Genes and you

Mitochondrial DNA

Mitochondria mean that there's a bit more of mum in all of us

There's another genome in all of our cells – it lies in the energy-generating organelles, the mitochondria (shown above). These vital accessories are almost certainly descendants of symbiotic bacteria that colonised larger cells more than a billion years ago. Most of a mitochondrion's essential functions depend on genes in the cell's nucleus (which have been transferred there over millions of years), but mitochondria retain and use a separate genome.

When a sperm cell unites with an egg, it brings some mitochondria from your dad. These are eliminated soon after fertilisation, however, so the hundreds of mitochondria in each of your cells are descended from your mum. The unusual maternal pattern of inheritance for these few mitochondrial genes is important in studies of evolution.

Mistakes in copying the mitochondrial DNA seem more common than mistakes made when copying nuclear DNA, at least in animals. The mutations this causes can lead to mitochondrial diseases – an often perplexing set of conditions that can have widely varying symptoms in humans. Not all mitochondria may be affected, and the consequences can be different in different tissues.

In the UK, the government has legalised an *in vitro* fertilisation technique for preventing mitochondrial diseases that relies on a 'third parent'. This involves transplanting nuclear DNA from the mother into an egg from a healthy donor (the extra parent) before fertilisation. The baby gets nuclear DNA from its two traditional parents plus mitochondrial DNA from its third parent. In 2016, for the first time, a baby was born using this technique.

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What is mitochondrial disease?

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World's first baby born with new '3 parent' technique

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Mitochondrial donation and 'three-parent' babies

What is mitochondrial donation – a process sometimes said to create 'three-parent babies' – and what does it involve?

Mitochondrial donation is an in-vitro fertilisation (IVF) technique that creates human embryos with three biological 'parents' to treat devastating mitochondrial diseases. The embryo contains DNA from two parents, plus DNA from an egg donor, although the term 'three-parent baby' is misleading because only a few genes come from the third parent.

The technique transfers DNA from one egg into a new denucleated egg (an egg with the nucleus removed) from a third person. Either both eggs are fertilised with the father's sperm before the donor egg's nucleus is removed, or just the donated egg containing the mother's nucleus is fertilised.

Following a public consultation on this process, in 2015 the UK became the first country to allow the technique to prevent life-threatening conditions. In late 2016, clinics in the UK were given the green light to start applying for licences to carry out the procedure, though the first licences weren't announced until 2018.

In the meantime, the first baby to receive a mitochondrial donation was born after scientists used the technique in Mexico, where it is unregulated. The parents had previously had four miscarriages and two children, both of whom had died, with genetic mutations in the mother's mitochondria suspected to be the cause.

The basics of mitochondrial DNA disease

People with mitochondrial diseases have problems producing enough energy to power their cells properly. Mitochondria are like tiny generators keeping all of our cells going: they carry out the reactions that extract the energy from our food through a process called aerobic respiration. Each cell contains many mitochondria, and those cells that need to produce a lot of energy contain the most. A single heart cell, for example, can contain 1,000–2,000 mitochondria.

It has been estimated that at least 3,500 women in the UK carry problematic mitochondrial DNA mutations. Around one in 6,500 babies develops severe forms of mitochondrial disease, and many of these children will die soon after birth. Others will grow up with a variety of difficulties, such as blindness or liver failure, and will need treatment to help their cells function more normally.

Sourcing a solution

Repairing mitochondrial faults does not involve making modifications to DNA sequences. However, DNA that is not from the mother or father is introduced from via egg donor – a third 'parent' – with healthy mitochondria, before or after being fertilised via in vitro fertilisation (IVF).

You might think the donor would be providing little more than a home for the DNA of the two 'real' parents, but in fact mitochondria have their own DNA. In babies without a donor, this DNA is simply passed down from the mother in her egg. In mitochondrial donation IVF, the baby would have nuclear DNA from its two parents, plus mitochondrial DNA from the third parent.

Mitochondrial DNA encodes proteins involved in the energy-generating process. Whereas the DNA in the nucleus of a human cell encodes more than 20,000 genes, which control everything from the colour of your hair to aspects of your personality, mitochondrial DNA encodes just 37 genes.

Although these 37 genes have an important job to do, they're limited to producing machinery for the mitochondria themselves. So replacing faulty mitochondria with properly functioning ones should mean they can do the job they're supposed to do without any effect on the vast majority of the cell's DNA.

Is there a downside?

