Genealogical Obscurement: Mitochondrial Replacement Techniques and Genealogical Research

Abstract

Mitochondrial Replacement Techniques (MRTs) are a new group of biotechnologies that aim to aid women whose eggs have disease-causing deleteriously mutated mitochondria have genetically related healthy children. These techniques have also been used to aid women with poor oocyte quality, and poor embryonic development, to have genetically related children. Remarkably, MRTs create humans with DNA from three sources: nuclear DNA from the intending mother and father, and mitochondrial DNA from the egg donor. In a recent publication Françoise Baylis argued that MRTs are detrimental for genealogical research via mitochondrial DNA, because they would obscure the lines of individual descent. In this paper I argue that MRTs do not obscure genealogical research, but rather that MRT-conceived children can have two mitochondrial linages. I argue for this position by showing that MRTs are reproductive in nature and thus they create genealogy.

Keywords: mitochondria**,** Mitochondrial Replacement Techniques, genealogy, reproduction, biotechnologies.

INTRODUCTION

Mitochondrial Replacement Techniques (MRTs) are a new group of biotechnologies that aim to aid women whose eggs have disease-causing deleteriously mutated mitochondria to have genetically related healthy children. These techniques have also been used to aid women with poor oocyte quality, and poor embryonic development, to have genetically related children. Due to the experimental nature of MRTs we still do not have solid data about their success rate, both for avoiding the birth of children with mtDNA diseases and for the treatment of infertility. However, both research programmes have ended up in live births.(1,2) The following is, in a very simplified manner, what happens when we resort to such biotechnologies. The nuclear DNA of an egg (or zygote) which has deleteriously mutated mitochondria is extracted and then transferred to a donated egg (or zygote) which has healthy mitochondria and has been previously enucleated.(3) MRT-conceived children have DNA from three sources: nuclear DNA from the intending mother and father, and mitochondrial DNA from the egg donor. These biotechnologies do not only radically depart from natural occurring human sexual reproduction, but they also raise new and interesting ethical questions.

The main ethical debate surrounding MRTs has centred, so far, on the following: if MRTs affect numerical or qualitative identity; safety; possible transgenerational health risks; the disclosure of MRT conception; and the ethics of long-term follow-up.(4) One issue that has

not received enough attention is what impact could MRTs have on genealogical research. Specifically, if they can be detrimental for genealogical research via mtDNA. Let us remember that mitochondria are passed down, most commonly, via the maternal line, and in very rare occasions mitochondria is passed down both via the maternal and paternal lines.(5)[1] Genealogical research via mtDNA, in the academic context, is valuable for studying the geographical origins of certain populations; migration patterns; and also the identification of human remains.(6) Genealogical research via mtDNA is also valued by people who want to: map their family trees; ascertain their belonging to a particular ethnic group; get to know who their genetic mother is; and reunite with long lost grandchildren.(7)

According to Baylis "Mitochondrial replacement technology represents a potential threat to genealogical research using mtDNA analysis, as it would obscure the lines of individual descent, thereby providing a false or confusing picture".(8) She presents two reasons in support of this claim. First, the mitochondria of an MRT-conceived child would come from the woman who donated the eggs, and not from the intending mother. Second, the children of female MRT-conceived individuals would inherit the third-party mitochondria, which in turn would be transmitted via the maternal line.

In this paper, I argue that MRTs do not obscure the lines of individual descent, and thus they are not detrimental for mtDNA genealogical research, both for academic and personal purposes. The paper is divided into four sections. In the second section, I present a brief overview of what mitochondria, mitochondrial diseases, and mitochondrial replacement techniques are. In the third section, I present the strongest and most compelling argument that has been advanced for concluding that MRTs obscure genealogical research via mtDNA. In the fourth section, I show that one of the key premises of this argument is false, and thus that only some MRTs obscure genealogical research via mtDNA. In the fifth section, I go even further: I identify and challenge an implicit premise of the argument against MRTs, and show that in fact MRTs do not obscure genealogical research. I argue for the former by showing that MRTs are reproductive in nature (i.e. the egg donor is a second genetic mother) and thus they create genealogy. In the conclusion, I do a recap of why MRT-conceived children have two mitochondrial linages.

