Human biology and ancient DNA: exploring disease, domestication and movement

Charlotte J. Houldcroft
Department of Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK Parasites and Microbes, Wellcome Sanger Institute, Hinxton, UK
Department of Archaeology, University of Cambridge, Cambridge, UK

Riaan F. Rifkin
Centre for Microbial Ecology and Genomics, Department of Biochemistry, Genetics and Microbiology, University of Pretoria, Hatfield, South Africa
Human Origins and Palaeo-Environments Research Group, Department of Anthropology and Geography, Oxford Brookes University, Oxford, UK

Simon J. Underdown
Human Origins and Palaeo-Environments Research Group, Department of Anthropology and Geography, Oxford Brookes University, Oxford, UK

Correspondence to: *sunderdown@brookes.ac.uk*

Introduction

The development of ancient DNA (aDNA) analysis has radically transformed how we think about and study the past. The use of aDNA technology has permeated almost every area of anthropology and archaeology and continues to radically alter how we understand the past (Paubo et al. 1989, 2004; Meyer et al. 2016; Slon et al. 2017). Ancient DNA has both vastly enriched and complicated the mosaic picture of the human story from Neanderthals and *Homo sapiens* interbreeding to the identification of the hitherto unknown Denisovan group (Slon et al. 2017). aDNA has revolutionised the fields of archaeology, population genetics and evolutionary biology, allowing us to directly test hypotheses about past populations which could formerly only be inferred from other lines of evidence. aDNA has also revealed new species, challenged assumptions about admixture and demonstrated that processes such as animal and plant domestication are even more complex than we had assumed. Currently, the oldest aDNA (from a horse) is dated to 700,000 years ago (Orlando et al. 2013) and the oldest human aDNA to 400,000 years ago (Meyer et al. 2016), potentially opening up much of human prehistory to this new field. However, there are also questions which cannot currently be answered by aDNA, whether because of the age or nature of a sample, the preservation conditions or ethical considerations, including engagement with indigenous and marginalised groups. These themes were explored by the participants of the 59th Society for the Study of Human Biology Symposium held in August 2018 at Oxford Brookes University, UK. Work presented at SSHB2018 included pioneering studies which have pushed the origins of human pathogens back to before the emergence of domesticated animals and agriculture (for instance, parvovirus B19 (Muhlemann et al. 2018b)), as well as uncovering the complex evolutionary history of chronic viral infections which will require further ancient genomes to resolve, such as hepatitis B virus (Krause-Kyora et al. 2018; Muhlemann et al. 2018a). The 59th SSHB Symposium explored how aDNA can help us to understand the human biology of disease (both chronic and infectious), the migration of groups and species, personal identity explored using genetics and domestication—including the ways in which humans have 'self- domesticated' through the origins of behaviours such as language. By bringing together an interdisciplinary team of researchers and practitioners, including not only archaeologists, geneticists and human biologists, but also anthropologists, population biologists and experts on the ethics of ancient and population DNA analysis, we tackled questions around what aDNA can add to our knowledge of human biology.

This special issue of the *Annals of Human Biology* includes papers from participants and selected papers which highlight the topics explored during the Symposium. The papers range from the analysis of introgressed SNPs from Neanderthals (Ham et al. 2019) to identifying genes associated with language disorders, although they can only encompass a fraction of the diverse ways in which aDNA technology is changing our views on human evolution years.

