# Differential Diagnosis of Complex Conditions in Paleopathology: A Mutational Spectrum Approach

by

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## Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

## Abstract

The expression of mutations causing complex conditions varies considerably on a scale of mild to severe referred to as a mutational spectrum. Capturing a complete picture of this scale in the archaeological record through the study of human remains is limited due to a number of factors complicating the diagnosis of complex conditions. An array of potential etiologies for particular conditions, and crossover of various symptoms add an extra layer of complexity preventing paleopathologists from confidently attempting a differential diagnosis. This study attempts to address these challenges in a number of ways: 1) by providing an overview of congenital and developmental anomalies important in the identification of mild expressions related to mutations causing complex conditions; 2) by outlining diagnostic features of select anomalies used as screening tools for complex conditions in the medical field ; 3) by assessing how mild/carrier expressions of mutations and conditions with minimal skeletal impact are accounted for and used within paleopathology; and 4) by considering the potential of these mild expressions in illuminating additional diagnostic and environmental information regarding past populations.

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# Chapter 1

## Public Issues Anthropology Relevance and Proposed Publication Venue

### 1.1 Introduction

Medical diagnostics is a process complicated by inherent biases, insufficient categorizations and time constraints that can lead to no diagnosis, misdiagnosis, and dangerously faulty treatments (Khullar et al. 2015). The research project that follows examines this process within both the medical field and paleopathology. It highlights the changes to the classification of complex conditions due to advances in molecular genetics, and explores the human environment relationship with physical development and gene expression. The challenges of interpreting symptoms within strict parameters and finding potential solutions for combating these limitations are also examined. All of these factors contribute to the complexity of diagnostics both within the medical field and in paleopathology. As they can impact the delivery and perception of health care, this is an issue that can permeate the public domain.

Diagnostic complexity is in part due to the features that make up known conditions and the way in which they are perceived within paleopathology and the medical field. In this study, the term complex conditions refers to common and rare diseases, malformation syndromes and disorders. There are a number of definitions for rare diseases depending on the country. In their global study of rare disease definitions, Richter et al. (2015) suggest 40-50 cases per 100,000 people. However, the definition in the United States involves any condition affecting under 200,000 individuals, and the European Union regards any condition affecting less than 1 in 2000 individuals as rare (GARD, Genetic and Rare Diseases Information Centre, 2017).

These conditions can be comprised of major anomalies requiring medical intervention and minor anomalies that are more benign in nature. Anomalies are further subdivided into congenital anomalies visible at birth and developmental anomalies that become evident later in life with growth (Barnes 1994; Saxen & Rapola 1969). The designation of these benign features as an anomaly or simply a less common variation often relies on prevalence thresholds and is population specific. All of these factors are important to consider when attempting a diagnosis and can open the door to additional biases. How all of these complexities interact, and the ultimate impact of these interconnections is an important public issue.

### 1.2 Definitions of Public Issues Anthropology

There have been many different conceptions of what it means to practice public issues anthropology. Some believe it involves producing research considered useful to the public in some way. Often this entails providing the public with an alternative view to what persists in popular thought. Others believe a public issues motivated anthropology should involve a more "militant" approach (Scheper-Hughes 2009; Robins & Scheper-Hughes 1996). This strategy views responsible anthropologists as engaging with the public in a manner that emphasizes the importance of morality and ethics in fieldwork (Scheper-Hughes 1995). Scheper-Hughes places the emphasis on questioning established ethics in the field, and the complex relationship between anthropologists, the truth, and those who are a part of their research (Scheper-Hughes 2009, 1995).

Another interpretation of public issues anthropology focuses on public participation and partial ownership of anthropological research. An example of this is evident in the growing popularity of public archaeology, which encourages those living within the community of a

project to contribute their efforts to decision-making and excavation (Shackel & Chambers 2004; Merriman & Schadla-Hall 2004). This is a particularly important aspect of bioarchaeological research, which has become enmeshed in the sphere of public involvement and mediation.

For the purposes of the research that follows, public issues anthropology provides perspective and information on an issue already impacting the public domain. In this case, that issue involves the limitations placed on the diagnostic process due to the influence of inherent biases.

### 1.2 Biomedical Approaches to Complex Conditions

In relation to diagnostics, there are a number of well known hinderances faced by physicians and paleopathologists on a routine basis. More than 40 different types of bias have been studied for relative influence on diagnostic reasoning (Mamede et al. 2010,). Some of the most consistent are **availability bias**, and **framing bias** (Mamede et al. 2010; Popovich et al. 2019; Howard 2019). These biases can have a profound influence on the process through which diagnostic decisions are made, both in the medical and paleopathological fields. When a physician or paleopathologist grasps at the first diagnosis that comes readily to mind, often one they have seen recently that has similar symptoms, it is referred to as *availability bias* (Mamede et al. 2010). Research suggests this type of bias is more present with experienced physicians or paleopathologists who can draw on years of exposure to various cases when making diagnostic decisions (Mamede et al. 2010). With paleopathologists, the types of conditions often discussed within reference texts, and those frequently chosen to be highlighted in case studies can impact the conditions considered in differential diagnoses.

When considering a diagnosis, physicians and paleopathologists can also be influenced by how they are informed of symptoms, which can result in **framing bias**. This can exclude harder to reach, though just as likely, diagnoses from consideration (Popovich et al. 2019). In other words, how information is provided or considered (i.e. negatively or positively) can impact the perception of diagnoses and treatments in the mind of a physician or paleopathologist. In some cases, this can be significant enough to deter a physician or paleopathologist from making sound judgment calls (Howard 2019). Likewise, if they have a particular diagnosis in mind, this could lead to framing, as any evidence supporting the favoured diagnosis may be given greater weight (Howard 2019). The limited symptoms on bone available to paleopathologists may also contribute to framing bias.

A means of combating these flaws of reasoning is generating an awareness of their impact within the medical community. Some researchers suggest the best means of accomplishing this is to examine the actual decision-making process both qualitatively and quantitatively to gain a better understanding of where the pitfalls occur, rather than simply focusing on accuracy (Mamede et al. 2019; Olson & Graber 2020; Croskerry 2003). A number of articles also address concerns regarding the diagnostic process in paleopathology and bioarchaeology (Mays 2018; Ortner 2016; Buikstra et al. 2017; Klepinger 1983; Lawler 2017; Snoddy et al. 2020). However, suggested approaches continue to be sporadically adopted.

This awareness should also extend to how conditions are classified in biomedical approaches. Biomedical definitions of complex conditions are crafted and developed as is any social construct; however, there is a prevailing sense that these constructs are a neutral or universal way of viewing a particular subject (Conrad & Barker 2010; van Bemmel & van der Weegen 2019). The case of nodding syndrome reflects the shortcomings of relying on a

single biomedical definition without evaluating individual cases that cast doubt on its universality. Nodding syndrome, a condition causing nodding of the head in the morning after food is consumed, has different regional definitions. There is no known genetic cause for the syndrome, some believe it is the result of war, others a side effect of contaminated food or perhaps a virus (van Bemmel & van der Weegen 2019).

For the biomedical community, common symptoms were agreed upon and shifting regimens of pharmaceuticals prescribed to patients. However, the medications prescribed do not seem to have a positive impact on the symptoms. The lack of progress would suggest a faulty definition of the condition based on a set list of expected symptoms, which overshadow the importance of understanding possible causes. This particular case would benefit from further investigation of local factors outside of the biomedical sphere yet, beyond anthropological investigations, there appears to be little incentive to incorporate these unknowns into the search for an effective treatment (van Bemmel & van der Weegen 2019). In this situation, over confidence in a socially crafted definition and globally accepted treatment practice has placed limitations on the potential usefulness of other perspectives.

How information is approached and presented is also a concern in paleopathology. Researchers can be motivated by publicity and funding opportunities to present inconclusive diagnoses as conclusive to the public. These cases can be linked to historical individuals, but if so, they raise ethical questions (Snoddy et al. 2020). It has been suggested these cases are susceptible to confirmation bias as researchers attempt to match study results within preconceived notions. As an example of this, the authors describe the case of a mandible without provenance reported to belong to King Louis IV of France. This mandible was used to confirm the narrative King Louis IV suffered from scurvy. According to the authors, there

are a number of ways this type of bias can impact the public. It can mislead individuals into thinking specific identities can be ascertained when the evidence to support it does not exist, and it perpetuates general misinformation (Snoddy et al. 2020).

As anthropology has a history of presenting an issue from a multitude of perspectives, it is well equipped for the task of creating awareness in this respect. Since its formative years, paleopathology has used prevailing medical techniques to diagnose conditions in past populations (Mays 2018). However, paleopathology is also an anthropological venture and, as such, is not restricted to the confines of medical practices; it is free to assess current techniques and explore alternative methods of diagnostics. This project is an attempt to examine the less likely diagnoses and to assess the current diagnostic process within paleopathology.

### 1.4 Proposed Publication Venue

The International Journal of Paleopathology is the proposed publication venue for this study. Articles published in this journal focus on theory and perspective, as well as methodological approaches to disease in the past. These interests align with the nature of this study. This journal also has an international reach and is available to a wide audience which is appropriate for a public issues related research project.

# Chapter 2

# Differential Diagnosis of Complex Conditions in Paleopathology: A Mutational Spectrum Approach

## 2.1 Introduction

The identification of syndromes and rare conditions is a complex process still in various stages of development within the medical and paleopathological fields. Assigning an accurate diagnosis can involve a network of medical professionals with specializations in genetics, radiology, pathology, clinical medicine, and histology among others (Brothwell 2010; Buikstra et al. 2017; Snoddy et al. 2020). Within the field of paleopathology, limited resources to work with make it even more difficult to confirm a diagnosis (Ortner 2011; Ortner 2016). Contributions of the environment, poorly understood genetic processes, and types of mutations add to the complexity of ordering conditions into neatly arranged categories. These factors also make attempts to broadly identify anomalies as syndromic or non-syndromic challenging.

This study attempts to address these complexities in a number of ways: 1) by providing an overview of congenital and developmental anomalies important in the identification of mild expressions caused by mutations resulting in complex conditions; 2) by outlining diagnostic features of select anomalies used in the medical field to identify potential complex conditions; 3) by assessing how mild/carrier expressions of mutations and conditions with minimal skeletal impact are accounted for and used within paleopathology; and 4) by considering the potential of these mild expressions in illuminating additional diagnostic and environmental information regarding past populations. These steps are intended to contribute

to a diagnostic approach that accommodates the full spectrum of mutations, including mild expressions.

The role of minor anomalies as clinical screening tools suggesting potentially severe conditions and the application of this to paleopathology is an important component of this research. Minor anomalies have been addressed in bioarchaeological and paleopathological literature for a number of reasons. Due to their typically benign or minor health effects, Barnes suggests developmental anomalies are a potential solution to studying more severe congenital anomalies. Her reasoning for this relates to the lower survival rate of children born with more serious anomalies, which results in fewer major anomalies detectable in the archaeological record (Barnes 1994). As minor defects also appear more frequently in human remains from archaeological contexts, they can provide valuable information regarding variation in the expression of conditions (Barnes 1994). Barnes' work creating a system to evaluate these defects builds on previous work by Brothwell and Powers (1968), Zimmerman and Kelley (1982), and Manchester (1983) (Barnes 1994). All felt that research focused on more severe congenital anomalies was limited due to their rarity.

These efforts parallel studies concentrating on minor anomalies produced within the medical field. Many of these studies examine the relationship between minor and major congenital anomalies (Leppig et al. 1987) or the number of minor congenital anomalies not firmly linked with a syndrome present in populations (Marden et al. 1964; Shapira et al. 2019; Miles et al. 2008). In some of these studies the objective is also to determine if a greater number of anomalies is indictive of an associated major malformation that could have more severe health consequences (Leppig et al. 1987). However, in anthropology, especially

within biological anthropology, more emphasis is placed on distinguishing variants in morphology from congenital anomalies.

### 2.2 Definitions

A significant part of the complexity inherent in recognizing syndromes is understanding their composition and clinical classification. A syndrome is comprised of a number of symptoms reliably occurring together (Martini et al. 2009). Key components of syndromes are referred to as congenital anomalies, malformations, or variations that occur as the result of disruptions in expected intrauterine development (Aufderheide et.al. 1998). A spectrum of variations in morphology can occur at different stages of intrauterine development and derive from a number of etiologies. The stage of intrauterine development during which these disruptions occur can have a profound impact on the severity of the outcome (Barnes 1994).

A **congenital anomaly** is described as a visible anatomic characteristic that differs greatly from a reference population (Hennekam et al. 2013). Conditions that could significantly impact the health of an individual to the extent they could be lethal or require medical intervention to correct are classified as **major** congenital anomalies (Hennekam et al. 2013; Shapira 2019). Often co-occurring alongside major congenital anomalies are **minor congenital anomalies** which have little to no significant impact on health (Hennekam et al. 2013; Shapira 2019; Marden et al. 1964). Minor and major anomalies can be malformations, which involve a single part of the body and do not worsen. They can also involve deformations, which are caused by mechanical stress that results in altered morphology (Hennekam et al. 2013).

Although congenital anomalies may be visible at birth (Turkel 1989), they can also take many years to noticeably manifest. This is the case for a specific category of congenital

anomalies referred to as **developmental defects**. These anomalies are generally less severe in expression and appear years after birth when impacted by growth or traumatic events (Barnes 1994; Saxen & Rapola 1969). In this study, **congenital anomaly** and **developmental anomaly** are used to refer to variations both minor and major, present at birth and later in life respectively.

### 2.3 Congenital Anomalies vs. Anatomical Variants

Once a congenital anomaly is determined to be major or minor, there is still the question of whether it is a true anomaly, a less common variation of a trait, or what is considered a "normal" trait. This categorization separates anomalies that could indicate a significant disturbance during intrauterine development resulting in a greater health risk, from what is simply a consistent, though less common, variation within a population that has no discernable impact on the individual (Leppig et al. 1987). There are defined guidelines to assist in this process although, similar to the line between etiologies of congenital anomalies, it can be difficult to confidently decipher (Oostra et al. 2016, 879).

Researchers have used prevalence of a particular anomaly within a specific population as a means of determining its significance to the diagnosis of syndromes. Certain prevalence thresholds in a population are used to separate true anomalies from examples of human variation. Leppig et al. suggest a prevalence of less than 4% indicates a minor anomaly, those appearing in between 4% and 50% of the population are "normal variants" and those in greater than 50% of the population are too common to be considered anomalies or variants and are classified as "normal traits" (1987, 532).

Some anomalies, such as characteristic facies linked to specific mutations, require comparison to family members and evaluation of facial proportions. Measurements are

required in these cases and anomalies are classified as such if the measurements fall outside the mean by greater than or less than two standard deviations (Hennekam et al. 2013). Of course, these medical practices do not necessarily transfer well to paleopathology. In the examination of archaeologically derived human remains, the advantages of a living patient with known family histories, direct comparison of phenotypes to family members, and access to DNA analysis are lost or difficult to obtain. Even if these aids are available, determining what is "normal" can become an exercise in social constructions, and traits that are outliers in a sample do not necessarily have pathological associations. In short, both paleopathologists and clinicians must take care when defining what is and is not considered a "normal" trait.

Although most variants and traits are common, some can be the result of pathological and environmental factors (Berry & Berry 1963). The works of Brothwell (1967), Brothwell & Powers (1968), Finnegan (1978), and (Barnes 1994) are essential references for paleopathologists that define variation and its application on a population level; however, they do not fully express its usefulness on a diagnostic level. More specifically, the opportunity exists to build on how these anomalies in their variable expressions relate to each other and factor into the classification of complex conditions.

