from a C–G base pair to T–A, occurred about 5–50% of the time. The efficiency of editing was influenced by various factors: the spacing between the two DdCBE subunits; TALE design; orientation of the split-DddA$_{tox}$ halves; and the position of the target cytosine relative to the TALE bindings sites.

A major consideration for all genome-editing tools is whether they modify DNA at unintended sites. Mok and colleagues compared treated and untreated cells, and found no off-target effects in the nuclear genome. Off-target activity in mtDNA was low, except in the case of one gene, in which off-target edits were linked to the TALE design.

Next, Mok *et al.* examined the therapeutic potential of DdCBE. The authors reported that cytosine base editing has the potential to correct 49% of known harmful mtDNA mutations. However, in its current form, DdCBE can efficiently edit only C bases that are preceded in the genome by a T, narrowing its range.

The reliance of DdCBE on DNA replication to implement the C–G to T–A conversion implies a theoretical maximum editing efficiency of 50%. To explain, the two newly replicated mtDNAs each receive a parental DNA strand, one of which will be unedited, containing G, which becomes paired with a C. However, Mok *et al.* find that the activity of DdCBE persists over several days, potentially offering the opportunity for further editing during subsequent replication events. Whether off-target effects increase during prolonged exposure to DdCBE will be a key consideration for the future.

These caveats mean that DdCBE might cause a reduction in — rather than complete elimination of — mtDNA mutations. But given that the severity of the symptoms of mtDNA diseases increases with mutation load[8], the ability to reduce the mutation level in itself holds therapeutic promise.

Mitochondrion-targeted nucleases have previously been used to eliminate specific mtDNA mutations in mice[9,10]. This is possible because the double-strand breaks they create lead to mtDNA degradation. Cells contain many copies of their mtDNA, and only the copies that carry the harmful mutation are degraded. But there is a risk that, in cases of high mutation load, elimination of mutated mtDNA could reduce the mtDNA copy number to harmfully low levels. And the nuclease approach could not be used if all copies of mtDNA carry the same mutation. By contrast, base editing could reduce the fraction of mtDNA that carries a mutation without reducing the copy number. It might therefore be the preferred (or the only) option when the mutation load is high.

Does DdCBE have the potential to prevent the transmission of mtDNA disease? MtDNA is typically inherited only from mothers, and current mitochondrial-replacement procedures reduce the transmission of mtDNA mutations by transplanting the nuclear genome from the egg of a woman who carries the mutated mtDNA into an unaffected donor egg[11]. Base editing to reduce the mutation load in eggs or early embryos could theoretically be an alternative approach. However, mtDNA replication is thought not to occur during the first five to six days of human development[12], and so success might hinge on prolonged protection of U.

Mok and colleagues' work is a key advance towards the development of gene therapies for mtDNA diseases. In addition, by using the tool to experimentally alter the mitochondrial genome, we could gain a better understanding of the relevance of mtDNA mutations in complex diseases, cancer and age-related cellular dysfunction. The study is also likely to inspire further developments in protein engineering and evolution that increase the range and efficiency of DdCBE, and to intensify the search for other promising candidate base editors.

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Historical climatology

A flood history of Europe

Francis Ludlow & Rhonda McGovern

Europe's rich heritage of historical documents has been used to reconstruct the flooding history of the continent for the past five centuries. This could help policymakers to develop flood-management strategies for the future. **See p.560**

On page 560, Blöschl *et al.*[1] capitalize on a vast assembly of written historical observations to provide a history of flooding for 103 major European river reaches between AD 1500 and 2016. In doing so, they reveal nine flood-rich periods that affected extensive regions in distinct areas of Europe — and find that the most recent of these periods, which might not yet be over, differs in key respects from the others.

Some 0.03% of the European population, on average, are thought to have been affected by flooding annually between 1870 and 2016, at a yearly average cost of 0.08–0.09% of gross domestic product[2]. Increased flood hazards are widely expected in the future for a substantial area of Europe as a result of climate change[2], and so, without effective management and adaptation, these losses will potentially be even greater.

Such measures must be based on the best available knowledge, and require an understanding of long-term flooding patterns. Decision makers must know whether they are living in a flood-rich period (more-frequent flooding, of higher magnitudes or greater extent than usual) or a flood-poor one (fewer floods, with lower magnitudes or less-than-usual extent). Extreme floods in any one river basin in a given year are inherently rare, but the risk is cumulatively higher across large regions such as Europe — so the longer and more spatially extensive these flood histories are, the better.

Fortunately, Europe hosts some of the most abundant and diverse historical documentary sources for any world region, ranging from annals and chronicles to administrative and legal records, correspondence and newspapers (Fig. 1). These sources are replete with observations of extreme weather and hazards such as flooding, given their often severe human impacts, spectacular effects and religious significance as portents or vehicles of divine retribution[3]. For example, the Gaelic Irish *Annals of Connacht* for AD 1471 reports[4]: "Showers of hail fell [on] each side of Beltaine [1st May], with lightning and thunder, destroying much blossom and beans and fruits in all parts of Ireland where they fell. One of these showers, in the east, had stones two or three inches long, which made large

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wounds on the people they struck ... There was another ... at the monastery of Boyle; and a boat could have floated over the floor of the great church of the monks, as we have heard from the folk of that place."

