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REVIEW

Paleodysmorphology and Paleoteratology:
Diagnosing and Interpreting Congenital Conditions of the Skeleton in Anthropological Contexts

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Most congenital conditions have low prevalence, but collectively they occur in a few percent of all live births. Congenital conditions are rarely encountered in anthropological studies, not least because many of them have no obvious effect on the skeleton. Here, we discuss two groups of congenital conditions that specifically affect the skeleton, either qualitatively or quantitatively. Skeletal dysplasias (osteochondrodysplasias) interfere with the histological formation, growth and maturation of skeletal tissues leading to diminished postural length, but the building plan of the body is unaffected. Well- known skeletal dysplasias represented in the archeological record include osteogenesis imperfecta and achondroplasia. Dysostoses, in contrast, interfere with the building plan of the body, leading to e.g. missing or extraskeletal elements, but the histology of the skeletal tissues is unaffected. Dysostoses can concern the extremities (e.g., oligodactyly and polydactyly), the vertebral column (e.g., homeotic and meristic anomalies), or the craniofacial region. Conditions pertaining to the cranial sutures, i.e., craniosynostoses, can be either skeletal dysplasias or dysostoses. Congenital conditions that are not harmful to the individual are known as anatomical variations, several of which have a high and population-specific prevalence that could potentially make them useful for determining ethnic origins. In individual cases, specific congenital conditions could be determinative in establishing identity, provided that ante-mortem registration of those conditions was ensured. Clin. Anat. 00:000–000, 2016. © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

Congenital anomalies have intrigued mankind since the earliest times. Initially considered to result from divine intervention or maternal imagination, their true nature has been progressively unraveled since the late 17th century. Physical conditions are considered "congenital" if they result from a prenatally present cause. This does not necessarily imply that the conditions themselves are always apparent before or at birth. Conditions with an insidious onset can show their first symptoms in childhood, adolescence, or

even adulthood. The collectively recorded prevalence of all congenital conditions is around 2.4% of live births (Dolk et al., 2010). However, there is a transitional region rather than a sharp boundary between normal morphology and congenital anomalies, which encompasses the so-called anatomical variations. Although they deviate from the default building plan of the human body, these variations are not significantly disadvantageous to the affected subject.

Congenital conditions in humans are studied by two overlapping disciplines: dysmorphology and teratology. Dysmorphology is a medical, mostly pediatric, discipline that focuses on the clinical diagnosis and symptomatology of physically apparent patterns of congenital anomalies, whereas teratology, a biological discipline, deals with the epidemiology and pathogenesis of congenital conditions. This review surveys what these two disciplines can offer to physical and forensic anthropologists in assessing skeletonized human remains presenting with congenital anomalies.

CONGENITAL CONDITIONS: CAUSES, DISTRIBUTIONS, AND ARCHAELOGICAL REPRESENTATION

The cause of a congenital condition can be endogenous (i.e., fetal), exogenous (i.e., maternal) or a combination of both, although in many cases no exact cause can be established. Endogenous causes include >5,000 presently known genetic conditions and many chromosomal anomalies (aneuploidies) and sporadic conditions with no clear-cut genetic involvement. Exogenous causes mainly comprise placentally transmittable infections, intoxications and metabolic conditions that render the fetus either deprived of or overexposed to certain metabolites. Well-known examples of exogenously induced conditions are congenital syphilis (which is discussed elsewhere in this issue of the journal) and fetal alcohol syndrome.

Congenital conditions are not distributed equally over the global population. Depending on the causes, their prevalences can differ profoundly among population groups. For instance, certain genetic conditions are significantly more (or less) prevalent in geographically and/or culturally isolated, hence inbred, communities in which ancestral mutations are preserved in subsequent generations and become part of a stagnant and increasingly homogeneous gene pool. This phenomenon is known as the "founder effect". Exogenous causes, especially maternal infections and intoxications, can also show community-specific prevalences in relation to health care provision and socioeconomic stratification.

Apart from the fact that pathology, whether acquired or congenital, can be difficult or even impossible to assess in skeletal remains, there are several reasons for the paucity of congenital conditions in the anthropological record. First, most congenital and genetic conditions are rare, with incidences well below 1 in 50,000. Moreover, a substantial portion of these, e.g., cardiovascular and genitourinary defects, cause no skeletal lesions. Secondly, most individuals with

congenital anomalies, in particular the more severely affected ones, die in infancy or while they are juvenile. These age groups are underrepresented in the archaeological record (Pinhasi and Bourbou, 2008). Thirdly, several skeletal conditions such as skeletal dysplasias affect the histological architecture of bones, rendering them vulnerable to diagenetic processes. Finally, in some instances, seemingly congenital conditions can in fact have postnatal causes.

Several excellent papers have been published on the archeological presentation of certain congenital conditions, including neural tube closure defects (Kumar and Tubbs, 2011), Down syndrome (Rivollat et al., 2014) and orofacial clefts (Tur et al, 2016). Leaving aside conditions with a predominantly extraskeletal focus, the remainder of this review will focus on the morphological characteristics of congenital conditions that directly and specifically concern the skeleton, qualitatively and/or quantitatively. These conditions are known, respectively, as skeletal dysplasias and dysostoses, of which >400 are presently known and categorized in accordance with their radiographic, biochemical and genetic characteristics (Warman et al., 2011). Although most of these conditions are quite rare, their overall prevalence is around $2.3 - 7.6$ per 10,000 (Panda et al., 2014). However, since mildly affected individuals often remain undiagnosed, the actual prevalence could be higher.

SKELETAL DYSPLASIAS

Skeletal dysplasias (osteochondrodysplasias) mostly originate from genetic defects resulting in abnormal histological formation, growth and maturation of cartilaginous and/or osseous tissues. They usually affect most skeletal elements equally, leading to diminished postural length (dwarfism). Skeletal dysplasias are therefore a generalized qualitative disorder of the skeleton, but the building plan of the body, including four extremities and pentadactylous hands and feet, is unaffected.

