Sequencing the COVID-19 virus from positive patient samples. Image credit: Dan Ross

COVID-19 Sanger Science

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# 20 Things We Learned in 2020

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This has been a year that none of us will forget in a hurry. At the Sanger Institute, much of our research has had to pause, with wet lab scientists unable to do their work from home, and many of our staff redeployed to work on the sequencing of COVID-19 viral genomes taken from positive patient samples.

The Institute is immensely proud of the way that our staff have pulled together, and the work we have managed to achieve. Here are just 20 of the many things we learned in 2020:

# 1. The genomic secrets of scallops

Our mission to map the genetic codes of 60,000 eukaryotic species in Britain and Ireland – as part of the Darwin Tree of Life Project – is now well underway. This year, our partners continued sample collection for future genome sequencing, and we celebrated the release of the scallop genome.

Scallops feed on planktonic algae that produce domoic acid, a poisonous chemical that can cause vomiting, and in severe cases, disorientation, memory-loss, seizures, and sometimes death in humans. Consequently, public health authorities now monitor levels of the toxin in shellfish to protect human consumers. Domoic acid mimics a neurotransmitter called glutamate, which has been linked to Parkinson's disease and Alzheimer's. Given scallops' immunity to the effects of domoic acid, researchers are optimistic that the genome might provide new insights into how humans might avoid these illnesses.

*The gene-rich genome of the scallop* Pecten maximus from the Natural History Museum and Wellcome Sanger Institute can be viewed in *GigaScience*

# 2. Virtual Collaboration

Collaborating virtually isn't anything new to researchers, with projects spanning continents being the norm, but it's undeniable that 2020 took virtual collaboration to a new level.

A success story of virtual collaboration, borne from a tweet and a blog post, featured on our blog this year. The team was able to pool their expertise to discover the genome of *Hepatocystis* (a parasite that can cause malaria-like symptoms)within the genome of a red colobus monkey, and become the first to sequence the DNA of a *Hepatocystis* species.

*Genomic and transcriptomic evidence for descent from* Plasmodium *and loss of blood schizogony in* Hepatocystis *parasites from naturally infected red colobus monkeys* from

the Francis Crick Institute, Duke University, and Wellcome Sanger Institute can be read in *PLOS Pathogens*

# 3. It's never too late to quit smoking

A study this year found that in ex-smokers, healthy cells can replenish the lining of lungs damaged by smoking, and the shift in proportion of healthy to damaged cells could help protect against lung cancer.

9 out of every 10 lung cells in current smokers were found to have up to 10,000 mutations, caused directly by the chemicals in tobacco smoke. Ex-smokers were found to have up to 40 per cent of their total lung cells replenished and healthy, proving that it really is never too late to give up smoking.

*Tobacco smoking and somatic mutations in human bronchial epithelium* from Cancer Research UK, University College London, University College London Hospitals NHS Foundation Trust, National Institute for Health Research and the Wellcome Sanger Institute can be read in *Nature*

# 4. How we can use artificial intelligence in cancer diagnosis, prognosis, and treatment

Researchers repurposed an algorithm that was originally used to identify everyday objects such as fruit and radiators to distinguish cancerous tissue from healthy tissue. They showed that the algorithm could even be used to predict survival, and show the patterns of mutational changes, just from images of the tumour tissue.

The more information you have about a tumour - its origins, features, and how it is interacting with the host, the better chance clinicians have at tailoring treatments to the needs of the patient.

*Pan-cancer computational histopathology reveals mutations, tumor composition and prognosis* from EMBL-EBI, Wellcome Sanger Institute and Addenbrooke's Hospital can be read in *Nature Cancer*

# 5. How antibiotic resistance genes have been able to spread at a continental scale

For the first time, researchers were able to identify the pathways by which antibiotic resistance genes spread via plasmids through bacterial populations. Plasmids can 'jump' between different species and strains of bacteria, so the genes that confer resistance to antibiotics can spread quickly among bacteria, allowing superbugs to spread.

*Integrated chromosomal and plasmid sequence analyses reveal diverse modes of carbapenemase gene spread among* Klebsiella pneumoniae from the Centre for Genomic Pathogen Surveillance, Big Data Institute, University of Freiburg Medical Centre, and Wellcome Sanger Institute can be read in *PNAS*

Image credit: Wellcome Sanger Institute, Genome Research Limited

# 6. Mysteries of the mouse immune system

Researchers have created the first full dynamic map of how genes in immune cells in mice respond over the course of an infection, learning to fight invading pathogens, and then preserving memory of this in case they encounter the pathogen again in future. This information could be used to develop new vaccines and treatments for diseases, as scientists can better pinpoint where medical interventions would most help the patient's immune system.

