A probable case of gigantism/acromegaly in skeletal remains from the Jewish necropolis of "Ronda Sur" (Lucena, Córdoba, Spain; VIII–XII centuries CE)

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With 6 figures and 3 tables

Abbreviated title: A case report of gigantism/acromegaly

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Abstract

Pituitary gigantism is a rare endocrine disorder caused by hypersecretion of growth hormone during growing period. Individuals with this disorder have an enormous growth in height and associated degenerative changes. The continued hypersecretion of growth hormone during adulthood leads to acromegaly, a condition related to the disproportionate bone growth of the skull, hands and feet.

The skeletal remains belong to a young adult male from the Jewish necropolis of "Ronda Sur" in Lucena (Córdoba, Spain, VIII–XII centuries CE). The individual shows a very large and thick neurocranium, pronounced supraorbital ridges, an extremely prominent occipital protuberance, and an extremely large and massive mandible. Additional pathologies include enlargement of the vertebral bodies with degenerative changes, thickened ribs, and a slight increased length of the diaphysis with an increased cortical bone thickness of lower limbs. Comparative metric analysis of the mandible with other individuals from the same population and a contemporary Mediterranean population shows a trend toward acromegalic morphology. This case is an important contribution in paleopathological literature because it is a rare condition that has not been widely documented in ancient skeletal remains.

Introduction

Human overgrowth is a complex multi–factorial process, involving physiological interaction between nutritional, metabolic, and endocrine factors, on a wider background of variation in genetic traits and environmental exposure (Sabin et al. 2011). Due to the complexity to attain normal growth, usually disturbance of even a single factor results in a delayed growth velocity and short stature, being less common conditions that cause increased height (Visser et al. 2009).

Longitudinal bone growth during childhood is due to growth hormone (GH)–dependent stimulation of precursor cells in epiphyseal cartilage, while maintenance of adult bone mass results from GH–driven bone modelling processes. These effects are the consequence of a complex interaction between circulating GH and insulin–like growth factor type I (IGF–I) produced peripherally (Colao et al. 2004, Morselli et al. 2006, Ueland 2004). Disorders of the GH/IGF–I system result from excessive GH secretion or GH deficiency (Ayuk & Sheppard 2006).

GH hypersecretion has several potential causes and may occur in the context of a number of heterogeneous disorders (Eugster & Pescovitz 1999), but the vast majority of cases (more than 95% of cases) are due to benign pituitary adenoma (Chanson & Salenave 2008, Chanson et al. 2009).

Pituitary gigantism is a rare endocrine disorder caused by excessive secretion of GH by the adenohypophysis during growing period, which causes prolonged stimulation at the endochondral growth plates (Melmed 2011, Schmidt et al. 2007). During childhood, the epiphyseal lines have not been yet closed and bones continue to growth in length and width (proportional growth of bones) (George et al. 1983), presenting the affected subjects an excessive growth in stature and degenerative changes associated.

The continued hypersecretion of GH during adulthood leads to acromegaly. After the closure of the epiphyseal lines, this condition hinders any further overgrowth of the bones in length, being only possible the periosteal apposition of bones and cortical thickening (George et al. 1983). The most characteristic skeletal changes are a disproportionate growth of the skull with coarse facial features, mandible, hands and feet (Ayuk & Sheppard 2006, Resnick 1988). If hypersecretion of GH occurs during childhood and continues into adulthood, both features of gigantism and acromegaly are expressed.

Manifestations of the acromegaly include skeletal and soft tissue growth and deformities and cardiac, respiratory, neuromuscular, endocrine, metabolic, and neoplastic complications (Chanson & Salenave 2008, Colao et al. 2004). The most typical skeletal signs are the coarse facial features, large spade–shaped hands and enlarged feet resulting from soft tissue swelling and bony enlargement. The craniofacial features include thickening of the cranium vault, frontal skull bossing, prominent supraorbital ridges, mandibular overgrowth, and large external occipital protuberance. Growth of the mandible results in prognathism, malocclusion, and widened interdental spaces (Chanson & Salenave 2008, Chanson et al. 2009, Lugo et al. 2012). Other common feature includes functional disability caused by arthropathy, which affects up to 70% of patients and involves both the axial and peripheral skeleton (Barkan 1997, Colao et al. 2004, Morselli et al. 2006, Scarpa et al. 2004). The underlying pathophysiology is not entirely understood, but it has been hypothesized that GH excess stimulates local production of IGF–I in cartilage, resulting in thickening of the cartilage, change of the normal joint geometry, and joint hypermobility (Colao et al. 2004, Morselli et al. 2006). Radiological findings include narrowing of the joint spaces, osteophytes, and other features seen in osteoarthritis (Scarpa et al. 2004).

Material and Methods

Archaeological context

The archaeological remains of Lucena (Córdoba, Spain) consist of the several partially ruined structures of a Jewish necropolis, one of the most ancient Jewish cemeteries of the Iberian Peninsula, which was used between the VIII–XII centuries CE (Botella & Riquelme 2008, De Luca et al. 2013). In 2007, arising from the construction of the "Ronda Sur" ring road, an extensive archaeological excavation took place and 346 graves were discovered, of which 201 had skeletal remains. In the inhumation funerary ritual documented, the bodies were

placed in simple undecorated wooden coffins without funerary offering, according to the Jewish religion. Mortuary customs consisted of an inhumation ritual with the body in a supine and extended position, orientated with the head to the west and looking to east, to the Holy City of Jerusalem.