One concern is that mitochondrial and nuclear DNA may interact in ways that depend on some level of shared inheritance. However, studies in non-human primates have shown no adverse effects and the first human babies born using this technique are healthy. In April 2019, the first use of the technique to treat infertility – as opposed to mitochrondrial disease specifically – resulted in a healthy baby being born to a woman in Greece who had struggled to conceive via standard IVF.

From a technical point of view, though, the procedure is not foolproof and there is no way to ensure that all the mother's mitochondria are removed from her nucleus before it is transplanted into the donor egg. In which case, disease mutations would be passed along. We do not yet know if any remaining "faulty" mitochondria could have an affect later in life or future generations. Female babies born as a result of this method will pass on the mitochondrial DNA to their own children. Because egg cells act as carriers for mitochondrial DNA, it is always inherited from the mother without mixing with the father's DNA.

Ethical considerations

As with many scientific procedures, there are ethical considerations to take into account.

Some people worry that this procedure may pave the way to 'designer babies'. Others point out that in addition to only being available to people in rich nations, it is unnecessary – because parents could choose to conceive with a donor egg and nucleus rather than using their own.

There are some religious and ethical objections, as there are to IVF: not all the embryos created are used, so some people see terminating those that aren't used as immoral. Others disagree, suggesting a merciful and loving God would want humans to use their knowledge and ability to alleviate the suffering of others.

Others have warned about the status of the donor – in terms of both the medical procedure she will undergo and her rights. Although egg removal is minimally invasive, no surgery is without risk, and some individuals worry about women being exploited for their eggs if institutions are willing to pay women to donate them.

As for the donors' legal status: under UK law they are not regarded as having the same status as the parents; rather, they are regarded similarly to organ or tissue donors. Any children conceived using this technique are allowed to access 'non-identifying' information, such as medical information, about the donor from the age of 16.

While the Nuffield Council on Bioethics has said that "if these novel techniques are adequately proven to be acceptably safe and effective as treatments, it would be ethical for families to use them", the Human Genetics Alert group has warned that "the techniques are unethical according to basic medical ethics, since their only advantage over standard and safe egg donation is that the mother is genetically related to her child".

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Mitochondrial donation: the making of three-parent babies

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HFEA - Mitochondrial donation treatment

https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/mitochondrial-donation-treatment/

What is mitochondrial disease?

https://www.umdf.org/what-is-mitochondrial-disease/

QUESTIONS FOR DISCUSSION

- Do you think the creation of a child with DNA from three people is ethical? Consider and discuss reasons why some people may think it is ethical and others disagree.
- Do you agree that the donor should not receive the same legal status as the parents and instead have a status more like that of an organ donor?
- It would be possible to use sex selection to allow only male embryos to be conceived, to prevent the donated mitochondria being passed down to future generations. Discuss the advantages and disadvantages of not incorporating this into the law.

FURTHER READING

Healing broken batteries – a Wellcome Trust film about mitochondrial donation

https://www.youtube.com/watch?v=Sr7Jnr9qn44

Genes vs environment

How do researchers tease apart genetic and environmental factors?

Before the genome era, twin studies helped researchers to assess the relative influences of genes and environment – without knowing details of particular genes. Researchers can record

what happens to lots of pairs of identical twins and similar numbers of non-identical, same-sex twins when each pair is raised together in a similar environment. If a characteristic differs more in non-identical twins, this is likely to be because of some genetic effect.

Better, but more difficult to arrange, is to look at identical twins who have been raised in different households (and, therefore, different environments). If they nevertheless turn out very alike, the likeness will be at least in part because of genes shaping their development.

Identifying the genes involved requires a different kind of study. For example, the EPIC-Interact project led by the Medical Research Council's Epidemiology Unit in Cambridge seeks to understand the complex interactions between genes and lifestyle factors such as diet, exercise and other behaviours on the risk of developing type 2 diabetes.

The researchers used a mega-database of 350,000 people across Europe from the existing 'EPIC' study on cancer and nutrition. The records were so detailed that the Cambridge team were able to pull out over 12,000 people with diabetes as well as over 16,000 diabetes-free controls. With such a large sample, it is possible to give good indications of which genes and lifestyle differences are important contributors to diabetes risk, and the results could feed into health policies for tackling what is becoming one of the most common conditions of middle age.

More than 25 studies have already been published as a result of this work. One 2014 study, for example, supported the idea that eating a lot of meat increases your risk of type 2 diabetes. Another, published in 2017, identified regions of the human genome associated with insulin resistance (when the body stops responding properly to the hormone that regulates blood sugar levels) suggesting that these regions, which had functions related to fat storage, could be important in diabetes risk.

