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medplag
The medieval plagues: ecology, transmission modalities and routes of the infections.

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MedPlag (AdG 2013-2018)

Panel: SH6 The Study of the Human Past: Archaeology, history and memory.

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The PI

- Takes responsibility of the whole project (competence, inclination to Multidisciplinarity, strong cooperation network)
- Manages and organizes the team: Attitude to leadership (Publications without tutor -> PI of different projects + senior authorship)
- Ability in negotiating conditions (the best work environment with the institutions - infrastructures)
- Mobility (portability of grants)
- Discusses on a regular basis with in-house team members about the project (not less than 60-65%)
- Organizes and participates to workshops (dissemination)
- Writes up (financial & scientific) reports to the ERC
- Reviewer activity for ERC

- Develops theories
- Writes up publications (as senior author)

- Impact on the career

Ancient DNA from the First European Farmers in 7500-Year-Old Neolithic Sites

Wolfgang Haak,[1]* Peter Forster,[2] Barbara Bramanti,[1] Shuichi Matsumura,[2] Guido Brandt,[1] Marc Tänzer,[1] Richard Villems,[3] Colin Renfrew,[2] Detlef Gronenborn,[4] Kurt Werner Alt,[1] Joachim Burger[1]

The ancestry of modern Europeans is a subject of debate among geneticists, archaeologists, and anthropologists. A crucial question is the extent to which Europeans are descended from the first European farmers in the Neolithic Age 7500 years ago or from Paleolithic hunter-gatherers who were present in Europe since 40,000 years ago. Here we present an analysis of ancient DNA from early European farmers. We successfully extracted and sequenced intact stretches of maternally inherited mitochondrial DNA (mtDNA) from 24 out of 57 Neolithic skeletons from various locations in Germany, Austria, and Hungary. We found that 25% of the Neolithic farmers had one characteristic mtDNA type and that this type formerly was widespread among Neolithic farmers in Central Europe. Europeans today have a 150-times lower frequency (0.2%) of this mtDNA type, revealing that these first Neolithic farmers did not have a strong genetic influence on modern European female lineages. Our finding lends weight to a proposed Paleolithic ancestry for modern Europeans.

Agriculture originated in the Fertile Crescent of the Near East about 12,000 years ago, from where it spread via Anatolia all over Europe (*1*). It has been widely suggested that the global expansion of farming included not only the dispersal of cultures but also of genes and languages (*2*). Archaeological cultures such as the Linear pottery culture (*Linearbandkeramik* or LBK) and Alföldi Vonaldiszes Kerámia (AVK) mark the onset of farming in temperate regions of Europe 7500 years ago (*3*). These early farming cultures originated in Hungary and Slovakia, and the LBK then spread rapidly as far as the Paris Basin and the Ukraine (*4*, *5*). The remarkable speed of the LBK expansion within a period of about 500 years, and the general uniformity of this archaeological unit across a territory of nearly a million square kilometers (Fig. 1), might indicate that the spread was fueled to a considerable degree by a migration of people (*6*–*8*). On the other hand, a number of archaeological studies suggest that local European hunter-gatherers had shifted to farming without a large-scale uptake of genes from the first farmers (*9*–*11*). Genetic studies carried out on modern Europeans have led to conflicting results, with estimates of Neolithic input into the present population ranging from 20 to 100% (*12*–*20*). A theoretical simulation study by Currat and Excoffier (*21*) has recently suggested a minor contribution, clearly less than 50%, and possibly much less. Conclusive ancient DNA studies on skeletons of the first European farmers have so far not been published to our knowledge.

Response to Comment on "Ancient DNA from the First European Farmers in 7500-Year-Old Neolithic Sites"

Joachim Burger,[1]* Detlef Gronenborn,[2] Peter Forster,[3] Shuichi Matsumura,[3] Barbara Bramanti,[1] Wolfgang Haak[1]

The discovery of mitochondrial type N1a in Central European Neolithic skeletons at a high frequency enabled us to answer the question of whether the modern population is maternally descended from the early farmers instead of addressing the traditional question of the origin of early European farmers.

