climate-model simulations to show (using further analysis) that human-induced greenhouse-gas emissions almost certainly contributed to these trends (Fig. 1). Their findings suggest that this human-caused loss of snow mass will accelerate in the coming decades. Perhaps more importantly, they note that many basins in populated areas in the Northern Hemisphere will approach an average winter temperature of −8 °C, causing a major decay of snow mass that will lead to drastic decreases in river discharges, especially in the heavily populated drainage basins of North America and Europe.

The authors' use of ensemble data necessarily combines sources with varying spatial resolution and uncertainties. There are substantial spatio-temporal differences in gridded snow-cover data and, for this reason, the trends suggested by different types of data are inconsistent with each other for some regions. In complex mountainous terrain, for example, these problems are amplified owing to the spatial variability of snow water equivalent on scales much smaller than those of the authors' gridded data, which have spatial resolutions of several to dozens of kilometres. These factors affect Gottlieb and Mankin's calculation of confidence in the trends identified in their analysis.

Owing to observational uncertainties, it is unclear how well ensemble approaches can represent spatial details on the scale of basins in the Northern Hemisphere. Thus, observational uncertainties limit the accuracy of climate reconstructions and predictions. One way to mitigate these issues could involve collating snow-cover data from satellite, ground-based and model-based information. This would in turn require new observational systems, such as satellite sensors with a high spatial resolution. Satellite missions that are currently being planned include radar sensors with a spatial resolution ranging from tens to hundreds of metres[8–10]. Such sensors also have the potential to improve calculations of the uncertainty associated with historical observations.

Gottlieb and Mankin's study underlines the impact that humans have had — and will continue to have — on heavily populated drainage basins in the Northern Hemisphere. However, the relevance of the authors' analysis extends beyond these regions to the Arctic and other sparsely populated high-latitude and mountainous regions. This is because Arctic temperatures, for example, are increasing four times more rapidly than is global mean temperature[11]. And, as well as affecting water availability for people, changes in seasonal snow cover directly affect ecosystems, both those in seasonal snow regions and those in snow-free downstream areas. Such changes, in turn, influence the efficacy of carbon sinks, and increase the likelihood of extreme events, such as wildfires or droughts.

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Ancient DNA

Multiple sclerosis rooted in European prehistory

Samira Asgari & Lionel A. Pousaz

An exploration of more than 1,600 ancient Eurasian genomes suggests that genetic changes that increase autoimmune-disease risk in modern Europeans could have protected ancient Europeans from pathogens. **See p.301, 312, 321 & 329**

Multiple sclerosis is an autoimmune disease that can affect all human populations, but its prevalence is the highest in white people, particularly northern Europeans. On page 321, Barrie *et al.*[1] examine the prehistoric origins of the genetic changes that might hold the key to understanding Europeans' elevated risk of multiple sclerosis. The researchers' work builds on three accompanying papers from members of the same team[2–4], presenting a deep dive into the genomic history of ancient Eurasian populations using data gathered from ancient DNA.

Multiple sclerosis is a complex disease, which is contributed to by environmental and heritable factors. Understanding the role of heritable factors in multiple sclerosis can help to predict an individual's risk of developing the disease and can even point to potential drug targets for its treatment[5]. So far, scientists have identified more than 230 genetic changes that can increase the likelihood of developing the disease (risk variants)[6]. For example, a genetic variant on chromosome 6 called HLA-DRB1*15:01 is present in up to one-fifth of northern Europeans, and individuals with this variant have a threefold higher risk of developing multiple sclerosis compared with those who do not have the variant[6]. The HLA-DRB1*15:01 variant is much less common in southern European populations and populations with non-European ancestry[6].

In the latest study, Barrie *et al.* sought to explore the origins of multiple sclerosis risk in northern Europeans. The researchers show that genetic risk is correlated with the proportion of ancestry from ancient pastoralists who introduced domesticated animals to Europe around 5,000 years ago. Moreover, they show that the proportion of ancient pastoralist ancestry is higher in northern Europeans than in southern Europeans, bringing answers to the debate about the origins of the north–south gradient in multiple sclerosis burden in Europe. Finally, they show that some risk variants have risen in frequency in Europeans over time, suggesting that these variants could have provided an evolutionary advantage in the context of the lifestyle of ancient Europeans (Fig. 1).

