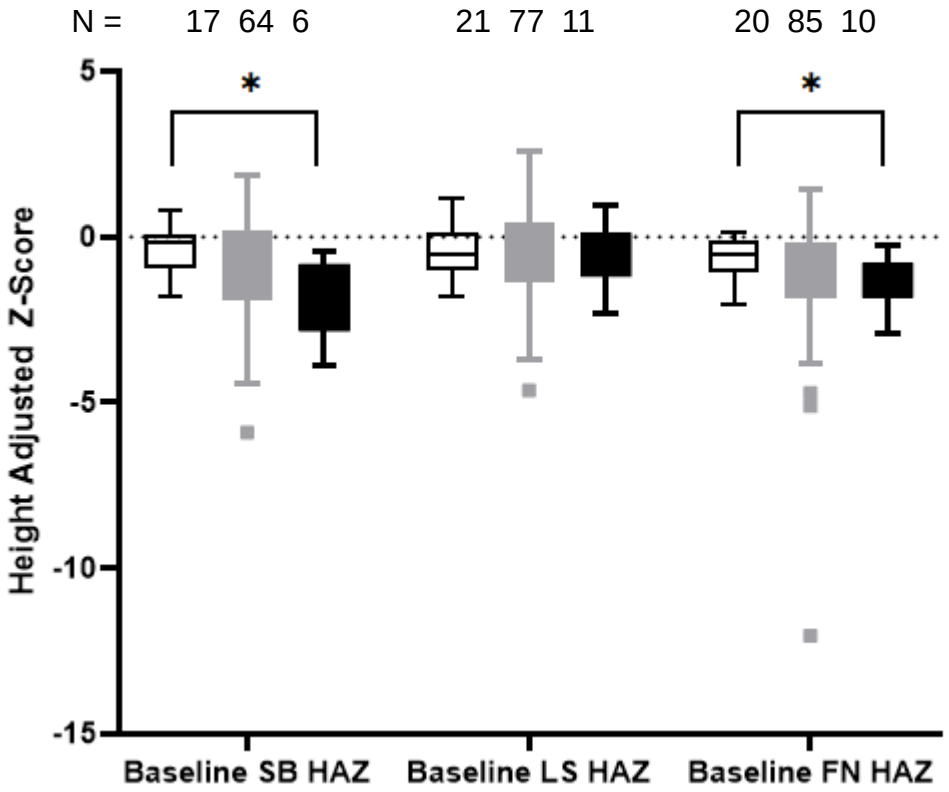
Paired Height-Adjusted Z Scores: Change Over Time (n = 78)

	n	Median Age at Baseline	Median HAZ at Baseline	Median HAZ at Most Recent Scan	Median Time between Scans	Median Difference
Subtotal HAZ	58	11.96	-0.95	-0.525	3.18	0.30*
Lumbar Spine HAZ	66	11.21	-0.31	-0.64	3.9	-0.23*
Femoral Neck HAZ	74	11.46	-0.94	-0.98	4.04	0.00

- No difference in change in HAZ over time by surgical, medical, or MEK inhibitor treatment status