All the burials were frequently poorly preserved because of the acidy of the soil and the shallow depth which did not protect them from recent agricultural activities (Botella & Riquelme 2008, De Luca et al. 2013).

The December 18 2011 was held the ritual reburial of the human remains in the original Jewish necropolis of Lucena, overseen by the Federation of Jewish Communities in Spain and the Hebrá Kadishá of Madrid (Spain). More than 40 representatives of national and international Jewish communities moved to Lucena to take part in the reburials under the Jewish rite.

Description of the individual TB.5

The individual reported in this study (TB.5) was inhumed in a tomb covered in large flat tiles or *tegulae*, in an extended supine position, with the head orientation to the west and the arms to the sides. No grave goods were associated with the burial (Botella & Riquelme 2008). Burial TB.5 was buried in a similar fashion to all other individuals in the necropolis, and its location within the necropolis did not distinguish it as being atypical. However, the degree of destruction of skeletal remains has been accused by the passage of heavy machinery over the burial and underlying structures during the initial stages of construction of the road, as well as the action of different taphonomic agents (Figure 1).

-----Insert Figure 1-----

Initially, the recovered skeletal remains were housed in the Archaeological and Ethnological Museum of Lucena (Córdoba) for further anthropological analysis. In 2010, while a study of oral pathology was conducting, the skeletal remains were cleaned to remove dirt and an extremely large mandible caught the attention of the researchers. Thus, the individual TB.5 was transported to the Laboratory of Anthropology (University of Granada) to conduct a more detailed analysis. The skeletal remains were very poorly preserved and highly fragmented and consisted of an incomplete skull (left parietal, occipital, and a small part of frontal bone), the mandible and isolated teeth. Regarding the postcranial skeleton, the individual is represented by the incomplete diaphysis of the right humerus and both femora, fragments of ribs and three vertebrae (C7, L4 and L5) (Figure 2).

Due to the reburial of the skeletal remains, these are not available for further studies.

-----Insert Figure 2-----

Methods

Sex was assessed according to the standard descriptive criteria (Buikstra & Ubelaker 1994, Ferembach et al. 1980). Due to the absence of the pelvis, cranial and mandible morphology were the main indicators of sex. In addition, discriminant functions of permanent dentition developed by Viciano (2012) with this same Jewish population were also applied to estimate sex. Age at death was based on the degree of occlusal dental wear following Brothwell (1981), Lovejoy (1985), Miles (1963), and Zoubov (1968) methods. Age was determined as an average of the ranges obtained by the different methods. Due to the incompleteness and alteration of the skull by postdepositional processes, the sutures were not used for age estimation.

Due to the integrity of the mandible, metric analysis was conducted according the definitions based in the descriptions of Buikstra & Ubelaker (1994) and Moore–Jansen & Jantz (1989) (Table 1). Data of mandible measurements for TB.5 were compared with measurements of other 21 males from the same Jewish population, as well as a sample of 35 male individuals from the Granada osteological collection of identified individuals (XIX–XXI centuries CE) housed at Laboratory of Anthropology (University of Granada), using *z*–scores. The standardization procedure of raw data to *z*–scores allows us to compare scores from different populations. The *z*–score indicates how far and what direction (positive vs. negative) a measured value deviates from the population mean, expressed in units of the population standard deviation. It is a dimensionless quantity derived from dividing the difference between the value of an observation (raw data; i.e. the mandible measurements of TB.5) and the population mean (i.e. the average of measurements collected from the same Jewish population and contemporary Mediterranean population) by the population standard deviation (SD; i.e. the standard deviation from both mentioned populations) (Bernard 2006, Wang & Chen 2012). A *z*–score close to 0 means that the raw score is close to the population mean. A negative or positive *z*–score means that the raw score is below or above the mean, respectively.

-----Insert Table 1-----

In addition, metric data of historical giants and acromegalic cases published in scientific literature were provided as mere comparative information. Unfortunately, the stature of TB.5 was not calculated because of the poor preservation of the long bones.

Results

Sex and age

The individual TB.5 is sexed as male, according to the descriptive criteria and the odontometric analysis. The estimated age at death was 22.22–33.74 years. Occlusal tooth wear is moderate and is consistent with the patterns observed in other 19 juvenile and adult individuals from the same population, whose age could be estimated more accurately by other skeletal observations.

Description of pathological findings

In general, each preserved bone of the skeleton is abnormal in shape, appearance, and/or size.

The bones of the neurocranium are remarkably thick and the left supraorbital ridge is large and very pronounced. The left mastoid process is large and bulky and the external occipital protuberance is massive and extremely prominent. The left glenoid fossa is large and deep, and in shape it resembles a circular fossa rather than a transverse groove (Figure 3).

-----Insert Figure 3-----

The mandible is extraordinarily large and massive, with a square and thick chin (Figure 4). Its angle is opened out to form a gentle curve. The rami show a greater increase in their vertical than in their antero–posterior diameter. The right coronoid process is thin and ascends to about a third more than its usual height. The condyles show a great increase in width and the height of the symphysis is markedly increased. The alveolar margin is partially destroyed and shows no pathological signs.