To reach these conclusions, the authors first had to step back and examine the genomes of individuals who lived several thousands of years before the arrival of pastoralists in Europe. Researchers in the same team as Barrie and colleagues (Allentoft *et al.*[2], on page 301, and Allentoft *et al.*[3], on page 329) generated a genomic data set using bones and teeth from the remains of 317 ancient inhabitants of Europe and western Asia. Combined with existing genetic data from more than 1,300 ancient Europeans, this data set is a unique resource that captures Europe's population history over the past 10,000 years.

This period encompasses major events in recent human evolution. Chief among these is the shift from hunting and gathering to farming and pastoralism. Although most of Europe's inhabitants were hunter-gatherers 15,000 years ago, by 5,000 years ago they had almost entirely shifted to farming domesticated crops that had been brought by Middle Eastern farmers. Around this time, pastoralists from the northern shores of the Black Sea and Caspian Sea (situated between Europe and Asia) introduced domesticated animals.

Major changes in the lifestyles of people in a population are often accompanied by changes

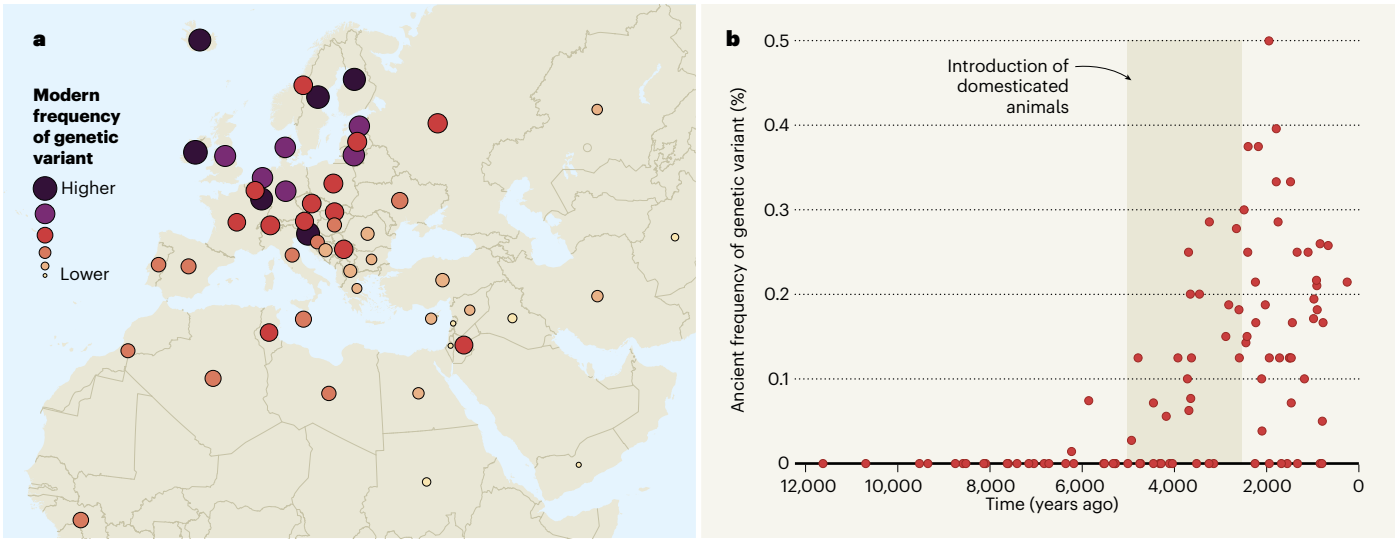

Figure 1 | The prehistoric origins of a genetic variant that elevates multiple sclerosis risk in northern Europeans. **a**, The genetic variant HLA-DRB1*15:01 is associated with an increased risk of developing the autoimmune disease multiple sclerosis. The frequency of HLA-DRB1*15:01 is higher in present-day northern Europeans compared with present-day southern Europeans, reflecting the north–south gradient of the multiple sclerosis burden in Europe. **b**, Barrie *et al.*[1] report that the frequency of HLA-DRB1*15:01 in the genomes of ancient individuals, sampled from across Europe, increased after the introduction of domesticated animals to Europe by pastoralists around 5,000 years ago. The authors suggest that HLA-DRB1*15:01 could have protected ancient Europeans against pathogens that came with the shift from hunting and gathering to farming and pastoralism. This could explain why the variant has been positively selected for in recent human evolution. (Adapted from Fig. 2 in ref. 1.)

in the genetic make-up of that population over time[7]. This is owing to evolutionary forces such as natural selection, as well as the production of offspring from the mixing of existing and incoming populations. Using their ancient-genome data set, and an analysis approach developed by Irving-Pease *et al.*[4] (page 312), the authors sought to quantify the proportion of genetic ancestries from different ancient European groups (hunter-gatherers, farmers and pastoralists) in almost 410,000 present-day self-reported 'white British' people. They then asked whether specific regions in the genomes of present-day white Europeans show unusually high or low proportions of ancient ancestry and whether such changes are associated with multiple sclerosis risk.