Ancient DNA: exploring disease, domestication and movement

The role of disease in the deep past is one that has often been overlooked, but an increasing body of research is revealing a much more complicated pattern of adaptation and selection (Wolfe et al. 2007; Trueba and Dunthorn 2012; Houldcroft and Underdown 2016; Pimenoff et al. 2018). The work of Underdown et al. (2017) has demonstrated that it is possible to use genetic data from diseases to reconstruct events that are completely invisible to the archaeological and fossil records and well beyond the 400,000 year old age of the oldest ancient human DNA. However, many human diseases are regarded as modern phenomena. For example, cancers are generally thought of as a *quid pro quo* of modern life. However, are neoplastic diseases effectively a product of post-industrial human society or can we trace their origins further back into deep (prehistoric) time? It is a common misconception that cancers associated with infectious agents were rare or non-existent in human pre-history (Rifkin et al. 2017). Similarly, it is often, incorrectly, argued that cancer was essentially selectively neutral in the past, with the absent or low rates of oncogenesis normally attributed to the combination of short hominin lifespans and a (perceived) lack of exposure to causative agents inherent to modern human society. However, evidence for neoplastic tumours in Australopithecines *c.* 2 million years ago, Neanderthals at 12c0000 years ago and anatomically-modern humans at 100,000years ago, establishes the antiquity of human cancers (Randolph-Quinney et al. 2016). The impact of infectious disease generally and oncogenic infection specifically can, therefore, be traced across multiple hominin species over at least 2 million years. This demonstrates a chain of infection transmission from Pleistocene Africa to Palaeolithic Europe and, ultimately, to modern human populations (Houldcroft and Underdown 2016). While intrinsic risk factors contribute a relatively small amount (<30%) to the lifetime risk of oncogenesis, 70-90% of cancers have been attributed to extrinsic (largely environmental and also microbial) factors (Plummer et al. 2016). Approximately 45 species of bacteria, viruses and parasitic microorganisms have been implicated directly in oncogenesis. In sub-Saharan Africa, nearly 33% of cancers are thought to be infection-related. However, when combined with data for sub-Saharan African HIV infection-related cancers, these figures suggest as much as 44% of the burden of cancer in sub-Saharan Africa can be associated with infection, of viral, bacterial and parasitic origin (Rifkin et al. 2017). There are also numerous pathogens not currently thought of as oncogenic (in particular HIV), which may play a major or synergistic role in carcinogenesis (Jacqueline et al. 2017; Dai et al. 2019); combined with the likelihood that now-extinct oncogenic pathogens infected hominins during the Pliocene and Pleistocene, the incidence of cancer in pre-history is almost certainly hugely under-estimated. Similarly, the discovery of multiple examples of cancer in an extremely fragmentary fossil record argues for a much greater incidence of cancer than can be assumed from a simple skeletal 'body-count'. As our understanding of human exposure to pathogens in prehistory becomes clearer (e.g. Muhlemann et al. 2018a, 2018b), a more detailed picture of the role these microbes played in our evolution is gradually developing. The role of aDNA will be crucial in shining a light on not just where and when these microorganisms became human pathogens, but also in revealing how they have evolved to exploit human biology and behaviour (Bennett and Baker 2019; Rascovan et al. 2019).

Ham et al. (2019) examine patterns of Neanderthal allele variation in modern humans in order to explore hypotheses for selective pressures. The SNP rs3917862 is associated with hypercoagulability and, while it can be deleterious, it can also help to prevent blood loss. Ham et al. test two very different selective pressures: death from interpersonal violent trauma (or what might be thought of as the orthodox view of male-led violence) and death from blood loss during childbirth. Their results suggest that women are more likely to die in childbirth in populations lacking rs3917862, while deaths due to violence show no correlation with rs3917862. Their results challenge the assumption that Neanderthal admixture has negatively impacted on modern human health, and suggest that maternal survival may have been an important selective pressure for the persistence of hypercoagulability alleles in modern Europeans.

Mountford et al. (2019) examine the genetics underlying our ability to communicate and interact with the world. They ask whether small population isolates help us to detect genes associated with developmental disorders of language and, thus, better understand their evolution in ancient genomic data. Language is not a phenotype which fossilises well and studies of modern populations are crucial if we are to properly understand what data from the fossil, archaeological and aDNA records reveal about the development of language and how humans effectively self-domesticate through niche construction.

Donoghue (2019) uses aDNA to examine variation in ancient strains of tuberculosis (MTB) and leprosy (ML). While both diseases are well known from the palaeopathological record, what is less well understood is how the diseases differed across time and space. Using data from 18th century Hungary Donoghue reports that many individuals were co-infected with up to three MTB sub-genotypes. In C8th-C14th Europe, significant differences in ML genotypes were found between north-western Europe compared with central, southern or eastern Europe. Comorbidities can also be detected using aDNA, as several co-infections of MTB and ML were detected in historical samples. This provides an important layer of detail that is all but invisible to conventional macroscopic examination of skeletal lesions.

Santander et al. (2019) review the state of research for archaic introgression in African populations and explore recent developments. They make the important point that, while much research has focused on the modern human populations that left Africa and subsequent introgression between *Homo sapiens,* Neanderthals and Denisovans, little attention is paid to the deep genetic diversity of African human populations. They compellingly argue that future studies should concentrate on unravelling the complicated demographic history of Africa through means of aDNA where possible and through more focused efforts to sequence modern DNA from more representative populations across the African continent, an approach other researchers are already taking to heart (Lorente-Galdos et al. 2019).