### 2.4 Changing Approaches to Differential Diagnosis

In paleopathology, as in the medical field, approaches to diagnostics are constantly changing due to a number of complicating factors. Crossover of many congenital and developmental anomalies among various conditions makes it difficult to accurately identify specific conditions without verification through DNA analysis (Ortner 2003; Ortner 2011). For paleopathologists, the degree of difficulty is also increased by a lack of soft tissue, and incomplete skeletal remains from archaeological contexts. As a number of researchers have

noted, direct comparison to medical reference texts when trying to identify a condition is fraught with risk. Among these risks is the tendency of traditional clinical classification systems to highlight the most likely set of symptoms. Medical literature also focuses on soft tissue-related conditions, leaving some of the more nuanced aspects of bone conditions still to be discovered (Ortner 2011; Ortner 2016; Mays 2016; Mays 2018).

Before the advent of molecular genetics, complex conditions were identified and categorized through a clinical approach to diagnostics. This approach focuses on phenotypic expression of conditions by analyzing incidence rates and pattern presentation of congenital and developmental anomalies. Conditions are both classified and diagnosed using this technique (Wright et al. 2019). Conditions were typically named after the original investigators. For example, in the case of Ehlers-Danlos syndrome, a physician named Frederick Parkes-Weber thought it was appropriate to name the syndrome after dermatologists Edvard Ehlers and Henri-Alexandre Danlos. In the early 20$^{th}$ century, these men aided in identifying the characteristic features that make it a distinct syndrome (Liakat & Jackson 2008).

Conditions are also named after the type of biological alteration characteristically present, such as osteogenesis imperfecta. The history of this condition highlights the challenges of integrating new mutations causing similar effects to established classification systems. Originally identified clinically through macroscopic and radiographic features in the classification system for osteogenesis imperfecta developed by David Sillence, another "genetic classification" emerged as new genetic mutations were discovered. The new genetic classification organized types of osteogenesis imperfecta by the gene involved, adding to the Sillence classification (Forlino & Marini 2016). The infinite nature of this type of

classification led some researchers to consider a “functional metabolic” classification, focusing on similar functions of genes within the same signalling pathway (Forlino & Marini 2016). A similar approach was also attempted for new forms of Ehlers-Danlos syndrome (Depaepe & Malfait 2012). This type of reorganization will likely become more frequent as research in molecular genetics progresses.

Advances in molecular genetics also continue to complicate tidy concepts of Mendelian inheritance in relation to complex conditions. Mendelian inheritance refers to more predictable patterns of complex condition inheritance typically caused by a single gene mutation or, less frequently, digenic mutations (van Heyningen & Yeyati 2004). In contrast to this, non-Mendelian inheritance can be irregular. Examples of non-Mendelian inheritance include sporadic single gene mutations; interaction with environmental triggers; triplet repeat expansions; chromosomal aberrations, such as mosaicism; and polygenic inheritance (van Heyningen & Yeyati 2004).

Chromosomal aberrations are represented by conditions such as Turner syndrome, which is sex-linked and caused by complete or partial chromosomal deletions. There are also instances when these chromosomal alterations are only present in some cells; this is referred to as mosaicism. As a result of all these different modes of causation, there can be a wide range of variation in the phenotype of this particular condition. Fragile X syndrome also occurs through the non-Mendelian mechanism of triplet repeat expansion (van Heyningen & Yeyati 2004). All of these mechanisms increase phenotypic variation of complex conditions, making them more difficult to predict and diagnostically interpret.

Even among complex conditions of Mendelian inheritance patterns, incomplete penetrance can produce mild expressions with only one or two congenital/developmental anomalies.

These cases have forced the medical community to recognize manifestations of conditions that would not have been considered without proven association to genetic mutations (Teber et al.2004). Some have classified these mild phenotypes as "non-syndromic traits of the causative gene" since they do not fit into traditional definitions of syndrome groups, which typically involve two or more structures (Wright et al. 2019, 444).

The paleopathological literature does not typically include these milder expressions alongside descriptions of more severe versions of the condition (Drtikolová et al. 2020). Research classifying and recording minor anomalies in isolation or within developmental fields has been produced; however methods of assessing these minor anomalies accurately within the context of syndromes is less explored. Applying this new information and the inevitable changes to classificatory systems that result from it in a way that is meaningful to the study of archaeological remains is important to the future development of paleopathology (Snoddy et al. 2020; Zuckerman 2016).

### 2.5 Methods and Materials

The purpose of this study is to add to this knowledge by engaging with both paleopathological case studies and reference texts addressing mild anomalies. This is combined with medical literature focusing on cases of mild expressions in general and more specific diagnostic potential of select minor anomalies. I review the minor anomalies used as diagnostic indicators of mild and novel skeletal expressions within medical literature. This provides a reference specific to skeletal anomalies, and promotes awareness of these expressions and their potential use in the diagnostic process of paleopathological cases. In addition, 118 paleopathological case studies with skeletal changes potentially due to genetic

mutations causing complex conditions were analyzed to determine the frequency and use of these minor anomalies within the field.

Examination of remains from archaeological contexts was not possible due to COVID-19 restrictions. Therefore case studies were selected through a search of the Omni Library database available through the University of Waterloo, Google Scholar, and the Wellcome Osteological Database. Articles from any type of journal (i.e. medical or anthropology related), pertaining to archaeologically derived human remains from any time period prior to 1920 CE, and any geographic location were included in the study. Examples of variations in morphology were included alongside congenital and developmental anomalies. Conditions suspected to be the result of birth trauma and those of inconclusive etiology are not excluded as they can be similar to congenital and developmental anomalies as the result of a complex condition. These cases also include congenital conditions in their differential diagnoses, which is relevant to the study.

The information provided in each case study was then entered into an Excel spreadsheet with information arranged under the following headings: author, publication title, site, time period or specific date, number of individuals (included in the study and the number with a suspected complex condition), age, sex, conditions, differential diagnosis (list of potential diagnoses), final diagnosis (the most likely of the diagnoses presented according to the author), diagnostic methods used, and how it was sourced (i.e. reference text, OMNI search) (see Appendix, Table 1, pp.72-74). From this information, the number of conditions included in differential diagnoses was quantified.

To determine relative occurrences of congenital and developmental anomalies and body regions, results from case studies were recorded on a specialized form of skeletally focused

congenital and developmental anomalies separated into body regions (Appendix Table 2 pp. 76-95). The congenital and developmental anomalies included in this form were sourced from studies by Miles et al. (2008), Shapira et al. (2019), Castriota-Scanderbeg and Dallapiccola (2005) and the sample case studies. The results of these forms were then entered into spreadsheets to determine the frequency of co-occurrence between anomalies, trends in the selection of diagnoses, trends in identification of specific anomalies, and how frequently anomalies are found in each body region.

## 2.6 Results

### 2.6.1 Mild Skeletal Expressions in Differential Diagnosis

Investigators were able to suggest a probable final diagnosis in the majority of case studies (n=76, 64%). The remainder of case studies listed the anomalies present as idiopathic or isolated (n=42, 36%). Of the suggested final diagnoses, complex conditions easily detectable in bone, such as those involving hyperostosis (15%, n=12), and short-stature dysplasias (30%, n=23) represent a notable portion of the cases. Many of the conditions selected multiple times as the most likely diagnoses are well-known from paleopathological literature. The following table provides a list of the conditions most cited as suggested final diagnoses.

| Condition | # of Cases | Case Study |
|---|---|---|
| Leri-Weill<br><br>Dyschondrosteosis | 8 | Lagier et al. 1978; Bianucci et al. 2012; Cummings & Rega 2008; Titelbaum et al. 2015b; Waldron 2000; Cormier et al. 2017 (combined achondroplasia and Leri-Weill dyschondrosteosis) |
| Klippel-Feil syndrome | 6 | Pany & Teschler-Nicola 2007; Fabra & Selega 2016; Drupka et al. 2019; Arriaza et al. 2019; Marchewka et al. 2017; Kieffer 2017 |
| Fibrous dysplasia | 5 | Traversari et al. 2019; Canalis et al. 1980; Wells 1963; Milella et al. 2016; Willmon et al. 2013 |
| Gigantism and acromegaly | 5 | Gladykowska-Rzeczycka et al. 1998; Minozzi et al. 2015; Mulhern 2005; Bartelink et al. 2014; Canci et al. 1992 |
| Paget's disease | 4 | Wells & Woodhouse 1975; Aaron et al. 1992; Burrell et al. 2019; Kesterke & Judd 2019 |
| Osteogenesis imperfecta | 3 | Wells 1965; Vairamuthu & Pfeiffer 2018; Darcy & Dupras 2011 |
| Thalassemia | 3 | Thomas 2016; Hershkovitz et al. 1991; Rohnbogner 2016 |

Table 1: Most frequently noted conditions as suggested final diagnoses in paleopathological case study sample.

These results suggest paleopathologists and bioarchaeologists are potentially influenced by availability bias (grasping at the first diagnosis that comes to mind) and framing bias (weighing symptoms based on a selected diagnosis) when making diagnostic decisions. This is further supported by the 38% of all case studies presented without a differential diagnosis. As no other diagnostic possibilities are presented in these cases, it is reasonable to assume the investigators had a specific diagnosis in mind against which symptoms may have been weighed.

Of the conditions that will be discussed below in relation to mild skeletal expressions, only Turner syndrome (n=1) (Ottini et al. 2001) and Gorlin-Goltz/Nasal Cell Nevus syndrome

(n=2) (Satinoff & Wells 1969; Ponti et al. 2016) are selected as probable final diagnoses. Overall, the range of conditions discussed in the differential diagnoses of cases is broader. It includes conditions such as pseudohyperparathyroidism (n=1) (Cybulski 1988), CHARGE syndrome (n=1) (Hoffman et al. 2019), as well as other less commonly noted conditions. The results also indicate that without aDNA analysis, conditions with mild skeletal expressions are less frequently detected with confidence than those with more recognizable skeletal manifestations. Even if aDNA were less susceptible to poor preservation and contamination (Pilli et al. 2013; Sampietro et al. 2006; Mulligan 2006; Kolman & Tuross 2000), it is unlikely individuals with very mild expressions will be identified as candidates for this type of analysis. Although confirmation of mild expressions of complex conditions may not be possible, an improved screening process tailored to skeletal remains may assist in identifying individuals with unspecified mild expressions. Similar to the process in a clinical setting, this can flag remains for further investigation.

### 2.6.2 Anomalies Associated with Mild Skeletal Expressions

In an effort to record the skeletal expressions of known mutational spectrums and associated skeletal anomalies, an extensive review of medical case studies presenting mild or novel cases of complex conditions was undertaken. These conditions may present mildly in terms of skeletal anomalies; however, the impact on soft tissue structures can be severe. An example of this is the variable expression of Ehlers Danlos syndrome. This condition causes laxity in connective tissues that can produce serious heart defects (Girotto et al. 2000); and increased danger during pregnancy (Volkov et al. 2007). Although mildly expressed in human skeletal remains, these conditions can profoundly compromise life expectancy and

quality of life. The results of this review suggest the following anomalies should be flagged as potential screening indicators falling within the spectrum of complex conditions.

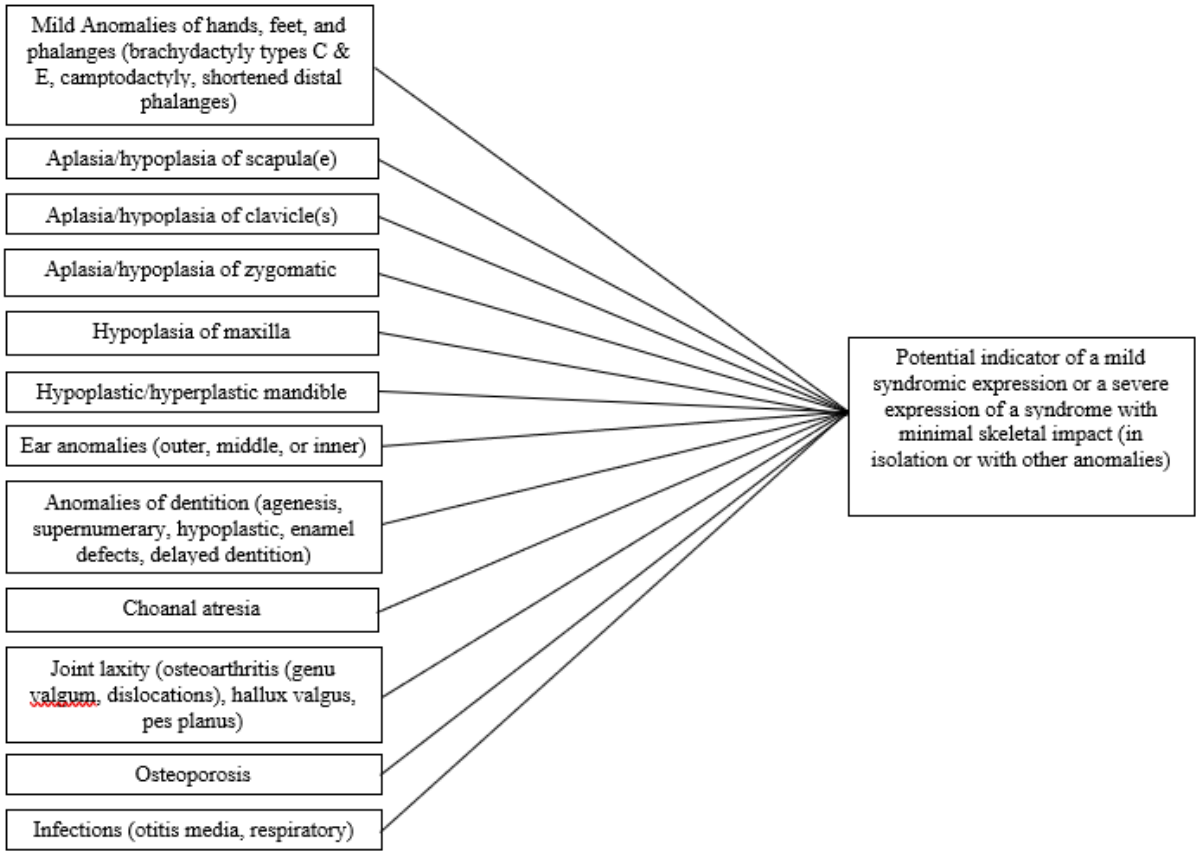


Figure 1: Summary of anomalies connected to known mild expressions of complex conditions. Adapted from Orphanet (2020); Stelzer et al. (2003); Bergendal (2014); Lexner (2007); Jaruga et al. (2016); Teber et al. (2004); Passos-Bueno et al. (2009); Davids et al. (1990); Singh et al. (2015); Weber & Kousseff (1999).

As these expressions present so mildly, it can be difficult to deduce isolated anomalies from those indicative of a complex condition, let alone a specific condition. In this study, I attempt to broadly identify these anomalies as syndromic or non-syndromic in certain contexts. A brief review of conditions with mild expressions involving these anomalies, and the frequency of these anomalies in paleopathological case studies is also provided. The

potential of these mild indicators as aids to the diagnostic process as well as in defining the environment in which development occurs is also briefly examined.

### 2.6.3 Mild Anomalies of the Hands, Feet, and Phalanges

The term **brachydactyly** refers to unusually short hands and feet (Temtamy et al. 2008, 15). This condition can occur in isolation or as part of a complex condition and includes the shortening of both metacarpals/metatarsals and phalanges (Pereda et al. 2013). Brachydactyly types E and C are known to consistently occur within the context of complex conditions (Pereda et al. 2013; Stelzer et al. 2003; Farooq et al. 2013). Although it can be difficult to determine if brachydactyly type E and C are isolated or part of a complex condition, there are some subtle features of the hands and feet, as well as other skeletal elements, reviewed later in this section that could aid in this determination.

Although there are multiple subtypes of brachydactyly type E (Bell 1951) (see figures below for some examples), it is mainly characterized by shortening of the fourth, and often the fifth, metacarpals and metatarsals (Pereda et al. 2013, 1). Brachydactyly type C, on the other hand, typically manifests as a shortening of the second, third and fifth middle phalanges, leaving the fourth digit within average measurements (Stelzer et al. 2003).

