Translated Article

A bioethical discussion of issues inherent to mitochondrial replacement and having "three genetic parents"*

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Abstract

In February 2015, the U.K. became the first nation in the world to legalize the so-called "mitochondrial replacement" procedure for egg cells of patients with mitochondrial disease. Given the possibility that Japan may also seek approval to use this technology, the present study aimed to organize thoughts and discussion points put forth by previous studies concerning the ethical aspects of mitochondrial replacement technology. One main consideration presented here pertains to the unique bioethical issue created by this technology; namely, the birth of children with "three genetic parents." I have added my thoughts and discussion points.

With regard to mitochondrial replacement technology, I conclude that the following four issues should be taken into consideration: 1) safety, 2) the likelihood of further application, 3) the child's identity, and 4) "three genetic parents." This paper takes a particularly close look at 4), as I consider whether mitochondrial replacement would in fact create "three genetic parents," and whether it would even be ethically problematic if a child was born to "three genetic parents."

Key words: mitochondrial replacement, three genetic parents, mitochondrial DNA, assisted reproduction technology (ART), bioethics

1. Introduction

1-1. Background

Diseases caused by reduced function of mitochondria, organelles that produce energy in cells, are collectively named "mitochondrial disease" [1-6]. The pathology of mitochondrial disease varies, with some affecting nerves or muscles, others causing severe symptoms in organs such as the heart, and some that can be fatal.

In February 2015, the U.K. passed the first bill ever to allow the use of egg cells in new technologies that would prevent mitochondrial disease to be passed on genetically to the children of women with mitochondrial disease [7]. These new technologies can be described as those that aim to prevent the onset of mitochondrial disease by replacing

mitochondria in an egg cell from a mother who could genetically pass on mitochondrial disease, with that donated by a third party. Collectively, these technologies are known as mitochondrial replacement or mitochondrial transplantation.

While mitochondrial replacement is anticipated by patients and their families to bypass the possibility of mitochondrial disease onset while still having a child with the same genetic background as the parents, some voices within the U.K. remain opposed to this. For example, the Church of England has spoken out against the technology, on the grounds that mitochondrial replacement will lead to the genetic alteration of the next generation [8].

According to a survey conducted in 2012, the number of patients with mitochondrial disease in Japan was reported to be 1087 [9], but given the difficulty of diagnosing this illness, some have estimated higher numbers [1]. In the U.K. and other Western nations, it is said that 1 in anywhere from several thousand to 10-20,000 patients is afflicted [1]. Regardless, a good number of those afflicted by or who are carriers of mitochondrial disease face the risk of genetically passing this disease on to their offspring. Thus, Japan may also seek to use this technology in the future.

As mentioned above, passage of the bill in the U.K. was accompanied by an examination of this issue by the Nuffield Council on Bioethics (an independent council that specializes in debates on bioethical issues), and the Human Fertilisation and Embryology Authority (HFEA), the latter of which includes laypersons. Thus, legalization was preceded by years of cumulative arguments surrounding this matter [10-12]. If Japan is headed toward considering the introduction of this technology, then we anticipate that serious ethical evaluation will become necessary. In addition, close scrutiny over the ethical aspects of mitochondrial replacement may help to shed some light on issues that have not yet been considered much in the field of bioethics. One topic that will be discussed below is that of potential issues involved in creating a child with “three genetic parents.” In addition to mitochondrial replacement presenting new issues to the field of bioethics, this issue also simultaneously asks a question that cannot be ignored or addressed by conventional perspectives concerning the value of genetic linkages in our society and the ideal relationship between parent and child. In past ethical discussions on assisted reproductive technology, the arguments about genetic associations were based on the nuclear DNA and its dissociation within the lineage. However, mitochondrial replacement technology brings into question genetic associations based on mitochondrial DNA as well as the significance/implications of dissociation.

1-2. Present study objectives and methods

Against this backdrop, I conducted a literature review and present a critical discussion of ethical issues surrounding mitochondrial replacement when this technology is used as a way to prevent the genetic continuation of mitochondrial disease. My specific aim with the present study was to clarify the following two points. First, I aimed to understand and organize the main arguments that have been made thus far concerning ethical issues with mitochondrial replacement. Building

upon this, I aimed to evaluate specifically the discussion thus far concerning the creation of a child with "three genetic parents" and the bioethical ramifications unique to the technology of mitochondrial replacement. I also present my own opinions and thoughts on this matter. The current reality in Japan is that very little ethical discussion has occurred surrounding mitochondrial replacement. As such, the ultimate objective of article below is to pave the way for discussions to progress on the pros and cons of mitochondrial replacement in Japan.