The human microbiome

Like it or not, our bodies are teeming with billions of microorganisms

We carry many more genomes than just our own. Thousands of different kinds of bacteria live on and in humans, and there are perhaps ten times as many bacterial cells present as there are cells in our bodies. About 1% of your bodyweight is bacteria.

The Human Microbiome Project is an international effort uniting the labs sequencing the genomes of these passengers, both welcome and unwelcome. In our guts alone, we house bacteria carrying more than three million genes – 150 times as many as in the human genome.

Meanwhile, the number of studies of what these bacteria do for us – or to us – is growing. Some bacteria are essential, such as those needed for digestion. Some are harmful. Some can be benign but turn nasty.

An example of the last kind is *Neisseria meningitidis*, which lives in the throats of as many as one person in every ten, mostly harmlessly. But the bacterium (the genome of which was sequenced in 2000) also causes meningitis if it gets into the brain. Each year, meningococcal bacteria causes 30,000 cases of meningitis across 26 countries in sub-Saharan Africa, despite the introduction of a new vaccine. Without treatment, half of those affected will die and many are left with brain damage.

Much current research focuses on the bacteria in our intestines, most of which cannot live anywhere else. There's a whole ecosystem in there, and it varies from person to person. A 2012 study showed that the DNA belonging to all the bacteria in one person's gut microbiome was substantially different to another's. Variations in this vast population – the gut microbiota – seem to affect our risk of obesity, as well as subtler responses to our diet. They could also suggest approaches to personalised medicine and nutrition.

The microbial populations in other areas of our body vary too. One 2019 study that sequenced the DNA of bacteria in men's prostate glands found that those with prostate cancer had less diverse microbiomes when compared to those without cancer. The results suggest bacteria may have a role to play in cancer, for example, changing the environment for tumour growth, but also provide a possible new tool for diagnosing the disease.

A growing number of serious medical conditions that were formerly thought to be unlinked to microbes may actually have bacterial culprits. For instance, a gut bacterium called *Helicobacter pylori* can cause stomach ulcers, and the bacteria in hardened arteries – when disturbed by stress – may play a part in triggering heart attacks.

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The body's ecosystem

https://www.the-scientist.com/features/the-bodys-ecosystem-37085

The Human Microbiome Project

https://www.hmpdacc.org/

The genetic origins of humans

How DNA studies help to trace the origins of modern humans

Following individual genes down more than a few human generations is next to impossible. Egg and sperm are each made in a specially orchestrated cell division, and their paired genes – one copy from each parent in the previous generation – are thoroughly shuffled before their single sets of chromosomes are assembled.

These then combine to create a new person's genome. That happens in every round of reproduction, so clear lines of descent get very blurred. Both sexes, though, contribute portions of DNA that escape this mixing. Only males have a Y chromosome and it passes from father to son without any recombination; it never mixes its genes with the X chromosome, it's partner. Meanwhile, mitochondrial genes are passed from a mother to her children; they are passed to the next generation in the egg not the sperm, meaning only females' mitochondrial DNA is inherited. So, there are two sets of genes that are normally passed cleanly from one generation to the next. Analysis of both kinds has been used to track the history of human migration out of Africa. More recently, it has been extended to more detailed tracking of who may have been where and when.

More subtle traces of our past can also be found in the bacteria in our guts, and sampling shows they differ from place to place. Genome analysis of samples of a single species recovered from two different human populations can indicate when the populations became separated, assuming the bacteria are undergoing a roughly constant rate of mutation. In 2007, one study traced the lineage of *Helicobacter pylori* (the bug that causes stomach ulcers) from European, African and Asian populations. The researchers established similar patterns of migration for the bugs as for their human hosts, indicating that people and *H. pylori* have probably been living with each other ever since the first modern humans left Africa.

More recently, research in mice and insects has shown that animals that are more closely related have more similar communities of bacteria living on them, suggesting that bacteria can be used to understand evolutionary relationships.

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The history of the Y chromosome in man

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How genetics affects physical characteristics

Small genetic changes can mean big physical differences

We are fascinated by people who are different, but genetically humans are really rather similar. We are all over 99 per cent similar (identical twins excepted). Many human characteristics vary continuously – there are people at many different points on the scale. Height is a typical example, and research from a study of more than 250,000 people suggests at least 400 different gene regions (as well as environment) affect how tall a person grows.