Our study (*1*) described the discovery of the mitochondrial type N1a in 6 out of 24 Central European Neolithic skeletons, which was unexpected because today this type is found at 150-times lower frequency in Europe. We offered two possible explanations for our observations. First, female Early Neolithic farmers could have been replaced by immigrant women after the early Neolithic (post–early-Neolithic replacement theory). Second, the female early Neolithic farmers could have been genetically diluted by resident native hunter-gatherers (Paleolithic survival theory). Both interpretations are compatible with our genetic data. Because there is so far no archaeological evidence for a major post–early-Neolithic population replacement, we suggested that the Paleolithic survival theory is more likely.

In their comment, Ammerman et al. (*2*) raise concerns about our study and call for further ancient DNA studies. First, the authors may have misread the central question asked in our study. We tackled the question of the fate of the early European farmers [as represented by the Neolithic skeletons of the Linear pottery culture (LBK)], that is, whether modern central Europeans are descended from them or not. In contrast, Ammerman *et al.* imply that our study deals with questions on the origin of the early European farmers, such as whether the female lineages in the farmer skeletons were immigrants from southeastern Europe or whether they were local Mesolithic women who intermarried with incoming males. Irrespective of this misunderstanding, the origin of the farmers remains an important question, and the plight of the early farmers' descendants outlined in our study, along with the intriguing ancient DNA data, may one day contribute to a better understanding of farming origins.

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We believe it is worthwhile to clarify the points that Ammerman and colleagues usefully raise. Regarding the point that we should have analyzed far more than 24 samples, we point out that our main conclusions (*1*) were based on statistically significant results. Furthermore, we carefully examined the sample locations and mitochondrial DNA types to exclude the possibility of biased sampling. Ammerman *et al.* (*2*) are correct that one of our 24 skeletons, namely the one from Escegfalva, is not a "first" farmer but only an "early" farmer, as far as eastern Hungary is concerned. We included this skeleton in our analysis because it is culturally and chronologically closely related to our actual focus, the first farmers in the LBK area of neighboring Central Europe (Fig. 1). The other 23 skeletons represent the first full farming populations in their local LBK regions; this is particularly the case for the Flomborn site, which is among the first LBK colonies west of the Rhine and is also the type-site for the "Flomborn"

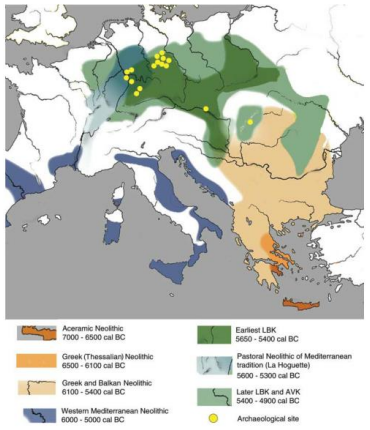

Fig. 1. The spread of farming across Europe. The colors indicate time scales for the spread of the early Neolithic in Europe. All 24 samples of our ancient DNA study belong to the same LBK/AVK (Linear pottery and Alföld linear pottery culture) chronostratum, representing the first farmers in much of central Europe.

Genetic Discontinuity Between Local Hunter-Gatherers and Central Europe's First Farmers

B. Bramanti,[1]* M. G. Thomas,[2] W. Haak,[1]† M. Unterlaender,[1] P. Jores,[1]‡ K. Tambets,[3] I. Antanaitis-Jacobs,[4] M. N. Haidle,[5] R. Jankauskas,[4] C.-J. Kind,[6] F. Lueth,[7] T. Terberger,[8] J. Hiller,[9]§ S. Matsumura,[10,11]‖ P. Forster,[12] J. Burger[1]

After the domestication of animals and crops in the Near East some 11,000 years ago, farming had reached much of central Europe by 7500 years before the present. The extent to which these early European farmers were immigrants or descendants of resident hunter-gatherers who had adopted farming has been widely debated. We compared new mitochondrial DNA (mtDNA) sequences from late European hunter-gatherer skeletons with those from early farmers and from modern Europeans. We find large genetic differences between all three groups that cannot be explained by population continuity alone. Most (82%) of the ancient hunter-gatherers share mtDNA types that are relatively rare in central Europeans today. Together, these analyses provide persuasive evidence that the first farmers were not the descendants of local hunter-gatherers but immigrated into central Europe at the onset of the Neolithic.