Silva et al. (2019) demonstrate how a detailed mitochondrial DNA (mtDNA) phylogeographic approach, using both modern and ancient variation, can provide evidence of population movements. They focus on the phylogeographic patterns of mitochondrial haplogroups H2 and H13 in the Indian Subcontinent and incorporate evidence from recently released ancient genomes from Central and South Asia. Their results indicate signals of Neolithic arrivals from Iran and later movements in the Bronze Age from Central Asia that derived ultimately from the Steppe. Their approach shows that, even in the face of strong male-bias such as during the Bronze Age Steppe dispersals, mtDNA analysis can shed light on complex population movements and help to answer key questions about the shaping of the South Asian gene pool over the last 10,000 years.

Scheib et al. (2019) use aDNA to understand kin relationships in an East Anglian Neolithic burial, supporting recent hypotheses that patrilineal burials were common in Atlantic facade and British megalithic burials and providing genetic predictions of key phenotypes such as lactase persistence which can inform the dietary isotopic data which this study also provides. This study is a perfect example of the power aDNA has to inform skeletal biographies which are already possible for human remains, by adding data on predicted hair, eye and skin pigmentation, dietary intolerances and even susceptibility to selected infectious and chronic diseases (Pfeiffer et al. 2019).

Conclusions

The themes explored and the questions posed at the 2018 SSHB symposium reflect the exciting directions the field is moving in, namely: ancient population genetics, sedimentary and pathogen aDNA and the integration of phenotype and function with aDNA discoveries. Ancient DNA is able to answer old and ask new questions across the breadth of human biology and the interdisciplinary nature of this symposium reflects the complexities of trying to understand the selective pressures that shaped modern humans.

The 59th SSHB Symposium successfully brought together researchers from a wide range of scientific disciplines and research methods, who were ultimately all focused on the role that aDNA has in understanding what it means to be human. This special issue of the *Annals of Human Biology* is intended to mirror the themes and questions posed at the symposium and hopefully to showcase new ideas, perceptions and research applications for aDNA to human biology and beyond.

Acknowledgements

We would like to extend our thanks to Oxford Brookes University for hosting the meeting and their assistance in helping to deliver the 59th SSHB Symposium. We would also like to thank all of the presenters, especially the early career researchers, who gave papers and posters and the participants who helped to make the symposium such a great success. We should also like to thank Taylor & Francis for their help in producing this special issue and their financial contribution to the symposium's reception. Finally, we would like to thank Rachel Deevey and Noel Cameron for their help and support throughout the editorial process.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Bennett RJ, Baker KS. 2019. Looking backwards to move forward: the utility of sequencing historical bacterial genomes. J Clin Microbiol. [Internet] [cited 2019 May 24]:JCM.00100-19. http://www.ncbi.nlm.nih. gov/pubmed/31092597

Dai L, Qiao J, Yin J, Goldstein A, Lin H-Y, Post SR, Qin Z. 2019. KSHV and Staphylococcus aureus co-infection in oral cavities of HIV + patients: a unique niche for oncogenic virus lytic reactivation. J Infect Dis. [Internet] [cited 2019 May 24]. https://academic.oup.com/jid/advance- article/doi/10.1093/infdis/jiz249/5491269

Donoghue HD. 2019. Tuberculosis and leprosy associated with historical human population movements in Europe and beyond - an overview based on mycobacterial ancient DNA. Ann Hum Biol 46:120-128.

Ham E, Underdown SJ, Houldcroft CJ. 2019. The relative roles of maternal survival and inter-personal violence as selection pressures on the persistence of Neanderthal hypercoagulability alleles in modern Europeans. Ann Hum Biol. 46:99-108.

Houldcroft CJ, Underdown SJ. 2016. Neanderthal genomics suggests a pleistocene time frame for the first epidemiologic transition. Am J Phys Anthropol. 160:379-388.

Jacqueline C, Tasiemski A, Sorci G, Ujvari B, Maachi F, Misse D, Renaud F, et al. 2017. Infections and cancer: the "fifty shades of immunity" hypothesis. BMC Cancer 17(1):257.

Krause-Kyora B, Susat J, Key FM, Kuhnert D, Bosse E, Immel A, Rinne C, et al. 2018. Neolithic and Medieval virus genomes

