

**Dear Dr. Nolan,**

Thank you very much for the opportunity to examine the radiographic images of this specimen.

I have examined in the course of my career many skeletal and other pediatric bone anomalies and dysmorphias, especially in the field of skeletal dysplasias & syndromes. This specimen does not fall under any known, to me, class of disorders or syndromes. As I told you during our last meeting (when I formally went over the images in preparation for the formal report) -- there is no known form of dwarfism that accounts for all of the anomalies seen in this specimen. Most interestingly, based on knee epiphyseal standards, the specimen appears to be 6-8 years of age. While there remains a possibility this latter result is due to some form of unknown progeria (accelerated aging syndrome), in my opinion this is a low probability.

In many respects the proportions of the spine and extremities are normal. The major abnormalities appear to be (1) the size of the specimen, which is not in accordance with an apparent age of 6-8 years, (2) mid-face hypoplasia and underdevelopment of the jaw, and that the specimen has only 10 ribs (humans normally have 12, rarely 11).

I look forward to your genetic analyses of the specimen. I have listed for you at the end of the report a number of mutations of which I am aware that are known to affect the skeletal regions that show mutations in the specimen. While none of those mutations are known to cause all the anomalies observed, they are provided as reference points in your continued examination of the specimen.

Good luck with your work on this.

Best,  
Ralph Lachman MD



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# BARCELONA PROJECT RADIOGRAPHIC EVALUATION

- EXTREMELY TINY PROPORTIONATE SHORTENING
  - [NO EVIDENCE OF RHIZO/MESO/ACROMELIA]
- CALCULATED BONE AGE [FROM KNEE EPIPHYSEAL STANDARDS]
  - ABOUT 6-8 YEARS

## SKULL

- APPARENTLY POST MORTEM (PM) CRUSHED SKULL
- CORONAL SUTURE SYNOSTOSIS [?]; TURRENCEPHALY
- MILD/MODERATE MIDFACE HYPOPLASIA
- LOSS OF MANDIBULAR ANGLE
- AT LEAST 1 TOOTH NOTED IN MANDIBLE [Lack of teeth could be due to post-mortem loss]

## SPINE

- NORMAL [INTACT BUT SMALL STRUCTURES]
- NORMAL INTERPEDICULATE WIDENING [L1-L5]

## THORAX

- 10 RIBS
- NARROW THORAX WITH OTHERWISE NORMAL RIBS
- ELONGATED CLAVICLES [Post-Mortem FRACTURE]
- NORMAL SCAPULA

## PELVIS

- FLAT ACETABULAR ROOF
- OTHERWISE NORMAL ILEUM/ISCHIUM
- PUBIS NOT WELL SEEN [? UNOSSIFIED]

## EXTREMITIES

- ALL LONG BONE DIAPHYSES ARE PROPORTIONATELY VERY SHORT BUT NORMALLY FORMED

## FEMUR

- CAPITAL FEMORAL EPIPHYSES NOT WELL SEEN [PROBABLY NORMAL]
- DISTAL EPIPHYSES NORMAL [PM FRACTURE THRU GROWTHPLATE WITH RESULTANT WIDENING]

## TIBIA

- NORMAL PROXIMAL & DISTAL EPIPHYSES

## FIBULA

- NORMAL /EXPECTED PROPORTIONATE LENGTH

## HUMERUS

- NORMAL PROXIMAL EPIPHYSIS
- NO ELBOW DISLOCATIONS

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## RADIUS/ULNA

- NORMAL INCLUDING AT LEAST 1 ULNA EPIPHYSIS

## HANDS

- RELATIVELY NORMAL PROPORTIONATELY SHORT HANDS
- CARPALS NOT WELL SEEN BUT CARPAL SPACE IS NORMAL IN SIZE
- NORMAL NUMBER OF METACARPALS/PHALANGES

## RADIOGRAPHIC IMPRESSION/CONCLUSIONS:

- AN UNBELIEVABLY TINY PROBABLE 6-8 YEAR OLD WITH PROPORTIONATE SHORTENING
- NO EVIDENCE OF EPIPHYSEAL/METAPHYSEAL/DIAPHYSEAL DYSPLASIA & WITHOUT ANY SPINE CHANGES
- POSSIBLE CRANIAL SUTURE ABNORMALITY & DYSMORPHISM
- DOES NOT APPEAR TO REPRESENT A SKELETAL DYSPLASIA

## SOME THOUGHTS:

Speculative mutations based on knowledge to date:

- IF SUTURAL CLOSURE IS REAL SUGGESTS POSSIBLE FGFR [2, 3] MUTATION
- LOSS OF MANDIBULAR ANGLE SUGGESTS PYCNODYSTOSIS [CATHEPSIN GENE]; NO OTHER ASSOCIATED FINDINGS IN THIS CASE
- 10 RIBS SUGGEST CHROMOSOMAL SYNDROME [IE TRISOMIES ETC]
- COULD THIS BE ADVANCED BONE AGE IN MUCH YOUNGER INDIVIDUAL SUGGESTING A PROGEROID OR OTHER SYNDROME?
  - I REALLY DOUBT THAT.
- I THINK THE MONEY IS ON SOMETHING NEW BUT THE CLOSEST KNOWN ENTITY IS SOME FORM OF OSTEODYSPLASTIC DYSPLASIA
- MOPD 1
  - RNU4ATAC GENE ENCODING SMALL NUCLEAR RNA[sn RNA] COMPONENT OF U12 DEPENDENT SPLICEOSOME ON CHR 2q14.2
- MOPD 2
  - PCNT GENE CHR 21q22
- \*MOPD 3 [CAROLINE CARACHI TYPE]
  - BUT, NO KNOWN GENE

\* NOTE: 1 KNOWN DWARFISM CASE, BUT NOT SAME SIZE - 7 INCHES AT BIRTH; 20 INCHES AT 12 YEARS