Europe has witnessed several changes in archaeological cultures since anatomically modern humans displaced the Neandertal population 30,000 to 40,000 years ago (*1*, *2*). Palaeolithic hunter-gatherers survived the Last Glacial Maximum (LGM) about 25,000 years ago in southern and eastern refugia (*3*) and resettled central Europe after the retreat of the ice sheets. With the end of the Ice Age at ~9600 B.C.E., their Mesolithic descendants or successors had recolonized large parts of the deglaciated northern latitudes (*4*, *5*). From around 6400 B.C.E., the hunter-gatherer way of life gave way to farming cultures in a transition known as the Neolithic Revolution (*6*). The extent to which this important cultural transition was mediated by the arrival of new peoples, and the degree of Mesolithic and early Neolithic ancestry in Europeans today, have been debated for more than a century (*7*–*10*). To address these questions directly, we obtained mitochondrial DNA (mtDNA) types from 22 central and northern European post-LGM hunter-gatherer skeletal remains (Fig. 1) and compared 20 of these (those for which full sequence information was available) to homologous mtDNA sequences from 25 early farmers (*11*, *12*) and 484 modern Europeans from the same geographic region (*13*). Our ancient sample spans a period from circa (ca.) 13,400 to 2300 B.C.E. and includes bones from Hohler Fels in the Ach valley (Late Upper Paleolithic) and Hohlenstein-Stadel in the Lone valley (Mesolithic). Extensive precautions were taken to ensure sequence authenticity (*14*), including extracting independent samples from different skeletal locations of the same individuals and examining remains only from high latitudes or cave sites with good biomolecular preservation.

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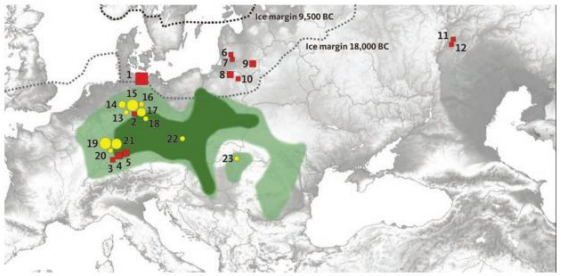

Fig. 1. mtDNA types from prehistoric samples of hunter-gatherers and farmers. The green shading represents the first farming areas [dark green: early LBK, 5650 to 5400 calibrated years B.C.E. (calBC); light green: LBK, 5400 to 4900 calBC] in central Europe, based on archaeological finds, whereas squares represent successfully analyzed Late Palaeolithic, Mesolithic, and Ceramist hunter-gatherers dating from 13,400 to 2300 B.C.E. The term "Neolithic" is sometimes applied to the n European Ceramlture because of their use of pottery, but this does not imply a farming omy (*21*). Previously analyzed (*11*, *12*) LBK farming sites are marked with s for comparison. The area of each square or circle is proportional to the er of individuals successfully investigated. In red are labeled archaeologtes with one or more U4/U5 individuals; in yellow, sites with other mtDNA , highlighting the specificity of U types in the prehistoric hunter-gatherers. The sites are as follows: 1, Ostorf; 2, Bad Dürrenberg; 3, Falkensteiner Höhle; 4, Hohler Fels; 5, Hohlenstein-Stadel; 6, Donkalnis; 7, Spiginas; 8, Dudka; 9, Kretuonas; 10, Drestwo; 11, Chekalino; 12, Lebyazhinka; 13, Unseburg; 14, Unterwiederstedt; 15, Derenburg/Meerenstieg; 16, Eilsleben; 17, Halberstadt; 18, Seehausen; 19, Flomborn; 20, Vaihingen an der Enz; 21, Schwetzingen; 22, Asparn/Schletz; 23, Ecsegfalva.

