Abrupt warming events in the Arctic pull the meteorological equator — a band of tropical storm clouds that circle the globe near the Equator — farther north, and, along with it, the rainfall patterns associated with the Asian summer monsoon. In 2017, a reinterpretation of water-isotope signals in an Antarctic ice core identified a near-instantaneous response of atmospheric circulation to changes in Arctic climate that occurred in the most recent ice age, all the way south to West Antarctica[8]. However, whether this response occurred throughout the Southern Hemisphere, or was more localized, remained unclear.

Buizert and colleagues present the first Antarctic-wide evidence for a rapid atmospheric coupling of the position of the westerly winds around the whole of the Southern Ocean to past abrupt climate events in the Arctic (Fig. 1). Identifying these pervasive fluctuations in wind position, which happened on a decadal timescale tens of thousands of years ago, required the precise synchronization of ages for ice cores from across the Antarctic continent.

Ice-core ages from Greenland have been linked to those from Antarctica using the methane composition of bubbles in the exceedingly well-resolved ice core from the West Antarctic Ice Sheet Divide[5]. Atmospheric methane is quickly mixed across the hemispheres, and so can be considered as globally synchronous. Past fluctuations in methane abundance mimicked abrupt changes in Greenland temperature and therefore provide a way of precisely interrogating the timing of climate events between the Arctic and the Antarctic.

Buizert *et al.* took the next step in synchronizing the West Antarctic Ice Sheet Divide record with four other Antarctic ice cores by identifying characteristic sequences of volcanic eruptions preserved in the sulfate levels in Antarctic ice. Only then were the authors able to identify the superimposed oceanic and atmospheric signals that occurred across Antarctica in response to past rapid changes in Arctic climate.

The classic see-saw of heat between the hemispheres through the ocean can explain the delayed and gradual changes in Antarctic temperature that accompanied past abrupt shifts in Greenland temperature. But Buizert and co-workers' study suggests that superimposed on these slow ocean changes were an almost synchronous northward shift in the westerly winds circling Antarctica when Greenland moved into its warm phase — and, vice versa, a southward shift in these winds during cool Greenland events. This atmospheric response modulated the latitude in the Southern Ocean that formed the source of the moisture that fell as snow over Antarctica.

A one-to-one relationship has previously been identified between the duration of Greenland temperature events and the magnitude of the ensuing temperature response in Antarctica through the ocean mechanism[7]. Similarly, the authors find that the atmospheric response seems to scale so that stronger Greenland events result in a larger climatic signal in Antarctica and the Southern Ocean. An atmospheric link tying changes in Arctic climate to the Antarctic has previously been hypothesized on the basis of climate-model responses in experiments designed to mimic aspects of Dansgaard–Oeschger events[6]. The current work provides the observational data to prove the existence of this link.

It is time to move beyond considering only the Atlantic Ocean and century-scale time lags when thinking about how the Arctic and the Antarctic are climatically connected[5]. Buizert and colleagues' identification of a rapid atmospheric link between climates at the poles has implications for our understanding of current climate change. Today, the Arctic is warming at about twice the rate of the global average; however, continent-scale warming of the Antarctic that is expected from climate simulations has not yet been clearly observed[9,10]. Changes in Antarctic sea ice are also not following expectations based on models[10]. Meanwhile, the westerly winds of the Southern Hemisphere have been shifting rapidly southwards, affecting water security in cities such as Perth in Australia and Cape Town in South Africa, and potentially having global consequences by altering the movement of heat and carbon dioxide between the atmosphere and the ocean[11].

Many challenges remain in accurately predicting how, and how quickly, the behaviour of Antarctica and the Southern Ocean will change in a warming climate. Nevertheless, the authors have provided a glimpse of the natural changes in behaviour — both rapid and slow — that occurred tens of thousands of years ago. These results provide a basis for progress in unravelling the current scientific mysteries of how the ocean and the atmosphere at the poles respond to rapid changes in climate. ■

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1. Fischer, H. *et al. Nature Geosci.* **11**, 474–485 (2018).
2. Kindler, P. *et al. Clim. Past* **10**, 887–902 (2014).
3. Buizert, C. *et al. Nature* **563**, 681–685 (2018).
4. Stocker, T. F. & Johnsen, S. J. *Paleoceanography* **18**, 1087 (2003).
5. WAIS Divide Project Members. *Nature* **520**, 661–665 (2015).
6. Pedro, J. B. *et al. Quat. Sci. Rev.* **192**, 27–46 (2018).
7. EPICA Community Members. *Nature* **444**, 195–198 (2006).
8. Markle, B. R. *et al. Nature Geosci.* **10**, 36–40 (2017).
9. Abram, N. J. *et al. Nature* **536**, 411–418 (2016).
10. Jones, J. M. *et al. Nature Clim. Change* **6**, 917–926 (2016).
11. Toggweiler, J. R. & Russell, J. *Nature* **451**, 286–288 (2008).

