International Journal of Paleopathology 33 (2021) 1–12

Contents lists available at ScienceDirect

International Journal of Paleopathology

journal homepage: www.elsevier.com/locate/ijpp

Research article

# An isthmus of isolation: The likely elevated prevalence of genetic disease in ancient Panama and implications for considering rare diseases in paleopathology

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ARTICLE INFO

*Keywords:*
Bioarchaeology
Genetic drift
Developmental anomalies
Osteogenesis imperfecta
Isthmo-Colombian Area

ABSTRACT

*Objective:* This study considers the evidence for elevated frequencies of "rare" diseases in ancient Panama. Indications of population isolation by multidisciplinary sources allow for the possibility that rare inherited conditions may have been maintained at relatively high prevalences in the region due to gene flow restriction.
*Materials:* A sample of 267 skeletal human remains with diverse demographical characteristics from Pre-Columbian archaeological sites throughout Panama.
*Methods:* Remains were analyzed macroscopically and hard tissue developmental anomalies were documented.
*Results:* Frequencies of developmental anomalies and hard tissue changes consistent with specific rare genetic diseases, such as osteogenesis imperfecta, on the comparatively few human remains recovered from pre-Columbian archaeological sites are elevated as compared with global averages.
*Conclusions:* The paleopathological evidence is concordant with a scenario of isolation in Pre-Columbian times and with an increased presence of genetic disorders in the population.
*Significance:* This study advocates for the special consideration of rare diseases by paleopathologists in regions where populations may have experienced prolonged geographical or social isolation in the past.
*Limitations:* A dearth of local modern epidemiological data and low sample sizes of preserved human remains in certain regions of the country limited the possibilities of spatiotemporal comparisons of rare disease prevalence.
*Suggestions for further research:* Further scrutiny of developmental anomalies of genetic origin on ancient Panamanian remains and biomolecular testing of remains for specific disorders should be pursued to confirm the findings of this study.

## 1. Introduction

Modern rare diseases (MRD) affect less than 0.0005 % of the total population and are often neglected in clinical research and public health funding due to their infrequency (Richter et al., 2015). Similarly, ancient rare diseases (ARD) are often thought to be unlikely causative agents or discarded entirely by paleopathologists for the same reason. Nevertheless, global prevalence averages of MRD may mask variation at the regional, populational, or community level. Particularly in the case of inherited genetic diseases, communities or populations experiencing prolonged isolation due to social or geographical barriers may maintain higher frequencies of these diseases due to genetic drift.

Understanding potential gene flow limitations within past populations over time is essential for considering the plausibility of ARD in paleopathology. This paper reviews the published literature across multiple disciplines to consider the specific circumstances leading to isolation and restricted gene flow among the Pre-Columbian populations inhabiting the Isthmus of Panama. Specifically, local historical, epidemiological, linguistic, archaeological, and genetic data are compiled to investigate ARD in ancient human remains from Panama.

### *1.1. Historic and modern regional epidemiological data*

Paleopathological consideration of inherited genetic conditions termed "rare" in modern times, requires assessing their local presence and prevalence in both historic and modern times. Local prevalences higher than the global average, and perhaps above the accepted threshold for consideration as a "rare" disease, will influence the consideration of inherited conditions in differential diagnoses within past populations that inhabited the region.

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https://doi.org/10.1016/j.ijpp.2021.01.002
Received 30 September 2020; Received in revised form 11 January 2021; Accepted 23 January 2021

Within the surviving indigenous groups of Panama, one of the most visible and frequently noted congenital disorders is that of albinism (specifically, oculocutaneous albinism type II, or OCA2; OMIM #203200), estimated to affect more than 0.06 % of the *Guna* people of Eastern Caribbean Panama (Keeler, 1964). The estimated prevalence of this autosomal recessive disorder is magnitudes higher than the global average, and is thought to result from high rates of consanguinity among this population, allowing several identified mutations of the P gene responsible for OCA2 to be retained as polymorphic variants within the gene pool due to genetic drift (Carrasco et al., 2009; Woolf, 2005). Guna individuals with OCA2 were first referenced by the Welsh buccaneer Lionel Wafer who lived in a Guna village in the late 17th century (Wafer, 1729). Wafer's allusions to a high prevalence of the disorder at that time (less than 200 years after first Spanish contact), coupled with the existence of Guna oral legends featuring protagonists with albinism, points to the likelihood of a genetic bottleneck event prior to Spanish arrival (Guionneau-Sinclair, 1991; Woolf, 2005).

Another highly prevalent inherited disorder in Panama is Kindler syndrome (OMIM #173650), specifically among the *Ngäbe* people of western Panama and southern Costa Rica (Penagos et al., 2004; Siegel et al., 2003). Again, this syndrome comprises an autosomal recessive disorder known to cause a variety of skin changes, such as skin fragility and blistering. The incidence of Kindler syndrome among the Ngäbe is approximately 0.021 %, while only a few cases have been reported in the literature at a global scale (Siegel et al., 2003). Penagos and colleagues (2004) found that this syndrome was caused by an identical mutation of the KIND1 gene in 26 patients, suggesting that a founder effect due to isolation likely led to the high prevalence.

Public attention has been garnered recently regarding the lack of epidemiological data accounting for the incidence and prevalence of MRD within the Panamanian population at large (Pérez Sánchez, 2017; Reyes, 2020; TVN, 2020). To date, the number of individuals living with MRD in the country is unknown, partly due to the absence of technical equipment in local medical centers with which to confirm diagnoses (TVN, 2020). Nevertheless, congenital abnormalities identified at birth in Panama City are notably higher than the global average (Stevenson et al., 1966; Turkel, 1989).