-----Insert Figure 4-----

The dentition recovered from this individual is composed of 13 isolated teeth. Teeth 11, 12, 17, 18, 21, 22, 23, 24, 25, 26, 27, 28, 31, 32, 33, 34, and 41 (following the nomenclature of the FDI 1971) have been lost postmortem. Teeth 35 and 38 are missing, leaving an empty cavity in which there are signs of remodeling (antemortem tooth loss). Teeth 36 and 37 show a stained opaque area of enamel in both mesial and distal interproximal contact areas (following Hillson 2001). No calculus deposits were observed. Tooth 43 exhibits enamel hypoplasia with two horizontal grooves (FDI 1982) on buccal surface between 3.26 and 4.55 mm from the cervico–enamel junction. Moderate occlusal wear was observed, from full cusp removal and/or some dentine exposure (teeth 14, 15, 36, 37, 42, 43, 44, 45, 47 and 48) to large dentine exposure with a complete enamel rim (teeth 13, 16 and 46) (following Smith 1984). Roots of all molars appear to be bulky, suggestive of hypercementosis.

Regarding the postcranial skeleton, vertebrae C7, L4 and L5 show marked periosteal buildup with anteroposterior and lateral enlargement of the vertebral bodies, with degenerative arthritic lipping. Osteophytes are present on the superior and inferior rims of L4 and L5, with Schmörl nodes on the inferior end plates (Figure 5). Ribs are big and thickened.

-----Insert Figure 5-----

The right humerus (Figure 6) and both femora show a slight length of the diaphysis, with an increased cortical bone thickness.

-----Insert Figure 6-----

Metric analysis

Table 2 shows the measurements of the mandible for TB.5 as well as comparative data for other males from the Jewish necropolis of "Ronda Sur", males from a contemporary Mediterranean population and other metric data from historical cases of acromegaly to comparison.

In general, the mandibular measurements of TB.5 are larger than the mean values of males from the same Jewish population. As shown in Table 2, three of 10 measurements showed significant differences. The *z*–score indicate that bigonial width, maximum ramus height, and mandibular length are significantly different ($z \geq 1.96$ SD) between TB.5 and other males from the same population. Similarly, six of 10 measurements collected showed significant differences with the contemporary Mediterranean population. These measurements correspond to mandibular body height, bicondylar breadth, minimum and maximum ramus breadth, maximum ramus height, and mandibular length. The *z*–score indicate that for these measurements, TB.5 exhibits significantly larger values than the contemporary Mediterranean sample ($z \geq 1.96$ SD). On the other hand, the mandible angle of TB.5 is smaller in comparison with the mentioned populations above, although is not statistically significant.

-----Insert Table 2-----

Is important to highlight that the mandible was complete at the time of the measurements collection. However, due to their poor state of preservation it became brittle in the course of time until the photographs were taken. For this reason the images show that the mandible has fragmented both condyles, and the right mandible angle. Only the right side of the mandibular body and the left coronoid process were already broken at the time of the morphological and metric studies.

Discussion

The incomplete and fragmentary nature of the skeletal remains underscores the difficulty of estimating sex and age of the individual with accuracy. The robustness of the skull and mandible, following descriptive criteria, appear to correspond with a male individual. Nevertheless, these features seem to correspond to a pattern of the disease process. It is noteworthy that sex estimation also was conducted using odontometric analysis with the application of specific discriminant functions of this population, and sex male was confirmed. However, some odontological literature correlate true generalized macrodontia with acromegaly (Bricker et al. 2001, Mainali et al. 2011, Purkait 2011, Schuurs 2013). Therefore, the estimated sex should be taken with caution, although no significant differences were found between the size of the dentition of individual TB.5 and the average size of the dentition of the entire Jewish population. Regarding the age, occlusal tooth wear analysis seems to correspond to a young–adult individual. Furthermore, the observation of sagittal and lambdoid sutures not obliterated also confirm this estimation (although the sutures were not used for age estimation in the present case study due to postdepositional changes that altered partially their morphology). Nevertheless, there are pronounced degenerative changes in spine, which are usually indicative of more advanced age; but in this case appear to be part of an overall pattern of pathological processes and, therefore, the estimated age should also be considered with caution.

It is also important to note that excessive growth of the skeleton in gigantism depends on the age of onset of the disorder. If the condition begins at an early age, growth is extreme, but if it starts closer to puberty, the increased growth is not as pronounced (Resnick 1988). TB.5 individual's stature could not be estimated. However, the diaphysis of the right humerus show

that the degree of bone growth is located on the lower end of the range of modern giants, suggesting the onset of disease around late childhood.

The persistence of hypersecretion of GH in adulthood can lead to acromegaly. The skeletal effects include an overgrowth of the skull, mandible, vertebral bodies, hands and feet (Cunningham 1903, Dostálová et al. 2003, Geddes 1911, Gosau et al. 2008, Hinsdale 1898, Kashyap et al. 2011, Marie 1891, Minozzi et al. 2012, 2013, Mulhern 2005, Souza–Leite 1891, Sternberg 1899, Thomson 1890). In the case of the craniofacial region, this condition leads to the presence of coarse features, which are reflected especially in the large size of the mandible and the supraorbital ridges, and large external occipital protuberance, as is observed in the individual TB.5.

The secretion of GH can be caused by a primary intrasellar pituitary tumor, which is usually a benign pituitary adenoma, but occasionally may be caused by diffuse hyperplasia (Aegerter & Kirkpatrick 1975). If a tumor is causing the pathological condition, the sella turcica can show evidences of increased diameter and lytic destruction (Chang et al. 2005, Cunningham 1903, Dostálová et al. 2003, Gosau et al. 2008, Hinsdale 1898, Marie 1891, Minozzi et al. 2012, 2013, Souza–Leite 1891, Sternberg 1899). However, in the case study could not be observed the sella turcica due to incomplete preservation of the skull.

