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A paleoepidemiological approach to the challenging differential diagnosis of an isolated 1500-year-old anomalous molar from Panamá

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ABSTRACT

Objective: This study seeks to quantify the presence and prevalence of specific genetic and infectious diseases in the pre-Colombian Panamanian population and uses these data to consider the plausibility of these diseases as causative factors in the development of an abnormal supernumerary cusp morphology in a 1500-year-old isolated molar recovered from Cerro Juan Díaz (Los Santos, Panama).
Materials: 267 individuals from pre-Columbian sites throughout Panama.
Methods: The anomalous tooth was analyzed through macroscopic, odontometric, and radiographic means. Tentative differential diagnosis was performed using inferences from paleopathological features of the broader regional population.
Results: The regional sample showed evidence of treponemal infection and developmental anomalies in 10.1% and 10.9% of individuals, respectively.
Conclusions: While not able to rule out three potential genetic conditions, more evidence was found to support the differential diagnosis of congenital syphilis as the causative agent leading to the development of abnormal supernumerary cusps in the isolated molar.
Significance: This study demonstrates how characterizing disease experience in the population can assist in differential diagnoses at the individual level and cautions against the assumption that any one lesion in isolation is unique to only one specific pathological condition.
Limitations: The timing discrepancy between clinical descriptions of congenital syphilis and genetic disorders, lack of knowledge on pathophysiological mechanisms of the former, poor preservation of *Treponema* pathogen ancient DNA, and deficiencies in modern public health data from Panama limit the differential diagnosis.
Suggestions for further research: Inclusion and serious contemplation of genetic diseases in paleopathological differential diagnoses is necessary.

SECONDARY ABSTRACT

Objetivo: Este estudio busca cuantificar la presencia y prevalencia de enfermedades genéticas e infecciosas específicas en la población panameña precolombina y utiliza estos datos para considerar la plausibilidad de estas enfermedades como factores causales en el desarrollo de una morfología anormal que abarca cúspides supernumerarias en un molar aislado de 1500 años de antigüedad recuperado del sitio arqueológico Cerro Juan Díaz en Los Santos, Panamá.
Materiales: 267 individuos de sitios precolombinos a lo largo de Panamá.
Métodos: El diente anómalo se analizó por medios macroscópicos, odontométricos y radiográficos. El diagnóstico diferencial tentativo se realizó considerando inferencias de las características paleopatológicas a nivel poblacional con uso de la muestra regional.
Resultados: La muestra regional mostró evidencia de infección treponémica y anomalías del desarrollo en 10.1% y 10.9% de los individuos, respectivamente.

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Conclusiones: Si bien no se puede descartar la posibilidad de tres condiciones genéticas, se encontró más evidencia para apoyar el diagnóstico diferencial de sífilis congénita como agente causal que conduce al desarrollo de cúspides supernumerarias anormales en el molar aislado.
Importancia: Este estudio demuestra cómo la caracterización de las enfermedades en la población puede ayudar en los diagnósticos diferenciales a nivel individual y advierte contra la suposición de que cualquier lesión aislada es exclusiva de una sola condición patológica específica.
Limitaciones: La discrepancia temporal entre las descripciones clínicas de la sífilis congénita y los trastornos genéticos, la falta de conocimiento sobre los mecanismos fisiopatológicos de la primera, la mala conservación del ADN antiguo del patógeno *Treponema* y las deficiencias en los datos modernos de salud pública de Panamá limitan el diagnóstico diferencial.
Sugerencias para futuras investigaciones: Es necesaria la inclusión y contemplación seria de las enfermedades genéticas en los diagnósticos diferenciales paleopatológicos.

1. Introduction

Tooth crown development is influenced both by genetic and environmental factors during the gestation and early childhood of the individual (Hughes and Townsend, 2013; Townsend et al., 2012). Teeth are arguably one of the most important biological structures due to their necessity in processing food, in turn providing energy to the body. Without teeth, survival of the individual is incredibly difficult; thus, odontogenesis and morphogenesis is governed by strict control via multiple genetic signaling pathways (Hillson, 2005; Jernvall and Thesleff, 2012). Consequently, this genetic control creates incredibly similar dental phenotypes within populations that share the same gene pool, allowing bioarchaeologists and forensic anthropologists to use metric and non-metric characteristics of teeth to estimate ancestry and biodistance in skeletal assemblages (Scott and Turner, 1997; Stojanowski and Schillaci, 2006).

Nevertheless, disruptions of normal dental development may lead to changes in expected dental crown and root morphology. These disruptions may occur as the result of genetic mutations or from environmental effects, such as infection or trauma on the developing dental structures (Brook, 2009; Townsend et al., 2012). In the case of genetic mutations, many of the induced changes to dental morphology overlap between different types of mutations, perhaps due to alterations in the same signaling pathways (Townsend et al., 2012). Further, many of the morphological changes caused by infection or trauma to the developing tooth may appear similar or identical to those caused by genetic mutations (Hoehndorf et al., 2015).

This situation presents a predicament for paleopathologists who, unlike clinical practitioners, cannot ask specific questions about disease and family histories to inform their diagnoses. Further complicating matters, researchers often refer to morphologically identical variants in the literature using various terms, the distinction of which is often based on the inferred causation or physiological manifestation of the dental aberration (de La Dure-Molla et al., 2019). This in turn leads to challenges in understanding the past and present prevalence, definition, and pathophysiology of rare forms of these anomalies, signaling that extreme caution must be taken in approaching these cases from a paleopathological perspective.

This study takes a paleoepidemiological approach in considering the case of an isolated human molar with an aberrant crown morphology from a commingled burial context at the pre-Columbian archaeological site of Cerro Juan Díaz in central Panama. Possible etiological factors leading to the development of this tooth's morphology are explored at the level of the population, including causative factors of both genetic and infectious origin. The characterization of the possible presence and prevalence of specific possible causative agents in the population are then used to assist the tentative differential diagnosis of this individual case.

2. Materials and methods

2.1. Archaeological background

The site of Cerro Juan Díaz is located on a hill on the southern banks of the La Villa River (what is today part of the province of Los Santos, Panama), approximately 5 km from the Bay of Parita on the Pacific coast (Fig. 1). The site was heavily looted in recent history, leading to one small professional excavation in 1980 by archaeologist Tomás Winter, and a much larger archaeological investigation under the direction of archaeologist Richard Cooke, spanning ten years from 1992 to 2001 and exposing contexts which date from 200 BCE to the time of Spanish contact (ca. 1500 CE; Cooke et al., 1998). A plethora of human remains representing upwards of 400 individuals were recovered during Cooke's excavations, and are currently undergoing osteological analysis by the author. A shell-bearing layer above the mortuary contexts at the site allowed for an unusually high preservation of osseous material in this tropical region, which is characterized by a preponderance of acidic soils.

The ongoing osteological analysis of the human remains from Cerro Juan Díaz is being performed systematically, having begun with the earliest mortuary contexts at the site (ca. 100–600 CE) and continuing towards the later contexts. These early funerary features are characterized by multiple secondary burials in common graves, often including patterns of mortuary space re-utilization and disruption of original grave occupants. Although the resulting high levels of commingling and fragmentation of skeletal elements presented challenges to the osteological analysis, details of disease and biocultural markers left on the bones have provided new insight into the lives of the first inhabitants of this site (Smith-Guzmán et al., 2021).

One of the early multiple secondary burial contexts at Cerro Juan Díaz is known as Feature 2 of Operation 3, excavated in 1992 by Luis Sánchez and Adrian Badilla. This context was spared between two large looter's pits, and contained at least eight bundle burials, one primary flexed burial, and a disturbed cluster of human remains likely pertaining to individuals originally buried in Feature 1, through which Feature 2 cut. Recent analysis of the remains in Features 1 and 2 revealed that at least 29 individuals are represented by the osteological material from these contexts combined, dating between 129 and 588 cal CE (Smith-Guzmán et al., 2021). At the bottom of this burial, which contained Bundles 10 and 13, as well as the continuation of the disturbed cluster, a molar tooth with an abnormal crown morphology was found in apparent association with Bundle 13 (see Fig. 2).

However, the association of this tooth with the individual in Bundle 13 was not confirmed due to the challenging nature of the excavation. Sánchez noted a lack of clear separation between the individuals at the bottom of the tomb and related the necessity of rapid excavation without enumerating the elements removed due to a heavy downpour as the contents of Bundles 10 and 13 were being removed (Sánchez Herrera, 1992). It is also possible that this tooth came from one of the individuals located superficially, as nearly all individuals interred comprised either

secondary or disturbed burials. An attempt was made to re-associate the tooth with a mandible or maxilla from the same burial context; however, fitting the tooth into a preserved socket was not possible due to the postmortem damage of the root, and there were no other teeth present of similar size or morphology. Therefore, this tooth was analyzed here as an isolated entity without confirmed association with any other dental or skeletal remains.