The Panamanian government passed a law in 2014 guaranteeing social protection for individuals with MRD, defined by a prevalence threshold of 0.05 % (Ley N° 28 de 28 de octubre de 2014). The associated bylaws, passed in 2015, recognize 10 types of MRD specifically within the national territory: hereditary angioedema, arthrogryposis multiplex congenita, Batten disease, lysosomal storage diseases (including six subtypes), motor neuron diseases (including seven specific disorders), Rubinstein–Taybi syndrome, tuberous sclerosis, myopathies (including eight subtypes), osteochondrodysplasias (including five specific diseases), and other genetic disorders (including 11 specific syndromes).

Of particular importance to paleopathologists (i.e., potentially identifiable on human skeletal remains) are the osteochondrodysplasias, including achondroplasia, hypochondroplasia, osteogenesis imperfecta, osteopetrosis, and Marfan's syndrome, within the modern Panamanian population (Decreto Ejecutivo N° 1217 de 7 de diciembre de 2015). Additionally, some lysosomal storage disorders present in Panama, including Morquio syndrome, may have marked skeletal manifestations. Osteogenesis imperfecta, in particular, seems to be quite prevalent nationally, currently estimated to affect approximately 175 Panamanians (0.004 % of the population) in unofficial reports (Pérez Sánchez, 2017; TVN, 2016, 2020).

### 1.2. Evidence for past social or geographic barriers

Panama is situated centrally within the Isthmo-Colombian Area that spanned from northwestern Colombia, encompassing both Panama and Costa Rica, as well as southern Nicaragua in Pre-Columbian times (Hoopes and Fonseca, 2003). In contrast to other areas of the Americas, no substantial archaeological evidence exists to suggest that the Isthmo-Colombian Area participated in long-distance exchange networks, and ample multidisciplinary evidence exists pointing towards both an inter- and intra-regional isolation of its ancient inhabitants (Cooke, 2016; Geurds, 2017).

Linguistically, the surviving indigenous groups of Panama speak languages corresponding to Chibchan and Chocoan language families. Only two groups speak Chocoan languages (i.e., the *Emberá* and the *Wounaan*), and they are both thought to have only recently migrated to the Isthmus in the last several centuries (Pardo Rojas, 1987). Nevertheless, archaeological evidence and scant linguistic evidence points to the plausible presence of Chocoan-speakers in Eastern Pacific Panama and extending to the Chocó region of Pacific Northwest Colombia at the time of contact (Constenla Umaña, 1991). The situation for the Chibchan-speaking groups is more clear-cut. The majority of the surviving indigenous groups in Panama are Chibchan-speakers and are thought to have a deep history in the region (Cooke, 2016). Linguists have estimated that the proto-Chibchan language diverged from the Lenmichí Micro-Phylum in the heart of the Isthmo-Colombian Area (southern Costa Rica and western to central Panama) around 10,000 years ago (Constenla Umaña, 2012, 1991; Grugni et al., 2015, sec. S1; Hoopes and Fonseca, 2003). Although there were several hypothetical migration events associated with the subsequent division of the proto-Chibchan language into subgroups, these are thought to correspond to groups of people migrating *away* from this central area. Thus, from a linguistic standpoint, the surviving indigenous peoples inhabiting southern Costa Rica, as well as western and central Panama, are thought to be the descendants of groups that have remained in the same region over many thousands of years.

The linguistic diversity in this region did not go unnoticed by contact-period Spanish chroniclers, who remarked on the variety of languages present along the Panamanian Caribbean coast and the Pacific coast to the west of Chame. The Parita Bay communities of Central Pacific Panama, consisting of numerous territories along several large river basins, apparently spoke different languages and necessitated the use of interpreters when traveling between them (Jopling, 1994). Chroniclers also noted the ubiquity of warfare between neighboring communities in the central region of Panama (Espinosa, 1994; Fernández de Oviedo, 1851), which suggests this linguistic heterogeneity may have resulted from intra-regional isolation. Many archaeologists have used this purported inter-community warfare to explain temporal increases in regional social complexity (Hoopes, 2005; Ibarra Rojas, 2012; Lothrop, 1937; Mayo and Carles, 2015:92–94); however, it is noteworthy that physical evidence of interpersonal violence on human remains regionally is rarely encountered (Díaz, 1999; Huard, 2013; Rojas-Sepúlveda et al., 2011; Smith-Guzmán and Cooke, 2018).

Notwithstanding this purported isolation, there is some evidence for attempted incursions of foreigners to Panama prior to Spanish contact. Contact-period writings relate the landing of a group of foreigners to Parita Bay two years prior to Spanish arrival in this area (Andagoya, 1994). According to this second-hand account, the foreigners came from the direction of Nicaragua and upon landing in Panama became ill with a gastrointestinal ailment (i.e., *enfermedad de cámaras*) (González Herrada, 2013). The chief of this territory, Cutatara, taking advantage of their weakened state, killed the entire encampment of foreigners. While this was not a primary observation, it is plausible that both defensive military actions and endemic tropical diseases contributed to the isolation of the Pre-Columbian Isthmians for a very long time.

Panama does not seem to have participated in the proposed long-distance maritime networks of material culture exchange between Mesoamerica and the Pacific coast of South America (Geurds, 2017). Evidence for the import of trade goods sourced from outside of the Isthmo-Colombian Area into Panama is absent, including at large ceremonial sites containing massive deposits of hoarded material goods such as Sitio Conte and El Caño in Central Pacific Panama (Cooke et al., 2003; Cooke and Ranere, 1992; Mayo and Carles, 2015). Clearly the exchange


**Fig. 1.** Map of Panama showing the locations of the 12 archaeological sites mentioned in the text. Adapted from Wikimedia Commons map - Alexrk2 (Bathymetry: NGDC ETOPO2v2 (public domain); Topography: NASA Shuttle Radar Topography Mission (SRTM30 v.2) (public domain); Shoreline and additional data: VMap-0 (public domain).

of ideas into Panama, both on an intra- and interregional scale (i.e., agriculture and metalworking) did occur at several points in prehistory (Cooke and Sánchez, 2001). Maritime trade of goods, including prized thorny oyster shells (*Spondylus* spp.), throughout the Gulf of Panama, for example, is thought to have been intense during specific pre-contact periods (Martín-Rincón and Sánchez Herrera, 2007). Nevertheless, the uniformity of iconographic motifs apparent on multiple types of material goods over thousands of years points to a local production adapted to new learned technological knowledge (Cooke and Sánchez Herrera, 1997). Thus, the material culture evidence supports a scenario involving the transfer of ideas between adjacent communities rather than through long-distance contacts (Cooke and Ranere, 1992).

