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A migration-driven model for the historical spread of leprosy in medieval Eastern and Central Europe

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ABSTRACT

Leprosy was rare in Europe during the Roman period, yet its prevalence increased dramatically in medieval times. We examined human remains, with paleopathological lesions indicative of leprosy, dated to the 6th–11th century AD, from Central and Eastern Europe and Byzantine Anatolia. Analysis of ancient DNA and bacterial cell wall lipid biomarkers revealed *Mycobacterium leprae* in skeletal remains from 6th–8th century Northern Italy, 7th–11th century Hungary, 8th–9th century Austria, the Slavic Greater Moravian Empire of the 9th–10th century and 8th–10th century Byzantine samples from Northern Anatolia. These data were analyzed alongside findings published by others. *M. leprae* is an obligate human pathogen that has undergone an evolutionary bottleneck followed by clonal expansion. Therefore *M. leprae* genotypes and sub-genotypes give information about the human populations they have infected and their migration. Although data are limited, genotyping demonstrates that historical *M. leprae* from Byzantine Anatolia, Eastern and Central Europe resembles modern strains in Asia Minor rather than the recently characterized historical strains from North West Europe. The westward migration of peoples from Central Asia in the first millennium may have introduced different *M. leprae* strains into medieval Europe and certainly would have facilitated the spread of any existing leprosy. The subsequent decline of *M. leprae* in Europe may be due to increased host resistance. However, molecular evidence of historical leprosy and tuberculosis co-infections suggests that death from tuberculosis in leprosy patients was also a factor.

1. Introduction

Leprosy (Hansen's Disease) is primarily a disease of peripheral nerves and skin but also affects bones. In the multi-bacillary

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lepromatous state there is direct invasion of soft tissues around the face and mouth by *Mycobacterium leprae* and spread via the peripheral nerves to the long bones and extremities. These changes in physical characteristics enabled the disease to be recognised in antiquity (Skinsnes and Chang, 1985). Although diagnoses based only on written reports remain questionable, they suggest that leprosy existed in ancient times in Egypt, India and China (Lechat, 1999; Mark, 2002). There is possible skeletal evidence of leprosy from 2000 BC Rajasthan and the late Indus civilisation from 2500–1700 BC (Robbins Schug et al., 2013). The most diagnostic bone changes are found in the skull, described as the rhinomaxillary syndrome, that involves the destruction of the anterior nasal spine, the rounding and widening of the nasal margins, the partial resorption of the pre-maxillary alveolar process and in some cases the loss of the upper incisors (Møller-Christensen, 1961; Ortner, 2003). Additional changes include deformities of the hands and feet, which are usually symmetrical and involve joint destruction, resorption of the fingers and toes, with potentially partial dislocation and bone fusion (Ortner, 2003).

A major difficulty in diagnosing leprosy in skeletal remains is that syphilis may cause similar changes in the rhinomaxillary region, while psoriatic arthritis, septic arthritis and other joint diseases may cause identical changes in the hands and feet (Ortner and Putschar, 1985). Hence a clear diagnosis of leprosy based solely on paleopathology can be made only if the typical facial changes are found in combination with atrophy and truncation of the fingers and toes. Not all leprosy cases display changes in both the rhinomaxillary region and the hands and feet, making paleopathological diagnosis difficult. Furthermore, as skeletal collections often comprise incomplete and damaged bones, paleopathological diagnosis is likely to overlook many true leprosy cases due to insufficient evidence. As *M. leprae* is an obligate pathogen, its presence in ancient human remains provides clear evidence of infection (Donoghue et al., 2002). Ancient DNA (aDNA) and/or lipid biomarker analyses enable identification of *M. leprae*, thereby confirming the antiquity of the disease. If aDNA preservation is sufficient, phylogenetic data may be obtained, but analysis is often restricted to the confirmation of probable leprosy cases, identified by paleopathological features.

Only about 5% of lepromatous leprosy, diagnosed in the 20th century before the introduction of antibiotics, involved bone changes (Faget and Mayoral, 1944). Therefore, the number of leprosy cases diagnosed by paleopathology will always be an under-estimate. However, comparison of the number of leprosy cases based on paleopathology against the number of skeletons systematically examined for typical lesions for a given period in antiquity, gives a glimpse of changes in the prevalence rates of the disease over space and time. In Britain the earliest evidence of leprosy was found in 2/1480 specimens from Romano-British sites (0.14% prevalence), in 18/2031 specimens from the 5th–11th centuries AD (0.89% prevalence) and in 108/4742 specimens dated from the 12th–16th centuries (2.28% prevalence) (Roberts, 2002). This is consistent with the historical accounts and suggests that the earliest appearance of the disease in Europe occurred during the Roman period (Pinhasi et al., 2006).