Before the 1860s, children born with neonatally apparent skeletal dysplasias were considered to suffer from a congenital form of rickets, a common disease in those days, because of their shortened and often curved extremities. However, true congenital rickets is rare, with only 25 cases reported to date (Paterson and Ayoub, 2015), and is one of the very few skeletal dysplasias that may result from an exogenous cause (i.e., maternal vitamin D deficiency). The Dutch anatomist Willem Vrolik (1801–1863) was one of the first to consider an alternative diagnosis in a stillborn child with numerous congenital fractures (Fig. 1), which he considered to result from imperfect bone formation rather than rickets (Oostra et al., 1998). He named the condition "osteogenesis imperfecta" (Vrolik, 1849). Still known as such today, osteogenesis imperfecta (OI) is a genetic disease mainly caused by dominant mutations in genes encoding subunits of collagen type I, a structural protein crucial for the architecture of bone and various other mesenchymal tissues. Mutations in other genes involved in collagen
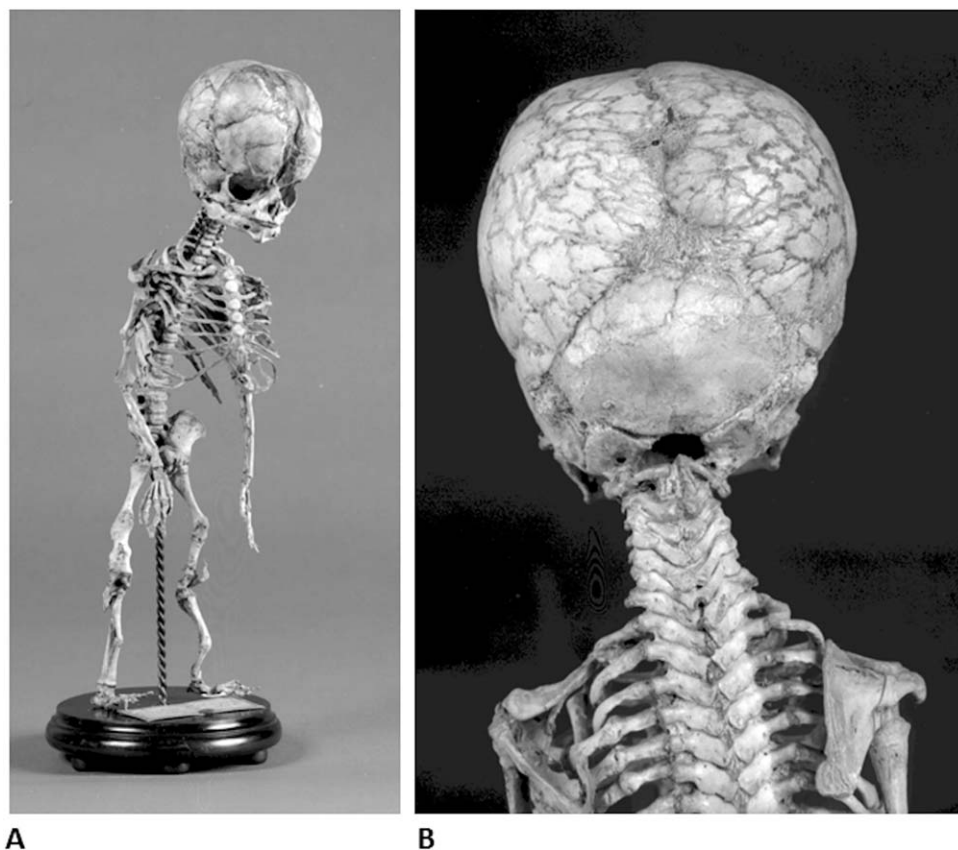
Fig. 1. Osteogenesis imperfecta type II. **A**: Complete macerated skeleton, showing numerous fractures in all tubular bones and ribs. **B**: Detail of the occipital part of the skull, showing many Wormian bones. Museum Vrolik, Amsterdam, The Netherlands (Oostra et al., 1998).

metabolism are increasingly being recognized as causal in different OI types (Shaker et al., 2015).

Occurring in 1 in 15–20,000 births (Forlino and Marini, 2016), OI is rare, yet it is one of the most common skeletal dysplasias. Its most important feature is the fragility of bones, leading to an increased tendency to fracture and to bow after healing. Shortening of the long bones, which is the main characteristic of most other skeletal dysplasias, occurs only secondarily in OI, i.e., when fractures fragment the diaphyses or destroy the growth plates. Depending on the severity of the condition and the mutations responsible, at least four different types are recognized, type II being lethal within the first two years of life while type I can have up to normal life expectancies. Several archaeological cases of what seems to be OI are known. These include mainly young adults with a mild phenotype, and a two year old child and a near-term fetus with presumably OI type II or III (reviewed by Cope and Dupras, 2011). The latter is exceptional considering the frailty of fetal bones in general, and especially when affected by OI. Nevertheless, in none of the described cases could the diagnosis of OI be established with certainty, leaving room for differential diagnoses that include other skeletal dysplasias.