Several biodistance studies have been published in recent years using Pre-Columbian human craniofacial metrics to evaluate archaeological and genetic evidence for population movements based on biological relationships throughout Central and South America and the Circum-Caribbean. In such studies, individuals from the Pre-Columbian component of the Panama Viejo site are consistently shown to be divergent from other groups, more so than those groups are from each other (Ross et al., 2020; Ross and Ubelaker, 2019). This evidence appears to support the hypothesis that populations living in Pre-Columbian Panama were genetically isolated from those of neighboring regions; however, caution in interpretation is needed given the small sample size ($n<10$) and geographic location (Pacific coastal site). Indeed, inclusion of individuals from Pre-Columbian sites on the Caribbean coast of Panama and Costa Rica may tell a very different story than the purported isolation of communities on the Pacific coast.

Although many attempts have been made to extract aDNA from ancient human tissue from Panama, poor preservation has led to successful genome extraction in only one very recent project so far (Capodiferro et al., 2020). This study showed a distinct genetic signature (mtDNA haplogroup A2af1) separating both ancient and modern indigenous Isthmians from other indigenous groups of the Americas, again suggesting isolation of Pre-Columbian indigenous groups on the isthmus of Panama from the early Holocene to the time of contact and beyond. A logical next step for pursuing evidence for ARD through aDNA would be to identify specific deleterious mutations known to cause specific genetic disorders in ancient human tissues. Though the aforementioned preservation issues characterizing human remains from this region complicates this goal, high-coverage whole genome sequencing could provide viable avenues for future research.

### 1.3. Modern genetic variation

Modern Panamanian genetic studies have consistently reported a general lack of genetic diversity among surviving indigenous groups (Baldi and Barrantes, 2019; Barrantes et al., 1990; Grugni et al., 2015; Kolman et al., 1995; Kolman and Bermingham, 1997; Melton et al., 2007; Perego et al., 2012). These studies provide further evidence supporting a scenario of a small founding population of Chibchan-speakers that was subsequently isolated and contained over a long period of time without major incursions or migrations of peoples from outside of the Isthmo-Colombian Area. Perhaps the most illustrative evidence in support of this genetic isolation is the complete or near absence of mitochondrial haplogroups C and D among modern Chibchan-speakers, whereas all four indigenous American haplogroups (i.e., A, B, C, and D) are present elsewhere (Melton et al., 2007; Morales-Arce et al., 2017; Perego et al., 2012). The low variability of the Q-DYS391-6 sub-lineage present in the modern Panamanian gene pool is interpreted by Grugni et al. (2015) to provide further evidence in support of population isolation in Pre-Columbian times (Alonso Morales et al., 2018).

An alternative hypothesis to the widely accepted scenario of in-situ microevolution of Chibchan-speakers in the Isthmo-Colombian Area from the early Holocene to the time of contact advocates for a back-migration event from South America to areas throughout the isthmus (Reich et al., 2012). However, this proposed back-migration hypothesis ignores the multitude of aforementioned multidisciplinary evidence pointing to the deep history of stable cultural and linguistic development in the region.

There has been discussion in the literature questioning whether local mutations in the genome of isthmian indigenous people may have deleterious effects (Achilli et al., 2008; Carvajal-Carmona et al., 2003). The question of rare disease and congenital anomalies provoked by a founder's effect has been addressed for modern populations in Colombia, where there is evidence from Pre-Columbian art for genetic syndromes prior to Spanish contact (Castro and Restrepo, 2015; Pachajoa and Rodriguez, 2014; Sotomayor Tribín, 1990). No genetic syndromes on anthropomorphic effigies have been identified in Pre-Columbian art from central Panama, where ceramic styles tend to be more stylized and abstract, and more often feature zoomorphic designs

(Biese, 1964; Linares, 1977; Sánchez, 2000).

### 1.4. Bioarchaeological evidence

Bioarchaeological evidence for ARD in Panama has never been explored. Based on the multidisciplinary evidence for isolation presented above, the likelihood of an increased retention of particular genes among ancient Panamanian populations due to restricted gene flow is high, and may have led to the maintenance of ARD above average levels. This potentially elevated prevalence is assessed in this study through the analysis of the available ancient human remains from Panama.

## 2. Materials and methods

Many human remains have been excavated by archaeologists from various Pre-Columbian archaeological sites in Panama over the last century and are curated currently by national and foreign institutions. Typical of the tropics, many archaeological sites in Panama do not preserve osseous remains due to the acidity of the soils and frequent rains (Briggs, 1993). Bones recovered from shell-bearing middens at coastal sites fare better; however, frequent fragmentation and commingling of human remains in multiple burial contexts complicates osteological analysis.

For this study, basic osteological analyses of Panamanian Pre-Columbian human remains, compiled over the past four years, have yielded a database of information comprising 267 individual skeletons recovered from 12 sites (Fig. 1). The sites in the western region of Panama (i.e., the "Greater Chiriquí" cultural region) include Sitio Drago and Cerro Brujo on the Caribbean coast, and La Pitahaya on the Pacific coast. The central region (or "Greater Coclé") included the sites of Río de Jesús (Ve-7), Punta Blanca, Cerro Juan Díaz, Sixto Pinilla (He-1), Cerro Girón, Sitio Sierra, and Sitio Conte. The eastern, or "Greater Darien," sites included Playa Venado and Panama Viejo. Chronologically, individuals recovered from these sites date between approximately 2500 BC – 1500 AD.

