Molecular archaeology

The genomic history of ice-age Europeans

Ludovic Orlando

An extensive genomic time series has been produced for 356 humans from across ice-age Europe. The data reveal how climate change affected the ranges of hunter-gatherer populations as they developed diverse cultures. **See p.117**

For most of the past 100,000 years, the glacial conditions of the last ice age prevailed across Europe. About halfway through this period, the first anatomically modern humans arrived on the continent[1,2]. Groups of hunter-gatherers developed breathtaking art, diverse lithic industries (which made tools from stone) and funerary practices across Europe. Then, around 9,000 years ago (9 ka), farmers from Anatolia started to settle[3]. Whether the pre-farming cultures reflect isolated biological entities or regional differences between highly interconnected groups is highly debated. Also unknown is what happened as the climate changed, including during the Last Glacial Maximum (LGM; between about 26 and 19 ka)[4], when large parts of the continent became uninhabitable. On page 117, Posth *et al.*[5] provide unprecedented insight into the genomic make-up of ice-age European hunter-gatherers, clarifying the biological underpinnings of several cultures and the relationships between them.

The authors report new genomic data for 116 ancient humans and reanalyse a further 240 specimens. These 356 specimens were from 34 countries. In doing this, Posth and colleagues add substantially to the genetic atlas of ancient Europe between 45 and 5.2 ka (Fig. 1). The analyses include the first examples of genomes from individuals of two south-western cultures — European Gravettian and Solutrean.

To obtain these data, Posth *et al.* relied on established, cost-effective methodologies that generate sequence data across 1.24 million locations in the human genome at which single DNA letters are known to show variability between individuals[6] — even for samples that show minimal DNA preservation or are contaminated by soil microorganisms. The authors also restricted their analyses to sequences that carried hallmarks of post-mortem DNA damage, to avoid risk of contamination from living people.

Posth and colleagues' work shows that the Gravettian lithic industry was developed by two main groups that populated Europe during the 10,000 years or so before the LGM. The first group — named Věstonice, in reference to the earliest associated site — stretched across present-day Italy, the Czech Republic and Austria. Věstonice people were descended from earlier groups found farther east, including those from what is now western Russia. The second group, called Fournol, inhabited western and southwestern Europe (present-day France and Spain), and were descended from earlier local hunter-gatherers, such as those from the Goyet Caves in Belgium (around 35 ka)[7]. The authors showed that six individuals from Goyet dated to 27 ka had mixed Fournol and Věstonice ancestries, indicating an east-to-west range expansion of the Věstonice group right before the LGM.

During the LGM, human populations retreated to glacial refuges on the southern fringe of Europe. In what is now southern France and Iberia (Spain and Portugal), this movement was accompanied by the development of Solutrean flint tools, which Posth *et al.* reveal to have been produced by people deriving from local Fournol groups. This model of population continuity between western Gravettian and Solutrean toolmakers is supported by a study in *Nature Ecology and Evolution*[8], which describes the genetic profile of an individual dated to 23ka from present-day Andalusia in southern Spain.

Posth and colleagues next demonstrated that, after the LGM and before 17 ka, non-local groups entered present-day Italy from the Balkans. These individuals showed 'near-Eastern' genetic affinities that define a cluster called Villabruna, and spread farther south in small groups that reached present-day Sicily around 14 ka. The implication is that the post-LGM 'Epigravettian' industry did not, as was previously thought[9], develop *in situ* from earlier local Gravettian groups in Italy — suggesting that the peninsula might not have offered a glacial refuge to humans. The Villabruna influence also extended outside Italy — Posth and colleagues found evidence of this ancestry in an individual dated to 19 ka found at El Mirón in Spain. This reveals a southern edge of Europe that acted as a corridor from the Balkans to Iberia.

Posth *et al.* also show that, after the LGM, populations expanded farther outside their glacial refuges, forming a new genetic blend derived from the Villabruna and Fournol ancestries. In present-day France, Belgium, Germany and Poland, these groups formed the 'Goyet Q2' cluster, which is associated with the Magdalenian lithic industry. The new data also show that it was around 14 ka that one of

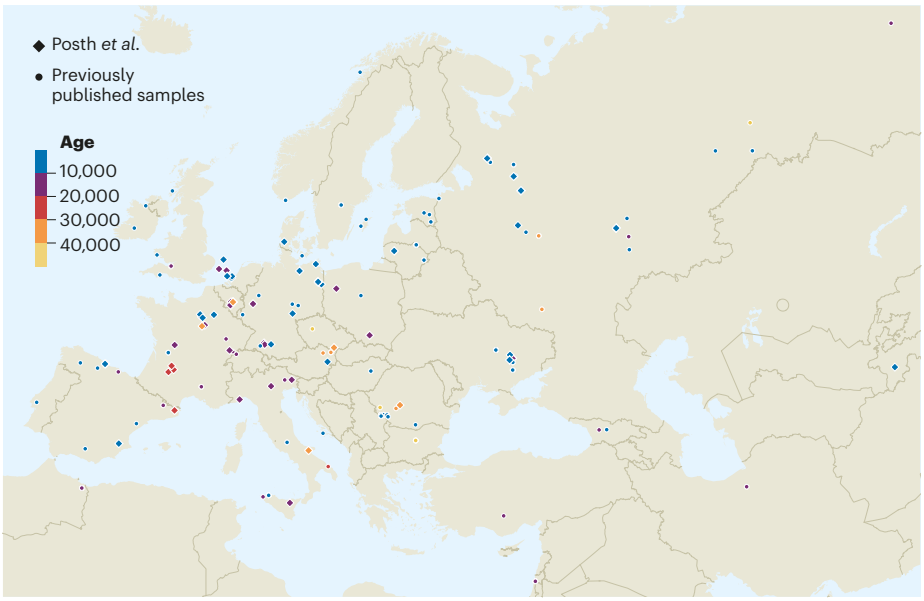

Figure 1 | A map of ancient human populations from across Europe. Posth *et al.*[5] analyse the genomes of 356 ancient human individuals. Of these, 102 had not been analysed previously, and improved data for 14 more increased the amount of genomic information available; 240 were previously published. The map shows the locations of these ancient individuals. Colours reflect a sample's age in years.