To this end, I must first acquire an accurate understanding of mitochondrial disease and the technology of mitochondrial replacement. The following chapter presents an overview of this technology and a basic explanation of mitochondrial disease.

2. Mitochondrial disease, mitochondrial replacement, and alternative measures

Genes of the several hundred proteins that reside in mitochondria are encoded by nuclear DNA, but each mitochondrion also houses 5-10 mitochondrial DNA (mtDNA). The mitochondrial genome is roughly 16.6 kbp in length and encodes 13 types of proteins [2-6][i]. Mitochondrial disease can be caused by genetic mutations in nuclear DNA as well as qualitative/quantitative abnormalities in mtDNA. Some also suspect an interaction between nuclear DNA and mtDNA.

At the time of fertilization, mitochondria within the father's sperm either never enter the egg or are destroyed in the process of doing so. Consequently, mitochondria within an individual's cells originate from the maternal egg cell, and each mature egg typically contains several hundred mitochondria. However, the proportion of mitochondria with abnormalities differs even between eggs from the same mother; therefore, even fertilized eggs from the same mother vary in the likelihood for mitochondrial disease onset.

Representative mitochondrial diseases include chronic progressive external ophthalmoplegia (CPEO); mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); myoclonus epilepsy associated with ragged-red fibers (MERRF), and Leigh's disease. The pathology and progression of mitochondrial disease vary widely, but many forms of the disease result in the onset of disorders in emotional, cognitive, or muscular development; MELAS and Leigh's disease in particular can be fatal. With the exception of CPEO, the diseases mentioned above involve specific mutations in mtDNA, and it is known that a mutation in mtDNA is involved for CPEO as well. Curative treatments are not currently available for these diseases, and thus treatment focuses on supportive measures.

Onset of mitochondrial disease brought about by mutations in mtDNA might be prevented by replacing the mutated mitochondria within the egg cell with healthy mitochondria. The two specific mitochondrial replacement methods approved for use in the U.K. include maternal spindle transfer (MST) and pronuclear transfer (PNT)[13][ii]. In MST, the

[i] Details related to mitochondrial disease below are summarized from References 2-6.

[ii] Descriptions hereafter on methods of mitochondrial replacement are based on explanations from Reference

spindle that contains nuclear DNA is removed from an egg donated from a third party, and the spindle extracted from the intended mother's egg cell is transplanted into the donor's egg. Sperm from the intended father is then used to create a fertilized egg through in vitro fertilization. In PNT, the egg from a donor undergoes in vitro fertilization with sperm from the intended father to create a fertilized egg, from which the two pronuclei (the nuclei from the sperm and the egg that have not yet fused after fertilization) are removed. Meanwhile, the two pronuclei harvested from a fertilized egg from the intended parents are transplanted into the enucleated fertilized egg (created by the donor and father).[iii]

Aside from mitochondrial replacement, preimplantation genetic diagnosis (PGD) or prenatal diagnosis (or elective abortions) may also prevent mitochondrial disease from being genetically transmitted to future generations. Using an egg donor is certainly possible, but this approach would mean that the intended mother would have no genetic link to the child. Needless to say, each of these alternative technologies comes with its own unique set of ethical challenges.

3. Ethical concerns with mitochondrial replacement

The main ethical issues about mitochondrial replacement as highlighted by previous studies are 1) safety, 2) the likelihood for further application of this technology, 3) identity of the child created by this technology, and 4) "three genetic parents." Below, I organize some simple argument points.

3-1. Issues related to the safety of mitochondrial replacement

When applying a novel medical technology to humans, the first issue to emerge is safety. Mitochondrial replacement is no different, and voices of concern have been raised about the safety of this technology. Baylis organized concerns about the dangers of mitochondrial replacement in the following four categories: 1) harm toward the egg donor, 2) harm to the child or future generations, 3) harm to select individuals with special interests in mitochondria-based lineage research, and 4) harm to society [14]. While 1) represents a problem that resides in the entire area of assisted reproductive technology that requires egg donors, 2)-4) are issues unique to mitochondrial replacement.