A few characteristics of appearance vary more simply. Red hair, for example, is associated with having two altered copies of a gene known as MC1R, which is involved in making the pigment melanin. (Having just one 'red' allele may affect skin tone and freckling.) There is some evidence for a number of the other characteristics often said to be associated with red hair, such as a lower tolerance for pain. The MC1R gene encodes a receptor that seems to interfere with pain circuits in the brain. However, redheads' reputation for 'fiery' temperament probably has more to do with the associations of the colour than with anything in the DNA.

Less obvious personal differences, such as having wet or dry earwax, have been tied to a specific gene. Wet earwax is harmless, but the same genetic variation has been linked with a slightly increased risk of breast cancer. However, dry earwax is much less common, so it's difficult to find large enough groups to compare.

Meanwhile, genomics is uncovering more details of the small differences in genes that can make a big difference to your appearance. For example, researchers recently identified 15 genes involved in face shape – 7 of which were involved in determining nose shape. They did this by looking at 3D scans of 2,329 people's faces and mapping the differences in their faces to single-"letter" changes (single nucleotide polymorphisms or SNPs) in their DNA. The study raises the interesting possibility of archaeologists being able to reconstruct people's noses from their remains – as long as they can extract DNA from the bones. This would not ordinarily be possible because noses, which are made of cartilage, are lost when a body decomposes.

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Myths of human genetics: earwax

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Scientists connect 15 genes with our facial features

https://www.futurity.org/15-genes-facial-features-1683492-2/

Genes and personality

How much of 'me' is determined by my genome?

Our personalities and behaviours are undoubtedly influenced by our genomes, but there are real difficulties in studying the links. A lot of the personality traits you might potentially want to study – such as optimism or aggression – can be hard to define. And, as with complex physical traits, genomic analysis typically finds many DNA variations that only have weak associations with the behaviours in question.

Geneticists who work in the area seem to have a persistently optimistic trait, though, and are continuing to work on the origins of a whole range of behaviours, including abilities such as reading and maths. They continue to find new clues to the connections between genetics and life histories.

For example, there is evidence from psychological studies that children's school performance is influenced by how smart they think they are – their 'self-perceived ability' (SPA). In 2009, Robert Plomin and colleagues at King's College London and Goldsmith's University, who work with a large database of twins, reported that SPA is highly heritable. So, while there is still a self-fulfilling prophecy involved, it may be at least partly due to some genetic influence on self-belief, rather than solely the messages children get from teachers or parents about their ability.

Researchers have also identified regions of the human genome that seem to be involved in determining certain personality traits, such as extraversion, neuroticism and conscientiousness. These studies are possible using genome-wide association studies, which search many small variations in DNA for associations with specific characteristics. With growing databases of data from private and public genome sequencing projects, it is increasingly possible to find large volumes of DNA to interrogate. However, it will always be difficult to say that we have found all the genes associated with a particular trait. For example, in a 2016 study, scientists identified variations in two genes that they linked to extraversion, but there are undoubtedly more.

It seems that the more we delve into our genomes, the more we realise how important it is in determining our personalities. For example, it was previously thought that genes had almost no influence on how much we tend to trust other people. One 2014 study in more than 1,000 twins and relatives suggested that trust is a trait shaped almost solely by the experiences we have during our lives. In 2016, however, another study took a closer look at the DNA of 7,000 twins and concluded that – on the contrary – trust is a trait that is strongly influenced by our genes, but that interactions between our genes and our lifestyles play an important role.

The Y chromosome and our evolutionary history

How we can use male chromosomes to chart the history of our ancestors

The male Y chromosome contains more DNA than the mitochondrion, which is passed on down the female line. It carries more than 59 million base pairs and between 50 and 60 genes – compared with 16,000 base pairs and 37 genes in a mitochondrion. That difference provides greater scope for variation, meaning it is more useful for detailed analysis of how DNA markers have been carried down the generations. Such analysis can even shed light on aspects of individual ancestry, as well as tracking population movements.

As many countries share our custom of passing surnames from father to son, DNA results can be compared with old-fashioned genealogies and used to see whether two people with the same surname are genetically related. More remarkably, DNA profiles from crime scenes might be useful in predicting the possible surnames of men who were there.

A team led by Professor Mark Jobling at the University of Leicester looked at the Y chromosome DNA of 1,678 men with 40 different British surnames, including Smith, Ravenscroft and Attenborough. Two men who shared a common surname, like Smith, were no more likely to have similar Y chromosome DNA that any two random men. However, when the surname was rarer, like Attenborough, their Y chromosomes were much more similar.

Researchers have also used analysis of the Y chromosome to dig much deeper into our evolutionary past. A 2016 study of Y-chromosome sequences from 1,244 men identified a group that emerged 55,000 years ago containing the ancestors of nearly all non-African males.