ALZHEIMER'S DISEASE

A mosaic mutation mechanism in the brain

Variable brain-specific mutations have been observed in Alzheimer's disease. One mechanism underlying this mosaicism involves integration of variant gene copies back into the neuronal genome. SEE ARTICLE P.639

GUOLIANG CHAI & JOSEPH G. GLEESON

Genetic mutations can arise not only in fertilized eggs, affecting all cells of an organism, but also in a subset of an organism's cells[1–3]. The latter phenomenon, called mosaicism, is prevalent in the brain, and has been associated with several neurological disorders, including sporadic Alzheimer's disease, the most common form of the disease[1,3,4]. In 2015, it was found[5] that neurons from people with sporadic Alzheimer's contained more DNA and had more copies of the Alzheimer-related gene *amyloid-β precursor protein* (*APP*) than did neurons from people without the disease. However, the exact genomic changes underlying this mosaicism remained unresolved. Lee *et al.*[6] follow up on that work on page 639, providing a mechanism for increased *APP* mosaicism in the brains of people with sporadic Alzheimer's disease. The study could alter our understanding of the roots of neurodegeneration.

First, Lee *et al.* set out to analyse *APP* variants in neuronal messenger RNA. In each experiment, the authors used mRNA from just 50 neurons from the brains of people with or without sporadic Alzheimer's, because averaging across large neuronal populations could mask variants present in only a few cells. The researchers' analysis revealed many *APP* mRNA variants. As expected, the variants lacked introns — non-protein-coding regions that are removed during gene transcription through a process called splicing, leaving only protein-coding exons. However, the variants were shorter than expected, and contained single-nucleotide mutations, inserted and

deleted exons, and larger deletions that led to the formation of new exon–exon junctions between missing multi-exon regions. Some of the mutations the authors observed have been previously implicated in familial Alzheimer's disease[7].

Lee and colleagues found the same short variants when they analysed genomic DNA from the neurons, suggesting that *APP*-variant mRNAs might be transcribed from matching genomic DNA sequences — named genomic complementary DNAs (gencDNAs) by the authors — that had become permanently embedded in the genomes of neurons. To further validate the existence of *APP* gencDNAs in neurons, the authors used two independent approaches: a technique called DNA *in situ* hybridization (DISH), in which fluorescent molecules were bound to gencDNA-specific exon–exon junctions in DNA; and sequencing of short sections of *APP* DNA. Both approaches confirmed the existence of gencDNA variants.

The researchers next investigated the extent of gencDNA diversity using DNA sequencing. In total, they identified 6,299 different *APP* gencDNA variants in 96,424 neurons from the brains of 5 people with sporadic Alzheimer's — approximately 10 times more than they found in the brains of people without the disease. In agreement, DISH also revealed substantially more gencDNAs in Alzheimer's neurons.

The authors demonstrated that *APP* gencDNAs were present in the neurons of a mouse model of Alzheimer's disease, but rarely in non-neuronal cells or neurons from control animals. Moreover, gencDNA variants accumulated with age. These findings are consistent with a role for *APP* gencDNA variants in the development of Alzheimer's. Indeed, the authors found that some *APP* mRNA variants are translated into proteins that are toxic to cells, further strengthening this possibility.

Finally, Lee and co-workers showed that gencDNAs could be generated in cells in culture, provided that two conditions were met. First, the cells' DNA had to contain breaks in its strands, and, second, the enzyme reverse transcriptase had to be active. This enzyme is responsible for a process called reverse transcription, in which matching DNA sequences are produced from mRNA. The data indicate that gencDNAs arise from reverse-transcribed mRNA intermediates, which are incorporated into the genome in a process that might be promoted by breaks in DNA (Fig. 1). In support of this idea, the authors detected reverse transcriptase activity in the human brain samples, and a previous study has shown the presence of DNA breaks in developing brains[8], whereas this phenomenon is rarely observed in other tissue types.

The incorporation of gencDNAs into the genome might share some mechanisms with retrotransposition — a process in which RNA transcribed from DNA sequences called transposable elements can reintegrate into new genomic regions to generate mosaicism[3]. But how gencDNAs become mutated from the original *APP* sequence remains unknown. Perhaps the mutations arise from mis-splicing of mRNA, or during genomic integration of gencDNAs.

Taken together, Lee and colleagues' work reveals the surprising existence of a phenomenon known as somatic gene recombination in the brain. This phenomenon, which has previously been reported only in antibody generation in immune cells[9], increases the diversity of proteins encoded by a given gene through DNA-shuffling mechanisms.