reveal complex evolution of Hepatitis B. Elife 7:e36666. https://elifesciences.org/ articles/36666
Lorente-Galdos B, Lao O, Serra-Vidal G, Santpere G, Kuderna LFK, Arauna LR, Fadhlaoui-Zid K, et al. 2019. Whole-genome sequence analysis of a Pan African set of samples reveals archaic gene flow from an extinct basal population of modern humans into sub-Saharan populations. Genome Biol. 20(1):77.
Meyer M, Arsuaga J-L, de Filippo C, Nagel S, Aximu-Petri A, Nickel B, Martinez I, et al. 2016. Nuclear DNA sequences from the Middle Pleistocene Sima de los Huesos hominins. Nature 531:504-507.
Mountford HS, Villanueva P, Fernandez MA, De Barbieri Z, Cazier J-B, Newbury DF. 2019. Candidate gene variant effects on language disorders in Robinson Crusoe Island. Ann Hum Biol 46:109-119.
Muhlemann B, Jones TC, Damgaard P. d B, Allentoft ME, Shevnina I, Logvin A, Usmanova E, et al. 2018a. Ancient hepatitis B viruses from the Bronze Age to the Medieval period. Nature [Internet] 557: 418-423. [cited 2018 May 10]. http://www.nature.com/articles/s41586-018-0097-z
Muhlemann B, Margaryan A, P de B D, Allentoft ME, Vinner L, Hansen AJ, Weber A, Bazaliiskii VI, et al. 2018b. Ancient human parvovirus B19 in Eurasia reveals its long-term association with humans. Proc Natl Acad Sci U S A. 115:7557-7562.
Orlando L, Ginolhac A, Zhang G, Froese D, Albrechtsen A, Stiller M, Schubert M, et al. 2013. Recalibrating Equus evolution using the genome sequence of an early Middle Pleistocene horse. Nature 499: 74-78.
Paabo S, Higuchi RG, Wilson AC. 1989. Ancient DNA and the polymerase chain reaction. The emerging field of molecular archaeology. J Biol Chem. 264:9709-9712.
Paabo S, Poinar H, Serre D, Jaenicke-Despres V, Hebler J, Rohland N, Kuch M, et al. 2004. Genetic analyses from ancient DNA. Annu Rev Genet. 38:645-679.
Pfeiffer S, Harrington L, Lombard M. 2019. The people behind the samples: Biographical features of Past Hunter-Gatherers from KwaZulu- Natal who yielded aDNA. Int J Paleopathol. 24:158-164.
Pimenoff VN, Houldcroft CJ, Rifkin RF, Underdown S. 2018. The role of aDNA in understanding the coevolutionary patterns of human sexually transmitted infections. Genes (Basel). 9(7):E317.
Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. 2016. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Heal. 4:e609-e616.
Randolph-Quinney PS, Williams SA, Steyn M, Meyer MR, Smilg JS, Churchill SE, Odes EJ, et al. 2016. Osteogenic tumour in Australopithecus sediba: Earliest hominin evidence for neoplastic disease. S Afr J Sci. 112:7.
Rascovan N, Sjogren K-G, Kristiansen K, Nielsen R, Willerslev E, Desnues C, Rasmussen S. 2019. Emergence and spread of basal lineages of yersinia pestis during the neolithic decline. Cell 176: 295-305.e10.
Rifkin RF, Potgieter M, Ramond J-B, Cowan DA. 2017. Ancient oncogenesis, infection and human evolution. Evol Appl. 10:949-964.
Santander C, Montinaro F, Capelli C. 2019. Searching for archaic contribution in Africa. Ann Hum Biol 46:129-139.
Scheib CL, Hui R, D'Atanasio E, Wilder Wohns A, Inskip SA, Rose A, Cessford C, O'Connell TC, Robb JE, Evans C, Patten R, Kivisild T. 2019. East Anglian early Neolithic monument burial linked to contemporary Megaliths. Ann Hum Biol 46:145-149.
Silva M, Justeau P, Rodrigues S, Oteo-Garcia G, Dulias K, Foody G, Fichera A, Yau B, Rito T, Wilson JF, Gandini F, Edwards CJ, Pala M, Soares PA, Richards MB. 2019. Untangling Neolithic and Bronze Age mitochondrial lineages in South Asia. Ann Hum Biol 46:140-144.
Slon V, Hopfe C, WeiG CL, Mafessoni F, de la Rasilla M, Lalueza-Fox C, Rosas A, et al. 2017. Neandertal and Denisovan DNA from Pleistocene sediments. Science (80-). 356(6338):605-608.
Trueba G, Dunthorn M. 2012. Many neglected tropical diseases may have originated in the Paleolithic or before: new insights from genetics. PLoS Negl Trop Dis. 6:e1393.
Underdown SJ, Kumar K, Houldcroft C. 2017. Network analysis of the hominin origin of Herpes Simplex virus 2 from fossil data. Virus Evol. 3(2):vex026.
Wolfe ND, Dunavan CP, Diamond J. 2007. Origins of major human infectious diseases. Nature [Internet] 447:279-283. [cited 2014 May 27].