### 2.1. Osteological analysis

The remains were assessed for demography, osseous and dental pathological lesions, and biocultural markers. For immature individuals, age estimation based on the dental development stage (AlQahtani et al., 2010) was the preferred method, but was supplemented by age estimation based on long bone length and epiphyseal union (Cunningham et al., 2016; Maresh, 1970). For adults, the pelvic features (Brooks and Suchey, 1990; Lovejoy et al., 1985) were preferred, but supplemented by cranial indicators of age (Meindl and Lovejoy, 1985). Sex estimation was only attempted for individuals 15 years of age or older, and favored pelvic indicators (Buikstra and Ubelaker, 1994; Phenice, 1969) supplemented secondarily by cranial indicators of sex (Acsadi and Nemeskeri, 1970). Paleopathological analysis recorded any abnormal bone growth or resorption following the North American Standards for specific lesion description (Buikstra and Ubelaker, 1994). Further diagnostic insight was gathered using compiled descriptions of common health afflictions on the hard tissues (Aufderheide and Rodríguez-Martín, 1998; Brickley and Ives, 2008; Ortner, 2003).

High relative frequencies of congenital anomalies present in ancient skeletal assemblages have been used by several researchers to suggest the presence of small, isolated populations (Turkel, 1989). Although the Panamanian assemblage has not yet been subjected to a specific study targeting congenital anomalies, many such anomalies were anecdotally noted during routine osteological analysis and provide useful preliminary information with which to assess the question of past genetic isolation regionally.

**Table 1**
Frequencies of individuals affected by single or multiple dental and skeletal developmental anomalies in Pre-Columbian Panama by site.

| Site | None | Single | Multiple | Total |
|---|---|---|---|---|
| Playa Venado | 66 (89.2 %) | 8 (10.8 %) | 0 | 74 |
| Panama Viejo | 54 (87.1 %) | 7 (11.3 %) | 1 (1.6 %) | 62 |
| Cerro Juan Díaz | 47 (94 %) | 2 (4%) | 1 (2%) | 50 |
| Sitio Sierra | 41 (85.4 %) | 6 (12.5 %) | 1 (2.1 %) | 48 |
| La Pitahaya | 9 (100 %) | 0 | 0 | 9 |
| Sitio Conte | 7 (87.5 %) | 1 (12.5 %) | 0 | 8 |
| Cerro Girón | 3 (75 %) | 1(25 %) | 0 | 4 |
| Sixto Pinilla | 4 (100 %) | 0 | 0 | 4 |
| Punta Blanca | 3 (75 %) | 1 (25 %) | 0 | 4 |
| Sitio Drago | 2 (100 %) | 0 | 0 | 2 |
| Cerro Brujo | 1 (100 %) | 0 | 0 | 1 |
| Río de Jesús | 1 (100 %) | 0 | 0 | 1 |
| **Total** | **238** (89.1 %) | **26** (9.7 %) | **3** (1.1 %) | **267** |

**Table 2**
Frequencies of individuals affected by dental and skeletal developmental anomalies in Pre-Columbian Panama by specific anomaly. Terminology *sensu* Barnes, 2012.

| | n[a] | N[b] | % |
|---|---|---|---|
| *Dental anomalies* | | | |
| Ectopic eruption | 7 | 212 | 3.3% |
| Supernumerary teeth | 5 | 212 | 2.4% |
| Notched incisors | 3 | 160 | 1.9% |
| Supernumerary cusps | 2 | 203 | 1.0% |
| Defective enamel | 2 | 212 | 0.9% |
| Transposition | 2 | 212 | 0.9% |
| Oligodontia | 1 | 212 | 0.5% |
| Root flexion | 1 | 212 | 0.5% |
| **Total** | **17** | **212** | **8.0%** |
| *Skeletal anomalies* | | | |
| Sternal foramen | 2 | 40 | 5.0% |
| Fused vertebrae | 5 | 150 | 3.3% |
| Bending deformity | 4 | 175 | 2.3% |
| Unfused sternal elements | 1 | 40 | 2.5% |
| Precondylar tubercle | 3 | 168 | 1.8% |
| Cleft neural arch | 2 | 159 | 1.3% |
| Fused ribs | 1 | 96 | 1.0% |
| Facial cleft | 1 | 163 | 0.6% |
| **Total** | **15** | **267** | **5.6%** |

[a] Note that "n" represents individuals affected; thus, totals reported here refer to total individuals, rather than total anomalies. Several individuals contained more than one type of anomaly overall.
[b] "N" represents the total number of individuals with at least one element specific to the respective anomaly observable (at least two for failure of segmentation anomalies). Total skeletal anomalies frequency based on individuals with at least one skeletal element (N = 267).

## 3. Results and discussion

### 3.1. Developmental anomalies

Of the 267 individuals represented in the sample, 29 individuals (10.9 %) displayed at least one dental or skeletal developmental anomaly (Tables 1 and 2). This preliminary prevalence estimate greatly exceeds the estimated 0.027 % incidence for congenital anomalies on a global scale (Aufderheide and Rodríguez-Martín, 1998). In an attempt to contextualize the frequencies of the specific anomalies observed in this assemblage, reported frequencies from the published literature are compiled in Supplemental Table 1. However, caution is warranted, as modern studies tend to exclude individuals with genetic syndromes and paleopathologists tend to publish cases of relatively high frequencies or case-studies in isolation. Additionally, extrinsic factors (i.e., infectious disease, nutritional stress, and trauma) can contribute to the development of some of these anomalies. However, five individuals showed multiple dental and skeletal anomalies which appeared to align with a


**Fig. 2.** Posterior (left) and anterior (right) views of the laminae of two thoracic vertebrae from Skeleton B-9 showing congenital fusion between the two contiguous vertebral arches along the midline. Photographs by Leslie Naranjo.

genetic syndrome. These cases are detailed in the following section.