2.2. Odontological and osteological features of associated individuals

The anomalous tooth was stored with the remains of the individual buried in Bundle 13 of Feature 2, who was estimated to correspond to a female over the age of 50 years at death (Smith-Guzmán et al., 2021). This individual was only missing the anterior maxillary teeth, the left maxillary third molar, and the right mandibular third molar. However, all teeth associated with this individual were much smaller in size than the molar with the abnormal crown morphology, leaving room for doubt as to the association of this tooth with this individual. No maxillary fragments belonging to this individual were recovered from this bundle burial. The mandible contained a dental anomaly consisting of an inverted left mandibular third molar that was embedded (Smith-Guzmán et al., 2021, Fig. 6c). The crown of this third molar contained a normal "Y-5" cusp pattern.

Adjacent to Bundle 13 was Bundle 10, which contained a male over the age of 50 with extensive periosteal reactions and abnormal bone apposition that affected nearly all of the long bones and resulted in generalized thickened cortical bone, often punctuated with circular focal cavitations, and slight anterior pseudo-bowing of the tibiae (Smith-Guzmán et al., 2021, Fig. 8). The bilateral nature of the periosteal reactions and diaphyseal enlargement and anterior apposition of bone on the tibiae is suggestive of treponemal disease (Baker et al., 2020; Buikstra, 2019; Hackett, 1976; Harper et al., 2011). The dentition of the individual in Bundle 10 was characterized by the antemortem loss of nearly all mandibular teeth (excluding the right canine and first premolar), as well as the antemortem loss of all left maxillary molars. The right side of the maxilla was not present, and thus, could have potentially housed the molar with abnormal crown morphology. However, this is not likely, in the opinion of the author, as the only tooth recovered from Bundle 10—the left maxillary canine—contained a heavily worn occlusal surface.

Other dental anomalies found present in the other teeth recovered from Feature 2 include mesial bending of the left lateral maxillary incisor from Bundle 5 resulting in a tilted appearance of the crown toward the mesial aspect from the long axis of the root (Smith-Guzmán et al., 2021, Fig. 6b). This incisor also contains an interruption groove extending from the mesial aspect of the root onto the enamel of the tooth, as well as a horizontal ridge on the labial root surface. The left maxillary first premolar of this individual is also rotated 45-degrees towards the mesial aspect.

2.3. Dental analysis and regional comparison

The anomalous tooth was analyzed macroscopically, and its morphology documented and compared with other reports of similar anomalous teeth in both the clinical and paleopathological literature. This macroscopic analysis was accompanied by an odontometric characterization of the tooth, followed by radiographic assessment. Odontometric characterization included six standard and alternative dental measurements (Buikstra and Ubelaker, 1994; Hillson et al., 2005): crown height, buccolingual crown diameter, mesiodistal crown diameter, buccolingual cervical diameter, mesiodistal cervical diameter, mesiolingual-distobuccal crown diameter, and mesiobuccal-distolingual crown diameter. Additionally, two measurements of the occlusal surface were taken, which were defined by the author as follows: the maximum distance between the buccal and lingual cusp tips (buccolingual occlusal diameter) and the maximum distance between the mesial and distal cusp

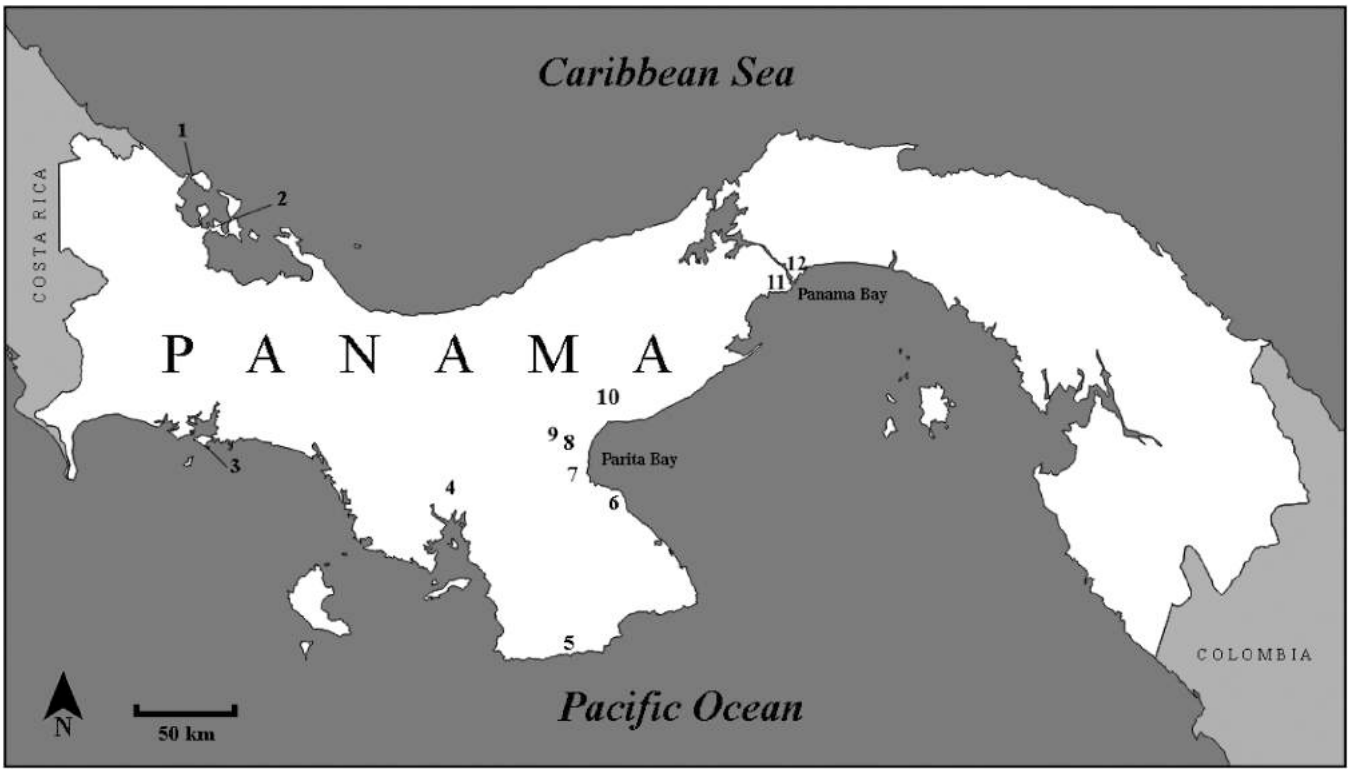

Fig. 1. Map of Panama showing the location of archaeological sites from which the human remains used in this study were recovered. Sites are numbered as they appear on the map from West to East: 1 – Sitio Drago, 2 – Cerro Brujo, 3 – La Pitahaya, 4 – Río de Jesús (Ve-7), 5 – Punta Blanca, 6 – Cerro Juan Díaz, 7 – Sixto Pinilla (He-1), 8 – Cerro Girón, 9 – Sitio Sierra, 10 – Sitio Conte, 11 – Playa Venado, 12 – Panama Viejo. Map created by Nicole Smith-Guzmán.