Similarly prevalent as OI is a condition known as achondroplasia, which occurs in 1 in 10,000 to 1 in 30,000 births (Horton et al., 2007). Initially described by Parrot (1876), it inappropriately became a generic name for any short-limbed skeletal dysplasia, even well after the advent of radiology, leading to much misdiagnosis. Achondroplasia is characterized by an average adult stature of 120–130 cm, rhizomelic shortening of the limbs (the upper arms and thighs being more affected than the forearms and legs), which is disproportionate to the shortening of the trunk, and macrocephaly with bulging forehead (Jones et al., 2013) (Fig. 2). Intellectual development and lifespan are usually within normal ranges. Other features include midfacial retrusion, exaggerated lumbar lordosis, limitation of elbow extension, genu varum, brachydactyly, and trident appearance of the hands (Pauli, 2012). The short stature results not only from the diminished length of the tubular bones in the lower extremities but also from the reduced height of the vertebral bodies, which is known as platyspondyly. This is found in most skeletal dysplasias that are characterized by short stature. Radiographically, the short and relatively thick tubular bones in achondroplasia show metaphyseal flaring and cupping (reviewed by Cheema et al. 2003). Typically,
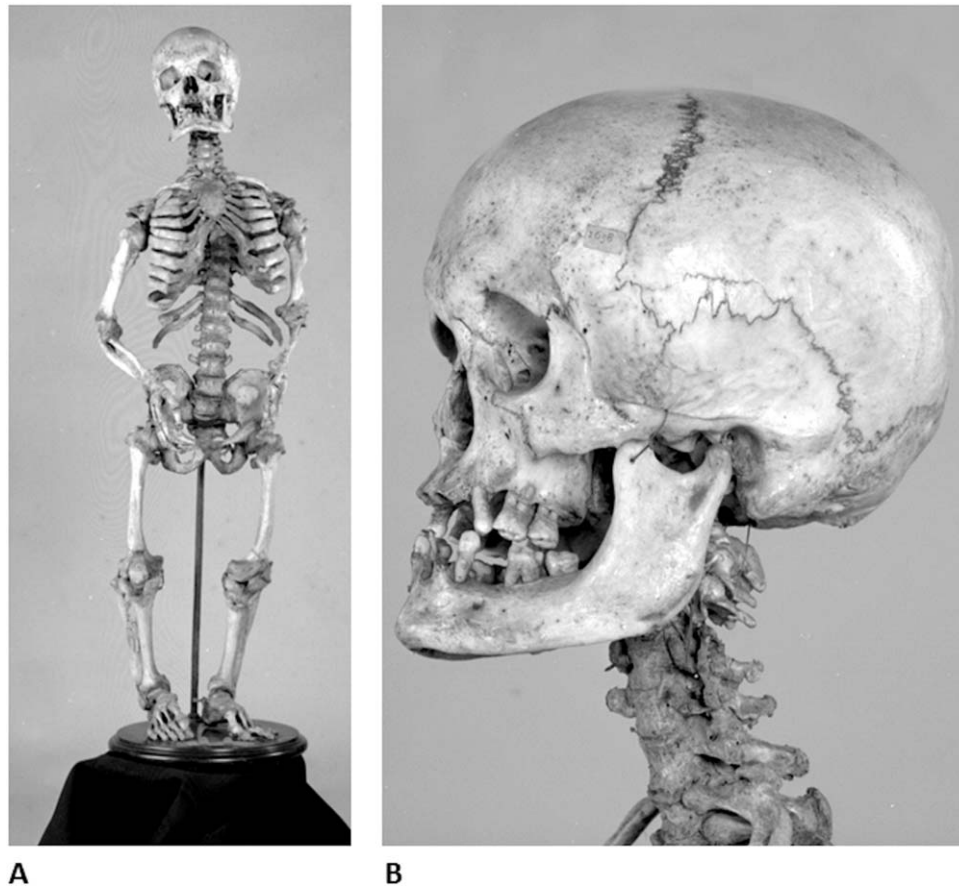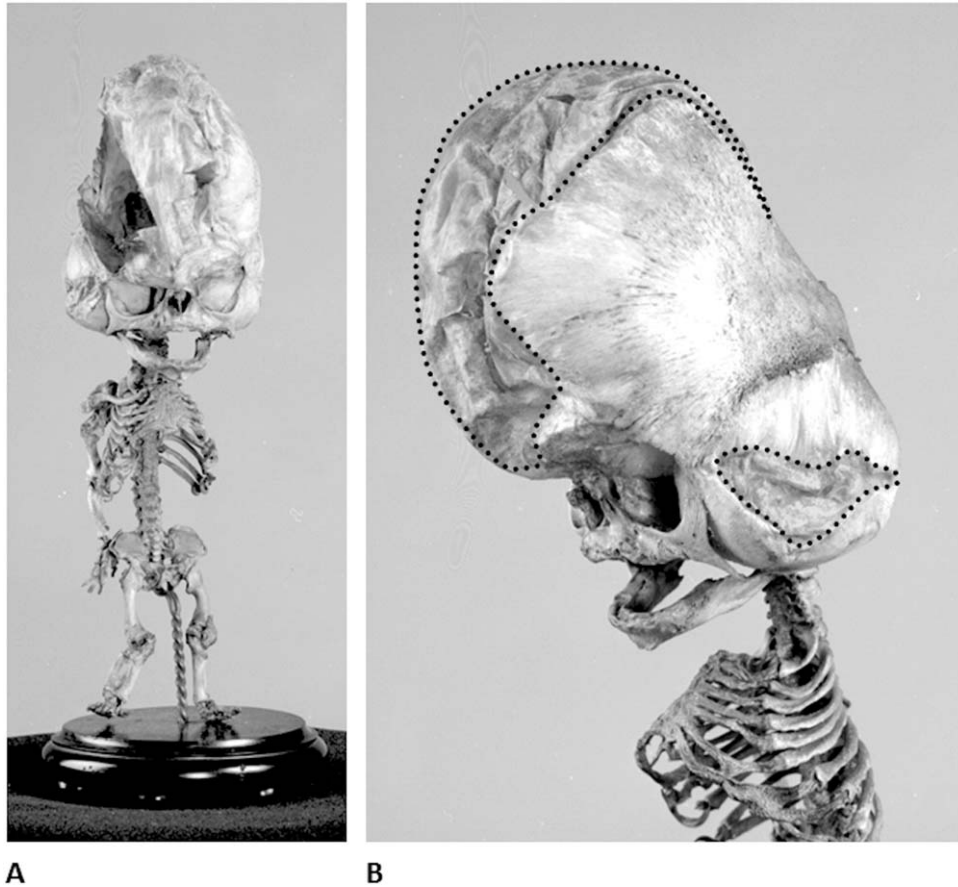
Fig. 2. Achondroplasia. **A**: Complete macerated skeleton, showing rhizomelic shortening of the extremities. **B**: Detail of the skull, showing relative macrocephaly and retracted cranial base. Museum Vrolik, Amsterdam, The Netherlands (Oostra et al., 1998).

there is overgrowth of the fibula, which correlates strongly with the degree of genu varum (Lee et al., 2007). Like many skeletal dysplasias, achondroplasia mainly affects enchondrally rather than intramembranously ossifying skeletal elements, hence the bulging forehead and midfacial retrusion.

Achondroplasia is caused by mutations in a gene encoding a receptor of fibroblast growth factors (FGFR3) (Shiang et al., 1994), the same dominant mutation being found in nearly all affected individuals (Bellus et al., 1995). However, since most of them are born to healthy, noncarrying parents, especially with increased paternal age (reviewed by Crow, 2000), it has long been assumed that this gene locus is a highly mutable "hotspot" in the human genome. Nevertheless, it appears that spermatogonial stem cells carrying the mutation have a proliferative advantage over non-mutated cells, thereby selectively increasing the number of mutated sperm cells (Shinde et al., 2013). As a result of the mutation, FGFR3 can be activated without binding to fibroblast growth factors (Webster and Donoghue, 1996), and since FGFR3 normally inhibits cartilage proliferation, diminished diaphyseal growth ensues (Deng et al., 1996).

Some other skeletal dysplasias are also caused by dominant germline mutations in FGFR3. They all resemble achondroplasia in their clinical and radiographic characteristics but they differ in severity. Intriguingly, the same mutations that repress cartilage proliferation can stimulate (malignant) proliferation of other tissues when they occur somatically, indicating that FGFR signaling dynamics are much more complex than originally assumed (Goriely et al., 2009; Foldynova-Trantirkova et al., 2012; Krejci 2014). Hypochondroplasia is the mildest FGFR3-related skeletal dysplasia. Whereas achondroplasia is usually recognized at birth, hypochondroplasia can go unnoticed until early childhood and is one of the conditions that mainly accounts for initially undiagnosed skeletal dysplasias in idiopathic short stature (Flechtner et al., 2014). As a result, the actual incidence and prevalence of hypochondroplasia are unknown (Wynne-Davies et al., 1981), but it is generally assumed that these numbers approach those of achondroplasia. Although its symptomatology is similar to but mostly milder than achondroplasia, it typically lacks the cranial dysmorphology, which was the key feature in differential diagnosis prior to the discovery of their

Fig. 3. Thanatophoric dysplasia. **A**: Complete macerated skeleton, showing severe rhizomelic shortening of the extremities. **B**: Detail of the skull, showing pansynostosis and bulging of the brain at the sites of the anterior and mastoid fontanelles (dotted lines). Museum Vrolik, Amsterdam, The Netherlands (Oostra et al., 1998).

molecular causes (Specht and Daentl, 1975; Oberklaid et al., 1979).