[1] In those very rare instances where there is paternal inheritance of mitochondria what happens is that the mitochondria contained in the sperm, which is usually degraded after the sperms enters the oocyte, survive and multiply.

MITOCHONDRIA, MITOCHONDRIAL DISEASES AND MRTS

The human body needs adequate supplies of energy to carry out its functions, and such energy is produced by the mitochondria. These cellular organelles not only produce energy in the form of adenosine triphosphate (ATP) but also partake in cellular processes such as cellular apoptosis and lipid metabolism.(9) Mitochondria are the only cellular organelles with their own DNA, mitochondrial DNA (mtDNA). Thus, in nucleated human cells there is mtDNA in each mitochondrion (in fact, there are several copies of the mtDNA in each mitochondrion) and there is DNA in the nucleus (nDNA). Mitochondria are also interesting in that nucleated human cells contain many of them. A human oocyte, for example, contains approximately 100,000 mitochondria.(10) Even when they exist in such large numbers mitochondrial DNA just encompasses .1% of the human cell's DNA, nDNA comprises the other 99.9%.(11)

The name 'mitochondrial diseases' has been employed to refer to those diseases caused by mitochondria not working as they should. Mitochondrial diseases can originate per malfunctions in the nDNA and/or malfunctions in the mtDNA. This is so because mitochondrial function depends on the jointly expression of nDNA and mtDNA genes. There are "more than 1500 mitochondrial proteins, most of which are nuclear-encoded, with only 13 encoded by mitochondrial DNA (mtDNA)".(12) Henceforth, I will only focus on diseases caused by pathogenic mutations of the mitochondrial DNA: mitochondrial DNA diseases (mtDNA disease).

Deleterious mtDNA mutations can occur throughout all mitochondria, or only in some of them. Let us remember that each nucleated cell has many mitochondria, and that each mitochondrion has many copies of the mtDNA. The term homoplasmy is employed when the mutation occurs throughout all mitochondria. The term heteroplasmy is employed when the mutation occurs only in some mitochondria. In the latter case the number of mutated mitochondria can diverge across cells and tissues. And, as Craven et al. point out, this is "complicated further by the presence of a 'genetic bottleneck' during development of the female germline, which means that women who carry a pathogenic mtDNA mutation can transmit different levels of mutant mtDNA to their children".(13) The maternal line of a woman with deleteriously mutated mtDNA can have individuals with deleterious mtDNA mutations and individuals with healthy mitochondria. This is due to the stochastic segregation of mitochondria during the development of the germ cell precursors, which will then develop into gametes.

Organs that require vast amounts of energy are the most affected by mitochondrial dysfunction, for example the brain and the muscles. The severity of mtDNA diseases varies from devastating to mild, and their onset can happen at any time. Pathogenic mutations in the mtDNA cause, among other conditions and syndromes: Leigh syndrome, Pearson syndrome, Kearns-Sayre syndrome, and MELAS syndrome (mitochondrial myopathy, encephalopathy with lactic acidosis and stroke-like episodes).(9) All the aforementioned cause suffering and pain, and they negatively affect the wellbeing of the people affected by them. Since there is currently no cure for such mtDNA diseases medical treatments focus on easing the symptoms caused by them.

Several techniques have been recently developed in order to aid women whose oocytes have pathogenic mutations of the mtDNA to have genetically related children absent such conditions. Here I will focus on the two most mature ones: maternal spindle transfer (MST) and pronuclear transfer (PNT).