Brachydactyly type E factors into the skeletal expression of a number of known mutations causing complex conditions (Pereda et al. 2013). It has also been suggested brachydactyly type E occurs less often as an isolated anomaly than as part of a complex condition (Temtamy & Aglan 2008). For this reason, it is included in the list of anomalies potentially indicative of a mild expression of a complex condition or a predominantly soft tissue condition with little to no skeletal impact. A number of medical publications highlight

brachydactyly type E as a variably consistent part of Turner syndrome (Zelinska et al. 2018), Pseudohypoparathyroidism (PHP) (De Sanctis 2004), Pseudohypoparathyroidism Ia (PHP-Ia) with AHO phenotype (Pereda et al. 2013), Tricho-renal-phalangeal syndrome (Ludecke 2001), and Bilginturan BD (Bilginturan 1973) among others (Pereda et al. 2013). The association with severe soft tissue anomalies and its potential impact on perceptions of life experiences of individuals from past populations make investigation of the diagnostic value of brachydactyly type E worthwhile. This is particularly true if occurring with other minor anomalies, which could suggest the presence of a mutation potentially impacting bone development genes.

A number of gene mutations and chromosomal alterations are implicated in these disorders. Caused by partial or complete deletions of the X chromosome, Turner syndrome is typically associated with short stature, fertility issues, and cardiovascular disease (Clement-Jones 2000; Mortensen et al. 2012). A number of skeletal anomalies have also been noted in some patients. Specific anomalies of the musculoskeletal system can include discrepancies in upper and lower leg/arm lengths, cubitus valgus, micrognathia, shortened metacarpals, genu valgum, scoliosis, and Madelung deformity. The partial or complete chromosomal deletions causing this condition are believed to negatively impact SHOX functions essential to bone development in some cases. This can possibly explain the range of skeletal anomalies that can accompany this condition (Clement-Jones 2000). A study by Zelinska et al. (2018) has shown brachydactyly type E1 to be over 70% consistent among a sample of over 500 patients with this condition.

Pseudohypoparathyroidism is connected to alterations involving chromosome 20 and the locus GNAS which is integral to a variety of cellular processes (Pereda et al. 2013). Tricho-

renal-phalangeal syndrome is caused by mutations to the gene of the same name (TRPS1), and in specific types can extend to the EXT1 gene. TRPS1 is known to facilitate chondrocyte cell division (Wuelling 2013). The chronic renal failure resulting from this condition poses a serious threat to life expectancy (Tasic et al. 2014). The cause of Bilginturan BD has not been confirmed; however, chromosome 12 is believed to be a potential source (Schuster 1996). This condition is known to cause hypertension throughout life and could result in death due to stroke by 50 years of age (Bilginturan 1973). Specific skeletal anomalies occurring with these conditions are outlined in figures 3 and 4 below.

These conditions have life threatening risks, often with minimal skeletal impact. A detailed understanding of minor anomalies present with these conditions can provide a means of incorporating these life experiences into the archaeological record. Some medical studies have been produced addressing the diagnosis of brachydactyly type E as isolated or as part of a complex condition. In their article, Pereda et al. (2013) highlight a number of distinctions between complex conditions potentially involving brachydactyly type E that may be useful to paleopathology.

Of particular importance are features indicative of brachydactyly as part of a complex condition within the hands and feet. An example of this includes cone-shaped epiphyses in subadults, with outcarving (excavation) of metaphyses in older children and adults (Giedion 1998). This is described as a concavity that develops over the course of a few years in childhood typically in cases of cartilage hair hypoplasia and tricho-renal-phalangeal syndrome. The metaphysis associated with the affected epiphysis will also show this concavity/excavation. Data has shown the mesophalanges, especially of the second and third digits, are most often impacted by this feature (Giedion 1998). Other anomalies associated

with these changes include asymmetrical trochlea, osteoarthritis in these joints, and exostoses on metacarpals and phalanges of children (Giedion 1998). Although these features can be isolated, studies suggest they are rarer and less pronounced than those related to a complex condition (Giedion 1998). In the case of Tricho-renal-phalangeal syndrome, the cone-shaped epiphyses and exostoses that can accompany them are attributed to a dysfunction in suppressor genes due to chromosomal deletion (Giedion 1998). These features suggest it is possible to consider a syndromic relationship when remains are incomplete or the anomaly appears isolated. The following charts are adapted summaries of anomalies that could suggest brachydactyly type E is part of a complex condition even when skeletal impact is minimal.

i. ii.

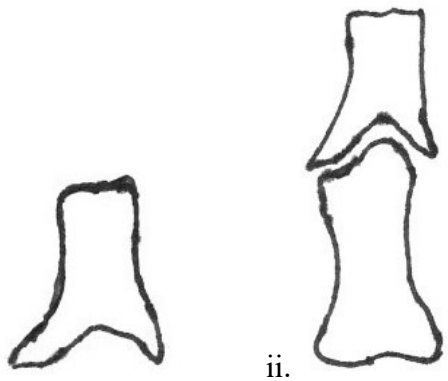

Figure 2: Examples of excavation/outcarving of the middle phalanx (i, ii) and asymmetry of the trochlea (ii) (modeled after Giedion 1998, 756).

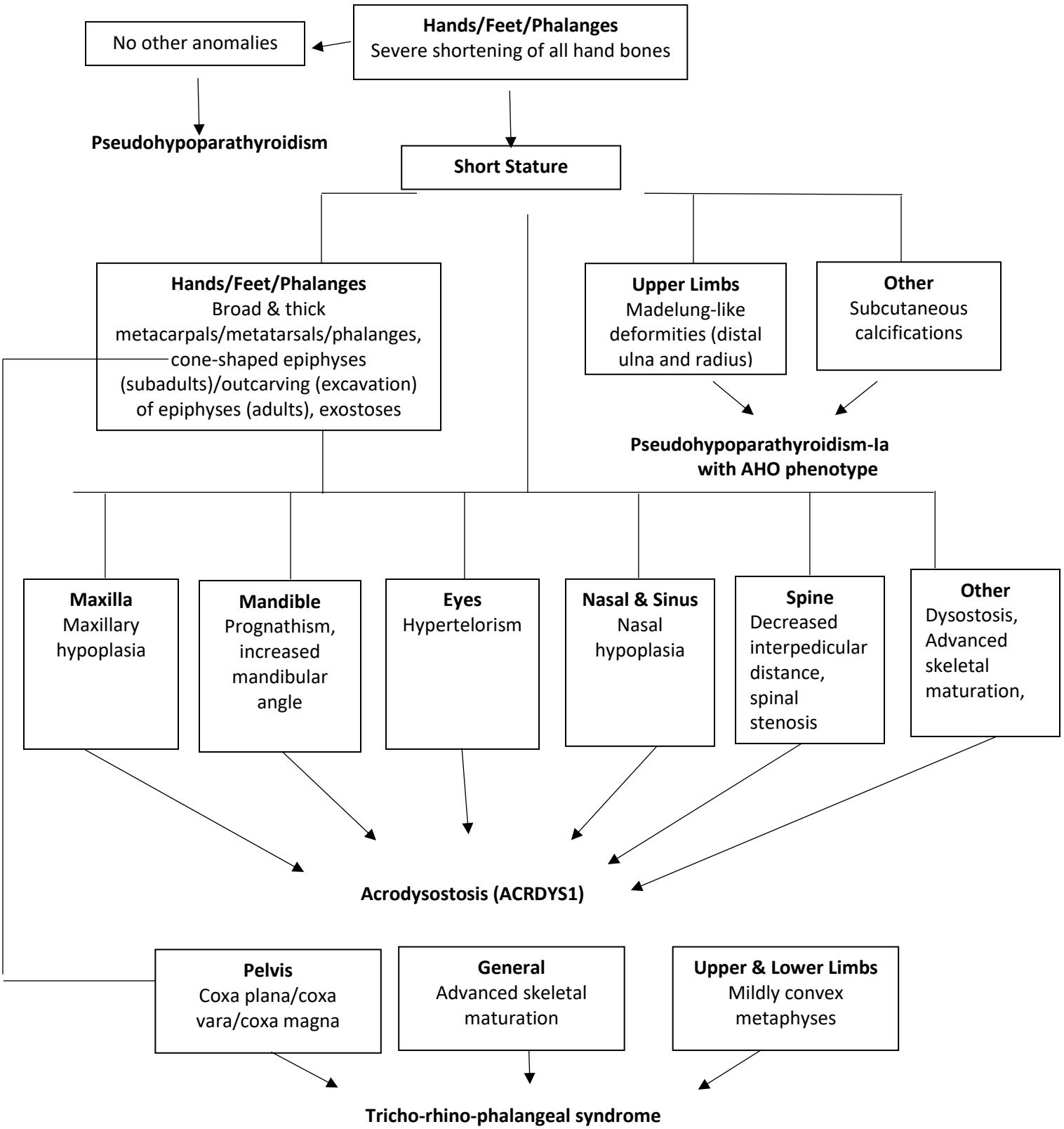


Figure 3: Types of brachydactyly type E and related anomalies associated with syndromes (adapted from Pereda et al. 2013, Orphanet 2020).

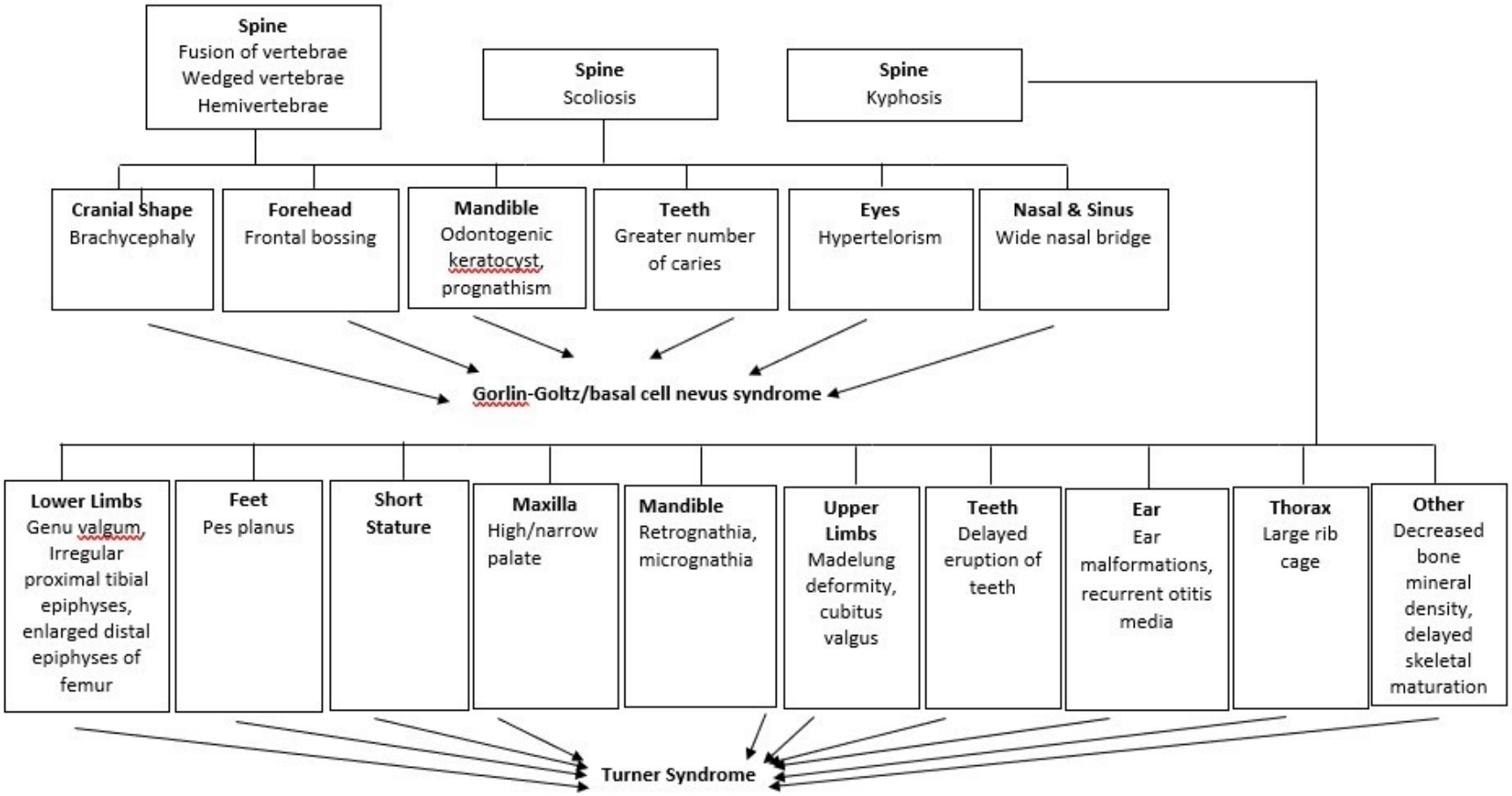


Figure 4: Anomalies known to be present with brachydactyly type E in relation to specific syndromes (adapted from Pereda et al. 2013; Orphanet 2020).

Another mild connection to a severe condition involving a type of brachydactyly is the heterozygous carrier phenotype of acromesomelic dysplasia, Grebe type. The latter condition typically consists of a severe growth disorder mainly directed at the hands, feet, and lower limbs (Stelzer et al. 2003). Brachydactyly type C is found consistently in heterozygous/carrier mutations of the CDMP1 gene, which is essential in both pre-cartilaginous and cartilaginous stages of structural development. This type of brachydactyly typically presents as hypoplastic second, third and fifth intermediate phalanges, as well as the first metacarpal (Stelzer et al. 2003). Although this form of brachydactyly can appear without the presence of any other anomalies, it is considered by some researchers to be part of the mutational spectrum of acromesomelic dysplasia, Grebe type. Some carriers of this mild mutation can have no physical signs or symptoms (Stelzer et al. 2003; Farooq et al. 2013).

Although this type of brachydactyly may be less accessible to bioarchaeologists due to the partial recovery of phalanges, its strong connection to potentially lethal recessive disorders such as acromesomelic dysplasia, Grebe type can contribute to the paleopathological discussion of these conditions. Recognition of its inclusion within this particular mutational spectrum can place it, even if tentatively, within a broader context than viewing it as simply an isolated feature allows. The implications this can have regarding interpretations of past life experiences can be significant.

In general, anomalies of the phalanges (fingers n=8, toes n=7) are among the lowest noted body regions in the sample of paleopathological case studies. Anomalous features of fingers and thumbs noted are brachydactyly (shortened phalanges) (n=2), phalanges that appear longer than average (n=1) (Minozzi et al. 2015), asymmetry of the phalanges (n=3), bony knots (n=1) (Arcini & Forlung1996), flaring of the epiphyses (n=1) (Lieverse et al. 2008),

and camptodactyly (n=1) (Panzer et al. 2018). Anomalies of the toes noted by investigators include postaxial polydactyly (n=3) (Hussein et al. 2013), preaxial polydactyly (n=1), symphalangism (n=1), slender toes (n=1), short toes (n=1), and long toes (n=1) (Minozzi et al. 2015). Serious anomalies such as missing toes or fingers, are not mentioned in any of the case studies included in the sample. A number of factors could contribute to the low numbers of anomalies identified in these elements, these include selective preservation, failure to recognize more subtle anomalies (Barnes 2012), or less overall presence.

Anomalies of the hands and feet have been covered in detail by Case (1996) who noted that metacarpals and metatarsals are the most useful in recognizing brachydactyly in archaeological remains (Case 1996 as cited in Barnes 2012). Cybulski (1988) explores the possibility of brachydactyly due to complex conditions in his study presenting multiple cases of shortened fourth metacarpals and metatarsals at the site of Prince Rupert Harbour. He provides a brief summary of select conditions and some associated skeletal anomalies in his appendix. However, he concludes the medical literature available does not confirm or deny a concrete relationship to particular conditions. He also eliminates some conditions because the classic signs are not present (1988). I identified additional anomalies not included in the review by Cybulski and the connection of brachydactyly to mild skeletal expressions of conditions more generally. It is possible to suggest that brachydactyly indicates bone development genes have been compromised due to genetic mutations or chromosomal aberrations, even if a specific condition can not be confidently identified.

