feat of detecting CNO neutrinos. The resulting measurements are not yet precise enough to resolve the question of solar metallicity, but they offer a path towards this objective.

Future experiments will seek to improve on the precision achieved by Borexino, by developing innovative methods to identify and reject background noise caused by radioactive contamination. In the meantime, the Borexino Collaboration's tremendous accomplishment moves us closer to a complete understanding of our Sun, and of the formation of massive stars, and is likely to define the goal in this field for years to come.

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1. The Borexino Collaboration. *Nature* **587**, 577–582 (2020).
2. Ahmad, Q. R. *Phys. Rev. Lett.* **87**, 071301 (2001).
3. Ahmad, Q. R. *Phys. Rev. Lett.* **89**, 011301 (2002).
4. Ashie, Y. *et al. Phys. Rev. D* **71**, 112005 (2005).
5. Aharmim, B. *et al. Phys. Rev. C* **72**, 055502 (2005).
6. Adelberger, E. G. *et al. Rev. Mod. Phys.* **83**, 195 (2011).
7. Davis, R. Jr, Harmer, D. S. & Hoffman, K. C. *Phys. Rev. Lett.* **20**, 1205 (1968).
8. Agostini, M. *et al. Nature* **562**, 505–510 (2018).
9. Asplund, M., Grevesse, N., Sauval, A. J. & Scott, P. *Annu. Rev. Astron. Astrophys.* **47**, 481–522 (2009).

Genetics

Neanderthal DNA raises risk of severe COVID

Yang Luo

A genetic analysis reveals that some people who have severe reactions to the SARS-CoV-2 virus inherited certain sections of their DNA from Neanderthals. However, our ancestors can't take all the blame for how someone responds to the virus. **See p.610**

A key part of tackling COVID-19 is understanding why some people experience more-severe symptoms than do others. Earlier this year, a segment of DNA 50,000 nucleotides long (corresponding to 0.002% of the human genome) was found to have a strong association with severe COVID-19 infection and hospitalization[1]. Zeberg and Pääbo[2] report on page 610 that this region is inherited from Neanderthals. Their results not only shed light on one reason that some people are more susceptible to severe disease, but also provide insights into human evolutionary biology.

DNA sequences that are physically close to one other in the genome are often inherited (linked) together. These blocks of DNA, known as haplotypes, therefore contain tightly linked variants — DNA sequences or nucleotides that vary between individuals in a population. For example, the COVID-19 risk haplotype described earlier this year[1] harbours variants across its entire 50,000-nucleotide span that are inherited together more than 98% of the time. Long haplotypes such as this could be a result of positive selection, maintained in our genomes because they contributed to our species' chances of survival and reproductive success. They could also be introduced as a result of interbreeding with archaic hominin species such as the Denisovans and Neanderthals.

Some 1–4% of the modern human genome comes from these ancient relatives[3]. Many of the surviving archaic genes are harmful to modern humans, and are associated with infertility and an increased risk of disease[4]. But a few are beneficial. Examples include the Denisovan-like version of a gene called *EPAS1* that helps modern Tibetans to cope with life at extremely high altitudes[5], a Neanderthal gene that increases our sensitivity to pain[6] and others that help us fend off viruses[7].

To investigate whether the COVID-19 risk haplotype might have been introduced from our ancient relatives, Zeberg and Pääbo compared the region with an online database of archaic genomes from around the world. They found the region to be closely related to that in the genome of a Neanderthal individual that lived in modern-day Croatia around 50,000 years ago, but it was not related to any known Denisovan genomes.

The authors next checked the prevalence of the Neanderthal-derived haplotype in the modern human population. They report that it is rare or completely absent in east Asians and Africans. Among Latin Americans and Europeans, the risk haplotype is maintained at a modest frequency (4% and 8%, respectively). By contrast, the haplotype occurs at a frequency of 30% in individuals who have south Asian ancestry, reaching as high as 37% in those with Bangladeshi heritage (Fig. 1).

The researchers therefore speculate that the Neanderthal-derived haplotype is a substantial contributor to COVID-19 risk in specific groups. Their hypothesis is supported by hospital data[8] from the Office for National Statistics in the United Kingdom, which indicates that individuals of Bangladeshi origin in the country are twice as likely to die from COVID-19 as are members of the general population (although other risk factors will, of course, contribute to these statistics).

