

Comparative Skeletal Features Between *Homo floresiensis* and Patients With Primary Growth Hormone Insensitivity (Laron Syndrome)

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ABSTRACT Comparison between the skeletal remains of *Homo floresiensis* and the auxological and roentgenological findings in a large Israeli cohort of patients with Laron Syndrome (LS, primary or classical GH insensitivity or resistance) revealed striking morphological similarities, including extremely small stature and reduced cranial volume. LS is an autosomal recessive disease caused by a molecular defect of the Growth Hormone (GH) receptor or in the post-receptor cascades. Epidemiological studies have shown that LS occurs more often in consanguineous families and isolates, and it has been described in several countries in South East Asia. It is our conclusion that the findings from the island of Flores, which were attributed to a new species of the genus *Homo*, may in fact represent a local, highly inbred, *Homo sapiens* population in whom a mutation for the GH receptor had occurred. *Am J Phys Anthropol* 000:000–000, 2007. © 2007 Wiley-Liss, Inc.

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In 2004, based mainly on the finding of skeletal remains of a female in the Liang Bua cave on the Island of Flores (Indonesia), an Australian–Indonesian scientific team announced the discovery of a new species within the genus *Homo*, identified as *Homo floresiensis* (Brown et al., 2004). These findings disconcerted the scientific world: not only did another species coexist with *Homo sapiens* until very recently (ca. 18,000 yrs BC), but these people had a diminutive body (106 cm in height) with an extremely small head and brain (380 cc). The origin of this species was uncertain; however, it was assumed that they were dwarfed descendants of the Javanese *Homo erectus*. Further, archeological excavations revealed additional findings and further characterization of this species (Morwood et al., 2005) and its culture (Brumm et al., 2006).

Soon after the publication by Brown et al. (2004), Henneberg and Thorne (2004) suggested that the female from Liang Bua cave is not a new species of the genus *Homo*, but rather a microcephalic individual. Following, most supportive studies for the *Homo floresiensis* hypothesis focused on the issue of microcephaly. Falk et al. (2005), based on endocast comparison with great apes, *Homo erectus*, *Homo sapiens*, a human pygmy, a human microcephalic, *Australopithecus africanus* and *Paranthropus aethiopicus*, refuted the possibility that Liang Bua 1 (LB1) was microcephalic or a pygmy. They further claimed that despite the minute size of the brain, the endocast shape resembled that of *Homo erectus*. Arque et al. (2006) explored the affinities of LB1 with early *Homo*, two microcephalic humans, a “pygmoid”, *H. sapiens*, *Australopithecus*, and *Paranthropus*, using cranial and postcranial metric and nonmetric traits. The authors concluded that it was unlikely that LB1 was a microcephalic human, and that since she could not be

attributed to any known species she must therefore represent a new species, *Homo floresiensis*. Recently, Taylor and Schaik (2007) suggested, based on the association of a relatively small brain and poor diet quality in Pongo, that ecological factors may plausibly account for “such a reduction in brain size as observed in the recently recovered *Homo floresiensis* from Indonesia” (p. 59).

Two major studies tried to refute the notion that LB1 is a new species. In response to the contention by Falk et al. (2005) that *Homo floresiensis* endocast analysis implied that the hominid was an insular dwarf derived from *H. erectus*, Martin et al. (2006a,b) raised several contradictory arguments, to wit: body size reduction in mammals is usually associated with only moderate brain size reduction, and therefore the tiny cranial capacity of LB1 could not be attributed to a specific type of dwarfism in *H. erectus*; The microcephalic plaster-based cast (not the original skull) used in the study by Falk et al. (2005) was problematic; the study by Falk et al. (2005) was based on a single microcephalic skull, yet large variability exists in the morphology of microcephalic skulls. Additionally, Martin and colleagues claimed that the

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stone tools reported at the LB1 site included types that are consistently associated with the *Homo sapiens* and that have not previously been linked with *H. erectus* or other early hominids. They therefore concluded that LB1 could represent a microcephalic individual (because of gene mutation) from a small or normal sized human population.

Jacob et al. (2006) claimed that LB1 is an Australomelanesian *H. sapiens* who manifested microcephaly, associated with other developmental abnormalities. Their major arguments were: Except for LB1, “there is no support for exceedingly small brain size, the focal characteristic of the postulated new species” (p. 13421); The mandible showed no traits that are unknown among modern Australomelanesians; all the descriptive features of the LB1 cranium and mandibles were within the range for modern humans from the region; LB1 facial and calvarial asymmetry exceeded clinical norms, providing evidence that the LB1 cranium was developmentally abnormal; the dentition of LB1 exhibited modern human traits; bilateral rotation of the upper fourth premolars and tooth shape deviations in lower premolars occurred at elevated frequencies in the Rampasasa (the local pygmy) population; there is considerable evidence from the long bones to suggest disordered growth, and the evolutionary scenario of *H. floresiensis* as described by Brown et al. (2004) is not in line with the geographical and ecological history of the region. Additionally, Jacob and colleagues raised several intriguing questions, for example, with a brain size smaller than average for a chimpanzee, how were these hominins able to manufacture sophisticated microblades? Assuming isolation for more than 800k years, how can shared traits with *H. sapiens* be explained?

Our hypothesis is that LB1 suffered from a congenital deficiency of insulin-like growth factor (IGF-I), because of inbred genetic defects of the growth hormone (GH) receptor gene recognized as Laron Syndrome (LS). This hypothesis is testable by comparing the body structure and skeletal features of the Liang Bua remains with LS characteristics.