My review of case studies also shows a higher number of anomalies of the metacarpals including shortened metacarpals (n=10), long metacarpals (n=1) (Minozzi et al. 2015), and broad metacarpals (n=1) (Garcia & Santos 2019). Of the 10 case studies with shortened

metacarpals, the 4th metacarpal of 5 individuals is affected (Satinoff & Wells, 1969; Ponti et al., 2016; Kozieradzka-Ogunmakin, 2011), with multiple cases of shortened 1st and 4th metacarpals and metatarsals (Cybulski 1988). The rest of the cases reported generalized shortening of all metacarpals and metatarsals (Cormier et al. 2017), unilateral shortening of metatarsals and phalanges (Lieverse et al. 2008); and a missing styloid process (Museum of London, Wellcome Osteological Database, Bermondsey Abbey; Cormier et al. 2017; Roberts et al. 2004). Otherwise, asymmetry of the hands (n=4) (Lieverse et al. 2008), bony knots (n=2) (Arcini & Forlung1996), and carpal coalition (n=1) (Rubini et al. 2013) are mentioned.

Similar to metacarpals, shortening of the metatarsals (n=5) (Cybulski 1988) is recognized more frequently than other foot anomalies in this sample of case studies. Other anomalies include pes planus (n=2) (Hussein et al. 2013; Wilbur 2000), talipes equinovarus (clubfoot) (n=4) (Roberts et al. 2004; Hussein et al. 2013; Wilbur 2000; Anderson & Thomas 1998), asymmetry of the foot (n=1) (Knüsel & Bowman 1996), broad metatarsals (n=1), and long metatarsals (n=1) (Minozzi et al. 2015). It is also interesting to note that anomalies of the feet (n=10) are among the most cited in cases identified as idiopathic or isolated, along with anomalies of the dentition (n=9) and the spine (n=15). The mild, perceived non-specific nature of these anomalies and incomplete skeletal remains may be a factor in the high number of foot anomalies among idiopathic and isolated conditions.

The table below highlights the conditions selected as probable final diagnoses for cases involving likely cases of brachydactyly type E (shortened 4th and 5th metacarpals/ metatarsals). The majority of case studies do not offer a differential diagnosis. When it is offered, as in the case of Cybulski (1988), isolated anomaly is still selected above these conditions. The author cites an absence of classic characteristics of the syndromes included

in the differential diagnosis and the high occurrence at the site as reasons supporting a diagnosis of isolated. This reasoning does not necessarily eliminate novel expressions of complex conditions or complex conditions not yet identified as such. It also does not account for the possibility of an inherited complex condition contributing to the occurrence of brachydactyly type E at this site. Defaulting to a diagnosis of isolated simply because the presence of a complex condition is inconclusive can be reflective of the tendency to grasp at diagnoses that are most familiar.

| **Final Suggested Diagnosis** | **Differential Diagnosis** | **Case Study** |
|---|---|---|
| Gorlin-Goltz syndrome | N/A | Ponti et al. 2016 |
| Inherited isolated anomaly | Trauma; infarction or infection; Turner syndrome; pseudohyperparathyroidism/Albright's hereditary osteodystrophy; Laurence-Moon-Biedl-Bardet syndrome; basal cell nevus syndrome; inherited isolated anomaly | Cybulski 1988 |
| Multiple epiphyseal dysplasia | N/A | Kozieradzka-Ogunmakin 2011 |
| Basal cell nevus syndrome (Gorlin-Goltz) | N/A | Satinoff & Wells 1969 |

Table 2: List of suggested final diagnoses and differential diagnoses of case studies with shortened 4$^{th}$ metacarpals.

### 2.6.4 Anomalies of the Dentition

Similar to brachydactyly, anomalies of the dentition can be mild indicators of more severe soft tissue anomalies and it is often difficult to distinguish isolated forms from those related to complex conditions. However, not all forms of dental anomalies are equally good indicators of complex conditions. As the mutational spectrum of ectodermal dysplasias includes mild forms with minimal skeletal impact and prominent cases of oligodontia (Bergendal 2014), these conditions will be the focus of this section.

Over 100 conditions are classified under the grouping ectodermal dysplasias. These conditions all share similar symptoms affecting the skin, hair, teeth, and fingernails, which can often produce only subtle changes to the skeletal structure. Genes and signalling pathways impacted include NFkB, EDA, EDAR, NEMO, or transcription/regulatory genes such as p63, DLX3, MSX1, EVC2, and EVC (García-Martín et al. 2011).

The X-linked form and autosomal dominant/recessive forms of hypohidrotic ectodermal dysplasia and incontinentia pigmenti are caused by mutations impacting different genes on the ectodysplasin-EDAR-EDARRADD signaling pathway. This pathway facilitates the formation of elements deriving from the ectoderm. The X-linked form specifically results from alterations to the ED-1 gene. The connection of these mutations to a signaling pathway rather than transcription results in a milder presentation (García-Martín et al. 2011). More specifically, incontinentia pigmenti can occur when a section of the NEMO gene has been deleted (Bailleul-Forestier et al. 2008,). The NEMO/NFkB gene is a significant contributor to parts of the body related to the ectoderm, including teeth (Wright et al. 2019). Despite its seemingly mild manifestations, X-linked ectodermal dysplasia can involve health issues such as blocked airways, infections, fevers, and delayed psychomotor development (Wohlfart et al. 2020). All of these conditions can affect quality of life for those who suffer from it.

Autosomal dominant or recessive hypohidrotic ectodermal dysplasia is very similar to X-linked hypohidrotic ectodermal dysplasia, although it is believed to be less common. It is caused by mutations to the WNT10A, EDAR and EDARRADD genes as opposed to the ED-1 gene of the X-linked type (García-Martín et al. 2011; Plaisancié et al. 2013).

The position, size and number of dental anomalies are essential in the diagnosis of an ectodermal dysplasia. This is particularly true of X-linked hypohidrotic ectodermal dysplasia,

which is characterized by oligodontia along with unusually shaped teeth. Differences in the expression of these features can vary between males and females (Shalk-van der Weide et al. 1994; Lexner 2007). In her review, Bergendal (2014) notes a study by Lexner (2007) that found females with this condition presented with 4 absent teeth, in contrast to 22 absent teeth in males.

All of the males in this study also showed a remarkable consistency in the type of teeth remaining: the first molars, both maxillary and mandibular, as well as the maxillary incisors and mandibular second molars (Lexner 2007). All of the remaining teeth had an unusual morphology including maxillary incisors that were tapered and conical. In the female subjects there was a difference in the shape of mandibular and maxillary incisors with the former being more conical and the latter tapered (Lexner 2007). The unusual consistency of these dental anomalies extends to female carriers of this condition 70% of the time, although the degree to which the individual is affected may be less pronounced (García-Martín et al. 2011). Carriers will also typically have an unusual shape to the remaining teeth, especially the incisors and canines, and taurodontism (teeth with larger bodies than roots) of the second molars has been noted (Bailleul-Forestier et al. 2008). Despite the consistency of these features, Bergendal suggests it is not possible to distinguish isolated hypodontia from hypodontia caused by complex conditions based on tooth number and morphology alone (2014).

Fortunately, other anomalies can aid in making this distinction. One of the recognizable features of oligodontia due to X-linked ectodermal dysplasia is its strong penetrance over multiple generations of the same family (Bergendal 2014). This can be a useful feature to bioarchaeologists studying a group of archaeologically derived human remains. If various

degrees of hypodontia are present in the burial group, it could indicate carrier and full mutation expressions of the same complex condition. This is particularly true if other subtle indicators are present. These can include respiratory infection, and a greater number of caries. Features such as these have been linked to salivary gland issues producing a drier mouth in those with ectodermal dysplasia, which increases susceptibility to dental disease and respiratory infection (García-Martín et al. 2011). The latter can be studied more readily in mummified remains where the lung is available to be examined; however, in skeletal remains osteomyelitis as the result of respiratory infection causing septicemia may be present (Aufderheide et al.1998). Sinusitis has also been noted as occurring with ectodermal dysplasia (Orphanet 2020).

Incisal notching, similar to that found in connection with congenital syphilis, has been noted in a small number of incontinentia pigmenti patients (Bergendal 2014; Holmstrom et al. 2012). Tapered canines and incisors that are conical in shape have also been found in connection with this condition (Bergendal 2014; Holmstrom et al. 2012). Anomalies of the hand and phalanges, both mild (camptodactyly, syndactyly) and severe (absent hand), may also be present. Unusual vertebrae and ribs also characterize this condition and can aid in diagnosis if present (Orphanet 2020).

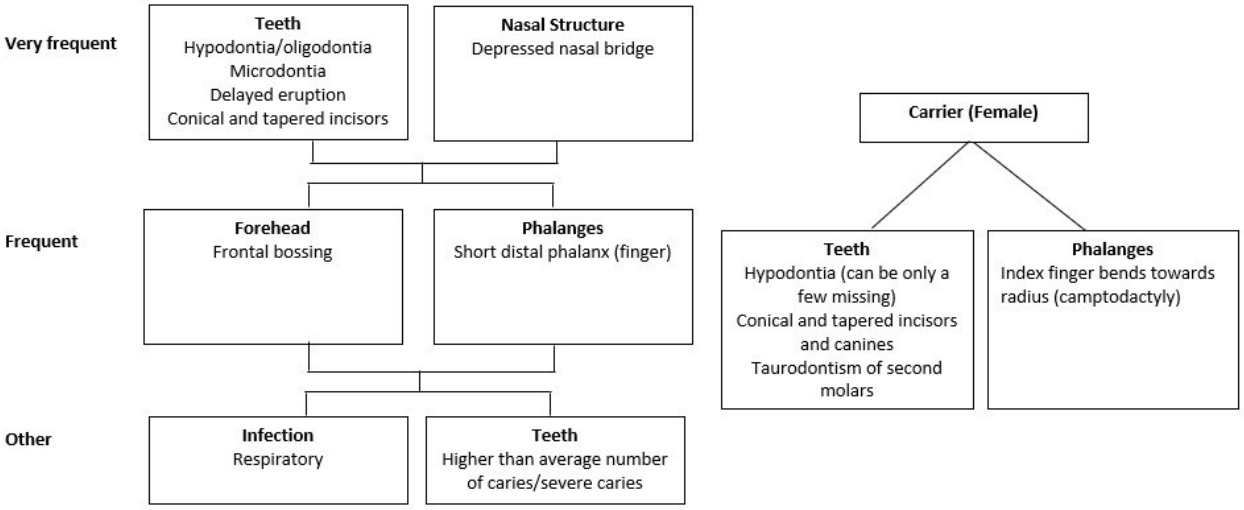


Figure 5: Skeletal anomalies of X-linked hypohidrotic ectodermal dysplasia and carrier (adapted from Bergendal 2014; Lexner 2007; García-Martín et al. 2011; Bailleul-Forestier et al. 2008; Orphanet 2020.

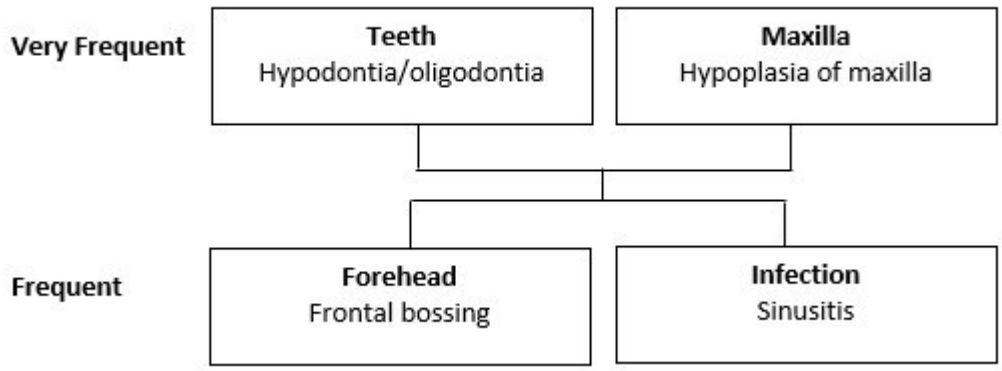


Figure 6: Skeletal anomalies of hypohidrotic ectodermal dysplasia (adapted from Lind et al. 2006; Orphanet 2020).

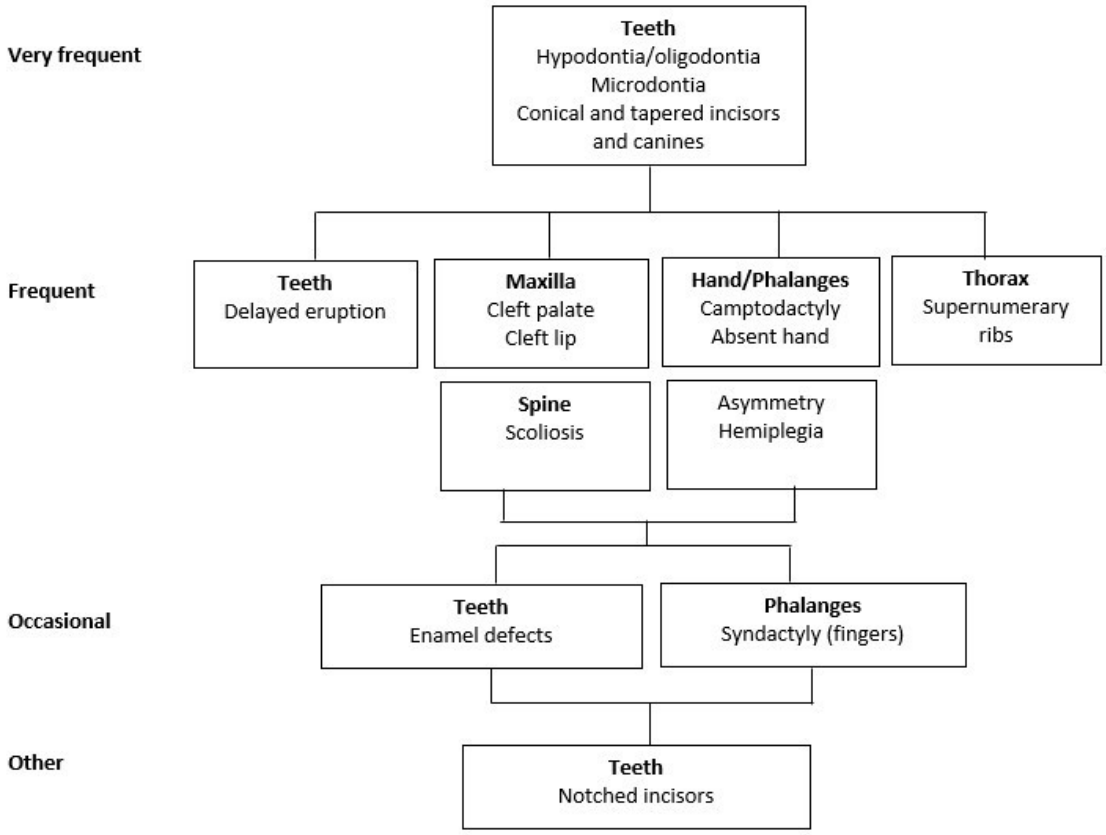


Figure 7: Skeletal features of Incontinentia Pigmenti (adapted from Bergendal 2014; Orphanet 2020).


Figure 8: i) tapered incisor; ii) tapered/concave canine iii) incisal notching (modeled after Bergendal 2014, 2469).

Hypodontia has been addressed in the dental anthropology literature. In their dental anthropology reference text, Brothwell et al. (2014) mentions the association of ectodermal dysplasias with hypodontia briefly; however, specific features and associations with other skeletal elements are not discussed. Nelson (2015) also covers an array of conditions associated with anomalies of the teeth and their prevalence. These sources provide valuable

information as it relates specifically to teeth; however, diagnostic information relating to other skeletal elements is lacking. This section details occurrences in paleopathological case studies specifically involving likely individuals with mutations causing complex conditions.