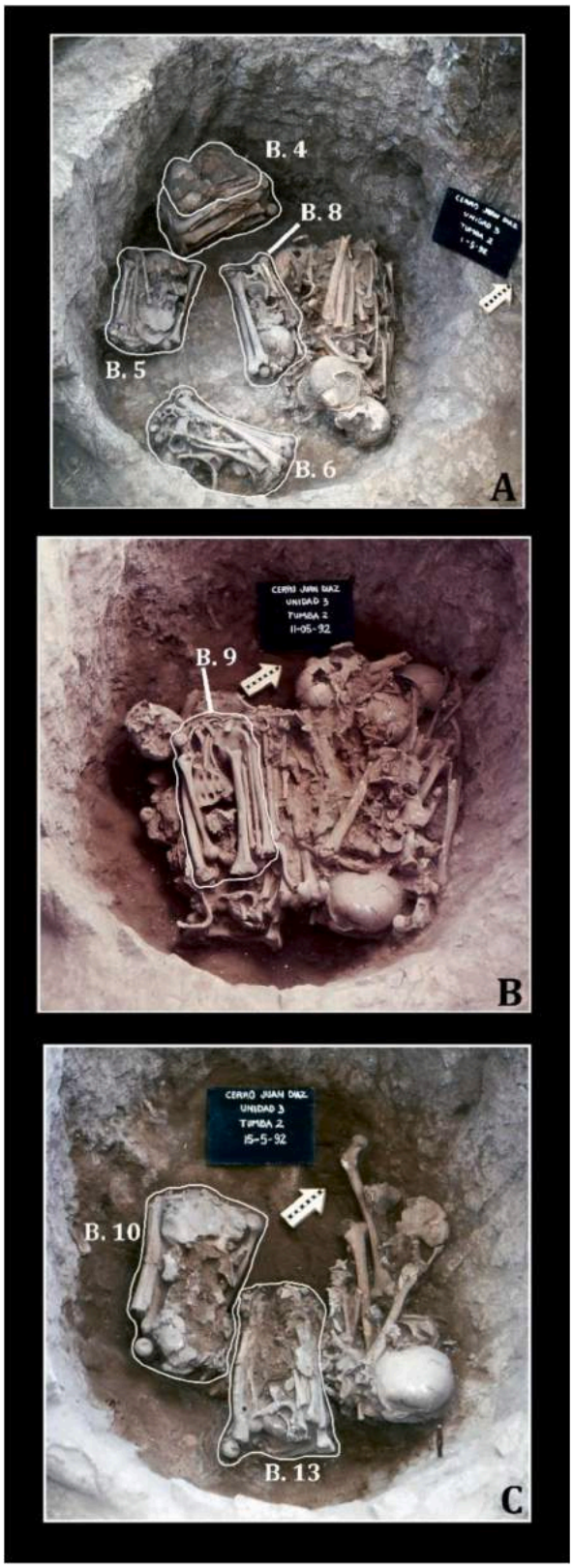

Fig. 2. Field photographs of three sequential phases of excavation of Feature 2 from Operation 3 at Cerro Juan Díaz. Human bundle burials within each phase are outlined in white and identified by their specific number. Panel C shows the last phase of excavation at the bottom of the burial feature wherein the aberrant tooth was found. Photographs by Luis Sánchez and Adrian Badilla.

tips (mesiodistal occlusal diameter). Measurements were taken for all other molars from the Feature 2 context and compared with of the isolated molar. All measurements were taken to the nearest 0.01 mm with a Mitutoyo 573 Series Absolute Point digital caliper.

Due to the isolated nature of this tooth, a differential diagnosis based on other skeletal and dental features found in the same individual is not possible. In an attempt to understand the potential for infectious or genetic diseases leading to the aberrant morphology of this tooth, this study utilized data from a previous survey of hard-tissue anomalies potentially associated with genetic disorders in a sample of 267 individuals from 12 pre-Columbian sites across Panama (Smith-Guzmán, 2021), with the addition of new data on osseous evidence of treponemal infection from the same regional sample (see Table 1 for site details). This multi-site perspective provides a way to bolster the findings of the differential diagnosis for the isolated anomalous tooth at a regional level. Further, the broader assemblage used should function as an unbiased sample of the overall regional population, since the majority of the individuals originate from common community burial grounds that are thought to contain local individuals of various demographic and social affiliations (Sharpe et al., 2021; Smith-Guzmán and Cooke, 2018; Smith-Guzmán et al., 2021, 2022).

During the basic osteological assessment of the regional sample, age and sex estimations were made for each individual using the following criteria. For non-adults, age was estimated using the dental development stage preferentially (AlQahtani et al., 2010); however, epiphyseal closure and long bone length were used when the teeth were not observable (Cunningham et al., 2016). In fully-developed adult individuals, the morphological changes of the pubic symphysis and the auricular surface of the pelvis were used preferentially (Brooks and Suchey, 1990; Lovejoy et al., 1985), while cranial suture closure stages were used in the absence of observable pelves (Meindl and Lovejoy, 1985). Sex was only estimated on individuals over the age of 15 years, and utilized the five-scale morphological differences in the pelvis laid out in Buikstra and Ubelaker's (1994) *Standards* text, with emphasis placed on the Phenice (1969) traits of the pubis where observable. In the absence of pelves, sex estimation used cranial morphological differences (Acsàdi and Nemeskéri, 1970) but proceeded cautiously given the cranial modification practices in the Central Panama region

Table 1
Site and sample size data for individuals included in the regional pre-Columbian Panamanian sample.

Site	Location	Date range	Sample size
Sitio Drago	Western Caribbean Panama	892 – 1262 CE	2
Cerro Brujo	Western Caribbean Panama	1267 – 1388 CE	1
La Pitahaya	Western Pacific Panama	893 – 1026 CE	9
Río de Jesús (Ve-7)	Central Pacific Panama	[unknown: ceramic period]	1
Punta Blanca	Central Pacific Panama	1047 – 1261 CE	4
Cerro Juan Díaz (early)	Central Pacific Panama	33 – 648 CE	50
Sixto Pinilla (He-1)	Central Pacific Panama	[500 – 800 CE]	4
Cerro Girón	Central Pacific Panama	[200 BCE – 500 CE]	4
Sitio Sierra	Central Pacific Panama	39 BCE – 1158 CE	48
Sitio Conte	Central Pacific Panama	[800 – 1200 CE]	8
Playa Venado	Eastern Pacific Panama	223 – 565 CE	74
Panamá Viejo (pre-contact)	Eastern Pacific Panama	545 – 1479 CE	62
Total			267

(Smith-Guzmán et al., 2021; Smith-Guzmán et al., 2022).

Briefly, the dental anomalies recorded in the regional survey recorded the presence of any developmental defect in the teeth, which included molars having supernumerary occlusal cusps, incisors with notched incisal edges, dental transposition, root flexion, supernumerary teeth, congenital absence of teeth, ectopic eruption, and defective enamel (outside the realm of the common stress-induced hypoplastic defects). Ectopic eruption and congenital absence of third molars were not considered in this study due to the common occurrence of impaction and congenital absence of these teeth. It should be noted that some cases of root flexion or ectopic eruption of supernumerary teeth may have been concealed within the alveolar bone and missed by the observers; thus, the frequencies of these anomalies are minimum counts, but are nonetheless useful as conservative indicators of actual prevalence.

Skeletal developmental anomalies included in the survey consisted of sternal foramina, fusion of contiguous ribs, fusion of contiguous vertebrae, facial clefting, precondylar tubercles (mild cranial shifting of the occipital-cervical border; cf. Barnes, 2012, fig. A-5.3.2)), unfused sternal elements in mature individuals, neural arch clefting in vertebrae, and long bone bending deformities (excluding anterior bowing consistent with saber shin). The anomalies comprise all of the observed anomalies consistent with developmental defects noted during routine osteological analysis of the sample population. Absence, fragmentation, and taphonomical damage to the cortex of skeletal elements may have prevented the observation of some of these anomalies in many of the individuals analyzed; thus, frequencies of these anomalies again represent minimum counts within the population.

Evidence for skeletal manifestation of treponemal disease followed standards laid out for meta-analyses of treponemal prevalence in which individuals are divided into categories by pathological lesions consistent with or strongly suggestive of treponemal disease (cf. Harper et al., 2011 and Baker et al., 2020). For the pre-Columbian Panamanian individuals, at least one tibia had to be present and observable to be scored for periosteal reaction. Individuals with bilateral periosteal reaction affecting the long bones, including the tibiae minimally, which appeared to be the result of a systemic inflammatory process were considered "consistent with" treponemal infection. Individuals deemed with higher confidence to have lesions "strongly suggestive of" the severe sequelae of treponemal infection during life included those with cranial lesions consistent with Hackett's (1976) characterization of caries sicca, as well as those with tibiae containing anterior apposition of bone (i.e., "saber shin") or enlarged diaphyses with nodes and superficial cavitation as characterized by Hackett (1976). The author prefers not to use the "pathognomonic" categorization of lesions used by other researchers given that other pathological conditions (potentially including those not yet described in the paleopathological literature) may cause very similar lesions.[1] Therefore, individuals containing these "pathognomonic" lesions were placed within the category of lesions "strongly suggestive of" treponemal disease. If, indeed, only 5–15% of infected individuals will go on to develop skeletal lesions in the tertiary stage of yaws or syphilis (Ortner, 2003), frequencies of lesions consistent with and strongly suggestive of treponemal disease in this ancient sample should represent a conservative figure of overall infection prevalence within the population.

[1] There appears to be some disagreement regarding the definition of the term "pathognomonic" as used within paleopathology. According to the unpublished document entitled "Nomenclature in Paleopathology," which is advocated for by the Paleopathology Association and hosted on their website (Manchester et al., 2016, p. 28), this term refers to "pathological features characteristic of (but not exclusive to) a specific disease." However, a recent publication addressing the paleopathology of treponemal disease defines the term as follows: "A pathognomonic lesion is one that occurs only in a single condition" (Baker et al., 2020, p. 28).