In PNT two zygotes are created *in vitro*. One is produced with the intending parents' sperm and egg (or a sperm from a donor), and the other one with a donated egg and the intending father's (or donor's) sperm.[2] Between 8 and 20 hours after sperm penetration, the maternal and paternal pronuclei, which are adjacent but contained within separate membranes, are removed from both zygotes.(14) The pronuclei that were contained in the cell produced with the donor's oocyte and the enucleated cell produced with the intending mother's egg are discarded. Afterwards, the intending parents' (or intending mother and donor's) pronuclei are ferried into the enucleated cell produced with the donor's oocyte. The reconstituted zygote is then transferred to the intending mother or a surrogate.(15)

In MST eggs are obtained from the intending mother and a donor. The chromosomes from both the donor and the intending mother's oocytes are removed. The intending mother's enucleated oocyte and the donor's chromosomes are discarded. Afterwards, the intending mother's chromosomes are ferried into the enucleated donor's oocyte. The reconstructed oocyte is fertilised *in vitro* and then transferred to the intending mother or a surrogate.(16)

If the techniques are successfully carried out, and everything goes according to plan, then the couples will end up with healthy children whose healthy mitochondria will be passed down via

[2] In this case the intending parents are also the genetic parents.

the maternal line to subsequent generations. However, it is important to notice that during the chromosome transfer it is possible for the carryover of deleterious mutated mitochondria to occur. If this happens and the carryover is significant, then the MRT-conceived child could develop an mtDNA disease.(17)[3]

GENEALOGY AND MRTS

In recent work Baylis has argued that genealogical research that relies on mtDNA faces a potential threat by MRTs. The threat stems from MRTs obscuring the lines of individual descent. According to her, genealogical information obtained via the mtDNA of MRT-conceived children would provide a false or confusing picture of genealogical relations. Why? Because genealogical research via mtDNA "presumes 'the genetic continuity of humans from a single ancestral group and facilitated by the remarkable conservation of gene sequences through evolutionary history'. This presumption is disrupted with intentional genetic modification of which mitochondrial replacement technology is but one instance". (8)

Baylis identifies two groups which could be harmed by such obscurement: i) people interested in tracing their ancestry and ii) DNA genealogists. She asserts:

> For some, genealogical information of the type available through ancestry tracing is important for identity. (…) Historical and anthropological research on human population migration patterns and demographic history uses mtDNA analysis and provides useful evidence of the geographical origins of humans, likely population sizes, and migration patterns.(8)

Even when Baylis accepts that preserving the ability to carry out research on migration patterns and demographic history might not be of the highest social priority, she concludes by pondering why should we employ a biotechnology that has this detrimental effect when there are other means to create a family, for example adoption. If we were to accept her position then we would have to conclude that opting for a non-MRT reproductive option is the alternative that causes the least issues, since couples could still have children (genetically related to them or not) and the genealogical lines would not be obscured.

[3] In this paper, I focus on MRTs and mtDNA diseases, however, the arguments that I present equally apply to the use of MRTs to treat infertility caused by poor oocyte quality and poor embryonic development.

Baylis' argument can be presented in the following way:

1. Genealogical information provided by mtDNA is valuable for identity and research purposes.
2. MRTs obscure the genealogical information provided by mtDNA.
3. There are family making options that do not obscure the genealogical information provided by mtDNA.
4. When choosing between two options we should choose that which, other things being equal, creates the least disvalue.

From 1 to 4.

5. We should choose those family making options that do not obscure the genealogical information provided by mtDNA.

From 1 to 5.

6. We should not choose, other things being equal, MRTs as family making options since they obscure the genealogical information provided by mtDNA.

Let us, very briefly, examine the four premises: (1) is true in terms of genealogical research and in terms of narrative and social identity; (2) can be easily challenged, and I will do so in the next sections; (3) is true for reproductive choices such as adoption and full egg donation, for example; and (4) seems to be an intuitively plausible moral principle.

Before I move to the next section, I must clarify that the cross-generational effects of any genealogical obscurement are asymmetrical in respect to male and female MRT-conceived individuals. In the case of male MRT-conceived individuals, their mtDNA genealogical information would be, in the vast majority of cases, the only one that could be obscured. In the case of female MRT-conceived individuals, theirs and all their children's mtDNA genealogical information could be obscured, and this effect would spread across the maternal line.

