

The rediscovery of smallpox

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Abstract

Smallpox is an infectious disease that is unique to humans, caused by a poxvirus. It is one of the most lethal of diseases; the virus variant *Variola major* has a mortality rate of 30%. People surviving this disease have life-long consequences, but also assured immunity. Historically, smallpox was recognized early in human populations. This led to prevention attempts—variolation, quarantine, and the isolation of infected subjects—until Jenner's discovery of the first steps of vaccination in the 18th century. After vaccination campaigns throughout the 19th and 20th centuries, the WHO declared the eradication of smallpox in 1980. With the development of microscopy techniques, the structural characterization of the virus began in the early 20th century. In 1990, the genomes of different smallpox viruses were determined; viruses could be classified in order to investigate their origin, diffusion, and evolution. To study the evolution and possible re-emergence of this viral pathogen, however, researchers can only use viral genomes collected during the 20th century. Cases of smallpox in ancient periods are sometimes well documented, so palaeomicrobiology and, more precisely, the study of ancient smallpox viral strains could be an exceptional opportunity. The analysis of poxvirus fragmented genomes could give new insights into the genetic evolution of the poxvirus. Recently, small fragments of the poxvirus genome were detected. With the genetic information obtained, a new phylogeny of smallpox virus was described. The interest in conducting studies on ancient strains is discussed, in order to explore the natural history of this disease.

Keywords: Ancient DNA, evolution, palaeomicrobiology, smallpox, Yakut population

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Introduction

Smallpox (*variola*) is an acute infectious disease of viral origin (genus *Orthopoxvirus*) that has caused devastating epidemics. During the 20th century, it was responsible for 300–500 million deaths, and in the last millennium it is estimated to have been responsible for 10% of deaths worldwide. Thus, it is highly probable that this disease has strongly selected human populations, but there is no current evidence to validate this hypothesis. Following a global pandemic in the 18th century, vaccination against smallpox began in the early 19th century, and the last case was reported in Somalia in 1977. In 1980, the WHO declared that smallpox had been eradicated. It is not clear what role population selection and the general improvement in hygiene conditions played in this eradication process,

but the extensive vaccination programme conducted by the WHO certainly accelerated the process (www.who.int/csr/disease/smallpox/en/). In the modern era, although populations worldwide have been affected by smallpox, it is the isolated non-occidental populations that have been affected the most; some New World and Siberian populations have been decimated by the virus.

Today, the study of smallpox has various challenges. (i) Social and medical challenges: many populations living in remote areas, where smallpox has become endemic only recently, will migrate to live in urban or suburban environments. Thus, minor cases of the disease could result in epidemics through the gradual reduction in the number of vaccinated people, and the major environmental changes that affect them. Moreover, humans constitute the only known

reservoir of the virus, but the emergence of an animal reservoir or a very closely related animal virus that could adapt to humans is not excluded. Note that current animal poxvirus strains can infect humans, but that virulence differs between strains [1]. Governments must therefore control live strains of the poxvirus (see below), and remain informed about the hazards of the virus, its mutation potential during epidemics (which can speed up the epidemic and/or make it last longer), and the potential for competition between different strains. It is also necessary to identify these strains, and to distinguish between the natural re-emergence of the disease and its genetic manipulation in the laboratory. This is also of importance because smallpox could be developed for acts of bioterrorism. (ii) It is also a biological challenge, owing to co-evolution between humans and the environment. What

genes were selected by smallpox epidemics during human evolution? How has the virus evolved? In human population histories, what were the relationships between the major human-killers (plague and tuberculosis) and smallpox?

Recently, we demonstrated a case of smallpox through molecular analysis; an autochthonous subject who died in Yakutia, Eastern Siberia (Fig. 1), between 1628 and 1640, during a significant tuberculosis epidemic [2]. On the basis of small fragments of degraded DNA, we proposed a new phylogeny of the virus. This research gave new perspectives on the genetic study of smallpox; ancient smallpox samples are now considered to be safe to work on, owing to the degraded nature of their DNA. There is no doubt that the discovery of ancient smallpox cases and the sequencing of ancient strains will give further insights into the natural history of this disease.

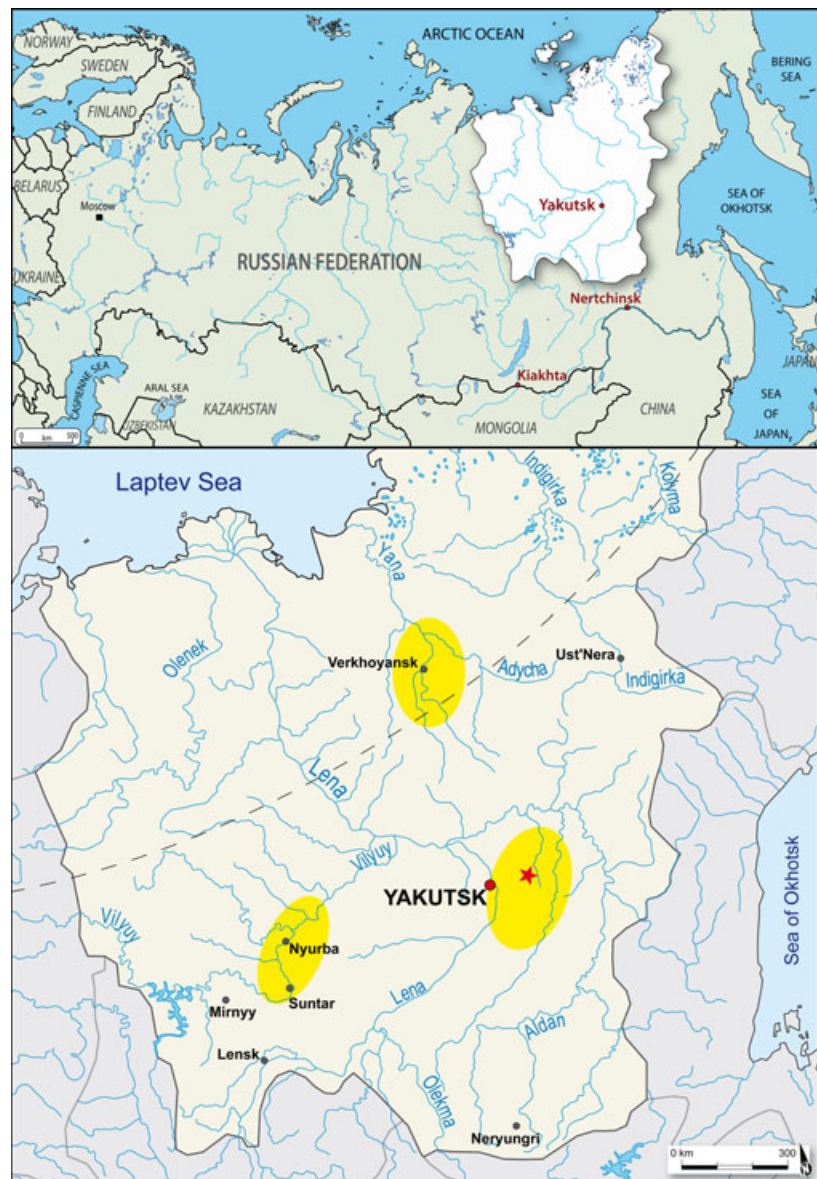


FIG. 1. Location of Yakutia in Siberia. Map of the three initial regions occupied by ancient Yakut populations excavated during MAFSO archaeological campaigns. The star shows the location of the shamanic tree grave, © Patrice Gérard CNRS.

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