

*Mitochondrial donation*

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# Q&A: Mitochondrial donation

## Mitochondrial donation

# What is mitochondrial DNA disease?



“Around 1 in 6500 children is thought to develop a serious mitochondrial disorder. There is no cure and our current treatments only focus on managing the symptoms.”

### 1. What are mitochondria?

Mitochondria are small structures found in our cells which generate the energy required to allow our bodies to function (see Figure 1). They sit outside the nucleus, which houses almost all of the cell's DNA (99.9%). Mitochondria also have their own DNA, which makes up only 0.1% of the total cell DNA and controls mitochondrial function and energy production. Mitochondrial DNA does not affect the features that make each person unique, such as appearance and personality, which are controlled by the nuclear DNA.

### 2. What causes mitochondrial DNA disease?

Mitochondrial DNA disease is caused by genetic defects in mitochondrial DNA, which mean the mitochondria do not work properly or produce enough energy.

There are many different genetic defects that can cause mitochondrial DNA disease, and multiple different organs can be affected as mitochondria are present in all tissues of the body. The symptoms and severity of disease therefore vary considerably between patients.

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### 3. What are the symptoms of mitochondrial DNA disease?

Mitochondrial DNA disease commonly affects multiple different organs, with symptoms including loss of movement control, muscle weakness and pain, diabetes, heart problems, brain disease such as epilepsy and stroke-like episodes, and stomach and intestinal problems. The severity of mitochondrial DNA disease varies from mild to extremely debilitating, and it can result in childhood death.

### 4. Can mitochondrial DNA disease be treated/cured?

There is no cure for mitochondrial DNA disease at present. Current treatments aim to decrease the effect of the symptoms but do not change the course of the disease.

### 5. How is it passed on?

Mitochondrial DNA is maternally inherited and so genetic defects that lead to mitochondrial DNA disease are often passed down from mother to child. Women who inherit faulty mitochondrial DNA can develop symptoms or be carriers of the condition without experiencing symptoms, and in both cases they can pass the defects on to their children.

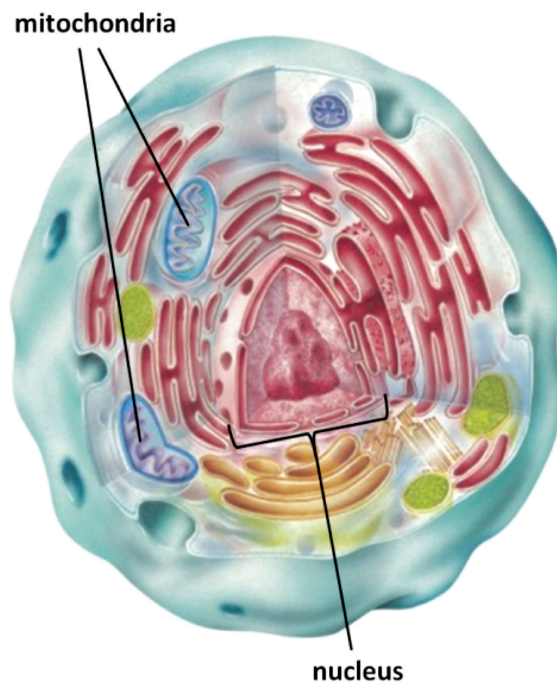


Figure 1. Cutaway of a human cell. Miles Kelly Art Library/Wellcome Images

## What can be done to prevent it?



The donor mitochondrial DNA will not affect the child's appearance, personality or any other features that make a person unique."

### 6. What is mitochondrial donation?

Nuclear DNA (the unique genetic information that makes us who we are) is taken out of a patient's egg containing faulty mitochondria and put into a donor egg, containing healthy mitochondria, which has had its nuclear DNA removed. This prevents mitochondrial DNA defects from being inherited, so the child that develops from the egg would not get mitochondrial DNA disease.