### 3.2. Description of individuals with pathologies of possible genetic causation

#### 3.2.1. Sitio Sierra, Skeleton B-9

Skeleton B-9 is a primary flexed burial of a child dating to approximately 40 BC - AD 400. The age of this individual was estimated at 7–9 years based on the dental development. The long bone lengths were consistent with those of a healthy 4–5-year-old (Maresh, 1970), suggesting a delay in normal growth and development for this child, which is arguably consistent with the pathological lesions observed on this individual's skeleton. Such dental and skeletal age discrepancies are understood to be provoked by growth attenuating physiological stress (i.e., malnutrition or disease), which affects dental development to a lesser extent than long bone growth (Cardoso, 2007; Cunningham et al., 2016; Hoppa and Fitzgerald, 1999).

Dental pathologies included linear enamel hypoplasias on the maxillary central incisors, carious lesions on the mandibular first molars and maxillary deciduous canines, and calculus on the maxillary central incisors and first molars. The unerupted maxillary right lateral incisor (visible within the crypt) appears to contain a notch along the incisal edge. Since the tooth is not fully visible, it is uncertain if this notch represents a developmental defect (i.e., "Hutchinson's incisor"), or simply normal variation, such as an interruption groove.

Osseous pathologies and anomalies present include porotic hyperostosis (occipital, near lambdoid suture), cribra orbitalia (right orbit only; left fragmented), and bilateral femoral cribra. Vascular impressions appear on the anterior maxillae, just inferior to the nasal apertures. There was an instance of congenital vertebral fusion (i.e., "block vertebrae") affecting two upper thoracic vertebrae, which were fused along the midline of the neural arches (spinous processes and laminae; Fig. 2). It is possible that the intervertebral facets were also fused or fusing, but there was at least some separation here with soil between the facets. Another vertebral developmental anomaly was noted in a fragment of the left side of the lamina of an upper thoracic vertebrae. Here, the lamina medial to the inferior intervertebral articular facet is rounded, suggesting incomplete fusion with the right half of the neural arch (cleft neural arch).

The presence of both cleft neural arch and block vertebrae in the same individual, along with evidence for congenital block vertebrae at other sites in Pre-Columbian Panama (Table 2), suggests an underlying genetic component to which these anomalies may be attributed in the regional population. Titelbaum (2020) notes a high prevalence of block vertebrae and other axial developmental anomalies among northern Peruvian populations, as well. Klippel-Feil syndrome (OMIM #118100) should be considered among potential associated syndromes leading to the development of block vertebrae.


**Fig. 3.** Anterior view of the mandible from Individual PV-14 P showing congenital absence of both primary and secondary dentition with associated lack of alveolar bone. Photograph by Leslie Naranjo.

#### 3.2.2. Cerro Juan Díaz, Operation 3 Feature 2 Bundle 13

This individual is a 50+ year old female within a bundle burial dating to about 200–600 AD (Smith-Guzmán et al., in review). It remains uncertain if the teeth curated with this skeleton belong to this individual due to the lack of maxillary bone and mandibular condyles with which to associate them with the cranium. Nevertheless, dental pathologies include slight to moderate dental calculus affecting most of the teeth, especially the anterior dentition. The mandibular left third molar shows ectopia, being rotated 180° within the alveolar bone so that the occlusal surface faces the inferior aspect. The only osseous abnormalities present in the elements associated with this individual include slight lipping of the joint margins (potentially due to age-related degenerative joint disease) and a sternal aperture. The presence of ectopic tooth eruption and a sternal aperture in the same individual suggests these may be linked to a common developmental disruption.

#### 3.2.3. Panama Viejo, Centro de Visitantes Unit 192N-298E Individual PV-14P

Individual PV-14 P is a primary, extended burial dating to 1170–1377 cal AD (Beta-168850, 770 ± 50 BP conventional, calibration with IntCal20). The age of this individual was estimated at 3–4 years based on dental development.

Dental pathologies present in this individual include antemortem absence of all mandibular teeth, including both primary and secondary dentition resulting in a flat, edentulous mandible (Fig. 3). Although this child retained four deciduous and five permanent maxillary teeth, the maxillae were not preserved and thus, the presence or absence of a facial cleft was unobservable. Nevertheless, the absence of more than six teeth constitutes oligodontia, or the congenital absence of nearly all of the


**Fig. 4.** Field photograph of Individual 1 from Tumba 8 at Plaza Casas Oeste of Panama Viejo in situ, showing abnormal bending of the hands and elevated position of the right shoulder. Photograph taken from excavation report on file at Patronato Panama Viejo, used with permission from Álvaro Brizuela.

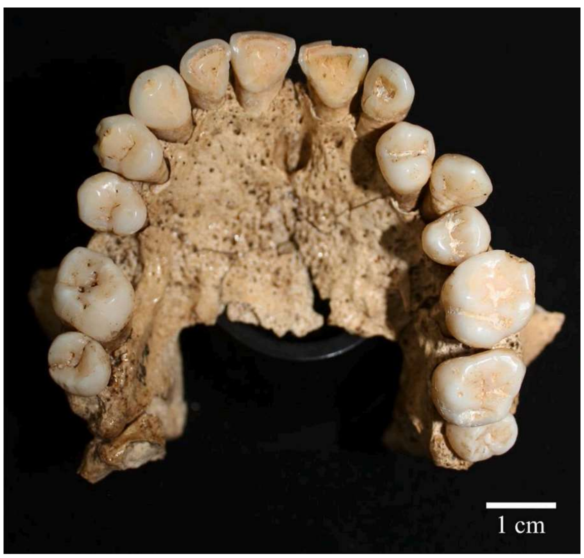


**Fig. 5.** Occlusal view of the maxillary dentition of Individual 1 from Tumba 8 at Plaza Casas Oeste of Panama Viejo, showing antemortem tooth loss of the right first molar and transposition and rotation of the left canine with the third premolar teeth. Photograph by Leslie Naranjo.