MATERIALS AND METHODS

To examine our hypothesis, we compared the “diagnostic” morphological features of *Homo floresiensis* as described by Brown et al. (2004) and Morwood et al. (2005) with those of LS patients. Our analysis is based on the skeletal material available from the Liang Bua Cave (mainly of LB1, the adult female partial skeleton) and growth and physique data of 64 LS patients followed for the past 45 years by one of the authors (LZ) from infancy to adulthood, direct observations of radiographs and CT images (including three-dimensional rendering method) of 15 adult (age 21–68 years) patients (seven males, 8 females) with LS, as well as from data from the literature (Rosenfeld et al., 1994; Kornreich et al., 2002).

RESULTS

The major diagnostic criteria applied are listed in Table 1. The data presented follow two lines of thought in favor of our hypothesis: the existence of morphological similarity between individuals with LS and LB1, and the many “primitive” features or the combination of “unique” features assigned to LB1 deriving from her small skull and stature.

TABLE 1. Comparison between the skeletal morphological characteristics in LB1 and Laron syndrome (LS)

Traits	LB1	LS
Stature (cm)	106	95–136
SD below local population	3.3 SDs ^a	4–10 SDs
Skull size and shape		
Skull size	Small	Small ^b
SD below local population	5.5 SD ^c	Up to –5 SD
Cranial bone thickness	Normal	Normal
Area of maximum cranial breadth	Supramastoid region	Supramastoid region
Cranial height/breadth ratio	Reduced	Reduced
Cranial base	Flexed	Flexed
Foramen magnum size (mm)	21 × 28	20 × 27
Facial height	Reduced	Reduced
Prognathism	Slight	Slight
Supraorbital rim	Rounded	Rounded
Supraorbital ridges	Pronounced	Pronounced
Frontal sinuses	?	Absent/ undersized
Infraorbital region	Retracted	Retracted
Infraorbital fossae	Marked	Marked
Zygomatic ridges	Arched	Arched
Pillars (nasal aperture)	Present	Present
Maxillary axis (P3-M3)	Laterally convex	Laterally convex
Mandible size	Small	Small
Coronoid relative height	>Condyle	>Condyle
Mental protuberance	Absent	Underdeveloped/ absent
Bifurcated root of premolar P3	Present	Present
Rotated maxillary premolars	Present	Present
Congenital absence of third molars	Yes	Yes
Fissure separating the mastoid process from the petrous crest of the tympanic plate	Present	Present
Recess between the tympanic plate and the entoglenoid pyramid	Present	Present
Post cranial bones		
Clavicle size and shape	Short and shallow	Short and shallow
Humerus shaft thickness	Pronounced	Pronounced
Humeral torsion	Limited	Limited
Lateral flaring of ilium	Marked	Marked
Bicondylar angle	14°	10°–16°
Femoral neck-shaft angle	130°	118°–134°
Tibia long axis	Curved	Curved
Limb proportion	Abnormal	Abnormal

^a Below mean Rampasasa height.

^b Relates to skull circumference.

^c Compared to combined sex Rampasasa mean.

Morphological comparison between LS and LB1

Congenital IGF-I deficiency produces two major auxological body characteristics: small stature and small head (Laron et al., 1993, p. 151). These are also the same two basic traits that characterize LB1 (Brown et al., 2004).

General features

Stature. In the Israeli cohort the adult height of female individuals with LS varies from 95 to 136 cm, and that of males from 116 to 142 (i.e. –5 to –10 SDS) (Laron,



Fig. 1. Facial architecture of LS patients: Note the pronounced supraorbital ridges, the extremely short face, small mandible and undeveloped mental protuberance.

2004). In the Ecuadorian cohort adult stature varies from -5.3 to -12 SDS (using United States standards), a range of 95–124 cm for women and 106–141 cm for men (Rosenbloom et al., 1999). Similar short stature has been reported for LS patients in other parts of the world and for untreated adults with congenital isolated GH deficiency (IGHD). Pakistani patients with GHRH-R (GH releasing hormone) defect have an average height of 130 ± 10.6 cm for men and 113.5 ± 0.7 cm for women (Maheshwari et al., 1998). The reconstructed height of LB1 (106 cm) fits the lowest centile of the specific growth charts for female LS patients (Laron et al., 1993; Laron, 2004).

Small brain. The most outstanding feature of LB1 is the extremely small endocranial volume ($410\text{--}380\text{ cm}^2$). Although not to the same extent as LB1, LS patients and patients with cIGHD due to GH gene deletion or GHRH-R defect also have much smaller heads compared to the norm; their head circumference is 2–5 SD below the norm (Konfino et al., 1975; Laron et al., 1993; Woods et al., 1996; Maheshwari et al., 1998). It is noteworthy that primary microcephaly has been reported in IGF-I gene deletion (Woods et al., 1996), and also in children with growth retardation because of GH deficiency (Dacou-Voutetakis et al., 1974; Spadoni et al., 1989; Kauschansky et al., 1993; Baumann, 1999).

Specific anatomical features: Axial skeleton

Cranial features. *Face:* Patients with LS manifest considerably short faces and slight prognathism, similar to LB1 (Scharf and Laron, 1972; Konfino et al., 1975) (Fig. 1). These two major facial characteristics are also evident in patients with GH deficiency (Spiegel et al., 1971; Nagasaka et al., 1977). Other cranial features shared by both LS and LB1 are: rounded supraorbital rims with pronounced supraorbital ridges (Figs. 1 and 2), absence of or undersized frontal sinuses (Figs. 1 and 2), retracted infraorbital region with marked infraorbital fossae, and arched zygomaxillary ridge. Also common to both are the