Dental agenesis (or hypodontia) is noted in the sample of paleopathological case studies (n=5) (Usher et al. 2000; Curate 2008; Laffranchi et al. 2015; Tur et al. 2017; Arriaza et al. 2019); however, oligodontia (more than six missing teeth) is not mentioned. Dental agenesis is most often associated with cases offering no diagnosis of a complex condition (n=4) (Usher et al. 2000; Curate 2008; Laffranchi et al. 2015; Tur et al. 2017). The only case offering a diagnosis attributes the anomalies present (curved fibulae, agenesis of central maxillary incisor, moderate kyphosis, fusion of vertebrae) to Klippel-Feil syndrome (Arriaza et al. 2019).

The type of teeth missing among these cases are the third molars, second molars and incisors. There is no mention of missing canines among these cases. Congenital anomalies of the spine, specifically block vertebrae, extra vertebrae, hemivertebrae, cleft vertebrae, and kyphosis, are mentioned most frequently in association with dental agenesis (n=4). The only other body regions mentioned alongside dental agenesis in more than one case study are the phalanges (toes specifically) (n=2). Congenital anomalies of the toes mentioned in these case studies include symphalangism (fusion), and bilateral post-axial toe polydactyly. Notching or tapering of incisors and/or canines is not noted among the case studies.

Infections were unexpectedly low considering the close correlation of rhinitis, sinusitis, otitis media, and respiratory illness with a number of conditions. Sinusitis is only mentioned in two case studies (Gladykowska-Rzeczycka et al. 1998; Phillips & Sivilich 2006), rhinitis in one (Charlier et al. 2012), and otitis media is not noted in this sample. Failure to

incorporate radiographic analysis into skeletal examinations may be associated with the minimal detection of these infections.

### 2.6.5 Anomalies of Ear Structure and Choanal Atresia

Detecting ear anomalies with no external indicators and identifying whether the anomaly is isolated or part of a complex condition are two key challenges faced by both paleopathologists and clinicians. Many conditions involving ear anomalies are particularly heterogeneous and/or mild in skeletal expression and anomalies of the middle and inner ear can come from numerous environmental and genetic etiologies (D'Arco et al. 2020). Anomalies that are not isolated are typically part of an autosomal dominant condition (Huang et al. 2012a).

Inner ear anomalies can be due to mutations in various genes including CHD7, HDAC8, MITF, NEFL, OTOF, SF3B4, SLC26A4, TECTA, TMPRSS3, USH2A (Likar et al. 2018). Environmental factors such as high altitude, and maternal diabetes can result in external and middle ear anomalies (Lammer et al. 1985; Wang et al. 2002; Castilla et al. 1999; Passos-Bueno et al. 2009). Infections during life, such as meningitis can result in inner ear damage (Huang et al. 2012b).

There are also conditions including outer and middle ear anomalies such as oculo-auriculo-vertebral syndrome (OAVS) that can be particularly informative to bioarchaeologists. In the case of OAVS, maternal diabetes has been suggested as a potential cause. This connection can be informative of other conditions present in the community (Grix 1982; Siebold et al. 2019; Wang et al. 2002; Johnson et al. 1982; Berkenstadt et al. 1991). The phenotype of OAVS is typically defined by facial asymmetry, atresia of the external auditory canal, vertebral and eye anomalies; however, it can be quite heterogeneous (Barisic et al. 2014).

This makes it difficult to detect in skeletal remains particularly when facial asymmetry is not present. This is an example of how genetic and environmental factors can overlap, making it difficult in most cases of mild skeletal involvement to distinguish isolated anomalies from anomalies that together can indicate a complex condition. However, if carefully studied, there are some symptoms that can suggest one type over another.

This is particularly true of inner ear anomalies, which can express in specific combinations occuring consistently due to infection or certain types of mutations causing complex conditions. For example, CHARGE syndrome (CHD7 gene mutation), BOR syndrome (EYA1, SIX1, SIX5 gene mutations), and Waardenburg syndrome (SOX10, PAX3, MITF, EDN3, EDNRB, and SNA12 mutations) all have specific sets of inner ear anomalies that if detected could suggest a syndromic association and the presence of severe soft tissue anomalies (Huang et al. 2012; D'Arco et al. 2020) (see figures 8-10).

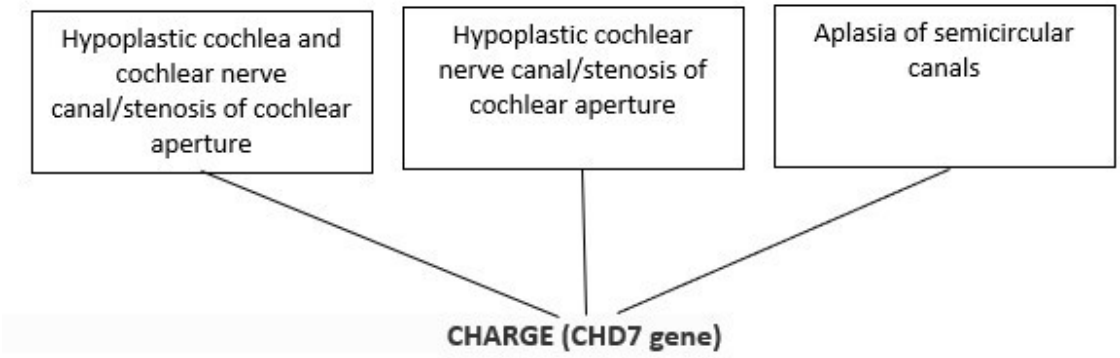


Figure 9: Combination of inner ear anomalies consistently occurring with CHARGE syndrome (adapted from Huang et al. 2012b; D'Arco et al. 2020).

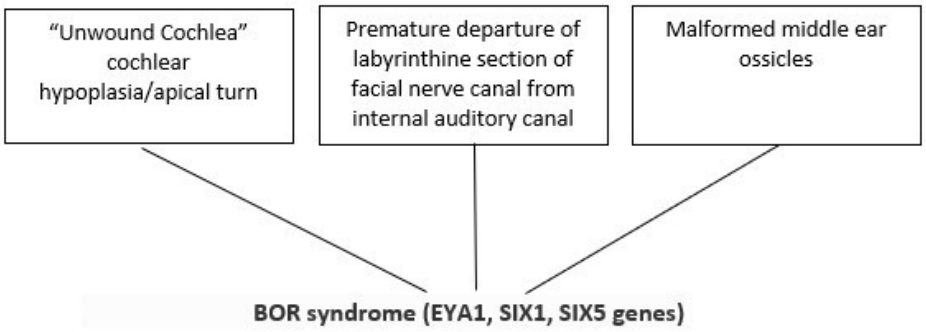


Figure 10: Combination of middle and inner ear anomalies consistently occurring with BOR syndrome (adapted from Huang et al. 2012b; D'Arco et al. 2020).

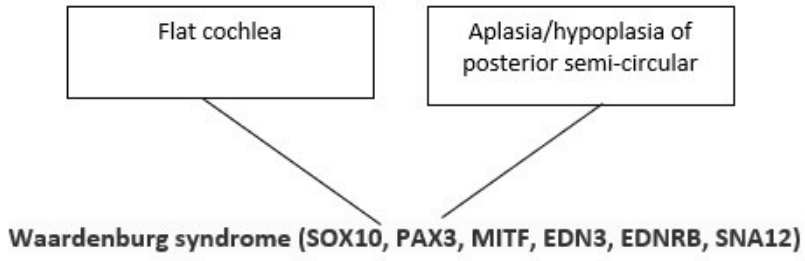


Figure 11: Combination of inner ear anomalies consistently occurring with Waardenburg syndrome (adapted from Huang et al. 2012b; D'Arco et al. 2020).

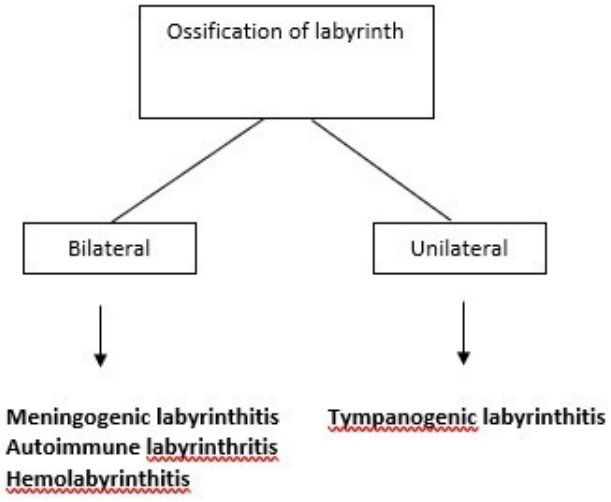


Figure 12: Inner ear damage caused by infection (adapted from Huang et al. 2012).

As radiographic examination is not always a standard part of skeletal examination in paleopathology (Chhem 2006), determining when to employ this type of method can prove difficult. Although it would be ideal to use radiographic technology on all remains examined, if this is not possible the presence of any anomaly should flag the remains as a candidate for radiographic examination of ear structures. Many syndromes with ear pathology involve anomalies of the spine, hands/feet/phalanges, cranial structure, maxilla, mandible, nasal and sinus structure, eye structure, and teeth (see figures 13-15 for examples).

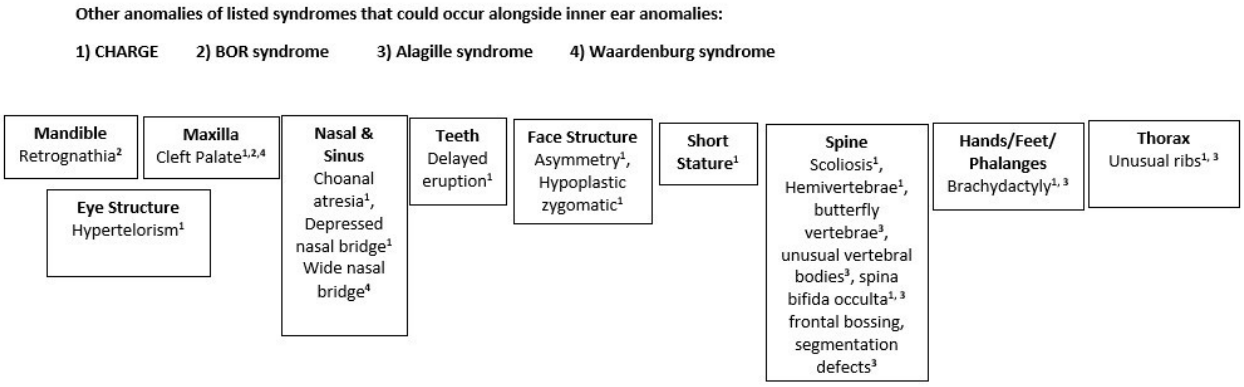


Figure 13: Anomalies occuring in syndromes with consistent anomalies of the inner ear (adapted from Orphanet 2020).

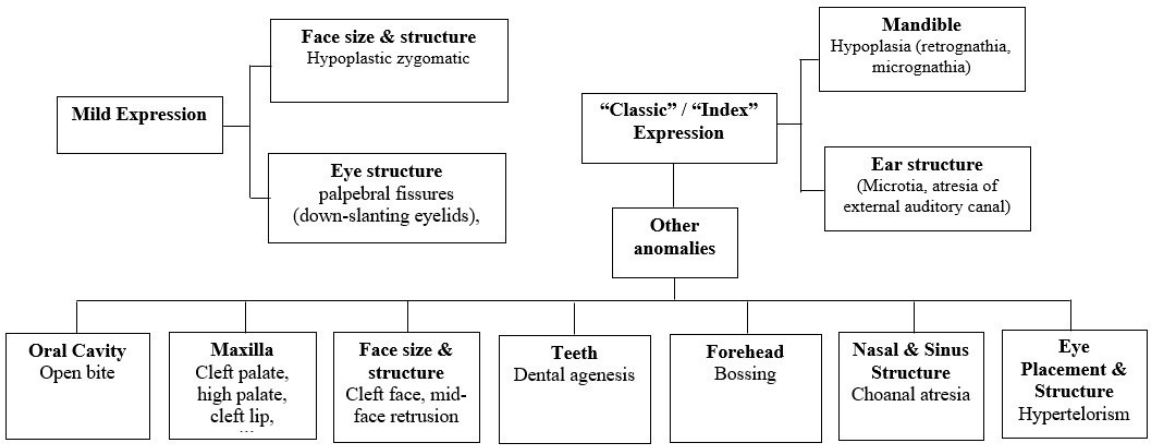


Figure 14: Various expressions of Treacher-Collins syndrome (adapted from Orphanet 2020 and Teber et al. 2004).

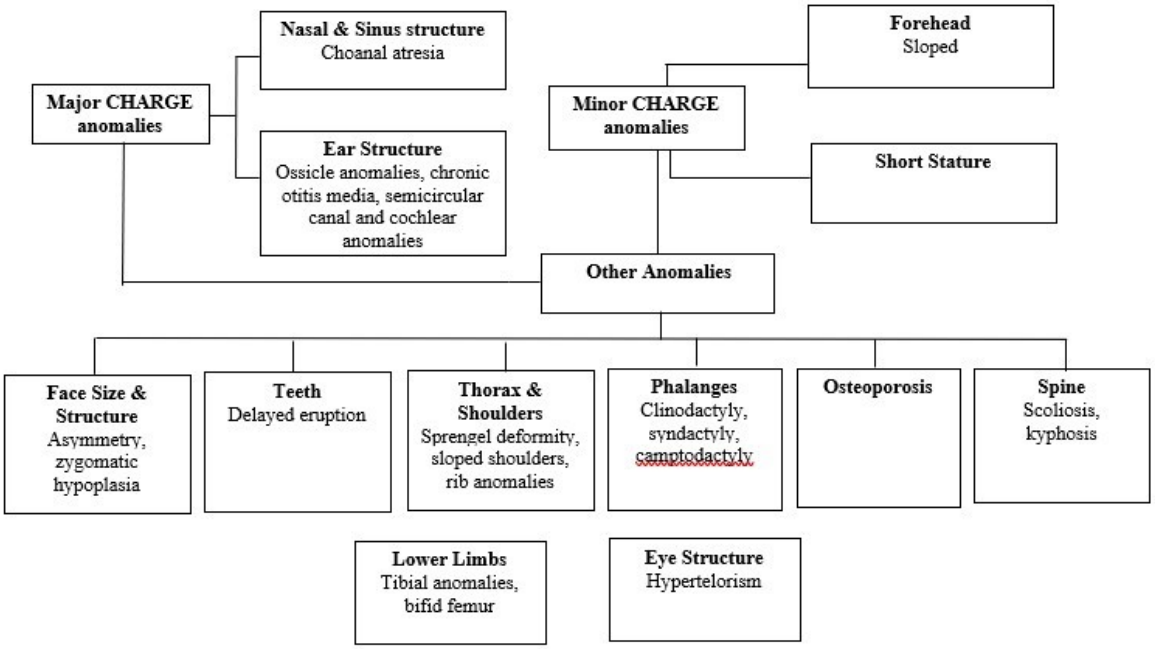


Figure 15: Minor and major anomalies of the skeletal structure only consistent with CHARGE syndrome (adapted from Orphanet, Blake & Prasad 2006).