**Fig. 6.** Posterosuperior view of the cranium of Individual 1 from Tumba 8 at Plaza Casas Oeste of Panama Viejo, showing accentuated parietal bosses creating an overall angular appearance. Photograph by Leslie Naranjo.

teeth, in this individual. There were no osseous pathologies noted on the elements present (Fig. 4).

Cleidocranial dysplasia (OMIM #119600) should be considered as a possible diagnosis for the oligodontia seen in this individual. The clavicles of this individual were not present during lab analysis; however, the archaeologist remembers these as being present but extremely fragile during excavation and not conserved post-excavation (Personal communication with Juan Guillermo Martín-Rincón, September 2020).

#### *3.2.4. Panama Viejo, Casas Oeste Tumba 8 Individual 1*

Individual 1 from Tumba 8 is a primary, extended burial dating to 898−1014 cal AD (date reported as coded individual "PAPV137" in Capodiferro et al., 2020: suppl info, fig. S1-c). The age of this individual was estimated at 15-19 years and although the sex was indeterminate osteologically, recent aDNA analysis revealed that this individual is male (Capodiferro et al., 2020).

Dental pathologies present include antemortem tooth loss (AMTL) of the right upper first molar. There was also likely AMTL of both mandibular first molars, as well, but a socket with resorbing alveolar bone remains, so the timing of the loss of these teeth is uncertain. The left maxillary canine and third premolar were transposed (Fig. 5). Carious lesions affected the mandibular left fourth premolar and both mandibular second molars, and linear enamel hypoplasias affected all canines and premolars. Interestingly, the incisors were unaffected.

Pathological lesions affecting the axial skeleton include bilateral cribra orbitalia and slight porotic hyperostosis of the cranial vault. Porosity was also noted on the sphenoid, and in the maxillary hard palate and other portions of the maxilla. A small patch of woven bone overlies the surface of the alveolus directly below the right mandibular second molar, and is likely related to the carious lesion affecting this tooth. The cranium is notably angular in shape, which seems to be produced by accentuated parietal bosses (Fig. 6). Abnormal porosity affects both ventral and dorsal aspects of the sternum. The mesosternum has also not commenced fusion of the sternebrae, which typically occurs


**Fig. 7.** A: Superior view of the left third rib of Individual 1 from Tumba 8 at Plaza Casas Oeste of Panama Viejo showing porosity and flaring of the sternal end. B: Focal, inferior view of the sternal end of the same rib. Photographs by Leslie Naranjo.


**Fig. 8.** Anterior (left) and posterolateral (right) views of the right humerus of Individual 1 from Tumba 8 at Plaza Casas Oeste of Panama Viejo. Note the posterior torsion of the proximal end of the bone and the abnormal protuberance inferior and lateral to the humeral head. Photographs by Leslie Naranjo.

for the inferior sternebrae by age 15 (Cunningham et al., 2016). Inferior to the manubrium, there are five sternebrae present, with the three inferior elements leaving a sternal aperture when combined. The ribs are generally very light-weight, with some areas of porosity, particularly


**Fig. 9.** Anterior (left) and medial (right) views of the right tibia from Plaza Casas Oeste, Tumba 8, Individual 1, showing medial and anterior bending deformities and enlarged areas of the diaphysis (arrows) from either antemortem fractures or remnants of metaphyseal flaring due to metabolic deficiency during development. Photographs by Leslie Naranjo.

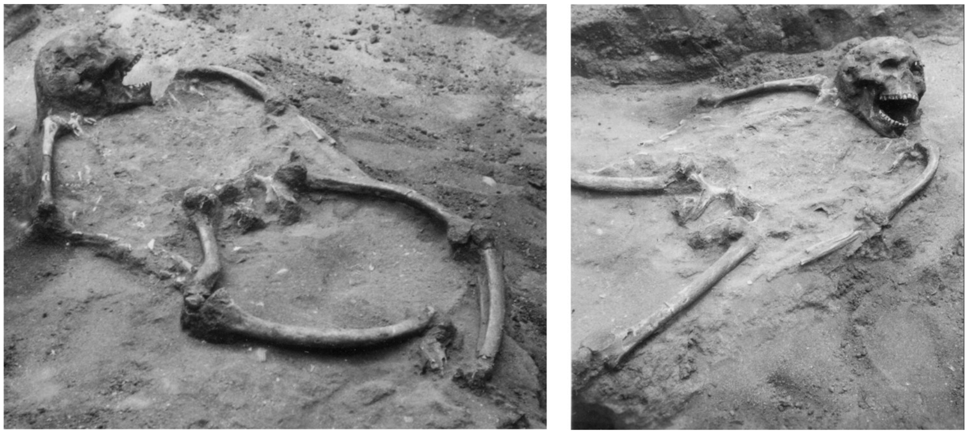

**Fig. 10.** Field photographs of Skeleton 8 from Area B, Trench 4 at Playa Venado in situ. Note abnormal bending deformities of the limb bones, antemortem fracture of the right femur, and extreme angle of the feet to the legs. Photographs courtesy of the Smithsonian's National Museum of Natural History, Washington, D.C.

towards the sternal ends, which have a flared and irregular appearance (Fig. 7). There appears to be a slight inferior bending of all rib heads, suggesting this individual might have had a barrel-chested appearance during life. Abnormal porosity also affects the bodies of all vertebrae present, with the largest pore measuring 9.86 mm x 3.81 mm in the first lumbar vertebra. The sacrum contained a complete cleft neural arch; however, the posterior structures of the fifth lumbar vertebra are not affected.