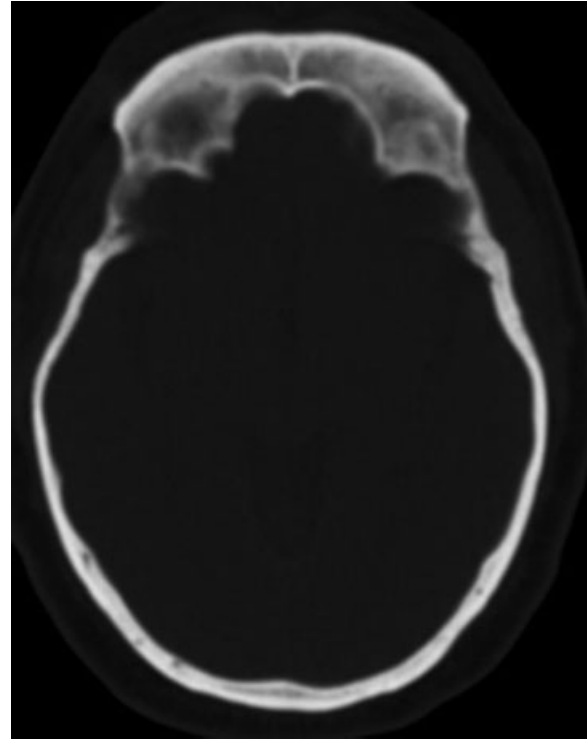


Fig. 2. Transverse CT section of skull of patient with LS: Note the absence of frontal sinuses and the developed supraorbital ridges.

distinct pillars on both sides of the nasal aperture, resulting from prominent maxillary canine juga, which are attributed, in LS patients, to underdevelopment of the maxilla (Konfino et al., 1975; Kornreich et al., 2002). The maxillary axis of $P_3\text{--}M_3$ is laterally convex (Fig. 3).

Vault: The thickness of the bones of the cranial vault is normal in LS (Figs. 1 and 2) and LB1. In both LS and LB1, the maximal cranial breadth is located in the supramastoid region and cranial height is reduced relative to cranial breadth.

Base: The cranial base is flexed (Fig. 1), yet the most striking features in LS individuals are the well developed juxtamastoid eminence and the shape of the foramen magnum (Figs. 3 and 4). The foramen magnum is small and similar in size in both LB1 ($21 \times 28\text{ mm}^2$) and LS ($20 \times 27\text{ mm}^2$) (Fig. 4). The two “unique” characteristics seen in LB1, namely a deep fissure separating the mastoid processes from the petrous crest of the tympanic plate and the presence of a recess between the tympanic plate and the entoglenoid pyramid, are also present in LS (partially seen in Figs. 3 and 4). Unfortunately, no radiographs of LB1’s skull are as yet available and therefore appreciation of the extent of pneumatization in the LB1 skull is impossible. Non-pneumatized (acellular) mastoid process (Fig. 4), lack of (or minimal) frontal sinus (Fig. 2), and small paranasal sinuses are characteristic of LS (Kornreich et al., 2002). Pneumatization (mainly of the mastoid process) is highly variable within the adult human population and is probably of genetic origin (Schulter-Ellis, 1979; Sherwood, 1999).

Mandible and teeth. The mandible in LS (and congenital GH deficiency) patients is very small because of underdevelopment in the forward direction (Laron et al.,

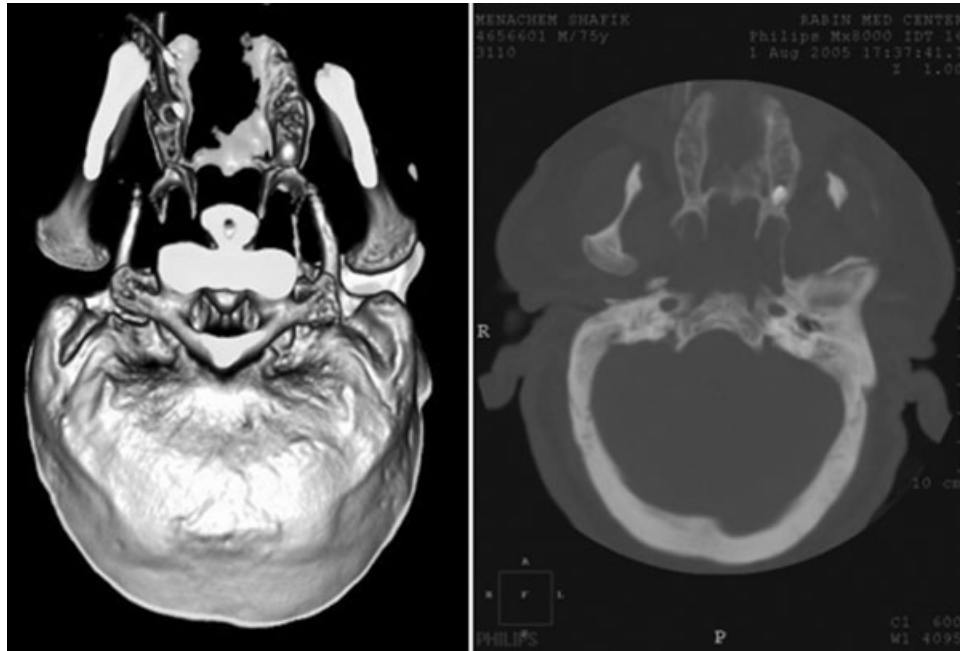


Fig. 3. Base of skull in LS. Note the well developed juxtamastoid eminence and the “notched” shape of the posterior rim of the foramen magnum. Maxillary dental arches are laterally convex.