Absence of the lactase-persistence-associated allele in early Neolithic Europeans

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Lactase persistence (LP), the dominant Mendelian trait conferring the ability to digest the milk sugar lactose in adults, has risen to high frequency in central and northern Europeans in the last 20,000 years. This trait is likely to have conferred a selective advantage in individuals who consume appreciable amounts of unfermented would have provided a selective advantage in the absence of a supply of fresh milk, and because of observed correlations between the frequency of LP and the extent of traditional reliance on animal milk, the culture-historical hypothesis has been proposed (8–12). Under this model, LP was driven from

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Distinct Clones of *Yersinia pestis* Caused the Black Death

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Abstract

From AD 1347 to AD 1353, the Black Death killed tens of millions of people in Europe, leaving misery and devastation in its wake, with successive epidemics ravaging the continent until the 18th century. The etiology of this disease has remained highly controversial, ranging from claims based on genetics and the historical descriptions of symptoms that it was caused by *Yersinia pestis* to conclusions that it must have been caused by other pathogens. It has also been disputed whether plague had the same etiology in northern and southern Europe. Here we identified DNA and protein signatures specific for *Y. pestis* in human skeletons from mass graves in northern, central and southern Europe that were associated archaeologically with the Black Death and subsequent resurgences. We confirm that *Y. pestis* caused the Black Death and later epidemics on the entire European continent over the course of four centuries. Furthermore, on the basis of 17 single nucleotide polymorphisms plus the absence of a deletion in *glpD* gene, our aDNA results identified two previously unknown but related clades of *Y. pestis* associated with distinct medieval mass graves. These findings suggest that plague was imported to Europe on two or more occasions, each following a distinct route. These two clades are ancestral to modern isolates of *Y. pestis* biovars Orientalis and Medievalis. Our results clarify the etiology of the Black Death and provide a paradigm for a detailed historical reconstruction of the infection routes followed by this disease.

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Introduction

Of the numerous epidemics in human history, three pandemics are generally accepted as having been caused by plague. Justinian's plague (AD 541–542) spread from Egypt to areas surrounding the Mediterranean [1]. In 1347, an epidemic known as the Black Death spread from the Caspian Sea to almost all European countries, causing the death of one third of the European population over the next few years [2]. This second pandemic persisted in Europe until 1750, causing successive and progressively declining epidemic waves. A third plague pandemic began in the Yunnan region of China in the mid-19th century, and spread globally via shipping from Hong Kong in 1894. During this last pandemic, the etiological cause of plague was identified as *Yersinia pestis*, a Gram-negative bacterium [3,4]. Most microbiologists and epidemiologists believe that *Y. pestis* was also the etiological agent of the first two pandemics. This belief is supported by ancient DNA (aDNA) analyses which identified sequences specific for *Y. pestis* in the teeth of central European plague victims from the first and second pandemics [5–7]. Moreover, the *Y. pestis* F1 protein capsule antigen has been detected in ancient plague skeletons from Germany and France by immunochromatography [8,9].

Based on studies on modern strains, microbiologists have subdivided *Y. pestis* into three biovars: Antiqua, Medievalis, and Orientalis. These biovars can be distinguished depending on their abilities to ferment glycerol and reduce nitrate [10]. The Medievalis biovar is unable to reduce nitrates due to a G to T mutation that results in a stop codon in the *napA* gene [11], while the Orientalis biovar cannot ferment glycerol because of a 93 bp deletion in the *glpD* gene [11,12]. Conversely, the Antiqua biovar is capable of performing both reactions [10]. An apparent historical association of the routes of the three pandemics with the modern geographical sources of the three biovars led Devignat to propose that each plague pandemic was caused by a different biovar [10]. There is no doubt that the ongoing third pandemic

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Yersinia pestis DNA from Skeletal Remains from the 6th Century AD Reveals Insights into Justinianic Plague

Michaela Harbeck[1]*, Lisa Seifert[2], Stephanie Hänsch[3,4], David M. Wagner[5], Dawn Birdsell[5], Katy L. Parise[5], Ingrid Wiechmann[6], Gisela Grupe[1,2], Astrid Thomas[7], Paul Keim[4], Lothar Zöller[7], Barbara Bramanti[3,4]*, Julia M. Riehm[7], Holger C. Scholz[7]*