The researchers noticed that an increase in pastoralist ancestry in a region on chromosome 6 was associated with a higher risk of developing multiple sclerosis. Interestingly, this is the same region that harbours the HLA-DRB1*15:01 risk variant. They also observed a higher proportion of pastoralist ancestry in this genomic region in northern than in southern Europeans, mirroring the north–south gradient for multiple sclerosis risk. They concluded that the increased proportion of pastoralist ancestry in present-day northern Europeans might be partly responsible for the higher prevalence of the disease in that population than in southern Europeans.

One common approach when looking at population history is to search for signatures of natural selection, which involves analysing changes in the frequency of genetic variants over time. In principle, the frequency of a variant increases when it has been favoured by evolution, or 'positively' selected – presumably because it has been advantageous. A decrease in frequency over time is a sign of 'negative' selection, an evolutionary mechanism to limit the effects of harmful variants.

When the authors carried out this analysis, they observed signs of positive selection for HLA-DRB1*15:01 and some other multiple sclerosis risk variants[4]. Why would a variant bearing such a health risk be favoured by evolution? To answer this, it is important to remember that traits that are beneficial in one context might be detrimental in another.

Previous evidence suggests that some of the variants that increase the risk of multiple sclerosis and other autoimmune diseases could be protective against infectious disease[8]. This is probably because the genetic changes that contribute to mounting effective immune responses in the face of infections can also lead to overactivity of the immune system in reaction to the body's own proteins. The authors speculate that having these variants might have been advantageous in the era that followed hunting and gathering, when agriculture, animal domestication and a higher population density increased the chances of contracting pathogens. This is a valid hypothesis, although more concrete evidence is needed to prove it.

"The study brings answers to the debate about the origins of the north–south gradient in multiple sclerosis burden in Europe."

Some of this evidence could be provided by further studies of ancient genomes, which would help scientists to better understand the extent to which pathogens exerted selective forces on the human genome, and the resulting effects on genetic diversity and disease risks in present-day humans. In addition, future experiments are needed to establish the biological mechanisms that connect the risk of specific autoimmune diseases with immune responses to certain pathogens.

Finally, it is crucial to extend these studies to diverse human populations to better understand how differences in population history might have contributed to the risk of autoimmune diseases such as multiple sclerosis. Although human biology is shared, each population has a unique history and focusing on a single population limits opportunities for discoveries that can bring insights that advance medicine.

In summary, the research teams behind these papers developed a comprehensive resource[2,3] along with several analytical approaches[4] to explore the origin of the genetic risk of multiple sclerosis in Europe more extensively than ever before[1]. Their findings reveal the reasons that underlie the north–south gradient in Europe and point to the potential evolutionary advantage that multiple sclerosis risk variants could have had in the post-hunting-and-gathering era. However, future work is needed to confirm the suggested association between infectious diseases and multiple sclerosis risk.

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S.A. declares competing interests, see go.nature.com/3rkqacu for details.

Engineering

A 2D route to 3D computer chips

Tania Roy

Ultrathin materials have long been touted as a solution to the problems faced by the ever-growing semiconductor industry. Evidence that 3D chips can be built from 2D semiconductors suggests that the hype was justified. **See p.276**

Silicon is the electronics equivalent of the steam engine. This amazing material is the reason for the decades-long boom in semiconductor technologies, which now grants many people the technology required to work from home. But as devices become ever more powerful, the number of transistors that can be packed onto a tiny 2D computer chip is nearing its limit. The only way is up, it seems: silicon-based chips are already being reduced in size by taking advantage of the third dimension. However, silicon might not be the best candidate for the job. On page 276, Jayachandran *et al.*[1] present a 3D device built from 2D materials — ultrathin layers of non-silicon semiconductors that solve many of the problems posed by silicon.