3. Results

The morphological characteristics of the isolated molar tooth include an outer ring of ten cusplets of variable heights, which terminate into 16 occlusal pits that encircle a conical central cusp (see Fig. 3). The crown reaches its greatest width (maximum crown diameters of 14.65 mm mesiodistal and 13.03 mm buccolingual) at a distance of 2.06 mm from the cemento-enamel junction (CEJ), or around one-third of the total crown height. The occlusal aspect is constricted (10.00 mm mesiodistal occlusal diameter). There was no evidence of a linear hypoplastic defect to the enamel surface; however, the pits within the occlusal surface of the tooth appear to represent non-carious hypoplastic defects. The occlusal surface of the tooth did not contain any observable wear facets, suggesting that it was not in proper occlusion, either due to the tooth being unerupted (i.e., impacted or embedded) within the alveolar bone or from the absence of the molar in the opposing jaw, or that the tooth had only recently erupted in the mouth of a very young individual.

The abnormal crown morphology of this tooth and its unobservable

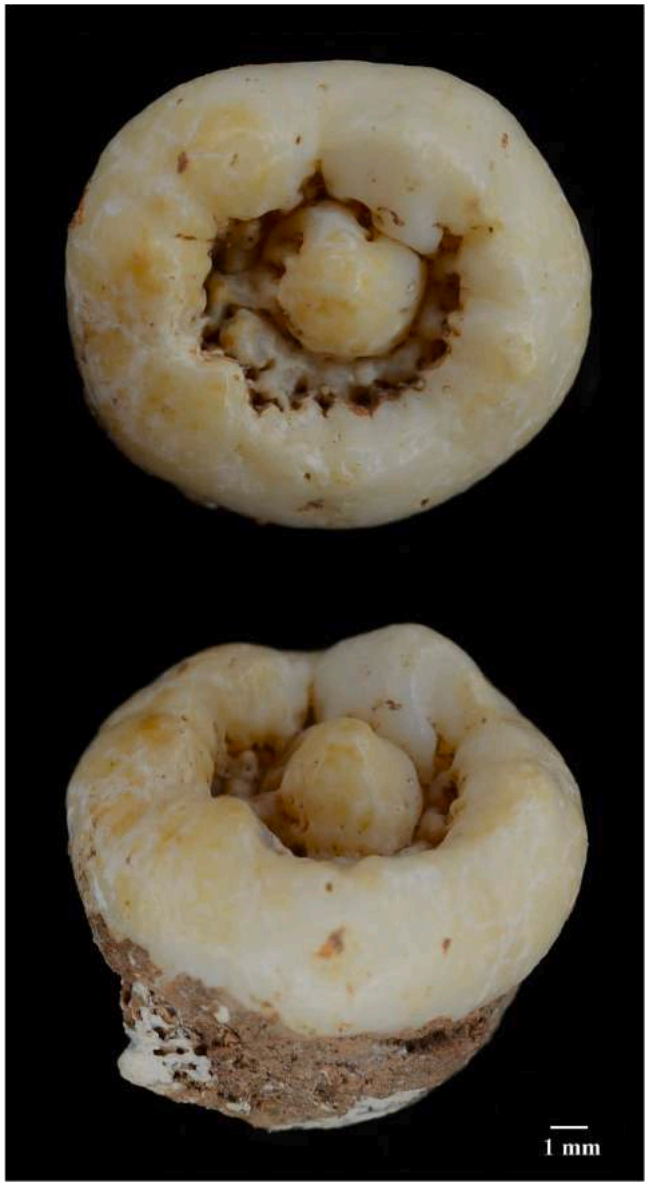

Fig. 3. Molar with abnormal supernumerary occlusal cusp morphology recovered from Feature 2 of Operation 3 at Cerro Juan Díaz, shown in both occlusal (above) and lateral oblique (below) aspects. Photographs by Raiza Segundo.

root morphology due to postmortem damage presented a challenge in discerning its specific position in terms of maxillary or mandibular arch and number (i.e., first, second, or third molar). The radiographs (Fig. 4) show a pulp chamber that appears to lead to a single root canal, suggesting that this molar contained a single, fused root – a morphology seen more commonly in third molars, generally (Scott and Irish, 2017). The radiographs also show pulp horns at the buccal, lingual, mesial, and distal aspects, but a flat roof to the pulp chamber with no sign of pulp extension to the central cusp, nor an internal structure suggestive of a dens-in-dente (tooth within a tooth) or dental fusion that might explain the appearance of this cusp (de Siqueira et al., 2004).

In comparing the metric characteristics of this molar with those of all permanent molar teeth from other individuals with measurable teeth within the same temporal context at Cerro Juan Díaz (n = 88), the anomalous molar appeared as an outlier in its mesiodistal cervical and crown dimensions, and was at the upper limits of the distribution for buccolingual cervical and crown dimensions (Figs. 5 and 6). That its mesiodistal crown diameter is more than two standard deviations above the mean of the comparative sample molars for each type of molar places this tooth within the realm of macrodontia (de La Dure-Molla et al., 2019, p. 1962).

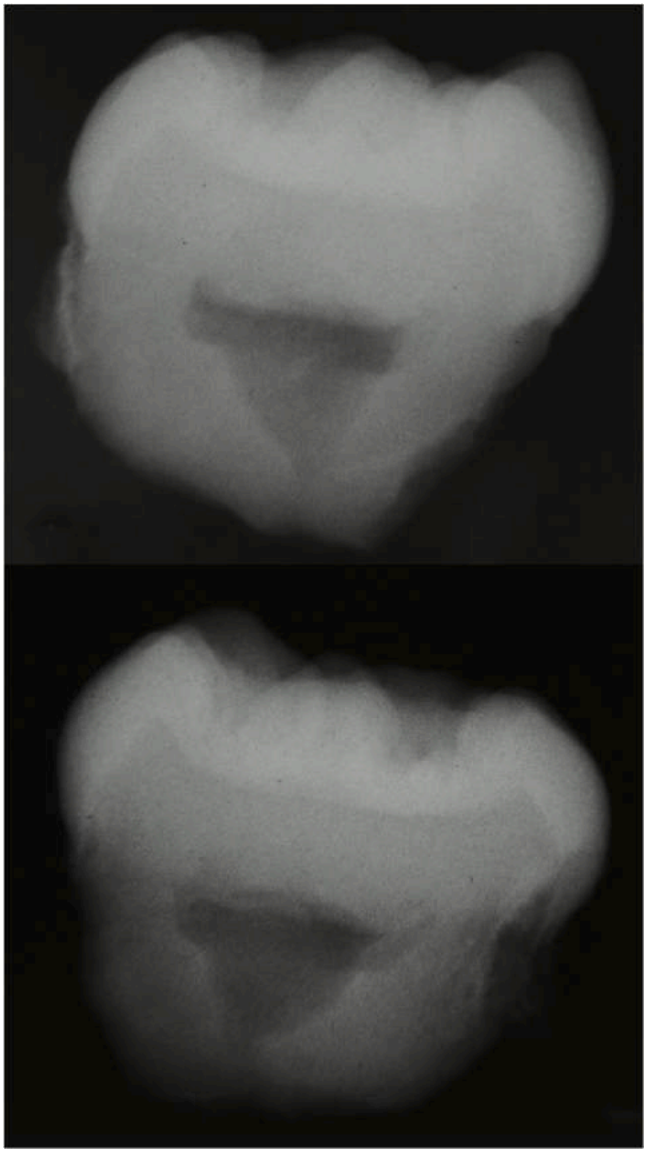

Fig. 4. Radiographs of the aberrant molar tooth from mesiodistal (above) and buccolingual (below) aspects.

3.1. Populational evidence of treponemal disease and developmental anomalies

Descriptive statistics were performed to identify the demographical characteristics of the pre-Columbian Panamanian sample used in this study (Fig. 7 and Tables S1 and S2). While both males and females are represented fairly evenly in the sample, there is a significant association between sex and age group when considering individuals over 14 years and of determinate age and sex (Chi-square = 8.903, df = 3, p = 0.031). This association is driven by a preponderance of middle adult males in the sample (28 individuals, representing 26.4% of the total 106 individuals of determinate age and sex considered). Although this demographical bias should be noted, there were no statistical differences between age or sex among adult individuals with evidence for developmental anomalies or treponemal lesions, as detailed in the paragraphs to follow.