Why has this haplotype been retained in some populations? The authors posit that it might be protective against other ancient pathogens, and therefore positively selected for in certain populations around the world[9]. But when individuals are infected with the SARS-CoV-2 coronavirus, the protective immune response mediated by these ancient genes might be overly aggressive, leading

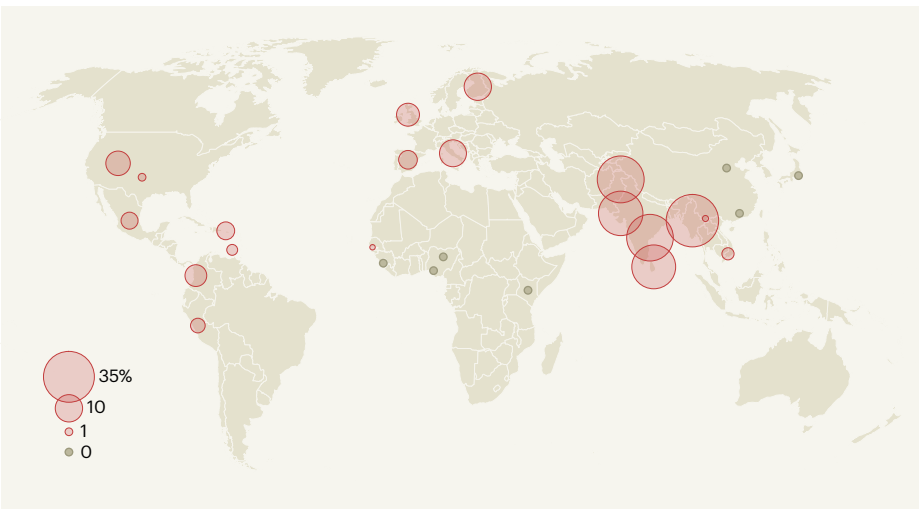

Figure 1 | Uneven global spread of a genetic risk factor for COVID-19. Zeberg and Pääbo[2] report that a long sequence of DNA that is associated with severe COVID-19 infection and hospitalization is derived from Neanderthals. The sequence is unevenly distributed across modern human populations. This map shows the frequency at which the risk factor is found in various populations from around the world. The sequencing data for these populations were gathered by the 1000 Genomes Project[10]. (Adapted from Fig. 3 of ref. 2.)

to the potentially fatal immune response observed in people who develop severe COVID-19 symptoms. As a result, a haplotype that at times in our past might have been beneficial for survival could now be having an adverse effect.

Despite the correlation between this risk haplotype and clinical outcomes, genetics alone do not determine a person's risk of developing severe COVID-19. Our genes and their origins clearly influence the development and progression of COVID-19 (and other infectious diseases), but environmental factors also have key roles in disease outcomes.

For example, although the Neanderthal-derived risk haplotype is almost completely absent in people with African ancestry, this population has a higher COVID-19 mortality rate than do people of other ethnic backgrounds, even after adjusting for geography and socio-economic factors (see go.nature.com/3jcxezx ('Demographics' tab) and go.nature.com/2h4qfqu, for example). Social inequality and its repercussions seem likely to account for a larger proportion of the risk of COVID-19 death than does Neanderthal-derived DNA.

It is fascinating to think that our ancestor's genetic legacy might be playing a part in the current pandemic. However, the underlying impact of the inherited DNA on the body's response to the virus is unclear. Ongoing global efforts to study associations between our genetics and COVID-19 by analysing more individuals from diverse populations, such as that being undertaken by the COVID-19 Host Genetics Initiative (www.covid19hg.org), will help us to develop a better understanding of the disease's aetiology. It is important to acknowledge that, although genes involved in the COVID-19 response might be inherited, social factors and behaviours (such as social distancing and mask wearing) are in our control, and can effectively reduce the risk of infection.