### 7. What techniques are used in mitochondrial donation?

Two techniques could be used for mitochondrial donation:

#### **Maternal spindle transfer**

Maternal spindle transfer involves removing the nuclear DNA (which amounts to 99.9% of the total cell DNA) from the donor egg, leaving the part of the cell containing the healthy mitochondria. The nuclear DNA from the mother's egg is then inserted into this cell. The healthy egg is fertilised and is then implanted into the mother's uterus in the same way IVF is carried out already.

#### **Pronuclear transfer**

Pronuclear transfer is similar to maternal spindle transfer but involves fertilising the mother's egg with the father's sperm first and then transferring the nuclear DNA to the donor egg containing healthy mitochondria, which has had its nuclear DNA removed. The healthy fertilised egg is then implanted into the mother's uterus in the same way as in maternal spindle transfer.

### 8. How safe are the techniques?

Maternal spindle transfer has been successfully performed in monkeys, leading to the birth of healthy offspring. Pronuclear transfer has been performed in mice and is successful in preventing mitochondrial DNA disease in mice that carry a genetic defect in their mitochondrial DNA.

Maternal spindle transfer has been used on human eggs and pronuclear transfer on human zygotes (fertilised eggs), in both cases leading to the successful development of a bundle of cells (blastocyst). This suggests that they would develop as normal if implanted in the uterus.

Safety is and will always be of paramount importance and the techniques have received unprecedented scrutiny by the Human Fertilisation and Embryology Authority's (HFEA) specially convened Expert Scientific Review panel. Through three separate reviews, the panel found no evidence to suggest that the techniques are unsafe for clinical use and concluded that both techniques have the potential to be used in patients with mitochondrial disease. Never before has a new reproductive technology been subjected to such thorough investigation before it has been approved.

It is never possible to answer every safety question before new medical procedures are used in people, but the scientific evidence suggests that any risks of mitochondrial donation are proportionate to the severity of mitochondrial disease and the well-recognised significant risk that children will continue to be born who will die in infancy if these techniques are not used.

### 9. Why does the law need to be changed?

The law does not currently allow an egg or an embryo which has had its mitochondrial DNA substituted to be used in treatment in humans. In 2008, when the Human Fertilisation and Embryology Act was amended, Parliament did, however, foresee that techniques such as those described above were being developed to prevent mitochondrial DNA disease. It therefore provided the Parliament of the day the power to pass regulations to enable techniques which prevent "serious mitochondrial disease" to be used for patients in the clinic.

## What are the principles behind the new regulations?

### 10. What are the ethical arguments in favour of allowing the techniques to be used?

Although mitochondrial DNA disease affects a small number of individuals, it has extremely disabling and often devastating effects on families. Mitochondrial donation will enable mothers to choose to have children who are genetically related to them but free from mitochondrial disease, preventing the transmission of a fatal disease in much the same way as organ donation. Doing nothing in the face of this suffering would be unethical if a safe and effective way of preventing it is available.

Throughout 2012 the HFEA conducted extensive public debates and engagement events concerning the ethical issues that surround the two mitochondrial donation techniques and in March 2013 they published a report demonstrating broad public support for the use of these techniques, providing that their use would be carefully controlled. Similarly in June 2012 the Nuffield Council on Bioethics held a discussion and lively debate at Westminster Palace on the two novel techniques, which again revealed broad public support for the use of mitochondrial donation techniques in the UK, within a robust regulatory framework. In a recent evaluation by Sciencewise the public consultation exercises were commended as excellent public engagement. Such broad public support suggests it would be unethical if the techniques were not made available if they are classified as sufficiently safe and effective.

### 11. Should we be creating 'three-person' babies?

Scientists estimate that our DNA is made up of ~30,000 genes. In mitochondrial donation, almost all of the child's genes will come from its parents; the mitochondrial donor will only contribute 37 genes (0.1% of total DNA), which enable the mitochondria to produce energy. The donor mitochondrial DNA will not affect the child's appearance, personality or any other features that make a person unique – it will simply allow the mitochondria to function normally and the child to be free of mitochondrial DNA disease. Mitochondrial donation involves two-parent fertilisation in the same way that IVF does, and any

child would be genetically unique, with a natural combination of nuclear genes from both parents.