Although the mandible of TB.5 shows no extreme characteristics, associated with advanced acromegaly, comparative measurements (with individuals of the same population and individuals of contemporary Mediterranean population) reveal a pattern suggesting an acromegalic morphology. Overgrowth disorders are those in which all or most of the parameters of growth and physical development exceed 1.96 SD (generally rounded to 2 SD) above average for that age and sex (Visser et al. 2009, Weaver 1994). Mandibular measurements of TB.5 show significant differences in the overall size, as reflected by other

authors (Dostálová et al. 2003, Geddes 1911, Hinsdale 1898, Minozzi et al. 2013, Mulhern 2005, Thomson 1890).

Regarding the differential diagnosis, there are several syndromes associated with an overgrowth, including Sotos, Beckwith–Wiedemann, Weaver, Simpson–Golabi–Behmel, Fragile X, McCune–Albright, Marfan, Klinefelter, Beals, and Lujan–Fryns syndromes, Homocystinuria and Pseudoacromegaly. Table 3 shows the most common causes of overgrowth and the principal skeletal findings. Although the clinical features of these syndromes differ from those associated with endocrine diseases, they share certain similarities regarding some skeletal and craniofacial features. Nevertheless, there are some distinctive features that allow us to exclude some of these syndromes when compared with our case study. For example, Beckwith–Wiedemann syndrome is characterized by an advanced skeletal age and microcephaly (Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009). In Weaver syndrome is characteristic an advanced skeletal age, flat occiput, micrognathia and a prominent chin (Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009). Other syndromes also differ in some skeletal features with individual TB.5 as an advanced skeletal age (Sotos and McCune–Albright syndromes) (Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Cole & Hughes 1994, Dumitrescu & Collins 2008, Gorlin et al. 2001, Hernández et al. 2012, Melo et al. 2002, Visser et al. 2009), microcephaly (Klinefelter syndrome) (Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009), micrognathia (Beals, and Lujan–Fryns syndromes) (Tunçbilek & Alanay 2006, Viljoen 1994, Visser et al. 2009), and overgrowth of the lower compared to the upper limbs with long and slender limbs (Marfan syndrome) (Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009). However, it is not possible to exclude other syndromes by only some skeletal characteristics; the best method of diagnosis

is the analysis of clinical features of the pathologic soft tissue overgrowth. Thus, for example, insulin–mediated pseudoacromegaly shares skeletal features with acromegaly. Although the most cause of acromegaly is due to a GH hypersecretion and high serum concentrations of IGF–I, some authors (Yaqub & Yaqub 2008, Agha et al. 2009, Sam et al. 2011) describe several clinical patients with insulin resistance showing features of acromegaly with the absence of elevated levels of GH and IGF–I. However, the insulin–mediated pseudoacromegaly is a very rare condition in the current population, and it is more probable that individual TB.5 suffered acromegaly.

-----Insert Table 3-----

Conclusions

Individual TB.5 exhibits extended longitudinal growth associated with appositional growth and degenerative bone changes, indicating the coexistence of gigantism and acromegaly in the expression of morphological and metric skeletal traits. The pathological features described are related to an abnormal skeletal growth and are typical of gigantism/acromegaly. Although other diagnostic anatomical regions are not preserved and is not possible to perform an analysis of the pathologic soft tissue overgrowth to confirm the etiology, it is clear that these features are compatible with this overgrowth disorder.

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Conflict of interest statement

All authors have not financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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Figure 1. Burial of individual TB.5 during the archaeological excavation. Note that the bottom of the burial was sectioned during the initial work of the road (it is indicated by a white dashed line).