This account highlights the strengths of documentary evidence: it is precisely dated, highly spatially resolved, generally unambiguous about the meteorological conditions involved and explicit regarding human impacts. Such evidence is used as the basis of historical climatology, a field whose origins date back to at least the 1920s (ref. 5), and which accelerated in the 1960s and 1970s, thanks to pioneers such as Hubert Lamb and Hermann Flohn. Their work furthered the growing recognition that societally meaningful changes in climate had occurred throughout the past few centuries, eroding the idea that the long-term climate was more or less constant during that period[6].

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Yet despite continued development of the field, historical climatologist Christian Pfister and climate scientist Heinz Wanner remarked[7] in 2002 that "many scientists are of the opinion that observations made before the instrumental period are "subjective" and less reliable than natural proxies ...". They went on to argue that "once calibrated and verified ... the data are precise and have a spatiotemporal resolution unmatched by any other climate proxy". Since then, historical climatologists have continued to identify evidence, develop methods to assess its credibility and quantify it to reconstruct past climates[8–10]. With their compilation of 9,576 floods, Blöschl *et al.* have built on this foundation to deliver a major contribution to our understanding of European flood history.

Patterns of past precipitation are inherently more spatially variable, and hence harder to reconstruct, than are those of temperature. Reconstructing flooding is even more challenging, because flooding depends not only on precipitation, but also on human landscape usage, from upstream deforestation to damming, bridging and urbanization. It is also related to prevailing temperatures, which have a seasonally and regionally varying role across Europe, influencing evaporation and soil moisture and the timing of spring snowmelt[11]. Importantly, therefore, Blöschl and colleagues establish an association in timing between all but one flood-rich period and the prevalence of lower-than-usual average temperatures. By contrast, the most recent flood-rich period in Europe (1990 to 2016, when the available data end) — for a region stretching into western and central Europe and northern Italy, and defined by the authors as being one of the most severe — is exceptional for occurring in a warming climate.

Just one highlight of this work is the care taken to control for biases arising from variability in the type and abundance of sources through space and time, a persistent challenge often acknowledged but infrequently addressed[3]. A further standout feature is the authors' 3D visualization of the magnitude, duration and geography of each flood-rich period (see Fig. 1 of the paper[1] and Supplementary Video 1). This invites a consideration of the internal and external climate processes that potentially drove these periods, and how their regional expression was manifested in, or mediated by, the behaviour of major modes of ocean and atmospheric circulation.

Figure 1 | Historical evidence of flooding. This reproduction of a woodcut depicts inundation of the streets of Glauchau in Germany in 1854. Blöschl *et al.*[1] have used information from historical records to construct a flood history for Europe from 1500 to 2016.

One key suspect noted by Blöschl *et al.* is the North Atlantic Oscillation (NAO), a fluctuation in the atmospheric pressure gradient between Iceland and the Azores that governs the strength and positioning of moisture-laden winter westerlies (and accompanying storm tracks) over Europe. Depending on the strength of this gradient, the westerlies either bring relatively warm wind and rain to northern and northwestern Europe, leaving southern Europe dry and cool, or flow towards southern Europe, leaving northern and northwestern Europe to experience incursions of cold and dry Arctic air.

But ambiguities remain regarding the mechanisms at play. With the dominant flood season differing by region (winter for northern and northwestern Europe, but summer for central Europe, for example), the wintertime NAO can explain only part of this story. The related role of prevailing temperatures in the observed flood-rich periods also remains an open question. Earth-system modelling, twinned with process-based hydrological models (as the authors note) could be used to capture the complexity of natural and human processes on the ground that enhance or suppress flooding. It could also provide further insight into the extent to which the association of cooler-than-usual conditions with most flood-rich periods is causative or correlative, and how much the most recent flood-rich period is a result of human-induced climate warming.

Blöschl *et al.* clearly demonstrate the potential of historical climatology, but there are yet more avenues by which to advance this approach to reconstruct past climate. Written evidence of climate can become particularly discontinuous in the deep past, but tree-ring evidence, for example (measurements of tree-ring widths, densities and isotopic composition, which correlate with climate conditions), is more continuous over long periods. However, tree-ring evidence usually reflects only the growing-season climate, whereas written evidence can attest to weather for all seasons. If both sources were more regularly used in a complementary manner[12], it would improve our understanding of the climatic signals preserved in each source, and help to resolve perceived conflicts — for instance, the great European drought of AD 1540 is readily apparent in written records, but more ambiguously represented in certain tree-ring evidence[13].

