# One baby, two mums

Creating kids with two genetic mothers could save them from dreadful disease. But will the next step be designer babies, asks **Nick Lane**

CHILDREN with three parents might sound like monstrous chimeras, but they are among us already. In the late 1990s, an American team created the first genetically engineered humans by adding part of the egg of one woman to the egg of another, to treat infertility. When the US Food and Drug Administration got wind of the technique it was promptly banned, though related methods have been used in other countries.

Now a research team in the UK is experimenting with creating three-parent embryos. This time, the goal is to prevent children inheriting a rare group of serious diseases caused by faulty mitochondria, the powerhouses in our cells. Mitochondrial diseases affect at least 1 in 8000 people, probably more, and there are no treatments.

Mitochondria are always inherited from the mother, so for women in whom they are faulty replacing the mitochondria in their eggs with healthy ones from a donor would help ensure their children are healthy. What makes the idea controversial is that mitochondria contain DNA of their own, meaning babies created this way will have genes from a "second mother".

Supporters of this approach point out that mitochondria contain a mere 37 of the 20,000 or so human genes. Changing them is akin to changing a battery, they argue. Yet it is becoming increasingly clear that the influence of mitochondrial genes extends far further: different variants can affect our energy, athleticism, health, ageing, fertility, perhaps even our intelligence, all of which help make us who we are as individuals.

The prospect of trying to prevent mitochondrial diseases by creating babies with two mothers raises a host of issues. On the one hand, if the FDA felt that three-parent embryos were unsafe, what's changed? On the other hand, if this approach really is safe, wouldn't it make sense to equip our children to live longer, healthier and more active lives by giving them the best possible mitochondria? The answers to these questions offer insights into some of the most intriguing aspects of sex, health, disease and longevity – and even into the origin of species.

## Mixed up

Male mitochondria are an evolutionary dead-end. While there are 100 or so in the tail of every sperm, powering its motility, they are destroyed when the winning sperm gets inside the egg, which is stocked with 100,000 or more mitochondria of its own. As a result, mitochondrial DNA almost always passes from egg to egg, mother to daughter.

This is the deepest distinction between the sexes. Forget the Y chromosome, which is a genetic johnny-come-lately, restricted to mammals: reptiles, insects and plants all have different systems of sex determination. Even many simple algae and fungi have two sexes, but the only thing their sexes have in common with ours is the passage of mitochondria down the "maternal" line.

How this came about is still hotly debated. The leading hypothesis, proposed in 1992, is that if mitochondria from the father and mother had to compete with each other for survival, "selfish mitochondria" would evolve to the detriment of the entire organism: the mitochondria that are best at proliferating are not necessarily best at providing a cell with the right amount of energy. Whatever the reason, all the mitochondria in our cells are normally identical.

In the 1990s, however, the fertility technique pioneered by Jacques Cohen at the Institute for Reproductive Medicine and Science of St Barnabas in Livingston, New Jersey, resulted in children with cells containing a mixture of mitochondria from different individuals – something that almost never happens naturally. The technique, known as ooplasmic transfer, involves transferring tiny extracts of healthy donor eggs into the eggs of infertile women, with the vague aim of "pepping them up" a little. It boiled down to injecting a bit of good egg into a bad egg, and hoping for the best. Surprisingly, it seemed to help, although no controlled trials were done to show this for sure.

The group suspected it was transferring mitochondria, but didn't anticipate the consequences. Despite injecting less than 5 per cent of the egg-cell volume, when blood cells were taken from two of the 30 babies born this way, about a third of the mitochondria were found to come from the donor egg.

While there is no evidence that these children will suffer from diseases as a result of their cells having a mixture of mitochondria from two different women, there is no guarantee that they won't, either. This is why most researchers think the FDA was right to ban ooplasmic transfer, at least until a lot more basic research has been done to fully investigate the technique. However, Jonathan Van Blerkom, a developmental biologist at the University of Colorado in Boulder, who sat on that FDA committee, sees the work now taking place in the UK in a different light. The approach holds enormous promise he says, and it would be "criminal" to ban it.