It is not necessarily clear how the child born from mitochondrial replacement will be affected, if at all, and whether the effects (if any) will be observed in their own children. This concern for harm to the child or future generations is at the heart of 2) and has become a major focal point of the discussion in the U.K.. There is some concern that the original (mutated) mitochondria are not eliminated completely, which would allow for the development of mitochondrial disease, or that the complexities of the mutual interactions between nuclear DNA and mtDNA will create some other effects beyond what could be anticipated [11]. Various effects have been reported in experiments using

13.

[iii] Therefore, while the present paper cannot provide details on this, as one fertilized egg is destroyed through the process of mitochondrial replacement in cases of PNT, issues emerge concerning the moral status of the fertilized embryo.

mouse models [15].

The individuals noted in 3) with special interests in this matter include genealogical researchers and historical/anthropological researchers of human migration, for whom mitochondrial replacement technology that severs the mtDNA of the maternal line may disrupt their research. Baylis acknowledges that this risk is extremely low, but still questions whether obstructing their freedom in research is acceptable, especially if there are alternate ways around the use of this technology (e.g., PGD).

Japan is considering the possibility of using autologous transplantation of mitochondria as infertility treatment [16], but there are so many other applications of mitochondrial replacement technology to which this could lead, and the effects on society from some of these would not be small—this is concern 4): harm to society. In section 3-2, I discuss the effects of this technology on other technologies and point out that perhaps I should be spending human and financial resources on more highly prioritized diseases affecting a greater number of patients [14].

Some have argued that the concerns described above are significant enough to keep this technology from moving forward [14, 17]. On the one hand, some would argue that new medical technology is going to accompany risk, and what is needed is not so much a prohibition altogether, but rather an extremely careful approach to research [18, 19]. The U.K. Department of Health and the Nuffield Council have called for careful execution of the procedure and follow-up with children born using this technology, acknowledging that its safety cannot be guaranteed 100% [13, 20].

3-2. Concerns that this technology will lead to further applications

As noted above, in addition to the risk to the child created by this technology, other concerns remain about the possibility of mitochondrial replacement leading to the application of other technologies as well. One example is using this technology as an infertility treatment (see above), but of the various applications, the biggest concern is its use in genetic engineering [10, 14, 21]. Even though the contribution of mtDNA to phenotype is small, we are certainly manipulating and changing genetic information that is to be inherited by the next generation(s). The first question is whether or not an important moral difference exists between the manipulation or engineering of mtDNA versus that of nuclear DNA. The British Department of Health and some others have established that the two are clearly different issues [20]. Bredenoord et al. state that, from the perspective of “the child’s right to an open future,” there is no critical or moral difference in manipulating mtDNA versus nuclear DNA [22]. The argument is ongoing among medical specialists about whether or not a delineation should be made between diseases involving mtDNA and those that do not [23]. Clearly, the question about whether manipulation of mtDNA differs from that of nuclear DNA is not easily answered.

In addition, even if a delineation could be made, some concern remains about the possibility that permitting mitochondrial replacement would pave the way for genetic engineering of nuclear DNA as well. Even if mitochondrial replacement does not serve the

purpose of genetic enhancement or engineering, the aim of disease prevention alone—as an attempt to manipulate the next generation's genetic characteristics—opens up the possibility for genetic engineering of the next generation, as well as enhancement-type interventions such as designer babies or the practice of eugenics [10, 14, 21, 24].

The concerns described thus far do not deem mitochondrial replacement as unethical, but rather represent some hesitancy to open the door to other potentially unethical acts that would be enabled by permitting mitochondrial replacement—in other words, it is a slippery slope argument. In general, for a slippery slope argument to become validated, the validity of the speculative theory and the unethicality of the premise become important [25]. While I will not argue the validity of the speculative theory of the present argument, I do wish to point out the importance of knowing whether or not the unethicality of the premise is clear. In other words, mitochondrial replacement to increase the chances of getting pregnant, genetic engineering of nuclear DNA, enhancement interventions and (new) eugenics practices are all technologies that could be argued both for and against, and we may not be able to state firmly that any one of these is necessarily unethical. Because of this, the unethicality of the premise may not always be obvious, and the slippery slope approach may present insufficient grounds for this argument. At the very least, this warrants a discussion centered on the ethics of mitochondrial replacement and careful scrutiny of the practice of technologies that involve these matters.

