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RESEARCH ARTICLE

Diverse variola virus (smallpox) strains were widespread in northern Europe in the Viking Age

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RE: Diverse variola virus (smallpox) strains were widespread in northern Europe in the Viking Age

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Mühlemann et al. ("Diverse variola virus (smallpox) strains were widespread in northern Europe in the Viking Age," Science 369 (2020), eaaw8977) report the capture, sequence and reconstruction of 4 Variola virus (VARV) genomes, the oldest yet drafted (600-1050 CE). While advancing markedly our knowledge of the evolutionary history and genomic content of VARV, the explanation and contextualization offered for their findings requires further clarification. The origins of smallpox have been debated for centuries. Before the disease was understood to be pathogenic, physicians and polymaths employed vague descriptions of pustular epidemics and pox-like endemic illness to comment on the location and age of smallpox's cradle.(1,2,3) Like purported soft tissue and skeletal evidence for the disease,(4,5) the interpretation of early 'poxes' is complicated and has precluded definitive diagnosis. At the same time, recent attempts to use sequence data and a 'molecular clock' to date VARV's emergence,(6,7,8) are subject to ascertainment bias and very distant outgroups (camelpox virus and taterapox virus), complicating VARV's origins.(12) The use of equivocal evidence for historical smallpox as calibration points has likewise confounded emergence estimates.(9) Lack of DNA-based unambiguous VARV detections pre-dating

the 17th century has further problematized attempts to better characterize VARV evolution. For this reason, the new study adds considerable time depth and context to the evolutionary history of VARV. The question remains, however, did the VARV strains Mühlemann et al. report cause smallpox?

Although coverage depth of 3 of 4 genomes is low enough (<8x) that identified gene (in)activations remain tentative, the reconstructed VARV strains very clearly sit, as Mühlemann et al. observe, in a previously unknown and extinct sister clade. These VARV strains are not the direct ancestor of the VARV known to have caused smallpox, and importantly their gene content and active/inactive state, as the highest-coverage sample (VK382, 45x) confirms, contrasts sharply with both VARV eradicated in the twentieth century and VARV drafted using 19th- and 17th-century samples.(9,10) Consequently, the disease caused by the newly reconstructed VARV would have differed, perhaps significantly, both clinically and epidemiologically, from the disease we know and recognize as smallpox. The authors' repeated assertion, therefore, that they identified 'smallpox' in Northern Europe, 600-1050, is an overstatement of the evidence they present and regrettably misleading. They do not address the origins of smallpox sensu stricto. The data they present neither put smallpox in Europe more than a millennium ago nor 'disprove' earlier claims regarding when smallpox first appeared in Europe. In fact, the phylogenetic placement of the distinct clade Mühlemann et al. identify, suggests that the clade currently comprising 17th-20th century VARV strains, the only VARV strains unquestionably associated with smallpox, emerged sometime after these two clades diverged. Mühlemann et al. estimate the lower bound of that divergence to date to ca. 1,700-to-1,400 years ago (95% highest priority density). Importantly, VARV that lead to a disease clinically and epidemiologically recognizable as smallpox may have emerged at any point along the branch leading to the 17th-20th century VARV clade. Previous studies have proposed that that emergence took place centuries later.(9,11) Establishing when and where it occurred are critical questions.

Interdisciplinarity will be vital in reconstructing the evolutionary history of VARV as well as the history of smallpox. That the 'Viking' VARV study would have benefitted from more collaboration with historians and archaeologists is apparent in the supposition that the extinct VARV was widespread. Mühlemann et al. impressively recovered VARV sequences from 11 out of 525 individuals spanning 600-1050 and much of northern Europe. False negatives are the norm in ancient DNA and the sample size Mühlemnann et al. describe represents a vast undersampling of the lives lived across those centuries and thousands of kilometres. Yet, with thousands of premodern European skeletons now analyzed for pathogen DNA (12) widespread and persistent VARV would likely have been detected already.

Further, and contrary to what the authors suggest, the written evidence for European pustular epidemics in the 570s and 580s (13,14), which they do not consult, cannot confirm the reconstituted VARV was present in the 6th century or that it was at an any point 'pan-European'. The reported VARV did not originate from known epidemic contexts (Mühlemann et al. "Diverse variola virus (smallpox)", SI: Site Descriptions), its clinical manifestation is completely uncertain, confounding attempts to draw linkages with documented disease, and there were then no settlements in northern Europe with anywhere near the >200,000 inhabitants required to ensure long-term smallpox maintenance.(15) If this VARV sister-clade was indeed widespread and long persistent, and if 6th-century authors did observe the disease that these 4 Northern Europeans would later suffer, there would be, in fact, more reason to argue that the VARV Mühlemann et al. report was epidemiologically distinct from smallpox as we know it. How else to explain the persistence of VARV for centuries in a sparsely populated rural region? That some of the samples the

authors present are described as ‘predating’ the Viking Age, but all are ultimately characterized as ‘Viking’ is, in this regard, also misleading. There was no singular ‘Viking’ Age. Bookends of the era vary region-to-region and disciplines delineate the period differently. VK388 died upwards of 190 years, and VK382 possibly 150, before the Viking Age as historians define it. VK281 and VK470 fit the periodization, but identifying these or the other nine VARV sequences as ‘Viking’ speciously reinforces the conjecture that the drafted VARV was widespread. ‘Viking’ to many conjures up images of frequent raids in foreign lands, long-distance trade, and exploration, but the great majority of northern Europeans then led far less eventful lives and were not superspreaders of exceptional potential.

Crucially, the identification of a pathogen must not be conflated with the identification of a disease and not all VARV would have caused smallpox as we understand it. As a pathogen evolves over centuries so too can the disease it causes, both clinically and epidemiologically. This is particularly true for viral pathogens, including DNA viruses like VARV. With this in mind, it is worth considering whether the novel ‘Viking’ virus should be labelled VARV at all. How we dub evolutionary relatives of contemporary pathogens from the past requires more reflection. There is no doubting, though, that as remarkable as the VARV Mühlemann et al. identify is, it was not smallpox.

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