The most severe, neonatally lethal skeletal dysplasias associated with FGFR3 mutations are thanatophoric dysplasia (TD) types I and II. The incidence of TD has been investigated in different populations and seems to be equal to or somewhat less than that of achondroplasia, though it is likely that other lethal skeletal dysplasias are sometimes misdiagnosed as TD (Donnelly et al., 2010; Moffitt et al., 2011; Stevenson et al., 2012). As with hypochondroplasia, TD resembles achondroplasia but the symptoms are much more severe. The lethality results from the ribs being extremely short—as are all other enchondrally ossifying bones—and this is accompanied by pulmonary hypoplasia, which leads to perinatal suffocation. A comparable clinical phenotype can occur in patients born to parents who are both affected with achondroplasia or hypochondroplasia, from whom they have inherited two mutated alleles. The two types of TD, each caused by specific FGFR3 mutations, differ especially in the morphology of the femur, which is profoundly curved in TD type I and straight in type II (Fig. 3). Also, type II is often accompanied by premature closure of all calvarial sutures. This indicates that FGF signaling is also involved in intramembranous ossification, which will be discussed further.

The occurrence of achondroplasia is relatively frequent in all times and all places, as reflected by its abundant representation in archaeological artifacts, especially in cultures with a positive appreciation of dwarfing conditions (Kozma, 2006, 2008; Rodriguez et al., 2012). The oldest skeletal remains that have been diagnosed with achondroplasia are of two Egyptian adults—a 45- to 50-year-old male and a 25- to 30-year-old female—dated to the third millennium BCE (Kozma et al., 2011). Several other osteoarcheological cases of achondroplasia have been reported (reviewed by Woo et al., 2015) but, to the best of our knowledge, none of hypochondroplasia or TD, which is surprising considering their equally frequent occurrence.

DYSOSTOSES

In contrast to skeletal dysplasias, dysostoses result from localized quantitative developmental disorders, with exogenous and endogenous causes that affect

the building plan of the body, leading to e.g. missing or extra skeletal elements. However, the histology of skeletal tissues is unaffected. Dysostoses are usually categorized in terms of their effect on the building plan, which can involve an excess of elements (e.g. polydactyly), a shortage of elements (e.g. oligodactyly, phocomelia and peromelia) or a persistence of embryonic morphology (e.g. syndactyly). They can occur as solitary entities or as parts of complex conditions such as malformation syndromes and disruptions. They can also co-occur with skeletal dysplasias. A well-known example of this is Ellis Van Creveld syndrome, a skeletal dysplasia characterized by short ribs, mesomelic shortening of the limbs, polydactyly, cleft palate and several other anomalies. Like most other recessively inherited conditions it is rare but its occurrence differs among populations as a result of the founder effect (see previously). Ellis Van Creveld syndrome is particularly prevalent among the Old Order Amish in Pennsylvania (McKusick et al., 1964).

Polydactyly—an excess of fingers and/or toes—is a relatively common dysostosis, occurring in 19 per 10,000 births (Castilla et al., 1996, 1998). They range from a barely visible pedunculated skin tag or a partially duplicated distal phalanx to multiple completely developed and articulated extra digits, which can occur unilaterally or bilaterally on the radial/tibial (preaxial) and/or ulnar/fibular (postaxial) side of the hands and feet or in their center (mesoaxial). Many categories can be recognized depending on the location of the extra elements, their extent, and the co-occurrence of other anomalies such as syndactyly (Temtamy and Mc Kusick, 1969; Losch et al. 1984; Castilla et al., 1996). More and more genes involved in hand and foot development are being recognized and mutations in them could cause a whole range of (syndromic) forms of polydactyly (Biesecker, 2002). Many of these genes are implicated in the embryonic development of the anteroposterior (radio-ulnar) axis of the hand and foot. By far the most frequent type, either isolated, monogenetic or part of a syndrome, is postaxial polydactyly, which occurs in 6–15 per 10,000 births (Castilla et al., 1996). Remarkably, the incidence of this type is ten times higher in Negroid populations than Caucasoids, although this only concerns the pedunculated type (Woolf and Myrianthopoulos, 1973; Buck-Gramcko, 1998). Archaeological reports of polydactyly (reviewed by Wrobel et al., 2012) are scarce, despite the rather high incidence of polydactylous conditions. This is no surprise with respect to the pedunculated type, which usually lacks osseous elements. However, completely formed extra digits can also go unnoticed if the investigated remains are disarticulated or arise from more than one individual. In fact, the most consistently recognizable types are those involving a bifurcated phalanx or an osseous branch attached to a metacarpal or metatarsal.

Oligodactyly, the lack of (parts of) fingers and/or toes, also is common dysostotic condition, ranging from shortness to complete absence of one or more digits, involving either the forearms or legs or both. The prexial, postaxial and/or mesoaxial regions of the extremities can be affected. Conrad and Ezaki (2002) reviewed the condition and recognized four categories, with incidences ranging from 1 in 10,000 to 1 in 100,000. Unless they are bilateral, most cases of oligodactyly occur sporadically and can result when an initially normal developmental process is disrupted. Such disruptions are considered to arise from e.g. necrosis caused by vascular malformations. Heritable forms of oligodactyly can show population-specific prevalences. Explicit examples include the various reports on (large) kindreds presenting with "split hand-foot" syndrome (mesoaxial oligodactyly), including an African village inhabited by an "ostrich-footed" tribe (Viljoen and Beighton, 1984). As with polydactyly, and for similar reasons, oligodactyly is scarcely represented in the archeological record. Additionally, it can be difficult if not impossible to differentiate between congenital reductions of the digits and postnatal traumatic amputations. It is claimed that the pharaoh Tutankhamun (14th century BCE), who suffered from several, mostly acquired conditions, had a mild form of oligodactyly, manifest in the absence of the middle phalanx of his left second toe (Hawass et al., 2010).