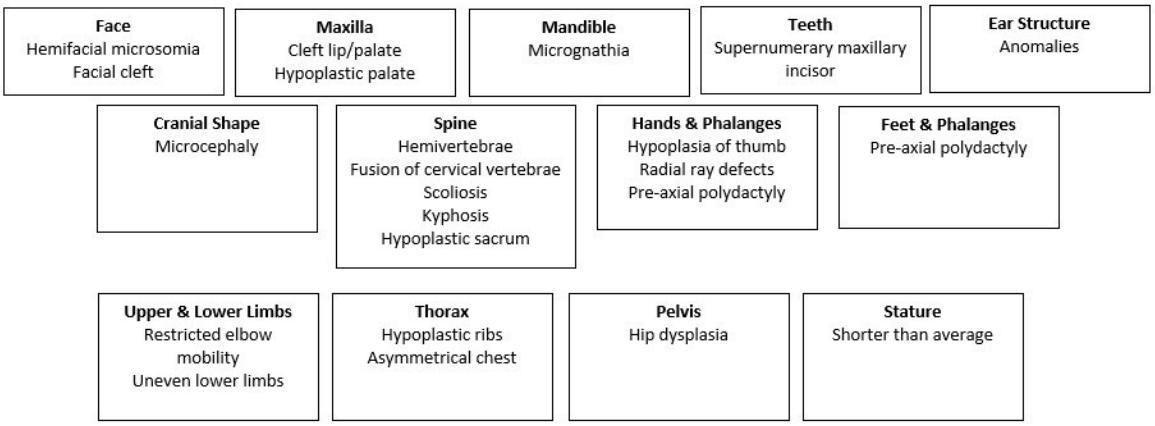


Figure 16: Skeletal anomalies known to occur with OAVS (adapted from Beleza-Meireles 2015, 457-459).

Choanal atresia refers to a bone or cartilaginous blockage of the passage between the nasal cavity and the vomer, although the blockage can also be membranous (Castriota-Scanderbeg 2005a,). This anomaly can occur as an isolated event 50% of the time. It can be bilateral

(although this can often be fatal) or unilateral, and is detectable in skeletal remains if the blockage is osseous (Castriota-Scanderbeg 2005a). As noted in the figure above, choanal atresia can occur alongside multiple anomalies. However, its relationship with the CHARGE syndrome anomalies, particularly those of the head, eyes, stature, and heart, is best known (Hall 1979; Harris et al. 1997). The same anomalies listed above for ear structure can be used as screening indicators for this anomaly; however isolated cases may still go undetected.

In paleopathology, anomalies of the middle ear have been noted (Barnes 2012; Arensburg et al. 2005; Panzer et al. 2008; van Duijvenbode 2015; Keenleyside 2011; Swanston 2011); however, anomalies of the inner ear are less frequently discussed (Spoor et al. 1998). In the paleopathological case study sample examined, there are relatively fewer cases involving the ear structure in general (n=9) (Panzer et al. 2008; Hoffman et al. 2019; Knusel et al. 1996; Kesterke & Judd 2019; Vairamuthu & Peiffer 2018; van Duijvenbode et al. 2015; Keenleyside 2011; Pany & Teschler-Nicola 2007; Swanston et al. 2013).

The types of ear anomalies identified by investigators are restricted to the external auditory canal and middle ear. These consist of hypoplasia or atresia of the ear canal (n=6) (Panzer et al. 2008; Knusel et al. 1996; van Duijvenbode et al. 2015; Keenleyside 2011; Pany & Teschler-Nicola 2007; Swanston et al. 2013), fused ossicles (n=2) (van Duijvenbode et al. 2015; Swanston et al. 2013), stapedial footplate fixation (n=2) (Kesterke & Judd 2019; Vairamuthu & Peiffer 2018), and an asymmetrical external auditory meatus (Hoffman et al. 2019). No inner ear anomalies or instances of choanal atresia are noted among the case studies. Other anomalies noted in association with middle and external ear anomalies predominantly include asymmetry of the skull (plagiocephaly) (n= 3) and upper and lower limbs (n=3). Conditions selected as most likely final diagnoses are Goldenhar syndrome

(Panzer et al. 2008), FAVS (Hoffman et al. 2019), neurofibromatosis (Knusel et al. 1996), Paget's disease (Kesterke & Judd 2019), osteogenesis imperfecta IV (Vairamuthu & Pfeiffer 2018), aural atresia (van Duijvenbode et al. 2015; Keenleyside 2011; Swanston 2011), and Klippel-Feil syndrome (Pany & Teschler-Nicola 2007).

Although generally considered a rare anomaly, choanal atresia could be underrepresented due to non-osseous forms that allude detection in skeletal remains (Castriota-Scanderbeg 2005a) and/or a failure to recognize its presence. As nearly all of the case studies including ear anomalies used radiographic equipment during analysis (n=7), and just under half of the total case studies did not use radiographic equipment, it is highly likely ear and sinus anomalies are also underrepresented in this sample. This is unfortunate as recording the prevalence and nature of ear anomalies can provide information on prenatal environmental stresses and rates of specific infections within a population.

### 2.6.6 Joint Laxity

Joint laxity characterizes multiple disorders known to have a spectrum of expression that can include minimal skeletal manifestation (Zannolli et al. 2002; Russek & Errico 2015; Kosho et al. 2010; Caraffi et al. 2019). Conditions caused by mutations to genes involved in the production of collagen, particularly types of Ehlers-Danlos syndrome, represent some of the best examples of joint laxity due to genetic causes. Similar to those presented above, these conditions often have related soft tissue anomalies that can severely impact life experience (Jørgensen et al. 2015; Ghali et al. 2019). There are nine types of Ehlers-Danlos caused by mutations to an array of genes including COL5A1 and COL5A2. These genes are essential to the development of type V collagen and cause the "classic" form of Ehlers-Danlos. When a mutation is present, it can result in delicate skin that is easily damaged and heals less

efficiently, along with generalized joint hypermobility, and indented (atrophic) scarring (Beighton 1970; Beighton et al. 1998; Symoens et al. 2009; Ritelli et al. 2013).

Other genes implicated in types of Ehlers-Danlos are B3GALT6 and COL3A1. Mutations to the gene B3GALT6 present as more severe than those of COL5A1 and COL5A2, causing both a pleiotropic type of Ehlers-Danlos and spondyloepimetaphyseal dysplasia. The main defect producing this type is a disruption in the proper functioning of proteoglycans, which aid in cell communication, development, tissue reconstruction, and morphogenesis (Van Damme et al 2018). Another form of Ehlers-Danlos described as "vascular" is caused by a mutation to the COL3A1 gene (Ghali et al. 2019).

In the case of pleiotropic Ehlers-Danlos symptoms, complex conditions are more likely to be considered based solely on skeletal remains as the result is more severe. However, the milder type of Ehlers-Danlos caused by COL5A1 and COL5A2 could be overlooked in skeletal remains as the main indicators are osteoarthritic patterns indicating joint laxity. Additional indicators of joint laxity can include scoliosis, kyphosis, vertebral fractures, low bone mineral density, pes planus (flat feet), genu recurvatum (a backward bend of the knee), and hallux valgus (bunions) (Castriota-Scanderbeg 2005b, 486; Beighton 1969; Hennekam et al. 2013; Formenti et al. 2018; Henderson et al. 2017).

The combination of these anomalies could suggest joint laxity. This is also true of complex conditions such as Fragile X. Although known for anomalies in brain development, subtle skeletal anomalies have been consistently reported for decades (Davids et al. 1990; Kjr et al. 2001; Kidd et al. 2014). As this condition can also involve heart malformations (Sreeram et al. 1989; Hagerman & Synhorst 1984; Loehr et al. 1986), its consideration in cases with signs of joint laxity can add to knowledge of life experience in the past. The following diagrams

provide an overview of joint laxity key indicators. If these are discovered in paleopathological settings a syndromic cause of joint laxity should be considered outside of typical activity-related or age-related contributors.

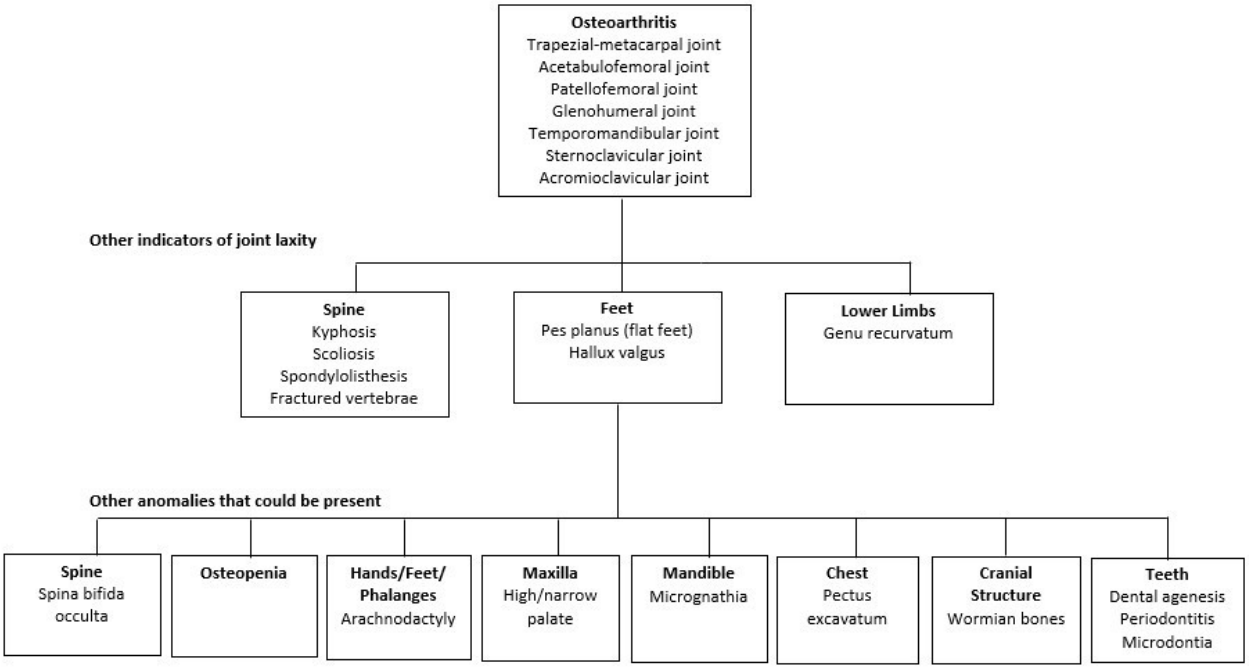


Figure 17: Mild forms of Ehlers-Danlos syndrome, combined symptoms (adapted from Orphanet 2020; Beighton 1969; Hennekam et al. 2013; Formenti et al. 2018; Henderson et al. 2017)

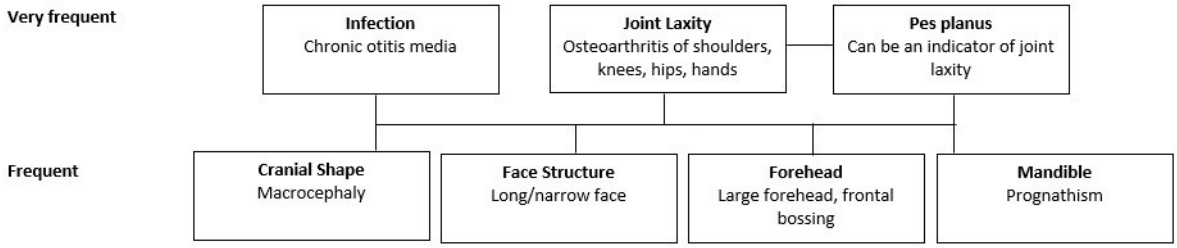


Figure 18: Skeletal anomalies of Fragile X full mutation and carrier (adapted from Orphanet 2020; Davids et al. 1990; Kidd et al. 2014)

Mild expressions of complex conditions causing premature osteoarthritis are discussed to a limited extent in paleopathological literature. A recent case study by Drtikolová et al. (2020) presents multiple individuals with evidence of osteoarthritis on several joints. Multiple complex conditions are considered in the differential diagnosis including a brief mention of Ehlers-Danlos and Marfan syndrome (Drtikolová et al. 2020). Drtikolová et al. encourage the study of mild skeletal anomalies in their article and suggest hip dysplasia as a potential anomaly to include in these indicators. The indicators mentioned in the figures above are provided as additional criteria in support of this direction.

A detailed comparison among the sample of paleopathological case studies analyzed for this paper was undertaken for mentions of joint degeneration indicating osteoarthritis. A total of 41 out of 132 skeletal remains examined (31%) and 27 differential diagnoses noted the presence of osteoarthritis. Single joint involvement was found in 49% (n=20) of the cases and involvement of four or more joints was found in 20% (n=8). The spine was the most frequently mentioned body area to be impacted by osteoarthritis in the case studies (n=24). This is followed by the knee (n=9), hip (n=7), feet (n=6) and elbow (n=6).

The conditions associated with osteoarthritis were reviewed for any indications of specific patterns. A number of short stature-related dysplasia cases showed indications of osteoarthritis including Leri-Weill Dyschondrosteosis, achondroplasia (Lagier et al. 1978; Titelbaum et al. 2015; Bianucci et al. 2012; Cummings & Rega 2008), spondylo-epiphyseal dysplasia (Arcini & Forlund 1996), and multiple epiphyseal dysplasia (Kozieradzka-Ogunmakin 2011). The age ranges estimated by investigators for these individuals varies from middle aged to older adult. This would suggest these individuals did not suffer from early onset osteoarthritis. Joints noted by investigators to be impacted by osteoarthritis

among individuals with these conditions are the radioulnar articulation, knee, carpal/metacarpal articulation, shoulder, elbow, ankle, talocalcaneal articulation, hip, and toes.

Signs of osteoarthritis were noted in all individuals with acromegaly, gigantism, or a combination of both. These individuals are also estimated by the authors of the studies to be under 40 years of age at the time of their death, which could qualify the osteoarthritis seen in this group of individuals as early onset (Bartelink et al. 2014; Charlier & Tsigonaki 2011; Gladykowska-Rzeczycka et al. 1998; Mulhern 2005). Also qualifying are two cases of potential Fibrous Dysplasia, both of which fall into younger estimated age ranges with one case below 20 years (Traversari et al. 2019) and the other below 40 years of age (Wells 1963).

Overall, the number of cases with a maximum estimated age of 40 years or less (n=13) is nearly equivalent to the number of cases with a maximum estimated age of over 40 years (n=18). There is a greater number of estimated males (n=10) among the individuals falling within the 40 years or less age range compared to estimated females (n=2) and unknown sex (n=1). Those above 40 years of age show the same number of males (n=9) as females (n=9) with signs of osteoarthritis.

## 2.7 Discussion

This analysis of paleopathological case studies suggests minor expressions of syndromes are difficult to detect and/or there are aspects of these syndromes which are not well recognized that are often viewed as isolated by default. This tendency to default to a diagnosis of isolated when complex conditions can not be confidently ruled out suggests the influence of availability and framing bias impacts diagnostic decision making in paleopathology. These

biases can also be seen in cases that dismiss diagnoses based on incomplete matches to index expressions of complex conditions.

The results also indicate the inner ear is particularly underrepresented among the case studies analyzed. This is likely due to the sporadic use of radiographic equipment within paleopathology (Chhem 2006). Another contributor could be a gap in knowledge concerning anomalies occurring frequently with inner ear defects, which can be used as screening tools. The review of medical literature suggests it is possible to assess whether these anomalies could be part of a complex condition with only a single element present and that some anomalies may be more indicative of a specific type of mutation than others. Anomalies of the inner ear also have the potential to inform on maternal health.

There are a number of reasons to improve detection of these anomalies and minor expressions of mutations in general. Careful attention to specific features of seemingly isolated anomalies and combinations of minor anomalies in archaeological populations could aid in determining possible relationships to complex conditions. From the application of this knowledge there is the potential to expand the types of complex conditions and mutations causing isolated anomalies in differential diagnoses. Recognition of variable expressions of conditions such as OAVS could also allow for more accurate inferences concerning other associated conditions, such as prenatal diabetes, within an archaeological population. Understanding the relationships between anomalies associated with mild expressions can also be beneficial in detecting anomalies not visible macroscopically. Better detection of anomalies of the inner ear in particular can aid greatly in our understanding of infection rates in a population and can drastically change concepts of life experience in particular cases.