The research is led by Patrick Chinnery and Douglas Turnbull of Newcastle University in the UK, who see people with some of the most dreadful congenital diseases known. Leigh syndrome, for instance, occasionally affects adults but usually strikes children under 2 years old. Sufferers have difficulty moving, swallowing and breathing. The symptoms come and go but inevitably worsen, leading to mental impairment, seizures and death ▶

BRIAN GRIMWOOD

HYBRID MEDICAL ANIMATION/SPL

## Mitochondria – the basics

- Each of our cells contains anything from one to thousands of mitochondria
- Mitochondria 'burn' food to produce the fuel that powers cellular processes
- Their size and shape varies from cell to cell
- Each contains up to 10 copies of a piece of circular DNA encoding 13 proteins
- These proteins are produced within the mitochondria
- However, the vast majority of the 1500 or so mitochondrial proteins are encoded in nuclear DNA and exported to mitochondria

within months or years. Leber's hereditary optic neuropathy causes blindness, usually in young men. Another syndrome, called MELAS, can involve everything from diabetes and mild deafness to digestive problems, seizures and stroke-like episodes.

"In mice it is possible to prevent the transmission of often disabling and sometimes fatal disease," Turnbull says. "The only focus of our laboratory is to try and determine if this is a valid treatment for our patients." Chinnery and Turnbull are experimenting with a method originally proposed in the 1980s by the guru of mitochondriacs, Doug Wallace, who is now at the University of California, Irvine. The trick, he suggested, is not to transplant any mitochondria, just the nucleus – the repository of the main genome in cells.

## Peculiar inheritance

Soon after an egg is fertilised, the nucleus is taken from an embryo with faulty mitochondria and injected into a donor egg cell whose nucleus has been removed. The outcome is an embryo with nuclear genes from the prospective parents, and mitochondrial DNA from the second mother. In principle, all the mutant mitochondria should be left behind; in practice, however, a few mutant mitochondria may stick to the transplanted nucleus. Even though their numbers start off small, as the embryo grows the proportion of mutant mitochondria could be ramped up in some cells, as happened after ooplasmic transfers.

Typically the proportion of mutant mitochondria per cell has to exceed a certain threshold before problems begin. This means people with the same mitochondrial mutation can have quite different symptoms, or none at all, depending on the fraction of mutant mitochondria in cells in different parts of the body. Chinnery and Turnbull are now investigating whether the transfer of a handful of mutant mitochondria along with the nucleus could result in some cells having a dangerously high proportion of mutant mitochondria. The early results suggest not, but they are in the middle of more systematic studies, and don't want to speak too soon.

Even if children conceived in this way are healthy and stay that way, Van Blerkom points out that a disease might reappear generations later. The problem is the random segregation of mitochondria into developing egg cells, which are then amplified in numbers from as few as 10 to the 100,000 in a mature egg cell. If even a handful of faulty mitochondria get into the germline, they could be amplified to a level high enough to cause a recurrence of disease in descendants of the female line.

This might seem to be a serious argument against three-parent embryos until you consider the alternative. At the moment, women who discover that their mitochondria bear dangerous mutations face a terrible dilemma when it comes to having children. The peculiar nature of mitochondrial diseases means that even when all a woman's mitochondria are mutant, a child could be anything from perfectly healthy to suffering from a far more severe form of the disease than the mother. In some cases doctors can give more precise odds, but often they can't.

