Science shows ethical questions remain unanswered with 3-person IVF

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Time for human trials? Credit: Halfpoint

Diseases caused by genetic mutations in the mitochondria – the powerhouses of the cell – can be disabling, or even deadly. That is why mitochondrial replacement therapy (MRT), otherwise also known as three-person IVF (*in vitro* fertilisation), is being touted as a much-needed option for women carrying mitochondrial mutations.

Most genes in a cell are trapped in the nucleus, but a tiny fraction are present in the mitochondria too. When eggs are fertilised, the genes in the nucleus of the egg combine with the genes in the nucleus of the sperm to create a new cell. However, mitochondrial genes do not undergo this mixing and are passed on from mother to child.

The idea behind three-person IVF is to find a way of replacing the mitochondrial genes in an affected egg cell before they are passed on to the child. This is done by acquiring a donor's egg cell and removing the nucleus from it to leave a cell with healthy mitochondria. Then the mother's nucleus, which is unaffected, is removed and placed in the donor's egg cell, creating an egg cell that should contain healthy genes both in the nucleus and in the mitochondria.

The procedure has been performed in animals with some success, and now there is a motion in the UK parliament to allow experiments to be done in humans. This may seem like a reasonable step ahead, but I feel a lot more work needs to be done before we can go to human trials.

Genes are a complex beast

Genes interact with one another. That's not really surprising – the complex range of processes that cells engage in, such as respiration or cell division, are unlikely to be accomplished by single genes acting in isolation. So genes act in networks or pathways, each one contributing some particular component.

Genes are also variable. This means that no two individual genomes are alike. As a consequence the outcome of a particular interacting pair of genes will sometimes differ between individuals. Geneticists call this kind of effect epistasis. It is the dark side of genetics, in the sense that it is poorly studied and we know very little about how widespread it may be, but a recent study suggests it is important.

Epistasis can occur between individual genes, between sets of genes, or even between whole genomes. This latter kind of epistasis is of relevance to the discussion on the safety and ethics of MRT. This is because when a mitochondrial genome from a donor replaces the diseased mitochondria, the nuclear DNA from the parents must now converse with a completely novel genomic partner. But, although epistasis has formed part of the debate over safety, the ethical implications of changing epistasis between mitochondrial and nuclear DNA have so far been ignored.

Ethics first

The ethical review of MRT within the UK was carried out by the Nuffield Council on Bioethics in 2012. Its conclusion was straightforward: provided it was safe, it was ethical. In short, if human trials showed that the treatment was safe then the council considered it to be ethical too.

An important part of the review revolved around whether the therapy might alter the individual's identity in some significant way. The report cites the view of the Medical Research Council and the Wellcome Trust that:

We do not believe the transfer of mitochondrial DNA raises issues around identity, since it does not carry any genetic data associated with the normally accepted characteristics of identity. An analogy could be drawn with replacing the battery in a camera – the brand of the battery does not affect the functioning of the camera.

The rationale for this is that the mitochondrial genome contains only 37 genes out of the 20,000 genes in the human genome, and that these genes are involved in mitochondrial functions and nothing else. Others see things differently. For instance bioethicist Annelien Bredenoord argued

that, in terms of a person's genetic identity, the distinction between the nuclear and mitochondrial genomes is a false one:

No matter whether one modifies a (pathogenic) nuclear gene or a (pathogenic) mitochondrial gene, the identity of the future person will be changed.

In fact there is growing evidence that mitochondrial DNA has far-reaching effects on a range of traits, from the core "battery" functions, to fertility, cognitive ability, ageing and even personality. One key feature of this extensive scientific literature is that the effect of the mitochondrial genome is sometimes surpassed by the effect of it interacting with the nuclear genome. So epistasis matters, although in ways that we don't fully understand.

This is a clear shortcoming of the ethical review, since it apparently did not explore in depth the substantial literature on this topic, which goes back decades. So while the battery analogy gives people a rough idea of what mitochondria do, it really is a highly simplified version of reality. It ignores the fact that batteries don't do anything by themselves, their function only being fully evident when placed within a device.

This issue is likely to crop up again when other technologies that allow scientists to literally re-write the genetic code are up for ethical approval. So bioethicists, policy makers and the general public need to appreciate that genes act in networks and if pathogenic genes are edited this may have unpredictable effects on processes and traits that do not form the target of the intervention. That is the reality of biological complexity. Whether that is ethical or not is up for discussion.

Source: The Conversation