The vertebral column can also be involved in dysostotic conditions that result in either an excess or a shortage of vertebrae—together known as meristic or numerical anomalies (see below)—or in a persisting embryonic morphology such as butterfly vertebrae, which results from notochordal remnants that interfere with the positions of ossification centers (Postma et al., 2014). Other conditions result from an aberrant segmentation of the mesoderm that gives rise to the alternating pattern of vertebrae and intervertebral discs, leading to hemivertebrae, block vertebrae and other dyssegmentations. These conditions usually occur sporadically but can also be components of more complex (syndromic) conditions. A particular group of vertebral dysostoses result from aberrant expression of homeotic selector (Hox) genes along the anteroposterior body axis of the early developing embryo. On each transverse level a specific set of Hox genes is expressed that determines the phenotypic identity of the vertebra formed at that level. Alterations in the expression of Hox genes - resulting either from functional mutations in those genes or from longitudinal shifts in their expression patterns - will therefore cause phenotypic changes in the vertebrae affected. Typically, the phenotypic characteristics of these vertebrae resemble those of adjacent vertebrae. These changes, known as homeotic transformations, are best recognized at the level of regional transitions (i.e., occipitocervical, cervicothoracic, thoracolumbar, lumbosacral and sacrococcygeal) (Fig. 4). In anterior homeotic transformations (AHT), the affected level phenotypically resembles the level above it. An example of this is lumbar ribs, in which the first lumbar vertebra resembles the twelfth thoracic and hence features true ribs (thoracalization) (Figs. 5A and 5B). Comparably, cervical ribs are an example of a posterior homeotic transformation (PHT), because the seventh cervical vertebra resembles the first thoracic (Figs. 5C and 5D). Although the number of vertebrae does not change in homeotic transformations, it can be difficult or even impossible to differentiate them
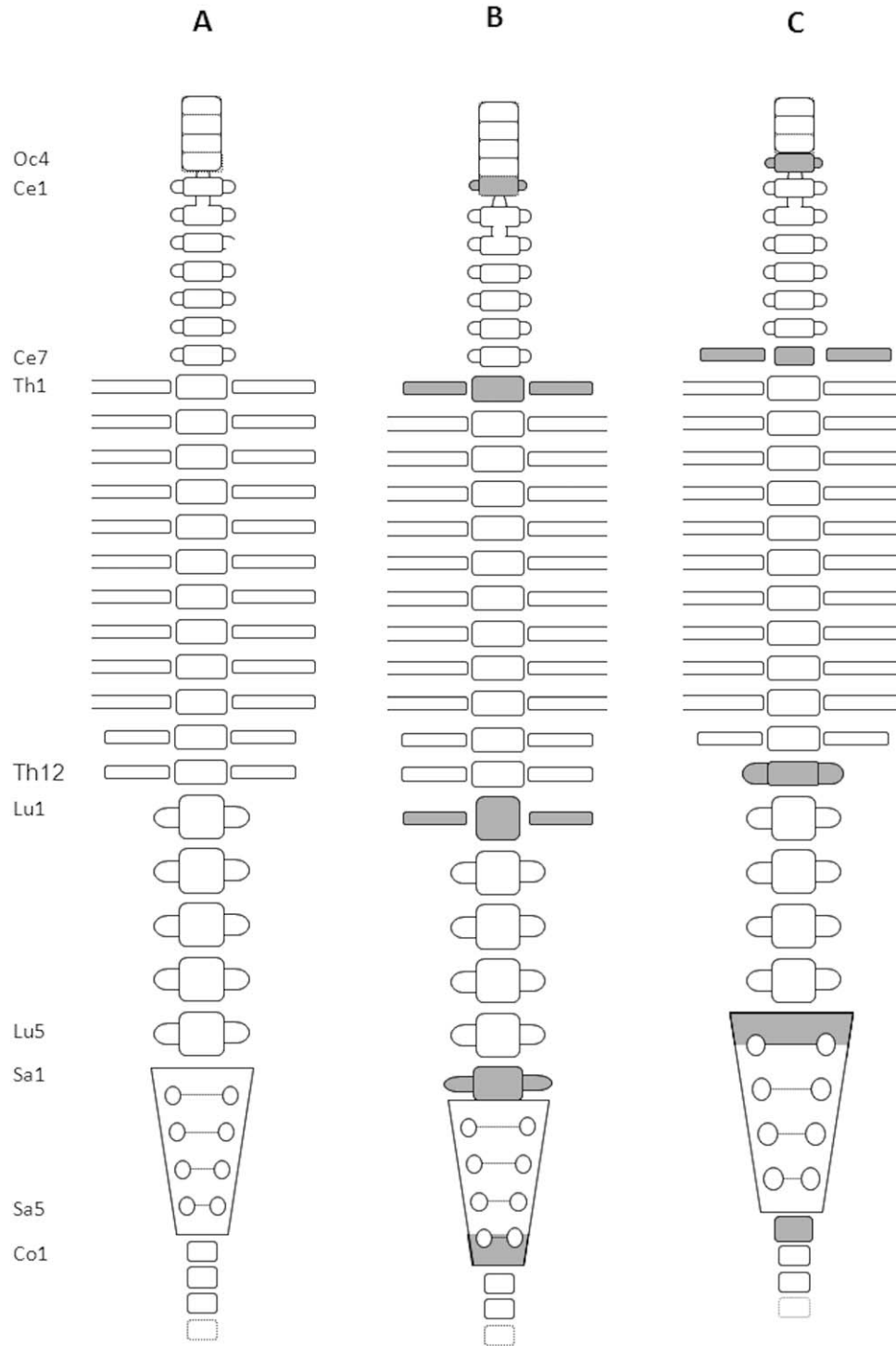
Fig. 4. Schematic representation of the interregional effects of homeotic transformations (in gray). **A**: Normal situation. **B**: Anterior transformations include: occipitalization of the first cervical vertebra (atlas assimilation), cervicalization of the first thoracic vertebra (hypoplastic first ribs), thoracalization of the first lumbar vertebra (lumbar ribs), lumbarization of the first sacral vertebra, and sacralization of the first coccygeal vertebra. **C**: posterior transformations include: cervicalization of the last occipital segment (occipital vertebra), thoracalization of the seventh cervical vertebra (cervical ribs), lumbarization of the twelfth thoracic vertebra, sacralization of the fifth lumbar vertebra, and coccygealization of the fifth sacral vertebra. (Adapted from Oostra et al., 2005a.).
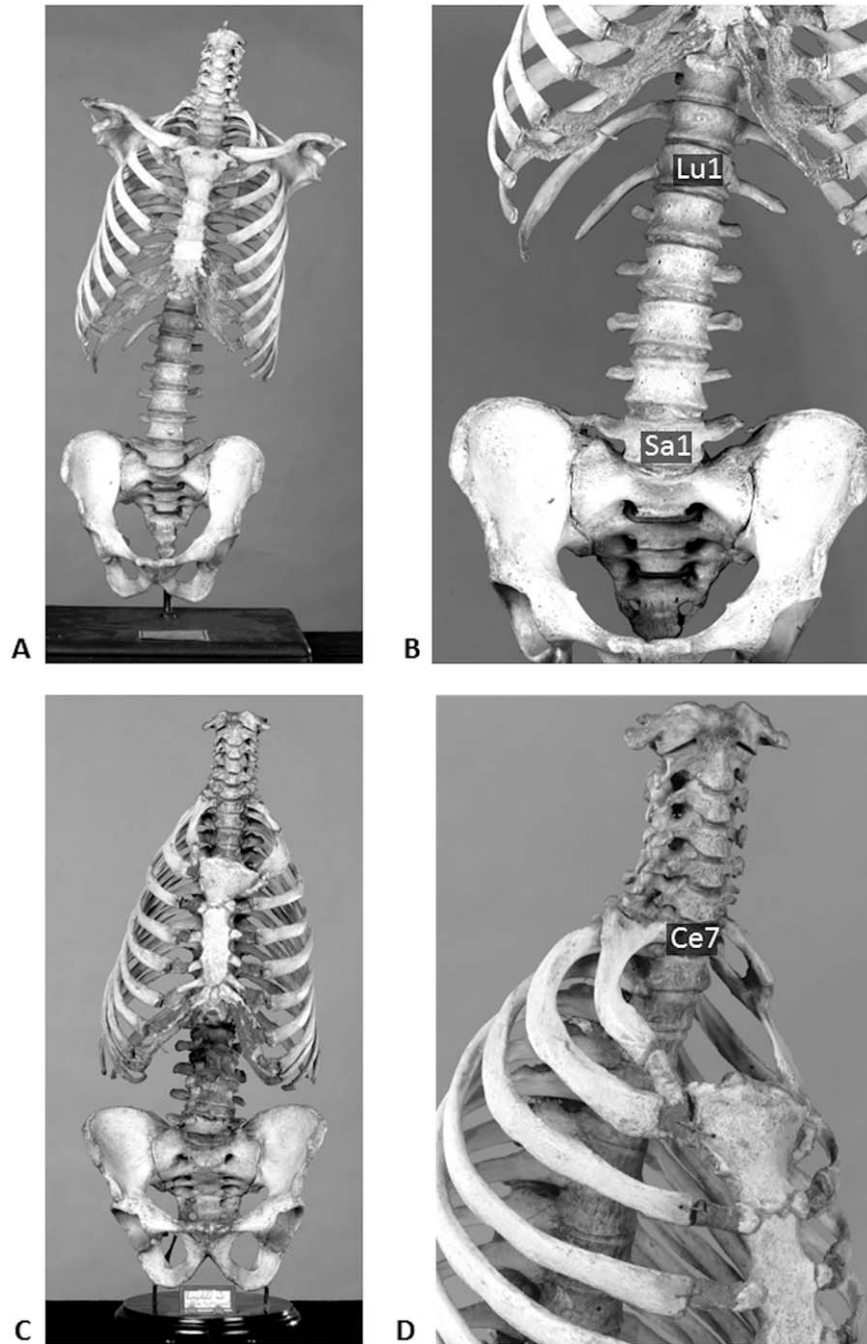
Fig. 5. Homeotic transformations. **A**: Macerated trunk skeleton with multi-level anterior homeotic transformations. **B**: Detail of the lower part of the vertebral column, showing thoracalization of the first lumbar vertebra (Lu1) and lumbarization of the first sacral vertebra (Sa1). **C**: Macerated trunk skeleton with multi-level posterior homeotic transformations. **D**: Detail of the upper part of the vertebral column, showing thoracalization of the seventh cervical vertebra (Ce7). Museum Vrolik, Amsterdam, The Netherlands (Oostra et al., 2005a).