3-3. Mitochondrial replacement and identity issues in a child screated by this technology

Another issue is the identity of the child born as a result of mitochondrial replacement. In other words, can a child born from an embryo that underwent mitochondrial replacement embody the same identity as if s/he had not undergone mitochondrial replacement? According to the Nuffield Council, 99.9% of the genetic characteristics of a child are determined by nuclear DNA, so mtDNA would not influence an individual's identity [13].

In the above argument, the debate focuses on the issue of numerical identity—i.e., identity in the sense that at two separate points in time, one's existence remains the same. However, as the Nuffield Council has widely discovered, there is great diversity in the concept of identity. Therefore, if, for example, an individual's identity is determined by the world in which s/he lives, or by their own personal narrative rather than by their genes (i.e., narrative identity), then we could conclude that their identity would be changed by the presence or absence of mitochondrial replacement [14]. This is because the raw narrative of Child α born from Mr. A's sperm and Ms. B's egg versus that of Child α' born from Mr. A's sperm, Ms. B's egg nucleus, and Ms. C's mitochondria will be different, particularly with regard to the presence of mitochondrial disease, whether a non-parent third party was involved in their birth or not, and issues with the disclosure of these facts.

Of course, some questions remain as to whether this sort of influence on identity is always unethical or not [26]. To use an example of someone undergoing an organ transplant, as

long as receiving a transplanted organ will not (figuratively, at least) render an individual as a different existence, then we cannot conclude that one's numerical identity has undergone a change before and after the transplant. On the other hand, if the individual's life narrative and world are changed dramatically by undergoing the transplant or not, then we would conclude that the narrative identity is changed by the transplant. Generally speaking, this type of change in narrative identity is not considered to render transplant medicine unethical. If a similar argument can be made for mitochondrial replacement, then trying to decree that this technology is unethical due solely to changes in narrative identity would be difficult.

3-4. Issues with "three genetic parents"

As described above, a child born as a result of mitochondrial replacement has nuclear DNA from the sperm, nuclear DNA from the intended mother's egg, and mtDNA from the donor. This has led to the criticism that mitochondrial replacement is the first technology ever to create a child with "three genetic parents" [27]. The term "three genetic parents," or "tri-parent" has become commonplace among the press both domestically and abroad, when commenting on mitochondrial replacement [7, 28, 29]. The U.K. Department of Health and the Nuffield Council have criticized the use of this term, however, opining that it is inappropriate [13, 20].

At least two thoughts must be considered when offering the criticism that "mitochondrial replacement creates a child with three genetic parents." The first is the obvious matter of whether or not mitochondrial replacement does, in fact, create a child with "three genetic parents." Second, even if we can affirm that it does give rise to a child with three genetic parents, is this in it of itself unethical? As discussed in section 1-1, these points are new issues that have been presented to the field of bioethics by the arrival of mitochondrial replacement technology. They are also questions that should be considered from non-conventional angles with regard to the value of genetic linkage and the ideal relationship that should exist between parent and child. For the remainder of this paper, I will focus the discussion on these two specific points.

4. "Three genetic parents," the value of genetic linkage, and the implications of severing this

4-1. Does mitochondrial replacement lead to the birth of a child with "three genetic parents?"

As discussed above, the U.K. Department of Health and the Nuffield Council have expressed some negative opinions pertaining to the term, "three genetic parents":

> *"Genetically, the child will, indeed, have DNA from three individuals but all available scientific evidence indicates that the genes contributing to personal characteristics and traits come solely from nuclear DNA, which will only come from the proposed child's mother and father. The donated mitochondrial DNA will not affect those characteristics."* (U.K. Department of Health, 2014, page 15).

As reflected in this excerpt, the U.K.

Department of Health and the Nuffield Council consider it problematic to label a mitochondrial donor as a 'parent,' given the low power of influence that mtDNA has on an individual's characteristics and form. At a workshop targeting individuals from the general public that was conducted by the HFEA as part of the process of policy-making, participant responses were consistent with this opinion, as demonstrated by the high number of those who felt that the term "three genetic parents" was inappropriate, based on the little amount that would be contributed genetically to the child from the donor's mtDNA [30]. However, while both the U.K. Department of Health and the Nuffield Council have these opinions concerning genetic linkages, they also do not necessarily deny the presence of emotional linkages altogether. Actually, that which partially protects a child's right to know their origins (albeit in a limited manner from anonymous information, etc.) offers medical benefits in addition to the emotional linkages.

