Linking genes and health

Genes and resistance to disease

Genetic variations can make us immune to certain diseases

Some gene variants are good news. Take one associated with HIV/AIDS – a disease that in 2018 affected 38 million people and was responsible for 770,000 deaths globally.

A genetic mutation called CCR5-delta 32 causes immune system cells called CD4+ T cells to lack working copies of the CCR5 receptor. This receptor plays a key role in allowing entry of the HIV virus into CD4+ T cells during HIV infection. Scientists have suspected for a long time that people with this mutation are resistant to HIV infection, though studies have been generally small and inconclusive. In 2018, a review of 24 separate studies that took place over two decades suggested that it does indeed protect against HIV, as long as you have two copies of the mutate gene. According to work carried out in 2017, around 1 per cent of people in northern Europe carry two mutated copies of the CCR5 gene but fewer in southern Europe and sub-Saharan Africa.

Stem cell transplants from people with the CCR-delta 32 mutation are being investigated for their potential to treat people with HIV. In one case, an AIDS patient who also had leukaemia was treated with stem cells from a donor who had two copies of the mutation and afterwards showed no sign of HIV. More recently, in 2019, scientists edited the CCR5 gene in human cells and transplanted the cells into mice, showing that they were more resistant to HIV than untreated mice. Some scientists have suggested that the CCR5-delta 32 variant offered protection from other diseases in the past - for instance, small pox or plague – and that this is why the mutation spread across Europe. However, historians point out that if this were the case, the mutation should more common in southern Europe and Africa, where the death toll was even greater than in northern Europe.

Genes and the environment in disease

Most conditions involve an interaction between genes and environment

Almost everything to do with health is affected by genes. Most often, the effect of an individual genetic variation is small and influenced by additional external factors: diet or exercise; exposure to a virus, bacterium or radiation; or a more general challenge, such as heat stress or exhaustion.

For example, people who develop the cancer mesothelioma have almost always been exposed to asbestos, the fibres of which lodge in the lungs. Some people who are exposed will be at a higher risk because of minor genetic differences. A 2013 study identified ten genetic variants that may contribute to a person’s risk, although they might not be the only ones.

Some genetic differences have mixed costs and benefits. There are a number of known mutations in the gene for the blood’s oxygen-carrying DNA haemoglobin. Carrying one altered copy of the gene can help to protect against infection by the parasite that causes malaria. However, carrying two altered copies (and hence no normal haemoglobin) can lead to diseases, including sickle-cell anaemia or thalassaemia.

Cancer cells develop from cells that have mutations in genes involved in regulating cell division. These mutations can be inherited, they may happen by chance, or they may occur when cells are exposed to chemicals that damage DNA, or interfere with its repair.

The genes that could lead to a cure

Why finding the genes linked to a particular disease is just the beginning of finding a treatment or cure

Once a particular condition is linked firmly to a gene (or several genes), this might lead to a genetic test to assess disease risks. Going beyond that can prove a lengthy effort. Sometimes, over the course of years, identifying the genes and gene variants involved in diseases can lead to improved understanding of their mechanisms and treatments targeting, for example, aberrant proteins made by those genes. However, we are also beginning to test treatments that can correct the disease-causing genes themselves. Nevertheless, the process of developing a new treatment is rarely a short one.

Leber congenital amaurosis (LCA) a hereditary disease that causes childhood blindness. In 2006, Dutch and German researchers discovered that, in some cases, the disease was the result of mutations in a gene called CEP290. It later emerged that around a fifth of cases are caused by CEP290 mutations. Although these insights did not lead directly to a cure, in the following years, the development of new technologies for editing genes opened the door to new possibilities for treating hereditary conditions. Fast forward to 2017 and a company called Editas Medicine was testing a gene-editing approach for correcting CEP290 mutations in mice. The treatment, now also tested in monkeys is due to move to small-scale clinical trials in humans by the end of 2019, well over a decade after the gene target was initially identified. If these early trials are a success, larger trials will follow and eventually the treatment may get approval for use in patients – or not. It is by no means unusual for the process of drug development to take this long, or much longer, even when the cause of a disease is known and many potential treatments that look promising initially will fall by the wayside.

When the causes of disease are complex, involving several or many different genes, developing treatments is far less straightforward. At least 70 different genes and their variants may play a role in potential targets for Type 2 diabetes – mutations in these genes often lead to impaired insulin production but on their own they do not cause diabetes. Lifestyle factors such as diet also play a crucial role in determining whether someone develops the condition. As yet, there is no cure for the condition, but over the course of many years of research, piecing together the mechanisms of disease through some of the genes involved may lead to better treatments.

Whole genome sequencing of the agents of disease

Knowing the genetic sequence of an organism can help us trace how it spreads

Whole-genome sequencing of bacteria and viruses is changing the way we tackle outbreaks of infectious disease.