HAPLOGROUPS AND MRTS

Before I explain why (2) is false let me first take a brief detour and say something about mitochondrial haplogroups and haplotypes. A haplotype is a group of DNA variations that tend to be inherited together. These variations in the DNA are so close that they tend not to recombine. In the case of mtDNA:

> There is substantial mtDNA sequence diversity between individuals and across human populations. Individuals can be classified by their mtDNA haplotypes, corresponding to the set of variant sequences, which in turn fall into particular haplogroups, based on characteristic sets of these polymorphisms. These haplogroups arose during human evolution and, in association with migrations of populations across the globe, became enriched in certain geographic regions".(3)

We could maintain that a haplogroup is a population who shares a common ancestor, and we know that haplogroups correlate with the geographic origins of populations as identified through maternal lineages. Currently over 5,400 haplogroups have been identified.(18)

Now, premise (2) fails because there are three possible relations between the haplotype of the MRT-conceived child and that of the intending mother and Baylis just pays attention to one: i.e. the case where the MRT-conceived child and the intending mother belong to different haplotypes. The second possibility is that the MRT-conceived child and the intending mother belong to the same haplotype. This situation attains, for example, if the intending mother asked someone from her maternal line (e.g. her sister), who she knows has healthy mitochondria, to donate eggs to her.[4] In this particular instance (2) would be false, since the genealogical information that could be obtained via the mtDNA of the intending mother and that which could be obtained via the mtDNA of the MRT-conceived child (i.e. via the egg donor's mitochondria) would be the same. Therefore, we need to conclude that not all instances of MRTs obscure the genealogical information provided by mtDNA.

A third possibility is that where the MRT-conceived child is heteroplasmic and thus has mitochondria that belongs both to the haplotype of the intending mother and the egg donor. In a previous publication I noted that "If very mild mitochondrial heteroplasmy [caused by mitochondrial carryover] is sufficient to identify both genealogical lines then the use of MRTs for reproductive purposes, as it caused such heteroplasmy, would not necessarily imply the obscurement of genealogical lines". (19) If we can identify the egg donor and the intending mother's mitochondria, then it might be possible to carry out un-obscured genealogical research. Of course, this depends on scientists being able to identify which mitochondria belongs to the intending mother and which to the egg donor.

What does current research on MRTs tell us about these three possibilities? All post MRT examined human embryos, so far, have been found to be *heteroplasmic* due to mitochondrial carryover. (15,17,20–23) There are several points to note. First, further refinement of such techniques could prove that it is possible to carry out an MRT where there is no mitochondrial carryover. At present, however, the amount of carryover depends on how each MRT procedure is carried out. Whereas Tachibana et al.'s MST experiments reported a maximum carryover of

[4] As previously stated, due to the way in which mitochondrial inheritance occurs not all members of a maternal line would necessarily have deleteriously mutated mitochondria.

.2%, the mitochondrial carryover in the first MST-conceived child was 5.7%.(22,23) Second, from the fact that we can identify heteroplasmy in the embryo it does not follow that we will be able to easily identify heteroplasmy in an adult, since mitochondria segregate stochastically among daughter cells during the development of the embryo.(24)

We must conclude that premise (2) is too strong and leads to the failure of Baylis' argument. In order for her argument to work she needs to amend (2) along the following lines:

> 2'. MRTs obscure the genealogical information provided by mtDNA when the MRT-conceived child and the intending mother do not belong to the same haplotype.

Once we have modified (2) we also need to soften the conclusion.

1. Genealogical information provided by mtDNA is valuable for identity and research purposes.
2'. MRTs obscure the genealogical information provided by mtDNA when the MRT-conceived child and the intending mother do not belong to the same haplotype.
3. There are family making options that do not obscure the genealogical information provided by mtDNA.
4. When choosing between two options we should choose that which, other things being equal, creates the least disvalue.

From 1 to 4.

5. We should choose those family making options that do not obscure the genealogical information provided by mtDNA.

From 1 to 5.

6'. We should not choose, other things being equal, MRTs when the MRT-conceived child and the intending mother would not belong to the same haplotype.

This conclusion (i.e. 6') leaves the door open for certain MRT procedures to be carried out. However, it is important to notice that if the above was accepted then the actual access to such biotechnologies will depend on other practical considerations, such as the availability of egg donors who match the intending mother's mitochondrial haplotype.

