**////Title: A Missed Opportunity: Reports of Ancient Rare Diseases in the Paleopathological Literature**

**////Stand-first**: Dr Julia Gresky of the German Archaeological Institute and her colleagues examined the frequency and content of accounts of ancient rare diseases in the paleopathological [pay-le-o-path-uh-lodge-ikal] literature. By studying published records over the past 45 years, the researchers provide a long-term perspective on the reporting of rare diseases in archaeological contexts. Despite methodological advancements, their work shows that there is much still to be achieved in this fascinating but understudied field.

**////Body text:**

The term ‘rare disease’ was first used more than 40 years ago in medical research, and currently, rare diseases are primarily defined by their prevalence. In Europe, a rare disease is considered one that affects no more than 1 in every 2,000 individuals. However, a universally accepted definition of rare disease has not yet been established, and definitions vary considerably across the world.

We do know between 5,000 and 8,000 different rare diseases exist at the current time and at least 80% of these have a genetic origin. This means that they may also have occurred in ancient times, albeit infrequently.

Paleopathology is the study of ancient diseases and injuries through the examination of human and animal remains such as skeletons, and allows us to find out more about rare diseases in archaeological contexts.

It comes as a surprise, however, that the existing literature on this topic is scant the number of bone disorders which have a genetic basis is huge. Skeletal dysplasias [dis-pley-zhuh-us], for example, in which the development of bones, joints and cartilage in infants is abnormal, account for more than 450 hereditary bone disorders alone.

Dr Julia Gresky of the German Archaeological Institute and her colleagues wanted to determine whether rare diseases are underrepresented in the paleopathological literature. They undertook a bibliometric analysis, in which a statistical approach was used to evaluate the content of articles published in the last 45 years across seven leading peer-reviewed bioarchaeological journals, along with a further two journals and editorial groups of broader scientific focus.

The researchers selected four rare diseases for their analysis (achondroplasia [ay-kon-droh-play-zee-uh], osteogenesis [o-stee-ow-jeh-nuh-sus] imperfecta [im-puh-fek-tuh], autosomal [aw-to-soo-mal]-dominant osteopetrosis [os-teo-pet-rosis] and osteopoikilosis [o-stee-op-ee-kill-oh-sis]. These four diseases represent a wide range of rare diseases readily detectable in human skeletons and meet the criteria of ‘rare’ by current definitions with an estimated prevalence today of 40 to 50 cases in every 100,000 individuals. Although having the same prevalence today, achondroplasia is more frequently detected in archaeological contexts than the other three rare diseases.

Tuberculosis [tyoo-bur-kyuh-loh-sis] was used for comparison purposes because although it is defined as rare today, it was likely to have been very common across continents throughout historic and prehistoric periods before antibiotics were at our disposal.

The researchers searched for reports of each of the four rare diseases in the identified publications, looking specifically at the type of publication in which it featured (e.g., an original research paper or a review paper) and also how it was discussed. They classified the content as relating to main diagnosis, differential diagnosis or marginal interest.

The researchers were not able to systematically discuss the findings concerning each type of article and each diagnostic grouping due to the overall lack of papers available. However, they were able to synthesise their observations across the relevant literature, and noted that in over 70% of the cases, rare diseases were mentioned as part of differential diagnosis and in around 25% of cases, rare diseases were mentioned as a topic of marginal interest. In only a very small number of cases, rare diseases comprised the specific diagnostic target of the paper, and when this did occur, most of these were cases of achondroplasia. The type of articles were often original contributions in the form of case reports in specialised journals and there were very few review articles.

As expected by the researchers, tuberculosis was frequently reported in the bioarchaeological literature, providing a useful comparison in terms of placing the coverage of rare diseases into an appropriate context. They concluded that the four rare diseases they studied are significantly under-represented in both the archaeological/bioarchaeological literature and the wider scientific literature. However, this under-representation was more pronounced for osteogenesis imperfecta, autosomal-dominant osteopetrosis and osteopoikilosis than for achondroplasia. The bone changes of individuals with achondroplasia are more easily recognisable, increasing the chances of identification and thus, being written up for publication.

Dr Gresky and her colleagues also sought to determine whether key advances in paleopathological research such as the introduction and now widespread application of biomolecular methods increased the number of published reports of ancient rare diseases – and found that it did not.

While there are many more rare diseases known to cause bone changes detectable in archaeological human remains than were studied in this work, the current lack of published literature points to an abundance of missed opportunities in paleopathological research.

Dr Gresky and her colleagues conclude that while ancient rare diseases represent an important part of human history, there is much yet to be achieved in terms of the genetic identification and understanding of their long-term evolution.

This SciPod is a summary of the paper ‘How rare is rare? A literature survey of the last 45 years of paleopathological research on ancient rare diseases’, published in the International Journal of Paleopathology. DOI: https://doi.org/10.1016/j.ijpp.2021.03.003

For further information, you can connect with Julia Gresky at Julia.Gresky@dainst.de