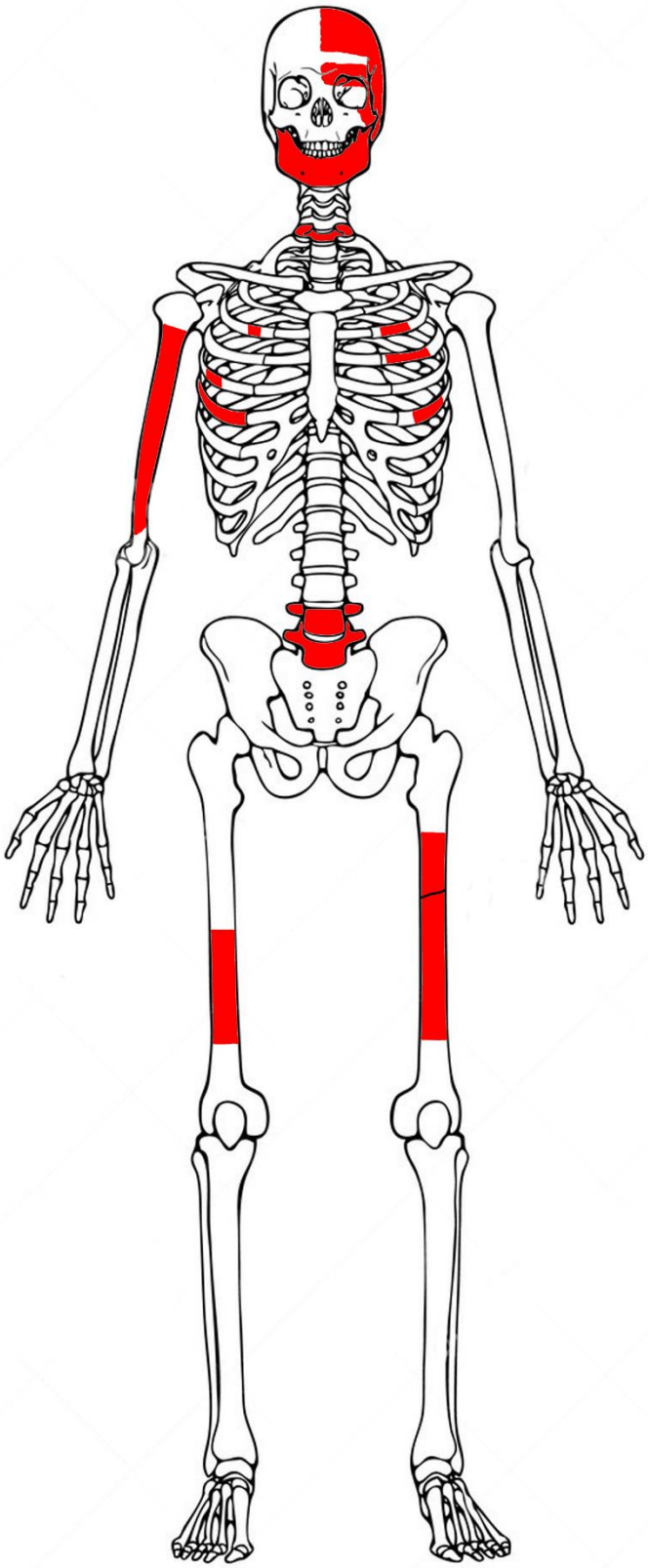

Figure 2. Skeletal diagram of the individual TB.5. The preserved remains are represented in red.

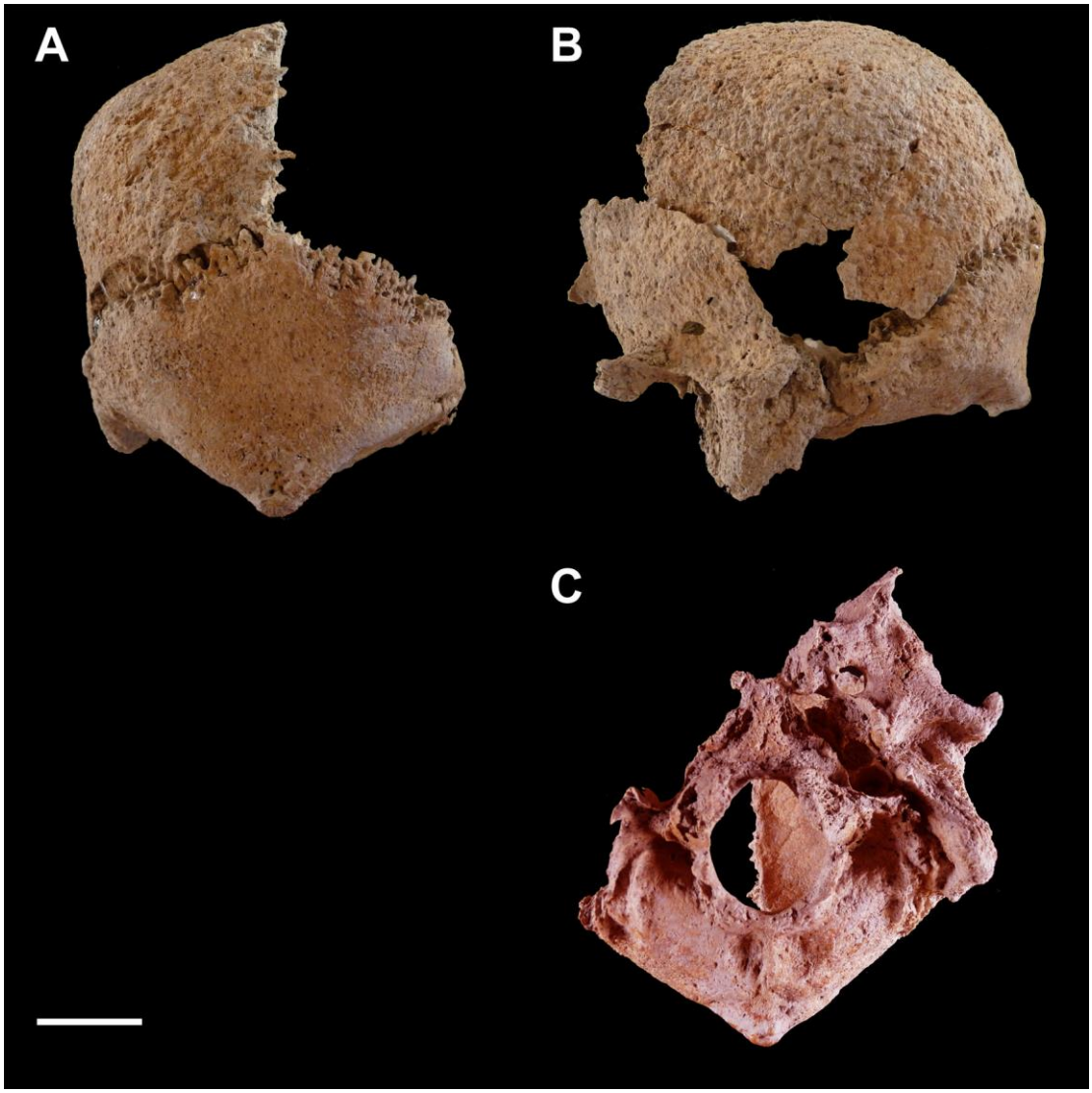

Figure 3. Skull of TB.5. A, posterior view. B, lateral view. C, inferior view. Scale bar, 5cm.