from meristic anomalies (reviewed by Oostra et al., 2005a), especially if the vertebral column cannot be completely retrieved. An isolated sacral bone consisting of six vertebrae, for example, could have resulted from sacralization of either the first coccygeal (AHT) or the fifth lumbar (PHT) vertebra or from an extra vertebra. A block vertebra of the second and third cervical vertebrae, although generally resulting from either segmentation defects or from degenerative (hence acquired) conditions, can result from an anterior homeotic transformation that causes the third cervical vertebra to resemble an axis with the body of

the second cervical vertebra as its dens (Oostra et al., 2005a).

Homeotic and meristic anomalies of the vertebral column are remarkably common, with a reported prevalence as high as 17% (Bornstein and Peterson, 1966). Although they result from aberrations early in embryonic development, their direct clinical implications seem quite limited, except for cervical ribs, which can occasionally lead to thoracic outlet syndrome. However, they appear to be associated with both malignancies (Merks et al., 2005) and several congenital malformations, and have a prevalence of 75–80% in stillborn and therapeutically aborted fetuses (Ten Broek et al., 2012; Castori et al., 2016). This implies that either the Hox genes themselves—and their targets—or their upstream enhancers are more intricately involved in tissue and organ development and proliferation than has yet been established. In accordance with their high prevalence, homeotic and meristic anomalies are frequently encountered in archeological settings, often in combination with other vertebral anomalies. Barclay-Smith (1911) described an AHT ranging from the atlanto-occipital down to the lumbosacral junction, together with several cleft neural arches, in the skeleton of a young Egyptian female dating from 500–600 BCE. An unusual case of meristic anomalies was described by Usher and Christensen (2000), who found no fewer than three additional vertebrae in the skeleton of a 12th century Danish female.

CRANIAL SUTURES IN DYSPLASIAS AND DYSOSTOSES

It is often less straightforward to recognize and distinguish between dysplasias and dysostoses in the craniofacial region than in the postcranial skeleton. For instance, facial and palatal clefts could be considered as dysostoses though they are generally not categorized as such, whereas hypoplasias such as mandibulofacial dysostosis usually are. Sutural disorders of the cranial vault, with or without concomitant macro- or micro-cephaly, can result from both dysplasias and dysostoses.

Unlike the postcranial skeleton, the bones of the cranial vault develop without a cartilaginous intermediate, i.e., intramembranously instead of enchondrally, and are therefore among the first osseous elements to be formed during late embryonic and early fetal life. The appearance of ossification centers is followed by the radial expansion of bone formation. Where the ossification fronts of adjacent calvaria meet, a type of fibrous joint called a cranial suture is formed. During subsequent pre- and post-natal development the proliferating mesenchyme of which these sutures consist serves as a source of new bone tissue, thereby allowing the cranial vault to expand in directions perpendicular to the sutures. This process ends as soon as the mesenchyme of (parts of) a suture ceases to proliferate and consequently ossifies. In most cranial sutures this will occur when the cranium has reached its final size. Physiological obliteration of cranial sutures is therefore age-related, but because the time-course of

initiation, progression and completion of closure is variable, its value for estimating age is rather limited. By contrast, sutures between the bones of the facial cranium remain open throughout life. While most calvarial sutures start closing after the 3rd decade of life, some close much earlier, including the metopic suture between the two halves of the frontal bone, which normally closes during the first 3–9 postnatal months (Vu et al., 2001). The various ossification centers in the squamous part of the occipital bone even coalesce during early fetal life (Srivastava, 1992).