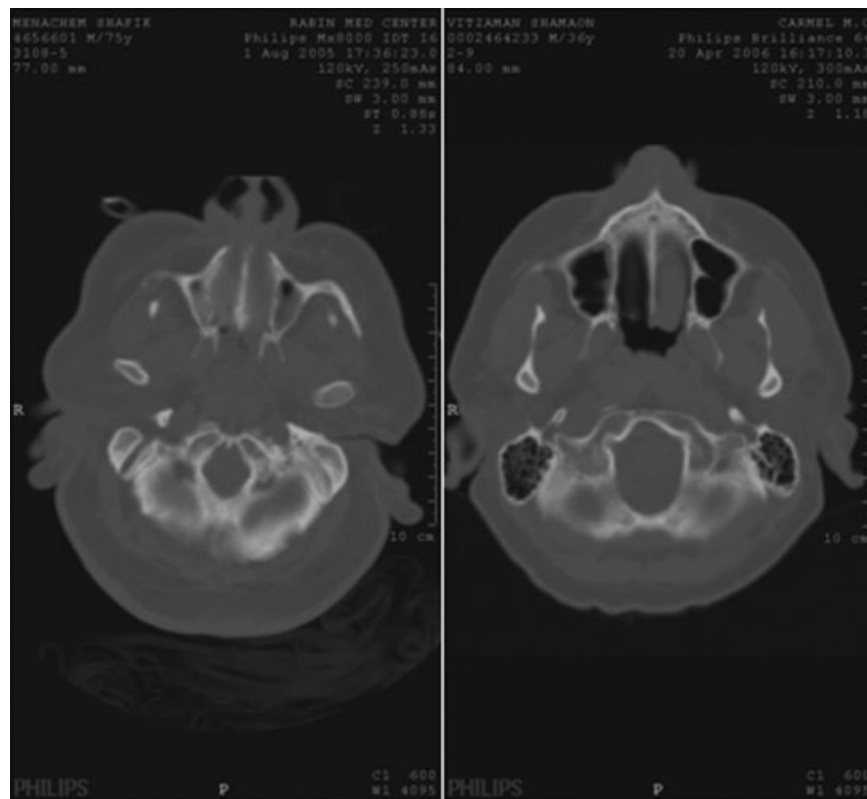


Fig. 4. Structure of the base of the skull in LS (left) and normal (right) individuals. Note the small foramen magnum in LS, the small maxillary sinuses and lack of mastoidal air cells (similar scale).

1968; Scharf and Laron, 1972; Takano et al., 1986), yet it retains its normal shape (Fig. 1), i.e., the coronoid process is higher than the condyle, the ramus has a posterior orientation (Fig. 2) and the chin is under-developed

(part of the characteristic acromicria typical in GH/IGF-I deficiency) (Konfino et al., 1975; Rosenbloom et al., 1999; Laron, 2004). The teeth are either normal or slightly smaller than normal (Sarnat et al., 1988), the second

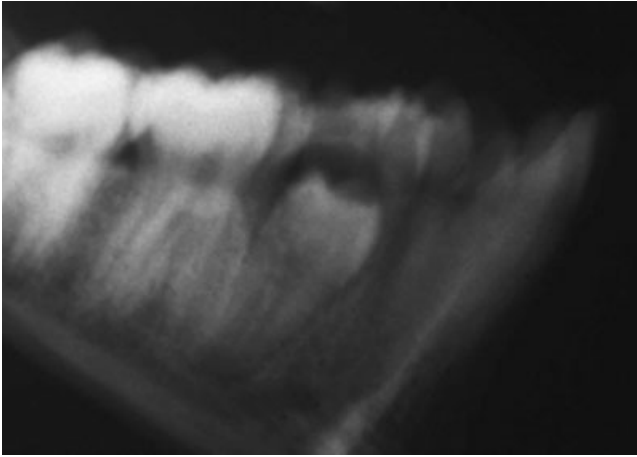


Fig. 5. Mandible of a child with LS. Note the double roots of the second premolar and that it is rotated parallel to the tooth row.

mandibular premolars have double roots (Fig. 5), and, as in LB1, the maxillary premolars are rotated parallel to the row of teeth (Fig. 5). Finally, congenital absence of a third molar and hypodontia are very common in LS patients (Sarnat et al., 1988) and this was also described in LB1 (Brown et al., 2004).

Rib cage and vertebrae. The rib cage of LS patients manifests a “fan-shaped” appearance, which is expressed as a pronounced deep (dorsoventrally) funnel-shaped thorax (rather than the “barrel-shape” that is characteristic of modern humans) with obliquely oriented ribs and narrow sternum (Fig. 6a–c). The cross-section of the ribs is generally rounded. Thoracic vertebrae manifest relatively very small spinal foramina. It is noteworthy that the flaring contour of the lower part of the LS thorax corresponds to the flaring ilia in these patients.

Appendicular skeleton

Shoulder girdle and upper limb bones. The scapulae of LS patients are normal in shape and size (relative to body size). Radiographs and CT reconstruction suggest a slightly protracted scapular position (Fig. 6). The clavicles are short relative to humeral length with shallow arcs (Fig. 6). Similar characteristics have been reported for LB1 (Larson et al., 2006). The most striking features of the LB1 humerus are the considerable thickness of the shaft (relative to length) in contradistinction to the very weakly marked muscle attachment sites, and the limited degree of torsion, traits which are also characteristic of the humeri of LS patients. Regarding the bones of the lower arm, the ulna of an individual with short stature of undetermined diagnosis recovered in an archaeological site near Jerusalem (ulna physiological length = 15.5 cm; maximum length = 18.5 cm, dated ca. 2,000 PB) was available for comparison with similar bones found in LB1 (maximum length ca. 20.5 cm). Albeit very short, the mid sagittal diameter of the control ulna was normal (Fig. 7), and areas of attachment for flexor digitorum, brachialis, and pronator muscles were developed (Fig. 7), similar to LB1.