MRTs, REPRODUCTION, AND GENEALOGY

There is an implicit premise in Baylis' argument that she, and the objection that I raised in the previous section, accept as true. This is, in the case of MRT-conceived children the only *true* (i.e. un-obscured) mtDNA genealogical information is that which comes from the intending mother's mitochondrial haplotype. What reason(s) can be provided for accepting such implicit premise?

The reason that needs to be provided for accepting it is that MRTs are not reproductive in nature, and thus no genealogy is created. In other words, in PNT and MST the egg donor *does not reproduce*. John Harris, for example, is among those who think that MRT-conceived children do not have three genetic parents: "Although children might be confused if they are told that they have three genetic parents [due to MRTs], only a very confused person would think—let alone say—any such thing".(25) If this were true, and since it is reproduction which establishes genealogical lines, then we have to accept that the information that can be obtained from the MRT-conceived child (supposing it comes from the egg donor's mitochondria) is, in strict sense, non-genealogical. An analogy here might be helpful, trying to obtain mtDNA genealogical information from an MRT-conceived child, whose mitochondria have their origin in the egg donor's mitochondria, would be analogous to trying to obtain someone's mtDNA genealogical information from cells sampled from a transplanted kidney which was donated by a non-relative. It is true that the organ donor and the organ recipient could belong to the same haplogroup but this would only be accidental.

What Harris, and others, defend is that the egg donor, for an MRT procedure, is a type of organ donor. This position has been endorsed most recently, for example, by the Community Affairs References Committee of the Australian Senate: "The committee considers that an mtDNA donor should be conceptualised as being similar to an organ donor".(26) And it is true that organ donation does not establish genealogical lines.

Interestingly, Baylis does not accept the organ donation position. She asserts:

> while it is undeniably true that the egg provider who contributes the healthy mtDNA provides less than 0.1% of the total genetic make-up of the newborn, this fact is irrelevant to the accuracy of the claim that there are three genetic parents. All that is relevant to this issue is the presence or absence of identifiable genetic material from someone other than the two individuals identified as genetic parents.(8)

Baylis holds a contradictory position here. On the one hand, she holds that MRTs generate children with three genetic parents, and, on the other, that the mitochondria of MRT-conceived children (which originated in the egg donor) produce false genealogical information. In order to be consistent she needs to reject one of such stances, and which stance is to be rejected seems to depend on which account of reproduction we consider to be the correct one. If MRTs are indeed reproductive in nature then any mtDNA genealogical information obtained from an MRT-conceived individual would not obscure the lines of individual descent.

Baylis does not explicitly present an account of reproduction, however, we could try to guide ourselves by the previous quote to further elaborate on whether MRTs are reproductive. A problem with the previous quote is that it is too ambiguous. For example, it leads to the implausible conclusion that unrelated organ donors *become* genetic parents of the people to whom they donate organs. If a 20-year-old donates a kidney to a 40-year-old then the former becomes the genetic parent of the latter. Why? Because in the 40-year-old we would be able to identify three sources of genetic material. But this would be absurd. Now, given that Baylis has not presented a fully fleshed out account of reproduction, we can turn to other accounts of reproduction.

Heidi Mertes and Guido Pennings (27) have tried to answer the question of whether new 'reproductive techniques' are indeed reproductive in nature. In order to achieve this, they have offered a criterion of genetic parenthood that establishes three conditions: a) the passing of genetic information, as physical entities, to the next generation; b) causing existence; and c) the reshuffling of different genomes. They formalized their account in the following way:

> *X is considered a genetic parent of Y if (i) X passes on genetic information to Y, (ii) X is a physical cause of Y's existence, and (iii) X's physical genes were reshuffled once to constitute Y* [emphasis in the original].(27)

According to such an account the MRT egg donor is not a genetic parent, and thus genealogy is not established. She is not so because she does not meet the third condition (i.e. that her physical genes were shuffled once to constitute the MRT-conceived child), in that the mtDNA does not reshuffle at all. However, the egg donor meets the first condition in that she passes genetic information to the MRT-conceived child, and she meets the second condition in that she is a physical cause of the MRT-conceived child's existence, as I will explain next. If we were to accept Mertes and Pennings account of genetic parenthood then we would have to accept that MRTs are not reproductive in nature, and they do in fact obscure genealogical research via mtDNA. One exception to the obscurement point, albeit accidental, is when the intending mother and egg donor's mitochondrial haplotype match.