Baylis rebuts this from the perspective of narrative identity [14]. Specifically, she argues that Child α, born as a result of Mr. A's sperm and Ms. B's egg, will constitute an entirely different individual from Child α', born from Mr. A's sperm, Ms. B's egg, and Ms. C's mitochondria. In so far as Child α and Child α' are different individuals, it can be said that there are three parents, including the mitochondrial donor Ms. C.[iv]

Indeed, while the contribution of mtDNA to an individual's phenotype is low, there are cases in which mtDNA plays a decisive role in the development of mitochondrial disease. Therefore, in some cases, an entirely different life could be anticipated as a result of the influence of mtDNA; naturally, a different personality and identity would also develop [22].

That said, even if Child α and Child α' were to have different identities, this is not a valid reason to conclude that mitochondrial donor Ms. C should be labeled as a parent to Child α'. At the very least, most would generally be reluctant to call her a genetic parent, primarily because if Ms. C should be considered a genetic parent in these instances, then there are others to whom the same label should be applied. However, labeling the mtDNA donor as a parent in some of those cases may force us to make some conclusions that would generally go against our intuition.

Such cases would include those of somatic cell cloning with the aim to reproduce (hereafter, reproductive cloning). In reproductive cloning, mtDNA has a different origin from that of the nuclear DNA, unless the woman uses her own egg cell or another egg donor such as her mother or sister with the same maternal genetic background. Therefore, if the mitochondrial donor in mitochondrial replacement is labeled a genetic parent, then the egg donor in reproductive cloning should also be labeled as such, to avoid inconsistencies. However, within the context of reproductive cloning, those who would consider a mtDNA donor (i.e., an egg donor) as a parent are certainly not in the

[iv] In cases for which the mitochondrial donor is from the same maternal lineage as the egg donor (e.g., a mother or sister), they will have similar if not the same mtDNA. Thus, in actuality, there will be two genetic parents. However, most of these cases do not allow for the possibility of bypassing mitochondrial disease, so I have excluded them from my present discussion.

majority.

Of course, with reproductive cloning, dramatic differences in phenotype are not anticipated simply due to differences in mitochondria. In this regard, one may argue that an important moral difference exists between reproductive cloning and mitochondrial replacement. Conversely, perhaps some would advocate that egg donors in reproductive cloning are labeled parents as well. However, (while this is doubtful given the argument trajectory thus far), even if a child were to be born with "three genetic parents" through mitochondrial replacement, we could not confidently conclude that something unethical has occurred. If this is true, then the simple fact that a child is born with "three genetic parents" cannot be the sole reason to deem mitochondrial replacement an unethical procedure.

4-2. Revisiting the ethics of creating a child with "three genetic parents"

Let us open up the discussion anew with regard to whether there are any ethical issues with creating a child who would be born to "three genetic parents." First, unless we feel the need to adhere so tightly to the original definition of the term "genetic," then it could be said that many children in modern-day society have three or more people whom they could call 'parents' [31]. For various reasons and circumstances, there are some children for whom their so-called biological/genetic parents differ from those who raised them (i.e., social or 'adopted' parent). For example, the couple that gave birth to the child may encounter a situation in which they are forced, for whatever reason, to leave the child to be raised by another couple. In this case, this child would have four adults that could be considered "parents."

However, in the case described above, the child may not necessarily have three (or more) parents from the stage of birth and beyond. On the one hand, mitochondrial replacement necessitates that three human beings are involved in the child's birth. However, in modern-day assisted reproductive technology, similar circumstances can emerge in several cases. One typical example would be the case in which a sperm or egg is donated from a third party in order to have a child [31]. In this case, the child would have the two adoptive parents that raised him/her in addition to the genetic parent that is the donor for one of the spouses, resulting in a total of three or more parents. In cases involving surrogate mothers, one may even argue that multiple individuals could be considered parents to this child [32]. Admittedly, opinions are quite split in Japan with regard to the technology requiring a third-party egg or sperm donor and surrogate mothers. The problems embodied by this technology that would likely overlap with problems inherent to mitochondrial replacement include confusion about family values or discrimination toward children born through this technology. However, whether or not these demerits are so severe as to outweigh the alternative of the child not existing requires further discussion. In the context of mitochondrial replacement, if Child α and Child α' were to embody different numerical identities, then Child α' would essentially be non-existent if this technology was not employed. If different numerical identities are not assumed for Child α and Child α', then Child α (= Child α') would benefit from being able to avoid the serious

disease that is mitochondrial disease, through the application of mitochondrial replacement. Johnson opines that the ability to avoid mitochondrial disease in this manner, or, at the very least, to have the potential to do so, outweighs the demerits associated with having three parents [18].