Pelvic girdle and lower limb bones. LS patients manifest a marked lateral flare of the ilium, as measured from the lateral upper rim of the acetabulum (Figs. 8

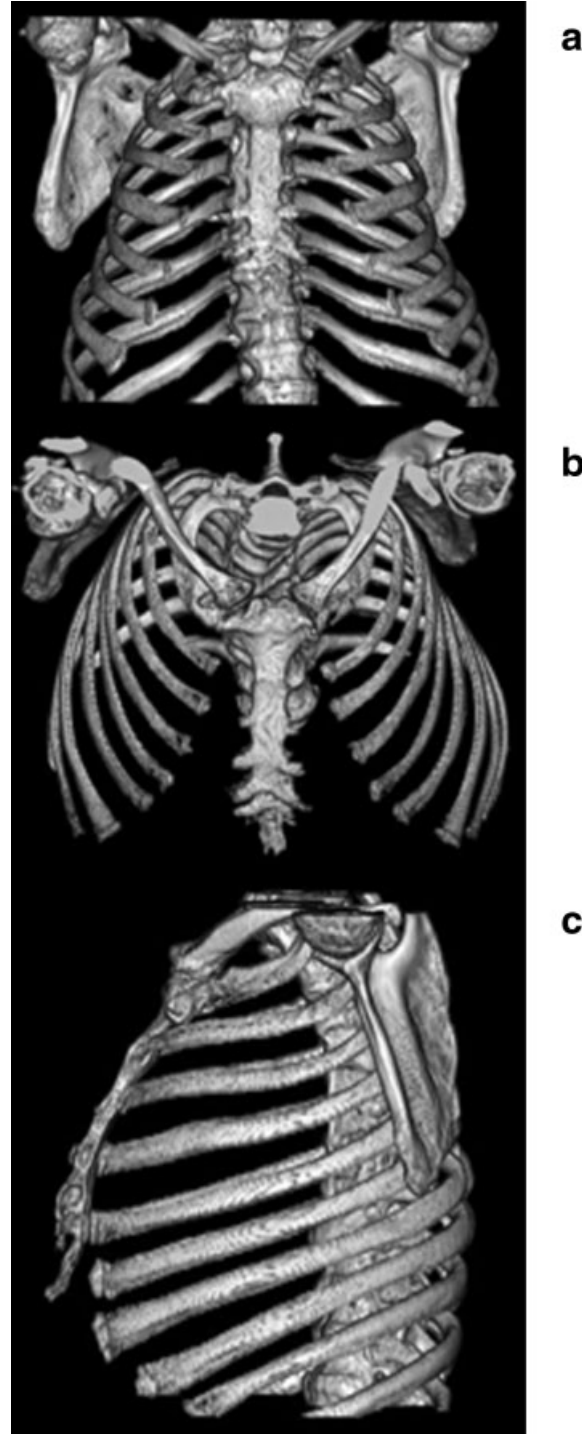


Fig. 6. CT reconstruction of the rib cage in a LS patient. Note: **a**) the funnel-shaped appearance of the thorax, **b**) the orientation of the ribs: supero-internal to infero-external plane, **c**) the deep rib cage.

and 9), and a pronounced oval-shaped pelvic inlet (Figs. 8 and 9), similar to LB1. Unfortunately, Brown et al. (2004) gives no explanation as to how the LB1 lateral pelvic flare was quantified, or how this was possible considering the nature of the relevant bones. The femoral shaft in LS patients is circular, the bicondylar angle



Fig. 7. Ulna of a small individual (shorter than the ulna of LB1) from archaeological site (ca. 2,000 BP) compared to an average normal ulna. Note the concave area for the attachment of the brachialis muscle (top), the pronounced bony ridge for the flexor digitorum superficialis (middle), and the large rugged area for the pronator quadratus muscle (bottom) in the small ulna.

ranges from 10° to 16° (14° in LB1), and the neck-shaft angle varies from 118° to 134° in LS patients (measured on radiographs) (130° in LB1). The long axis of the tibia is curved in both LS patients (Fig. 10) and LB1.

Body proportions

One of the most distinctive characteristics of LB1, according to Morwood et al. (2005), is the abnormal limb proportion. LS patients are also known to manifest abnormal body proportion, which is expressed by disproportionately short legs relative to the upper trunk, resulting in an abnormal upper/lower body ratio (Arad and Laron, 1979; Laron, 1984).



Fig. 8. CT 3-D pelvic reconstruction of an LS patient (top) and modern young male (bottom), superior view.

DISCUSSION

Laron syndrome

We suggest that LB1 is not a new *Homo* species but a local variant of LS. This thesis was presented at the 88th Annual Meeting of the Endocrine Society in Boston (Laron et al., 2006a), at the XVI Paleopathology Association European Meeting, Santorini, Greece (Hershkovitz et al., 2006) and in a preliminary report (Laron et al., 2006b). LS is a recessively inherited disease caused by molecular defects in the GH receptor gene (OMIM no. 262500) (Laron et al., 1966, 1968; Rosenbloom et al., 1990; Rosenfeld et al., 1994; Laron, 1999, 2004). The defects are either exon deletions or mutations in the gene or in the postreceptor cascade, resulting in lack of GH signal transmission and lack of IGH-1 generation in the presence of high levels of normal but inactive GH. The resulting phenotype is extremely low stature and small head, but otherwise normally shaped bones (Laron, 2004). LS is found mainly in subjects of Mediterranean, Mid-Eastern, and South Asian origin or their descendants (Rosenfeld et al., 1994; Rosenbloom and Guevara-Aguirre, 1998; Besson et al., 2004; Laron, 2004). Approximately 300 patients with LS have been reported so far, but we suspect that more remain undiagnosed, mainly in consanguineous communities and isolates. Both sexes are equally affected. The features, skeletal, and main biochemical characteristics of LS are indistinguishable from those of congenital IGHD; however, LS differs in that LS patients have a high serum GH which is unable to act because of its receptor defects, whereas in IGHD there is very low or undetectable serum hGH. Genetic analysis of 43 patients with LS belonging to 28