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Abstract

Yersinia pestis, the etiologic agent of the disease plague, has been implicated in three historical pandemics. These include the third pandemic of the 19th and 20th centuries, during which plague was spread around the world, and the second pandemic of the 14th–17th centuries, which included the infamous epidemic known as the Black Death. Previous studies have confirmed that *Y. pestis* caused these two more recent pandemics. However, a highly spirited debate still continues as to whether *Y. pestis* caused the so-called Justinianic Plague of the 6th–8th centuries AD. By analyzing ancient DNA in two independent ancient DNA laboratories, we confirmed unambiguously the presence of *Y. pestis* DNA in human skeletal remains from an Early Medieval cemetery. In addition, we narrowed the phylogenetic position of the responsible strain down to major branch 0 on the *Y. pestis* phylogeny, specifically between nodes N03 and N05. Our findings confirm that *Y. pestis* was responsible for the Justinianic Plague, which should end the controversy regarding the etiology of this pandemic. The first genotype of a *Y. pestis* strain that caused the Late Antique plague provides important information about the history of the plague bacillus and suggests that the first pandemic also originated in Asia, similar to the other two plague pandemics.

Citation: Harbeck M, Seifert L, Hänsch S, Wagner DM, Birdsell D, et al. (2013) *Yersinia pestis* DNA from Skeletal Remains from the 6th Century AD Reveals Insights into Justinianic Plague. PLoS Pathog 9(5): e1003349. doi:10.1371/journal.ppat.1003349

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Competing Interests: The authors have declared that no competing interests exist.

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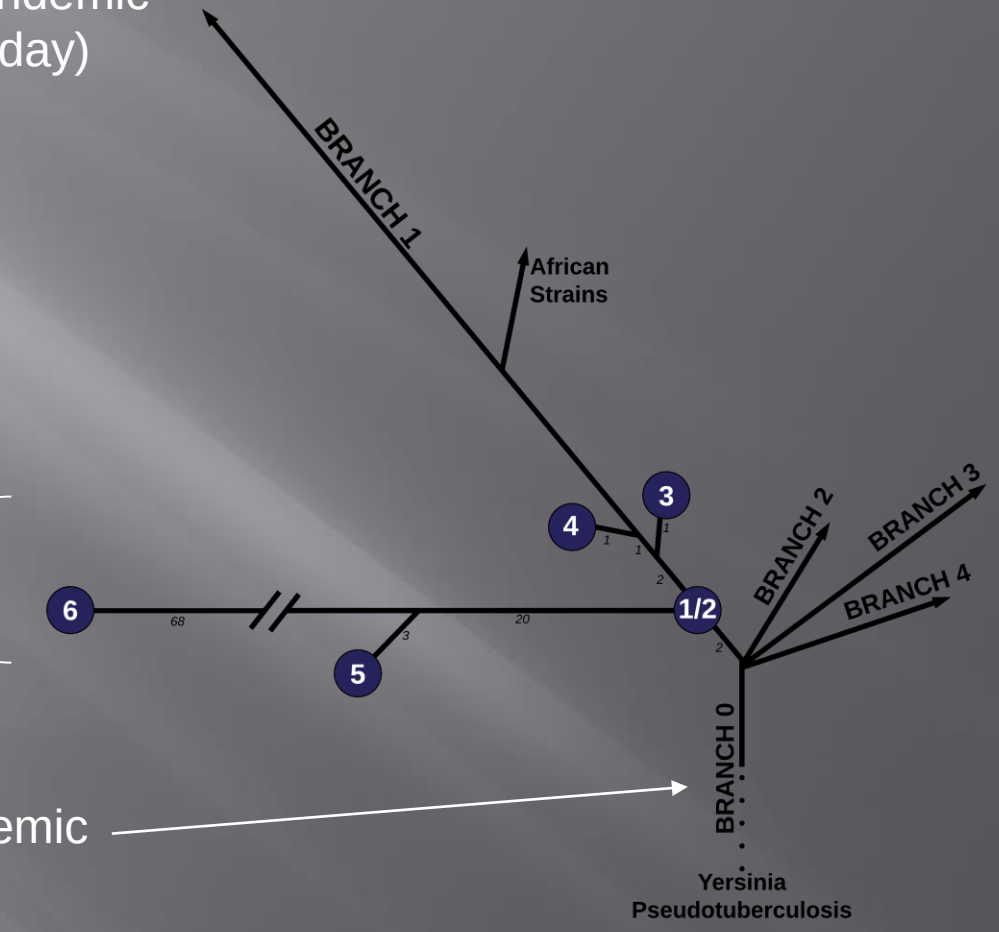
Introduction