Pathological lesions affecting the upper appendicular skeleton include porosity and bone enlargement affecting the acromia of both scapulae, as well as both clavicles circumferentially, but being more severe along the superior and lateral aspects. Abnormal porosity affects the posterior and proximal anterior surfaces of both humeral shafts. There is a large bony growth on the posterolateral aspect of the proximal third of the right humerus (23.53 mm x 22.4 mm), potentially associated with an abnormal torsion of the proximal humeral epiphysis (Fig. 8). The head of the right humerus is rotated 45° posteriorly. The proximal end of the left humerus is absent, preventing observation of bilateral abnormal growth and torsion. Abnormal porosity affects the posterior and proximal anterior surfaces of both radial and ulnar shafts, being more severe on the middle and distal thirds, and the distal metaphyses. There were antemortem fractures to the distal third of the left radius and ulna. The fractures appear to be oblique with the distal aspect overlapping the proximal. The cortical bone surface displays sclerotic reaction, suggesting a healing response to recent fractures. Based on the abnormal porosity to the bones, it is possible that these fractures were pathological rather than traumatic. A general cortical thinning and porosity was noted on most of the metacarpals (bilaterally), and there are antemortem (healing, perhaps pathological) fractures to the left second and right fifth metacarpals. A patch of woven bone is present on the dorsal surface of the right third metacarpal. Several hand phalanges contain abnormal new bone formation and porosity, particularly the proximal phalanges of the first digits bilaterally and distal phalanx of the right first digit. There are signs of pressure facets from flexion contractures on the palmar aspects of the proximal phalanges.

Pathological lesions affecting the lower appendicular skeleton include bilateral focal lesions along the anteroinferior aspect of the femoral necks, characteristic of "femoral cribra" (Djuric et al., 2008; Smith-Guzmán, 2015). Both tibiae are affected circumferentially by the same abnormal porosity as seen on the upper limb bones. The right tibia has extensive areas of enlargement, at the distal and proximal extremities of the middle third of the diaphysis (Fig. 9). These could be pathological fractures, but there is no clear fracture line. Alternatively, they could be areas of the diaphysis where the metaphysis was flared during development due to a metabolic condition. Potentially associated with the diaphyseal enlargement, the proximal end of the bone is bowed medially and anteriorly. The left tibia also appears to be bowed, but instead of widened focal areas, the diaphysis displays general enlargement with associated porous bone. Both fibulae show a similar general enlargement and bowing. The tarsal bones show abnormal porosity generally, and there was a healing fracture to the middle of the right second proximal foot phalanx. Again, the irregular bone texture appearing on this healing fracture suggests that it may have been pathological in nature, rather than traumatic.

Overall, the suite of pathological lesions observed on this skeleton appear consistent with a metabolic disorder. Specifically, the flared sternal ends of the ribs point to rickets (i.e., "rachitic rosary" phenotype), a conclusion reported by Martín and colleagues (2009:134–138) and attributed to limited mobility, perhaps associated with spina bifida. However, upon further evaluation, the sacrum of this individual appears to display a common cleft neural arch, rather than true spina bifida occulta (i.e., neural tube defect), which likely did not impact mobility for this individual during life. Nonetheless, this author agrees with Martín et al. (2009) that Vitamin D deficiency is an unlikely condition in a sunny, tropical environment, unless the individual stayed indoors constantly.

However, there are many anomalies present on the skeleton and dentition of this skeleton that do not align with metabolic conditions, and allude to an overarching problem during development. These lesions include the dental transposition of two teeth, the parietal bossing, the failure of the mesosternum and neural arch of the sacrum to fuse, the protuberance and torsion of the right humerus (perhaps representing a Sprengel deformity; OMIM %184400), and the pressure facets present on the proximal hand phalanges. These hard-tissue developmental anomalies align more closely with a disorder of genetic origin. Osteogenesis imperfecta should be considered among the potential causative agents; nevertheless, the range of hard-tissue anomalies seen in this case goes beyond those reported in modern cases of osteogenesis imperfecta, and may represent a yet unrecognized genetic disorder. It is hoped that forthcoming high coverage ancient genomic analysis will provide further evidence to elucidate a diagnosis for this individual.

*3.2.5. Playa Venado, Area B Trench 4 Skeleton 8 (NMNH no. P381828)*

Skeleton 8, a primary extended burial (Fig. 10), was referred to in print as a "dwarf" (Lothrop, 1954, p. 228), and dating to about 250–750 AD (Smith-Guzmán et al., in press). This individual was estimated to be a 20–35-year-old probable female. Dental pathologies included carious lesions affecting the maxillary left first molar and mandibular left third molar. There were no signs of physiological stress-related growth disruption to the enamel.

In general, all of the skeletal elements present were lightweight and osteoporotic, with loss of cortical and trabecular density. Pathological

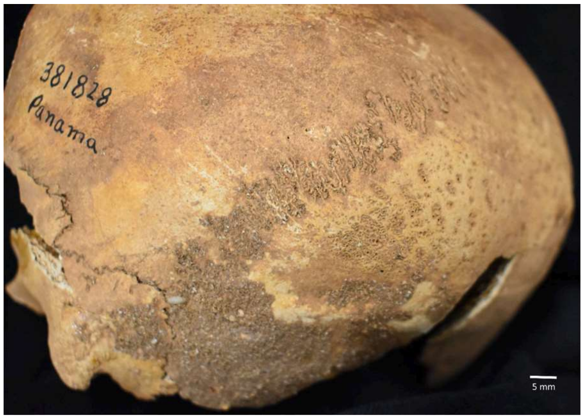


**Fig. 11.** Left posterolateral view of the cranium of Skeleton 8 from Area B, Trench 4 at Playa Venado showing severe cortical thinning, with patches of exposed diploë along the occipital squama. Note the complexity of the lambdoid suture. Photograph by the author.


**Fig. 12.** Anterior (left) and medial (right) views of the left humerus of Skeleton 8 from Area B, Trench 4 at Playa Venado showing abnormal lateral and anterior bending. Photograph by the author.

lesions noted on the axial skeleton include porosity of the cranial vault, including focal areas of severely thinned cortex on the occipital (Fig. 11). The cranium showed moderate obelionic-type artificial cranial


**Fig. 13.** Anterior view of the right and left femora of Skeleton 8 from Area B, Trench 4 at Playa Venado. Note the coxa vara angulation of the right femoral neck and antemortem fracture inferior to midshaft of the right femur, as well as the abnormal lateral and anterior bending of the left femur. Photograph by the author.

modification, which obscured the potential presence of congenital alterations. Extreme spinal curvature consistent with scoliosis was noted by field archaeologists, but the vertebrae were not retained for lab analysis. The right ischium shows some pitting and depression of the lunate surface and margin of the acetabulum, likely associated with pathologies noted on the right femur.