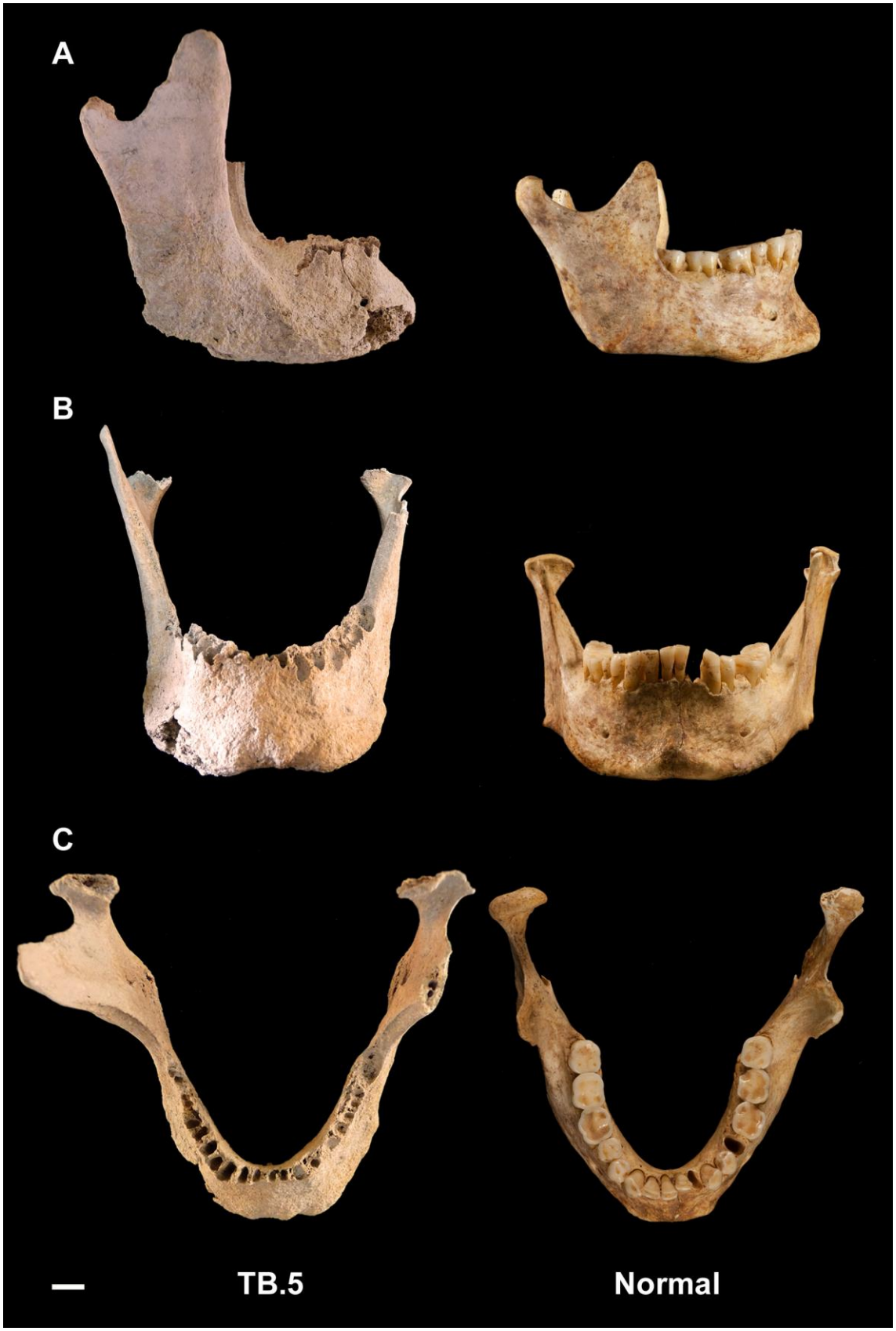

Figure 4. Comparison of the mandible of TB.5 and a normal male individual. A, lateral view. B, anterior view. C, superior view. Scale bar, 1cm.

Figure 5. Inferior view of vertebra L5 showing degenerative changes. Scale bar, 1cm.