*p<0.05

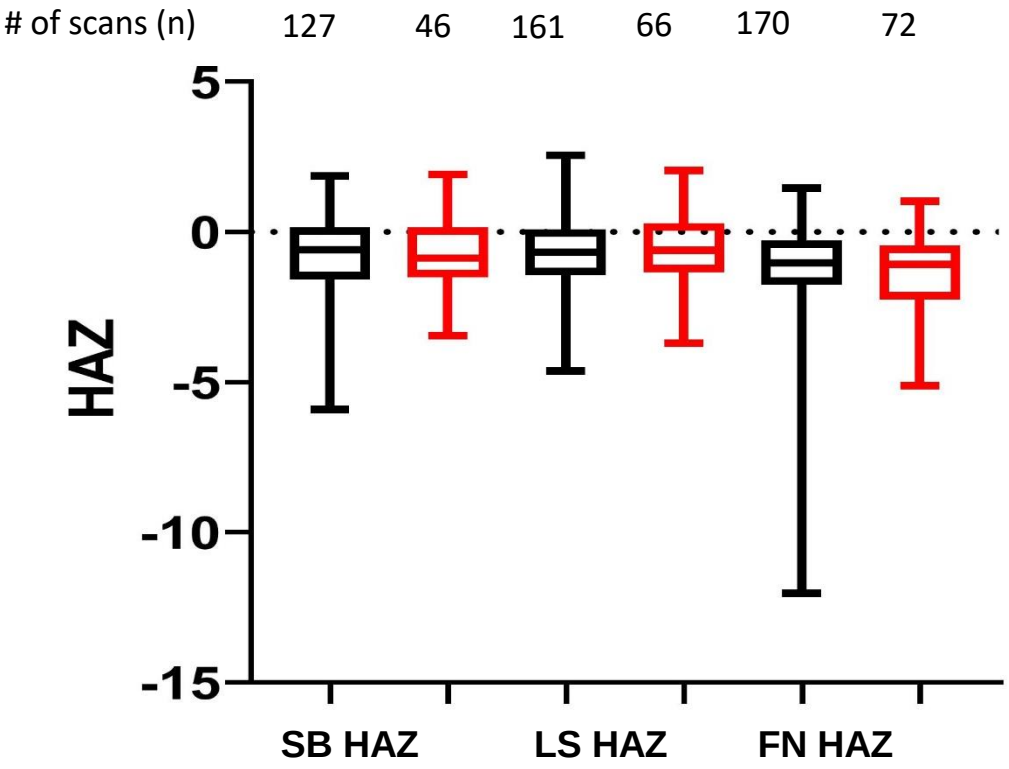
Bony Abnormalities at Baseline



- Subtotal Body and Femoral Neck HAZ significantly lower in subjects with 2 bony abnormalities

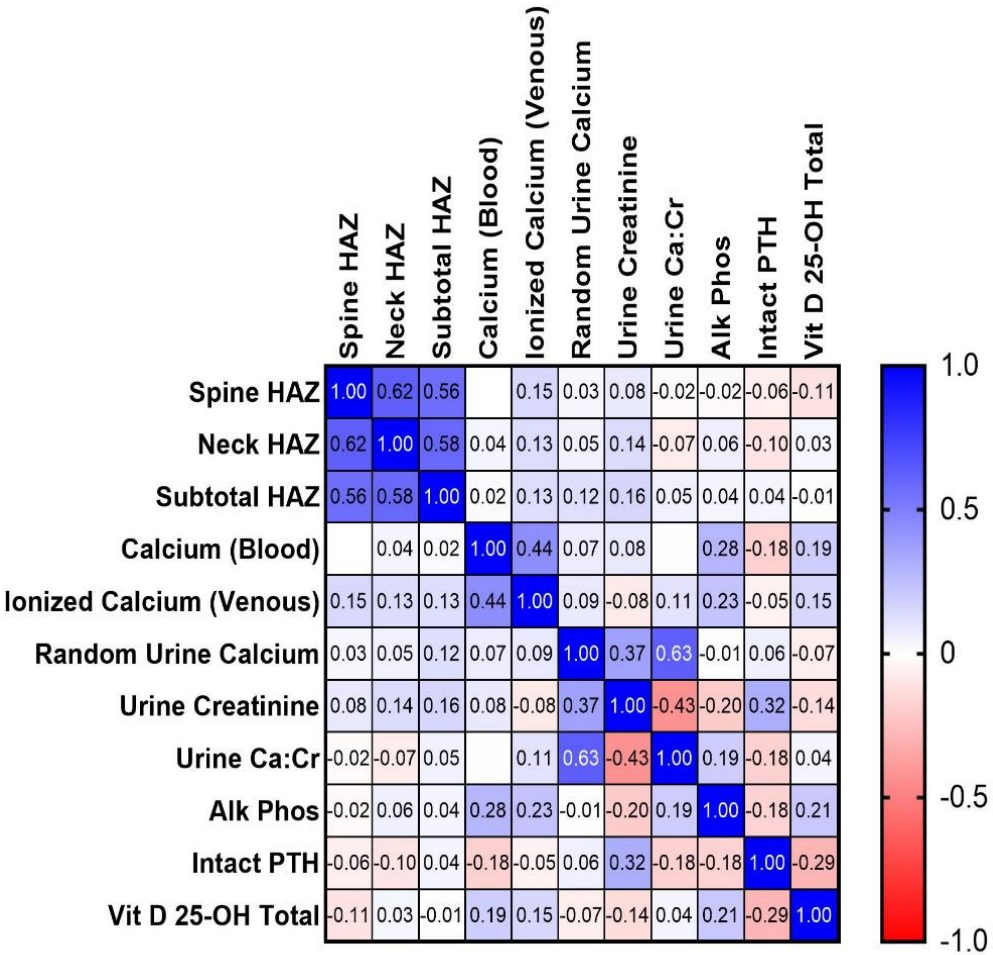
No significant difference in HAZ at baseline by type of bony abnormality: scoliosis vs. long bone dysplasia