the three main genetic ancestries found today in Europe (the western hunter-gatherers) was fully formed, when the Villabruna and Goyet Q2 mixed. This group — which Posth *et al.* now rename Oberkassel — seems to be genetically homogeneous from present-day Poland to the United Kingdom, indicating an expansion that was possibly related to the abrupt warming during the Bølling–Allerød period (14.8 to 12.9 ka).

Farther east, another population (in which individuals with lighter skin and darker eye colours were more frequent at the time than was the case in Oberkassel populations) eventually developed the Sidelkino culture of western Russia. Posth *et al.* detected Sidelkino-related genetic ancestry in individuals from northern Iberia,and its frequency increased in the Baltics shortly after the time of the thermal maximum approximately 8 ka — a period when the Oberkassel genetic influence also extended as far east as the Don–Volga region in Russia. Whether such population movements were the sole product of the warming climate, or a response to groups of farmers expanding outwards from Anatolia, remains unknown. Although the spread of Anatolian farmers into Europe changed the genetic make-up of local populations, Posth and co-workers found that individuals of mainly Oberkassel ancestry persisted in Germany until roughly 5.2 ka, in line with a previous study of northern France[10]. This could reflect local communities limiting admixture with incoming farmers but adopting a farming lifestyle.

Posth and colleagues have revealed population turnovers that shaped the European genetic landscape in the face of climate change. Their findings caution against simple narratives equating lithic industries and ethnicity. More genetic analyses are, however, needed to gain finer-grained resolution of the formation and expansion timing of several groups (such as the Villabruna) and their possible links to lithic industries currently omitted from genetic analyses (such as the Badegoulian). In the future, sequencing of DNA molecules preserved in cave sediments might help to overcome the limitations of sequencing only available skeletal samples[11], and could even reveal the social structure of the underlying human communities[12], including those that first entered Europe.

The European continent has a long tradition of archaeology, where excavation methods were developed in the early nineteenth century. It is therefore not surprising that this continent is also the best characterized archaeogenetically, with extensive genomic time series now extending from the present day to the Upper Palaeolithic period (50–12 ka). The resulting resources and increased understanding of the human past should be commended, but are also an invitation to redouble efforts outside Europe, to avoid developing a Eurocentric vision of human prehistory. For now, the fluidity of ancestries in the deep genetic history of Europe provides an important lesson: no modern population can claim a single origin from the human groups that first became established on the continent.

Ludovic Orlando is at the Centre for Anthropobiology and Genomics of Toulouse (CNRS UMR 5288), Paul Sabatier University, 31000 Toulouse, France.
e-mail: ludovic.orlando@univ-tlse3.fr

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Neurodegeneration

Drug trial for Alzheimer's disease is a game changer

Eric M. Reiman

An antibody treatment reduces measurements of brain abnormalities called amyloid plaques in people with Alzheimer's disease, and lessens clinical decline. This result will help in developing therapies to treat and prevent the disease.

Researchers have long sought a treatment for Alzheimer's disease that could target the biological underpinnings of the condition and slow cognitive decline and its disabling consequences in definitive clinical trials. Writing in the *New England Journal of Medicine*, van Dyck *et al.*[1] provide compelling evidence that an antibody treatment called lecanemab can drastically reduce measurements of a characteristic Alzheimer's brain abnormality called amyloid plaques, alter other biomarkers of the disease and reduce the clinical decline in people with the condition. Although lecanemab did not stop clinical decline completely, the trial results promise to have a profound effect on Alzheimer's research, patient care and the successful development of therapies that could modify or even prevent the disease.

"This treatment offers hope for many patients and family caregivers."

For more than 30 years, proponents of the 'amyloid hypothesis' have contended that the amyloid-β (Aβ) protein triggers a cascade of neurobiological changes that contribute to the development of Alzheimer's disease. The postulated cascade includes: aggregation of Aβ into soluble clumps and insoluble fibrils, the main component of plaques; phosphorylation, aggregation and spread of another protein called tau, the main component of tangles (a microscopic brain abnormality that, along with Aβ plaques, defines the disease); neuroinflammation; and neurodegeneration[2]. A growing number of drugs have been and continue to be developed to target Aβ and other elements of this cascade[3].

In 2016, the antibody aducanumab became the first drug shown to cause a notable reduction in Aβ plaques[4]. At the time, I suggested that it would be a game changer if the treatment's plaque-reducing effects were found to be linked with a clear clinical benefit in its phase III trials[5]. Unfortunately, those trials were discontinued early, after an interim analysis mistakenly concluded that aducanumab was unlikely to demonstrate sufficient clinical benefit. When remaining data from the two discontinued trials became available, one trial showed improvements, one did not. Post-hoc analyses suggested a clinical benefit in people who received the highest dose for at least one year[6].

In a review of aducanumab, the US Food and Drug Administration (FDA) conducted a meta-analysis of available findings from various anti-Aβ antibody therapy trials[7] and found a relationship between greater Aβ-plaque reduction and slower clinical decline. The meta-analysis included the aducanumab trials; phase II trials of lecanemab[8] and another antibody called donanemab[9,10] (both of which showed significant Aβ plaque reductions and suggested a clinical benefit); and trials of four other antibody therapies with more