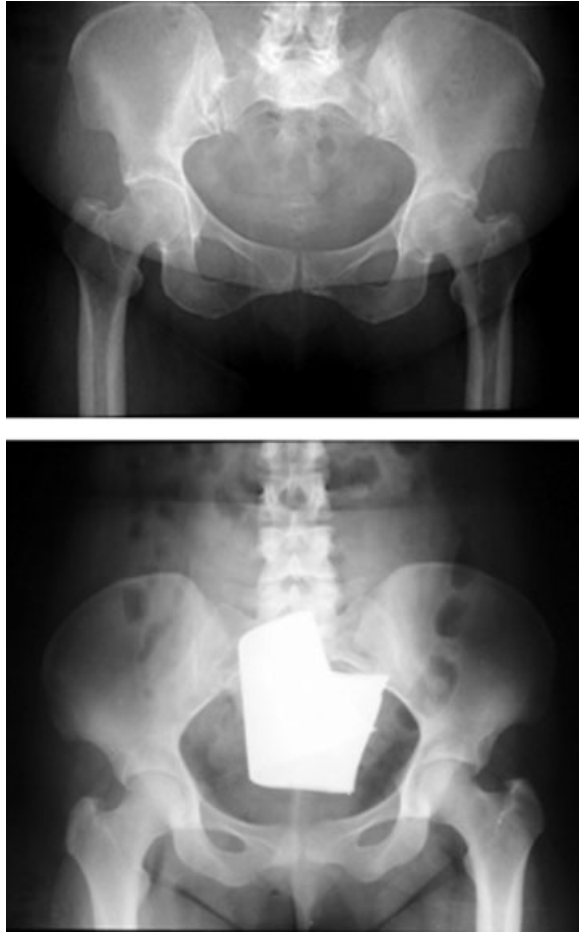


Fig. 9. Radiographs of pelvises of two LS patients. Note the lateral flaring of the iliac blade relative to the plane of the acetabulum and the marked oval shaped pelvic inlet.



Fig. 10. Radiograph of knee joint in an LS patient. Note the curved shape of the tibia.

families (11 of whom were consanguineous) of the Israeli cohort, and the study of their pedigrees (Shevah and Laron, 2006), confirmed an earlier report (Pertzalan et al., 1968) that LS is a recessively inherited disease. The heterozygote family members of the patients are within the low normal height range (Laron, 2004).

A genetic defect or a new species?

The "...mosaic of primitive, unique and derived features not recorded for any other hominin justify the assignment of this hominin to a new species, namely *Homo floresiensis*" wrote Brown et al. (2004, p. 1055). However, in contrast to this belief, the present study documents the high degree of morphological and metrical similarity that exists between the skeletal features of LB1 and LS patients; i.e., congenital IGF-I deficiency.

Cranial volume argument

There is no doubt that the most striking characteristic of LB1 is not small stature but rather the minute cranial capacity. Despite the fact that the cranial volume in patients with LS is usually not decreased to the same degree as observed in LB1, three points should be mentioned: a) skulls of LS patients manifest most of the unique LB1 cranial features, b) a small head is a major

characteristic of LS patients (up to 5 SD below the norm) and in IGF-I gene deletion (Woods et al., 1996). Jacob et al. (2006) reported that the LB1 cranial volume falls 5.5 SD below the combined sex Rampasasa mean, similar to what has been reported for LS patients, and c) there is a high degree of association between microcephaly and growth failure in general (O'Connell et al., 1965; Pryor and Thelander, 1968), GH deficiency (Dacuo-Voutetakis et al., 1974), and congenital IGF-I deficiency (Laron et al., 1968; Woods et al., 1996) in particular.

Additionally, many of the unique anatomical landmarks left by the brain of LB1 on the endocranial bony surface (Falk et al., 2005), are seen also in LS patients, and derived from the reorganization of the brain to fit into a small cranial space. An interesting question is what function can be expected from a small brain of 400–420 cc? Several studies on LS patients with extremely small head circumferences revealed a wide spectrum of intellectual abilities and deficits, ranging from normal to mental retardation (Galatzer et al., 1993; Kranzler et al., 1998), varying with the type of molecular defect in the GH-R gene (Shevah et al., 2005).

Finally, one should not expect complete cranial morphological similarity between our group of patients and the single LB1 skull for the following reasons: a) the basic cranial pattern of the Mediterranean population differs from that of the inhabitants of the islands of South

East Asia and the Pacific, especially if we relate to the local Ramapasasa pygmoid population. The differences are even more pronounced when it comes to prehistoric populations. The scant anthropological reports available on the skulls of the prehistoric island population of that region (Valentin et al., 2005) suggest a small cranium with projected face and posteriorly sloped frontal bone, b) the numerous GH-R mutations involved in LS produce large cranial morphological variability, and c) for comparative purposes we used radiographs of “normal” size skulls of LS individuals (Fig. 1), not the microcephalic cases.

Facial proportion-stature-small brain argument

To advance the concept of a unique morphological pattern in LB1, Brown et al. (2004) stated that “Although adult stature is reduced (in African pygmies), craniofacial proportions remain within the range of adjacent larger-bodied populations, as does brain size” (p. 1060). This key argument in Brown’s theory is solely based on comparison with certain African pygmies. Based on the incomplete data available, Merimee and Laron (1996) concluded that African pygmies have a partial defect in the GH receptors and therefore their growth disturbance and development are not as severe as in LS patients. LS patients manifest a complete block of the GH-Rs (Laron, 2004), resulting in a shorter stature than the African pygmies (the mean linear height in adult pygmy females from the Congo is 137.4 ± 4.36 cm while in LS it is 114 ± 3.9 cm for adult females of similar ages) as well as higher upper/lower body and craniofacial proportions than those found in normal humans (Laron et al., 1993; Laron, 2004). Thus, the statement by Brown and colleagues that “The combination of small stature and brain size in LB1 is not consistent with IGF-related post-natal growth retardation” (p. 1060) is incorrect. This also implies that the reconstructed height for LB1 (based on human pygmies) is greatly biased. Finally, Jacob et al. (2006) estimated that the stature of LB1 falls 3.3 SD below the local Ramapasasa pygmy average stature of 1.46 m, within the range of the deviation in stature reported in some of the Israeli LS patients (Laron, 2004).