**"Would-be mothers face a terrible dilemma, as their children could be anything from healthy to suffering from severe disease"**

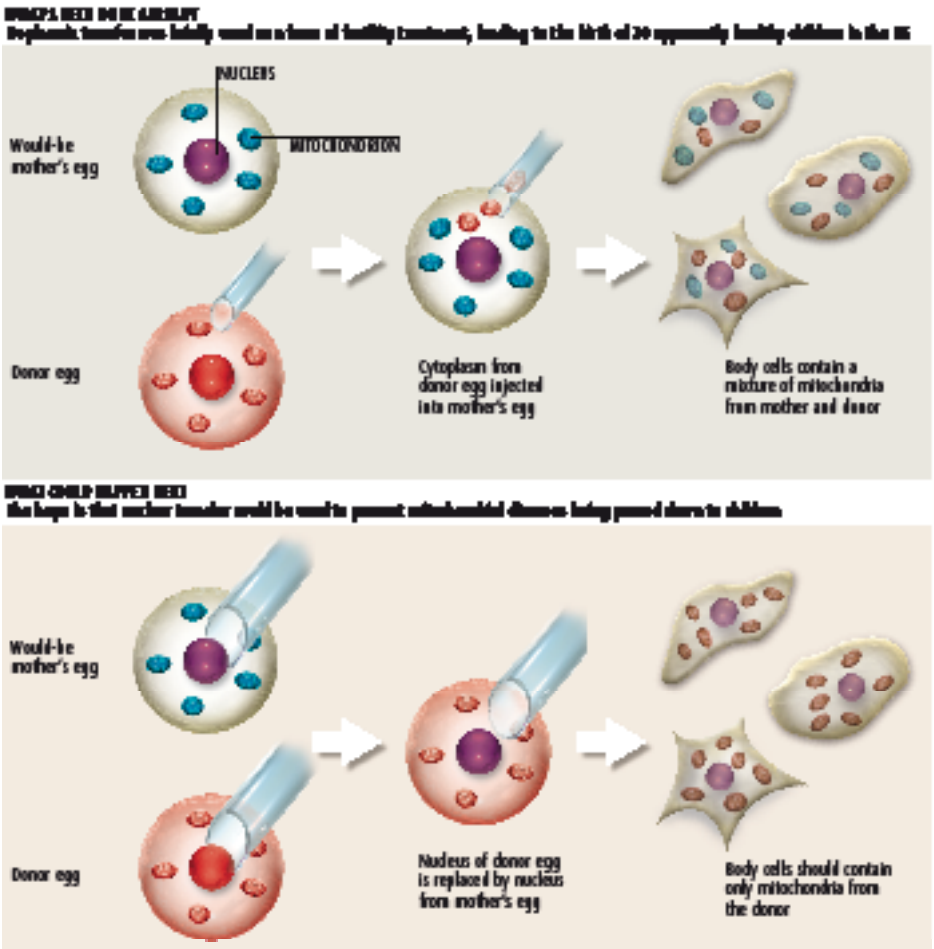
Prenatal testing, or IVF with pre-implantation genetic diagnosis (PGD), are not much help either. Such screening methods can detect some common mitochondrial mutations but cannot reliably reveal what percentage of mitochondria in cells bear these mutations. Neither method can help women whose mitochondria are all mutant. The bottom line is that the creation of two-mother embryos could provide would-be parents with by far the best chance of having healthy children – and healthy grandchildren and great-grandchildren.

So let's suppose that all the outstanding issues are solved in the next few years, and that the creation of two-mother babies to prevent mitochondrial diseases becomes routine in the next few decades. Will this be the first step on a slippery slope towards creating designer babies?

The idea is not beyond the pale, as we are learning that the role of mitochondrial DNA goes deeper than anyone thought. Perhaps the biggest surprise over the past decade is that mitochondria are responsible not merely for energy production in cells, but also for orchestrating programmed cell death. The state of mitochondria is the decisive factor determining whether cells live or die, with obvious implications for health and disease, from cancer to degenerative diseases such as Alzheimer's.

The most striking example comes from Japan. Here, there is a common variant in mitochondrial DNA, a change in a single DNA "letter". A decade ago Masashi Tanaka, now at the Tokyo Metropolitan Institute of Gerontology, and his colleagues reported that this tiny change almost halved the risk of being hospitalised for any age-related disease at all, while doubling the chance of living to 100. Most Japanese centenarians have the variant, but unfortunately for the rest of us it's very rare outside Japan.