Out of the 267 individuals in the sample population, 212 individuals contained at least one permanent tooth upon which to identify dental anomalies (comprised of 187 individuals with at least one anterior tooth and 203 individuals with at least one posterior tooth). Of this sample, 17 individuals (8.1%) had at least one dental anomaly, with the majority containing only one type of anomaly (11 individuals), and six individuals with two different types of dental anomalies. The majority of the 15 individuals showing signs of skeletal anomalies were affected by only one type of anomaly. However, five individuals contained multiple dental and skeletal anomalies suggestive of an underlying genetic syndrome (Smith-Guzmán, 2021). In total, 29 individuals were affected by skeletal or dental anomalies, comprising 10.9% of the total 267 individuals included in the study. This frequency is certainly an underestimate of prevalence given the issues of fragmentation and missing elements in many individuals in the sample, suggesting an unusually high rate of both skeletal and dental developmental defects in the sample population when comparing with prevalence rates from modern global epidemiological data (Anthonappa et al., 2012; Choi et al., 2017; Duque Parra et al., 2018; Hirst et al., 2020; Laganà et al., 2017; Lewis, 2019; Mastroiacovo et al., 2011; Oluwatoyin Folayan, 2019; Papadopoulos et al., 2010; Smith-Guzmán, 2021).

A total of 43 out of 121 observable individuals (35.5%) showed signs of periosteal reaction, of which only 29 were considered observable for treponemal infection. Of these 29 individuals, 14 (48.3%) were able to be placed within the category of “consistent with” treponemal disease, while a further 12 individuals (41.4%) had pathological lesions that were “strongly suggestive of” treponemal infection and the remaining three individuals (10.4%) did not meet the criteria for possible treponemal disease. Table S1 in the supplementary materials provides detailed information on the demographic characteristics and specific lesion types for each individual that showed signs of treponemal disease in the regional sample.

The majority of the 12 individuals with lesions considered strongly suggestive of treponemal disease showed the characteristic “saber shin” anterior apposition of bone on the tibiae (11 individuals, or 91.7%). Seven individuals (53.8%) showed enlarged diaphyses of the long bones characterized by undulating cortical surfaces suggestive of healed focal lesions, with the tibiae most severely affected. Four individuals (30.8%) also showed focal cavitations on these enlarged diaphyses. Two individuals (1.5% of 130 individuals total for which at least one fourth of the frontal bone was observable) had lesions characteristic of caries sicca of the cranium. The postcranial skeleton of one of these individuals with cranial lesions was unobservable and, thus, represents an additional individual with lesions strongly suggestive of treponemal disease, bringing the total count to 13 affected individuals in the sample studied when combined with the aforementioned 12 individuals with periosteal reactions on the long bones. Fig. 8 presents examples of the three pathological lesions considered suggestive of treponemal disease on human remains from the regional sample from Panama.

To consider the prevalence of treponemal disease, frequencies of

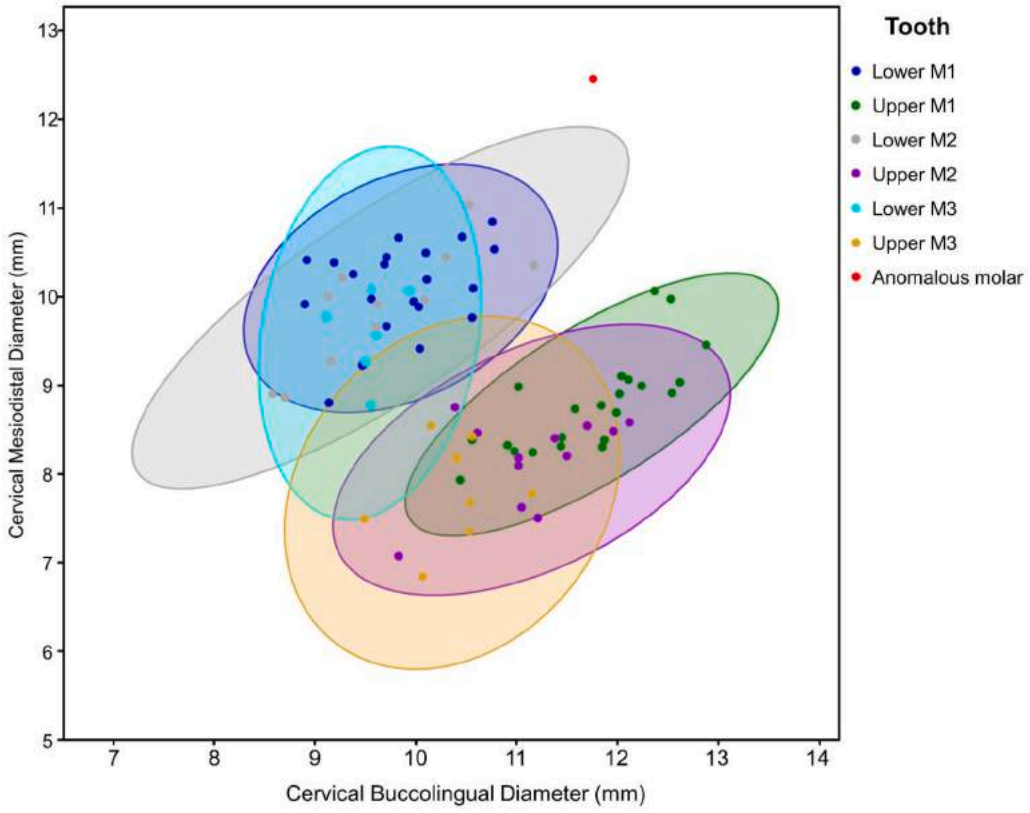

Fig. 5. Scatterplot showing a comparison of cervical diameters of molars from within Features 1, 2, and 16 from Operation 3 at Cerro Juan Díaz (n = 88). Shaded ellipses represent the 95% confidence interval around the centroid for each molar type by arch and position. Note that the anomalous molar (shown in red) represents an outlier.

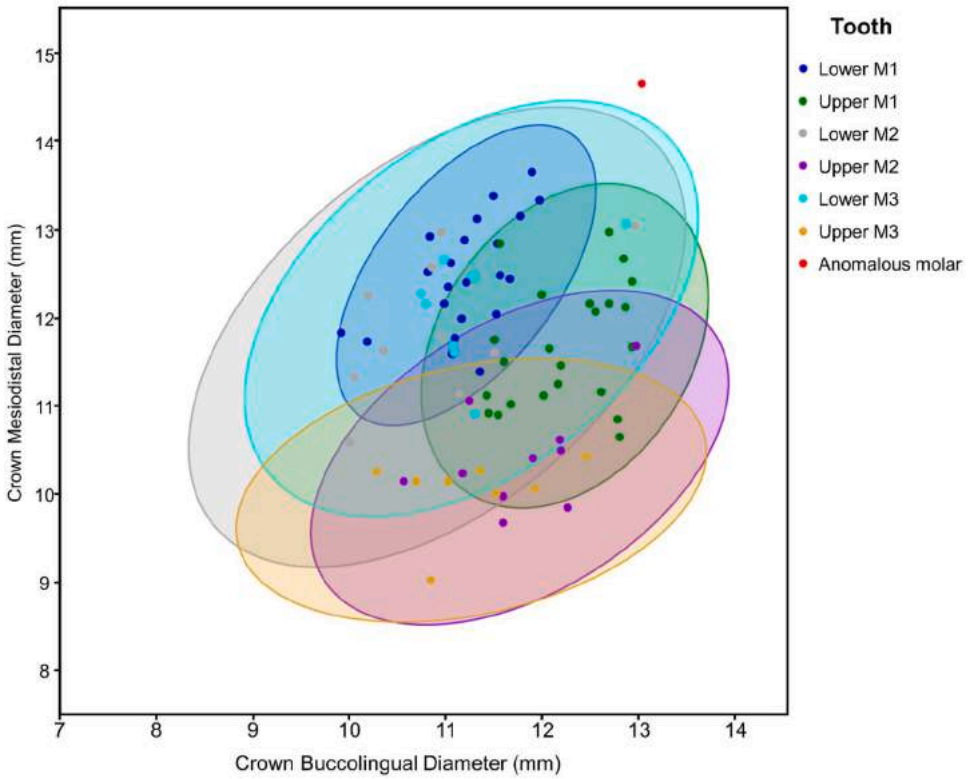

Fig. 6. Scatterplot showing a comparison of crown diameters of molars from within Features 1, 2, and 16 from Operation 3 at Cerro Juan Díaz (n = 88). Shaded ellipses represent the 95% confidence interval around the centroid for each molar type by arch and position. Note that the anomalous molar (shown in red) represents an outlier.