Nevertheless, Mertes and Pennings's account of genetic parenthood is found wanting, because it – incongruously – allows for someone to become the genetic parent of an already existing individual. Imagine the following case, Arnold and Alma approach Ben, a fertility specialist. In his fertility clinic he uses intracytoplasmic sperm injection (i.e. a technique where a sperm is injected directly into an egg) to produce embryo C. Rather than transferring embryo C, Ben

decides to wait until the third day and grafts C with one of his (Ben's) cells. This particular cell has been previously genetically modified. Ben has employed a gene editing technique to reshuffle his cell's nuclear genome. Finally, at the fourth day he transfers C to Alma's womb.

Under Mertes and Pennings' account Ben becomes the genetic parent of C at the third day of its existence. This is so given that Ben passes on genetic information to C; he is a physical cause of C's existence (he inserted Arnold's sperm into Alma's oocyte); and Ben's physical genes were reshuffled previous to the grafting.[5] Mertes and Pennings' account of reproduction allows for a fertility doctor to become the progenitor of *an already existing individual* but, as Peter Godfrey-Smith puts it, reproduction is making a new individual.(28)

Philosopher of biology James Griesemer (29–31) has advanced an account of reproduction that is all encompassing and not restricted to human reproduction, which is Mertes and Pennings' only aim. In order for his account to align with the theory of evolution by natural selection Griesemer's account admits novelty, is flexible, and it allows for progenitors and offspring to resemble. Griesemer's account entails two conditions:

> Reproduction is a process with two aspects: *progeneration* and *development.* Progeneration is the multiplication of entities with *material overlap* of old (parent) and new (offspring) entities. Material overlap means that some of the parts of the offspring were once parts of the parent. (29)

And

> The acquisition of the capacity to reproduce is the process of development.(29)

According to Griesemer's account of reproduction, the MRT egg donor *in fact reproduces,* she does so because there is material overlap between her and the MRT-conceived child, some parts of her are now parts of the offspring. Additionally, the energy production role of the mitochondria is necessary for the MRT-conceived child to develop her own capacity to reproduce (or in other words, to restart the process of material transfer). Finally, Griesemer's account of reproduction is not vulnerable to the previous counter-example. It is not so because

[5] At this point someone could argue that I am misinterpreting Mertes and Pennings' account, since (iii) states that the physical genes need to be reshuffled once to constitute Y. I am not being uncharitable. I have decided to interpret (iii) only as entailing reshuffling, because in human reproduction (which is what they are discussing) the reshuffling of genes does not happen during the fertilization process, but during gamete generation. This means that during fertilization no genes are reshuffled to constitute a new individual.

he defines 'multiplication' as "the process by which more entities are produced", and this does not happen in the fertility treatment case.(31)

Before I move forward, I need to answer the question of whether the different MRT procedures produce more entities or not. If it were to be the case that no more entities are produced then we would have to accept that MRTs are more akin to organ transplantation, since they do not satisfy Griesemer's first condition. However, PNT and MST indeed produce more entities, thus satisfying the first condition. This happens because the enucleation process destroys the eggs (qua cells) and zygotes (qua organisms), and the subsequent transfer of nuclear material creates new beings (i.e. a new egg or new zygote). This position has been successfully defended by Mathew Liao, who also argues that eggs are essentially cells and zygotes[6] are essentially organisms:

> a) an egg [zygote] begins to exist when the capacity to regulate and coordinate the various life processes is there; b) the egg [zygote] persists as long as there is what may be called 'cellular [organismic] continuity', which is the continuing ability to regulate and coordinate the various life processes; c) the egg [zygote] ceases to exist when the capacity to regulate and coordinate the various life processes is permanently gone." (34)

Now, the enucleation process destroys the eggs and zygote's ability to regulate and coordinate the different life processes, since it depends on the interaction between the nuclear DNA and the mtDNA. Most saliently, eggs and zygotes cannot carry out their metabolic processes without the correct interaction between the nuclear DNA and the mtDNA (which is why the MRT procedure is needed in the first place).