A major historic transition occurred when early Eurasian civilizations came into military and commercial contact some 1500–3000 years ago (McMichael, 2001, 2004). The east–west trade route, known as the Silk Road, was a means of spreading infections to and from China, the Eastern Mediterranean and Rome, to previously unexposed populations, including malaria, bubonic plague, leprosy, measles and smallpox. For example, McMichael (2001) states that smallpox entered the Roman Empire via troops returning from Syria in the second century AD. Mark (2002) suggested that the troops of Alexander the Great brought leprosy from eastern Asia to the Mediterranean, leading to its spread on a larger scale in Europe during the fourth century BC.

Skeletal cases with evidence of pathological lesions that are consistent with leprosy were reported from 4th to 3rd century BC Bologna, Italy (Mariotti et al., 2005) and 2nd century BC Roman Egypt (Molto, 2002). A case of lepromatous leprosy from mummified remains in early Christian Nubia (Elliot Smith and Dawson, 1924) and there are several reported cases from the Byzantine period (Zias, 1985). A child with characteristic leprosy paleopathology was found in Martellona (Rome, Central Italy), dated to the 2nd–3rd century AD (Rubini et al., 2012). An adult from Palombara, a poor rural site near Rome, Central Italy, showed paleopathology of the rhinomaxillary region typical of leprosy (Rubini et al., 2014). This case was C^{14}-dated to 475 ± 25 years CE (5th century AD). Among other early cases, Reader (1974) reported changes suggestive of leprosy in the right foot of an incomplete adult skeleton from a 4th century AD Romano-British cemetery. Also, a case from the Roman Iron Age (0–400 AD) has been reported in Sweden (Arcini and Artelius, 1993 cited by Kjellström (2010)). Hence, there is sporadic evidence of leprosy in the 'Roman World' that may have extended west to southern Britain and north to southern Sweden.

The diagnosis of *M. leprae* in specimens using both paleopathological diagnosis and aDNA analysis was first reported by Rafi et al. (1994) in archaeological skeletal samples from early Christian Palestine (600 AD). The earliest case confirmed by aDNA analysis, also from the Eastern Mediterranean, was dated to the 1st century AD (Donoghue et al., 2005a; Matheson et al., 2009). The *M. leprae* genome contains several repetitive sequences that enable the identification of the organism. Single nucleotide polymorphisms (SNPs) form the basis of molecular typing (Monot et al., 2005). There appears to be a clonal relationship between *M. leprae* and its human host, so determination of the genetic profiles of modern and extinct strains of *M. leprae* can illuminate the migration and spread of pathogen and host over time (Monot et al., 2009; Economou et al., 2013; Schuenemann et al., 2013; Taylor et al., 2013; Mendum et al., 2014). Archaeological studies indicate that the first significant appearance of leprosy occurred in northern Europe during the 9th–11th century AD (Schuenemann et al., 2013; Taylor et al., 2013). In Britain, the increase of lazar house foundations for the care of leprosy patients was maximal during the 12th and early 13th centuries (Manchester and Roberts, 1989). During the 15th–16th centuries the disease nearly disappeared from southern Europe and Britain, possibly linked to the increased level of tuberculosis in the community (Manchester, 1984).

Much less is known about the appearance and spread of leprosy in Eastern Europe and Western Asia. The paleopathological study by Blau and Yagodin (2005a) indicates evidence of leprosy from a nomadic burial mound located in the Ustyurt Plateau, Uzbekistan, radiocarbon dated to 80–240 AD (OxA-11792 on human tooth, 2 sigma) (Blau and Yagodin, 2005b). This suggests that leprosy prevailed among nomadic central Asian people and that one or more of these Asian populations may have either introduced leprosy for the first time in Eastern Europe by the 6th–8th century AD, or possibly re-introduced it as a later wave following the Roman period spread of the disease across Europe. However, there is a lack of evidence of leprosy from the skeletal population in the eastern parts of the Roman Empire, such as Croatia, where the earliest historical report of the disease was 804 AD and linked to contact with Byzantium (Bakija-Konsuo and Mulić, 2011).

The movement of peoples from Central Asia into the Great Hungarian Plain (Holló et al., 2008) and Northern Italy (Rubini and Zaio, 2011) may be relevant in relation to the spread of leprosy. Cases recognised by paleopathology were reported from cemeteries in 6th–8th century Central Italy (Belcastro et al., 2005; Rubini and