In sum, if we do not adhere too tightly to the semantics of the term "genetic" when describing parents, we must acknowledge the existence of quite a few children with three (or more) adults who could be called 'parents,' and that this is not unique to mitochondrial replacement. However, when considering a third-party egg or sperm donor through the same lens, having three parents from mitochondrial replacement is ethically problematic in cases for which A) the demerits are so severe that it would be better if the child did not exist, or B) the demerits far outweigh the merits associated with the ability to bypass mitochondrial disease. That said, it is not always obvious that the demerits associated with having three parents far outweigh the merits of being able to avoid mitochondrial disease.

4-3. The value of mtDNA linkage and nuclear DNA linkage

Thus far, I have delved into the two arguments of whether mitochondrial replacement will give rise to the birth of children with three genetic parents (section 4-1), and whether or not giving birth to a child with three genetic parents is, in fact, ethically problematic (section 4-2), both issues of which are related to the existence of "mitochondrial donors" and "genetic parents." Consider, however, how the "mitochondrial recipient," i.e., the woman or couple requesting the transplant, might view this issue. As mitochondrial replacement would involve a female seeking a nuclear DNA linkage, some might view this as a technology that (in the opposite manner) severs the mtDNA linkage. Thus, as a final argument, we will discuss issues with mitochondrial replacement and genetic parents as viewed from recipients of the mitochondrial replacement technology. However, given my limited ability to discuss this matter thoroughly, I will only briefly point out a few argument points to discuss the value of both mtDNA and nuclear DNA linkages, as well as the implications of severing each, ideally in a manner that contributes to future discussions on this topic.

Several infertility treatment technologies (e.g., in vitro fertilization for infertility, or pre-implantation genetic diagnosis to avoid habitual abortions) incorporate the practice of seeking a nuclear DNA linkage with the child. In other words, if nuclear DNA linkage was not so persistently sought after and a couple is having difficulty becoming pregnant, then their options would be to give up on having children, adoption, fostering, or using an egg donor. The same would apply to mitochondrial replacement [12]. Of course, some also view these desires for a nuclear DNA linkage and the technology that evokes this desire in some individuals with skepticism [33]. Even so, it is difficult to conclude that the desire to have a child with nuclear DNA linkage in its entirety is unreasonable or preposterous, or that such a desire is completely socially constructed [34]. If that is the case, at the very least, the possibility exists that our society does, in fact, perceive some form of value in

nuclear DNA linkage, despite the myriad of problems inherent to this.

What can we conclude about mtDNA linkage? One characteristic of mtDNA is that it is shared all along the maternal lineage; is it problematic to sever this linkage? Very few discussions are ongoing concerning this point, either within or outside of Japan, and Japan must also revisit this discussion and conduct bioethical research studies to this end. However, as stated in section 3-3, if mtDNA is responsible for 0.1% or less of phenotype, and the primary concern is to have a child who (phenotypically) resembles the parents, then the nuclear DNA linkage should be sufficient and mitochondrial replacement (which would sever mtDNA linkages while maintaining nuclear DNA linkages) should not be problematic to perform.

5. Conclusions

In the present paper, I have attempted to organize arguments from previous studies while providing a critical discussion of the ethical ramifications of allowing mitochondrial replacement to address the genetic issues of egg cells in women with mitochondrial disease. I am likely the first group from Japan to have examined the ethical aspects of mitochondrial replacement, particularly with regard to the ethical implications of giving birth to children with "three genetic parents." I was unfortunately unable to discuss all arguments in full, simply because I aimed to represent as many issues as possible that will serve as the foundation for future discussions in Japan. As mentioned in Section 4 above, a societal-level discussion is needed to evaluate the worth of mtDNA linkages and what it means to sever these, in a manner that incorporates deeper bioethical research studies and pays attention to the various stakeholders involved. In addition, in the event that mitochondrial replacement is implemented in Japan, it would likely begin as a clinical study, so a framework with research regulations must be organized for this technology. If the present paper could be used to help pioneer this discussion, then I have sufficiently accomplished my objectives.

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