Recognizing anomalies involved in mild expressions of complex conditions can also result in a more accurate record of the range of variation among complex conditions in the past. Improved screening of these cases could allow for more thorough examination through aDNA or radiographic methods. More integrated use of radiographic imaging to capture inner ear anomalies would be a substantial aid to this endeavor.

These strategies are especially significant in relation to conditions without a known etiology and heterogenous expression, such as OAVS. Multiple studies have been produced reflecting the environmental influence on the presentation of this very heterogeneous condition. Some of these influences include elevation levels (Castilla et al. 1999) and prenatal diabetes (Grix 1982; Siebold et al. 2019; Wang et al. 2002; Johnson et al. 1982; Berkenstadt et al. 1991). A solid understanding of the mild and extreme cases of this condition could allow for better geographical tracking. The ability to examine other members of the community and environment for potentially health-related risks could provide essential information as to its etiology.

Some researchers believe there is little value in studying in detail the nature of various complex conditions due to their rarity in the archaeological record (Oostra et al. 2016,), and others prefer to record the presence of anomalies in a population over attempting a diagnosis involving a complex condition (Barnes 2012). However, the information presented in this study suggests a better understanding of medical diagnostic features relating to minor anomalies could provide valuable information on the overall life experience and environments of past populations.

Next steps and future goals in relation to this topic include the development of a central reference focusing on diagnostic strategies and features of expressions on the mild end of the

mutational spectrum. Better recognition of these features can lead to better recording of mild expressions and their inclusion in future databases. As mentioned above, case studies can also be used to compare severity of expression and potential environmental factors.

Wood et al. (1992) astutely demonstrated the skeletal remains with the least obvious ailments did not necessarily belong to the healthiest individuals of a population. This is also true with the manifestation of complex conditions in skeletal remains, as a single minor anomaly visible can be indicative of more severe soft tissue malformations. Although it may not be possible to determine with any degree of confidence a particular condition is present without aDNA analysis, considering the full mutational spectrum of conditions can expand the current paleopathological database, enrich our understanding of the environment/genetic etiology of complex conditions, and aid in differential diagnosis.

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## Appendix

Appendix Table 1: List of conditions selected as final suggested diagnoses.

| Diagnosis | # of Articles/Listings (if online) | Case Studies |
|---|---|---|
| Blastogenetic developmental field defect/sequential developmental field defect | 1 | Usher et al. 2000 |
| Os odontoideum and developmental anomalies | 2 | Titelbau & Castillo 2015; Curate 2008 |
| FAVs | 1 | Hoffmann et al. 2019 |
| Cleidocranial Dysplasia | 1 | Sacks 2018 |
| Isolated Pre-axial polydactyly | 1 | Murphy 1999 |
| Bilateral post-axial polydactyly; dental agenesis; bipartite medial cuneiform | 1 | Laffranchi et al. 2015 |
| Gorlin-Goltz Syndrome | 1 | Ponti et al. 2016 |
| Multiple epiphyseal dysplasia | 1 | Kozieradzka-Ogunmakin 2011 |
| Impacted maxillary and mandibular canines | 1 | Rajić et al. 2019 |
| Non-syndromic brachycephaly | 1 | Giuffra et al. 2013 |
| Unconfirmed syndrome (Tutankhamun) | 1 | Hussein et al. 2013 |
| Dyke-Davidoff-Masson syndrome | 2 | Slon et al. 2012; Khudaverdyan et al. 2018 |
| Marfan Syndrome | 1 | Panzer et al. 2018 |
| Binder Syndrome | 1 | Mulhern et al. 2002 |
| Goldenhar syndrome | 1 | Panzer et al. 2008 |
| Leri-Weill Dyschondrosteosis | 8 | Lagier et al. 1978; Bianucci et al. 2012; Cummings & Rega 2008; Titelbaum et al. 2015; Waldron 2000; Cormier et al. 2017 (combined achondroplasia and Leri-Weill dyschondrosteosis) |
| Basal Cell Naevus Sydrome (also known as Gorlin Goltz) | 1 | Ponti et al.. 2016 |
| Stage 1-2 Müller-Weiss Disease | 1 | Chiavegatti et al. 2018 |
| Kartagener syndrome | 1 | Charlier et al. 2012 |
| Down Syndrome | 2 | Rivollat et al. 2014; Brothwell 1960 |
| Fibrous dysplasia | 5 | Traversari et al. 2019; Canalis et al. 1980; Wells 1963; Milella et al. 2016; Willmon et al. 2013 |
| Turner syndrome | 1 | Ottini et al. 2001 |
| Acromegaly | 2 | Bartelink et al. 2014; Canci et al. 2014 |
| Hyperpituitary Gigantism | 2 | Minozzi et al. 2015; Mulhern 2005 |
| Gigantism and Acromegaly | 1 | Gladykowska-Rzeczycka et al. 1998 |
| Thalassemia | 3 | Thomas 2016; Hershkovitz et al. 1991; Rohnbogner 2016 |
| Post-axial polydactyly type A, possibly syndromic | 1 | Case et al. 2006 |
| Probable Osgood-Schlatter's disease | 2 | DiGangi et al. 2010; Wells 1968 |
| Acromesomelic dysplasia | 1 | Frayer et al. 1987 |
| Achondroplasia | 2 | Waters-Rist & Hoogland 2013; Cormier et al. 2017 |

| Diagnosis | # of Articles/Listings (if online) | Case Studies |
|---|---|---|
| Idiopathic Short Stature | 1 | Waters-Rist & Hoogland 2013 |
| Madelung's Deformity | 1 | Canci et al. 2002 |
| Spondylo-epiphyseal Dysplasia with mild coxa vara | 1 | Arcini & Forlund 1996 |
| Gardner's Syndrome | 1 | Licata et al. 2016 |
| Type of lysosomal storage disease | 1 | Woo et al. 2015 |
| Caffey's Disease | 1 | Lombardo, et al. 2019 |
| Osteogenesis imperfecta | 3 | Wells 1965; Vairamuthu & Susan Pfeiffer 2018; Cope & Dupras 2011 |
| Paget's Disease (osteitis deformans) | 4 | Wells & Woodhouse 1975; Aaron et al. 1992; Burrell et al. 2019; Kesterke & Judd 2019 |
| Leontiasis Ossea | 1 | Mansilla-Lory, J et al. 2007 |
| Neurofibromatosis | 2 | Knusel et al. 1996; Murphy 1998 |
| Pituitary dwarfism | 1 | Roberts 1987 |
| Paediatric onset hypopituitarism and hypothyroidism | 1 | Halcrow et al. 2020 |
| Hypopituitarism | 1 | Molto & Kirkpatrick 2017 |
| Hydrocephalus | 3 | Richards & Anton 1991; Zeljika et al. 2019; Murphy 1996 |
| Cerebral Palsy | 1 | Tesorieri 2016 |
| Congenital and isolated aural atresia | 3 | van Duijvenbode et al. 2015; Keenleyside 2011; Swanston et al. 2013 |
| Neurogenic paralysis | 1 | Novak et al. 2014 |
| Congenital naviculocuneiform I coalition | 1 | Lieverse et al. 2012 |
| Talipes equinovarus | 1 | Wright 2011 |
| Congenital scoliosis | 1 | Kilgore & Van Gerven 2010 |
| Congenital upper limb synostosis | 1 | Swenson & Spinek 2020 |
| Congenital absence of patella | 1 | Patrick & Waldron 2003 |
| Congenital absence of ulna | 1 | Mann et al. 1998 |
| Sagittal cleft/butterfly vertebra(e) | 4 | Keenleyside 2012; Brasili et al. 2002; Anderson 2003; Fabra & Salega 2014 |
| Transverse basilar cleft | 1 | Semenovna et al. 2018 |
| Complete bilateral cleft palate | 2 | Phillips & Sivilich 2006; Tur at al. 2016 |
| Klippel-Feil Syndrome Type II/KFS/KFS Type I | 6 | Pany & Teschler-Nicola 2007; Fabra & Selega 2014; Drupka et al. 2019; Arriaza et al. 2019; Marchewka et al. 2017 |
| Spondylocarpotarsal synostosis | 1 | Rubini et al. 2013 |
| Os cuneiform mediale (bipartite medial cuneiform) | 1 | Kjellström 2004 |
| Transverse forearm deficiency | 1 | Gładykowska-Rzeczycka & Mazurek 2008 |
| Clubfoot, possibly due to Poliomyelitis | 1 | Roberts et al . 2004 |
| Complete brachial palsy | 1 | Lieverse et al. 2008 |

| Diagnosis | # of Articles/Listings (if online) | Case Studies |
|---|---|---|
| Hemivertebrae and sacral agenesis | 1 | Pitre & Lovel 2009 |
| Primary dysplasia of the scapula neck | 1 | Mays 2009 |
| Poliomyelitis | 1 | Ciesielska & Stark 2019 |
| Arthrogryposis multiplex congenita | 1 | Anderson & Thomas 1998 |
| Camurati–Engelmann disease | 1 | Giuffra et al. 2016 |
| Hypochondroplasia | 1 | Garcia & Santos 2019 |
| Pectus carinatum | 1 | Groves et al. 2003 |
| Bilateral Congenital Dislocation of the Hip, Spina Bifida Occulta and Spondylolysis | 1 | Wakely 1993 |
| Combined achondroplasia and Leri-Weill dyschondrosteosis | 1 | Cormier et al. 2017 |
| Osgood–Schlatter's disease & cartilaginous dysplasia | 1 | DiGangi et al. 2010 |
| Isolated Brachydactyly | 1 | Cybulski 1988 |
| Triplegia | 1 | Noval et al. 2014 |
| No diagnosis - wormian bones, palatine torus, hyperostosis, osteoarthritis, osteoma | 1 | Museum of London, Wellcome Osteological Database |
| No diagnosis - ribs fused to sternum, sternal aperture, hyperostosis | 1 | Museum of London, Wellcome Osteological Database |
| No diagnosis - wormian bones bones, parietal foramen, retained metopic suture | 1 | Museum of London, Wellcome Osteological Database |
| No diagnosis - short/hypoplastic metacarpals, osteoarthritis | 1 | Museum of London, Wellcome Osteological Database |
| No diagnosis - palatine torus, irregular/crowded teeth, supernumerary teeth, abnormally shaped teeth | 1 | Museum of London, Wellcome Osteological Database |

Appendix Table 2: Congenital Anomaly Recording Form (Adapted from Castriota-Scanderbeg & Dallapiccola 2005; Shapira et al. 2019; Miles et al. 2008)

| **Congenital Anomaly Recording Form** | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| Stature | | |
| | Tall Stature | |
| | Short Stature | |
| | **Body Region Total** | **0** |
| | | |
| Cranial Shape | | |
| | Plagiocephaly/asymmetric skull | |
| | Trigonocephaly | |
| | Turricephaly | |
| | Brachycephaly | |
| | Dolichocephaly | |
| | Cloverleaf skull | |
| | Macrocephaly | |
| | Microcephaly | |
| | Flat occiput | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Prominent occiput | |
| | **Body Region Total** | **0** |
| | | |
| Cranial Structure | | |
| | Large fontanelles | |
| | Wormian bones (specific if 10 + present, larger than 4-6 mm diameter) | |
| | Skull thickening | |
| | Calvarial thinning | |
| | Sella turcica abnormalities | |
| | Abnormalities of the foramen magnum | |
| | Basilar impression | |
| | Intracranial calcification | |
| | Wide cranial sutures | |
| | **Body Region Total** | **0** |
| | | |
| Forehead | | |
| | Frontal bossing | |

| **Congenital Anomaly Recording Form** | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Prominent forehead | |
| | Sloping forehead | |
| | Wide forehead | |
| | Narrow forehead/temporal narrowing | |
| | Vertical forehead crease | |
| | Depressed glabella | |
| | Metopic depression | |
| | Prominent metopic ridge | |
| | **Body Region Total** | **0** |
| | | |
| Ear Structure | | |
| | Auricular pits/fistulas | |
| | **Body Region Total** | **0** |
| | | |
| Eye Placement/Structure | | |
| | Orbital size abnormalities | |
| | Hypertelorism | |
| | Hypotelorism | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | **Body Region Total** | **0** |
| | | |
| Eyebrow | | |
| | Prominent supraorbital ridge | |
| | Underdeveloped supraorbital ridge | |
| | **Body Region Total** | **0** |
| | | |
| Nasal & Sinus Structure | | |
| | Small sinuses | |
| | Aplasia of sinuses | |
| | Choanal Atresia | |
| | Narrow nasal bridge | |
| | Broad/wide nasal bridge | |
| | Depressed/flat nasal bridge | |
| | Prominent/high nasal bridge | |
| | Bifid nose | |
| | **Body Region Total** | **0** |
| | | |

| **Congenital Anomaly Recording Form** | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| Face Size and Structure | | |
| | Asymmetric face | |
| | Flat face | |
| | Mid-face/malar hypoplasia | |
| | Mid-face/malar hyperplasia | |
| | Small face | |
| | Long face | |
| | Narrow face | |
| | Short face | |
| | Round face | |
| | Square face | |
| | Triangular face | |
| | Broad face | |
| | Coarse face | |
| | Prominent cheek bone | |
| | Underdeveloped cheek bone | |
| | **Body Region Total** | **0** |
| | | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| Maxilla | | |
| | Malar flattening | |
| | Malar prominence | |
| | Midface protrusion | |
| | Midface retrusion | |
| | Premaxillary prominence | |
| | Premaxillary underdevelopment | |
| | **Body Region Total** | **0** |
| | | |
| Mandible | | |
| | Broad jaw | |
| | Narrow jaw | |
| | Micrognathia | |
| | Retrognathia | |
| | Prognathism | |
| | Cleft mandible | |
| | **Body Region Total** | **0** |
| | | |