Abnormalities of sutural biology can be divided into premature closure, prolonged persistence and supernumerary ossification centers. In contrast to the latter two conditions, premature closure—known as craniosynostosis—leads to skull shape anomalies, especially in the cranial vault, that result from abolished growth across the closing suture and compensatory growth across the sutures that are still open (Fig. 6). Earlier onset generally results in more severe shape anomalies. Sagittal synostosis, the most common type of single-suture craniosynostosis, leads to a narrow but elongated skull (dolicho-, scapho- or clinocephaly, Figs. 6A–6C), whereas bicoronal synostosis results in a short but broadened skull (brachycephaly, Figs. 6D–6F). Asymmetry of the cranial vault can result from synostosis of one of the coronal or one of the lambdoid sutures, with compensatory growth across the still-open contralateral suture (plagiocephaly, Figs. 6G–6I). Closure of the metopic suture prior to birth results in a narrow, pointy forehead and compensatory widening across the sagittal suture, giving the cranial vault a triangular contour when seen from above. This condition is known as trigonocephaly (Figs. 6J–6L). If two or more sutures are involved, e.g. the coronal together with the sagittal or lambdoid sutures, a complex, more or less tower-shaped deformation results known as acro-, oxy-, turri- or hyps-encephaly (Figs. 6M–6O). This sometimes co-occurs with closure of the squamosal suture (Duncan and Stojanowski, 2008), which as an isolated condition is exceedingly rare (Tandon et al., 2014). If all calvarial sutures close prenatally, the growing brain can only expand at the sites of the anterior and mastoid fontanelles, resulting in a bizarre shape anomaly known as cloverleaf skull, with reference to its trilobed appearance (Fig. 3B). It should be noted that most shape anomalies described here can also result from other, non-suture-related conditions, most of which have a postnatal, exogenous cause. Well-known examples are the intentional skull deformations practiced by numerous cultures throughout history. Moreover, premature closure should be differentiated from early but adequate closure in response to cerebral growth arrest, in which case closure occurs secondarily and should not be considered a congenital or genetic condition per se.

Craniosynostoses involving one or more calvarial sutures can occur in isolation or as part of more complex congenital conditions (syndromes). Isolated craniosynostosis has an overall incidence of 1 in 2,000 and about half of all cases involve the sagittal suture (Kimonis et al., 2007). For unknown reasons, sagittal synostosis is three times more frequent in males (Hunter and Rudd, 1976), whereas coronal synostosis
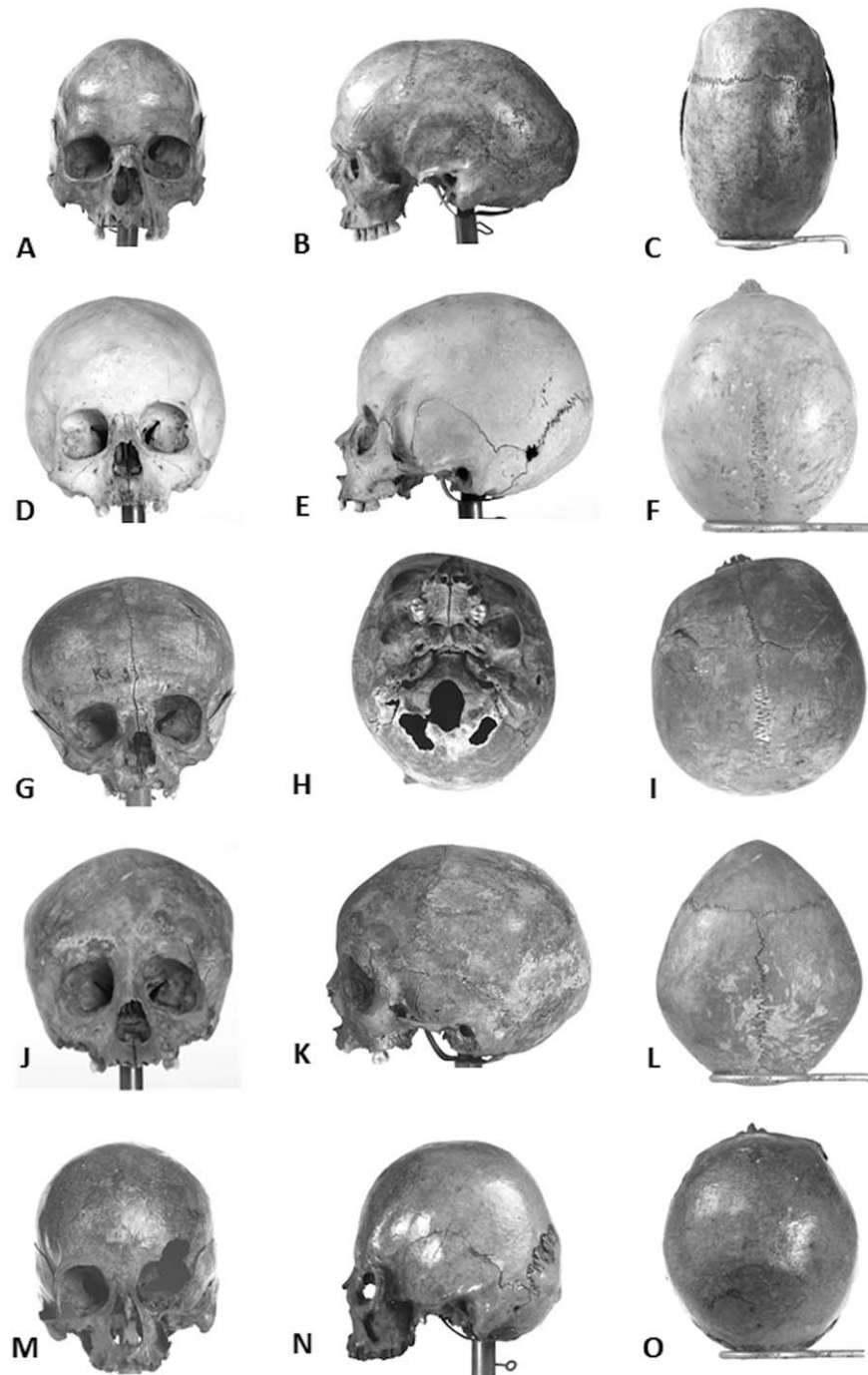
Fig. 6. Craniosynostoses. (**A-C**) sagittal synostosis (dolichocephaly); (**D-F**) bicoronal synostosis (brachycephaly); (**G-I**) unicoronal synostosis (plagiocephaly); (**J-L**) metopic synostosis (trigonocephaly); (**M-O**) sagittal and bicoronal synostosis (acrocephaly). Museum Vrolik, Amsterdam, The Netherlands (Oostra et al., 2005b).

is two to three times more frequent in females (Lajeune et al., 1995). Nonsyndromic, single-suture conditions rarely have a genetic cause or familial occurrence, in contrast to bi- and multi-sutural and syndromic conditions, in which an increasing number of genes appear to be causally involved (reviewed by e.g. Kimonis et al., 2007). Conditions in the latter group, which have much lower incidences, include some dysplasias as well as dysostoses. In TD type II (see above) a severe metaphyseal dysplasia occurs

together with pansynostosis, whereas in dysostotic syndromes such as Apert, Pfeiffer, Carpenter and Greig, multiple sutural synostoses are combined with mild to severe (poly)syndactylies. Intriguingly, there is not only a phenotypic but also a genetic overlap between dysplasias and dysostoses that feature craniosynostosis. Pathogenic mutations in e.g. FGFR genes are found in dysplasias, both with (e.g., TD type II) and without (e.g., achondroplasia) craniosynostosis, in dysostoses with craniosynostosis (e.g., Apert and Pfeiffer), and in craniosynostotic syndromes without other skeletal involvement (e.g., Crouzon and Beare-Stevenson). The effect of craniosynostosis on the neurocognitive development of the patient depends on several factors, including the age at onset and the number of sutures involved. Intracranial pressure is significantly elevated even when only one suture is involved (Thompson et al., 1995).