Morphology of the limb bones

Regarding the size and shape of the limb bones, Morwood and colleagues argued that “the most obvious differences are the greater thickness of the LB1 shaft and the limited degree of humeral torsion” (p. 1016) and that “In LB1, humeral torsion is approximately 110° , which is the norm for *Hylobates* and quadrupedal primates such as *Macaca*, but is significantly less than in large-bodied apes, modern humans (141° – 178°) and other known hominins, including *Australopithecus*” (p. 1016). Three counter arguments can be raised: First, the statement is incorrect. References cited by the authors themselves report that humeral torsion of 110° is outside the range of the *Hylobates* sp. manifesting a torsional range of 128° – 145° , and in *Macaca* is 112° – 128° . In fact, based on Evans and Krahl’s study (1945), humeral torsion of 110° is outside the primate range (Lemur excluded); this clearly implies that the humeral torsion of LB1 is of pathological origin rather than of an evolutionary outcome. Secondly, as has been demonstrated in the current study, humeral torsion and shaft thickness are also characteristics of LS patients. Thirdly, the humeral retrover-

sion angle (anthropologists express their findings as the obtuse of the angle that clinicians normally use) in human populations is much greater than reported in Morwood et al. paper, ranging from -8° to $+74^\circ$ (equivalent to a humeral torsion of 188° – 106°). Direct comparison of humeral torsion between studies is problematic as definition and measuring techniques vary greatly. Following the ontogeny of humeral torsion, limited torsional angle as observed in LB1 lends critical support to our argument: The mean retroversion angle in a fetal skeleton is only 102° ; with age, the humeral head derotates to reach the standard adult position at age 16 (Edelson, 1999, 2000). This process is not fully achieved either in LS patients or in LB1, as is indicated by the absence of the “twisting ridge”, judging by the published pictures in the absence of a detailed anatomical description, on the humerus. This twist, which defines the inferior aspect of the radial groove of the humerus, represents the point of cessation of the derotation process of the head on the shaft (Edelson, 2000; Saha, 1971). The failure of the humerus to derotate in individuals with growth disturbances is due to: a) as the site of humeral torsion is in the proximal epiphyseal cartilage, the extremely thin growth plate greatly hampers the plasticity of the region (Evans and Krahl, 1945) and b) the shape of the upper thoracic cage and the protracted scapula largely neutralizes the effect of the medial rotator muscles which exert the greater torsional force on the humerus (Evans and Krahl, 1945; Edelson, 2000). The early fusion of the proximal head to the shaft also limits the time in which these muscles can produce their effect. The faintly marked muscle attachment site on the LB1 humerus (characteristic also of LS patients) suggests weak muscle development (Jacob et al., 2006) which in turn is associated with an abnormally low degree of humeral torsion. Finally, judging by the photographs of the humerus, it is clear that the 110° mentioned is only an approximation and probably an underestimation, as an important part of the head required for adequate measuring is missing. Jacob et al. (2006) also suggested that the abnormally low degree of humeral torsion in LB1 is the result of abnormal development.

Our overall impression of the LB1 long bones, based on photographs and a short remark made by Brown et al. (2004) in the absence of a detailed anatomical description and radiographs, is of poorly developed muscle markings despite the ballooning appearance of the shaft in some of the bones. A poorly developed muscular system from longstanding GH and IGF-I deficiency is also characteristic of LS patients (Brat et al., 1997; Ben Dov et al., 2003). It is also noteworthy that in LS, as in LB1, despite the slender appearance of the long bones, mineralization and cortical thickness are normal (Bachrach et al., 1998; Benbassat et al., 2003).

Body proportions

Another important argument raised by Morwood et al. (2005) is related to the body proportions of LB1: “Abnormal growth seems an unlikely explanation (for LB1’s body proportions), as growth-hormone-related dwarfism and microcephaly in modern humans result in normal limb and pelvic proportions”. This statement is based solely on a single reference, namely Maheshwari et al. (1998), wrongly cited as Hiralal et al. (1998). Morwood et al. (2005), when referring to Maheshwari et al. (1998), do not indicate: a) that Maheshwari’s patients

suffered from a GHRH receptor defect, which is not the classical example of congenital IGF-I deficiency; b) that Maheshwari et al. specifically noted that their syndrome is distinct from other forms of GH deficiency with respect to microcephaly, absence of facial features, etc. (p. 4065); c) that the head circumference of these patients was 4.1 SD below the norm, testifying to the association between short stature and small head, d) from the body proportion indices reported in Maheshwari's paper (upper/lower; arm span/height; waist/hip) we cannot deduce the relationship of humerus and ulna length to femur length in these dwarfed individuals; e) Maheshwari and colleagues did not compare their data with normal Pakistani subjects, and thus were unable to conclude what is "normal body proportion", their sole "evidence" being a reference to a single picture of the patients (p. 4066). Maheshwari's raw data for adolescents and adults only gave a mean of 0.94 for the upper/lower segment ratio in the Sindh, which is significantly different ($P < 0.05$) from the norm. The range in a modern population varies from 1.13 to 1.16, indicating a disproportionately long leg relative to trunk. In sharp contrast, adult LS patients manifest a value of 1.38 for females and 1.26 for males (Arad and Laron, 1979), implying a short leg relative to trunk length. The difference between the two entities may be due to genetic differences rather than differences in degree of IGF-I deficiency.