In 541 AD, eight centuries before the Black Death, a deadly infectious disease hit the Byzantine Empire, reaching Constantinople in 542 and North Africa, Italy, Spain, and the French-German border by winter 543 [1]. The so called "Plague of Justinian", named after the contemporaneous emperor, led to mass mortality in Europe similar to that of the Black Death. It persisted in the territory of the Roman Empire until the middle of the 8th century and likely contributed to its decline, shaping the end of antiquity [1]. Based on historical records, this disease has been diagnosed as bubonic plague although discrepancies between historical sources and the progression of *Y. pestis* infections have led some authors to suppose that the Plague of Justinian was caused by a different pathogen (as discussed in [2]). This vivacious discussion was recently reinforced by an ancient DNA study of the second pandemic that also questioned whether *Y. pestis* was truly the causative agent of the first pandemic [3,4].

Western scientists have traditionally subdivided *Y. pestis* strains into three biovars: Antiqua, Medievalis, and Orientalis; depending on their abilities to ferment glycerol and reduce nitrate [5]. However, this system ignores many other *Y. pestis* biovars that have been designated and described by other scientists [see 6,7,8]. Biovars, which are based upon phenotypic properties, do not always correspond directly to specific molecular groups because the same phenotype can result from different mutations [9]. As a result, it has been suggested that groupings within *Y. pestis*, or assignment of unknown strains to specific populations should be based upon molecular signatures and not phenotypes [9]. Fortunately, the recent construction of highly-accurate rooted global phylogenetic trees for *Y. pestis* [10,11] (reproduced in Figure 1) have facilitated the assignment of isolates to distinct populations. The most recent global phylogeny is based upon single nucleotide polymorphisms (SNPs) identified from the genomes of 133 global strains [11]. All clones that caused the third pandemic belong to populations assigned to the molecular group 1.ORI [10,11]; the basal node for this group is N14 (Figure 1).

Two recent studies [3,12] have queried key SNPs in DNA samples obtained from victims of the second pandemic (14th century AD), facilitating the phylogenetic placement of these samples in the most recent global phylogeny [11]. These samples are along the branch between nodes N07 and N10 (Figure 1) close

Third pandemic
(1894-today)



Second pandemic
(1346-1720)

First pandemic
(6th-7th c.)

Guellil, Bramanti 2016

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Reservoirs of plague

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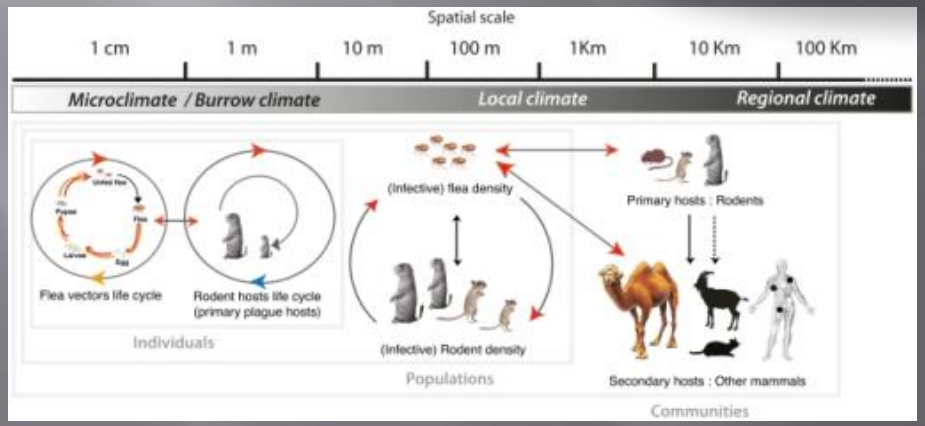