Since the late 1990s, other variants in mitochondrial DNA have turned out to be implicated in all kinds of traits. Several are linked with longevity, albeit less robustly than the Japanese type. Another common variation is associated with diabetes, while others increase the risk of neuro-degenerative conditions such as Parkinson's disease. Male fertility depends partly on sperm motility, which is also influenced by mitochondrial variants. Even IQ, Tanaka has found, is linked to mitochondrial variations, at least in Japan, though the differences are small.




So could we boost intelligence and lifespan, and prevent many diseases by creating "designer" three-parent embryos? The answer is probably not, at least in the foreseeable future. There are two main reasons. The first, Tanaka notes, is that old biological chestnut, trade-off: nothing comes without a cost. In Japan, the mitochondrial group with the highest IQ is most likely to get heart disease, for example.

Wallace, meanwhile, thinks that our mitochondria evolve to match our climate by regulating internal heat generation. Mitochondria may produce less heat in the tropics, but at the cost of leaking more free radicals, which predisposes individuals to diseases like diabetes. Conversely, people adapted to northern climates generate more heat internally and are less likely to get diabetes, but at the cost of more male infertility. So you choose a trait and pay the penalty. Would you opt for a mitochondrial variant that boosted your child's athleticism, for example, if you knew it would lead to poor health later in life?

Then there is an even more fundamental problem. Of the 1500 or so mitochondrial proteins, just 13 are encoded by mitochondrial genes and produced locally. The rest are encoded in nuclear DNA, made elsewhere in the cell and exported to mitochondria. These two sets of proteins, encoded by different genomes, have to work together intimately, yet mitochondrial DNA mutates around 20 times as fast as nuclear DNA. If such mutations mean the two genomes don't function well together, then an individual is more likely to suffer from a range of diseases. At worst, the embryo could die.

Ronald Burton, a marine biologist at the Scripps Institution of Oceanography in San Diego, California, has even suggested that such incompatibilities might be behind the origin of species, or at least some of them. He works with tiny marine copepods, shrimp-like crustaceans that live along the Pacific coast close to Scripps. Their populations don't interbreed much, and so steadily accumulate differences in their mitochondrial DNA. When Burton and his colleagues experimented with interbreeding between local populations, they discovered that mitochondrial incompatibilities undermined the health of offspring. The animals lacked energy, developed slowly, were less fertile and were also more likely to die early. It is only a matter of time before these incompatibilities reach a level that rules out successful interbreeding altogether – the very definition of a species. What's more, because mitochondrial genes evolve so quickly, they might even play the dominant role in natural speciation.

Wallace and others have found that these evolutionary patterns apply not only to crustaceans, but also to mammals – and notably to primates. Our genes show all the cardinal signs of selection for compatibility with mitochondria (*Gene*, vol 378, p 11), and mitochondrial incompatibilities might play a huge role in human health and happiness.

For example, around 40 per cent of all pregnancies end in early miscarriage for unknown reasons. Many could be caused by mitochondrial incompatibilities. Not only that, but Tanaka suspects the high incidence of diabetes among Californian Hispanics is related to incompatibilities between mitochondrial and nuclear genes due to the mixing of long-separated populations. If he's right, there could be many other examples.

The issue of compatibility means there is an inherent danger in any attempts to boost health, longevity, fertility, athleticism or IQ by transplanting mitochondria: putting the wrong mitochondria and nucleus together could harm children rather than improving them. Leaving aside the ethics, the risks appear to outweigh the benefits.

For those who risk passing on mutant mitochondria, however, the odds are very different. The Newcastle team plans to minimise incompatibilities by picking donors with a broadly similar mitochondrial genome, or haplotype. The risk cannot be completely eliminated but it is far lower than that of inheriting a mitochondrial disease. "It's inhumane not to treat such conditions if we can," says Van Blerkom. "There's no other reason to go into medicine at all." ●

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