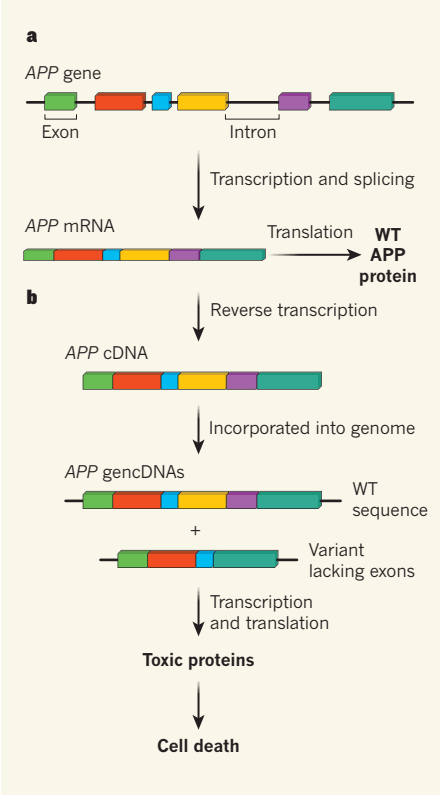

Figure 1 | Mosaic incorporation of *APP* variants into the neuronal genome. **a**, The gene *amyloid-β precursor protein* (*APP*) contains protein-coding exons (coloured blocks) and non-coding introns (this simplified schematic of the gene does not reflect the actual exon–intron composition). During transcription, introns are removed through a process called splicing to produce messenger RNA, which is translated to form the wild-type (WT) protein. **b**, Lee and colleagues[6] found that, in neurons in the human brain, *APP* mRNA undergoes a process called reverse transcription to produce a complementary DNA (cDNA). The cDNA can be reintegrated into the neuronal genome as a genomic cDNA (gencDNA). At some point in the process, mutations arise — perhaps when the cDNA is integrated into the genome, or at an earlier stage (not shown). This results in a range of gencDNA *APP* variants, some lacking one or more exons. Some gencDNA variants give rise to toxic proteins, leading to cell death. These processes might contribute to sporadic Alzheimer's disease.

The study hints at a previously unanticipated mechanism in the development of Alzheimer's, and expands our understanding of the genesis of brain mosaicism. But whether accumulation of gencDNAs in neurons is a cause of or is caused by Alzheimer's disease remains to be proved.

The techniques used here could be applied to investigate whether gencDNA mechanisms are at work in other genes in other tissues; this could provide insights into diseases such as cancer or other degenerative disorders. However, it remains possible that gencDNA production is specific to *APP* or to neurons. The authors did not find gencDNA variants in another gene involved in Alzheimer's, *presenilin*, but nor did they rule out the possibility that gencDNAs could arise from other genes. Neurons have many features that might make them particularly vulnerable to gencDNAs: they are long-lived, have mostly stopped dividing, and have higher levels of reverse transcriptase activity and DNA-strand breaks than do non-neuronal cells[8].

It is also unclear whether the integration of *APP* gencDNAs into DNA is random or is biased towards certain genomic regions. The development of more-powerful sequencing techniques should help to answer this question.

Of course, there are many other avenues for further research. For instance, whether gencDNAs co-opt the retrotransposition and integration pathways used by transposable elements remains to be tested. The fact that gencDNAs are found in normal neurons suggests that they could have some benefits — this possibility should be examined. Finally, it will be interesting to test whether inhibitors of reverse transcriptase can prevent the accumulation of gencDNAs. Only when these avenues have been explored will we be able to build a complete picture of the remarkable phenomenon observed by Lee and colleagues. ■

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1. Biesecker, L. G. & Spinner, N. B. *Nature Rev. Genet.* **14**, 307–320 (2013).
2. Freed, D., Stevens, E. L. & Pevsner, J. *Genes* **5**, 1064–1094 (2014).
3. Richardson, S. R., Morell, S. & Faulkner, G. J. *Annu. Rev. Genet.* **48**, 1–27 (2014).
4. Beck, J. A. *et al. Hum. Mol. Genet.* **13**, 1219–1224 2004).
5. Bushman, D. M. *et al. eLife* **4**, e05116 (2015).
6. Lee, M.-H. *et al. Nature* **563**, 639–645 (2018).
7. Murrell, J., Farlow, M., Ghetti, B. & Benson, M. D. *Science* **254,** 97–99 (1991).
8. Blaschke, A. J., Staley, K. & Chun, J. *Development* **122**, 1165–1174 (1996).
9. Tonegawa, S. *Nature* **302**, 575–581 (1983).

This article was published online on 21 November 2018.