The number of transistors on a computer chip doubles about every 18 months. This observation, known as Moore's law, is a nightmare for semiconductor engineers, who are tasked with building chips that are ever smaller and more powerful. But the electronics industry faces another challenge, which has been summed up as 'more than Moore'[2]: small devices, such as smartphones, can have multiple functions that require standard computer chips to have non-digital components (for example, sensors and actuators). Building tiered 3D chips is one way to address this challenge, but it is difficult, because the processing conditions that are needed vary between layers. For example, the temperature of the top layers must not exceed around 450 °C, which is relatively low for semiconductor processing. The quality of these layers is also compromised by rough surfaces that are created by the underlying layers.

Jayachandran *et al.* overcame these issues to fabricate a wafer (the substrate used to create chips) that consists of two integrated tiers of nanometre-scale transistors. Each layer contains more than 10,000 transistors made from sheets of molybdenum disulfide (MoS_2) of single-atom thickness. The authors grew the MoS_2 films separately before transferring them to the wafer, a process that does not require high temperatures.

Jayachandran and colleagues' achievement is sufficient in itself to incite the interest of the semiconductor industry in 2D materials. However, the authors then went further to prove the versatility of their process. They built a three-tier structure that combined MoS_2 transistors with those made from tungsten diselenide (WSe_2), and showed that all of the transistors could maintain a reasonably high performance in each level. They then scaled down the transistors in a two-tier configuration so that their channels (the structures through which charge carriers flow) were just 45 nanometres long — around one- sixth of the length of the smallest channels in the other two systems. The authors' technique could, in principle, be used to fabricate a fully functional 3D circuit (Fig. 1).

Each year, new ideas are formulated about which materials could form the basis of next-generation transistor channels. The excitement about the possibilities of 2D materials started with graphene, which is a single layer of carbon atoms that are arranged in a hexagonal lattice. After much research, graphene was relegated mainly to the realm of electrodes, because inducing it to have semiconducting properties is difficult. But other 2D materials, such as MoS_2, don't have this problem. And these materials also improve on semiconductors that aren't ultrathin, because they allow shorter channel lengths[3]. For these reasons, 2D materials have huge potential for electronics — as shown by the interest in MoS_2 and WSe_2 by semiconductor firms such as the Taiwan Semiconductor Manufacturing Company and Intel[4,5].

The process of building an integrated computer circuit is divided into two parts.

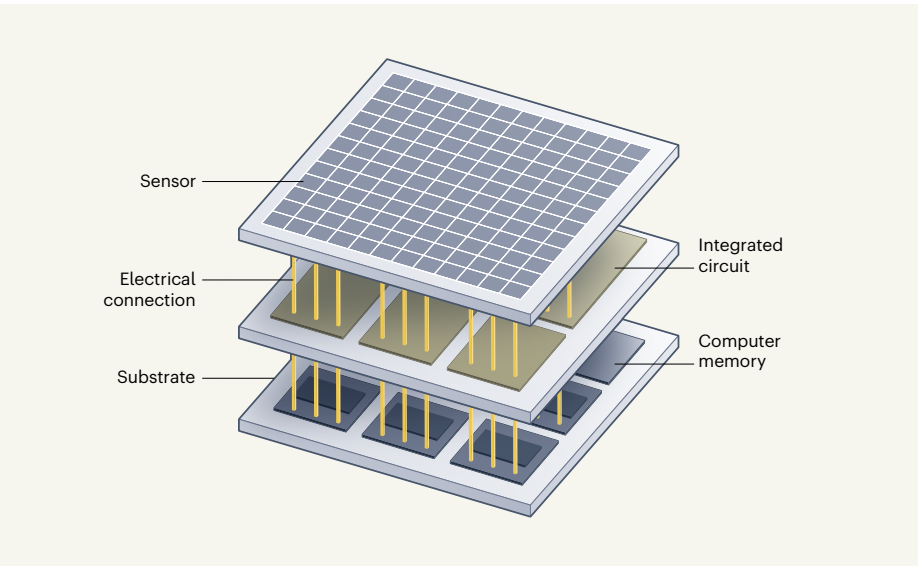

Figure 1 | A 3D circuit made from 2D materials. Jayachandran *et al.*[1] fabricated a tiered structure, in which each tier is made from ultrathin sheets of semiconductor materials, layered on a substrate, and is electrically connected to the next. The authors showed that the device could incorporate components with different functionalities, such as sensing and memory. The advance could give rise to fully functional 3D computer chips that include such components, as well as integrated circuits for computing. (Adapted from Fig. 1a in ref. 1.)