Further written sources remain to be discovered, including documents known as weather diaries, which are highly prized in historical climatology for their standardized systematic recording of weather conditions. These can be found not only in the most recent centuries, but sometimes much earlier — as with the incredible Babylonian 'astronomical diaries'[14], which boast systematic daily

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observations of weather during the first seven centuries BC, and which remain largely unexploited. As Pfister and Wanner stated[7] in 2002, "Worldwide, many thousand volumes with daily observations exist, but have not yet been analyzed for their climatic information. Let's get to work!"

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Human migration

Native South Americans reached Polynesia early

Paul Wallin

DNA analysis of Polynesians and Native South Americans has revealed an ancient genetic signature that resolves a long-running debate over Polynesian origins and early contacts between the two populations. **See p.572**

For many years, scholars have speculated about how Polynesia was initially populated. On page 572, Ioannidis *et al.*[1] now describe a genetic approach that they used to address the issue of Polynesian origins and interactions.

The early peopling of Polynesia attracted worldwide interest in 1947, when the Norwegian explorer Thor Heyerdahl set sail on the *Kon-Tiki* expedition to test his migration theory[2]. The crew left Peru on a wooden raft, and after 101 days and a voyage of more than 7,000 kilometres, they reached Polynesian shores, thus demonstrating the possibility of early travel from South America to these Pacific islands. Heyerdahl challenged the scientific community's view that evidence pointed instead to the peopling of Polynesia by people travelling east from Asia, and his idea that Polynesia was initially populated by South Americans was generally criticized by scholars.

The same scientific community nevertheless discussed cultural contacts between the two regions, because a South American plant, the sweet potato, has a long history of cultivation in eastern Polynesia. The idea that Polynesians voyaged to South America and introduced the plant on their return to Polynesia became the accepted explanation for this[3]. Rapa Nui (also known as Easter Island) is the best-known example considered concerning such contacts[4]. It is a part of Polynesia that is located relatively close to South America, and in Rapa Nui there is evidence of large, ancient sweet-potato fields, extraordinary old stonework and a specific birdman cult — all of which are features in common with those of South America.

Ioannidis and colleagues analysed the DNA of people from Rapa Nui, and also studied DNA of individuals from 17 populations of Pacific islands and 15 Native American populations from the Pacific coast of South America. Genome-wide DNA analyses of 807 people (analysing predominantly present-day individuals) enabled the authors to search for evidence of ancestors from different populations who produced offspring together — thereby generating a combined genetic signature of the two populations, described as an admixture. The authors compared the dominant Polynesian DNA markers with those of people from other regions, including Europe, America, Africa and Melanesia. A computational method called an ADMIXTURE analysis allowed Ioannidis and colleagues to work out a person's probable genetic ancestry and ancestral geographical origins through studies of gene flow. Their main discovery is that several eastern Polynesian populations have signs of a background signature (genetic traces from distant ancestors) that originated from Native South American people.

> **"Future research should assess the possibility of more than just one early contact from South America."**

How did Ioannidis and colleagues solve this complex task of genetic unravelling? In their admixture studies, they could trace and distinguish between different modern colonial admixtures; for example, in French Polynesia, there was a large French influence, whereas Spanish and Chilean groups were part of the population history in Rapa Nui. A key discovery came from their analysis of people from Rapa Nui — a signature could be assigned to Native South American populations from northern coastal regions of South America, and this component was independent of other large historical, or more-recent, admixture events. This signature exists in the genetic background, indicating that it is an old and stable hallmark of admixture. A surprising finding is that this signal was also identified in other eastern Polynesian populations, for example in populations in Mangareva, in North Marquesas and South Marquesas, and in Palliser in the Tuamotu Islands (Fig. 1). These other islands lie farther from South America than does Rapa Nui, although for people sailing from South America they are destinations that would be aided by favourable trade winds and currents.

Ioannidis *et al.* investigated the estimated timing of admixture events using a method called tract-length distribution analysis, which assesses the length distributions of the genomic segments inherited from different ancestral populations. As expected, this statistical approach suggests that the European admixtures in Polynesia first date back to colonial phases of AD 1750–1860.

The authors made the notable discovery that an initial admixture event between Native South Americans and Polynesians took place in eastern islands of Polynesia around AD 1150–1230. Previous work[3,5] is consistent with a model of populations spreading eastwards from Asia possibly having reached eastern Polynesia by that time. The exception to this South American admixture timeframe is Rapa Nui, which had a later admixture, dated to around AD 1380. This later date for Rapa Nui is surprising, because it is the closest site to South America studied and has been cited as the 'typical' example of a location with possible early connections to South America. However, the timing difference might be due to a more complex genetic history there because of relatively recent Chilean genetic input.

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Correction

A flood history of Europe

This News & Views article erroneously stated that the average yearly costs of flooding in Europe between 1870 and 2016 were 0.8–0.9% of gross domestic product. In fact, the range was 0.08–0.09%.

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