Furthermore, the Nuffield Council on Bioethics conducted an ethical review which concluded that "by the societal norms, [mitochondrial] DNA does not confer genetic identity". As a result, there is no reason why the techniques should affect the child's sense of identity. The term "three-parent children" is misleading. These children will only have two biological parents, with the donated mitochondria falling under the same category as organ donation.

### 12. Could allowing mitochondrial donation be the start of a 'slippery slope' towards allowing other techniques, such as nuclear genetic modification, which could be used to create 'designer babies'?

Mitochondria are separate structures from the nucleus (see Figure 1) and the regulations will only allow the techniques to be used on mitochondrial DNA, not on nuclear DNA. The ban on altering nuclear DNA will remain in place, and there is no intention of changing this.

### 13. Mitochondrial donation involves 'germline modification' (changes to sperm or egg cells), which enables DNA modifications to be passed on to children. Should we be changing future generations in this way?

DNA is not modified during mitochondrial donation; the techniques simply replace the mitochondria, and involve reconstruction (where nuclear DNA is moved from one cell to another). New combinations of mitochondrial DNA and nuclear DNA occur in nature every time an egg is fertilised. Mitochondrial donation will not alter physical or character traits; it will simply allow future generations to be born without mitochondrial DNA disease. It is not and cannot be used for 'eugenics' (deliberate alteration of physical traits).

## How will the regulations work in practice?

### 14. How will doctors be licensed to offer the techniques?

Once Parliament has passed regulations allowing mitochondrial donation, doctors will still need to obtain a licence from the HFEA in order to use the techniques, which will only be granted when the HFEA is satisfied that the use of the techniques is safe. The HFEA will carefully assess each application to use the techniques, so doctors will need to get specific approval and it will only be provided at specialist clinics.

### 15. What legal status will the mitochondria donor have?

Although women donating mitochondria would also be egg donors, only the mitochondria-containing part of their eggs would be used for the procedure. After extensive consultation the Government has proposed that the children born after mitochondrial donation should have a right to access non-identifying information about the donor but not identifying information.

## What happens next?

After three years of consultation and review processes, Government announced in July 2014 that it had carefully considered responses to public consultation and would proceed with laying the regulations before Parliament for debate and approval.

If these regulations are approved the HFEA will have responsibility for overseeing mitochondrial donation therapy. Specialist doctors will have to obtain a licence from the HFEA to use the techniques. This will only be granted once the HFEA is satisfied that any risk of their use is low. Approval of the regulations will allow more reproductive choice for parents at risk of having a child with mitochondrial DNA disease, giving them the possibility of having a healthy child free from a fatal disease.

### Links to further background information

Wellcome Trust Policy Spotlight on Mitochondrial Disease

[wellcome.ac.uk/About-us/Policy/Spotlight-issues/Mitochondrial-diseases/index.htm](https://wellcome.ac.uk/About-us/Policy/Spotlight-issues/Mitochondrial-diseases/index.htm)

Video from the Human Fertilisation and Embryology Authority: Mitochondrial Replacement – Some facts

[vimeo.com/49147390](https://vimeo.com/49147390)

HFEA advice to Government on the ethics and science of mitochondria replacement

[mitochondria.hfea.gov.uk](https://mitochondria.hfea.gov.uk)

Nuffield Council on Bioethics report ‘Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review’

[nuffieldbioethics.org/mitochondrial-dna-disorders](https://nuffieldbioethics.org/mitochondrial-dna-disorders)

Mitochondria: Nuts and bolts – What are mitochondria?

[wellc.me/MitoBolts](https://wellc.me/MitoBolts)

Healing Broken Batteries – a short film about mitochondrial disease and the new techniques being developed at Newcastle University

[wellc.me/brokenbatteries](https://wellc.me/brokenbatteries)

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