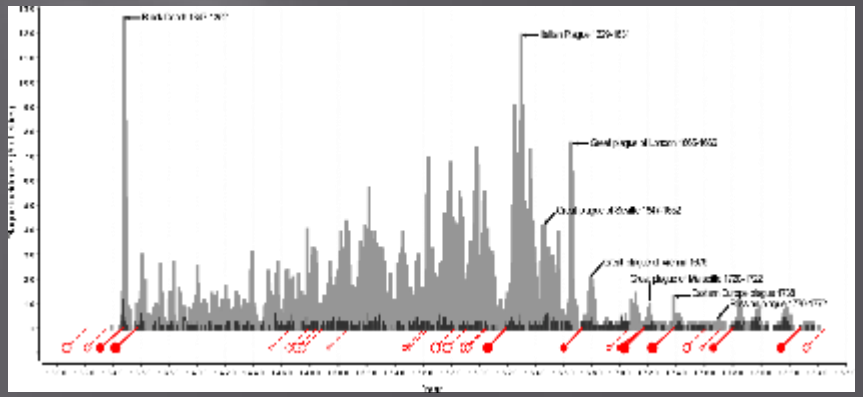

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The proposal

- Aiming for excellence
- Feasibility
- High risk / high gain
- Ground-breaking idea
- You (and collaborators) are the one(s)

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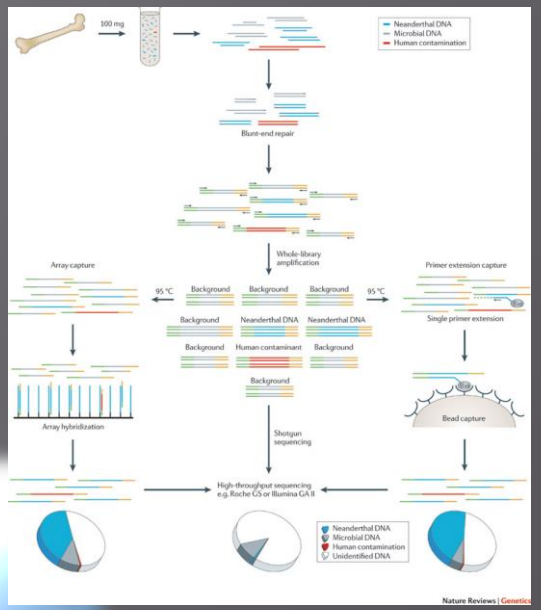
Ancient DNA

- Low amount
- Chemical changes
- Fragmentation
- Contamination



The aDNA Lab @ CEES, Oslo

Restricted area - specialised scientists

Fotos: Moritz Muschick

NORWEGIAN SEQUENCING CENTRE

Numbers

- Time Submission-Approval: April-November 2012
- Signature of the Agreement: May 2013
- 1st Amandment (PI @ Unife): 2015
- Now employed: PI (65%), 3 postdoc, 2 PhD-students, 1 technical assistent -> 3 persons in parental leave

- Putative plague samples: ca. 1,000
- Analysed: ca. 600
- Positive to plague: 10
- Genomes expected: at least 4 (total nr. of ancient genome published before: 5)

- Dissemination: >20 presentations of the project and several interviews
- Publications: 3 papers, 1 book chapter, >10 comunications and posters
- Other products: 1 thesis, 1 simulation program, official website of the project

UNIVERSITÀ DEGLI STUDI DI FERRARA
- EX LABORE FRUCTUS -

medplag

The medieval plagues: ecology, transmission modalities and routes of the infections.

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SEVENTH FRAMEWORK PROGRAMME


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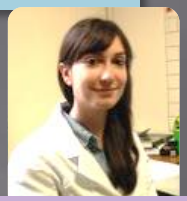
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