Pathological lesions present on the appendicular skeleton include abnormal lateral bowing of the left humerus, with posterior torsion of proximal epiphysis (Fig. 12). Abnormal lateral bowing of the left femur was present with associated antero-posterior flattening of the diaphysis. There was an antemortem healed displaced fracture along the distal third of the right femur, in which the distal portion had slipped over the proximal portion at the anterior aspect. The right femoral neck appears to contain a “shepherd’s hook deformity” (i.e., coxa vara), with a near 90° angle between the neck and shaft of the bone (Fig. 13). Both tibiae are bowed laterally, but this is very slight in the left bone. The right tibia shows extreme bowing, both laterally and posteriorly, which is similarly duplicated in the right fibula (Fig. 14). The left fibula is fragmented and unobservable. Radiographs of the long bones were taken, but the majority of the internal structural features were obfuscated by sediment contained within the shafts, which could not be removed without damaging the bones. Nevertheless, the radiographs confirmed the presence of cortical thinning observed during the osteological analysis.

Lothrop’s (1954) interpretation of achondroplasia for this


**Fig. 14.** Anterior view of the right tibia and fibula of Skeleton 8 from Area B, Trench 4 at Playa Venado, showing pronounced abnormal lateral bending of both bones. Photograph by the author.

individual's short stature and bending deformities is not substantiated by the characteristics of the skeletal anomalies present. The systemic cortical bone thinning and multiple fractures and pseudofractures align more closely with a collagen disorder. Metabolic deficiencies of an acquired nature (i.e., rickets) could possibly be implicated, but would likely cause less severe bending deformities, a more symmetric manifestation, and are not known to cause scoliosis (Brickley and Ives, 2008; Ortner, 2003). Nevertheless, the scoliosis could simply be a comorbid, unrelated condition. Osteogenesis imperfecta should be considered in differential diagnosis for this individual, but the absence of dentinogenesis imperfecta and survival to adulthood would restrict this potential affliction to Type I osteogenesis imperfecta.

## 4. Conclusions

MRD are considered "orphaned" due to the lack of attention they receive by scientists and medical professionals. These diseases also tend to be overlooked by paleopathologists in differential diagnosis due to the assumption that their global rarity greatly reduces the probability of finding evidence of their existence in ancient human remains. One of the goals of this study was to highlight the interregional variability of the prevalence of MRD and ARD, and the importance of their consideration in ancient populations that may have experienced substantial isolation over long periods of time.

In considering ancient Panamanian populations, a multidisciplinary assessment provided ample intersecting lines of evidence favoring the assertion of inter- and intraregional isolation in pre-contact times. Arguably, such isolation would have led to a reduction in genetic diversity, potentially amplifying the frequency of genetic mutations present in the founding population in subsequent generations. New preliminary evidence from Pre-Columbian human remains appears to coincide with this scenario, revealing an overall preponderance of developmental anomalies and several cases consistent with ARD. To further substantiate these findings, a survey of specific developmental anomalies associated with genetic etiologies is needed in order to differentiate them from bone changes linked to environmental conditions or infectious disease. The inclusion of additional individuals, specifically from the western region of Panama, would also help elucidate geographic and chronological differences in the frequencies of developmental anomalies.

More work is needed to address the question of whether individuals with ARD might have been afforded special burial, as seems to have been the case with an adolescent with a primary bone tumor recovered from the Cerro Brujo site in western Panama (Smith-Guzmán et al., 2018). Briggs' (1989) observation of a general trend for juvenile individuals to be buried with valuable material goods at sites in central Panama may also support this notion. If true, the frequency of individuals with developmental anomalies in skeletal assemblages might be misleading due to preferential preservation of these individuals from this cultural practice.

In examining the possibility that ARD existed in past populations at frequencies above the current global average requires a thorough literature review. Understanding the current epidemiological landscape can highlight potential MRD of unusually high prevalence locally. Linguistic, ethnohistorical, archaeological, and genetic data can further point to population dynamics in ancient and historic times, and provide evidence for the presence or absence of geographic or social isolation. Finally, accounting for developmental anomalies in ancient human remains, including anomalies found in isolation, can help provide a big-picture view of diseases that may be unusually common within a specific population or present on a regional scale.

## Acknowledgements

The data presented in this paper were collected during a postdoctoral fellowship funded by the Smithsonian Tropical Research Institute. Additional funding was provided by the Sistema Nacional de Investigación (SNI) of the Secretaria Nacional de Ciencia y Tecnología (SENACYT) of Panama. Osteological data collection by the author was assisted by Leslie Naranjo, Vanessa Sánchez, and Laura Schell. Thanks go to David Hunt (Smithsonian National Museum of Natural History), Julieta De Arango and Mirta Linero (Patronato Panama Viejo), Mary Suter (University Museum, University of Arkansas), and Loring Burgess (Peabody Museum of Archaeology and Ethnology) for allowing access to the human remains from institutions outside the Smithsonian Tropical Research Institute. The author would like to recognize the following archaeologists who oversaw the recovery of human remains utilized in this research: Adrian Badilla, Richard Cooke, Carlos Fitzgerald, Ilean Isaza, Olga Linares, Samuel Lothrop, Juan Guillermo Martín, Tomás Mendizábal, Álvaro Brizuela, Anthony Ranere, Luis Sánchez, Ashley Sharpe, and Tom Wake, as well as the technicians and students who formed part of the excavation crews. Helpful comments to an early version of this paper by two reviewers and an editor enhanced the clarity and depth of its content.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijpp.2021.01.002.

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