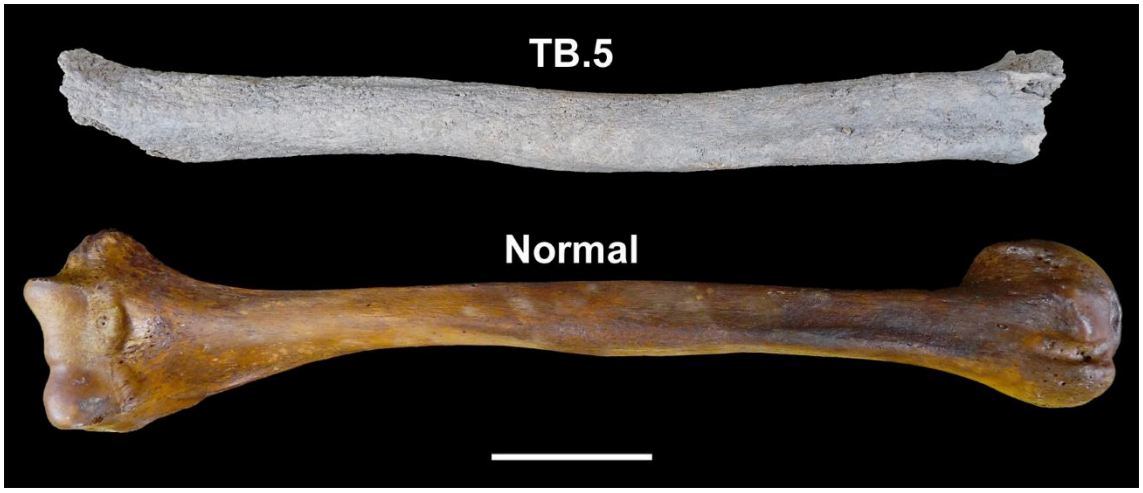

Figure 6. Comparison of the right humerus of TB.5 and a normal male individual. Posterior view. Scale bar, 5cm.

Table 1. Definition of mandibular measurements*

Measurement	Description	Instrument
Chin height	Direct distance from infradentale to gnathion	Sliding caliper
Mandibular body height	Direct distance from the alveolar process to the inferior border of the mandible perpendicular to the base at the level of the mental foramen	Sliding caliper
Mandibular body breadth	Maximum breadth measured in the region of the mental foramen perpendicular to the long axis of the mandibular body	Sliding caliper
Bigonial width	Direct distance between right and left gonion	Sliding caliper
Bicondylar breadth	Direct distance between the most lateral points on the two condyles	Sliding caliper
Minimum ramus breadth	Least breadth of the mandibular ramus measured perpendicular to the height of the ramus	Sliding caliper
Maximum ramus breadth	Distance between the most anterior point on the mandibular ramus and a line connecting the most posterior point on the condyle and the angle of the jaw	Sliding caliper
Maximum ramus height	Direct distance from the highest point on the mandibular condyle to gonion	Mandibulometer
Mandibular length	Distance of the anterior margin of the chin from a enter point on the protected straight line placed along the posterior border of the two mandibular angles	Mandibulometer
Mandibular angle	Angle formed by the inferior border of the corpus and the posterior border of the ramus	Mandibulometer

*Definitions based in the descriptions of Buikstra & Ubelaker (1994) and Moore–Jansen & Jantz (1989).

Table 2. Mandibular measurements for TB.5 compared with mean values for Jewish and contemporary Mediterranean male skeletal samples, and historical giants and acromegalic cases

	TB.5	Jewish from "Ronda Sur"				Mediterranean population				Historical giants and acromegalic cases						
	Measurements	Mean	n	SD	z–score	Mean	n	SD	z–score	EAS79[a]	EAS07[a]	Irish giant[a]	American giant[b]	Scotchman[c]	2507X[d]	Roman giant[e]
Chin height	35.02	30.47	6	2.92	1.56	31.21	16	2.09	1.82	46	46	46	40	46	42	31.0
Mandibular body height	35.68	27.68	8	4.39	1.82	29.28	16	1.97	3.25						44	
Mandibular body breadth	11.97[*]	10.54	21	1.44	0.99	10.82	25	1.02	1.13						16[§]	12.0
Bigonial width	112.71	99.69	8	5.73	2.27	97.46	33	8.70	1.75	113	100	113	113	101		
Bicondylar breadth	133.95	123.51	2	6.64	1.57	115.22	32	7.51	2.49				141			126.4
Minimum ramus breadth	35.95[*]	31.08	18	2.79	1.75	31.81	34	2.11	1.96						37[†]	37.25
Maximum ramus breadth	47.12[*]	42.47	11	5.24	0.89	43.28	33	3.87	3.96						51[†]	
Maximum ramus height	89.00[*]	62.50	9	3.07	8.63	64.26	33	5.10	4.85	93.5[*]	67[*]	95				
Mandibular length	99.00	75.60	15	5.68	4.12	76.27	33	4.47	5.09	109.5[*]	112[*]	113		103		
Mandibular angle	21.00	31.18	14	5.63	–1.81	32.24	33	6.31	–1.78							
Estimated stature	—	168.8				—				183.0	157.4	217.7	229.5	184.2	192.4	202.2

All the measurements are in mm, except the estimated stature, which is in cm.
[*]Average from the right and left side.
[†] Measurement from the right side.
[§] Measurement from the left side.
[a]Data from Geddes (1911).
[b]Data from Hinsdale (1898).
[c]Data from Thomson (1890).
[d]Data from Mulhern (2005).
[e]Data from Minozzi et al. (2013).