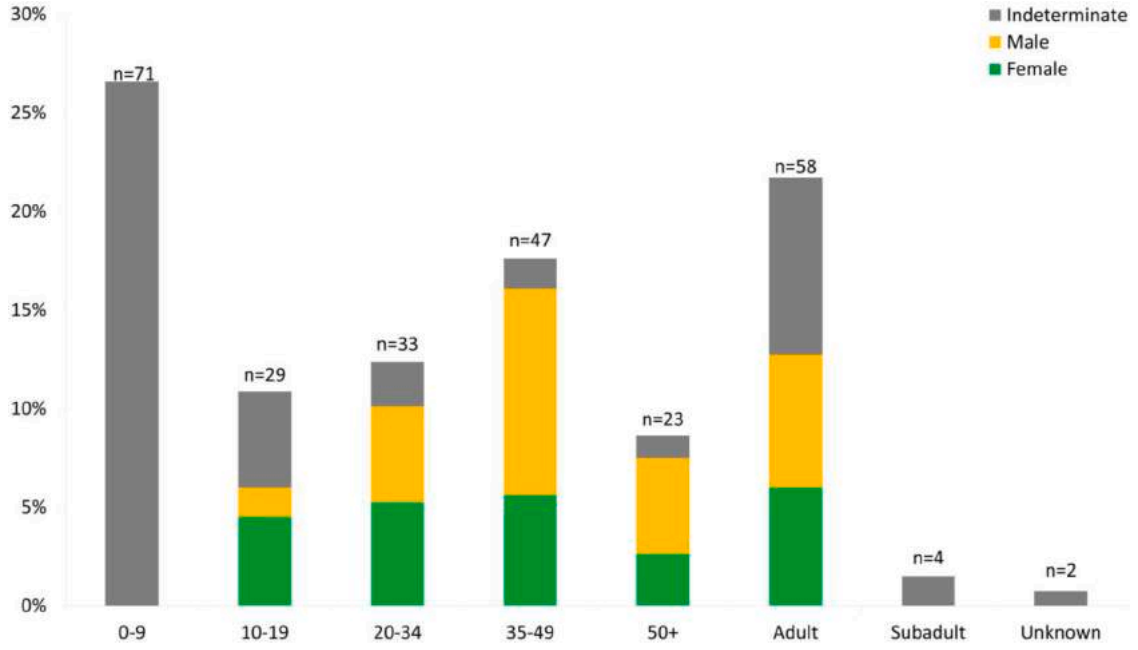

Fig. 7. Demographical characteristics of individuals included in the regional pre-Columbian Panamanian sample. See Tables S1 and S2 in the Supplemental Materials for age and sex distributions by site.

individuals with lesions consistent with and strongly suggestive of the disease out of the total number of individuals in the sample provide a conservative estimate. This is a particularly cautious estimate considering many individuals were represented by a limited number of skeletal elements observable for pathological lesions. Nevertheless, of the total sample of 267 individuals, the 14 individuals with lesions consistent with treponemal disease represent 5.2%, and the 13 individuals with lesions strongly suggestive of the disease represent 4.9%. Thus, if individuals consistent with and strongly suggestive of treponemal disease are considered together, they represent 10.1% of the total sample population. Bearing in mind that this 10.1% figure is undeniably affected by known biases in the observability of skeletal elements and the age of the individuals in the sample (since children and infants are unlikely to show the lesions considered herein), it is reasonable to infer that a large proportion of the population was affected by this disease. The specific prevalence estimates for both congenital anomalies and treponemal disease within the overall regional sample and within the four sites containing the largest number of individuals in the sample are given in Fig. 9.

Four individuals within the regional sample showed signs of both treponemal disease and congenital anomalies. Two of these were categorized as having periosteal reactions consistent with treponemal disease, and two had lesions strongly suggestive of the disease. The former group includes Skeleton A-4, a 40–50-year-old male from the late cemetery at Sitio Sierra with periosteal reactions affecting primarily both tibiae and clavicles, and whose mandible featured an ectopic supernumerary tooth that was rotated 180-degrees within the alveolus. It is important to note that anterior bowing in the tibiae of this individual was unobservable due to fragmentation and incompleteness of these bones. The second individual in the "consistent with" treponemal disease category is Individual 2 (a 35 + year old male) from Urna B2, recovered from Parque Morelos at Panama Viejo. In addition to healed periosteal reaction affecting both tibiae and femora, this individual had an ectopic supernumerary peg tooth positioned superior to the root apices of the left maxillary dentition with the long axis along the transverse plane (i.e., just inferior to the floor of the nasal cavity).

The two individuals with pathological lesions strongly suggestive of treponemal disease who also showed signs of congenital anomalies of the dentition or skeleton both originate from the Playa Venado site: Skeleton 13 from Area A-7 W and Skeleton 16 A from Area C-4. The former, a 19–23-year-old female, showed widespread periosteal reactions of upper and lower limb bones and extremities, associated with an overall enlarged, undulating appearance of the bones. The distal humeri showed bilateral bending deformities of the distal third toward the anterior aspect. The latter individual pertained to a 35 + year old individual of ambiguous sex for which only the skull and cervical vertebrae were recovered and available for study. Nevertheless, this individual showed clear signs of both active and healing phases of caries sicca on the cranium, and congenital fusion of the 2nd and 3rd cervical vertebrae along the vertebral arch.

Although it is known that congenital syphilis often leads to developmental anomalies, particularly involving the dentition, the anomalies present in these four individuals do not align with those reported in the clinical literature as being associated with the congenital form of the disease. Furthermore, statistical analysis failed to reveal any significant associations between individuals with signs of treponemal disease and those with developmental anomalies in the sample (χ^2 =1.819, df=1, p = 0.177). Thus, there is no evidence to suggest any particular causal association for the comorbidities detailed in the above paragraphs.

4. Discussion

The regional survey of ancient human remains from sites across Panama found evidence for treponemal infection in 10.1% and developmental anomalies in 10.9% of the 267 individual sample. Intrasite frequencies varied and there was no statistical association between the two conditions in the sample. The hard tissue indicators for both of these conditions are likely underestimates of actual condition prevalence, suggesting that neither treponemal disease nor developmental anomalies can be ruled out as plausible causative agents for the abnormal molar from Cerro Juan Díaz. The potential causes of the anomalous dental crown morphology characterized by this isolated tooth are considered in the paragraphs to follow.

Supernumerary cusps in molar teeth are often caused by genetic mutations associated with certain disorders. Specifically, Nance-Horan syndrome (MIM #302350), Goltz syndrome (or focal dermal hypoplasia; MIM #305600), and Ellis-van Creveld syndrome (MIM #225500) have all been implicated in the development of central occlusal cusps