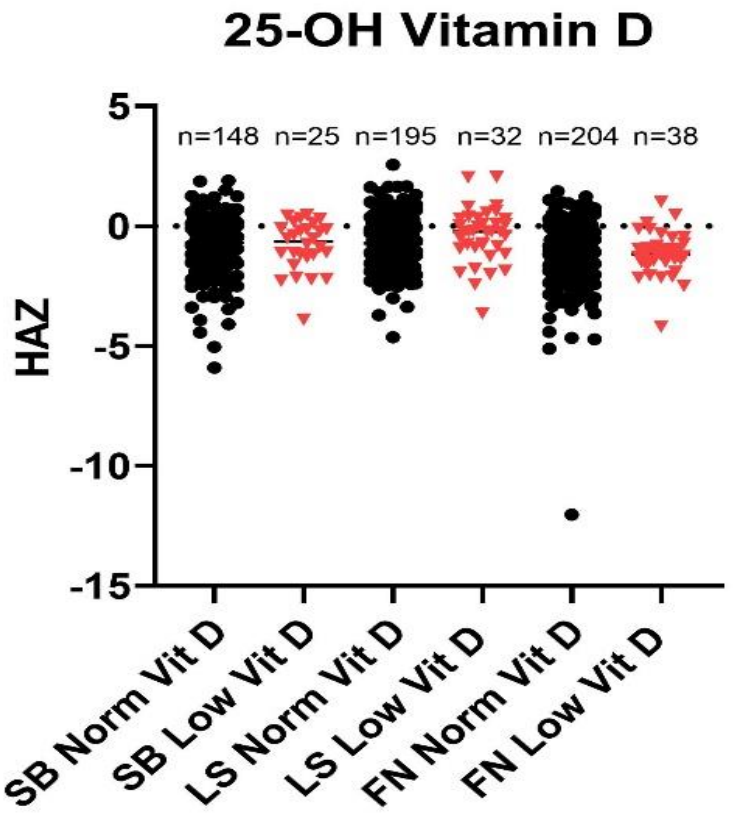
No Difference in HAZ BMD Between Patients with and Without Fracture



- **Black**: No history of fracture
- **Red**: History of fracture

BMD and Bone Lab Relationships





No significant correlations between HAZ BMD and bone-related labs

Limitations

- Multiple analyses may lessen statistical significance
- Excluding patients with hardware may skew results
- Significant number of patients with only single DEXA scan (35.5%)
- Subgroup analyses limited by small numbers
  - Bony abnormalities, especially multiple abnormalities

Conclusions and Future Directions

- 27% of subjects had at least one body region with abnormal HAZ (≤ -2) at baseline
  - <u>After ~4 Years of Follow up:</u>
    - If abnormal, more than half stayed abnormal
    - If normal, most stayed normal
- Subtotal body HAZ increased and lumbar spine HAZ decreased over time
- Did not find a relationship between HAZ BMD and bone-related labs, fracture history, or treatment between scans
  - Need further, targeted study of treatment effects

Extra Slides

Neurofibromatosis 1 (NF1) & Bone

- Spinal Deformities
  - Scoliosis; vertebral scalloping/wedging
- Long Bone Dysplasia/ Pseudoarthrosis
- Metabolic Bone Disease/ Decreased bone mineral density

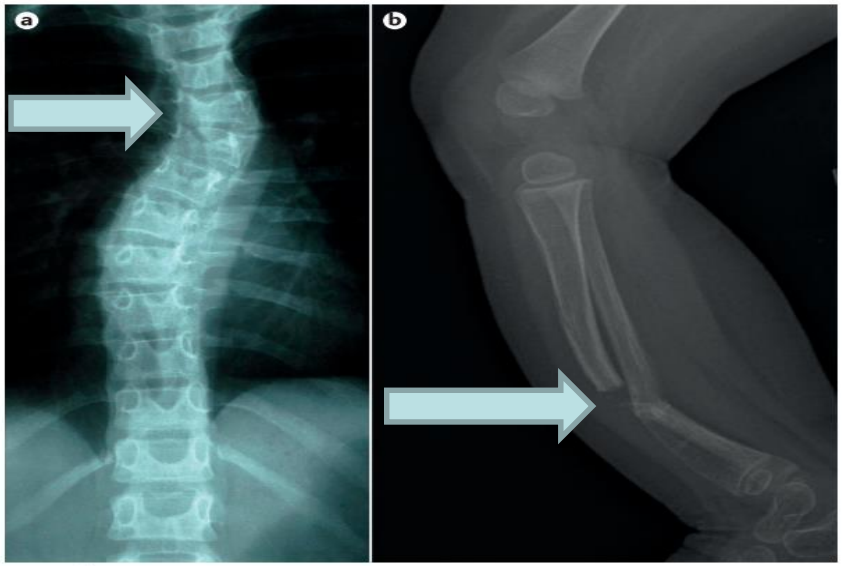
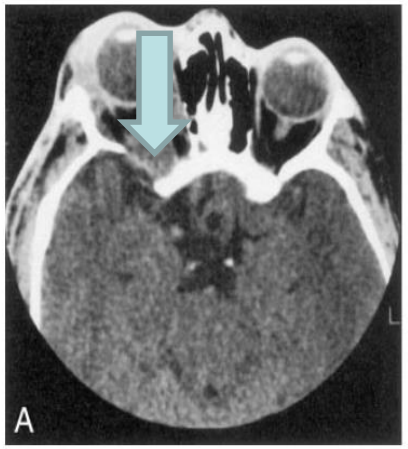


Figure 7 | **Skeletal defects in neurofibromatosis type 1.** Individuals with neurofibromatosis type 1 can present with a range of skeletal defects, including dystrophic scoliosis (part **a**) and tibial dysplasia (part **b**), which can be detected by radiographic imaging.

(Gutmann 2017)



(Jacquemin 2002)

Height-Adjusted Z Scores (HAZ)