Once we have concluded that the MRT egg donor in fact reproduces (i.e. there is progeneration and development) then we can further conclude that all the mtDNA genealogical information of an MRT-conceived individual is proper genealogical information. What happens here is that MRT-conceived individuals have two genetic mothers, the egg donor and the intending mother, and this opens the possibility for them to have one or two mtDNA lineages (let us remember that the genetic mothers could belong to the same or different haplotypes).

CONCLUSION

Since the MRT egg donor is in fact a genetic parent then all the genealogical information that could be obtained via the MRT-conceived individual is *true* genealogical information. This

[6] For a full defence of why zygotes are organisms see: (32,33)

entails that genealogical research via mtDNA, both for identity purposes and for historical and anthropological ends, is not upended by MRTs. What has happened here is that we have developed biotechnological means by which three people can reproduce. And MRT conceived children can have three ancestry lines: paternal line, the nucleo-mito-maternal line, and the mito-maternal line. How these lines are to be traced is a different question to how many ancestry lines exist. Finally, MRTs require that we make a small but substantial change in how we conceive our ancestry and the ways in which it can be traced.

References

1. Hamzelou J. Exclusive: World's first baby born with new "3 parent" technique [Internet]. New Scientist. 2016 [cited 2016 Oct 3]. Available from: https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/

2. Coghlan A. First baby born using 3-parent technique to treat infertility [Internet]. New Scientist. 2017 [cited 2017 Feb 21]. Available from: https://www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/

3. Greenfield A, Braude P, Flinter F, Lovell-Badge R, Ogilvie C, Perry ACF. Assisted reproductive technologies to prevent human mitochondrial disease transmission. Nat Biotechnol. 2017 Nov 9;35(11):1059–68.

4. Dupras-Leduc R, Birko S, Ravitsky V. Mitochondrial/Nuclear Transfer: A Literature Review of the Ethical, Legal and Social Issues. Can J Bioeth Rev Can Bioéthique. 2018 Feb 23;1(2):1–17.

5. Luo S, Valencia CA, Zhang J, Lee NC, Slone J, Gui B, et al. Biparental Inheritance of Mitochondrial DNA in Humans. Proc Natl Acad Sci. 2018 Dec 18;115(51):13039.

6. Bender K, Schneider PM, Rittner C. Application of mtDNA sequence analysis in forensic casework for the identification of human remains. Forensic Sci Int. 2000;113(1–3):103–7.

7. Duster T. Ancestry testing and DNA: Uses, limits–and caveat emptor. In: Genetics as social practice. Routledge; 2016. p. 75–88.

8. Baylis F. The ethics of creating children with three genetic parents. Reprod Biomed Online. 2013 Jun;26(6):531–4.

9. Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, McFarland R, et al. Mitochondrial diseases. Nat Rev Dis Primer. 2016 20;2:16080.

10. Babayev E, Seli E. Oocyte mitochondrial function and reproduction. Curr Opin Obstet Gynecol. 2015 Jun;27(3):175–81.

11. Taylor RW, Taylor GA, Durham SE, Turnbull DM. The determination of complete human mitochondrial DNA sequences in single cells: implications for the study of somatic mitochondrial DNA point mutations. Nucleic Acids Res. 2001 Aug 1;29(15):e74–e74.

12. Klopstock T, Klopstock B, Prokisch H. Mitochondrial replacement approaches: challenges for clinical implementation. Genome Med. 2016 Nov 25;8:126.

13. Craven L, Murphy J, Turnbull DM, Taylor RW, Gorman GS, McFarland R. Scientific and Ethical Issues in Mitochondrial Donation. New Bioeth. 2018 Jan 2;24(1):57–73.