In accordance with their relatively high incidences, isolated craniosynostoses are well represented in the archeological record (reviewed by e.g., Duncan and Stojanowski, 2008), in particular isolated sagittal synostosis. Pankowskà et al. (2010) described this condition in a >4,500 year old adult female skeleton. The oldest known case of craniosynostosis is that of a 500,000 years old *Homo heidelbergensis* child with a unilateral lambdoid synostosis, found at Atapuerca, Spain (Gracia et al., 2010). Syndromic craniosynostosis, which is rarely encountered in an archeological context, was described in a young adult 16th-19th century female from Siena, Italy, who was diagnosed with Crouzon syndrome (Giuffra et al., 2011).

Rather than closing prematurely, sutures that should close at a certain age can remain open for longer or even throughout life. Partial or complete persistence of the metopic suture beyond the first year of life—known as metopism—is a well-known phenomenon that has been extensively studied in numerous dry bone collections, making this one of the very few congenital conditions that is better known from the archeological record and anatomical collections than from living individuals. Its prevalence ranges from 1% to 10% depending on the population investigated and the definitions applied, without consistent gender differences (Da Silva Ido et al., 2013). The condition itself is harmless but it can co-occur with other more serious affections including hydrocephalus (Baaten et al., 2003), craniosynostosis (Giuffra et al., 2011), and basilar impression (Oostra et al., 2005b), in which cases metopic persistence could allow compensatory expansion. It was argued in the past that metopism is accompanied by agenesis of the frontal sinuses, although several subsequent studies failed to confirm this (reviewed by Marciniac and Nizankowski, 1959). The oldest known case of metopism, although diagnostically disputed (Holloway et al., 2014), concerns the 2.5 million year old skull of an *Australopithecus africanus* child aged 3–4 years and found near Taung, South-Africa (Hrdlicka, 1925). This ignited the idea that persistence of the metopic suture well beyond birth, as in modern humans and apparently in earlier hominids but not in chimpanzees or gorillas (our closest living relatives), reflects prolonged growth of the frontal lobes and hence advanced cognitive development (Falk et al., 2012).

Most variations in sutural morphology are found at the back of the skull, for example the occipital bone, which develops from several enchondral and intramembranous ossification centers. Four centers surrounding the foramen magnum give rise to the enchondrally ossifying basioccipital, left and right exoccipital, and squamous supraoccipital bones (Shapiro and Robinson, 1976). The remainder of the squamous part—the interparietal bone—develops from ten paired intramembranous ossification centers (Srivastava, 1992; Thanapaisal et al., 2013), although their number seems to vary (Niida et al., 1992). Around the beginning of the fetal period the first two ossification centers, one on either side of the midline, appear above the superior margin of the supra-occipital bone, giving rise to the intermediate segment between the future superior and highest nuchal lines (Srivastava, 1992). Subsequently, four sets of two centers each arise above the intermediate segment, giving rise to a lateral and a medial plate on either side of the midline. Normally, the borders between these centers and plates have disappeared by the end of the first trimester to form the interparietal bone *sensu stricto*, which in its lateral aspects is still separated from the intermediate segment (Srivastava, 1992). These lateral fissures are usually obliterated by the end of the second year (Shapiro and Robinson, 1976) but remnants can persist into adulthood (Tubbs et al., 2007).

This pattern varies when borders between ossification centers persist and subsequently give rise to additional sutures. A well-known example is the mendosal suture, which results from persistence of the fissure between the intermediate segment and the lateral plates. When the latter are normally fused with the medial plates a separate interparietal bone is formed. However, since any of the eight centers in the medial and lateral plates can either fuse or remain separate from the rest and/or from the intermediate segment, a vast number of bone and suture patterns results, as vividly illustrated by e.g., Srivastava (1992), Hanihara and Ishida (2001), and Thanapaisal et al. (2013). Collectively, these variations are known as Inca bones (*ossa incae*), since they were first described in skulls originating from the indigenous population of Peru (Rivero and Tschudy, 1851, cited by Oetteking, 1930). Indeed, the prevalence of ossification variations of the occipital bone differs markedly among populations worldwide, ranging from <1% to >10% (e.g., Hanihara and Ishida, 2001; Thanapaisal et al., 2013), but the incidence among South American natives has been reported as high as 27% (García-Hernández and Murphy-Echeverría, 2008). Apart from the demographic differences, interparietal bones seem to be more frequent in patients with craniosynostoses (Wu et al., 2011).

The variations in ossification patterns as described above, resulting in aberrant calvarial partitions, should be differentiated from Wormian bones, which are intrasutural (rather than intersutural) bones resulting from supernumerary (rather than generic) ossification centers. The presence of one or more Wormian bones, ranging in size from less than a millimeter up to

several centimeters, is so common, with prevalences ranging from 55% to 80% (reviewed by Cirpan et al., 2015), that it seems inappropriate to consider their presence rather than their absence as an anatomical variation. Wormian bones occur even more often in combination with sutural conditions such as cranio-synostosis (Sanchez-Lara et al., 2007) and metopism (Cirpan et al., 2016). Since they are mostly found within the lambdoid suture, co-occurrence with Inca bones can lead to very complex patterns, especially when the Wormian bones are formed not only in the lambdoid but also in the additional sutures. The fact that Wormian bones are associated with many other conditions, including skeletal dysplasias such as oste-ogenesis imperfecta (Fig. 1B) and Hajdu-Cheney syn-drome, and also with postural and intentional skull deformities, has led to the idea that their occurrence is triggered by mechanical stress on the forming bone tissue within the sutures in combination with an (epi)-genetic predisposition (reviewed by Bellary et al., 2013). This suggests that in certain cases, Wormian bones touch the limits of what can still be called a congenital and/or inherited condition rather than an acquired one.

CONCLUSIONS AND PERSPECTIVE

Most congenital conditions, especially those that are deleterious to the owner, have a low prevalence in extant populations and even more so in the anthropo-logical record. Nevertheless, as a group they occur in a few percent of all live births and their occurrence should be anticipated. Although it is therefore impor-tant to recognize anomalies as deviant from normal development, detailed knowledge of all these condi-tions is of limited value in archeological and forensic practice, considering their rarity. Specific diagnoses can sometimes be made in collaboration with patholo-gists, radiologists, and geneticists who have special-ized expertise in developmental osteology.

On the other hand, some anatomical variations per-taining to the skeleton have a high and population-specific prevalence which, in selected situations, could make them useful for determining ethnic origins. In this respect, although outside the scope of this article, creating a database of anatomical variations and their specific occurrence and prevalence in populations and geographical areas would be helpful for physical anthropologists. In individual cases the presence of specific congenital conditions could be determinative in establishing identity, provided that ante mortem registration of these conditions was ensured.

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