In a paper published in the ‘Lancet’ in 2013, researchers described how they sequenced the genomes of MRSA (methicillin-resistant *Staphylococcus aureus*) samples from babies in a hospital baby care unit, patients elsewhere in the hospital and people outside in the community during a suspected outbreak in 2011.

The results showed the paths of infection between babies, mothers on a postnatal ward and the community. The researchers found that a strain of MRSA responsible for an outbreak was a new sequence type that had originally been transmitted unknowingly by a member of hospital staff.

Then, the method was still novel, showing great promise as a tool to rapidly and accurately identify the potential source and people involved in an outbreak of MRSA – information that could be used when deciding how to control infections.

Today, whole genome sequencing is rapidly becoming the norm in disease outbreaks, from foodborne illnesses to Ebola. Epidemiologists use it to work out how related different strains are, where they have come from and how they spread. It can also be used to predict whether a bacterium will be resistant to a particular drug or not, based on features in its genome. In 2015, scientists travelling to the Ebola outbreak in Guinea put an entire genomic sequencing system on a plane in standard luggage. They used the

equipment to sequence viruses from every new case for five weeks, with each sequencing process taking less than an hour. Just a few years before, this would have been impossible.

Meanwhile, using whole genome sequencing in MSRA is beginning to uncover the complexity of developing outbreaks. Researchers hope its use will become routine in hospital and community outbreaks.

Genome-wide and whole-genome studies in humans

How searching the whole genome can uncover the genetic basis of disease

Access to data about the entire genome is increasing knowledge of many diseases, but it is also reinforcing our awareness of how complex cells, tissues and bodies are. Although the press may still report on a 'gene for' conditions like arthritis or depression, studies almost always show that there are multiple factors involved.

One research approach is to use genome-wide association studies (GWAS). These involve going through the genome looking for common genetic variants – usually single 'letter' differences known as single nucleotide polymorphisms (SNPs) – to see whether they are associated with a disease or physical trait.

Since the 2000s, GWAS have identified many thousands of genetic variants associated with disease and other traits important for our health. For example, researchers working as part of the Psychiatric Genomics Consortium have identified numerous genetic changes that increase the risk of schizophrenia. These include changes in the gene for mGlu3, a cell membrane receptor that is considered a potential target for drug treatment. Meanwhile, in 2017, researchers who looked at the body composition of over 38,000 people discovered 21 SNPs that were linked to lean body (muscle) mass – an advance that they suggested could benefit treatment approaches for older people who suffer muscle loss as they age.

However, since the SNPs identified in GWAS studies are markers for a wider region in which they sit, it's difficult to pinpoint exactly which variants within the region are the real causative agents. Moreover, most of the SNPs associated with particular diseases fall into regions outside of the protein-coding genes. And most effects are caused by combinations of variants, not single SNPs, which makes it difficult to untangle what mechanisms they use. In a 2017 study in the paper *Cell*, geneticists argued that many gene variants identified through GWAS actually have little influence on the diseases of interest and that their roles in these diseases depend on a much deeper understanding of biochemical pathways involved in disease than we currently have.

As the cost of sequencing drops – and methods become faster and more precise – whole-genome sequencing may complement or even replace GWAS studies. As the name suggests, these scans look at the entire DNA sequence in a person's genome, rather than merely looking for markers that flag up particular regions.

In 2011, researchers sequenced the genomes of 87 Icelanders and used that data in combination with GWAS to identify a rare variant of the gene MYH6 associated with a high risk of developing sick sinus syndrome, a common cause of abnormal heart rhythm. Since then, researchers have identified specific mutations in MYH6 and tried transferring them into heart cells, shedding new light on the cause of the condition.

An alternative to whole-genome sequencing is 'whole-exome' sequencing, which focuses only on the protein-coding regions of the genome. Stanford University, for example, runs a Clinical Genomics Program that offers whole-exome sequencing for patients with 'mystery diseases'. They say it leads to diagnoses in at least a quarter of cases. For example, in 2013, they used it to diagnose a rare form of epilepsy in a woman suffering from seizures. The downside to this approach, of course, is that it misses genetic variations in non-coding regions that do still play a role in regulating protein activity and, via that route, disease.

Single-gene and chromosome disorders

Some conditions are caused by genetic 'abnormalities'

Some conditions are so tightly tied to DNA mutations that they can be called genetic diseases. In a few cases, inheriting just one copy of an altered allele (ie a normal allele from one parent and an altered allele from the other) can lead to disease. These are known as dominant conditions, and they include Huntington's disease, an incurable condition that causes gradual deterioration of the brain (for more on this, see our Real Voices interview with Matt Ellison).