*Transcriptome dynamics of $CD4^+$ T cells during malaria maps gradual transit from effector to memory* from the Peter Doherty Institute for Infection and Immunity and Wellcome Sanger Institute can be read in *Nature Immunology*

# 7. How a neglected tropical disease made a comeback

Yaws is a neglected tropical disease that can cause chronic disfigurement and disability, most commonly in children in poor, tropical countries. The bacterium that causes the disease was tracked through genomic sequencing. Sequencing shed light on its re-emergence, as the DNA sequences of the bacteria in each patient show how cases are related to each other. The researchers were able to determine that the rise in cases was likely due to asymptomatic patients who didn't receive treatment, and passed the bacteria on to others.

*Yaws re-emergence and bacterial drug resistance selection after mass administration of azithromycin: a genomic epidemiology investigation* from the London School of Hygiene & Tropical Medicine, Fight AIDS and Infections Disease Foundation and Wellcome Sanger Institute can be read in the *Lancet Microbe*

# 8. Potentially cancerous cells can be kept in check

A study of the oesophagus has found that mutant cells that could lead to cancer can be kept from expanding by their healthy neighbours. By middle age, most cells in human tissues such as the oesophagus and skin are mutant clones, but most do not go on to become cancer. Competition between all of these clones can lead to them cancelling each other out, and so the tissue is able to remain healthy overall.

*Spatial competition shapes the dynamic mutational landscape of normal esophageal epithelium* from the Wellcome-MRC Cambridge Stem Cell Institute, University of Cambridge and Wellcome Sanger Institute can be read in *Nature Genetics*

# 9. How likely someone is to develop a blood disease

Researchers from 101 institutions studied hundreds of thousands of participants to identify over 7,000 regions of the human genome that control the characteristics of blood cells. All of this data show how someone's genetic profile contributes to them developing a blood disease, and brings us closer to predicting an individual's risk of developing blood disorders.

*The Polygenic and Monogenic Basis of Blood Traits and Diseases* from NIH, University of Cambridge and the Wellcome Sanger Institute can be read in *Cell*

# 10. Mysteries of the mosquito immune system

With hopes of combatting mosquito-borne diseases such as malaria, Dengue fever, and the Zika virus, researchers have mapped mosquito immune cells. With this in-depth knowledge of their immune response, including which cells and pathways are involved when infected with a parasite, scientists hope that the chain of transmission from mosquito to human can be broken.

*Mosquito cellular immunity at single-cell resolution* from Umeå University and Wellcome Sanger Institute can be read in *Science Magazine*

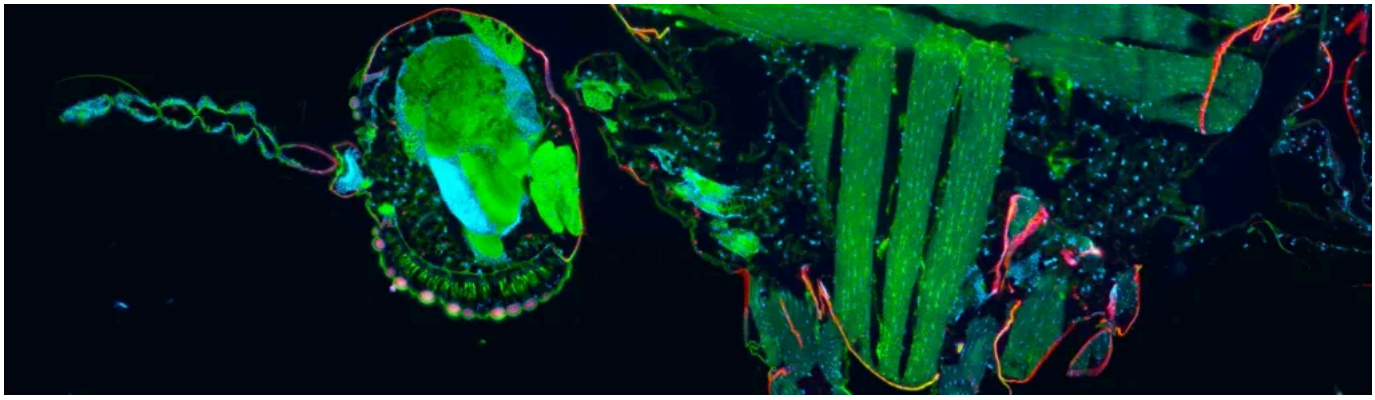

Image credit: Gianmarco Reddi, Wellcome Sanger Institute

# 11. How your gut is protecting your brain

The brain is protected from physical damage by the skull, and is wrapped up in three layers of watertight tissue known as the meninges. Beyond these physical barriers, it was unknown how the brain is protected against invading bacteria and viruses. This year, researchers learned that the meninges contain plasma cells that are positioned next to large blood vessels within the meninges. These plasma cells secrete antibodies that “guard” the perimeter of the brain, though these antibodies in particular are normally just found in the intestine. By being able to recognise and defend the brain against gut microbes, these antibodies are able to provide protection from the pathogens that are the most likely bodily invaders.