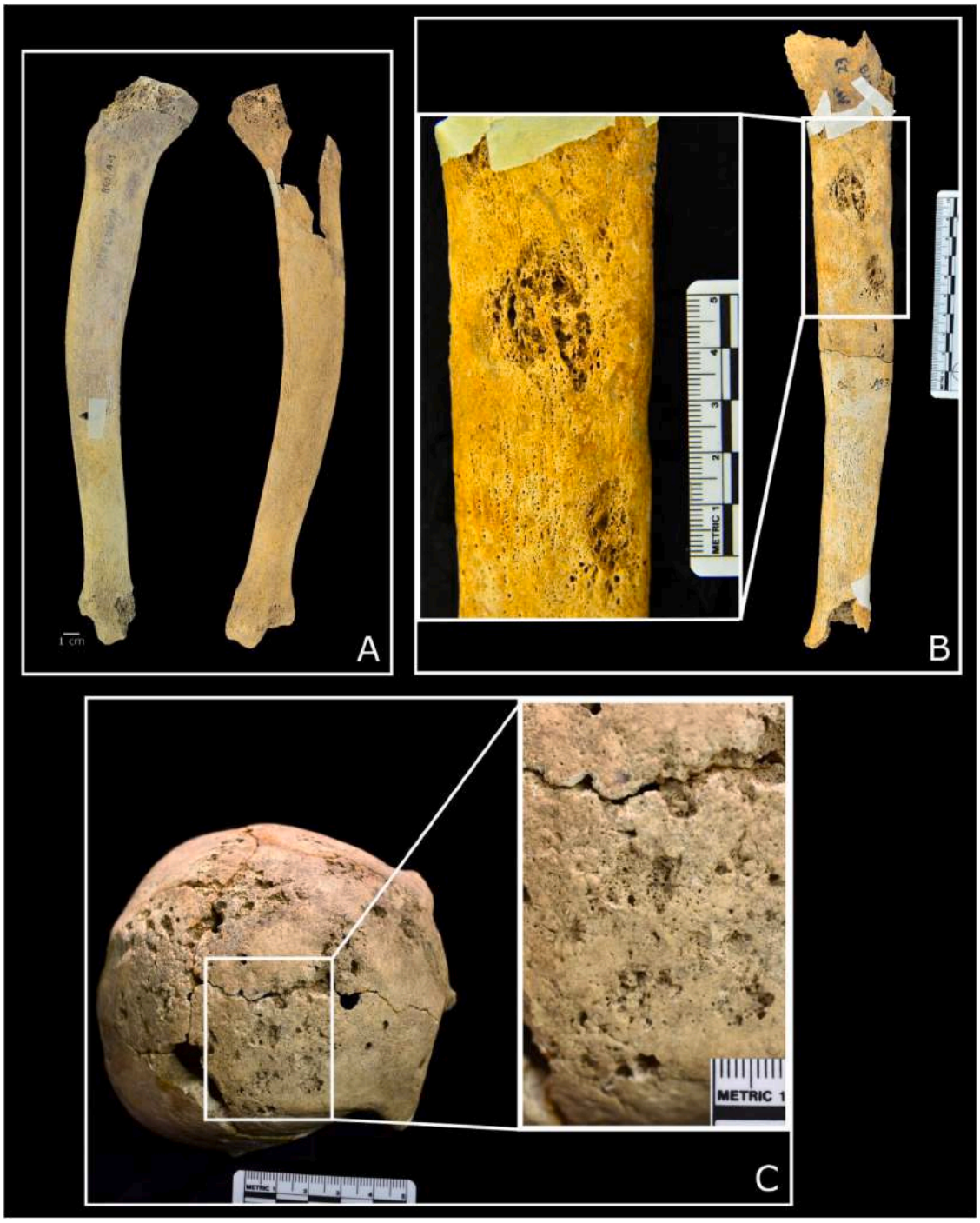

Fig. 8. Examples of pathological lesions strongly suggestive of treponemal disease within the regional sample from Panama. A - Medial views of the right and left tibiae from Skeleton A-1 from Sitio Sierra showing anterior bone apposition and bowing consistent with bilateral "saber shin" tibiae; B - Medial view of the left tibia of Skeleton B-23 from Sitio Sierra showing an enlarged diaphysis with nodes and active superficial cavitation; C - Superior oblique view of the cranium of Skeleton C4–16 from Playa Venado showing "caries sicca" lesions in both active and healing stages. Photographs by Leslie Naranjo (A) and Nicole Smith-Guzmán (B and C).

and supernumerary cusps in the posterior teeth (Gjørup et al., 2017; Hibbert, 2005). Other, more poorly understood rare inherited conditions have also been implicated in the formation of supernumerary cusps on molar teeth. A mutation of the gene *CACNA1S* (MIM #114208) was determined to cause such dental anomalies in a group of five non-consanguineous families from Thailand (Laugel-Haushalter et al., 2018). Molar teeth appearing morphologically identical to the anomalous molar discussed in this paper have often been reported in clinical cases of lobodontia (MIM %187000), an inherited disorder of uncertain etiology (Kocsis et al., 2002, Fig. 5).

However, in many cases, concurrent supernumerary and central occlusal cusps on molars have been reported in patients with no reported associated syndrome (Nagaveni and Umashankara, 2013, Fig. 1). The tooth reported on therein is similar in many ways to the anomalous molar from Cerro Juan Díaz, including the radiographic evidence of the lack of pulpal extension into the central cusp and the presence of a single, fused root. Interestingly, the authors also note that all cusps of the anomalous molar in this 56-year-old patient were unaffected by attrition, and that its antimere was congenitally absent.

Congenital syphilis is another agent commonly implicated in

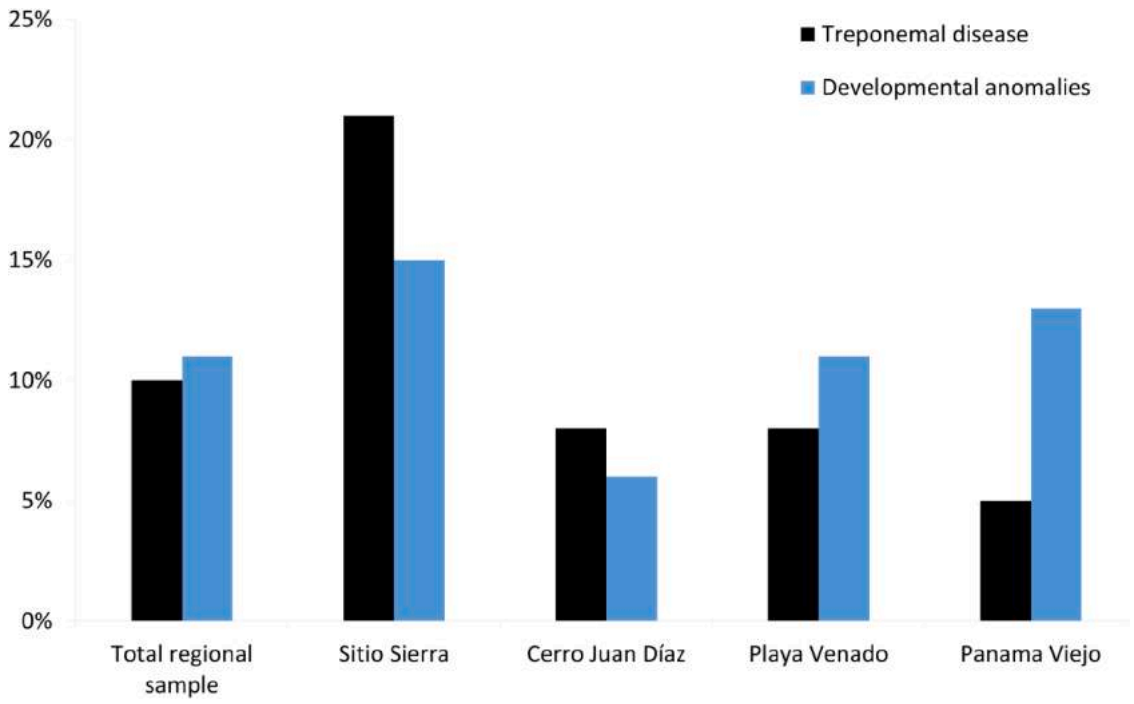

Fig. 9. Approximate prevalence estimates of treponemal disease and developmental anomalies within the total regional Panamanian sample, and at four sites with large (n > 30) sample sizes.

Table 2
A compilation of known dental and skeletal anomalies of reported association with (+) or characteristic of (++) congenital syphilis and five genetic syndromes associated with the development of bud-shaped (Moon's) molars, and a cross reference of the presence (✓), absence (×), or unobservability (?) of these hard tissue defects among the pre-Columbian Panamanian sample[a].

Hard tissue defect	NHS	FDH	EVC	CACNA1S	Lobodontia	Congenital syphilis	Panamanian sample
Dental							
Bud-shaped (Moon's) molars	++	+	+	+	+	++	✓
Mulberry (Fournier's) molars						+	✓
Notched (Hutchinson's) incisors	++					++	✓
Talon cusp		+	+		+		×
Conical anterior teeth	+		+	+	++		×
Hyperdontia	+	+	+	+			✓
Irregular diastemas	+	+	+	+			✓
Hypo-/oligodontia	+	+	+	+	+		✓
Enamel hypoplasias	+	+	+			+	✓
Blaschko vertical linear enamel defects		++					×
Microdontia	+	+	+		+		×
Taurodontism	+	+	+	+	+		✓
Ectopic eruption		+					✓
Fused teeth		+	+				✓
Dental transposition			+				✓
Skeletal							
Scoliosis	+	+					✓
Spina bifida	+	+					✓
Short fingers	+		+				×
Frontal bossing	+		+			+	✓
Cleft lip/palate		+	+				✓
Ectro-/syn-/poly-/oligodactyly		+	+				×
Osteopathia striata		+					?
Microcephaly		+					×
Genu valgum			+				✓
Short ribs			+				×
Short limbs			+				×
Flared scapulae						+	?
Periostitis/tibial bowing						+	✓
Enlarged sternal end of clavicle (Higouménakis' sign)						+	✓
Focal necrosis of medial aspect of proximal tibiae (Wimberger's sign)						+	?