Another major characteristic of LB1 according to Morwood et al. (2005) is that "all the major limb bones of LB1 have shaft and articular surface dimensions that are robust relative to length" (p 1016). If by "robust" the authors mean "great diameter" (as muscles markings are only weakly developed), then this phenomenon is commonly observed in many types of dwarfism including LS.

Dental features

Brown et al. (2004) assert that "Unusually, both maxillary P⁴s are rotated parallel to the tooth row, a trait that seems to be unrecorded in any other hominin" (p. 1058). This is a disturbing statement for three reasons: a) rotation of premolars is commonly seen in modern human populations (McMullan and Kvam, 1990; McMullan and Richardson, 1991). Furthermore, Jacob et al. (2006) documented the presence of such an anomaly particularly in the Rampasasa pygmies, who live today in close proximity to the Liang Bua Cave; b) the phenomenon has a strong genetic background (Hu et al., 1992; Baccetti, 1998), and c) rotation of maxillary premolars is strongly associated with maxillary I2 aplasia (Baccetti, 1998). Finally, it should be recalled that premolar rotation is also seen in LS patients.

SUMMARY

It is not the numerous conundrums that have been located by us and other researchers (Jacob et al., 2006; Martin et al., 2006a,b) in the *Homo floresiensis* publications which refute its status as a new species, but rather the wrong arguments brought to support it.

The combination of "modern" and "primitive" morphological characteristics is one of the major arguments raised by Brown et al. (2004) to differentiate LB1 from *Homo sapiens*. Nobody would argue, however, that LS patients who also manifest a similar combination (e.g., an extremely oval-shaped pelvic inlet, or a "bell-shaped"

form of the thoracic cage), are direct descendents of *Homo erectus* (an idea advocated strongly for LB1 in the first paper) nor of the australopithecines (a notion which appears in the second publication). Based on morphological comparison between LS patients and normal short children, it is clearly evident that many of the "unique" primitive morphological traits seen in LB1 are due to her small stature (Takano et al., 1986). This also explains why LB1 shares most of her features, including the most "unique" ones (e.g., the deep fissure separating the mastoid process from the petrous crest of the tympanic bone; the absence of a true chin etc.) with local pygmyoid populations (Jacob et al., 2006). Ignoring the possibility that LB1 is derived from a small stature population (Rampasasa pygmies are good candidates, as suggested by Jacob et al. in 2006) with its own distinct morphological features may lead to erroneous conclusions. For example, recently Larson et al. (2006) reported on a clavicle (short relative to humeral length) and scapula (normal) of LB1 and suggested that "A short clavicle may indicate a more protracted scapular position, raising the possibility of a previously unsuspected transitional stage in the course of hominin pectoral girdle evolution" (p A21). However, the length of the clavicle is mainly dictated by the shape and diameter of the upper thoracic cage. This is why both LS patients and KNM-WT 15000 *H. erectus* (both manifesting a very similar fan-shaped thorax) have a relatively short clavicle.

In contrast to Morwood's statement (2005) that LB1 manifests a combination of primitive and derived features that dictate exclusion from the species sapiens, we have herein offered evidence to suggest that LB1 is but a local individual in a highly inbred, probably pygmy-like population (of *Homo sapiens*) in whom a mutation of the GH receptor had occurred.

So far 57 mutations have been described in LS patients residing in various parts of the world including South Asia (Rosenfeld et al., 1994; Rosenbloom and Guevara-Aguirre, 1998; Laron, 1999; Shevah et al., 2005). These numerous molecular defects on the GH receptor gene or the postreceptor cascade (Elders et al., 1973; Godowski et al., 1989; Laron et al., 1992; Rosenbloom et al., 1999; Laron, 2004; Woods and Savage, 2004) produce a large variety of short stature phenotypes and a wide spectrum of intellectual abilities and deficits (Shevah et al., 2005), which may also explain the differences between the LS patients and LB1.

LS is a recessively inherited disorder that occurs predominantly in families with a high degree of consanguinity (Pertzalan et al., 1968; Rosenbloom et al., 1990; Shevah and Laron, 2006), and therefore it is also found in isolated populations. As LB1 replicates most of the diagnostic features of LS patients (Table 1), as well as those of pygmyoid Australomelanesians (Jacob et al., 2006), it can be assumed that the findings from the island of Flores represent a local, highly inbred, low stature *Homo sapiens* population in whom a mutation in the GH receptor had occurred. The long time presence of LB1-type humans on the island of Flores is not surprising considering that LS patients, and derived dwarfed populations with GHRH-R defect, reproduce normally (Laron, 2004).

For differential diagnosis, one could consider other molecular defects along the GH IGF-I axis. Untreated GH gene deletion patients are undistinguishable from patients with LS.

Previous researchers have looked into the issue of whether LB1 represents a developmentally normal holotype required for a new species or an abnormal member of our own species (Jacob et al., 2006; Martin et al., 2006a,b). The current study attempts to link the diagnosis of the skeletal remains of LB1 to a specific genetic syndrome. A recent article by Richards (2006) supports our initial thesis (Hershkovitz et al., 2006; Laron et al., 2006a,b) that LB1 probably suffered from a defect along the GH/IGF-I axis.

CONCLUSION

Proposing a molecular defect in the GH receptor as the diagnosis for the small statured population from the island of Flores, Indonesia, presents a challenge. Although only future DNA analysis may confirm our diagnosis, the manifold morphological resemblances leave little doubt that a congenital deficiency of insulin-like growth factor (IGF-I) is the major cause of their abnormal development.

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