Recessive conditions, such as cystic fibrosis, are a larger group of genetic disorders that only occur when someone inherits two copies of an altered allele (ie one from each parent).

There are also conditions caused by larger changes in the chromosomes. Down's syndrome, for instance, is caused by an extra copy of chromosome 21. In the UK, all pregnant women are offered screening for Down's syndrome.

Some women may choose to terminate their pregnancies when they learn that their babies are likely to be born with the syndrome. These decisions are difficult and controversial because many people with Down's syndrome lead happy and fulfilling lives. Richard Dawkins, the scientist and author of 'The Selfish Gene', was attacked by the media for advising a woman to have an abortion if she found her child had Down's syndrome.

Genetic diseases can be more complicated than they might seem at first glance. For example, there are more than 1,700 different mutations in the protein affected by cystic fibrosis that can lead to the disease. Some mutations cause more severe symptoms than others. The extent of symptoms can also be affected by other genes, which modify the effect of the cystic fibrosis gene. Meanwhile, although most people with Down's syndrome have an extra chromosome in all of their cells, around 1 in 100 only have the extra copy in some of their cells (Mosaic Down Syndrome), which usually results in fewer features of Down's syndrome.

FURTHER READING

- Mosaic: How close are we to a cure for Huntington's? https://mosaicscience.com/story/how-close-are-we-cure-huntingtons/

Personalised medicine

How genetic testing is leading to personalised treatment approaches

Genetic tests could help doctors to identify the best treatment for each patient. Some gene variants, for example, affect how the body breaks down or responds to different drugs. Giving the right drug to the right patient at the right dose, when there is a choice, should increase effectiveness and reduce adverse reactions. A more complete knowledge of how genetics affects our responses to drugs – pharmacogenetics – is driving progress towards an era of personalised medicine.

Cancer is one area in which it is hoped that personalised, individualised or 'precision' therapies can lead to improved treatment. For example, differences in a gene called CYP2D6 affect how different patients break down the breast cancer drug tamoxifen and whether they experience severe side effects. The gene makes an enzyme involved in metabolism of tamoxifen to endoxifen, the active form of the drug. It is hoped that genetic testing for this and other breast cancer gene variants will enable doctors to tailor drug regimens to individual patients.

Brain cancers called gliomas are another form of cancer that is amenable to personalised approaches. Already, patients are tested for a number of biomarkers, one of which is a gene called IDH, or its mutated versions. The information these tests provides can sometimes guide treatment. Now, however, researchers at the Massachusetts Insitute of Technology are trialling approaches based on rapid testing for IDH mutations in glioma tissue that is removed during surgery. Depending on whether the mutations are present, the researchers can implant slow-release drug particles directly into the brain before closing it up.

Many diseases, not just cancer, may be appropriate for personalised approaches. These approaches do not even have to be based on genetic tests. In the case of the neurodegenerative disease multiple sclerosis, for example, researchers suggest that tailored treatments could be offered based on biomarkers in patient's blood serum and spinal fluid, such as neurofilament light chain – a component of nerve cells that is released into the spinal fluid following nerve damage. However, in other diseases looking for genetic variations may help suggest the path the disease will take and therefore the best treatment approach for preventing damage before it occurs.

Long-term genetic studies

Large, long-term population studies help researchers plan for future discoveries today

The effects of interactions between genes and the environment are often long term, so the medical consequences – such as diabetes or cancer – don't appear until later in life. That means waiting a long time for research results, too. Nowadays, the collection of DNA samples from people who enrol in studies is done with plans to keep the samples for many decades and to make sure that any new tests that emerge along the way can still be applied to them.

One far-sighted study in the west of England began in 1991. The Avon Longitudinal Study of Parents and Children (ALSPAC) signed up more than 14,000 pregnant mothers before their babies were born. The children have been followed ever since – and as young adults, some are on the advisory panel that oversees the project. The research explores a range of social and medical issues.

ALSPAC's findings so far include that eating oily fish in pregnancy improves the child's eyesight, that children growing up in very hygienic homes are more likely to get asthma, and that men who smoked as children have fatter sons (and fatter daughters, but to a lesser extent). Now, by recruiting the children of the original children, the researchers hope to learn more about genetic influences on health. The aim is to use the results of the study to improve the health of future generations.

Larger still is UK Biobank, a national study that is following the health of 500,000 people. The participants have given health screening interviews, donated blood samples for genome sequencing or genotyping and agreed to allow their future medical records to be shared with the researchers. The big numbers should help to reveal the numerous factors (with small individual effects) that contribute to the development of a disease.

Data from these large genetic studies is already being pooled to generate more meaningful datasets. For example, in 2019, scientists searching for genes that affect the risk of mouth ulcers announced that they had found 97 genetic variations in the genomes of UK Biobank participants, results confirmed in the genomes of ALSPAC participants.