*Gut-educated IgA plasma cells defend the meningeal venous sinuses* from the University of Cambridge and Wellcome Sanger Institute can be read in *Nature*

# 12. Diagnoses for around 500 families living with children with rare conditions may now be possible

Globally, around 400,000 babies are born with new, unidentified mutations that can interfere with their development, causing disorders that might lead to conditions such as heart defects, learning disabilities, or epilepsy. Research into such disorders has led to the identification of 285 genes linked to these conditions, including 28 newly-associated genes. These insights will enable diagnoses for around 500 families living with children who have rare, previously unidentified conditions.

*Evidence for 28 genetic disorders discovered by combining healthcare and research data* from the Deciphering Developmental Disorders project, GeneDx, Inc., and the Wellcome Sanger Institute can be read in *Nature*

# 13. Molecular and cellular knowledge of the human heart

Scientists have created a map of cells in the healthy human heart, allowing better understanding of how the heart functions, what goes wrong in cardiovascular disease, and guiding personalised medicine. The atlas of the heart, which contributes to the Human Cell Atlas, shows the huge diversity of cells and reveals heart muscle cell types, cardiac protective immune cells, and the intricate network of blood vessels. It also predicts how the cells communicate to keep the heart working.

*Cells of the adult human heart* from the Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Harvard Medical School, Imperial College London, and the Wellcome Sanger Institute can be read in *Nature*

# 14. How the *EGFR* gene initiates brain cancer in mice

Glioblastoma is the most aggressive form of brain cancer, and researchers were able to create a new mouse model to show how a mutation in the *EGFR* gene initiates this cancer. More than 200 genes are associated with this cancer, and knowing about them allows researchers to develop drug treatments targeted at them specifically.

PiggyBac *mutagenesis and exome sequencing identify genetic driver landscapes and potential therapeutic targets of* EGFR*-mutant gliomas* from the University of Cambridge, Kymab, and Wellcome Sanger Institute can be read in *Genome Biology*

# 15. Cellular functions associated with childhood-onset Crohn's Disease

The causes of Crohn's Disease are not well understood, so it is difficult to find targeted treatments for patients. In this study, researchers were able to study the early stages of human gut development in minute detail, and found specific cell functions reactivated in the gut of children with Crohn's Disease. These findings may be an important step towards management and treatment of the condition.

*Single-Cell Sequencing of Developing Human Gut Reveals Transcriptional Links to Childhood Crohn's Disease* from the University of Cambridge and Wellcome Sanger Institute can be read in *Developmental Cell*