Table 3. Most common causes of tall stature/growth acceleration and main skeletal findings

Disorders	Description	References
Disorders without dysmorphic features		
Pituitary gigantism	*Growth and skeletal findings* Large joint arthropathy; Vertebral enlargement; Osteophytosis; Extremities (hands and feet) are broadened; Diaphyseal cortical thickening *Craniofacial features* Enlarged sella turcica; Thickening of the cranial vault; Coarse facial features; Prominent supraorbital ridges; Marked frontal bossing, prominent forehead; Mandibular overgrowth with prognathism; Malocclusion and overbite; Widened interdental spaces; Hypercementosis of dental roots	Ayuk & Sheppard 2006, Ben–Shlomo & Melmed 2008, Chang et al. 2005, Chanson & Salenave 2008, Chanson et al. 2009, Colao et al. 2004, Kashyap et al. 2011, Lugo et al. 2012, Morselli et al. 2006
Insulin–mediated "pseudoacromegaly"	*Growth and skeletal findings* Extremities (hands and feet) are broadened *Craniofacial features* Coarse facial features; Prominent supraorbital ridges; Marked frontal bossing; Enlargement of the mandible, with prognathism; Widened interdental spaces.	Yaqub & Yaqub 2008, Agha et al. 2009, Sam et al. 2011
Dysmorphic features without disproportions		
Sotos syndrome	*Growth and skeletal findings* Advanced bone age; Tall stature; Excessive growth; Disproportionately long limbs; Asymmetric lower limbs length; Large hands and feet; Kyphoscoliosis *Craniofacial features* Macrocephaly; Dolichocephaly; Marked frontal bossing, prominent forehead; Long, narrow (inferiorly), and prominent mandible, squared or pointed chin; True prognathism is rare; High–arched palate	Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Cole & Hughes 1994, Gorlin et al. 2001, Melo et al. 2002, Visser et al. 2009
Beckwith–Wiedemann syndrome	*Growth and skeletal findings* Advanced bone age; Metaphyseal widening and cortical thickening of long bones *Craniofacial features* Mild microcephaly; Midfacial hypoplasia; Coarse facial features; Prominent occiput; Mandibular prognathism	Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009
Weaver syndrome	*Growth and skeletal findings* Advanced bone age; Abnormal cervical vertebrae; Camptodactily	

	Craniofacial features Macrocephaly; Broad forehead; Flat occiput (plagiocephaly); Relative micrognathia; No prominent chin	Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009
Simpson–Golabi–Behmel syndrome	*Growth and skeletal findings* Overgrowth; Brachydactyly, polydactyly; Rib and vertebral abnormalities *Craniofacial features* Macrocephaly; Coarse facial features; Dental malocclusion; Macrognathia in older individuals; Cleft lip/palate	Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009
Fragile X syndrome	*Growth and skeletal findings* Adult height is somewhat decreased; Hand and foot lengths are slightly reduced; Scoliosis *Craniofacial features* Prominent and quadrangular forehead; Prominent supraorbital ridges; Prominent mandible; High and narrow palate; Tooth crown diameter asymmetry is frequent	Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009
Dysmorphic features with disproportions		
McCune–Albright syndrome	*Growth and skeletal findings* Advanced bone age; Polyostotic (more than one bone involved) fibrous dysplasia; Pathological fractures; Pseudoarthrosis; Bone deformities; Tendency to asymmetry; Scoliosis; Widened shaft of long bones, thin cortices; Enlargement of hands and feet; Arthritis *Craniofacial features* Coarse facial features; Skull base becomes thickened and dense; Calvaria may also become thickened, with marked occipital and frontal bulging; Unilaterally distributed areas of thickening, alternating with cyst–like lesions in cranial bones; Increased density of skull base and facial bones; Mandible may be enlarged, expanded, and distorted; Marked frontal bossing; Prognathism; Facial asymmetry	Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Dumitrescu & Collins 2008, Gorlin et al. 2001, Hernández et al. 2012
Marfan syndrome	*Growth and skeletal findings* Disproportionate skeletal growth with dolichostenomelia (limbs are disproportionately long compared with the trunk); Bone overgrowth; Individuals are tall and thin; Normal or advanced bone age; Kyphoscoliosis; Spondylolisthesis; Premature osteoarthritis; Enlarged vertebrae; Elongation of tubular bones in hands and feet; Long and slender limbs; Thin ribs; Overgrowth of the ribs	Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009

	Craniofacial features Dolichocephaly; Long and narrow face; Prominent supraorbital ridges; Micrognathia or retrognathia; High–arched palate; Dental crowding	
Homocystinuria	*Growth and skeletal findings* Excessive bone growth; Osteoporosis; Individuals are tall and thin; Long and slender limbs; Kyphoscoliosis; Widened metaphyses and epiphyses; Enlarged carpal bones; Elongated talus; Associated with biconcavity of the vertebral bodies *Craniofacial features* High and narrow palate; Mandibular prognathism; Teeth are crowded and irregularly aligned	Brenton 1977, Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Schedewie et al. 1973, Visser et al. 2009
Klinefelter syndrome	*Growth and skeletal findings* Usually taller than average; Disproportionately long arms and legs; Increased arm span and long legs *Craniofacial features* Microcephaly; Smaller calvarial size; Smaller cranial base angle; Larger gonial angle than normal; Mandibular prognathism; Macrodontia; Increased frequency of taurodontism	Castriota–Scanderberg & Dallapiccola 2005, Chen 2006, Gorlin et al. 2001, Visser et al. 2009
Beals syndrome	*Growth and skeletal findings* Tall stature with dolichostenomelia; Arm span exceeds body height; Long and slender limbs; Arachnodactily; Camptodactily; Kyphoscoliosis *Craniofacial features* Micrognathia; High–arched palate; Cranial abnormalities (including scaphocephaly, brachycephaly, dolichocephaly); Frontal bossing	Tunçbilek & Alanay 2006, Viljoen 1994, Visser et al. 2009
Lujan–Fryns syndrome	*Growth and skeletal findings* Tall stature *Craniofacial features* Long and narrow face; Prominent forehead; Maxillary hypoplasia; Small mandible	Visser et al. 2009