14. Hyslop LA, Blakeley P, Craven L, Richardson J, Fogarty NME, Fragouli E, et al. Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. Nature. 2016 Jun 8;

15. Craven L, Tuppen HA, Greggains GD, Harbottle SJ, Murphy JL, Cree LM, et al. Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. Nature. 2010 May 6;465(7294):82–5.

16. Tachibana M, Sparman M, Sritanaudomchai H, Ma H, Clepper L, Woodward J, et al. Mitochondrial gene replacement in primate offspring and embryonic stem cells. Nature. 2009 Sep 17;461(7262):367–72.

17. Yamada M, Emmanuele V, Sanchez-Quintero MJ, Sun B, Lallos G, Paull D, et al. Genetic Drift Can Compromise Mitochondrial Replacement by Nuclear Transfer in Human Oocytes. Cell Stem Cell. 2016 Jun 2;18(6):749–54.

18. Kivisild T. Maternal ancestry and population history from whole mitochondrial genomes. Investig Genet. 2015 Mar 10;6(1):3.

19. Palacios-González C. Mitochondrial replacement techniques: egg donation, genealogy and eugenics. Monash Bioeth Rev. 2016 Jul 28;34(1):37–51.

20. Hyslop LA, Blakeley P, Craven L, Richardson J, Fogarty NME, Fragouli E, et al. Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. Nature. 2016 Jun 16;534(7607):383–6.

21. Kang E, Wu J, Gutierrez NM, Koski A, Tippner-Hedges R, Agaronyan K, et al. Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. Nature. 2016 Dec 8;540(7632):270–5.

22. Tachibana M, Amato P, Sparman M, Woodward J, Sanchis DM, Ma H, et al. Towards germline gene therapy of inherited mitochondrial diseases. Nature. 2013 Jan 31;493(7434):627–31.

23. Zhang J, Liu H, Luo S, Lu Z, Chávez-Badiola A, Liu Z, et al. Live birth derived from oocyte spindle transfer to prevent mitochondrial disease. Reprod Biomed Online. 2017 Apr;34(4):361–8.

24. Wai T, Teoli D, Shoubridge EA. The mitochondrial DNA genetic bottleneck results from replication of a subpopulation of genomes. Nat Genet. 2008 Dec;40(12):1484–8.

25. Harris J. Germline Modification and the Burden of Human Existence. Camb Q Healthc Ethics CQ Int J Healthc Ethics Comm. 2016 Jan;25(1):6–18.

26. Community Affairs, References Committee of the Australian Senate. Science of mitochondrial donation and related matters. Australia; 2018 Jun.

27. Mertes H, Pennings G. Embryonic stem cell-derived gametes and genetic parenthood: a problematic relationship. Camb Q Healthc Ethics. 2008;17(1):7–14.

28. Godfrey-Smith P. Darwinian Individuals. In: Bouchard F, Huneman P, editors. From Groups to Individuals: Perspectives on Biological Associations and Emerging Individuality. Cambridge, Massachusetts: MIT Press; 2012. p. 17–36.

29. Griesemer J. Reproduction and the reduction of genetics. In: Beurton P, Falk R, Rheinberger HJ, editors. The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives [Internet]. New York: Cambridge University Press; 2000 [cited 2017 Jun 2]. p. 240–85. Available from: https://genericgenetic.umn.edu/content/reproduction-and-reduction-genetics

30. Griesemer J. Development, Culture, and the Units of Inheritance. Philos Sci. 2000 Sep 1;67:S348–68.

31. Griesemer J. The units of evolutionary transition. Selection. 2000;1(1–3):67–80.

32. Liao SM. The Organism View Defended. The Monist. 2006;89(3):334–50.

33. Liao SM. Twinning, Inorganic Replacement, and the Organism View. Ratio. 2010 Mar 1;23(1):59–72.

34. Liao SM. Do Mitochondrial Replacement Techniques Affect Qualitative or Numerical Identity? Bioethics. 2017 Jan 1;31(1):20–6.