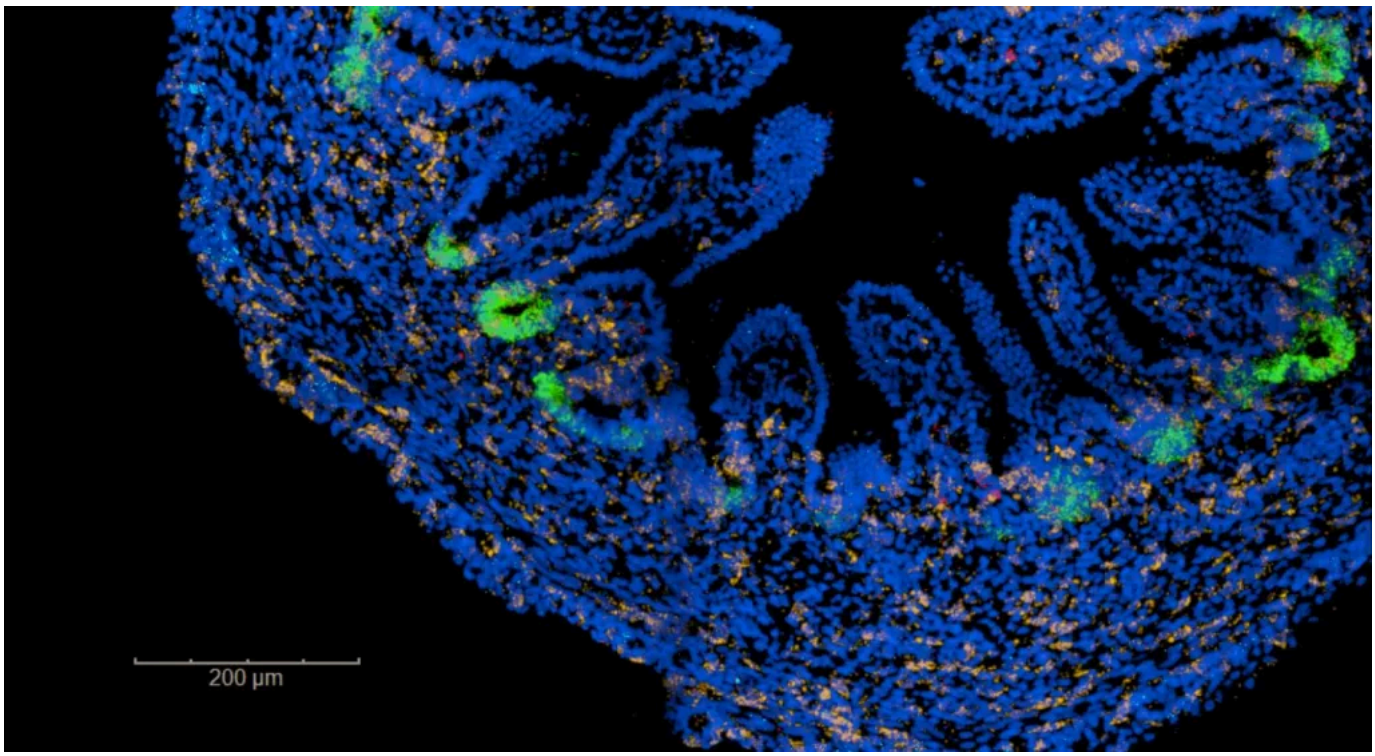


Image credit: Kenny Roberts and Sophie Pritchard, Wellcome Sanger Institute

# 16. How the Dantu blood mutation protects against malaria

People with the Dantu blood variant, usually found in East Africa, have been known to have protection against malaria for several years, and this year researchers learned why that is. Red blood cells with this mutation have a higher surface tension, which prevents the malaria parasite from invading the cell and causing the illness. It might be possible to design drugs that mimic this high surface tension to prevent malaria infection in others.

*Red blood cell tension protects against severe malaria in the Dantu blood group* from the KEMRI-Wellcome Trust Research Programme, University of Cambridge, and Wellcome Sanger Institute can be read in *Nature*

## 17. 4,000 years of conflict, contact, and cultural change had a negligible impact on the genetics of the Near East

You might expect that 4,000 years of invasions and conquests would have a large impact on the genetics of the Near East, but this is not the case. A study of the DNA of ancient skeletons in Beirut has found that only the start of the Iron Age, the arrival of Alexander the Great, and the dominion of the Ottoman Empire had any impact on the long-term genetics of ordinary people. Despite the huge cultural impacts of different leaders, religions, languages, and Crusades in this region, research has shown that 90 per cent of the genetic make-up of present-day people in Lebanon descends from their Bronze Age ancestors.

*A Genetic History of the Near East from an aDNA Time Course Sampling Eight Points in the Past 4,000 Years* from the University of Birmingham, Institut Francais du Proche-Orient, and Wellcome Sanger Institute can be read in the *American Journal of Human Genetics*

## 18. The most comprehensive analysis of human genetic diversity to date

Researchers sequenced the genomes of 929 humans to create the most detailed representation of worldwide population genetic diversity yet, allowing better study of genetic susceptibility to disease in different parts of the world. The study provided new

insights into humans' evolutionary past, showing the complex history of how our ancestors diversified, migrated, and mixed throughout the world.

*Insights into human genetic variation and population history from 929 diverse genomes* from the Francis Crick Institute, University of Cambridge, and Wellcome Sanger Institute can be read in *Science*

## 19. Changing our approach to vaccine development could halve rates of serious bacterial disease

Researchers have combined genomic data, models of how bacteria evolve, and predictive modelling to identify how vaccines could be optimised for people in specific age groups and geographic regions, against particular communities of bacteria. With this approach, they have identified new vaccine designs that could reduce overall rates of bacterial diseases.

*Designing ecologically optimized pneumococcal vaccines using population genomics* from Imperial College London and Wellcome Sanger Institute can be read in *Nature Microbiology*

## 20. Supporting the launch of a nationwide consortium to map how a virus creates a pandemic

In March, the Sanger Institute joined the COVID-19 Genomics UK Consortium (COG-UK), composed of the NHS, Public Health Agencies from England, Scotland, Wales and Northern Ireland, and numerous academic institutions, to deliver large-scale rapid whole genome sequencing of the COVID-19 virus from positive patient samples. At the time of writing, the consortium has sequenced 156,335 viral genomes.

By doing this, the consortium has been able to monitor changes in the virus at a national scale. This will provide a better understanding of how it is spreading and whether different variants are emerging. These insights will inform policy, public health strategies and clinical care of patients.

Read more about the work of COG-UK on the consortium's website

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