[a] NHS=Nance-Horan syndrome; FDH=focal dermal hypoplasia (Goltz-Gorlin syndrome); EVC=Ellis-van Creveld syndrome; CACNA1S=yet unnamed syndrome caused by mutation of the CACNA1S gene (cf. Laugel-Haushalter et al., 2018). It should be noted that skeletal manifestations associated with CACNA1S and lobodontia are not currently known.

provoking the development of molar teeth with an anomalous supernumerary cusp morphology, also characterized by a bulbous crown that is widest near the CEJ and narrowest at the occlusal aspect (Hillson et al., 1998; Moon, 1877). Many paleopathologists consider molars of this form to be "pathognomonic" for congenital syphilis (Baker et al., 2020; Buikstra, 2019; Ioannou et al., 2016; Lewis, 2017), probably due to the assumption that the potential for genetic causation of supernumerary occlusal molar cusps is very rare, and that in areas where venereal syphilis was endemic, congenital syphilis would have been common in the past.

4.1. Differential diagnosis

To narrow down the list of possible infectious or genetic causative factors in this case, all hard tissue anomalies characteristic of both congenital syphilis and the implicated inherited syndromes were compared with the anomalies seen in the Panamanian regional survey (Table 2). Although all of these conditions may lead to the development of multi-cusp or "bud" molars, rarely is this hard tissue manifestation found in isolation. Thus, the patterning of anomalies throughout the dentition and skeleton is fundamental to differential diagnosis between these. Further, the presence and especially absence of these other hard tissue anomalies in the regional pre-Columbian sample from Panama provides a way to weigh the likelihood of each as a causative agent in the case of the molar from Cerro Juan Díaz.

Dental anomalies common in many of the genetic syndromes but absent in ancient Panama include talon cusp, conical incisors (highly characteristic of lobodontia), Blaschko vertical linear enamel defects (highly characteristic of focal dermal hypoplasia), and microdontia. Thus, lobodontia and focal dermal hypoplasia are unlikely to have provoked this anomalous tooth. Several of the other hard tissue anomalies seen in Nance-Horan syndrome (NHS) and Ellis-van Creveld syndrome (EVC) have not been noted among the ancient Panamanian skeletal remains, including shortening or changes in the number of fingers and toes, and shortening of the limbs and ribs. Potential skeletal effects associated with the dental anomalies caused by a mutation of the CACNA1S gene have not yet been described in the literature.

While the absence of several of these characteristic skeletal anomalies would seem to rule out these genetic syndromes, it is notable that several of the dental and skeletal anomalies common in these syndromes but absent in congenital syphilis are present in the regional Panamanian sample. The known effects of congenital syphilis on the hard tissues are also present in the Panamanian sample, including Moon's and Fournier's molars, Hutchinson's incisors, severe enamel hypoplasias of the deciduous anterior teeth, frontal bossing, periostitis and bowing in the tibiae, and enlarged sternal ends of the clavicles (Higouménakis' sign). Certain stigmata such as flared scapulae and "Wimberger's sign" on the tibiae were not possible to assess in the sample due to post-depositional damage and fragmentation of these delicate zones.

In sum, the regional pre-Columbian Panamanian human skeletal sample contains examples of nearly each hard tissue manifestation of congenital syphilis, which provides support for the possibility of infectious causation for the anomalous molar tooth from Cerro Juan Díaz. Still, the possibility of genetic causation cannot be ruled out entirely as there is clear evidence for genetic developmental anomalies in the broader population (Smith-Guzmán, 2021). Nevertheless, the complete absence of conical anterior teeth and talon cusp formation in the sample advocates for a lower relative potential for the specific syndromic effects of Nance-Horan syndrome, Ellis-van Creveld syndrome, or a CACNA1S mutation in the population.

4.2. Limitations

The relative antiquity of the clinical literature on congenital syphilis (pre-1960 s) and novelty of the literature on genetic disease (post-1960 s) may present a bias affecting the precision with which one may perform differential diagnoses between them based on hard tissue signs alone. It is uncertain, for example, whether congenital syphilis might also be implicated in some of the other dental anomalies included in Table 2. This time discrepancy might also explain the absence of any mention of rare inherited genetic syndromes for consideration in differential diagnoses of congenital syphilis (Fournier, 1884; Hutchinson, 1858, 1857; Moon, 1877). Most of these clinical descriptions were written prior to the advent of penicillin and consequential reduction of the global prevalence of syphilis, at a time when the genetic syndromes included in Table 2 above had not yet been fully recognized nor described in the clinical literature (Ellis and Van Creveld, 1940; Goltz et al., 1962; Horan and Billson, 1974; Nance et al., 1974).

Similarly, the precise pathophysiology of congenital syphilis is poorly known. Unlike other forms of treponemal infection, congenital syphilis affects the body during the first stages of development, leading to various anomalies in the morphological appearance of the growing bones and teeth. However, the inability of *T. pallidum* to be cultured in a laboratory setting has historically hindered focused studies into the etiology and pathophysiology of these sequelae (but see promising recent progress toward this end by Edmondson et al., 2018). It has been hypothesized that the dental defects produced by congenital syphilis result from the invasion of the tooth germ by the pathogen, which seems to be based on tangential evidence of a preponderance of *T. pallidum* in the tooth germs of deceased infants (Bauer, 1944; Nissanka-Jayasuriya et al., 2016).

Bauer's (1944) interpretation that the pressure associated with the inflammation caused by this infection of the developing tooth leads to the morphological changes observed in congenital syphilis appears less likely when considering the recognition of genetic causation for the same phenotype. It seems that a re-assessment of historical understandings of the disease in the light of modern advances is warranted. Considering that both Nance-Horan syndrome and congenital syphilis are implicated in the development of bud-shaped molars, screwdriver-shaped incisors, and cataracts, one could hypothesize that these defects may result from a common point of disruption of the molecular signaling cascade controlling epithelial cell activity during early tooth bud development and later dentinogenesis (Hillson et al., 1998; Nance et al., 1974). This observation highlights a need for more clinical research into the precise pathophysiology of these dental defects.

Based on the current clinical evidence, it appears that not all children affected with congenital syphilis develop these dental stigmata. Furthermore, the effect of syphilis on the developing fetus frequently results in miscarriage or severe detrimental effects to the fetus leading to an elevated mortality early in life (i.e., before the child would have the chance to develop permanent teeth). The most recent global health data published by the World Health Organization estimates that only 16% of live births to untreated mothers with venereal syphilis result in congenital syphilis (World Health Organization, 2016, p. 24). These factors may explain why dental evidence of congenital syphilis in the archaeological record remains rare.

Furthermore, pinpointing the potential presence of genetic disease among the pre-Columbian inhabitants of Panama presents its own set of challenges. The identification of these diseases in past populations is limited to genetic diseases already identified and characterized in the clinical literature. At the local level, the identification of specific genetic diseases in Panama and the surrounding regions is also limited by poor preservation of osseous material due to the tropical environment and acidic soils, as well as the lack of modern epidemiological data from which to identify locally prevalent inherited conditions (Smith-Guzmán, 2021).

Over the past three decades, several researchers have attempted to extract ancient DNA (aDNA) from human skeletal samples recovered from archaeological sites in Panama with little success. The few successful samples have provided mostly low-coverage data, at times providing information on populational genetics from mitochondrial and nuclear DNA (Capodiferro et al., 2021; Rambaldi Migliore et al., 2021).

However, to date, this data cannot be used to identify mutations of specific genes and there have been no attempts to obtain pathogen DNA from these degraded samples. Even so, paleogeneticists have yet to identify *Treponema pallidum* DNA to the subspecies level in any pre-Columbian human remains, even in well-preserved samples, that would be able to resolve debates on the origin and antiquity of syphilis (Schuenemann et al., 2018).

Ideally, local public health data would be informative in considering specific genetic diseases present in the modern population of Panama that might have also affected pre-contact populations on the Isthmus. However, there is currently no system in place to track inherited genetic diseases in Panama, and even obtaining genetic testing to diagnose these diseases is problematic for many patients (Pérez Sánchez, 2017; Reyes, 2020). Nevertheless, at least one of the specific genetic diseases discussed in the present study has been identified in a Panamanian patient in recent years: Nance Horan syndrome (Ulate Jiménez and Gudiño Fernández, 2009). This finding suggests that this particular inherited mutation is present in the modern gene pool locally, and thus, could potentially have existed in pre-contact populations as well.

5. Conclusions

This study highlights the importance of considering both infectious and genetic causation for aberrant supernumerary cusps in archaeological contexts. Particularly in geographically and culturally isolated areas, as Panama seems to have been in the past, inclusion and serious contemplation of rare diseases in differential diagnoses by paleopathologists is vital. Considering potential causative factors leading to the development of the anomalous molar tooth at Cerro Juan Díaz from a conservative regional perspective, congenital syphilis appears to be the most likely candidate. A genetic causation for the crown anomaly was deemed less likely, but still cannot be ruled out based on the evidence at hand.

Declaration of interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found at doi:10.1016/j.ijpp.2022.07.002.

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