| **Congenital Anomaly Recording Form** | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| Chin | | |
| | Broad chin | |
| | Pointed chin | |
| | Short chin | |
| | Tall chin | |
| | **Body Region Total** | **0** |
| | | |
| Mouth | | |
| | Open-mouth/bite | |
| | **Body Region Total** | **0** |
| | | |
| Oral Cavity | | |
| | Thick/wide alveolar ridges | |
| | Paramedian cleft lip/palate | |
| | Oblique cleft lip/palate | |
| | Transverse/lateral cleft lip/palate | |
| | High palate | |
| | Narrow palate | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | **Body Region Total** | **0** |
| | | |
| Teeth | | |
| | Enamel abnormalities | |
| | Irregular or crowded teeth | |
| | Supernumerary tooth (teeth) | |
| | Abnormally shaped teeth (including peg shaped) | |
| | Small/dysplastic teeth | |
| | Missing tooth (teeth) | |
| | Widely-spaced teeth | |
| | **Body Region Total** | **0** |
| | | |
| Neck | | |
| | Short neck | |
| | **Body Region Total** | **0** |
| | | |
| Thorax & Shoulders | | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Small thoracic cage | |
| | Long, narrow thorax | |
| | Pectus excavatum | |
| | Pectus carinatum | |
| | Short rib(s) | |
| | Eleven pairs of rib(s) | |
| | Supernumerary rib(s) | |
| | Thin or twisted rib(s) | |
| | Broad and/or thickened rib(s) | |
| | Notched rib(s) - inferiorly | |
| | Notched rib(s) - superiorly | |
| | Fused rib(s) | |
| | Bifurcated rib(s) | |
| | Flared or cupped rib(s) | |
| | Rib gap | |
| | Slender clavicles | |
| | Wide and/or thickened clavicles | |
| | Lateral hooks on clavicles (handlebars) | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Shoulder shape abnormal | |
| | Narrow shoulders | |
| | Sloping shoulders | |
| | 'Hook-shaped' scapula | |
| | Duplicated scapula | |
| | Sprengel deformity | |
| | Scapula hypoplasia | |
| | Extra ossification centres - sternal manubrium | |
| | Decreased ossification centres - sternal | |
| | Failure of sternal mineralization | |
| | Sternal cleft | |
| | Short, bifid sternum | |
| | **Body Region Total** | **0** |
| | | |
| Back and spine | | |
| | Tall vertebrae | |
| | Beaked vertebrae | |
| | Vertebral body scalloping | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Platyspondyly | |
| | Hemivertebrae (same as butterfly/cleft) | |
| | Block vertebrae | |
| | Coronal cleft vertebra(e) | |
| | Sagittal cleft vertebra(e) | |
| | Absent or Minimal Vertebral Ossification | |
| | Odontoid Hypoplasia/Aplasia | |
| | Sacral agenesis | |
| | Narrow spinal canal (spinal stenosis) | |
| | Wide Spinal Canal | |
| | Atlanto-axial Instability | |
| | Disc calcification | |
| | Lordosis | |
| | Kyphosis | |
| | Scoliosis | |
| | **Body Region Total** | **0** |
| | | |
| Pelvis | | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Hypoplastic/small pelvis | |
| | Flared iliac wings | |
| | Abnormally small sciatic notches | |
| | Serration of iliac crest | |
| | Wide interpubic distance | |
| | Angle of acetabulum small | |
| | Protrusio acetabuli | |
| | Slipped Capital Femoral Epiphysis | |
| | Coxa vara | |
| | Coxa valga | |
| | Early Ossification of the Femoral Head | |
| | Irregular femoral head (fragmented, hypoplastic, aplastic | |
| | Subluxation/dislocation of hip | |
| | **Body Region Total** | **0** |
| | | |
| Upper Limbs | | |
| | Asymmetric arms | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Stippled Epiphyses | |
| | Hypoplastic, dysplastic,dysgenetic epiphyses | |
| | Large epiphyses | |
| | Broad metaphyses | |
| | Coarse/frayed metaphyses | |
| | Metaphyseal Cupping | |
| | Metaphyseal Spurs | |
| | Slender tubular bones | |
| | Bowed tubular bones | |
| | Cortical thickening, hyperostosis | |
| | Cortical thinning | |
| | Absent forearm (amelia) | |
| | Rhizomelia | |
| | Mesomelia | |
| | Radioulnar Synostosis | |
| | Humeroradial Synostosis | |
| | Humeroulnar Synostosis | |
| | Madelung Deformity | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Cubitus valgus | |
| | Limited movement/flexion deformity elbow | |
| | Broad tubular bones | |
| | Restriction of supination/pronation | |
| | **Body Region Total** | **0** |
| | | |
| Hands | | |
| | Radial Ray Deficiency | |
| | Ulnar Ray Deficiency | |
| | Large hands | |
| | Small hands | |
| | Absent hand (acheiria) | |
| | Split hand (Central Ray Deficiency) | |
| | Trident hand | |
| | **Body Region Total** | **0** |
| | | |
| Fingers and Thumbs | | |
| | Pseudoepiphyses | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Ivory epiphyses | |
| | Cone-shaped epiphyses | |
| | Acro-osteolysis | |
| | Camptodactyly | |
| | Clinodactyly | |
| | Tapering fingers | |
| | Clubbed fingers | |
| | Presence of os centrale | |
| | Other supernumerary carpal bones | |
| | Carpal coalition | |
| | Short/hypoplastic metacarpals | |
| | Short phalanges | |
| | Wide phalanges | |
| | Long phalanges | |
| | Overlapping fingers | |
| | Macrodactyly | |
| | Syndactyly | |
| | Symphalangism | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Angel-shaped phalanges | |
| | Broad thumbs | |
| | Clubbed thumb | |
| | Trident hand | |
| | Absent finger | |
| | Absent thumb | |
| | Triphalangeal thumb | |
| | Hypoplastic or truncated thumb | |
| | Preaxial thumb polydactyly | |
| | Postaxial polydactyly | |
| | Bi-fid thumb | |
| | Absent hand | |
| | Split hand | |
| | Absent finger(s) (aphalangism) | |
| | **Body Region Total** | **0** |
| | | |
| Lower Limbs | | |
| | Broad tubular bones | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Slender tubular bones | |
| | Bowed tubular bones | |
| | Cortical thickening, hyperostosis | |
| | Cortical thinning | |
| | Rhizomelia | |
| | Mesomelia | |
| | Asymmetrical lower limbs | |
| | Tibial hemimelia | |
| | Fibular hemimelia | |
| | Abnormal patella | |
| | Stippled Epiphyses | |
| | Hypoplastic, dysplastic, dysgenetic epiphyses | |
| | Large epiphyses | |
| | Metaphyseal Cupping | |
| | Broad metaphyses | |
| | Metaphyseal Spurs | |
| | Coarse/frayed metaphyses | |
| | Vertical striations near/on metaphyses | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Genu varum | |
| | Genu valgum | |
| | **Body Region Total** | **0** |
| | | |
| Feet | | |
| | Acro-osteolysis | |
| | Cone-shaped epiphyses | |
| | Pes planus | |
| | Club foot, varus | |
| | Rocker bottom foot | |
| | Large feet | |
| | Small feet | |
| | Wide feet | |
| | Hallux valgus | |
| | Toes, other | |
| | Short toes | |
| | Long toes | |
| | Slender toes | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Broad toes | |
| | Short toes | |
| | Long toes | |
| | Slender toes | |
| | clinodactyly | |
| | Tarsal fusion/coalition (synostosis) | |
| | Duplication of calcaneus / Bipartite calcaneus | |
| | Triplication of calcaneus | |
| | Stippled calcaneus | |
| | Syndactyly 2-3 of toes | |
| | Syndactyly not 2-3 of toes | |
| | Widely spaced toes | |
| | Hallux varus (sandal gap) | |
| | Camptodactyly/hammer toes | |
| | Metatarsus adductus | |
| | Absent foot | |
| | Split foot | |
| | Absent toe | |

| Congenital Anomaly Recording Form | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Absent great toe | |
| | Absent 2nd-5th toe | |
| | Hypoplastic or truncated great toe | |
| | Preaxial toe polydactyly | |
| | Bifid great toe | |
| | Great toe and second toe overlap | |
| | Other toes overlap | |
| | Postaxial toe polydactyly | |
| | Hypoplastic or truncated toe | |
| | **Body Region Total** | **0** |
| | | |
| Joints | Joint contractures | |
| | Joint laxity | |
| | **Body Region Total** | **0** |
| | | |
| | | |
| Various | Osteoporosis | |
| | Hyperostosis/osteosclerosis | |

| **Congenital Anomaly Recording Form** | | |
|---|---|---|
| **Body Region** | **Feature** | **Present 1=Yes** |
| | Fractures | |
| | Exostoses | |
| | Spurs | |
| | Horns | |
| | Multiple radiolucent bone defects | |
| | Osteolyses | |
| | Advanced skeletal aging | |
| | Delayed skeletal aging | |
| | Asymmetry | |
| | **Body Region Total** | **0** |
| | | |
| | **Overall Total** | **0** |
| | | |
| Other Conditions Not Listed: | | |

Appendix Table 3: Brachydactyly, Polydactyly (Short/Hypoplastic/Extra Metacarpals, Metatarsals and Phalanges) and Associated Anomalies (data collected from Minozzi et al. 2015; Garcia & Santos 2019; Satinoff & Wells, 1969; Ponti et al., 2016; Kozieradzka-Ogunmakin, 2011; Cybulski 1988; Cormier et al. 2017; Lieverse et al. 2008; Museum of London, Wellcome Osteological Database, Bermondsey Abbey; Roberts et al. 2004

| **Anomaly** | **# of Cases** | **Anomaly** | **# of Cases** | **Body Region** | **# of Cases** |
|---|---|---|---|---|---|
| Brachycephaly | 2 | Asymmetrical upper limbs | 2 | Cranial shape | 6 |
| Cleft palate | 1 | Asymmetrical lower limbs | 1 | Cranial structure | 7 |
| Retrognathia | 1 | Asymmetrical hands | 1 | Stature | 1 |
| Scoliosis | 7 | Asymmetrical phalanges (fingers & thumbs) | 1 | Forehead | 2 |
| Kyphosis | 2 | Dental Agenesis | 2 | Ear structure | 0 |
| Pes planus | 1 | Spina bifida occulta | 2 | Eye Structure | 0 |
| Club foot | 2 | Irregular/crowded teeth | 7 | Eyebrow | 0 |
| Post-axial toe polydactyly | 3 | Osteoarthritis | 6 | Nasal & Sinus | 0 |
| Calvaria thinning | 1 | Hyperostosis | 1 | Face Size & Structure | 0 |
| Sella turcica abnormalities | 3 | Narrow spinal canal | 1 | Maxilla | 4 |
| Wormian bones | 1 | Os odontoideum | 1 | Mandible | 4 |
| Skull thickening | 1 | Tubercle on foramen magnum | 1 | Oral cavity | 0 |
| Short stature | 1 | Symphalangism | 1 | Thorax | 5 |
| Short/hypoplastic metatarsals | 4 | Bipartite medial cuneiform | 1 | Shoulders | 1 |
| Short/hypoplastic metacarpals | 10 | Enamel defects | 1 | Spine | 11 |
| Bowed lower limbs | 1 | Slender tubular bones (upper) | 1 | Pelvis | 2 |
| Plagiocephaly | 4 | Mandibular cysts/Stafne defect | 3 | Upper limbs | 4 |
| Butterfly vertebrae | 1 | Bifurcated rib | 4 | Lower limbs | 2 |
| Asymmetry | 1 | Incomplete laminae fusion | 3 | Teeth | 8 |
| Asymmetrical clavicle and scapula | 1 | Maxillary cysts | 3 | | |
| Basilar impression | 1 | Rhizomelia (upper limbs) | 1 | | |
| Unfused left tibial epiphysis | 1 | Robust humeri | 1 | | |
| Frontal bossing | 2 | Deformed proximal tibia | 1 | | |
| Flared distal metaphyses | 1 | Genu varum | 1 | | |
| No other anomalies | 2 | Short ribs | 1 | | |

| Anomaly | # of Cases | Anomaly | # of Cases | Body Region | # of Cases |
|---|---|---|---|---|---|
| Flared iliac wings | 1 | Unusual development of distal articular surface of humeri and ulnae | 1 | | |
| Limited movement of elbow/flexion deformity | 1 | Short phalanges | 2 | | |
| Coxa valga | 1 | Abnormally shaped metatarsals | 1 | | |
| Slender clavicle | 1 | Small & flat humeral head | 1 | | |
| Bowed ulna & radius | 1 | Flared epiphyses | 1 | | |

Appendix Table 4: Dental Agenesis and Associated Anomalies (data collected from (Usher et al. 2000; Curate 2008; Laffranchi et al. 2015; Tur et al. 2017; Arriaza et al. 2019)

| **Dental Agenesis** | | | | | |
|---|---|---|---|---|---|
| **Tooth/Teeth Missing** | | **Number** | **Conditions** | | |
| Lateral Incisors | | 1 | Developmental Field Defects | | |
| Upper 3rd molars | | 1 | Congenital os odontoideum | | |
| Two lower 3rd molars | | 1 | Co-occuring anomalies | | |
| Right lower central incisor | | 1 | Co-occuring anomalies | | |
| Maxillary incisors | | 1 | Complete bilateral cleft of primary palate | | |
| Left second mandibular premolar | | 1 | Complete bilateral cleft of primary palate | | |
| Left lateral maxillary incisor | | 1 | Klippel-Feil syndrome | | |
| **Other Anomalies** | **# of Cases** | **Body Region** | **# of Cases** | **Condition** | **# of Cases** |
| Extra pair of ribs | 1 | Thorax & Shoulders | 1 | Developmental Field Defects | 1 |
| Asymmetrical sternum | 1 | Spine | 4 | Congenital os odontoideum | 1 |
| Block vertebrae | 2 | Osteolyses | 1 | Co-occuring anomalies | 1 |
| Extra vertebrae | 2 | Cranial shape | 1 | Complete bilateral cleft of primary palate | 1 |
| Plagiocephaly | 1 | Cranial structure | 1 | Klippel-Feil syndrome | 1 |
| Abnormal foramen magnum | 1 | Phalanges (toes) | 2 | | |
| Cleft vertebrae | 1 | Osteoarthritis | 1 | | |
| Os ondontoideum | 1 | Feet | 1 | | |
| Scoliosis | 1 | Teeth | 1 | | |
| Symphalangism | 1 | Nasal & sinus structure | 1 | | |
| Bipartite medial cuneiform | 1 | Face size & structure | 1 | | |
| Bilateral post-axial toe polydactyly | 1 | Maxilla | 1 | | |
| Microdontia | 1 | Mandible | 1 | | |
| Diastema | 1 | Lower limbs | 1 | | |
| Retained teeth | 1 | Spina bifida occulta | 1 | | |
| Aplasia/hypoplasia of sinus | 1 | Hemivertebrae | 1 | | |
| Wide/broad nasal bridge | 1 | Kyphosis | 1 | | |
| Underdevelopment of premaxilla | 1 | Bowed fibulae | 1 | | |
| Cleft palate | 1 | Retrognathia | 1 | | |

Appendix Table 5: Anomalies of the Ear Structure and Associated Anomalies (data collected from Panzer et al. 2008; Hoffman et al. 2019; Knusel et al. 1996; Kesterke & Judd 2019; Vairamuthu & Peiffer 2018; van Duijvenbode et al. 2015; Keenleyside 2011; Pany & Teschler-Nicola 2007; Swanston et al. 2013).

| **Anomaly** | **# of Cases** | **Anomaly** | **# of Cases** | **Body Region** | **# of Cases** |
|---|---|---|---|---|---|
| Brachycephaly | 1 | Asymmetrical upper limbs | 3 | Cranial shape | 3 |
| Cleft palate | 1 | Asymmetrical lower limbs | 3 | Cranial structure | 4 |
| Scoliosis | 1 | Spina bifida occulta | 1 | Stature | 1 |
| Kyphosis | 1 | Hyperostosis | 2 | Forehead | 0 |
| Calvarial thinning | 1 | Enamel defects | 2 | Eye Structure | 1 |
| Wormian bones | 1 | Slender tubular bones (upper) | 1 | Eyebrow | 0 |
| Skull thickening | 1 | Limited movement of elbow/flexion deformity | 1 | Nasal & Sinus | 2 |
| Plagiocephaly | 3 | Coxa valga | 1 | Face Size & Structure | 2 |
| Butterfly vertebrae | 1 | Basilar impression | 1 | Maxilla | 3 |
| Asymmetrical clavicle and scapula | 1 | Asymmetrical external auditory meatus | 1 | Mandible | 3 |
| Aplasia/hypoplasia of ear | 6 | Asymmetrical zygomatic | 1 | Oral cavity | 0 |
| Asymmetrical nasal bones | 1 | Narrow palate | 1 | Thorax | 1 |
| Asymmetrical mandible | 2 | Small sinuses | 1 | Shoulders | 1 |
| Orbital size anomalies | 1 | Unusually shaped teeth | 1 | Spine | 3 |
| Asymmetrical face | 1 | Cortical thickening of vertebrae | 1 | Pelvis | 0 |
| Hemivertebrae | 1 | Bowed tubular bones, lower | 1 | Upper limbs | 4 |
| Vertebrae fused with ribs | 1 | Asymmetrical tarsals | 1 | Lower limbs | 4 |
| Genu valgum | 1 | Stapedial footplate fixation | 2 | Hands/phalanges | 0 |
| Asymmetrical metatarsals | 1 | Hypoplasia of mandible | 1 | Feet/phalanges | 1 |
| Short stature | 1 | Slender tubular bones (lower) | 1 | | |
| Wedge-shaped vertebrae | 1 | Flat occiput | 1 | | |
| Fused ossicles | 2 | Dental/alveolar prognathism | 1 | | |
| Small/dysplastic teeth | 1 | Block vertebrae | 1 | | |
| Extra vertebrae | 1 | | | | |