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1. The Severe Covid-19 GWAS Group. *N. Engl. J. Med.* **383**, 1522–1534 (2020).
2. Zeberg, H. & Pääbo, S. *Nature* **587**, 610–612 (2020).
3. Green, R. E. *et al. Science* **328**, 710–722 (2010).
4. Sankararaman, S. *et al. Nature* **507**, 354–357 (2014).
5. Huerta-Sánchez, E. *et al. Nature* **512**, 194–197 (2014).
6. Zeberg, H. *et al. Curr. Biol.* **30**, 3465–3469 (2020).
7. Enard, D. & Petrov, D. A. *Cell* **175**, 360–371 (2018).
8. Public Health England. *Disparities in the Risk and Outcomes of COVID-19* (PHE Publs, 2020).
9. Browning, S. R., Browning, B. L., Zhou, Y., Tucci, S. & Akey, J. M. *Cell* **173**, 53–61 (2018).
10. The 1000 Genomes Project Consortium. *Nature* **526**, 68–74 (2015).

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Biochemistry

Isoforms combine for diverse signalling

Joshua C. Snyder & Sudarshan Rajagopal

Many receptor proteins of the GPCR family exist in multiple isoforms. A comprehensive analysis of different combinations of GPCR isoforms that produce diverse signalling patterns in cells has implications for drug development. **See p.650**

With more than 800 members[1], the G-protein-coupled receptor (GPCR) superfamily is the largest family of cell-surface receptor proteins in humans. GPCRs trigger intracellular signalling pathways in response to activation by extracellular factors. In doing so, they determine how a cell responds to and interacts with its environment, thereby influencing nearly every aspect of physiology. As such, they are excellent drug targets – at least 475 drugs approved by the US Food and Drug Administration (FDA) are aimed at GPCRs[2]. But many GPCRs exist in multiple isoforms, or variants, complicating attempts to find drugs that can bind to them. On page 650, Marti-Solano *et al.*[3] describe a catalogue of the structure and expression of GPCR isoforms in humans. This resource has been added to a GPCR database, called GPCRdb, and is already openly available to the scientific community[4] (https://gpcrdb.org/protein/isoforms).

One common hurdle when attempting to design drugs that control GPCR signalling is that the same GPCR can activate multiple intracellular signalling pathways[5]. Pharmacologically altering the receptor's activity can therefore lead to unforeseen side effects. Drugs called biased agonists that target just one pathway downstream of GPCRs have shown great promise[6,7]. However, they are effective in only some cases – perhaps because the genes that encode GPCRs can be processed in different ways during transcription, producing multiple versions of the final messenger RNA, called splice variants. Through this splicing mechanism, specific domains can be excluded from a GPCR or atypical ones added, producing a range of isoforms. Each one might preferentially activate alternative downstream signalling pathways. So far, our understanding of this key aspect of GPCR biology has been limited to studies of a few isoforms in unnatural settings[8,9].

Marti-Solano and colleagues set out to determine how the presence of various isoforms affects the signalling of around 350 GPCRs across tissues of the human body. First, they made use of information about GPCR structures and DNA sequences from GPCRdb to help them identify candidate GPCRs in a database called GTex – a catalogue of gene expression in human tissues. This produced a list of 625 GPCR isoforms, with 38% of GPCRs having more than one.

The group then systematically organized these GPCR isoforms according to their topology. They developed a set of 'structural fingerprints' for GPCR isoforms, based on the specific extracellular, intracellular and transmembrane domains present in each one (Fig. 1a). The most common structural fingerprints preserved GPCR topology, and the most frequent changes were seen only in the protein's extracellular amino terminus or intracellular carboxy terminus. The N-terminal alterations typically caused changes in the binding of ligand molecules or efficacy. By contrast, C-terminal alterations led to changes in the ability of the receptor to couple with other receptor monomers, or in alterations in the internalization or transport of receptors through the cell inside vesicles – all of which are key to downstream signalling.

The authors also found a few truncated isoforms, in which transmembrane domains were eliminated. They propose that these decrease receptor signalling. The truncated isoforms might be expressed only inside the cell, where they bind to more-complete versions – isoforms internalized in this way are unable to signal.

Next, to model the potential tissue-specific effects of different isoforms, Marti-Solano *et al.* generated tissue-expression signatures – maps of the expression of each isoform for each receptor across 30 tissues. This revealed different combinations across tissues. The authors confirmed that co-expressing various combinations of isoforms of a given receptor in cells in culture resulted in different patterns of downstream signalling (Fig. 1b). It is not surprising that isoforms have different signalling properties. Nonetheless, the demonstration that co-expression of different isoforms alters